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Polymorphism Arg290Arg in Esophageal-Cancer-Related Gene 1 (ECRG1) is a Prognostic Factor for Survival in Esophageal Cancer

Kai Bachmann · Shanly Shahmiri · Jussuf Kaifi · Paulus Schurr · Oliver Mann · Tamina Rawnaq · Suzette Block · Viacheslav Kalinin · Jakob R. Izbicki · Tim Strate

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Abstract
Background Esophageal cancer is one of the most frequent cancers worldwide and is associated with poor outcome. Besides clinicopathological data, few prognostic molecular markers exist. Esophageal-cancer-related gene1 (ECRG1) short tandem repeats are associated with higher risk for developing esophageal squamous cell carcinoma. The aim of the present study was to evaluate the impact of DNA polymorphisms in the coding region of ECRG1 in esophageal carcinoma.
Methods Genomic DNA of 107 patients with esophageal cancer that underwent complete surgical resection between 1997 and 2005 was extracted. DNA was analyzed for ECRG1 polymorphisms Arg290Arg, Arg290Gln, and Gln290Gln by PCR and gel electrophoresis. Polymorphisms were correlated with survival data by the Kaplan–Meier method, multivariate Cox regression analysis, and odds ratio were determined. For all variables, cross tables were generated, followed by calculation of the p value by using the chi-square test/Fisher-exact test.
Results Follow-up data of 102 patients with esophageal cancer were available after complete surgical resection for a median follow-up time of 24.3 months. Polymorphism Arg290Arg was found in 47 patients (46.1%), Arg290Gln in 48 patients (47.0%), and Gln290Gln in seven cases (6.9%). Arg290Arg polymorphism was significantly associated with reduced overall survival (p=0.01) and tumor-free survival (p=0.01) by the log-rank test. Multivariate regression analysis by Cox revealed polymorphism Arg290Arg to be a significant prognostic factor for survival (p=0.012).
Conclusions Polymorphism Arg290Arg in ECRG1 is associated with poor clinical outcome after complete surgical resection in patients with esophageal cancer.

Keywords Esophageal-cancer-related gene1 · ECRG1 · Prognostic factor · Risk factor · DNA polymorphism · Esophageal cancer

Introduction

Esophageal cancer ranks among the ten most frequent cancers worldwide and has a very aggressive clinical behavior.[1,2] In the United States and Western Europe, esophageal carcinoma is currently the most rapidly increasing cancer.[3–5] Risk factors include smoking, heavy consumption of alcohol, micronutrient deficiency, and dietary carcinogen exposure.[6–8] Usually, the tumor is detected in an advanced stage, and the reported 5-year survival rate ranges from 10% to 36% after surgical resection.[9,10]

The reason for poor outcome after surgical resection is the extensive local invasion and frequent regional lymph node metastasis. Age of the patient, depth of tumor invasion, and presence of metastasis in lymph nodes and peripheral organs are well-known prognostic factors. Besides these clinicopathological data, different molecular markers have been examined for their impact on prediction of development and prognosis in esophageal cancer. However, only few powerful markers currently exist.[11]

K. Bachmann (✉) · S. Shahmiri · J. Kaifi · P. Schurr · O. Mann · T. Rawnaq · S. Block · V. Kalinin · J. R. Izbicki · T. Strate
Department of General, Visceral, and Thoracic Surgery,
University Medical Center Hamburg-Eppendorf,
Martinistrasse 52,
20246 Hamburg, Germany
e-mail: k.bachmann@uke.uni-hamburg.de

Esophageal-cancer-related Gene1 (ECRG1) is a recently-found tumor suppressor gene that has an impact on the regulation of cell proliferation and cell cycle.[12] Previous studies have shown that ECRG1 is downregulated in esophageal cancer. Additionally in vivo and in vitro overexpression of ECRG1 was found to inhibit tumor cell proliferation.[13,14] Mutation and genetic polymorphisms in coding sequences of a gene may cause functional alterations. Screening the coding region of ECRG1 for single nucleotide polymorphisms, a variant allele in exon 8 resulting in expression of glutamine or arginine in codon 290 was identified by PCR-based SSCP and DNA sequencing.[15,16] The aim of this study was to reveal the impact of these DNA polymorphisms in the coding region of ECRG1 for the prognosis after complete surgical resection of esophageal cancer.

Materials and Methods

Study Design and Patients

This study was approved by the ethics committee of the Hamburg Medical Association (Hamburg/Germany). Patients with esophageal cancer that underwent surgery in the Department of Surgery at the University Medical Center Hamburg–Eppendorf between 1997 and 2005 were included after histopathological confirmation, if complete surgical resection with tumor-free resection margins on histopathological examination of the surgical specimen (R0) was performed. Patients that died during the hospitalization were excluded.

Written informed consent to follow up and genetic analysis on their blood and tumor was obtained from the patients. Overall, 107 consecutive patients meeting the inclusion criteria and signed the consent were included in this trial. All patients were Caucasian. Tumor stage and grade were classified according to the most recent TNM classification of the International Union Against Cancer.[17,18] Five patients had to be excluded in analysis of the survival because they were lost to follow-up.

Clinicopathological Data

All data including sex, histology, depth of tumor invasion, lymph node metastasis, grading, and disease stage were obtained from the clinical and pathological records. Clinical follow-up data were retrieved by reviewing the hospital records, direct communication with patients or the attending physicians, and from the Hamburg Cancer Registry. Tumor-free and overall survival was calculated from the date of surgical resection of the tumor to the date of death or last follow-up. Altogether, the median follow-up period was 24.3 (range 1.7–58.2) months.

Analysis of DNA Polymorphism

A 5-ml sample of peripheral blood was taken in the operation theater preoperatively in all patients. The time of taking blood has no influence on this analysis because the marker is genetically fixed. Genomic DNA was extracted from peripheral blood leukocytes and purified according to established protocols using the QIAamp Blood Tissue Kit (Qiagen, Hilden, Germany). The PCR amplification was accomplished with a 25-μl reaction mixture consisting of 50 ng template DNA, 0.4 μM each primer, 0.2 mM each deoxynuccleotide-triphosphate (dNTP), 2.0 mM $MgCl_2$ and 1.0 U Taq DNA polymerase with 1× reaction buffer (Takara, Japan). PCR primers for amplifying DNA fragment containing the polymorphism were 5-CAGGGCTTAGCGCTCTGTTA-3 and 5-GCTCATATACTTTGGGCAGCTT-3 that produce a 354-bp fragment. The reaction conditions consisted of an initial melting step of 2 min at 94°C; followed by 35 cycles of 30 s at 94°C, 30 s at 58°C and 30 s at 72°C; and a final elongation step of 7 min at 72°C. The 290 Gln/Gln genotype has a single band representing the entire 354-bp fragment, the variant 290 Arg/Arg genotype results in two fragments of 232 and 122 bp; the heterozygous 290 Arg/Gln genotype has all three fragments of 122, 232, and 354 bp. The restricted product was analyzed by electrophoresis in a 2% agarose gel stained with ethidium bromide. Three genotypes revealed by RFLP with MspI digestion were confirmed by DNA sequencing (Fig. 1). Positive and negative controls were used in the RFLP-PCR assay. All samples were analyzed in duplicate; the results were consistent in all cases. The agarose gels were read independently by two persons blinded to the study. The concordance of PCR analysis and sequencing was 100%.

Statistical Analysis

We used SPSS® for Windows® (Version 11.5.1; SPSS Inc., Chicago, IL) for statistical analysis. Survival curves of the patients were plotted using the Kaplan–Meier method and analyzed using the log-rank test. Cox regression analysis

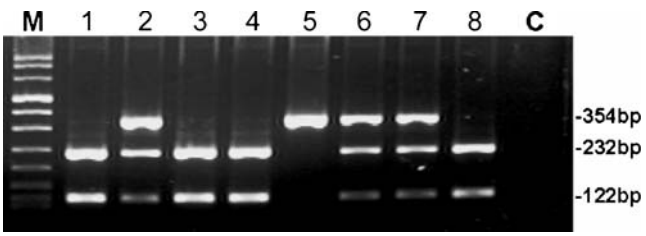

Figure 1 Electrophoresis of ECRG 1. Electrophoresis in a 2% agarose gel stained with ethidium bromide. The 354 bp fragment represents the Gln290Gln genotype; the variant Arg290Arg genotype results in two fragments of 232 and 122 bp; the heterozygous Arg290Gln genotype has all three fragments of 122, 232, and 354 bp.

was used for multivariate analysis to assess the independent influence polymorphism Arg290Arg simultaneously with other covariates. Significance statements refer to p values of two-tailed tests that were less than 0.05. For correlation analysis cross tables were generated for all variables, followed by calculation of the p value by using the chi-square test/Fisher-exact test. Patient's data and blood were collected prospectively, while no data of frequencies of the different alleles in the Caucasian population and impact on prognosis were available. Therefore, no statistical power analysis was performed prior to the study.

Results

Characteristics of the Patients

A total of 107 patients with esophageal cancer were chosen for this study. Characteristics of patients are listed in Table 1. The median age was 62 years; all patients were Caucasian. Eighty-seven patients (81.3%) were male and 20 patients (18.7%) female. Histopathological examination revealed adenocarcinoma in 41 (38.3%) patients and squamous cell carcinoma in 66 (61.7%) patients. Analyzing the distribution of the DNA polymorphism in adenocarcinoma and squamous cell carcinoma with Fisher's exact test showed no significant association (p=0.681). Therefore, both histologies were analyzed together as esophageal cancer. The invasion depth/tumor size was classified in histopathological examination as pT1 in 19 (17.8%) patients, pT2 in 30 (28.0%), pT3 in 46 (43.0%), and pT4 in 12 (11.2%) patients. Thirty-one (29.0%) of the patients had no lymph node metastases (pN0), while lymph node metastases were found in 76 (71.0%) patients. Tumor grading was classified as G1 in ten (9.3%) patients, G2 in 47 (43.9%), and G3 in 50 (46.7%) patients.

Transthoracic esophagectomy was performed in 68 patients, while transhiatal approach was used in 39 patients. A radical lymphadenectomy was performed in all patients. The median numbers of resected lymph nodes was 31 (19–43) in the transthoracic group and 25 (15–34) in the transhiatal group. The distribution of the number of resected lymph nodes and operative approach were comparable concerning the different alleles and had no significant influence on survival. Forty-five patients underwent adjuvant treatment, while no patient received neoadjuvant therapy.

The distribution of DNA polymorphisms in ECRG1 according to age, sex, tumor invasion depth (pT), and presence of lymph node metastasis (pN) is listed in Table 1. No clinical or pathological factor was associated with the polymorphism frequency in ECRG1 (age (p=0.847), sex (p=0.470), adjuvant therapy (p=0.654), tumor size (p=0.564), lymph nodes (p=0.288), grading (p=0.836), and histology of the tumor (p=0.564)) using the chi-squared/Fisher's exact test. Analyzing distribution of the concerning the univariate statistical analysis using the

Table 1 Clinicopathological Characteristics of Esophageal Cancer Patients' DNA Polymorphism in Esophageal Cancer Related Gene 1 (ECRG1)

Variable	No. of Patients		ArgArg		ArgGln		GlnGln		Gln allele	
Sex										
Male	87	81.3%	43	40.2%	40	37.4%	4	3.7%	44	41.1%
Female	20	18.7%	8	7.5%	9	8.4%	3	2.8%	12	11.2%
Age										
≤62	50	46.7%	23	21.5%	23	21.5%	4	3.7%	27	25.2%
>62	57	53.3%	28	26.2%	26	24.3%	3	2.8%	29	27.1%
Tumor depth										
Invading the submucosa (pT1)	19	17.8%	7	6.5%	10	9.3%	2	1.9%	12	11.2%
Invading the muscularis propria (pT2)	30	28,0%	17	15.9%	11	10.3%	2	1.9%	13	12.1%
Invading the adventitia (pT3)	46	43.0%	22	20.6%	22	20.6%	2	1.9%	24	22.4%
Invading contiguous structures (pT4)	12	11.2%	5	4.7%	6	5.6%	1	0.9%	7	6.5%
Lymph nodes										
No lymph node metastasis (pN0)	31	29.0%	12	11.2%	17	15.9%	2	1.9%	19	17.8%
Lymph node metastasis (pN1)	76	71.0%	39	36.4%	32	29.9%	5	4.7%	37	34.6%
Grading										
Well differenciated (G1)	10	9.3%	4	3.7%	5	4.7%	1	0.9%	6	5.6%
Moderate differenciated (G2)	47	43.9%	22	20.6%	21	19.6%	4	3.7%	25	23.4%
Poorly differenciated (G3)	50	46.7%	25	23.4%	23	21.5%	2	1.9%	25	23.4%
Histology										
Adenocarcinoma	41	38.3%	21	19.6%	18	16.8%	2	1.9%	20	18.7%
Squamous cell carcinoma	66	61.7%	30	28.0%	31	29.0%	5	4.7%	36	33.6%
Total	107	100.0%	51	47.7%	49	45.8%	7	6.5%	56	52.3%

log-rank test revealed a significantly poorer prognosis for survival for older patients (>62 years; $p=0.034$), patients with presence of lymph node metastasis ($p=0.024$), increasing invasion depth/tumor size ($p=0.046$), and grading ($p=0.047$). No significant differences were found comparing adenocarcinoma and squamous cell carcinoma ($p=0.175$). No significant impact on survival was found for the number of resected lymph nodes ($p=0.541$) or adjuvant treatment ($p=0.681$). Therefore, these parameters had to be excluded from multivariate Cox regression analysis.

DNA Polymorphism

Peripheral blood taken on the day of surgery was examined in 107 patients. Genomic DNA was extracted and analyzed for polymorphism in ECRG1. Arg290Arg was found in 51 (47.7%) patients, Arg290Gln in 49 (45.8%) and Gln290Gln in seven (6.5%) samples. The median overall survival in patients with Arg290Arg was 17.0 months (95% CI 9.6–24.4). The median survival for Arg290Gln was 30.8 months (95% CI 20.7–40.9), for Gln290Gln 39.9 months (95% CI 6.8–72.9), and for the presence of at least one Gln allele 30.8 months (95% CI 23.0–38. 6). Survival curves plotted by the Kaplan–Meier method for DNA polymorphism ECRG1 for overall survival are shown in Fig. 2 (Arg290Arg vs. Arg290Gln vs. Gln290Gln). In Fig. 3, the survival curves Arg290Arg versus presence of the Gln allele (Arg290Gln and Gln290Gln) in ECRG1 are plotted. Statistical analysis using the log-rank test revealed that patients with polymorphism Arg290Arg in ECRG1 had a significantly poorer prognosis ($p=0.038$); comparing Arg290Arg with Arg290Gln, significantly poorer prognosis was confirmed ($p=0.015$). Analyzing the impact of the presence of the Gln allele (Arg290Gln and Gln290Gln) in ECRG1 versus Arg290Arg, a significantly shorter overall survival was found in univariate analysis ($p=0.01$).

Multivariate analysis using Cox regression revealed Arg290Arg (versus Arg290Gln and Gln290Gln) as prognostic marker for survival ($p=0.012$) with a relative risk of 2.016 (95% CI 1.164–3.493; Table 2). Analyzing the DNA polymorphism (Arg290Arg vs. Arg290Gln vs. Gln290Gln), it was found to be a prognostic marker for survival ($p=0.046$) in multivariate analysis as well. The relative risk was found to be 1.630 (95% CI 1.009–2.633; Table 3). Age, grading, and invasion depth/tumor size (pT) were found to be prognostic factors for survival as well. Presence of lymph node metastasis was found to be a prognostic factor in univariate log rank test ($p=0.024$); it could not be identified as independent prognostic factor ($p=0.610$) in multivariate analysis.

Analyzing the tumor-free survival, DNA polymorphism of the ECRG1 ($p=0.01$), lymph node status (0.03) and tumor invasion depth ($p=0.02$) were identified to be prognostic factors in univariate log rank test. No significant impact on tumor-free survival could be detected for age ($p=0.12$), sex ($p=0.06$), grading ($p=0.12$), and histology ($p=0.39$). Therefore, the polymorphism, lymph node status, and tumor invasion depth were included in multivariate Cox regression analysis. In multivariate analysis, tumor invasion depth ($p=0.03$) and presence of Arg290Arg polymorphism ($p=0.01$) were confirmed as prognostic factors.

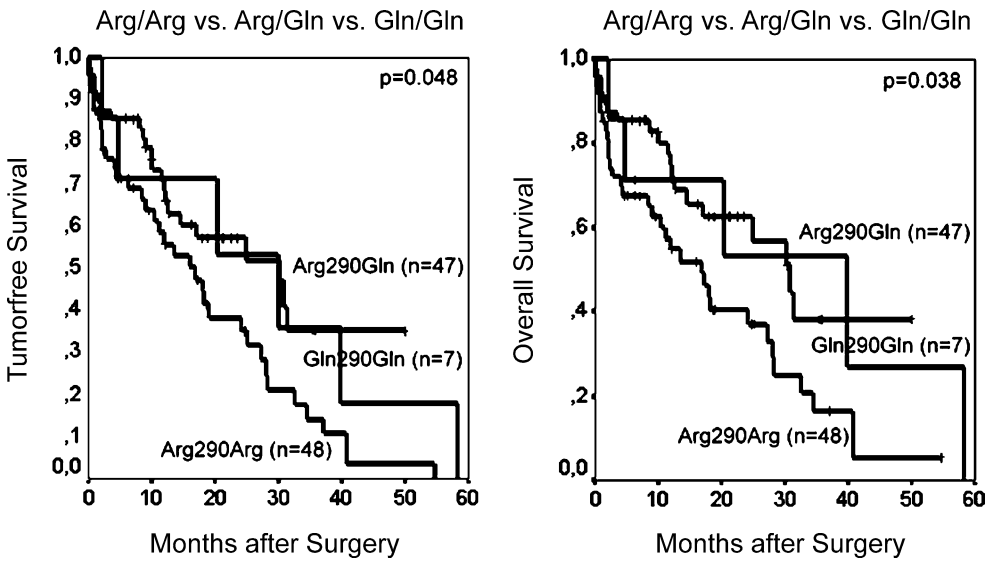

Figure 2 **a**, **b** Kaplan–Meier analysis for overall survival for DNA polymorphism in ECRG1. (Arg290Arg vs. Arg290Gln vs. Gln290Gln) in patients with esophageal cancer after curative esophagectomy. Kaplan–Meier analysis for tumor-free and overall survival for DNA-Polymorphism in ECRG1.P value was calculated with two-sided log-rank test. The median overall survival of patients with 290Arg290 was 17.0 months (95% CI 9.6–24.4). For Arg290Gln the median overall survival was 30.8 months (95% CI 20.7–40.9) and 39.9 months (95% CI 6.8–72.9) for Gln290Gln. The median tumor-free survival of patients with 290Arg290 was 17.0 months (95% CI 13.3–22.7). For Arg290Gln the median survival was 30.1 month (95% CI 15.0–45.3) and 30.0 months (95% CI 2.6–57.4) for Gln290Gln.

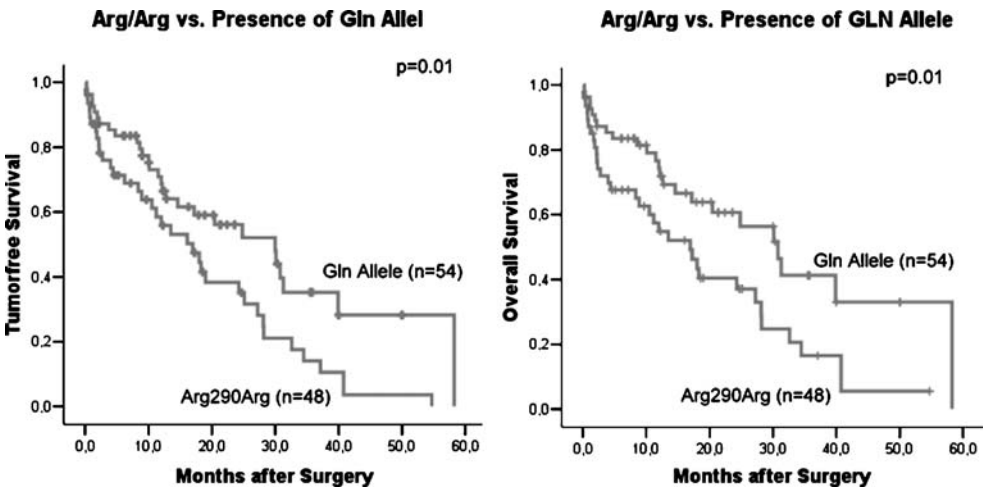

Figure 3 **a**, **b** Kaplan–Meier analysis for overall survival for presence of Gln allele in ECRG1. (Arg290Arg vs. Arg290Gln and Gln290Gln) in patients with esophageal cancer after curative esophagectomy. Kaplan–Meier analysis for tumor-free and overall survival for presence of Gln allele in ECRG1. P value was calculated with two-sided log-rank test. The median overall survival of patients with 290Arg290 was 17.0 months (95% CI 9.6–24.4), 30.8 months (95% CI 23.0–38.6) for presence of at least one Gln allele. The median tumor-free survival of patients with 290Arg290 was 17.0 months (95% CI 13.3.–22.7), respectively 29.1 months (95% CI 22.2–36.1) for presence of at least one Gln allele.

To analyze the impact of the polymorphism, the patients were grouped according to UICC classification. Twelve patients were grouped to UICC I. Due to a limited number of patients and number of deaths (only one patient died), survival analysis including Kaplan-Meier and calculation of log rank test is not possible. Analyzing the 40 patients with UICC II (A+B) stage, no significant impact of the ECRG1 polymorphism on survival was identified. In the 50 patients that were grouped to UICC III, Arg290Arg was found to be a predictor for poorer prognosis concerning tumor-free survival (p=0.008) and overall survival (p=0.025).

Discussion

This study detected ECRG1 polymorphism Arg 290Arg as prognostic factor for survival after complete surgical resection of esophageal cancer. The Arg290Arg polymorphism is associated with significantly poorer prognosis for tumor-free and overall survival. In multivariate analysis, age, grading, and tumor invasion depth were also found to be associated with prognosis concerning overall survival. It has to be mentioned that the size of the study population (n=107) is a limitation of the power of this trial, but even in patients with UICC III, the polymorphism Arg290Arg was identified as poor prognostic factor. In univariate analysis, positive lymph nodes were identified as poor prognostic factor for overall and tumor-free survival, but lymph node status was not significant in a multivariate model with other, more highly associated covariates. This might be caused by the association between tumor size and lymph node metastasis and the limited number of patients in this trial.

Table 2 Multivariate Analysis by *Cox* Regression for Overall Survival for Various Factors (n=102) for Presence of Gln Allele in ECRG1

Overall survival	Odds ratio/95%CI[a]	*P* value
Age(<62 vs. >62)	1.831 (1.047–3.202)	0.034
Tumor invasion depth (pT1/2vs. T3/4)	1.687 (1.135–2.510)	0.010
Lymph node metastasis (pN0 vs. N1)	1.266 (0.511–3.133)	0.610
Grading (G1/2 vs. G3)	1.765 (1.034–3.015)	0.037
AA vs. AG and GG	2.016 (1.164–3.493)	0.012

[a] *CI* Confidence interval. Statistics were done by multivariate Cox regression analysis. All statistical tests were two-sided. Odds ratio presented are for overall survival

Table 3 Multivariate Analysis by *Cox* Regression for Overall Survival for Various Factors (n=102) for DNA Polymorphism in ECRG1

Overall survival	Odds ratio/95%CI[a]	P value
Age (<62 vs. >62)	1.814 (1.035–3.179)	0.037
Tumor invasion depth (pT1/2 vs. T3/4)	1.635 (1.104–2.421)	0.014
Lymph node metastasis (pN0 vs. N1)	1.346 (0.546–3.320)	0.519
Grading (G1/2 vs. G3)	1.716 (1.009–2.917)	0.046
Polymorphism (AA vs. AG vs. GG)	1.630 (1.009–2.633)	0.046

[a] *CI* Confidence interval. Statistics were done by multivariate Cox regression analysis. All statistical tests were two-sided. Odds ratio presented are for overall survival

Besides age, tumor invasion depth, lymph node status, and presence of peripheral metastases, different predictive and prognostic markers in esophageal cancer have been described in the past without proceeding to widespread clinical use. In this trial, adenocarcinoma and squamous cell carcinoma were included and grouped together, because prognosis and surgical treatment are comparable; additionally, the expression of DNA polymorphism of the ECRG1 showed no significant difference between both groups.

Expression of different proteins such as EGFR, COX2, p53, and TGF β was found to be associated with the aggressiveness of tumors or shorter survival.[19–23] Therefore, these might be predictive markers for response to radiochemotherapy.[20,21,24–26]

Genomic DNA polymorphisms are stable and do not change throughout one's lifetime since they are genetically fixed. They can be detected consistently in contrast to protein expression analysis. Only few genetic markers have been evaluated for their clinical impact. Alterations of genes involved in the cell cycle control (p21, p27) are associated with outcome. Cyclin D1 polymorphisms were found to be associated with genomic instability and poorer prognosis in esophageal carcinoma in a recent study.[27] High levels of Bax and low levels of Bcl-X are associated with longer overall survival.[28–31] Recently polymorphism TCA_3/TCA_3 in exon 4 of the esophageal-cancer-related gene 2 (ECRG2) was found to be an independent prognostic factor for poor survival in esophageal and oral squamous cell cancer.[32–34] The use of diagnostic analysis of DNA polymorphisms is increasing rapidly in the last months. Different polymorphisms have been published in patients with cancer[35–37] but also in other diseases such as Parkinson's disease.[38]

ECRG1 is a member of the membrane anchored serine protease domains that play a role in proteolytic activity. In vivo and in vitro assays revealed that overexpression of ECRG1 protein inhibits tumor cell proliferation. ECRG1 was able to induce an arrest of the cell cycle in a cell line in an experimental setting. Therefore, ECRG1 might play a role in development of esophageal cancer.[39]

Li et al. found the polymorphism in codon 290 in exon 8 to be a predictive factor in the Chinese population in development of esophageal cancer in a study including 998 patients and 1,252 controls. The genotype Arg290Gln was associated with slightly higher risk for developing esophageal cancer. In association with smoking, the presence of this genotype Arg290Gln was a significant factor for development of squamous cell carcinoma.[16] No data of impact on survival was provided in this trial. This study is the first to analyze the impact of DNA polymorphism of ECRG1 on prognosis of the patients so no comparable results are available. Further trials are necessary to evaluate the impact of ECRG1 on developing esophageal cancer and its prognosis and potential therapeutic management.

Conclusion

In this trial, we could detect the genotype Arg290Arg to be a prognostic factor for poorer tumor-free and overall survival in esophageal cancer. The evaluation of the impact of the polymorphism of ECRG1 on development and prognosis of cancer has to be explored in the future. Further trials are needed to evaluate the potential of our findings and its possible impact as a new starting point for adjuvant or neoadjuvant therapy.

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2008 SSAT ANNUAL MEETING

Laparoendoscopic Single Site (LESS) Cholecystectomy

Steven E. Hodgett · Jonathan M. Hernandez · Connor A. Morton · Sharona B. Ross · Michael Albrink · Alexander S. Rosemurgy

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Abstract
Introduction The journey from conventional "open" operations to truly "minimally invasive" operations naturally includes progression from operations involving multiple trocars and multiple incisions to operations involving access through the umbilicus alone. Laparoscopic operations through the umbilicus alone, laparoendoscopic single site surgery (LESS), offer improved cosmesis and hopes for less pain and improved recovery. This study was undertaken to evaluate our initial experience with LESS cholecystectomy and to compare our initial experience to concurrent outcomes with more conventional multiport, multi-incision laparoscopic cholecystectomy.
Methods All patients referred for cholecystectomy over a 6-month period were offered LESS. Outcomes, including blood loss, operative time, complications, and length of stay were recorded. Outcomes with our first LESS cholecystectomies were compared to an uncontrolled group of concurrent patients undergoing multiport, multi-incision laparoscopic cholecystectomy at the same hospital by the same surgeon.
Results Twenty-nine patients of median age 50 years undergoing LESS cholecystectomy from November 2007 until May 2008 were compared to 29* patients, median age 48 years, undergoing standard multiport, multiple-incision laparoscopic cholecystectomy over the same time period. Median operative time for patients undergoing LESS cholecystectomy was 72 min and was not different from that of patients undergoing multiport, multi-incision laparoscopic cholecystectomy ($p=0.81$). Median length of hospital stay was 1.0 day for patients undergoing LESS cholecystectomy and was not different from patients undergoing standard laparoscopic cholecystectomy ($p=0.46$). Operative estimated blood loss was less than 100 cc for all patients. No patients undergoing attempted LESS cholecystectomy had conversions to "open" operations; two patients had an additional trocar(s) placed distant from the umbilicus to aid in exposure. Three patients undergoing LESS cholecystectomy had complications: two were troubled by pain control and another had urinary retention.
Conclusions LESS cholecystectomy is a safe and effective alternative to standard laparoscopic cholecystectomy. It can be undertaken without the expense of added operative time and provides patients with minimal, if any, apparent scarring. We believe LESS cholecystectomy will be driven by consumer demand, and therefore, laparoscopic surgeons will need to become proficient with LESS procedures.

Keywords Laparoendoscopic single site (LESS) Surgery · Cholecystectomy · Minimally invasive · Umbilicus · Laparoscopic cholecystectomy

S. E. Hodgett · J. M. Hernandez · C. A. Morton · S. B. Ross · M. Albrink · A. S. Rosemurgy (✉)
Department of Surgery, University of South Florida,
Tampa General Hospital,
P.O. Box 1289, Tampa, FL 33601, USA
e-mail: arosemur@health.usf.edu

Introduction

The first cholecystectomy was undertaken in 1882 by Langenbuch through a subcostal incision. His technique became the standard of care, remaining essentially unchanged for over a century. In 1987, Phillipe Mouret was credited with the first laparoscopic cholecystectomy using video technology, marking the beginnings of the minimally invasive revolution in General Surgery. Laparoscopic cholecystectomy is currently the standard of care for

gallbladder removal, with the open technique being largely reserved for failure of laparoscopic resection.[1] Today, we stand on the brink of a technological explosion that may drive surgery from small incisions to incisionless.[2–8]

Natural orifice transluminal endoscopic surgery (NOTES) may represent the final frontier for the minimally invasive revolution—surgery without incisions.[2,9–15] However, laparoendoscopic single site (LESS) cholecystectomy can be implemented now. LESS approaches "no scar" surgery and may not be associated with any significant learning curve beyond standard laparoscopic cholecystectomy. Furthermore, LESS offers the potential advantages of decreased postoperative pain and shortened, if any, postoperative hospitalization.

Our institution began focusing on LESS within the last year and subsequently developed a technique for laparoendoscopic single site cholecystectomy. We herein report our technique and results with the first 29 patients undergoing LESS cholecystectomy. Our hypothesis in implementing LESS cholecystectomy is that it would offer similar operative time, length of stay, and complication profile with improved cosmesis and less postoperative pain in comparison to traditional multiport, multi-incision laparoscopic cholecystectomy.

Methods

From November 2007 until May 2008, 29 patients referred with gallbladder pathology requiring cholecystectomy were operated upon with the general intent of undertaking LESS. One surgeon (MA) participated in all operations. Operative time, defined as the time from incision to time of closure, blood loss, complications, and length of stay were recorded. Outcomes of 20 patients undergoing multiport, multi-incision laparoscopic cholecystectomy during the same time period, by the same surgeon, were also recorded. In order to compare an equal number of patients, the last nine standard laparoscopic cholecystectomies undertaken prior to the time of first LESS cholecystectomy were included in the analysis. The results of patients undergoing LESS cholecystectomy or standard laparoscopic cholecystectomy were compared utilizing the Mann–Whitney *U* test. Data are presented as median, mean±SD.

Operative Technique

Patients were placed in supine position with the operating surgeon on the patients' left and the assistant on the patients' right. A 10-mm longitudinal incision is made through the umbilicus and the natural umbilical defect is used to enter the peritoneum. A 5-mm blunt port is inserted into the peritoneum and the abdomen is insufflated. Air leaks at port sites must be avoided. A 0°, 5-mm laparoscope is inserted into the port to assure adequate pneumoperitoneum. A second 5-mm working port (with a sharp trocar) is placed in the same incision superiorly to the camera port through a second fascial insertion. This technique diminishes the amount of air leak to a negligible level. Attention is then turned to the gallbladder.

Any adhesions to the fundus of the gallbladder are dissected free as the fundus is made visible. A 2–0 polyproprolene suture on a Keith needle is inserted through the abdominal wall subcostally at approximately the midclavicular line. This needle is then grasped intracorporally and placed through the fundus of the gallbladder. The needle is then returned through the abdominal wall near the original insertion. With retraction, the fundus of the gallbladder is lifted to the anterior abdominal wall, exposing the infundibulum of the gallbladder as well as the triangle of Callot (Fig. 1). A second suture is then inserted subxiphoid through the skin, grasped, and then placed through the infundibulum in a medial to lateral direction. This suture is then placed, quite laterally on the patient's right, through the abdominal wall. A 5-mm clip applier is then inserted through the working port, and clips are applied to the medial and lateral aspects of the infundibulum at the insertion and exit of the latter suture. This permits a "puppeteering" of the infundibulum to allow excellent exposure of Callot's triangle and the liver–gallbladder interface. Attention is then turned to the dissection of the cystic duct. This may be facilitated by the use of articulating laparoscopic dissectors. The cystic duct and artery are dissected free, clipped, and divided.

The gallbladder is then dissected free off the liver bed with hook cautery. After the gallbladder is free, it is grasped with a locking grasper and withdrawn through the umbilicus as both ports are removed. The umbilical port is dilated and, if needed, the two fascial incisions are joined and the gallbladder drained to facilitate removal. The umbilical incision is closed with fascial and skin sutures.

Results

Twenty-nine patients underwent LESS cholecystectomy from November 2007 through May 2008 (Table 1). Median age of patients undergoing LESS cholecystectomy was 51 years. Twenty-nine patients underwent standard laparoscopic cholecystectomy (three- or four-port cholecystectomy through three or four incisions, including the umbilicus). The median age of patients undergoing standard cholecystectomy was 46 years. Median body mass index (BMI) for all patients was 28 kg/m^2. No patients had acute cholecystitis; 22 patients undergoing LESS cholecystectomy and 21 patients undergoing multiport, multi-incision

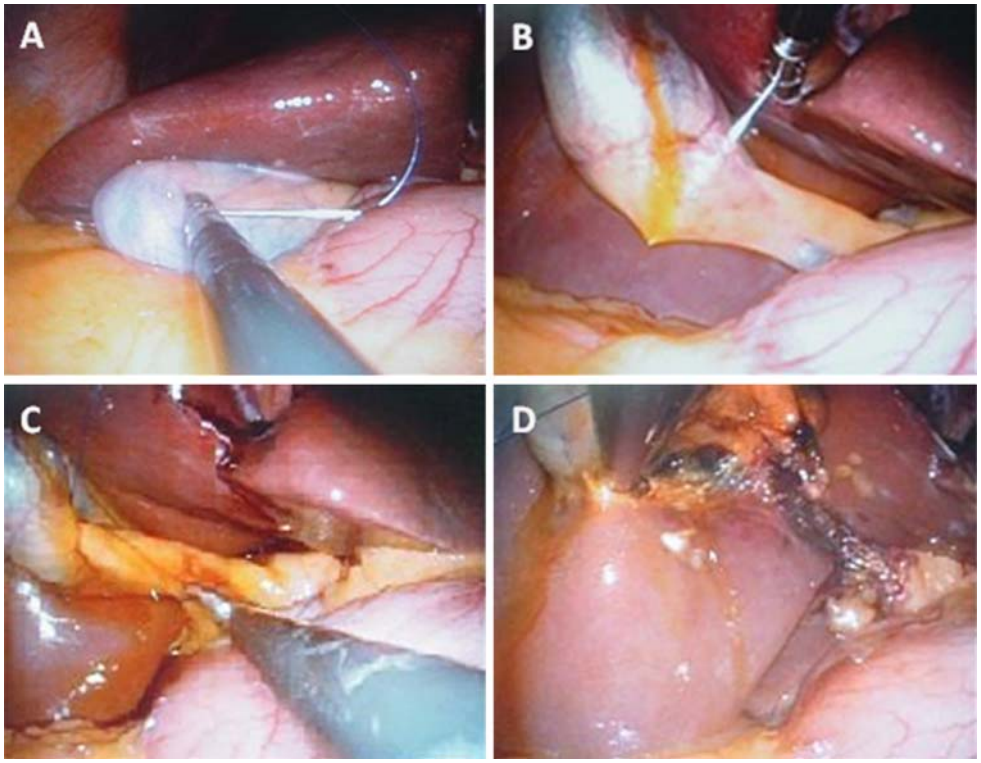

Figure 1 A Keith needle is placed through the fundus of the gallbladder to provide initial exposure (**a**). A second Keith needle is placed near the gallbladder infundibulum to facilitate exposure of the cystic duct and artery (**b**). Suture retraction of both the fundus and infundibulum provide excellent exposure for dissection (**c**). After identification and clipping of the cystic duct and artery, the gallbladder is dissected from the liver using electrocautery (**d**).

laparoscopic cholecystectomy had chronic cholecystitis. Operative time for patients undergoing LESS cholecystectomy was 72 min (74 min±17.3) vs. 66 min (71 min±16.3) for those undergoing standard laparoscopic cholecystectomy (p=0.46). All patients had less than 100 cc of estimated blood loss. No patients required conversion to an "open" operation. Two patients undergoing LESS cholecystectomy required placement of additional trocar(s) away from the umbilicus in order to facilitate exposure. These patients were considered to have undergone LESS cholecystectomy for the purposes of the comparison. No major postoperative complications occurred in any patients. Two patients undergoing LESS cholecystectomy required extended postoperative stays for pain control. One patient undergoing LESS cholecystectomy required catheter insertion for urinary retention. Length of stay for patients undergoing LESS cholecystectomy was 1 day (1 day±0.61) vs. 1 day (1 day±0.51) for those patients undergoing standard laparoscopic cholecystectomy (p=0.81). No biliary injuries or complications occurred in any patients.

Discussion

LESS, driven by consumer demand and fueled by technological explosion, is the next step along the path to incisionless procedures. LESS allows the incision to be hidden in the umbilicus. Unlike NOTES, which faces obvious hurdles in safety,[15] single incision transumbilical laparoscopy, e.g., LESS cholecystectomy, is ready for

Table 1 A Comparison of 29 LESS Cholecystectomies vs. 29 Multiport, Multi-incision Laparoscopic Cholecystectomies

	Single-incision laparoscopic cholecystectomy	Multiple-incision laparoscopic cholecystectomy	p value
Number of patients	29	29	N/A
Gender	6 males/23 females	9 males/19 females	NS
Age	51 years (50 years±16.2)	46 years (48 years±16.7)	NS
BMI	28 kg/m^2 (28 kg/m^2±5.5)	28 kg/m^2 (29 kg/m^2±7.0)	NS
Length of operation	72 min (74 min±17.3)	66 min (71 min±16.3)	NS
Blood loss	Minimal in 100%	Minimal in 100%	NS
Pathology	Chronic cholecystitis (76%)	Chronic cholecystitis (72%)	NS
Complications	Pain control (2) Urinary incontinence (1)	None	NS
Length of stay	1 day (1 day±0.61)	1 day (1 day±0.51)	NS

widespread implementation. We have outlined a safe technique for LESS cholecystectomy, which can be undertaken safely and with similar operative time. Exposure is nearly equivalent to standard laparoscopic cholecystectomy, and any inadequacies can be remedied with the addition of a 3- to 5-mm trocar away from the umbilicus. This report documents the largest LESS experience to date and serves as the prelude to a randomized prospective trial comparing LESS cholecystectomy with standard laparoscopic cholecystectomy.

The BMI of patients undergoing LESS cholecystectomy were similar to patients undergoing multiport, multi-incision laparoscopic cholecystectomy in this report. As a group, these patients are representative of the average patients presenting with complaints of biliary pathology to general surgeons across America. In other words, patients undergoing LESS cholecystectomy in this report did not represent a highly selected group of patients based upon anticipated technical ease, with the exception of patients with acute cholecystitis. All patients seen in clinic during the 6-month period specified were offered LESS cholecystectomy. After a detailed explanation of the procedure, 20 patients refused in favor of a standard laparoscopic cholecystectomy. The reason for this refusal varied from patient to patient but was felt by the surgeon obtaining consent to be related to the nascent procedure about which definitive conclusions regarding safety and complication rates could not be given. It was not and is not our practice to coerce patients after any hesitation or indecisiveness.

Additional 5-mm trocars were placed in two patients undergoing LESS cholecystectomy. An additional trocar was placed in one patient because of a bleeding cystic artery. Retrospectively, this was felt to be unnecessary by the operating surgeon but demonstrates the importance of a conservative approach during the learning curve for any procedure. In a second patient, an additional trocar was placed away from the umbilicus because of failure to adequately delineate the anatomy of Callot's triangle. This patient also had a second additional trocar placed away from the umbilicus to assure avoidance of injury to the common bile duct.[16] We did not consider placing a third trocar through the umbilicus, although this technique has been utilized at our institution for LESS Nissen fundoplications and LESS Heller myotomies (data not yet reported). In our experience, a third trocar through the umbilicus is technically more restrictive for the operating surgeon. Furthermore, with difficult exposure, we feel that the addition of trocar in a standard (i.e., non-umbilical) location is safest and more expedient, especially with this new technique.

Two patients undergoing LESS cholecystectomy requested to stay an additional night in the hospital for pain control. Both patients were discharged on postoperative day number two. Interestingly, both patients complained of subcostal pain despite only an umbilical incision. Although no conclusions can be drawn from two patients, the potential for better pain control with a single incision certainly will require formal evaluation to substantiate this claim.

Scattered reports of different techniques for LESS cholecystectomy have been reported in the literature and have utilized several acronyms including SILS (single-incision laparoscopic surgery) and SPA (single-port access).[3–6,8] The technique we have developed utilizes a single umbilical incision without the expense of increased operative time. There is essentially no learning curve to this approach; operative times were consistently similar from the time of the very first LESS cholecystectomy to the 29th LESS cholecystectomy. Only techniques necessary for standard laparoscopic cholecystectomy are required to undertake and complete LESS cholecystectomy. We believe that the ease of the operation is largely facilitated by the exposure provided by suture retraction. Furthermore, we do not feel that that the use of suture retraction away from the umbilicus detracts from this single site procedure any more so than percutaneous local anesthetic "needle-stick" injection at the end of the case.

We recommend LESS cholecystectomy for patients with uncomplicated gallbladder pathology and biliary anatomy not distorted by inflammation. This is a safe alternative to standard laparoscopic cholecystectomy and can be done with comparable operative times. Currently, provisions are underway at our institution to evaluate this technique in a randomized controlled trial to document, not only safety and feasibility but also patient satisfaction, postoperative pain, and cosmesis.

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2008 PANCREAS CLUB ANNUAL MEETING

Summary of the 42nd Annual Meeting of the Pancreas Club

William R. Schiller

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Abstract The annual meeting of the Pancreas Club, traditionally held during the same week as the meetings of the Society for the Surgery of the Alimentary Tract and Digestive Disease Week was held at the University of California San Diego on May 18, 2008 and consisted of both oral presentations and selected poster sessions. Submissions for the program numbered 143 abstracts of which 29 were chosen for oral presentation. There were 19 10-min presentations and ten were 3 min in length. Each was followed by 5- and 2-min discussion periods, respectively. In addition, 50 of the submitted abstracts were chosen for a designated poster session. Summaries of the presentations comprise the body of this report.

Keywords Pancreatitis · Pancreatic disease · Pancreatic cancer · Pancreatectomy

The annual meeting of the Pancreas Club, traditionally held during the same week as the meetings of the Society for the Surgery of the Alimentary Tract and Digestive Disease Week was held at the University of California San Diego on May 18, 2008 and consisted of both oral presentations and selected poster sessions. Submissions for the program numbered 143 abstracts of which 29 were chosen for oral presentation. There were 19 10-min presentations and ten were 3 min in length. Each was followed by 5- and 2-min discussion periods, respectively. In addition, 50 of the submitted abstracts were chosen for a designated poster session. Summaries of the presentations comprise the body of this report.

Session I, held in the morning, concerned the management of clinical pancreatitis. The first paper, *Timing of Cholecystectomy for Biliary Pancreatitis: Do the Data Support Current Guidelines?*, by Ito K., Ito H., and Whang E.E. consisted of a retrospective analysis of biliary pancreatitis patient records from 1999 to 2005. A total of 436 patients from Brigham and Women's Hospital were found to have biliary pancreatitis and were sorted into a group which underwent cholecystectomy during the initial admission (group A) or those who were discharged and then readmitted for definitive biliary surgery (group B). The two groups were similar in number (group A=162 vs group B=119) and had comparable demographic, comorbidity, and disease severity variables. The data revealed that, in those who underwent delayed cholecystectomy, the incidence of biliary complications and length of hospital stay were greater than those who underwent immediate biliary surgery. Endoscopic sphincterotomy protected against recurrent pancreatitis but was less effective against ongoing biliary events. This study provides evidence that delayed biliary operation is a suboptimal strategy when the patient groups were studied retrospectively. The follow-up discussion disclosed that, in the experience of many participants, the decisions for early discharge and readmission were often nonmedical and mandated by insurance and managed care concerns.

The next study, *Five-Year Outcome of a Randomized Trial Comparing Pylorus- and Duodenum-Preserving Pancreatic Head Resection for Chronic Pancreatitis*, concerned a 5-year randomized trial of the utility of either pylorus- or duodenum-preserving operations for the treatment of chronic pancreatitis. The authors included Adam U., Makowiec F., Fischer E., et al. who evaluated a total of

A summary of the work presented at the 42nd Pancreas Club Meeting, May 18, 2008, University of California San Diego.

W. R. Schiller (✉)
PMB 300 223 N. Guadalupe,
Santa Fe, NM 87501, USA
e-mail: wrschiller@hughes.net

85 patients surgically treated for chronic pancreatitis from 1997 to 2001. Either Whipple or pylorus-preserving pancreaticoduodectomy (PPPD, $n=43$) or duodenum-preserving pancreatic head resection (DPPHR, $n=42$) were utilized. The more conservative pancreatic head resections were performed using either the Frey ($n=22$) or Beger ($n=20$) procedures. Focusing on outcomes such as pain control, incidence of diabetes, exocrine insufficiency, and weight gain, the results were found to be similar when both types of operations were compared. There were no differences in outcome between Frey and Beger procedures. The 5-year survival rate was 80%, most deaths a result of concomitant disease processes, often exacerbated by alcohol or tobacco use. A focus of discussion included speculation as to how surgical treatment has evolved for chronic pancreatitis since the introduction of more aggressive use of nonsurgical therapeutic modalities as practiced by gastroenterologists and radiologists.

The following paper, *A Unifying Concept: Pancreatic Ductal Anatomy both Predicts and Determines the Major Complications Resulting from Pancreatitis*, by Nealon W. H., Bhutani M., Riall T.S., et al. explored the relationship between pancreatic ductal inflammatory abnormalities and the behavior of pseudocysts and associated pancreatitis. From 1985 to 2006, the authors performed ERCP or MRCP or both in patients with chronic pancreatitis, acute pancreatitis, and necrotizing pancreatitis. The purpose was to correlate altered ductal anatomy in these conditions with the presence of pseudocysts in whom percutaneous drainage was performed as the chosen means of treatment. Necrotizing pancreatitis patients were monitored for episodes of acute pancreatitis, sepsis, or persistent fistula after operative or percutaneous drainage. Ductal anatomy was classified into four groups. Type I displayed normal ducts while type II images revealed ductal stricture. In type III, the pancreatography demonstrated the presence of ductal occlusion or disconnection was revealed and type IV duct images were interpreted as representing the presence of chronic pancreatitis. Persistence, complications, and failed percutaneous drainage of pseudocysts were correlated with ductal stricture or occlusion. The progressive abnormalities observed in severe pancreatitis such as persistent pain, weight loss, recurrent pancreatic inflammation, sepsis, and development of a pancreatic fistula after necrotizing pancreatitis were associated with ductal injury by the inflammatory process. Discussion following the presentation focused on the best method to be used to evaluate the pancreatic duct anatomy and ERCP seemed to be the preferred technique.

The next presentation, *Probiotic Prophylaxis in Acute Pancreatitis; A Placebo Controlled Randomized Clinical Trial*, reported on an attempt to modulate the inflammatory response and reduce infectious complications early in the course of patients with predicted severe acute pancreatitis by means of jejunal intraluminal administration of a culture suspension of lactobacilli (probiotic) in an attempt to modify the adverse infectious complications caused by increased mucosal permeability. The authors from the Dutch Acute Pancreatitis Study Group reported on a multicenter, prospective, double-blind, placebo-controlled trial in which 297 patients were randomized to receive either a multispecies probiotic suspension ($n=152$) or a placebo ($n=145$) through a nasojejunal tube into the intestinal lumen twice daily for 28 days. Endpoints recorded during the course of a 90-day follow-up included a range of infectious complications, urosepsis, infected ascites, infected pancreatic necrosis, bacteremia, mortality, and adverse events. The groups were judged to be comparable for disease severity and patient characteristics. While infectious complications were not distinctly different in the two groups, mortality in the probiotic group was significantly greater than the placebo group (16% vs 6%; relative risk=2.5; 95%CI=1.2–5.3). While bowel ischemia was not observed in the placebo group, there were nine cases in the probiotic group, eight of which were fatal. Organ failure was also frequent in the probiotic compared to the placebo group. In summary, probiotic administration had no positive effect on outcomes and was thought to be directly responsible for increased mortality and development of bowel ischemia.

Another report from the Dutch Acute Pancreatitis Study Group, *Early ERCP is only Beneficial in Predicted Severe Acute Biliary Pancreatitis in Presence of Concurrent Cholestasis*, concerned the results of early ERCP as a means of reducing complications and mortality in acute biliary pancreatitis (ABP). A prospective multicenter study involving matched groups with cholestasis ($n=78$) or without associated cholestasis ($n=75$) were studied to document the results of early ERCP compared to conservative management as a means of reducing complications and mortality. Patients with actual cholangitis were excluded from this study. In patients with predicted severe APB with cholestasis, but not cholangitis, early ERCP was associated with reduced complications. Patients without cholestasis had no benefit from early ERCP.

Nordback I., Lappalainen-Lehto R., Pelli H., et al. presented, *Repeated Intervention Against Alcohol Use at 6 Month Intervals is Better than Initial Intervention Alone During Hospitalization in Reducing Recurrent Episodes of Alcoholic Pancreatitis—Prospective Randomized Controlled Trial*, from Tampere University Hospital, Finland, concerning the efficacy of strategies for intervention in patients with alcoholism. Prior to hospital discharge, 120 patients recovering from their first episode of acute alcoholic pancreatitis were randomized into two different intervention groups. Group I ($n=59$) were to receive repeated intervention, while a single initial intervention was assigned to group II patients ($n=61$). These patient groups

were followed up for a period of 2 years by a nurse coordinator. The group II patients received an initial intervention which consisted of education, motivation, and the importance of self-responsibility while the group I patients received the intervention at 6-month intervals over the 2-year study period. There were nine recurrent episodes of pancreatitis in five patients in the repeated-intervention group compared with 20 episodes in 13 patients in the initial intervention group. The authors reported that the repeated-intervention program seemed more likely to reduce the incidence of recurrent pancreatitis than the single-intervention protocol.

The first of the short oral presentations was a multicenter study from the University of Pittsburgh Medical Center and the Mayo Clinic, *A Comparison of Direct Endoscopic Necrosectomy and Usual Transmural Endoscopic Techniques for the Treatment of Walled Off Pancreatic Necrosis*, a comparison of direct endoscopic necrosectomy and transmural techniques for the treatment of walled off pancreatic necrosis by Gardner T.B., Chahal P., Papachristou G.I., et al. This report concerned a retrospective study of 45 patients referred to the Mayo Clinic for drainage of walled off pancreatic necrosis. In this selected group of patients, 25 underwent direct endoscopic necrosectomy, and in 20 patients, transmural endoscopic drainage was performed. Successful cavity drainage was accomplished in 88% of those who underwent direct endoscopic necrosectomy compared with 45% success rate for those in whom transmural drainage was performed ($p<0.01$).

Autoimmune Pancreatitis: Application of Current Diagnostic Criteria are Suboptimal addressed the issue of diagnostic criteria for autoimmune pancreatitis (AIP) presented by Giday S.A., Buscaglia J.M., Mukkai-Krishnamurty D., et al. from the Johns Hopkins Institute. The aim of this study was to retrospectively compare the 2006 Japanese diagnostic criteria with a cohort of 30 patients from Johns Hopkins Hospital who were histologically proven to have AIP. The results indicated that when using the Japanese criteria, only 44% of the histologically proven cases of AIP would have been accurately diagnosed prior to obtaining definitive tissue specimens. In conclusion, the study suggests the need for further revision of the Japanese diagnostic AIP criteria.

The final presentation of the morning session, *Combined Resection of Extrapancreatic Nerve Plexus may Improve the Survival After Pancreaticoduodenectomy for Small Pancreatic Cancer*, authored by Egawa S., Motoi F., and Unno M., contained data regarding the effect on survival of small pancreatic cancers by means of combined pancreatoduodenectomy (PD) and extrapancreatic nerve plexus resection. Data from 1,049 patients with tumors less than 2 cm in diameter were compiled by surgeons from Tohoku University, Sendai, Japan. While extended lymph node dissection and portal vein excision produced no improvement in survival compared to PD alone, the addition of pancreatic nerve resection in 88 of these patients produced a 5-year survival of 39% compared to 12% with PD alone ($p=0.0002$). This result seemed valid only for the small tumors of 2 cm diameter or less.

The remainder of the morning was devoted to a "How I Do It" session entitled "Clinical Trials in Pancreatology." A complete video of the three presentations from this session is available from http://www.PancreasClub.com. A 1-h poster session with Professor Rounds for the ten best posters completed the morning session.

The afternoon program was focused on basic science and clinical studies pertaining to pancreatic carcinoma. Christein J.D., Kojima K, Asmellash S., et al. reported on using biomarkers to improve the diagnosis of pancreatic cancer in their presentation, *Applying Proteomic Based Biomarker Tools for the Accurate Diagnosis of Pancreatic Cancer*. They endeavored to study proteomic biologic protein signatures as a means of differentiating patients with pancreatic disease from those without it. Serum, plasma, and urine specimens were collected from patients classified either as normal or as having chronic pancreatitis or pancreatic cancer. Six serum biologic protein features and 14 urine features produced a diagnostic differentiation between the three disease states with a sensitivity of 94%. By contrast, plasma specimens seemed not to produce any differentiating results. The authors will attempt to refine their technique sufficiently to produce detection of early pancreatic tumors.

The next paper, *Induction of Osteopontin Expression by Nicotine and Cigarette Smoke in the Pancreas and Pancreatic Ductal Adenocarcinoma Cells*, authored by Chipitsyna G., Gong Q., Anadanadesan R., et al., described an experimental study in rats wherein induction of osteopontin (OPN) expression in the pancreas and in pancreatic ductal adenocarcinoma (PDA) cells was accomplished by means of treatment with nicotine. OPN apparently activates signaling pathways that induce cancer cell survival, proliferation, invasion, and metastasis. OPN in rats was measured by real-time PCR and immunofluorescence staining, while in humans, PDA tissue was analyzed by immunochemistry. Rats exposed to cigarette smoke showed a dose-dependent increase in pancreatic OPN. In human PDA, intense OPN immunoreactivity was seen in ducts with malignant changes and in the surrounding pancreatic acini. The question which remains somewhat unclear is whether the OPN activity constitutes a tumor marker or is it directly tumorigenic?

The paper, *Epithelial to Mesenchymal Transition in Pancreatic Cancer: Expression and Role of Transcription Factors Snail, Slug, and Twist*, by Hotz H.G., Hotz B., Schellhaus E. et al., documented the mechanisms for cell

transitions from epithelial to mesenchymal (EMT) types in pancreatic cancer, a necessary event for tumor progression and metastasis. Specifically, inducers of EMT are transcription factors known as Snail, Slug, and Twist which seem to function by repression of the adhesive molecule, E-cadherin. Human pancreatic cancer cells have variable expression of these transcription factors with Snail present in 78%, Slug 50%, and minimal expression in Twist. When these tumor cells were implanted in the nude mouse model, it was found that Snail mRNA expression correlated positively with metastatic potential of the cancer cells and there was a negative correlation found between E-cadherin and metastasis. They concluded that Snail transcription factor may play a role in the metastasis of human pancreatic cancer.

A report concerning chromosomal aberrations in intraductal papillary mucinous neoplasms, *Recurrent Chromosomal Aberrations in Intraductal Papillary Mucinous Neoplasms (IPMNS)*, was presented by Fritz S., Fernandez-del Castillo C., Mino-Kenudson M., et al. Shared genetic mutations control the mechanisms responsible for the clinical behavior of IPMNs. Twenty such specimens were selected for study and graded as showing low or moderate dysplasia or high-grade dysplasia and invasive cancer. DNA was isolated from these tumors, and the chromosomal aberrations were analyzed using comparative genetic hybridization (CGH) array techniques. The incidence of chromosomal aberrational gains and losses became increasingly more common as the grade of dysplasia reflected more severe changes in cell morphology and behavior. These multistep chromosomal changes may add insight into the tumorigenesis of IPMNs.

Gene manipulation of pancreatic cancer cell growth was reported by Angst E., Hasan S., Kim M, et al. in *Pancreatic Cancer Cell Growth is Attenuated by the Expression of N-myc Downregulated Gene*. The presence in human tumors of N-myc downregulated gene-1 (NDRG1) has been reported as being associated with more differentiated tumors and improved clinical outcome. The aim of the present study was to elucidate the functional role of NDRG1 in human pancreatic cancer cells in vitro. The investigators studied the human pancreatic cancer cell line HPAF-11 with weak NDRG1 expression by transfecting the cells with NDRG1 cDNA, producing an altered population of cells with more than double NDRG1 expression compared to original cells. These altered cells displayed a statistically significant decrease in several metastasis-related genes. Therapeutic changes in this downregulated gene may represent an avenue of treatment for human cancers, particularly those of pancreatic origin.

Preoperative Detection of Familial Pancreatic Neoplasms by Endoscopic Ultrasonography(EUS), Multidetector Computed Tomography (CT), and/or Magnetic Resonance Cholangiopancreatography (MRCP) reported that the early diagnosis of pancreatic neoplasms in high-risk individuals (HRI) with a familial history of pancreatic cancer might improve the ultimate outcome in this group of pancreatic patients. Preoperative detection by means of endoscopic ultrasonography (EUS), computerized tomography (CT), or magnetic resonance cholangiopancreatography (MRCP) was studied by Canto M.I., Schulick R.D., Goggins M.G. et al. They reported results from 165 patients who fulfilled these categorical requirements. While most pancreatic neoplasms detected by screening tests are small and low-grade, EUS detected twice as many neoplastic lesions as CT/MRCP. Fine needle aspiration added little to the diagnostic accuracy of the detection protocol.

In the short presentation format, *Ascorbate-Induced Cytotoxicity in Pancreatic Cancer*, Du J., Levine M., Wagner B., et al. tested the hypothesis that pharmacologic blood levels of ascorbate might be cytotoxic to pancreatic cancer cells. Several in vitro pancreatic cancer cell lines were treated with ascorbate followed by tumor delivery into nude mice for evaluation of cell viability. The results showed that ascorbate treatment decreased experimental tumor growth in some tumors but not in others. It appeared that these results were dependent on whether the tumor cells had the biological ability by means of a mitochondrial mechanism to respond to the ascorbate by producing cytotoxic levels of hydrogen peroxide. In cells lacking this mitochondrial DNA mechanism, there was no sensitivity to the ascorbate administration. These results may suggest an additional therapeutic tactic in some forms of cancer.

Tumor-Derived ICAM-1 Mediates Tumor-Associated Leukocyte Infiltration, presented by Roland C.L., Dineen S.P., Toombs J. et al., explored the clinical observation that, in the setting of locally advanced pancreatic cancer, increased expression of intracellular adhesion molecule-1 (ICAM-1) on the tumor correlates with poor prognosis. The aim of this study was to investigate the function of host- vs tumor-derived ICAM-1 in pancreatic cancer progression and metastasis using ICAM-1 null mice in which the glycoprotein is not expressed. Murine pancreatic tumor cells found to be ICAM-1-positive were injected into the tail of either wild type of ICAM-1 null mice and allowed to grow for 6 weeks. Clinical growth characteristic and histologic findings of frozen tumor sections including PMN activity at the zone of tumor invasion were recorded. Following the observation that tumor weights and metastatic variables were similar in the two groups of mice, it was concluded that host ICAM-1 was not necessary for tumor progression. Tumor-derived ICAM-1 seemed sufficient as a docking site for PMNs at the tumor invasion front. There was some speculation as to the biologic function of these PMNs at the periphery of the growing tumor.

The concluding paper of this session, *Effect of Hospital Pancreatectomy Volume on Margin Status for Pancreatic Cancer Resections in the United States*, concerned the effect of hospital pancreatectomy volume on margin status for pancreatic cancer resections in American hospitals. The authors included Bilimoria K.Y., Talamonti M.S., Sener S. F. et al. who analyzed 15,507 patients from the National Cancer Data Base who had undergone pancreatic resection during the years 1998 to 2004. They observed that positive margin involvement was recorded at an incidence of 27% in lowest-volume hospitals as opposed to an incidence of 20% in the highest-volume hospitals. On multivariate analysis, margin involvement was associated with a 28% higher risk of death compared to margin-negative resections. However, their multivariate analysis indicated that margin status itself accounted for approximately 5% of the volume-based variation in long-term pancreatectomy outcomes.

The first paper of the second afternoon session, *Benefit of Adjuvant Therapy in Patients Undergoing Surgical Resection for Pancreatic Adenocarcinoma*, concerned the benefit of adjuvant therapy in patients following surgical resection of pancreatic cancer. The authors, including Vanderveen K.A., Chen S.L., Yin D., et al., reviewed patients from the California Cancer Registry who had undergone potentially curative resections for pancreatic cancer. From the years 1994 to 2002, it was possible to identify 3,196 pertinent patients of whom 58% had received adjuvant therapy. The adjuvant therapy included a 5-fluorouracil regimen and postoperative radiation. The overall survival of the resected group was reported as 16 months with adjuvant therapy seemingly adding approximately 2 months to the survival duration. There appeared to be no benefit in patients found to have negative lymph nodes or well-differentiated tumors. The follow-up discussion posed the question as to whether the slight improvement in outcome was a result of the adjuvant therapy or improved surgical techniques.

The Effect of Occupational and Environmental Exposures in Cases of Familial and Sporadic Pancreatic Cancer was presented by Yeo T.P., Hruban R.H, Brune K., et al. This retrospective cross-sectional case-only analysis included cases of familial pancreatic cancer (FPC, $n=569$) and sporadic pancreatic cancer (SPC, $n=689$) from the Johns Hopkins National Familial Pancreas Tumor Registry (NFPTR) enrolled between 1994 and 2005. Reported risk factors for PC included advancing age, family history of PC, high-risk inherited syndromes, cigarette smoking, exposure to occupational and environmental carcinogens, African-American race, high fat/cholesterol diet, obesity, chronic pancreatitis, and diabetes mellitus. The results of their analysis showed that exposure to occupational and environmental factors, especially cigarette smoke, is associated with a younger age of diagnosis in FPC and SPC cases. They advocated early screening in these high-risk cases.

The aim of the next presentation, *Feasibility and Safety of Radiofrequency Ablation for Locally Advanced Pancreatic Cancer: Result of a Pilot Study on 27 Consecutive Patients*, by Girelli R., Frigerio I., Salvia R., et al., was to evaluate short-term morbidity and mortality and to define a safe and standardized technique of radiofrequency tumor ablation (RFA) in locally advanced pancreatic cancer (PC). During a 1-year period of time, 27 patients with histologically proven PC were prospectively enrolled in this study. RFA was performed during laparotomy under ultrasonographic guidance and associated palliative surgery was also performed as clinically indicated. The tumors were reevaluated by computerized tomography 7 days after the procedure. The impact of the procedure on abdominal pain was recorded, along with other tumor indicators such as serum CEA and CA 19-9 levels. Patient interviews, physical examination, and abdominal MRI were also performed during the 30-day follow-up period. RFA was found to be clinically feasible and safe. Tumor indices decreased by half and abdominal pain scores decreased by 75%. The authors seemed optimistic about performing future studies to determine the effect of RFA on long-term survival. They advocated the systemic use of adjuvant chemoradiation therapy in association with the local use of RFA in advanced pancreatic cancer.

McElroy M., Kaushal S., Moosa A.R. et al., *Using Fluorophore-Conjugated Antibodies to Improve Surgical Navigation in Pancreatic Cancer*, investigated the use of fluorophore-labeled anti-CA 19-9 and anti-CEA monoclonal antibodies to aid in cancer visualization in nude mouse models of human pancreatic cancer. After tumor implantation into nude mice, the animals were given a single intravenous dose of conjugated antibody and were imaged using the OV-100 Small Animal Imaging System. Small (1–2 mm diameter) subcutaneous tumors were clearly visible with bright green fluorescence through the skin. Tumor fluorescence became more intense with increasing dosage. Fluorophore-labeled anti-CA 19-9 and anti-CAE offer a novel potential intraoperative imaging technique for the enhanced visualization of small tumors.

The next presentation, *Management of Suspected Pancreatic Cystic Neoplasms Based on Cyst Size*, was presented by Walsh R.M., Vogt D., Henderson J.M, et al. They evaluated a single institutional experience of 500 patients seen from 1999 to 2006. They compared the results of operations mandated by cyst size compared to those in whom cyst aspiration was performed or who exhibited symptoms related to the cyst. They concluded that management based on aspiration was significantly better in predicting mucinous neoplasms compared to size (75% vs 57%, $p<0.001$) including asymptomatic patients

with cysts less than 3 cm in diameter (78% vs 65%, $p=0.003$). Had patients been managed by size alone, in their experience, 20% would have received inappropriate treatment.

Pratt W.B., Callery M.P., and Vollmer C.M., *Prediction of Morbidity for Pancreatic Resection: The Influence of Surgical Performance on Baseline Physiology*, reviewed 379 pancreatic resections performed between 2001 and 2007 to determine the influence of surgical performance on baseline patient physiology as a factor in the prediction of morbidity for this type of operation. They found that, as baseline physiology declines, patients suffer more complications and require more therapeutic and invasive interventions. More severe operations are similarly associated with worse outcomes. Their analysis revealed that the primary issue in operative severity was blood loss. Conversely, they indicated that the effects of poor physiologic variables could be attenuated by improved operative performance.

In *Delayed Gastric Emptying (DGE) After Pancreaticoduodenectomy (PD)—The International Pancreatic Study Group (ISGPS) Definition is Very Useful*, Hashimoto Y. and Traverso L.W. reported on their study concerning delayed gastric emptying (DGE) after pancreatoduodenectomy (PD) as their experience related to the newly published International Pancreatic Study Group (ISGPS) definitions. As a basis for their presentation, they analyzed 416 consecutive cases which occurred during the time period of 1997 to 2007. The patient population was limited to those whose postextirpation reconstruction took the form of a pancreaticojejunostomy (PJ), 377 of which following a pylorus-preserving procedure. They calculated DGE, pancreatic anastomotic leak (LEAK), and median length of stay (LOS) in postoperative days (POD). LEAK was defined into four groups including none, grade A (any drain amylase >3 times upper limit of serum in any volume), grade B (an exclusive intermediate designation), and grade C (reoperation, sepsis, death). They also correlated their use of microsurgery to perform the PJ with the incidence of DGE and LEAK. Their report indicated that, following the introduction of microsurgical techniques, the incidence of DGE and LEAK dramatically decreased from 84% to 34% and from 70% to 26% for grade A, respectively. Grade B decreased from 14% to 8% and grade C decreased to zero. They also reported shortening of LOS as a result of these techniques.

The next paper in short format, *Frequency of Extrapancreatic Neoplasms in Intraductal Papillary Mucinous Neoplasm of the Pancreas Compared to Pancreatic Adenocarcinoma and Referral Patients*, concerned the frequency of extrapancreatic neoplasms in patients with intraductal papillary mucinous neoplasm (IPMN) of the pancreas compared to pancreatic adenocarcinoma and control general referral patients. The authors, including Mathis K.L., Lombardo K.R., and Sarr M.G., studied this issue in patients referred to their institution during the period of 1994–2006. They included 477 patients in the IPMN group, 471 in the pancreatic adenocarcinoma group (control group 1), and 1,431 in the general referral group (control group 2). The proportion of patients in the IPMN group having extrapancreatic neoplasm before or coincident to the reported study period was 52% compared to 36% in control group 1 and 43% in control group 2. Patients with IPMN are at greater risk for extrapancreatic neoplasms compared to both control groups. Colorectal neoplasms were common lesions found in the IPMN group and the authors recommended screening colonoscopy in these patients.

Hurtuck M.G, Hughes C, Shoup M., et al. addressed the question of whether the ratio of positive lymph nodes to total lymph nodes resected was an important factor in postoperative survival after ablative surgery for periampullary lesions in *Does Lymph Node Ratio (LNR) Impact Survival in Resected Periampullary Malignancies?*. They performed a retrospective review of 341 patients who had undergone pancreaticoduodenectomy for periampullary malignancies in the time period of 1998 to 2007. While positive lymph node status was found to be negatively related to survival, the absolute number of positive lymph nodes or lymph node ratio were found not to significantly change prognosis.

Twelve authors including Hsu C.C., Herman J.M, Corsini M.M., et al. presented their data concerning the effect of adjuvant chemoradiation therapy (CRT) after surgical resection for 1,092 cases of pancreatic adenocarcinoma. The review, *Adjuvant Chemoradiation Therapy After Surgical Resection for 1092 Cases of Pancreatic Adenocarcinoma: The Johns Hopkins Hospital–Mayo Clinic Collaborative Study of Pancreatic Cancer*, was provided by authors including Hsu C.C., Herman J.M., Corsini M.M., et al. They reported an overall median survival of 18.8 months. Matched-pair analysis demonstrated that survival was longer in those patients who received CRT compared to those who were treated by pancreaticoduodenectomy (PD) alone (21.9 vs 14.3 months, $p<0.001$). Adjuvant CRT was significantly associated with improved survival after PD regardless of age, tumor size, margin status, node status, or tumor differentiation.

The last oral presentation of the day, *Diagnostic Laparoscopy and Peritoneal Cytology in the Staging of Unresectable Pancreatic Cancer*, concerned the role of diagnostic laparoscopy and peritoneal cytology in the staging of unresectable pancreatic cancer, by Clark C.J., Bahireai F., Picozzi V., et al. The purpose of the study was to compute the incidence of occult stage IV pancreatic cancer by means of staging laparoscopy in patients with CT

findings of locally advanced disease (CT stage III). During an 8-year period, 183 patients, found by contrast-enhanced pancreas protocol thin cut CT to have locally advanced unresectable pancreatic cancer, underwent diagnostic laparoscopy and collection of peritoneal washings for cytology (CLPLC). The use of diagnostic laparoscopy and DLPLC in selected patients provides for additional accuracy in 23.5% of patients. The positivity of the peritoneal lavage cytology seems most strongly correlated with tumor size greater than 4.5 cm. Whether this diagnostic technique will change therapeutic and prognostic management in locally advanced pancreatic cancer remains uncertain.

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ORIGINAL ARTICLE

Prevention of Post-operative Leak Following Laparoscopic Heller Myotomy

Kelly R. Finan · David Renton · Catherine C. Vick · Mary T. Hawn

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Abstract
Purpose Laparoscopic Heller myotomy is the preferred treatment for achalasia. Post-operative leaks cause significant morbidity and impair functional outcome. This study assesses the efficacy of intra-operative leak testing on post-operative leak rate.
Methods A retrospective analysis of 106 consecutive patients undergoing laparoscopic Heller myotomy by a single surgeon between November 2001 and August 2006 was undertaken. Intra-operative leak testing was performed in all patients. Variables associated with intra-operative mucosotomy were assessed by univariate analysis and logistic regression modeling.
Results Intra-operative mucosotomy occurred in 25% of patients. All mucosotomies were repaired primarily and tested with methylene-blue-stained saline. Dor fundoplication was performed in 74% of the patients. There were no post-operative leaks and patients were started on diet day of surgery. Mean LOS was 1.4(±0.7) days. Logistic regression modeling demonstrated that prior myotomy was associated with a statistically significant increase in the rate of mucosotomy (p=0.033), while previous botox injection (p=0.193), pneumatic dilation (p=0.599) or concomitant hiatal hernia (p=0.874) were not significantly associated with mucosotomy.
Conclusion Laparoscopic Heller myotomy for the treatment of achalasia is a safe procedure. Intra-operative leak testing minimizes the risk of post-operative leaks and expedites post-operative management. Prior endoscopic treatment does not impair operative results.

Keywords Esophageal achalasia · Laparoscopic surgery · Post-operative complication · Intra-operative procedures · Heller myotomy

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K. R. Finan · D. Renton · C. C. Vick · M. T. Hawn (✉)
Section of Gastrointestinal Surgery, Department of Surgery,
University of Alabama at Birmingham,
KB 417 1530 3rd Ave S,
Birmingham, AL 35294, USA
e-mail: mhawn@uab.edu

C. C. Vick · M. T. Hawn
Deep South Center for Effectiveness Research,
Birmingham Veterans Affairs Medical Center,
Birmingham, AL, USA

Introduction

Achalasia is a rare primary esophageal motility disorder of the esophagus and is characterized by incomplete relaxation of the lower esophageal sphincter (LES) and loss of primary esophageal peristalsis. The principal therapeutic goal for patients with achalasia is to improve esophageal emptying by reducing lower esophageal sphincter pressure. Treatment options include medical management, endoscopic therapies (botulinum toxin and pneumatic dilation), and surgical intervention. Pharmacologic therapies aimed to decrease the LES pressure with smooth muscle relaxants such as calcium channel blockers and nitrates offer only modest symptom improvement and are only utilized in patients with contraindication or reluctance to undergo more invasive therapies.[1, 2] Endoscopic intersphincteric botulinum toxin injection inhibits acetyl-

choline release from presynaptic nerve endings, effectively "paralyzing" LES and lowering the LES pressure.[3] Multiple cohort studies have demonstrated acceptable immediate clinical response rates of 75–84%, but decreasing effectiveness with time as the effects of the botulinum toxin wanes.[4–7] Endoscopic pneumatic dilation stretches and ruptures the LES, making the sphincter incompetent. Success rates of 50–78% have been reported, but patients frequently require repeat dilations and can suffer the morbidity of iatrogenic esophageal perforation.[8–11] Until recently, endoscopic pneumatic dilatation and clostridium botulinum toxin injection had been the initial therapeutic interventions for these patients; however, a paradigm shift has occurred over the last decade, placing surgical intervention at the forefront of achalasia treatment.[12–14]

Heller myotomy has been performed for the treatment of achalasia since 1913, but recent developments in laparoscopic techniques have significantly reduced the morbidity and mortality of this procedure.[15] Laparoscopic Heller myotomy has emerged as the preferred first line treatment for patients with achalasia,[3] with reported success of 85–93%.[16–22] Gastroesophageal reflux is the most common consequence of myotomy, thus, a prophylactic antireflux fundoplication is commonly performed concomitantly with myotomy.[23]

Botulinum toxin injection and pneumatic dilation cause severe inflammation of the GE junction in animal studies.[20] It has been speculated that previous endoscopic treatments may, therefore, make dissection more difficult and increase operative risk of mucosal injury during myotomy. Contradictory reports exist in the literature regarding the effect of pre-operative endoscopic therapies on surgical difficulty of myotomy or outcomes.[13, 19, 24–29] Post-operative leaks from inadvertent enterotomy cause significant morbidity and impair functional outcome. Missed mucosal injury exposes patient to risk of sepsis, reoperation, and long-term complications including esophagectomy.[30, 31]

This study assesses the efficacy of intra-operative leak testing on post-operative leak rate and evaluates short-term outcomes. We further evaluate whether previous endoscopic therapies or surgical intervention are associated with intra-operative mucosotomy.

Methods

A retrospective analysis of all patients undergoing laparoscopic Heller myotomy by a single surgeon at a tertiary care center between November 2001 and December 2006 was conducted. The protocol was approved by the Institutional Review Board at the University of Alabama at Birmingham under a waiver of documented informed consent. A chart abstraction of all subjects was performed. Demographic data, history of previous treatment (including surgery, botox injection, and pneumatic dilatation), comorbid conditions, pre-operative evaluation, and peri-operative course were obtained from the medical record. Operative notes were physician abstracted to obtain surgical variables of interest, including length of myotomy, mucosal injury, type of leak test performed, and fundoplication performed.

Surgical Technique

Pneumoperitoneum is established by Veress needle. Five working ports are placed in the upper abdomen. Division of the phrenoesophageal ligament, mediastinal dissection, and mobilization of the gastroesophageal (GE) fat pad allows for identification of the GE junction. A 36–45 French bougie is placed across the GE junction. If pre-operative evaluation identifies an epiphrenic diverticulum or tortuous esophagus, an endoscope is placed under direct vision into the stomach in place of a bougie. The myotomy is begun on the anterior esophageal wall just above the GE junction. The longitudinal and circular muscle fibers are bluntly separated from the sub-mucosal plane and serially divided with an ultrasonic scalpel, approximately 5 cm cephalad. A hook cautery is used to continue the myotomy approximately 2 cm caudally across the GE junction. Care is taken to preserve the anterior vagus nerve throughout dissection and the myotomy. All recognized mucosotomies are repaired primarily with 3–0 vicryl suture. Leak test is performed on all cases to test integrity of mucosa by injection of 125 cc of methylene blue–saline solution via a nasoesophageal tube or endoscope in the distal esophagus. In the majority of cases, a Dor fundoplication is performed securing the fundoplication to either side of the myotomy and diaphragmatic crus with 0–0 Ethibond suture, as described by Richards et al.[23] Fundoplication is not performed in cases of greater than 2 cm hiatal hernia or severe esophageal dilation and tortuosity. All patients are started on clear liquids immediately post-operatively with advancement to a soft diet on post-operative day one. Gastrografin swallow was only performed on select patients with abnormal post-operative course.

Statistical Analysis

Pre-operative variables associated with mucosal injury were assessed by Students *t* test, Wilcoxon Rank Sum and Chi-square analysis, as appropriate. A logistic regression analysis was performed to identify significant predictors of mucosotomy during Heller myotomy. All analyses were performed using the SAS statistical package (SAS Version 9.1.3, SAS Institute Inc., Cary, NC, USA).

Results

One hundred and six patients were included in analysis (Table 1). The diagnosis of achalasia was made by barium swallow (91%), manometry (90%), and EGD (88%). Prior treatment for achalasia included Botox injection (31%), pneumatic dilation (37%), prior transabdominal myotomy (8%), and prior transthoracic myotomy (5%).

All cases were completed laparoscopically (Table 2). A Dor fundoplication was performed in 74% of the patients. Intra-operative mucosotomy occurred in 22 (21%) patients; all mucosotomies were immediately recognized and repaired. Intra-operative leak testing was performed with methylene-blue-stained saline injected via the nasogastric tube (90%) or endoscope (10%) in all patients. There were no post-operative leaks and patients were started on diet day of surgery. Three patients underwent post-operative upper gastrointestinal series on post-operative day 1 and all were negative for leak. Of the 22 mucosotomies, 16 involved the gastric mucosa, five the esophageal mucosa, and one both. Of the subjects with intra-operative mucosotomies, three patients had a hiatal hernia, five patients had undergone previous myotomy, and nine had undergone previous endoscopic therapies prior to surgery (five botulinum toxin, four pneumatic dilation, and three both). There was no significant variation in mucosotomy by year (2002: five, 2003: six, 2004: four, 2005: four, 2006: three). The mean length of stay was 1.4 (±0.7) days; and there was no difference in length of stay or complications between patients with and without mucosotomy. There were six intra-operative complications; and four post-operative complications.

On univariate testing, there were no risk factors independently associated with mucosotomy. Logistic regression modeling demonstrated that prior surgical myotomy was associated with a statistically significant increase in the rate of mucosal tear or injury (p=0.033), while previous botox injection (p=0.193), pneumatic dilation (p=0.599), or concomitant hiatal hernia (p=0.874) at time of myotomy were not significantly associated with mucosotomy (Table 3).

Table 1 Study Demographics of Consecutive Patients Undergoing Laparoscopic Heller Myotomy at the University of Alabama at Birmingham

Study population (*N*)	106
Age mean (+SD)	49
Gender	
Female	47 (44%)
Male	59 (56%)
Ethnicity	
White	73 (69%)
Black	32 (30%)
Weight loss in pounds mean(±SD)	20.3 (26.5)
Duration of symptoms years mean (±SD)	4.2 (6.1)
Pre-operative treatment	
Prior myotomy	12 (11%)
Botox	33 (31%)
Dilation	39 (37%)
Botox and dilation	15 (14%)
Pre-operative work-up	
EGD	93 (88%)
Manometry	95 (90%)
Barium swallow	96 (91%)

Table 2 Peri-operative Variables of Study Population (*N*=106)

Type of surgery	
Heller myotomy without fundoplication	28 (26%)
Heller with Dor fundoplication	78 (74%)
Conversion to open	0
Hiatal hernia	22 (21%)
Type 1	20 (19%)
Type 2	0
Type 3	2 (2%)
Intra-operative mucosotomy	22 (21%)
Leak test	
Methylene blue	91 (86%)
EGD	15 (14%)
Post op swallow	3 (3%)
Postop leaks	0
Complications	
Intra-operative	6 (6%)
Anterior vagus nerve injury	1
Apical pneumothorax, not requiring chest tube	1
Splenic rent	1
Mesenteric rent small bowel mesentary	1
Epigastric artery trocar injury	1
Aspiration on induction	1
Post-operative	4 (4%)
Urinary retention, discharged with catheter	1
Atrial fibrillation	1
Reintubation (acetylcholinesterase deficiency)	1
Myocardial infarction	1
Mean length of stay in days (+SD)	1.38 (0.70)

Discussion

Laparoscopic Heller myotomy has been demonstrated to be superior to endoscopic therapies and is favored as first line treatment in achalasia. This study confirms the safety of laparoscopic Heller myotomy for the treatment of achalasia. Previous transabdominal or transthoracic myotomy was the only significant predictor of mucosotomy. We found no association with previous endoscopic therapies and intra-operative complications. Intra-operative leak testing allows

Table 3 Predictors of Intra-operative Mucosotomy During Laparoscopic Heller Myotomy

		N	Odds ratio	95% CI	*p* value
Previous myotomy	Yes	12	4.47	1.13, 17.78	0.033
	No	94			
Botox injection	Yes	33	0.45	0.13, 1.50	0.193
	No	73			
Pneumatic dilation	Yes	39	0.75	0.025, 2.22	0.599
	No	67			
Hiatal hernia	Yes	22	0.89	0.21, 3.74	0.874
	No	84			

for immediate evaluation of mucosal integrity and early refeeding on the day of surgery. No delayed leaks were encountered. Leak testing further alleviates the need for post-operative radiologic evaluation and allows for early discharge from the hospital.

The incidence of mucosotomy during laparoscopic Heller myotomy has been reported from 5–33% in cohort studies.[13, 19, 26, 29, 32–34] Our data is consistent with the literature with a mucosotomy rate of 22% that can only be partially attributed to re-operative surgery, with no post-operative leaks. We did not identify any adverse events in patients that had a mucosal perforation. All perforations were immediately recognized and repaired laparoscopically. The key technical component is recognition of the perforation, proper repair with intra-operative confirmation of adequacy of repair with leak testing.

The only risk factor for mucosotomy we identified was previous abdominal or transthoracic surgical myotomy. Failure of myotomy to relieve symptoms of dysphagia post-operatively is multifactorial, but technical failures have been attributed to short and incomplete myotomy.[18, 19, 29, 31, 35] Although re-operative surgery may be subjectively more difficult, we found no difference in the ability to successfully complete the myotomy or in early post-operative outcomes. Pre-operative endoscopic therapies did not increase the risk of perforation or intra-operative complications in our patient population. These results are consistent with reports from a single institution cohort from Mayo Clinic.[13] They found no association with pre-operative bougie dilation, pneumatic dilation or botox injection on the rate of intra-operative mucosal perforation (16%), but did not analyze the impact of previous surgery on perforation rate. Iqbal et al. similarly reported a series of 15 re-operative Heller myotomies in 2006.[35] They did not find a difference in intra-operative mucosal perforation rate in patients with and without prior endoscopic therapies, nor did prior endoscopic therapies or intra-operative perforation affect functional outcome. Rakita et al. likewise found that inadvertent esophageal mucosotomy could not be predicted based on pre-operative endoscopic therapies and that post-operative dysphagia scores were equivalent to those patients without prior intervention.[28] Several other cohort studies have noted no difference in ability to perform a safe myotomy based on pre-operative endoscopic interventions, but there has been a trend for increase rate of peri-operative complications.[24, 27] A surgeon rated increased level of difficulty of laparoscopic myotomy and an increased risk of perforation in patients with pre-operative botox injection has also been reported, but no difference in early outcome was identified.[25] Contrary to above reports, a recent publication by Smith et al. reported increased intra-operative perforations (9.7% vs. 3.6%), post-operative complications (10.4%vs. 5.4%), and worse outcomes in patients with pre-operative endoscopic interventions (74%) compared to those undergoing primary myotomy (26%) for treatment of achalasia.[29] Therefore, there does not appear to be a strong level of evidence to consistently support the impact of endoscopic therapies on surgical outcomes of myotomy. There does appear to be evidence of increased difficulty of myotomy and increased rate of perforation, but there is no evidence that this affects surgical success.

We routinely perform intra-operative leak testing to minimize the risk of a potential missed injury as well as to ensure water-tight repair of all mucosal perforations. This is easily performed with injection of methylene-stained saline down a nasogastric tube by our anesthesiology colleagues, and requires little time to perform at negligible cost. We confirm adequacy of our myotomy by bulging of the mucosa. When a hiatal hernia is present, contorted anatomy or any uncertainty of the adequacy of our myotomy, we will then selectively perform upper endoscopy and perform a methylene blue leak test. Leak testing is not routinely performed by all centers in the operating room.[13, 19, 35] Unfortunately, the consequence of an unrecognized injury can be profound with peritonitis, mediastinitis, sepsis requiring drainage, and return to the operating room and can feasibly lead to esophagectomy. Therefore, we argue that routine leak testing can help decrease the possibility of post-operative leaks and subsequent morbidity to the patient.

We have shown that intra-operative leak testing with methylene-blue-stained saline is a safe technique. Others

incorporate routine upper endoscopy routinely during a laparoscopic myotomy and perform leak testing with air insufflation.[29, 31] While this is an acceptable technique, it is potentially cost saving to perform selective endoscopy and employ routine methylene blue injection for leak testing.

We only selectively perform contrast swallow studies (2.8%) when patients fell outside of normal post-operative parameters (fever, pain, tachycardia, etc.), and none of these patients had a post-operative leak. Several series report routine or regular post-operative contrast studies[13, 24, 26, 27] or delayed enteral intake after mucosal perforation.[36] We feel, with intra-operative leak testing, we can avoid routine radiologic exams for leak testing which allows for immediate refeeding and decreased length of stay with early discharge leading to reduced hospital charges.

This study is limited in the fact it is a single institution experience and may not be generalizable to the community. Long-term functional outcomes are lacking and would aid in assessment of the impact of pre-operative endoscopic therapies and mucosotomy. Further, most pre-operative interventions, endoscopic and surgical, were not performed at our institution and may introduce some bias.

Conclusion

Laparoscopic Heller myotomy for the treatment of achalasia is a safe procedure. Intra-operative leak testing minimizes, if not eliminates, the risk of post-operative leaks and expedites post-operative management with early refeeding and discharge. Prior endoscopic treatment does not impair operative results.

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ORIGINAL ARTICLE

Leiomyomatosis of the Esophagus: Experience over a Decade

Vikas Gupta · Anupam Lal · Saroj K. Sinha · Ritambhra Nada · Narendar M. Gupta

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Abstract
Purpose To assess the clinical, radiological findings, and treatment strategies in patients with esophageal leiomyomatosis.
Background Esophageal leiomyomatosis is a rare hamartomatous disorder with varied presentation. It is described mostly in children and is associated with Alport's syndrome.
Methods A retrospective analysis of three cases managed in the Department of General Surgery at Chandigarh over a period of 10 years.
Results The study involves three female patients of different generations within the same family with age range of 10–58 years. All presented with dysphagia of 2–7 years duration. Barium swallow revealed a long-segment stricture in two patients. Computed tomography (CT) demonstrated a circumferential mass lesion in the lower esophagus in all the patients. Esophageal resection was carried out in all the patients. All patients made an uneventful recovery.
Conclusions Esophageal leiomyomatosis should be suspected in patients with long-standing dysphagia. Barium findings are suggestive but can mimic achalasia. CT scan shows a circumferential esophageal wall thickening. Surgical resection and reconstruction of the digestive passage is the optimal treatment.

Keywords Leiomyomatosis · Esophageal resection · Alport's syndrome · Esophageal leiomyomatosis · Familial

V. Gupta (✉) · N. M. Gupta
Division of Gastrointestinal Surgery, Department of General Surgery, PGIMER,
Chandigarh 160012, India
e-mail: vggispgi@hotmail.com

A. Lal
Department of Radiodiagnosis, PGIMER,
Chandigarh 160012, India

S. K. Sinha
Department of Gastroenterology, PGIMER,
Chandigarh 160012, India

R. Nada
Department of Histopathology, PGIMER,
Chandigarh 160012, India

Introduction

Esophageal leiomyomatosis is a rare, benign neoplastic condition leading on to the proliferation of esophageal smooth muscle and thickening of sizable portion of the esophagus.[1–5] The condition is usually found in children and young adults.[3–5] The disease can be associated with leiomyomas at other sites or with nephropathy, defective hearing, astigmatism, and myopia (Alport's syndrome).[3–6] However, it can manifest in an isolated manner. The condition causes minimal symptoms.[5–7] The main abnormality is usually confined to the esophagus but the disease may extend to involve the stomach also. On contrast examination, it may mimic achalasia.[7–9] Length of the stricture can differentiate the condition from other benign strictures.[6–9] Cross-sectional imaging can delineate a circumferential thickening of the esophagus which is usually suggestive.[6–10] Esophageal resection and replacement is the optimal management.[3,5–11] We report our experience of managing esophageal leiomyomatosis.

Materials and Methods

From July 1998 to July 2008, three patients with esophageal leiomyomatosis were analyzed in a retrospective manner at Postgraduate Institute of Medical Education and Research—a tertiary care center in North India. Clinical data was reviewed to determine the demographic characteristics, clinical presentation, and treatment strategies. A diagnostic endoscopy was done in all the patients. All of them underwent barium swallow examination and contrast-enhanced computerized tomogram of the chest and abdomen. All patients underwent subtotal esophagectomy—transhiatal approach in two and transthoracic in one. The digestive passage was restored using stomach as a conduit. In all the patients, the diagnosis was confirmed on pathological examination.

Results

All the patients were females of three different generations from the same family—the maternal grandmother, mother, and the patient herself, with their respective age of 58, 38, and 10 years at presentation. All the patients presented with slowly progressive dysphagia of 2–7 years duration. Substernal chest pain and regurgitation was noticed in one patient. The general physical and the systemic examination including the genitourinary system was normal. The grandmother had undergone cholecystectomy about 3 years prior to the presentation. The biochemical, hematological, and coagulation parameters were normal in all the patients. Neither the family history nor the phenotypic expression of Alport's syndrome could be elicited in any of the patients.

A diagnostic upper gastrointestinal endoscopy revealed multiple submucosal extrinsic impressions in the middle and lower third of esophagus reaching up to the gastroesophageal junction. The overlying mucosa was normal. The stomach and duodenum were normal.

Radiological Findings

Barium Findings

Barium swallow examination (single contrast) was performed in all the patient. All patients had proximal dilatation of the esophagus ranging from 3–4.5 cm with one or multiple segments of smooth narrowing of lower thoracic esophagus. The involved segments varied in length from 4 to 9 cm. There were no mucosal destructions, ulcerations, or nodularity associated with the narrowed segments. The esophagus was displaced to the right in one patient (Fig. 1a). One of the lesions was mimicking achalasia (Fig. 1b,c).

CT Findings

There were circumferential masses of soft tissue attenuation ranging in the lower esophagus in all the patients. However, the lesion was smallest in the youngest patient. The mass lesion was reaching up to the gastroesophageal junction. The

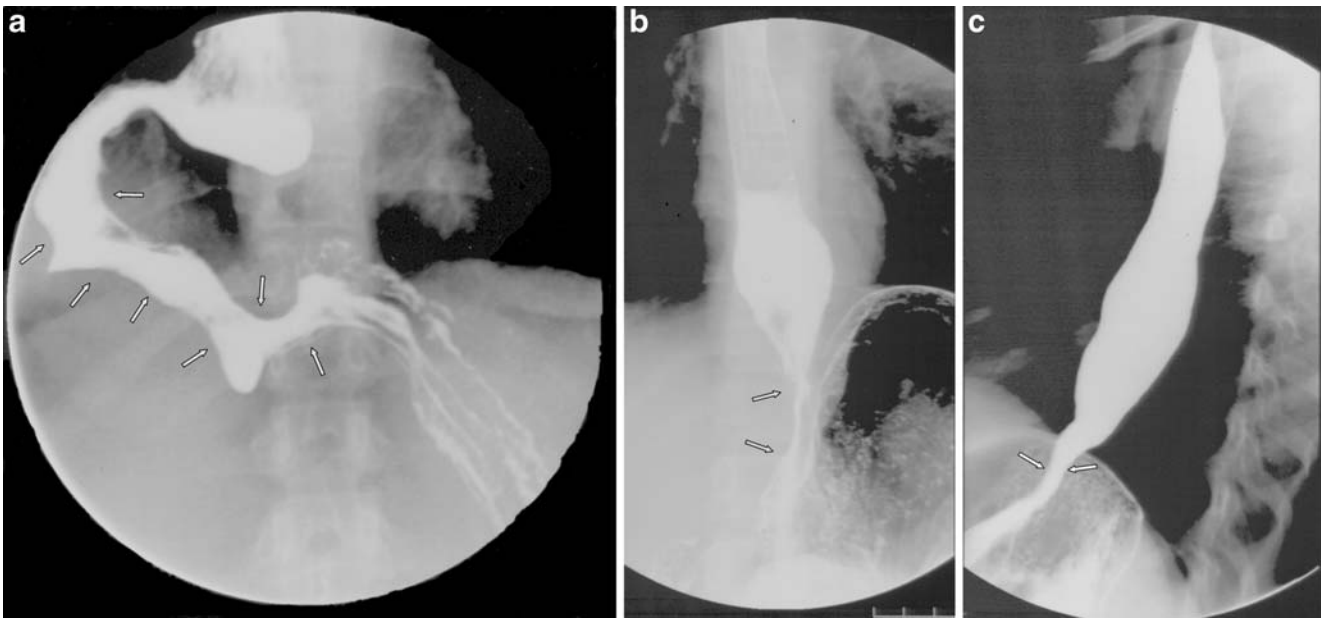

Figure 1 **a** Barium swallow study shows multiple submucosal lesions causing luminal narrowing (*arrows*) and deviation of lower esophagus to right. **b**, **c** Leiomyomatous lesion at gastroesophageal junction mimicking achalasia (*arrows*) on barium swallow study. A relatively long segment of narrowing and extension of narrowed segment above the diaphragm are points against the diagnosis of achalasia.

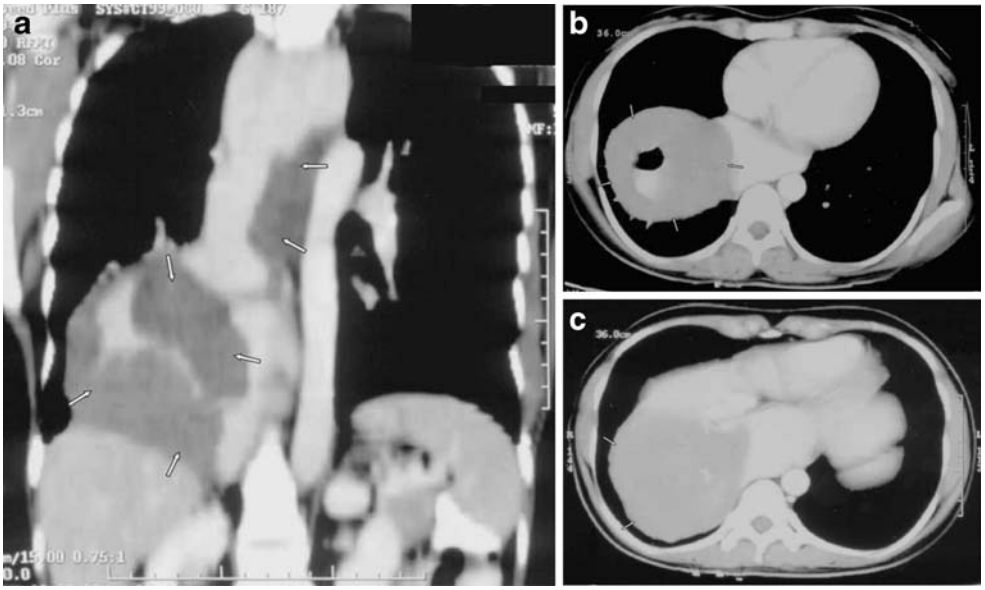

Figure 2 **a** Coronal reformatted CT image showing multifocal leiomyomas (*arrows*) of esophagus causing luminal narrowing and esophageal deviation to right. **b** Axial CT image showing marked circumferential mural thickening of esophagus (*arrows*) which is seen deviated to right hemithorax. **c** Axial CT *image*: Eccentric large leiomyoma of esophagus seen in right hemithorax (*arrows*). Note the dilated esophagus anterior to aorta.

proximal esophagus was dilated. At places, noncircumferential focal thickening of esophageal wall was also seen. The esophagus was diffusely thickened in its entire length. The stomach was normal in appearance (Fig. 2a,b).

Operative Findings

The stomach was normal in all the patients. There was circumferential mass lesion in the lower thoracic esophagus with flimsy adhesions with the surrounding structures which could be easily separated by blunt dissection. Nodularity was also appreciated in the midesophagus. The esophagus was thickened in its entirety. A transhiatal esophagectomy could be successfully accomplished in two patients. In one patient, a planned transthoracic (posterolateral thoracotomy) esophagectomy was performed owing to the large size of the lesion (Fig. 3).

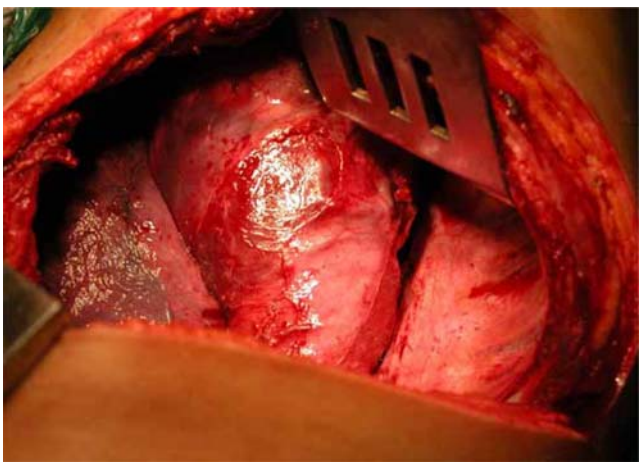

Figure 3 Intraoperative *photograph* (transthoracic) showing huge circumferential thickening of the lower esophagus.

The cut section of the specimen revealed a dilated esophagus. A large circumferential mass was seen in the lower esophagus with nodularity in the middle part. The overlying mucosa was normal. There was marked hypertrophy of the

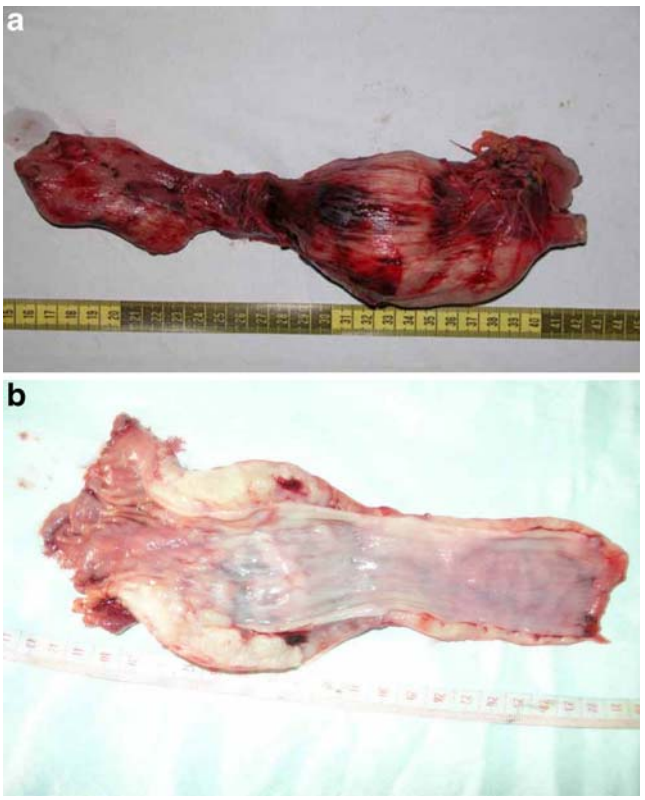

Figure 4 **a** Resected specimen showing a large circumferential tumor mass in the lower esophagus. Note the nodularity in the midesophagus. Diffuse muscular hypertrophy can also be appreciated. **b** Cut section of the specimen showing normal mucosa and diffuse muscular hypertrophy more prominent in the lower esophagus. Note is made on the normal stomach and gastroesophageal junction.

esophageal musculature (Fig. 4a,b). All patients made an uneventful recovery and were discharged after 9 to 14 days.

Histopathological Findings

The lesion appeared like circumferential mass predominantly occupying the lower third of the esophagus. The lesion appeared microscopically as a smooth muscle tumor with evidence of leiomyomatosis of the entire esophagus. Interweaving spindle cell fascicles without mitosis or atypia were observed in all the patients. The overall cellularity was low (Fig. 5).

Follow-up

All the patients remained well on follow-up for a period ranging from 2–9 years.

Discussion

Diffuse esophageal leiomyomatosis is a rare, benign hamartomatous condition in which there is proliferation of smooth muscle of the esophagus.[1,2] This leads to the thickening of the esophagus.[1,2] The condition may occur sporadically or on a hereditary basis with autosomal dominant inheritance.[3–7] It may have an association with other gastrointestinal leiomyomata (particularly small intestinal and rectal) along with widespread visceral leiomyomatosis,[12] tracheobronchial lesions,[13] genital lesions in women, including clitoral hypertrophy and vulval leiomyomatosis which constitutes the esophagovulvar syndrome,[14,15] and Alport's syndrome.[3–6] The latter one is an inherited (X-linked) disorder which is characterized by the triad of interstitial nephritis, sensorineural hearing loss, and ocular lesions.[3] The pattern of rectal involvement in leiomyomatosis

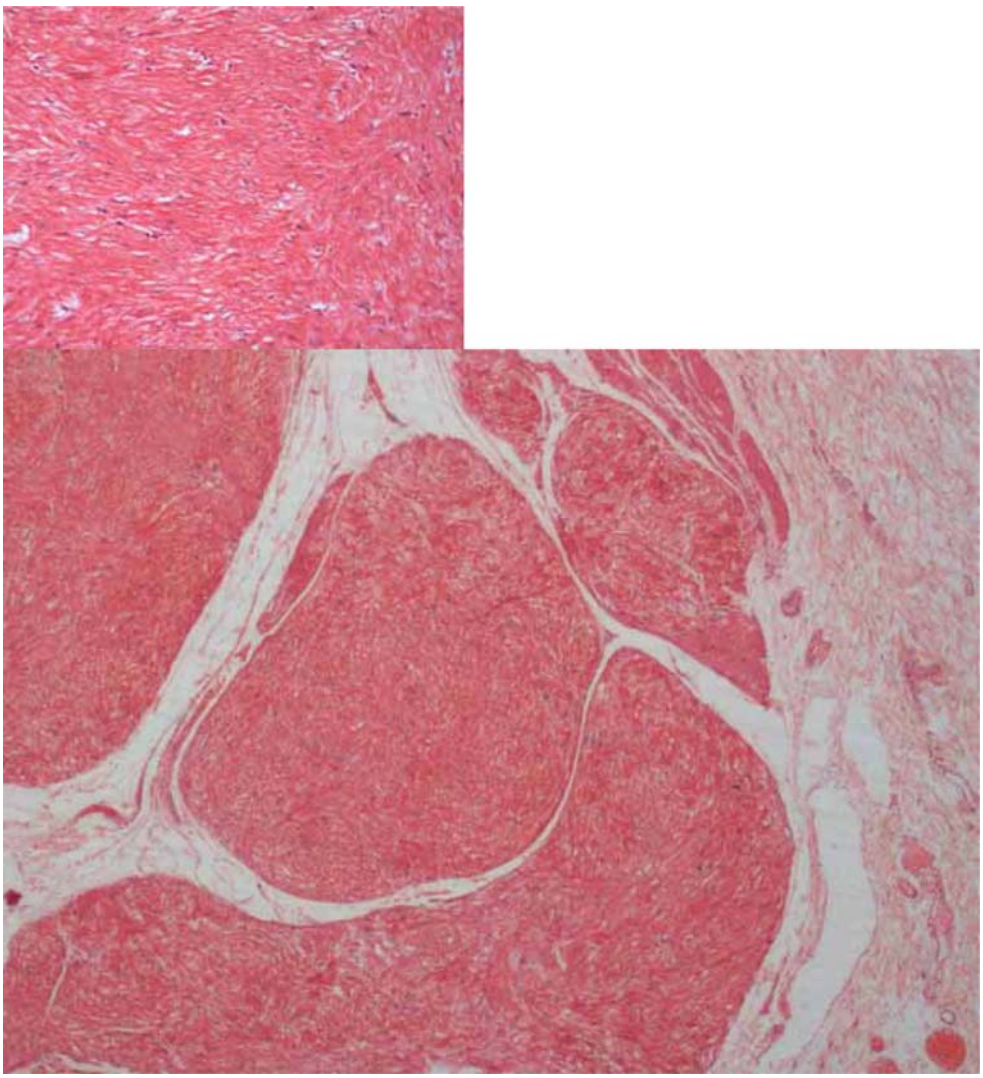

Figure 5 HPE photomicro shows nodules of tumor in the submucosa (hematoxylin and eosin, ×20) *Inset* spindle-shaped cells with moderate indistinct cytoplasm and no mitosis.

may mimic Hirschsprung's disease.[14] The condition has also been reported to be coexisted with other esophageal lesions like granular cell tumor[16] and pedunculated polyp.[17] Levine et al.[6] in a series of six patients reported half of them to have familial disease (siblings or two generations) while one third had diagnosed or suspected Alport's syndrome. The present series is different in this regard that the disease pattern was familial without evidence of expression of any associated lesions. The patients were from three different generations with in the same family. The inheritance diffuse esophageal leiomyomatosis with Alport's syndrome has been shown to be due to sis, contiguous gene deletions of the COL4A5 and COL4A6 genes while the inheritance of Alport's syndrome is associated with the mutation of gene for encoding type IV collagen (COL4A5 gene).[4,14,18]

It usually involves the distal esophagus but may extend throughout its entirety and into the proximal stomach.[1,6,19] Esophageal ulceration and bleeding caused by esophageal leiomyomatosis are uncommon. Minimal to moderate vascularization is seen in esophageal leiomyomatosis. Histologically, the condition is characterized by proliferation of circular and longitudinal smooth muscle within the esophageal wall. There is minimal or no cellular atypia, no detectable mitoses, and the overall cellularity is low. There may be nodularity superimposed on the diffuse esophageal process, and the leiomyomatosis lie beneath normal esophageal and gastric epithelium.[1,2,6]

The condition occurs approximately twice as frequently in males as in females. The onset of symptoms is usually in the first decade of life. However, in the present series, all patients were females and two of them presented after the third decade of life. The usual presentation is slowly progressive dysphagia over many years.[6,11] Dysphagia is the result of circumferential wall thickening that is caused by proliferation of the circular and longitudinal smooth muscle mostly located in the lower third of the esophagus, extending to the cardia of the stomach in some cases and obstructing the lumen.[6,8,9] A small number of patients develop prestenotic dilatation of the esophagus. Respiratory symptoms, such as dyspnea and recurrent pulmonary infections, may occur as a result of tracheobronchial involvement with leiomyomatosis or, possibly, due to aspiration.[13]

The diagnosis is suspected on the basis of the radiological findings. A chest radiograph may show a tubular posterior mediastinal mass.[5,6,9] A contrast study may show eccentric lumen with dilatation, tapering, tortuosity, and deviation of the axis of the esophagus. Such a radiological picture may mimic achalasia and hence has been described as one of the causes of pseudoachalasia.[6–9] However, the narrowed segment is much longer than that seen in achalasia.[6,8,9] In the present study, one patient had barium swallow mimicking achalasia.

Computerized tomogram (CT) of the esophagus may show luminal dilatation and gross circumferential thickening of the esophageal wall. The imaging studies may show soft tissue mass produced by the esophageal wall thickening into the cardia of the stomach. This can differentiate between leiomyomatosis and other benign esophageal strictures. CT can show the complete extraluminal extent of the tumor with the delineation of mediastinal and supra- and infradiaphragmatic structures.[6,7] Likewise, magnetic resonance imaging has also been used to demonstrate the thickness of the esophageal wall.[19] Endosonography, by virtue of its ability to define the layers of the gut wall, can localize these lesions that arise from the muscularis.[8,11]

The management of such cases usually requires surgery. Myotomy is an ineffective treatment. Partial or subtotal esophageal resection and replacement is recommended. Depending upon the gastric involvement, a partial gastrectomy can be added to the procedure. Esophagus can be substituted using stomach or colon.[3,6–9,11,13]

Concluding, leiomyomatosis is a rare benign disorder of the esophagus which can cause long-standing slowly progressive dysphagia. It is known to have familial inheritance. The disease may be associated with Alport's syndrome or leiomyomata elsewhere in the body including gastrointestinal tract, tracheobronchial tree, or female genitalia. The barium picture may mimic achalasia. CT findings of circumferential mass and thickened esophagus are usually suggestive. However, the diagnosis is established by histopathological examination. Esophageal resection is the optimal treatment.

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ORIGINAL ARTICLE

Bile Acid Alone, or in Combination with Acid, Induces CDX2 Expression Through Activation of the Epidermal Growth Factor Receptor (EGFR)

Nelly E. Avissar · Liana Toia · Yingchuan Hu · Thomas J. Watson · Carolyn Jones · Daniel P. Raymond · Alexi Matousek · Jeffrey H. Peters

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Abstract
Objectives Bile acids and acid are implicated in the development of Barrett's esophagus. Evidence suggests that Barrett's esophagus intestinal metaplasia may occur via induction of caudal homeobox gene 2 (CDX2). We hypothesized that induction of CDX2 by bile acids may be due to ligand-dependent transactivation of epidermal growth factor receptor (EGFR).
Methods Human mucosal epithelial cells (SEG-1) were treated for 0 to 24 h with up to 300 μM deoxycholic acid (DCA) at pH 7 or 5 with or without (w/wo) antibodies against EGFR ligand-binding site (Mab528, 3–5 μg/ml). Treatment with 100 ng/ml EGF served as control. CDX2 mRNA expression was determined by real-time polymerase chain reaction. EGFR activation was analyzed by Westerns of phosphorylated EGFR tyrosines.
Results Acid (pH 5) increased the induction of CDX2 mRNA expression caused by DCA. CDX2 mRNA induction was markedly reduced by EGFR blockade with Mab528. Each treatment (pH 5, DCA or pH 5 plus DCA) activated the EGFR on all tyrosines tested but in different time courses. Phosphorylation by DCA was inhibited by Mab528. Activation of EGFR by DCA at pH 5 resulted in EGFR degradation, while that by DCA alone did not.
Conclusion Thus, CDX2 induction by DCA w/wo acid occurs through ligand-dependent transactivation of the EGFR. The variations in EGFR degradation pattern with DCA or DCA at pH 5 indicate differential transactivation pathways. The molecular pathogenesis of Barrett's esophagus may occur via bile-stimulated cell signaling through the EGFR.

Keywords Barrett's esophagus · SEG1 · Bile acid and acid · CDX2 · Transactivation of EGFR

Introduction

Barrett's esophagus (BE) is a pathologic epithelial change occurring in a substantial minority of patients with chronic gastroesophageal reflux disease. It is characterized by the metaplastic change from the normally present squamous to intestinal epithelium, visually apparent as a columnar-lined esophagus and histologically characterized by the presence of goblet cells in cardiac-type epithelium. It is associated with considerable utilization of health care resources, including outpatient costs which are similar to those of insulin-dependent diabetes mellitus.[1] Its greatest significance however lies in the fact that it is the predominant risk factor for the development of adenocarcinoma of the esophagus, the fastest rising cancer in the USA.[2–4] Recent evidence implicates the induction of caudal homeobox gene 2 (CDX2), a transcription factor involved in embryonic intestinal development, as a likely key in the pathogenesis of the intestinal epithelial phenotype.[5–7] We, and others, have previously shown that bile acids and acids, known to be present in reflux, particularly in

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N. E. Avissar (✉) · L. Toia · Y. Hu · T. J. Watson · C. Jones · D. P. Raymond · A. Matousek · J. H. Peters
Department of Surgery, University of Rochester Medical Center, 601 Elmwood Avenue,
Rochester, NY 14642, USA
e-mail: nelly_avissar@urmc.rochester.edu

patients with BE, induce CDX2 in esophageal and mucosal epithelial cells epithelium.[2,8–13]

Acids and bile acids have been shown to activate the epidermal growth factor receptor (EGFR) under a variety of experimental conditions resulting in diverse physiological end points.[12,14–19] Further, bile-acid-induced EGFR activation may occur via both ligand-dependent[18] and independent mechanisms.[20,21] The first step in ligand-induced EGFR activation involves the autophosphorylation of multiple intracytoplasmic tyrosine residues by a tyrosine kinase (TK) intrinsic to the EGFR molecule[22] (Fig. 1). Transactivation of EGFR by other effectors can occur in a ligand-dependent or in ligand-independent pathways. Ligand-dependent transactivation pathways can be induced through non-EGFR ligands such as bile acids, stimulating activation of specific proteases which in turn evoke the autocrine release of one or more EGFR ligands, likely from precursors present in the cell membrane.[15–19,23] Ligand-independent transactivation may occur via phosphorylation of one or more of the EGFR's intracytoplasmic tyrosine residues by other intracytoplasmic kinase molecules.[20,21,24–27] For example, it has been shown in both normal hepatic and cholangiocarcinoma cells that bile acids induce activation of the cytoplasmic kinases Yes[28] or Src,[29] which phosphorylate tyrosine 845 on the EGFR. Phosphorylated EGFR tyrosines, whether autophosphorylated or transphosphorylated, serve as docking sites for specific downstream signal transduction molecules. It would appear that differential site-specific EGFR tyrosine phosphorylation may explain the observed differences in signaling induced by various effectors.

We hypothesized that, in mucosal epithelial cells, bile acids at neutral or acidic pH induce CDX2 through ligand-dependent EGFR phosphorylation. Investigating the mechanisms of bile-acid-induced CDX2 expression and intestinal metaplasia may lead to the discovery of molecular targets useful for diagnosis, risk assessment, and therapeutic intervention in BE.

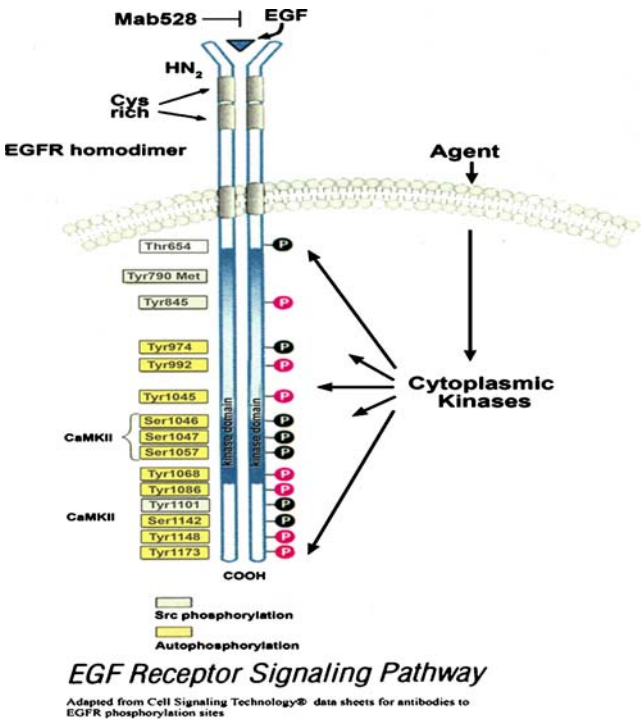

Figure 1 *A scheme of phosphorylation sites.* EGFR phosphorylation sites. Marked in *red* are phosphorylated tyrosines analyzed in the current study (adapted from Cell Signaling Technology® data sheets for antibodies against EGFR site-specific phosphorylated tyrosines).

Materials and Methods

Cell Culture and Treatments

We have previously reported the effect of multiple bile salts in a variety of human cell lines on CDX2 mRNA expression.[9] These studies showed that the combination of DCA and what was believed to be human esophageal adenocarcinoma cell line, SEG-1, was the most effective stimulator of CDX2 expression under the conditions tested. As such, SEG-1 cells and DCA were chosen for further studies to elucidate the mechanisms involved in CDX2 induction. SEG-1 is a human adenocarcinoma cell line (a kind gift from Dr. David Beer, University of Michigan, Ann Arbor, MI, USA). Of note, after completion of the experiments reported in this study, it came to our knowledge via personal communication from Dr. David Beer that genotyping suggested that SEG-1 cells were more consistent with the lung carcinoma cells, H460.

SEG-1 cells were cultured in low-glucose Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum and 100 U/ml penicillin G and 100 μg/ml streptomycin (all from Invitrogen, Carlsbad, CA, USA) at 37°C in a humidified incubator containing 5% carbon dioxide. For experiments, subconfluent cells were split and subcultured on plastic until 70% confluent and were serum-starved 24 h prior to experiments. When reported, 3 or 5 μg/ml of Mab528 (Abcam, Cambridge, MA, USA) or vehicle or a Mab528 isotype IgG2a was added to the cultures 1 h before the addition of 100 ng/ml EGF (Upstate USA, Inc., Lake Placid, NY, USA) or DCA (100 μM, 300 μM) at pH 7 or pH 5. For the experimental groups at pH 7 or pH 5, the media was titrated to corresponding pH before addition of the other components and the pH was verified also thereafter. The cells were then incubated for the indicated time points. Additional control experiments included polymyxin 100 U/ml to inhibit contaminating endotoxin, if present.

RNA Extraction and Complementary DNA Synthesis

Total RNA was extracted using RNeasy Plus Mini Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instruction manual. Total RNA concentrations were determined by spectrophotometric quantification at 260 nm, and the integrity of the bands were verified visually by agarose gel electrophoresis. For real-time reverse-transcription polymerase chain reaction (PCR), cDNA was synthesized from 0.125-μg total RNA using the iScript cDNA Synthesis kit (BioRad Laboratories, Hercules, CA, USA) according to the manufacturer's protocol, and the final reaction was diluted fivefold in RNAse-free water.

Real-time PCR

CDX2 mRNA expression was determined by quantitative real-time PCR in triplicate with 2 μl cDNA, 1× iQ SYBR Green Supermix (BioRad Laboratories, Hercules, CA, USA), and 0.5 μM primers (IDT, Coralville, IA, USA), in a final reaction volume of 20 μl using Mx3005P (Stratagene, La Jolla, CA, USA). The gene-specific primers for CDX2 were CDX2-F, 5′-ACCAGGACGAAAGACAAATATCGA-3′, and CDX2-R, 5′-TGTAGCGACTGTAGTGAAACT CCTTCT-3′. The primers for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were GAPDH-F, 5′-GGCTCTC CAGAACATCATCCCTGC-3′, and GAPDH-R, 5′-GGG TCTCGCTGTTGAACTCAGAGG-3′. The real-time PCR reaction includes initial denaturing at 95°C for 10 min followed by 34 cycles of 94°C for 1 min, 55°C for 1 min, and 72°C for 1 min followed by an extension at 72°C for 10 min to detect the fluorescent product. PCR products were subjected to a melting curve analysis. Agarose gel electrophoresis showed the expected band. The data were analyzed using MX3005P software.

Protein Concentration

Protein concentration was determined using bicinchoninic acid protein assay reagent kit (Pierce Biochemicals, Rockford, IL, USA) according to the manufacturer's instructions. Absorbance at 545 nm was measured using Benchmark Plate Reader (BioRad, Hercules, CA, USA). Bovine serum albumin (BSA) served as standard.

Preparation of Crude Extracts for Western Blot Analysis

Cells were lysed in a modified radioimmunoprecipitation assay buffer (10 mM Tris, 150 mM NaCl, 0.5% Nonidet p40, 1% Triton X 100, 1 mM ethylenediaminetetraacetic acid, pH 7.4) with protease and phosphatase inhibitors (1 mM activated sodium orthovanadate, sodium fluoride, and phenylmethylsulfonyl fluoride, 10 μg/ml of each aprotinin, pepstatin, and leupeptin and Sigma protease inhibitor cocktail diluted 1:10; Sigma Chemical Co., St. Louis, MO, USA). The lysates in Laemmli buffer were boiled for 5 min prior to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE).

Western Blot Analysis

Crude extracts (40 μg/lane) were analyzed by 7.5% SDS-PAGE according to the method of Laemmli.[30] Proteins were electotransferred to polyvinylidene fluoride membranes, and the membranes were blocked by incubation for 1 h at room temperature with blocking solution (3% nonfat dry milk in TTBS: 13 mM Tris, 150 mM NaCl, pH 7.5 containing 0.05% Tween-20). The membranes were incubated overnight at 4°C with the following primary antibodies: against total EGFR (Upstate USA, Inc., Lake Placid, NY, USA; 1:1,000); EGFR phosphorylated on tyrosine 1068 (1:2,000) and on tyrosines 1173, 1086, 1148, and 845 (1/1,000; Biosource, Camarillo, CA, USA) all diluted in 3% blocking solution; EGFR phosphorylated on tyrosine 1045 diluted in 5% BSA, 1× TBS and 0.1% Tween-20 (Cell Signaling Technology, Beverly, MA, USA). Blots were washed three times (2×5; 1×15 min) in TTBS and incubated with the appropriate secondary antibodies (Jackson ImmunoResearch, West Grove, PA, USA) usually diluted 1:5,000 (total EGFR 1:20,000). Prior to visualizing the autoradiograms on blue XAR ALF film (Labscientific; Livingston, NJ, USA), blots were washed again as previously described and incubated in SuperSignal (Pierce Chemical, Rockford, IL, USA) for 1–40 min. Benchmark standards (Invitrogen, Carlsbad, CA, USA) were used to determine apparent molecular weight. Because each antibody has its own sensitivity, comparisons of the intensities of the bands can be made only to each antibody's own control and not among bands of different antibodies. Total EGFR or β-actin was used as loading control on stripped blots as specified in the relevant experiments. Unsaturated (or saturated when specified) autoradiograms were scanned by Kodak Gel Logic100 Imaging System and densitometry was carried out using Kodak 1D image Analysis Software (Rochester, NY, USA). Membranes that were incubated without a primary antibody did not show any staining (data not shown).

Statistical Analysis

Results are reported as means±SEM. Data were analyzed by one-way analysis of variance (ANOVA; with Newman Keuls posttest) on GraphPad Prism® (San Diego, CA, USA) statistical software package. Differences were considered significant at $p<0.05$. Each value represents the mean of three experiments unless otherwise specified.

Results

CDX2 mRNA Expression Induced by 300 μM DCA at pH 7 Is Reduced by Blocking of EGFR Extracellular Ligands Binding Site

Our previous experiments have shown that DCA upregulation of CDX2 expression in SEG-1 cells is maximal with treatment with 300 μM DCA after 24 h with minimal effects on cell viability.[9] We hypothesized that EGFR transactivation by DCA involved the autocrine release of EGFR ligands. In order to test this hypothesis, SEG-1 cells were pretreated with Mab528 (3 μg/ml), known to block the EGFR extracellular ligand-binding site, for 1 h prior to and during 300 μM DCA exposure for 24 h. DCA treatment increased CDX2 mRNA by over tenfold. EGFR blockade resulted in approximately 50% decrease in DCA-induced CDX2 mRNA expression (Fig. 2). The presence of polymyxin during the incubation did not change this outcome. In addition, incubation with the isotype IgG2a was without any effect. These results suggest that DCA-induced CDX2 expression is partially mediated via EGFR signaling.

DCA at pH 7 (300 μM) Induces EGFR Phosphorylation on Multiple Tyrosines which Is Inhibited by Mab528

We initially investigated short-term (≤60 min) DCA-induced EGFR phosphorylation in SEG-1 cells treated with 300 μM DCA for 0 to 60 min. The phosphorylation of individual EGFR tyrosines represented in red in Fig. 1 was determined. Western blot analysis showed DCA-induced phosphorylation of all the EGFR tyrosines tested, including 1173, 1148 1086, 1068, 1045, 992, and 845 (Fig. 3a, right). DCA-induced EGFR phosphorylation peaked at 30 min, slightly slower than the EGF-positive control, which peaked at 5 min (Fig. 3a, left). DCA-induced phosphorylation level was at least three to nine times less than EGF-induced phosphorylation (Fig. 3b). We also examined the longer-term activation of EGFR by DCA (up to 24 h, Fig. 3c, left). These experiments confirmed the phosphorylation peak at 30 min and revealed a second peak 8 h after DCA addition (Fig. 3a–c). At both time points, all EGFR tyrosines were phosphorylated, suggesting that the intrinsic EGFR tyrosine kinase was activated in response to DCA treatment. EGF-induced phosphorylation had only one peak at 5 min (Fig. 3a) and declined afterwards (data not shown). As expected, the addition of Mab528 before and during incubation with DCA caused a decrease in the DCA-induced EGFR tyrosine phosphorylation at both time peaks (Fig. 3c, right). To quantify the degree of the decrease in phosphorylation, we determined the density of the bands induced by 30 min and 8 h of DCA and 5 min of EGF treatment with and without Mab528. Each band was normalized to total EGFR and to its own control under the same condition. The ratio of the band induced by DCA or EGF treatment (which was set as 1) to that of the bands in the presence of Mab528 was calculated. Mab528 treatment significantly reduced both EGF- and DCA-induced phosphorylation, almost by half (Fig. 3d). In concert, these experiments suggest that blocking EGFR ligand-binding sites partially inhibits the DCA-induced phosphorylation of EGFR and that DCA may act by inducing the release of EGFR ligands, which in turn activates the EGFR.

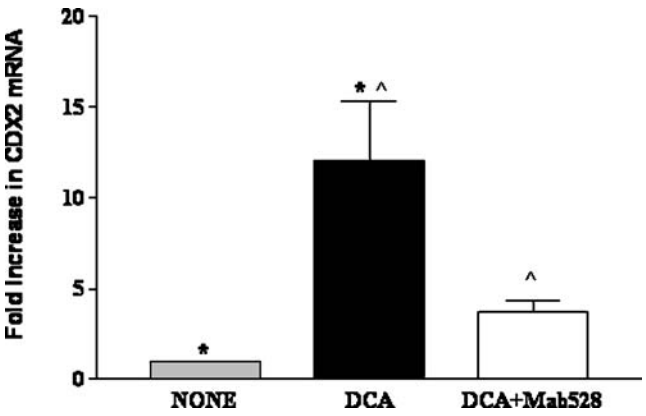

Figure 2 *Real-time PCR of relative CDX2 mRNA expression in SEG-1 cells treated with 300 μM DCA at pH 7 w/wo Mab528*. SEG-1 cells were incubated with 300 μM DCA with or without 3 μg/ml of Mab528 for 24 h. Total RNA was isolated from cell lysates, reverse-transcribed to cDNA and subjected to real-time PCR analysis ($n=3$, each in triplicates, ^*$p<0.01$).

DCA (300 μM, pH 7) Activation of EGFR Induces Minimal EGFR Degradation

We studied the autoregulatory ligand-binding-induced degradation of EGFR. It is known that EGFR signal transduction induced by EGFR ligands is autoregulated (stopped) by EGFR degradation.[31] As expected, EGF induced time-dependent degradation of EGFR. The decrease was significant by 2 h and by 24 h only minimal amounts of EGFR remained (Figs. 4a,b). In contrast, activation of EGFR by DCA resulted in only minimal EGFR degradation. Under the conditions studied, Mab528 did not inhibit EGF-induced EGFR degradation, but it significantly inhibited the minimal degradation induced by DCA (Fig. 6b).

CDX2 mRNA Is Synergistically Induced by a Combination of pH 5 Plus 100 μM DCA and the Increase Is Inhibited by 5 μg/ml Mab528; Real-time PCR of CDX2 mRNA

As both acid and bile acid are components of the refluxate, we investigated the treatment by the combination of the two

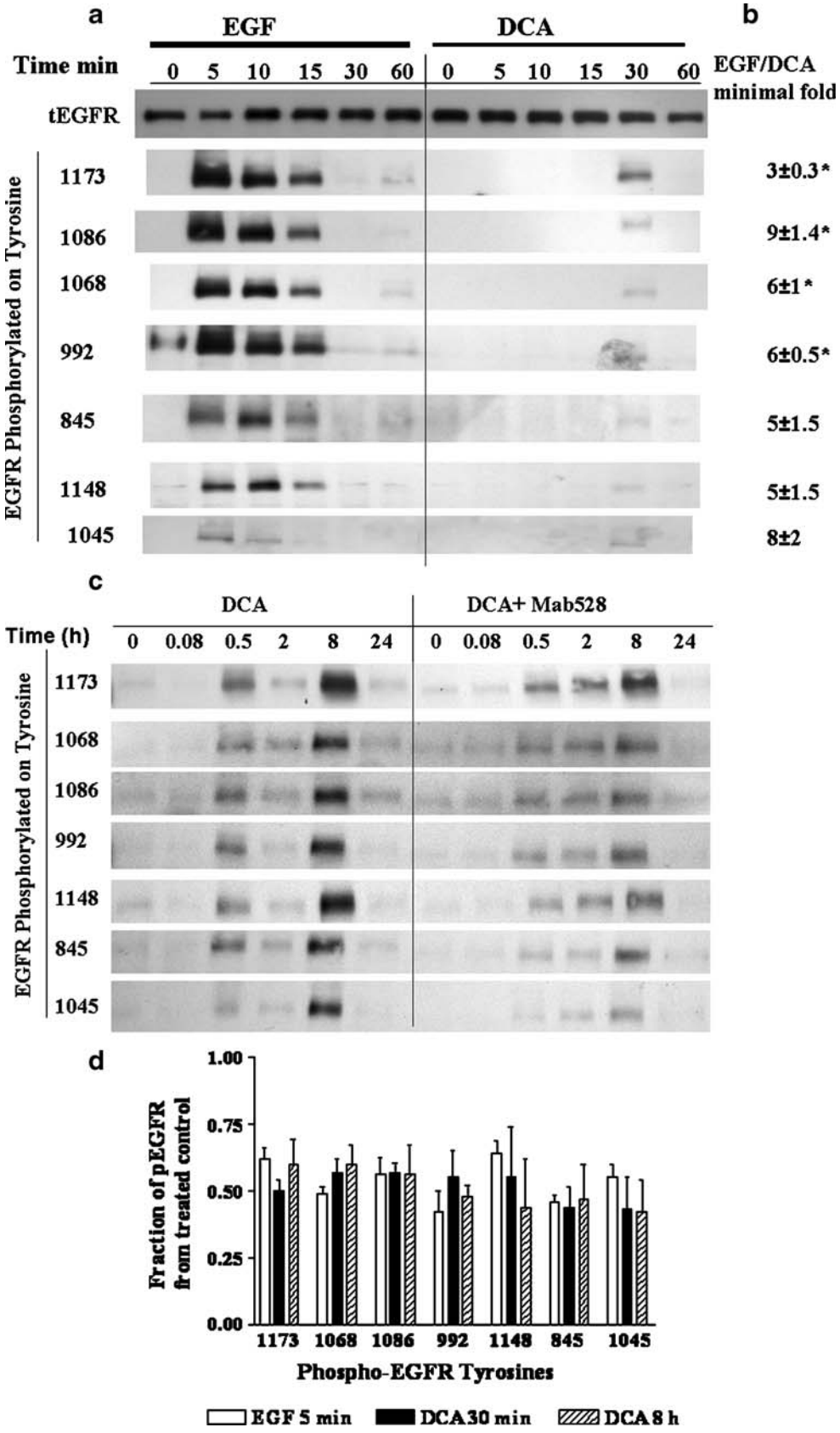

Figure 3 *Western blot analysis of EGFR phosphorylation induced by DCA (300 μM, pH 7) and its inhibition by Mab528 in SEG1 cells*. **a** and **b** *Short-term DCA- and EGF-induced EGFR tyrosine phosphorylation*. SEG-1 cells were incubated with or without EGF or DCA for up to 1 h. Crude extracts were subjected to Western blot analysis for **a** total EGFR (*tEGFR*) and EGFR phosphorylated on multiple individual tyrosines and **b** quantification of the minimal ratio of EGF-induced versus DCA-induced phosphorylation, $n=3$. **c** and **d** *Long-term EGFR phosphorylation induced by DCA and its inhibition by Mab528*. SEG-1 cells were incubated with 300 μM DCA with or without 3 μg/ml Mab528 for up to 24 h. Crude extracts were subjected to Western blot analysis for EGFR phosphorylated on multiple individual tyrosines. **c** Representative blot. **d** Autoradiograms of total EGFR and EGFR phosphotyrosines were quantified by densitometry for the following experimental conditions: EGF-treated cells at 5 min; DCA-treated cells at 30 min and 8 h. For every phosphotyrosine and each experimental condition, phosphorylated EGFR was normalized with total EGFR. For each phosphorylated EGFR tyrosine, the induced phosphorylation under a specific treatment condition was set at one. Phosphorylation fold decrease by Mab528 is presented ($n=3$, $p<0.01$ by one-way ANOVA for all tyrosines except 1148), $n=3$.

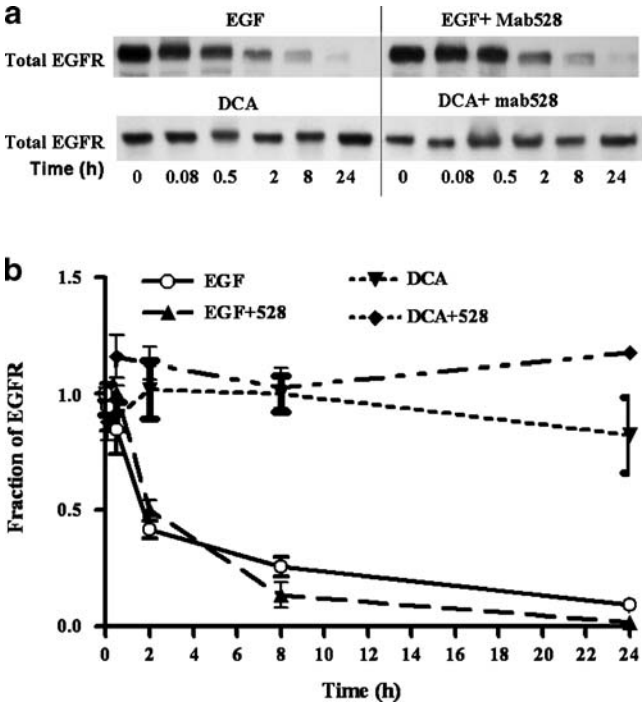

Figure 4 *Quantification of EGFR degradation following treatment with 300 μM DCA at pH 7***.** SEG-1 cells were incubated with 300 μM DCA w/wo 3 μg/ml Mab528 for up to 24 h. Crude extracts were subjected to Western blot analysis for total EGFR. **a** Representative blot. **b** Quantification of three experiments (n=3). EGFR level in each experimental control was set at one and the fold decrease calculated for each time point (p<0.01 for DCA±Mab528 versus EGF±Mab528, 2 h; p<0.001 for DCA±Mab528 versus EGF±Mab528, 8 and 24 h; p<0.05 for DCA versus DCA + Mab528).

on CDX2 induction. Combination of pH 5 plus 300 μM DCA was toxic to the cells and was not investigated further. Incubation of the cells for up to 24 h with 100 μM DCA or pH 5 each alone did not increase CDX2 message. However, the combination of the two was synergistic and increased CDX2 mRNA by up to 40-fold after 24-h incubation (Fig. 5a).

Blockage of EGFR Extracellular Ligand-Binding Site by 5 μg/ml Mab528 Inhibits CDX2 mRNA Expression Induced by 100 μM DCA at pH 5; Real-time PCR of CDX2 mRNA

To investigate whether the induction of CDX2 is via ligand-dependent EGFR transactivation, as it is for induction of CDX2 mRNA by 300 μM DCA at pH 7 (Fig. 2), we pretreated the cells with Mab528 (5 μg/ml) for 1 h prior and during incubation with acidic DCA. The antibody completely inhibited the increase in CDX2 mRNA expression induced by acidic DCA (Fig. 5b). Thus, the induction of CDX2 by acidic DCA occurs also via ligand-dependent transactivation of EGFR.

The Combination of pH 5 Plus 100 μM DCA Alters the Time Course of EGFR Phosphorylation on Multiple Tyrosines

Incubation of 24-h serum-starved SEG-1 cells for additional 24 h at neutral pH induced EGFR phosphorylation on all the tyrosines which peaked at 24 h (Fig. 6a, left). In contrast to the pattern obtained with addition of neutral 300 μM DCA to the cells (Fig. 3), the addition of neutral lower concentration of 100 μM DCA did not change the EGFR phosphorylation pattern (Fig. 6a, right). Incubation of the cells in an acidified medium caused the peak to shift and to appear earlier after 4–8 h (Fig. 6b, left, c). The combination of acidic pH plus 100 μM DCA shifted EGFR phosphorylation peak even earlier to appear at 30 min–2 h

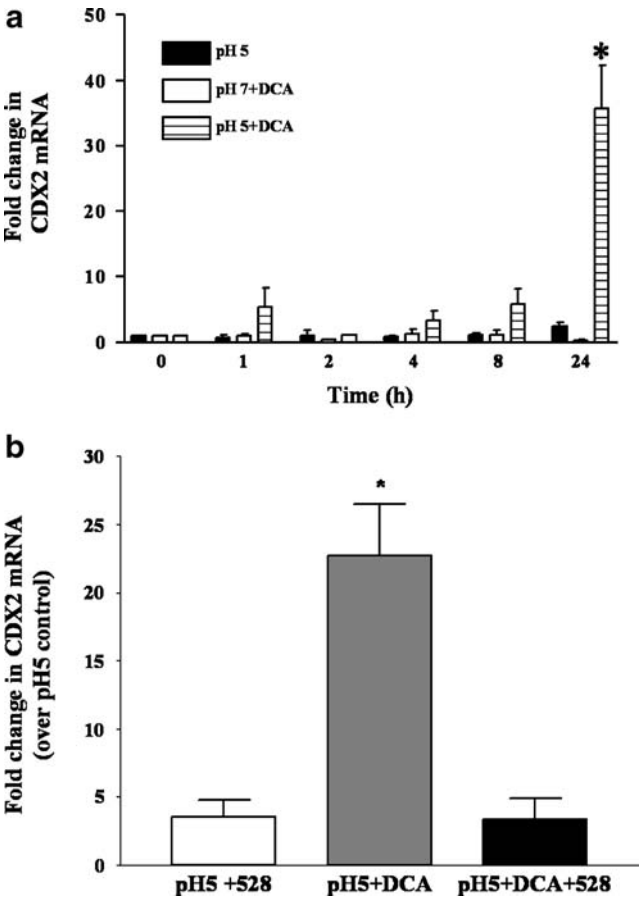

Figure 5 *Real-time PCR of relative CDX2 mRNA expression in SEG-1 cells treated with 100 μM DCA at pH 5 or pH 7 w/wo Mab528***.** **a** SEG-1 cells were incubated for up to 24 h at pH 5 or pH 7 w/wo 100 μM DCA or **b** for 24 h at pH 5 w/wo 100 μM DCA, w/wo 5 μg/ml Mab528 (528). Total RNA was isolated from cell lysates, reverse-transcribed to cDNA, and subjected to real-time PCR analysis. Values obtained for control at pH 7 alone were set at 1 for **a** and those obtained for control at pH 5 were set at 1 for **b**. Values are means± SEM; *p<0.001 compared to all others, n=3–8.

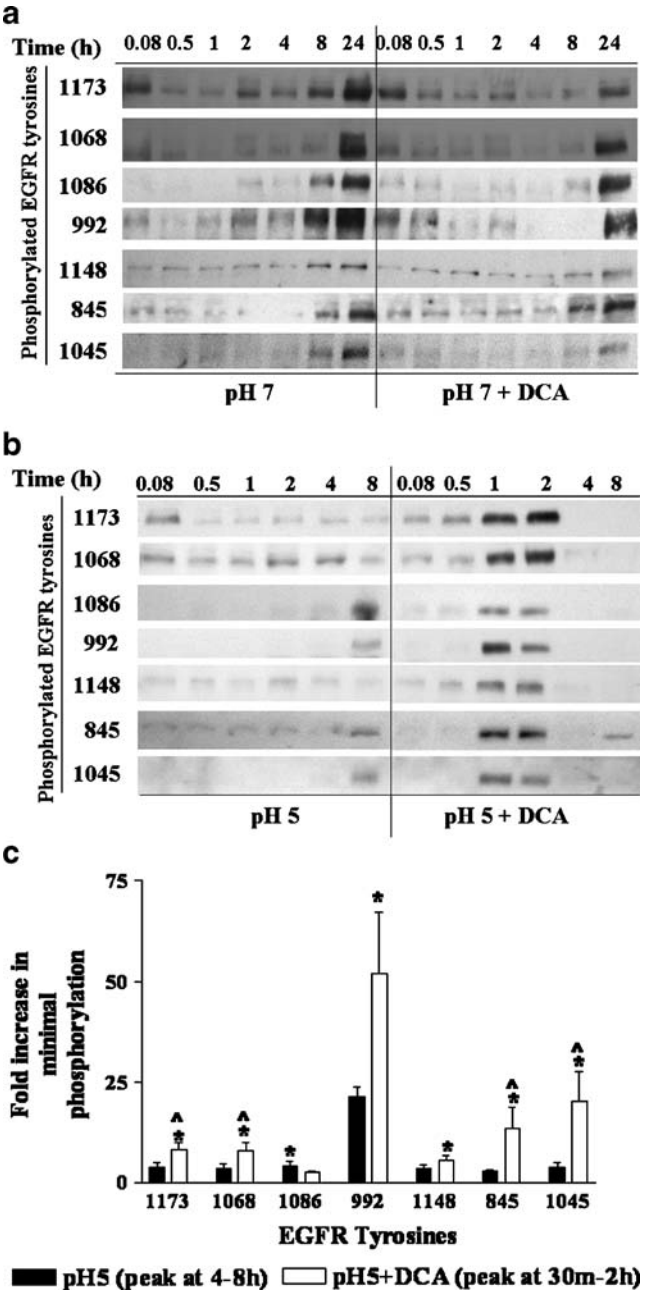

Figure 6 *Western blot analysis of EGFR phosphorylation induced at pH 5 or pH 7 w/wo 100 μM DCA in SEG-1 cells*. SEG-1 cells were incubated at pH 7 for up to 24 h (**a**) or pH 5 for up to 8 h (**b**) w/wo 100 μM DCA. Crude extracts were subjected to Western blot analysis for EGFR phosphorylated on multiple tyrosines. **a** and **b** are representative gels. **c** Quantitative results for **b**. Each tyrosine phosphorylation at 5 min under each condition was taken as control and set at 1. Values are mean±SEM. *$p<0.05$ versus control. ^$p<0.05$ for pH 5 versus pH 5 + DCA, $n=3$–7.

(Fig. 6b, right, c). Under each condition, all the tyrosines were phosphorylated in a similar time course, indicating that probably EGFR intrinsic TK was activated. Thus, DCA alone, depending on its concentration, or in combination with acid alters EGFR phosphorylation time course. The transactivation of EGFR occurs prior to the induction of CDX2.

Activated EGFR Is Degraded Only by the Combination Treatment of pH 5 Plus 100 μM DCA

Finally, we studied the degradation of EGFR under acidic DCA treatment of the cells. As for treatment with neutral 300 μM DCA (Fig. 4), treatment with neutral 100 μM DCA did not cause degradation (Fig. 7a,b). Likewise, incubating the cells at pH 5 alone over 8 h did not result in EGFR degradation. In contrast, acidic 100 μM DCA synergistically caused EGFR degradation (Fig. 7), in a mode similar to EGF-induced time-dependent EGFR degradation (Fig. 4a,b). For an unknown reason, in several of the experiments, actin level was also decreased over time with the combination treatment.

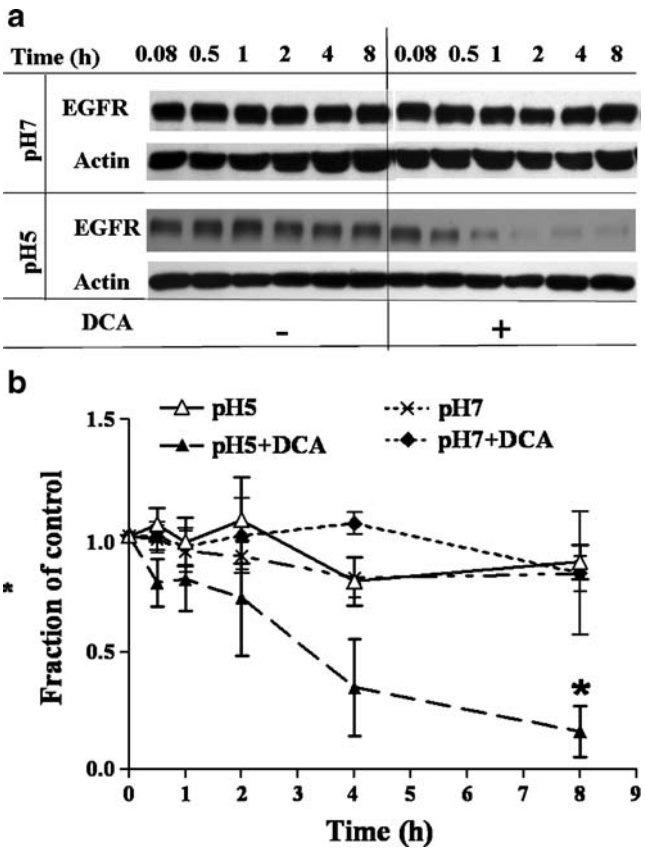

Figure 7 *Quantification of EGFR degradation following treatment with 100 mM DCA at pH 7 or pH 5*. SEG-1 cells were incubated at pH 7 or pH 5 w/wo 100 μM DCA for up to 8 h. Crude extracts were subjected to Western blot analysis for EGFR protein and β-actin. **a** Representative gels. **b** The ratio of EGFR/β-actin was calculated for each time point and the ratio at 0.08 h was set at 1 for each condition. Values are mean±SEM. *$p<0.01$ versus all except 4 h at pH 5 + DCA, $n=3$.

Discussion

Both acid and bile acids are components of the refluxate. Although DCA alone at high concentration can cause the induction of CDX2, the synergism between lower concentration of DCA and acid in inducing CDX2 has physiological and pathological significance. The mechanisms involved in the synergism are not known but could be due to the ability of acids to activate proteases and enhance penetration of bile acids across the mucosa.[2] In a similar manner, CDX1 is induced by bile acids or acidic bile but not by acid alone.[32] It was reported that the ability of acid alone or its synergism with bile to induce CDX2 is dependent on the cell type and the magnitude and the duration of acidification.[13,33,34] Hundreds of publications over the past one to two decades have utilized SEG-1 cells as a model for esophageal cellular biology. Although the recent suggestion that the genotype of SEG-1 cells is more consistent with a tracheobronchial origin, their foregut epithelial nature along with the basic nature of the investigations is unlikely to substantially alter the relevance of this in vitro model system. However, it should be noted that, although cell line experiments often enable elucidating mechanisms, the results may not directly apply in vivo in which the likely cell of interest is the esophageal stem cell.

We have shown that exposure of human mucosal epithelial cells to DCA in neutral and acidic pH results in activation of the EGFR. However, the time course of activation is variable and depends on both DCA concentration and the acidic environment. Multiple tyrosine residues were activated on EGFR under all conditions studied, suggesting activation of the intrinsic EGFR TK. Further, activation peaks were inhibited by a monoclonal antibody known to inhibit ligand binding to EGFR (Fig. 3d). Inhibition of CDX2 induction by Mab528 (Figs. 2 and 5b) provides a link between bile acid, or combination of bile and acid, to CDX2 upregulation and EGFR activation This is the first evidence linking activation of a putative receptor to the observation of DCA-stimulated CDX2 upregulation.

The first step in EGFR signal transduction induced by its ligands is its autophosphorylation by EGFR intrinsic tyrosine kinase on multiple tyrosines.[22] Transactivation of EGFR by other effectors, such as bile salts, can result in specific individual tyrosine phosphorylation.[27,28] Both autophosphorylation and transphosphorylation of the EGFR occur via a multistep process. Thus, the degree of phosphorylation is best measured site-specifically with attention to the time course to obtain functionally relevant information.[35] The simultaneous activation by DCA or acidic DCA of all tyrosine kinase sites on the EGFR suggests activation by a ligand-dependent mechanism.

These data are consistent with activation of the EGFR by several possible mechanisms (Fig. 8). Bile acids and particularly acidic bile may activate matrix metalloproteinases. Matrix metalloprotease may activate one or more dormant membrane EGFR ligands, which then bind to EGFR resulting in multiple tyrosine phosphorylations. This mechanism has been shown to underlie EGFR activation in several tissues.[16–18,23] Alternatively, membrane perturbation or transactivation of other receptors by bile acids or acidic bile may activate cytoplasmic kinases, which phosphorylate individual EGFR tyrosines. This mechanism has been shown to operate in primary hepatocyte stem cells and intestinal cells in response to several bile acids.[20,21] Our data suggest the former is more likely. Further, the delay in DCA or acidic DCA activation of the EGFR in comparison to EGF (30 vs 5 min) is consistent with the time needed for activation of primary alternate signaling mechanisms which then secondarily activate EGFR.

Activation of EGFR by hydrophobic bile acids in primary hepatocytes[24] or by tumor necrosis factor α and interleukin 1β in intestinal cells[36] also caused two phosphorylation peaks such as obtained by neutral 300 μM DCA. In contrast to our findings, Mab528 in these studies abolished only the later peak. The first peak in hepatocyte culture was shown to be secondary to the activation of another kinase (yes) which in turn specifically phosphorylated EGFR tyrosine 845.[24,28] The observation that both peaks were blocked in our studies can be explained by hypothesizing that the early activation occurs via activation of metalloproteinases and the second via de novo synthesis of EGFR ligands.

Mab528 only partially inhibited (50%) both neutral DCA-induced CDX2 expression and neutral DCA-induced EGFR phosphorylation. It is possible that signaling proteins, other than EGFR, participate in CDX2 induction (Fig. 8). Alternatively, the concentration of Mab528 used

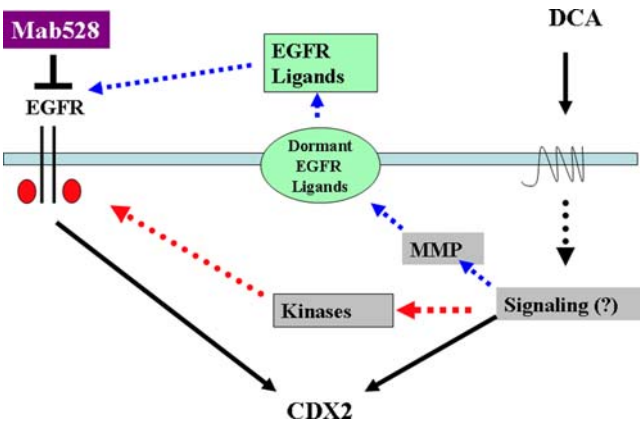

Figure 8 *Suggested mechanisms for CDX2 induction by DCA in SEG1 cells. Broken lines*, pathways not directly tested; *solid lines*, pathways tested; *red lines*, likely do not occur; *blue lines*, likely to occur.

may not have been sufficient to fully inhibit the process. Although we used an antibody concentration which has been reported to inhibit EGFR activation by 90%,[37] other reports have indicated that this concentration is not enough for full inhibition of EGFR activity.[38,39] Therefore, in the following set of experiments (Fig. 5b), we increased the antibody concentration and obtained complete inhibition of CDX2 induction, indicating that EGFR is the key signaling protein.

The transactivation of EGFR by neutral DCA in SEG-1 cells did not result in EGFR downregulation, while the transactivation by acidic DCA caused EGFR degradation. Phosphorylation of EGFR tyrosine 1045 is a crucial step for degradation of EGFR by either its direct ligands or as a result of transactivation.[40,41] Phosphorylation of EGFR tyrosine 1045 in acidic bile is in agreement with EGFR degradation. On the other hand, transactivation of EGFR in a variety of tissues by effectors other than its primary ligands[28,42,43] has been shown to result in minimal or slow EGFR degradation. In the studies referenced above, tyrosine 1045 activation was low or absent. In contrast, our data showed phosphorylation of tyrosine 1045 following also neutral DCA treatment. Other mechanisms inhibiting EGFR degradation rather than hypophosphorylation of tyrosine 1045 must be involved. For example, heterodimers of EGFR and ErbB2 (a member of the EGFR family of receptors) are known to be degraded at a much slower rate than EGFR homodimers.[44,45] The machinery responsible for EGFR degradation involves many proteins and steps. Other factors influencing degradation such as phosphatidylinositol 4-kinase type IIA translocation,[46] EGFR threonine 645 phosphorylation,[45] and sprout 2 activation[47] may have been affected by neutral DCA.

Successful translation of this knowledge into clinical benefit requires a number of clinical issues to be addressed. These include identifying (1) the appropriate timing of intervention, (2) the patients at risk for BE, and (3) the ideal point of pharmacologic intervention such as receptor blockade, pathway inhibition, siRNA administration, or others. While EGFR-inhibiting drugs are being used with significant success in the treatment of cancer, inhibiting the development of metaplasia is a completely different treatment paradigm. Finally, preventative treatment must be safe. Current EGFR inhibitors including monoclonal antibodies such as cetuximab, EGFR TK inhibitors such as Iressa™, and antisense oligonucleotides are reasonably well tolerated but do have several side effects including acne like rash, nausea, and vomiting.[45]

In summary, the study implicates activation of the EGFR by bile acids or acidic bile as a putative mechanism in the pathogenesis of the epithelial change occurring in BE. We have established a link between bile acids, EGFR activation, and CDX2 upregulation. We also showed that activation of EGFR by neutral bile acid caused a prolonged activation of EGFR. An increased amount of EGFR, prolongation of the activation of EGFR, and the presence of EGFR variants that are perpetually activated have been shown to be hallmarks of many neoplastic processes.[48] These data suggest that similar mechanisms may underlie the metaplastic evolution responsible for BE.

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ORIGINAL ARTICLE

Transthoracic Esophagectomy After Endoscopic Mucosal Resection in Patients with Early Esophageal Carcinoma

W. Schröder · K. Wirths · C. Gutschow · D. Vallböhmer · M. Bludau · B. Schumacher · H. Neuhaus · A. H. Hölscher

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Abstract
Introduction For patients with esophageal carcinoma limited to the mucosa endoscopic mucosal resection (EMR) is the therapy of choice whereas surgical resection is advocated for submucosal tumors.
Methods This study analyzes the histopathologic results of patients with early esophageal carcinoma who underwent EMR prior to transthoracic esophagectomy. Sixteen patients with early esophageal carcinoma and EMR as first line treatment were included in this retrospective study. Ten patients underwent transthoracic esophagectomy because of submucosal infiltration combined incomplete tumor resection at the lateral/basal resection margin. In one patient each, surgical therapy was indicated due to submucosal infiltration or incomplete resection only. Three patients underwent surgical resection due to residual neoplasia within an esophageal stenosis following EMR. Surgical specimens were examined for pT and pN stage according to the UICC.
Results Three patients had a squamous cell carcinoma (SCC) and 13 patients an adenocarcinoma (AC), nine patients with a long segment Barrett's esophagus. The distribution of the pT stages was as follows: 6× pT0 (no histopathologic evidence of residual tumor), 1× pT1m1, 1× pT1m2, 3× pT1m3, 1× pT1sm1, 1× pT1sm2, 1× pT2, and 2× pT3. Three of 16 patients (18.8%) with a pT1sm1, pT2, and pT3 stage had nodal metastases. In all three patients metastatic nodes were located in the mediastinum. In two patients, a second carcinoma was detected during histopathologic work-up (1× AC in the cardia and 1× SCC in the cervical esophagus).
Conclusion The data of this highly selected patients indicate that the boundary between the therapy of mucosal and submucosal tumors is not as clear as stated. Therefore, treatment of early esophageal carcinoma demands a close interdisciplinary cooperation.

Keywords Endoscopic mucosal resection · Esophagectomy · Early esophageal carcinoma

W. Schröder (✉) · C. Gutschow · D. Vallböhmer · M. Bludau · A. H. Hölscher
Department of Visceral and Vascular Surgery,
University of Cologne,
Kerperner Str. 62,
50937 Cologne, Germany
e-mail: Wolfgang.Schroeder@uni-koeln.de

K. Wirths · B. Schumacher · H. Neuhaus
Department of Gastroenterology,
Evangelisches Krankenhaus Duesseldorf,
Duesseldorf, Germany

Introduction

For patients with esophageal cancer the basic goals are a curative treatment with improvement of long-term prognosis and a reduction of treatment-associated morbidity and mortality. With respect to these goals endoscopic mucosal resection (EMR) and standardized surgical resection are possible treatment options for early esophageal carcinoma. It is generally accepted that EMR is the treatment of choice for mucosal carcinoma whereas submucosal carcinomas are best treated with a subtotal esophagectomy and lymphadenectomy.[1,2] The rationale for this different therapeutic strategy is the pattern of lymphatic spread observed for mucosal and submucosal carcinomas.[3–5] For mucosal esophageal carcinomas, a metastatic spread to the locore-

gional lymph nodes rarely occurs. On the other hand, the rate of nodal metastases increases with depth of submucosal infiltration and reaches up to 75% for the deepest layer of the submucosa.[4,6] This histopathologic observation is not different for adeno- (AC) and squamous cell carcinoma (SCC).[4]

However, this well-defined therapeutic concept for early esophageal carcinoma has still major difficulties for a successful implementation. Despite advanced diagnostic technologies the accuracy to safely differentiate between mucosal and submucosal carcinomas before endoscopic treatment is still limited. High resolution endoscopy (HRE) and endoluminal ultrasound (EUS) are the best diagnostic means available at present but their predictive values do not exceed 80–90%.[7] Histological assessment of complete tumor resection is another problem associated with EMR because larger lesions are resected in piecemeal fashion in the majority of patients.[8] In this setting, complete resection has to be confirmed by follow-up biopsies. On the contrary, standard surgical resection offers an almost 100% R0 resection rate but is still associated with a relevant postoperative morbidity and mortality.[9–11]

The present study retrospectively analyses the results of patients with early esophageal carcinoma who underwent a standardized surgical resection following EMR treatment. This analysis focuses on the comparison of histopathological results after EMR with definite histopathology obtained from the surgical specimen.

Material and Methods

From 02/05 to 12/07 a total of 172 patients with esophageal carcinoma underwent curative surgical treatment in the Department of Surgery, University of Cologne. Out of this consecutive series, 16 patients (9.3%) were identified who had one or more EMR prior to esophagectomy. Only these 16 patients were subject to further analysis. Thirteen of the 16 patients were treated in one single, highly specialized endoscopic unit. Three other patients were referred from three different gastroenterologic units. Thirteen patients were male, three patients female. The average age was 61.8 years (range, 49–79 years).

Endoscopic Treatment

The following description characterizes the endoscopic treatment of the specialized endoscopic unit.

All of the patients referred for EMR either had high grade intraepithelial neoplasia (HGIN) or early cancer in the biopsy specimen prior endoscopic treatment. Staging procedures before EMR comprised high resolution endoscopy (GIF Q 140, GIF Q 160, GIF H 180; Olympus Optical, Tokyo, Japan) with determination of the surface extension and macroscopic type due to the Paris classification.[12] The infiltration depth of the tumor was determined by endoscopic ultrasound (EUS), usually with a radial 7.5/12 MHz scanner (GIF UM 30, GF UE 160; Olympus Optical; Tokyo, Japan). Only patients with a lesion confined to the mucosal layer were treated in curative intention by EMR. In case of suspicion of submucosal infiltration resection was performed for staging purposes only. Patients with early cancer underwent a CT scan of the chest as well as abdominal ultrasound. Patients with evidence of lymph node metastasis were excluded.

EMR was performed using the cap technique described in detail by Inoue.[13] In this technique the lesion is marked, infiltrated with dye-diluted saline solution, and sucked in a transparent cap fixed onto the distal end of a regular endoscope. Resection is completed by closing a pre-looped snare lying in the distal rim of the cap and applying current. Resection is continued until the lesion is completely removed. Each specimen was removed and stretched onto cork and fixated in formalin, 4% for histopathological analysis. In order to assess the lateral resection margin tissue pieces collected by EMR were rearranged before fixation. Patients were followed with HRE and biopsies after 6 weeks, 3, 6, 9, and 12 months during the first year. In case of piecemeal resection complete resection had to be confirmed by two negative follow-up endoscopies with biopsy sampling. If endoscopy and/or biopsies showed evidence of residual tumor EMR was continued.

Indication for surgery included histopathological proof of submucosal infiltration and/or an incomplete resection at the basal or lateral resection margin (R1). Furthermore, surgery was indicated in case of residual or metachronous carcinoma according to biopsy results during follow-up endoscopies especially those not amenable for further endoscopic treatment due to stricture formation.

Surgical Treatment

After a standardized preoperative diagnostic work up all patients underwent a transthoracic en-bloc esophagectomy and reconstruction with a gastric tube and high intrathoracic esophagogastrostomy. In 15 of 16 patients this surgical resection was performed as a two-stage procedure with initial laparoscopic gastric mobilization followed by transthoracic resection and reconstruction.[14] Due to a previous laparoscopic fundoplication, one patient (patient no. 4) underwent a one-stage esophagectomy and reconstruction.[15] Irrespective of the surgical procedure, all patients had a two-field lymphadenectomy of the abdominal and the mediastinal compartment. The abdominal part included a partial lymphadenectomy of compartment I and II (lymph node group 1, 2, 3, 7, 8, and 9) which was performed as en-bloc resection and kept attached to the lesser curvature.

Mediastinal lymphadenectomy was performed as an extended resection including the lymph nodes of the right and left recurrent nerves in the upper mediastinum. The lymph nodes were dissected from the specimen in the operating theater to allow a precise assignment to the single lymph node groups. Abdominal lymph nodes were classified according to the Japanese Gastric Cancer Association.[16] Mediastinal lymph nodes were grouped according to the anatomical relation to the tracheal bifurcation.[17]

Post-EMR and postsurgery specimen were not evaluated by the same histopathologist. However, the vast majority of specimen were analyzed by a specialized and experienced GI pathologist.

The local Institutional Review Board (IRB) approved this retrospective study and indicated that individual consent could be waived because individual patients were not identified.

Results

Patient's Characteristics and Technical Data of EMR

Thirteen patients were diagnosed to have an adenocarcinoma (AC) and three patients had a squamous cell carcinoma (SCC). In nine of the 13 patients the AC was associated with a long segment Barrett esophagus, whereas four patients had a short Barrett esophagus. Three patients with a long segment Barrett esophagus (patient no. 5, 9, and 16) had a multifocal AC localized in the middle and distal esophagus. In these three patients, only the locally more advanced tumor was included for further analyses (Table 1). Except for one patient (patient no. 11) all diagnosed carcinomas were 2 cm in size or smaller. Ten of 14 tumors were located in the distal or middle esophagus. Two patients with SCC had the primary lesion in the upper esophagus (Table 1).

Nine patients had one EMR, seven patients (patient no. 3, 4, 5, 6, 14, 15, and 16) had at least two EMR sessions before they were referred for surgical therapy. Except for one patient (patient no. 7), EMR was performed as piecemeal technique with a median of five pieces per patient (range, 1–8).

Indication for Surgery

In 11 patients, indication for esophagectomy was infiltration of the submucosal layer, in many cases combined with an incomplete EMR at the lateral or basal resection margin. Three patients were referred to surgery because of an esophageal stenosis after EMR combined with residual carcinoma in follow-up biopsies (patient no. 3, 4, and 9). One patient, no. 6, had an incomplete EMR with HGIN at the lateral margin of the resected mucosa. In patient, no. 11,

Table 1 Histopathological and clinical data of 16 patients treated for early esophageal carcinoma

No	Age	Histology	Localization/ size	EMR[a]	EMR pathology	EMR R status	IFS	Surgical pathology	Postop. course
1	65	SCC	Proximal, 1 cm	4	pT1sm-x G2 L0 V0	Rx	1, 2	pT1sm1 pN1 (6/36)	Normal
2	49	AC long Barrett	Distal, 2 cm	1(4)	pT1sm-x G1 L0 V0	R1 basal	1, 2	pT0 pN0 (0/29)	Normal
3	64	AC long Barrett	Distal, 1 cm	2(7)	pT1m2 G1 L0 V0	R0	3	pT1m1 pN0 (0/25)	Severe
4	76	AC long Barrett	Distal, 2 cm	2(12)	pT1 G2 L0 V0	Rx	3	pT1m3 pN0 (0/26)	Normal
5	79	AC long Barrett	Multifocal, middle/distal	2(13)	pT1sm3 G4 L0 V0	R1 basal	1, 2	pT1m3 pN0 (0/44)	Prolonged
6	56	SCC	Middle, 2 cm	2(5)	pT1m2 G1 L0 V0	R1 lateral (HGIN)	2	pT0 pN0 (0/25)	Normal
7	71	AC short	Distal, 2 cm	1	pT1sm-x	R1 lateral	1, 2	pT3 pN0 (0/31)	Normal
8	52	AC short Barrett	Distal, 1 cm	1(2)	pT1sm1 G2 L0 V0	Rx	1, 2	pT0 pN0 (0/20)	Normal
9	58	AC long Barrett	Multifocal, middle/distal	1(4)	pTx	Rx	3	pT1m2 pN0 (0/28)	Prolonged
10	66	AC long Barrett	Middle	1(4)	pT1sm1 G2 L0 V0	R2	1, 2	pT2 pN1 (4/35)	Normal
11	60	SCC	Proximal, 3 cm	1(2)	pT1m1 (HIN)	R0	2	pT0 pN0 (0/25)	Fatal
12	67	AC short Barrett	Distal, 2 cm	8	pT1sm-x G3 L0 V0	R1 basal/lateral	1, 2	pT1sm2 pN0 (0/24)	Normal
13	45	AC short Barrett	Distal 1.5 cm	1(2)	pTsm3 G1 L0 V0	R1 lateral	1, 2	pT0 pN0 (0/30)	Normal
14	65	AC long Barrett	Distal, 2 cm	2(9)	pT1sm1 G2 L1 V0	R1 lateral	1, 2	pT0 pN0 (0/43)	Normal
15	49	AC long Barrett	Distal, 2 cm	2(7)	pT1sm1 G2 L0 V0	R1 basal	1, 2	pT1m3 pN0 (0/29)	Normal
16	67	AC long Barrett	Multifocal, distal	3(6)	pT1sm3 G2 L0	R1 lateral/basal	1	pT3 pN1 (7/33)	Normal

IFS Indication for Surgery: (1) infiltration of the submucosa, (2) infiltration of the lateral and/or basal resection margin (R1), (3) residual carcinoma in follow-up biopsies not amenable for further EMR due to stricture formation

AC adenocarcinoma, *SCC* squamous cell carcinoma, *EMR* endoscopic mucosal resection, *m* mucosa, *sm* submucosa

[a] Number of EMR sessions (total number of particles)

EMR showed HGIN in squamous epithelium. Because of the lateral widespread extension and a nonlifting sign, EMR was not continued. The average time interval between the last EMR and esophagectomy was 3.1 months (range, 1–9 months).

Results of Histopathological Work-up

The work-up of the surgical specimen showed the following pT results (Table 1): in six patients (38%) no residual tumor could be detected (pT0). In another seven patients, the primary tumor was classified as pT1 (1× m1, 1× m2, 3× m3, 1× sm1, and 1× sm2). Three patients had more advanced tumor stages, one patient with a pT2 (patient no. 10) and two patients with a pT3 tumor (patient no. 7 and 16). Patient no. 16 with a multifocal neoplasia initially showed mucosal neoplasia at one site but further resection revealed submucosal infiltration at another site thus resulting in a delay of correct staging and subsequent surgical therapy. In patient no. 10 a nonlifting sign indicated a more advanced tumor staging. Patient no. 7 was simply misdiagnosed prior and during EMR. In all 16 patients a complete surgical resection of the primary tumor could be achieved (R0 resection).

As a result of a two-field lymphadenectomy, the mean number of resected lymph nodes (LN) was 29.7 (range, 20–44). Three of 16 patients (18.8%) were classified as pN1. Patient no. 1 had six metastatic lymph nodes all of them located in the upper mediastinum close to a secondary SCC. Patient no. 10 with a pT2 adenocarcinoma at the level of the tracheal bifurcation had two metastatic LN at the left main bronchus, one in the lower mediastinum as well as one at the lesser curvature of the stomach (LN group No. 1). The third pN1 patient (no. 16) had seven nodal metastases which were located in the abdominal and mediastinal compartment.

Two patients had secondary carcinomas which were not detected endoscopically but during the work-up of the surgical specimen. Patient no. 1 had a second pT1sm SCC located in the upper esophagus at the level of the thoracic inlet. Patient no. 6 with an SCC in the middle esophagus was found to have an additional small AC in the cardia classified as pT1sm.

Postoperative Surgical Course

Table 1 summarizes the data which were obtained from each patient in this observational study. As described elsewhere the postoperative course was classified according to the duration of mechanical ventilation, the number of days stayed on the intensive care unit, readmission to ICU, and reoperations ('normal', 'prolonged', 'severe', 'lethal').[18] Twelve of 16 patients (75.0%) had an uncomplicated postoperative course classified as 'normal'. The mean hospital stay of these patients was 17 days (range, 10–27). Two patients (no. 5 and 9) had a 'prolonged' and one patient (no. 3) a 'severe' postoperative course. In one patient (no. 11) a gastric volvulus was diagnosed on the first postoperative day after laparoscopic gastrolysis which required relaparotomy with repositioning of the mobilized stomach. After transthoracic esophagectomy 4 days later the patient developed an anastomotic leakage due to a partial necrosis of the gastric tube and underwent rethoracotomy with resection of the gastric conduit. After complete recovery from a septic course the patient developed an acute myocardial infarction and died 26 days after esophagectomy.

Discussion

To our knowledge this is the first published series analyzing the clinical and histopathological data of patients who had EMR and subsequent subtotal esophagectomy for treatment of early esophageal carcinoma. Approximately 10% of the whole study population of patients with esophageal cancer underwent this combined treatment indicating an increasing frequency due to improved endoscopic techniques.

As known from many other studies EMR proved to be a feasible technique for local resection of early esophageal carcinoma which is associated with very little complications and therefore high patient's safety and comfort.[1,2] It is currently accepted as definitive treatment in case of a neoplasia limited to the mucosal layer since the risk of lymph node metastasis is low. So far, the calculated 5-year survival rate of patients with HGIN or adenocarcinoma confined to the mucosal layer treated by EMR has shown no differences between patients successfully treated by EMR and a matched normal population.[2] Furthermore, EMR is implemented in the diagnostic algorithm for patients with early neoplasia because staging procedures (EUS, CT-scan) do not offer an absolute accuracy.[19,20] The pretherapeutic differentiation between mucosal and submucosal tumors is crucial in the treatment of early esophageal carcinoma since these T categories are associated with two completely different treatment strategies. In general, indications for surgery after EMR can be divided into two groups: oncological reasons and technical reasons. Oncological reasons are submucosal infiltration and incomplete basal and/or lateral resection. Technical reasons comprise failure of EMR due to strictures or the risk of stricturing in case of widespread neoplasia.

Oncological Indication for Surgical Resection

The most common indication for referring patients to the surgeon is histopathological evidence of submucosal

infiltration associated with an incomplete basal resection. This was seen in almost 70% of the study population. Out of these patients, the majority demonstrated residual tumor and a smaller percentage lymph node metastases during histopathological work-up of the surgical specimen, confirming the need for surgical intervention and adequate lymphadenectomy.

However, almost 40% of the patients had no residual tumor in the resected specimen whereas 25% had locally advanced tumors (pT2–3) not suitable for EMR. This relevant percentage of 'over- and undertreatment' clearly demonstrates the main problem in the present treatment of early esophageal carcinoma, namely the lack of adequate methods to correctly stage the T and also N category prior to EMR.

This is particularly true for patients with deep submucosal infiltration pTsm2–3 and locally advanced tumors (pT2–3). The high frequency of this histopathological diagnosis in the surgical specimen should be a reminder to avoid repeated EMR in case of incomplete resection with delay of surgery. However, the most adequate staging information with regard to infiltration depth of early cancers, grade of differentiation, and local lymphatic- or vascular infiltration is provided by the EMR specimen therefore called diagnostic EMR.[21] This diagnostic EMR can help to determine the appropriate treatment of early neoplasia.

With respect to the N status, "over- and undertreatment" seems to be unavoidable because there are no diagnostic preoperative tools to safely rule out lymph node metastasis. With infiltration of the superficial submucosal layer lymph node metastases can be detected in patients with AC and SCC.[4,22] The frequency of metastatic nodes clearly correlates with the depth of submucosal infiltration ranging from 21% for the sm1 level up to 60% for the sm3 level.[4] In previous studies it could be demonstrated that for esophageal and also gastric cancer the majority of resected lymph nodes including the metastatic ones are smaller than 5 mm in diameter and therefore difficult to detect prior to EMR or surgical resection.[23,24] Therefore, at present no diagnostic tools including EUS in combination with histopathologic features of the biopsies are capable to safely predict the presence of metastatic lymph nodes. However, in patients with superficial submucosal infiltration the risk of metastasis must be balanced against the risk of surgery.

As expected in this patient series, the frequency of nodal metastasis was low but as demonstrated in previous studies nodal metastasis could be found in the mediastinal and abdominal compartment justifying the standard two-field lymphadenectomy.[25]

Comparing EMR and surgical pathology, it has to be taken into consideration that the work-up of the specimen was not done by the same histopathologists. To a certain degree this fact might explain the different tumor stages observed. However, a complete sectioning of the surgical specimen as done in this study reveals is technically easier and reveals an accurate tumor stage. Therefore, histopathology of the surgical specimen can be considered as gold standard.

Technical Indication

One of the most important disadvantage of EMR especially with regard to multifocal neoplastic lesions requiring multiple or widespread resections is the risk of stricture formation. Nineteen percent of patients in this series with mucosal adenocarcinoma underwent surgical resection due to stricture formation in combination with residual carcinoma. These results indicate that the EMR technique has to be improved or combined with adjunctive endoscopic modalities like additional ablative techniques to avoid technical failures with subsequent need for surgery.

Surgical Resection

In case of early esophageal carcinoma, a standardized esophagectomy with adequate lymphadenectomy fulfils all requirements of an adequate oncological procedure and offers long-term survival for patients with a potentially curable carcinoma. In contrast to EMR, a complete resection of early esophageal neoplasms is achieved in almost all patients undergoing subtotal esophagectomy.[26,27] Only patients with multifocal lesions or submucosal lymphangio invasion (L1) are at risk for a histopathologically incomplete (R1)-resection predominantly seen at the proximal resection margin. As in this series, for the majority of patients early adenocarcinoma is associated with a long segment Barrett esophagus and it is still a matter of discussion whether in these patients the remaining Barrett's mucosa as precancerous condition should be ablated. In favor of a complete ablation is the relatively high frequency of multifocal carcinoma in Barrett's mucosa detected during follow-up endoscopies or histopathological examination of the esophagectomy specimen.[28] The risk of subsequent HGIN or even invasive carcinoma is also resolved with an adequate surgical resection since the entire Barrett's segment with intestinal metaplasia is completely removed. Therefore, subtotal esophagectomy is the method of choice to significantly reduce the risk of subsequent malignant degeneration. It is also important to know that repeated EMR procedures do not increase the technical difficulty to resect the tubular esophagus.

One of the major advantages of EMR is its low complication rate contributing to the patient's safety.[1] Subtotal esophagectomy with an adequate lymphadenectomy is still associated with a considerable morbidity and even mortality. Though the mortality rate has constantly declined over the past decade even high volume centers

report a mortality rate of approximately 3% to 5%.[10,11,14,29] This reduction is mainly due to a strict selection of patients and an improved perioperative management.[18] However, the low overall mortality rate does not correlate with tumor stage so that even patients with mucosal or submucosal carcinomas can decease postoperatively from general or surgical complications. In this series, one patient with a complicated postoperative course due to a poorly vascularized gastric interposition finally died after a myocardial infarction resulting in a mortality rate of 6%. Unfortunately, this patient had no residual tumor in the esophagectomy specimen so that the indication for surgery is retrospectively debatable. On the other hand, even patients with a high preoperative risk in whom surgery was the only oncological option after failure of EMRs were safely managed.

Conclusion

These retrospective data do not allow determining the efficacy and safety of either EMR or esophageal surgery in general. This is a report on a highly selected group of patients who were referred to surgery because EMR indicated no potential for curative treatment because of histopathologically confirmed submucosal infiltration or technical failures of complete resection.

However, the results of this patient series indicate that the boundary between treatment of mucosal and submucosal tumors is not as clear as proposed demonstrating a relevant percentage of potential 'over- and undertreatment'. This is mainly due to a lack of adequate diagnostic imaging and difficulties associated with multifocal lesions in long segment Barrett's esophagus. Therefore, the study confirms the clinical value of EMR as diagnostic tool suggesting a need for surgery in case of submucosal infiltration. From an oncological point of view, the standard surgical esophagectomy is superior compared to therapeutic EMR but is associated with a relevant postoperative morbidity and mortality. Therefore, in order to offer patients with early esophageal carcinoma the optimal treatment individual decision should be based on an interdisciplinary judgment of gastroenterologists and visceral surgeons in high volume centers.

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ORIGINAL ARTICLE

An Effective Duodenum Bulb Mobilization for Extracorporeal Billroth I Anastomosis of Laparoscopic Gastrectomy

Naoki Hiki · Testsu Fukunaga · Masanori Tokunaga · Shigekazu Ohyama · Kazuhiko Yamada · Akio Saiura · Toshiharu Yamaguchi

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Abstract
Background Data Extracorporeal circular-stapled Billroth I (B-I) anastomosis is difficult in patients with obesity, a large body shape, or small remnant stomach, as it requires the duodenal stump to be lifted outside of the wound. The aim of this study was to evaluate the feasibility of circular-stapled B-I reconstruction for laparoscopy-assisted distal gastrectomy (LADG) with effective duodenal mobilization.
Methods Between March 2005 and December 2007, 199 patients with early gastric cancer underwent LADG with B-I reconstruction in the Department of Gastrointestinal Surgery at the Cancer Institute. The greater omentum, comprised of four membrane layers, was completely dissected for effective duodenal bulb mobilization to allow easy performance of extracorporeal end-to-end gastroduodenostomy. Several clinicopathophysiological features relating to anastomosis complications, including anastomotic leakage, stenosis, bleeding, and ulcers, were evaluated.
Results The success rate of extracorporeal circular-stapled B-I anastomosis was 100% for the 199 patients, 24% of whom had a body mass index greater than 25. The rate of anastomosis-related postoperative complications was 2%. Anastomotic leakage was not observed in this study. Anastomotic stenosis was observed in 2 (1%) patients, anastomotic bleeding was observed in 1 (0.5%) patient, and anastomotic ulcer was diagnosed in 1 (0.5%) patient. All these complications were managed conservatively. There was no postoperative mortality.
Conclusions Feasible duodenal bulb mobilization by complete dissection of the greater omentum allows easy performance of extracorporeal B-I anastomosis and minimizes complications related to anastomosis in LADG.

Keywords Double-stapling anastomosis · Laparoscopy-assisted distal gastrectomy · Gastric cancer · Billroth I anastomosis

Introduction

Since Theodor Billroth first performed a gastroduodenostomy after distal gastrectomy in 1881, several techniques referred to as Billroth I (B-1) anastomosis have been developed using either a linear[1] or circular stapler.[2–5] B-I gastroduodenostomy using a hemidouble stapling technique was firstly reported by Oka et al.[2] This technique was shown to be simple and safe for the open gastric cancer surgical procedure of distal subtotal gastrectomy.[4]

By comparison, the application of B-I anastomosis for laparoscopy-assisted distal gastrectomy (LADG) is a difficult procedure in patients with obesity, a large body shape, or small remnant stomach. This is because extracorporeal B-I anastomosis for LADG requires the duodenum stump to be lifted outside of the small laparotomy wound. The Kocher maneuver is used for mobilization of the second part of the duodenum for LADG,[2,3] but is not effective for mobilization of the duodenum bulb in the ventral direction. A further disadvantage of the

N. Hiki (✉) · T. Fukunaga · M. Tokunaga · S. Ohyama · K. Yamada · A. Saiura · T. Yamaguchi
Gastroenterological Center,
Department of Gastroenterological Surgery,
Cancer Institute Hospital, Japanese Foundation for Cancer Research,
3-10-6 Ariake, Koto-ku,
Tokyo 135-8550, Japan
e-mail: naoki.hiki@jfcr.or.jp

Kocher maneuver is the possible increase in duodenal juice reflux due to mobilization of the second part of the duodenum that may aggravate gastroesophageal reflux symptoms.

After complete dissection of the anterior and posterior lobes of the greater omentum, the membranes of which fuse with the pancreatic head, the duodenal bulb can be effectively mobilized in the ventral direction. Extracorporeal B-I gastroduodenostomy using the hemidouble stapling technique is easily and safely performed after duodenal bulb mobilization. In the present study, the feasibility of the extracorporeal hemidouble stapling technique for B-I gastroduodenostomy in LADG with effective duodenal bulb mobilization is evaluated in 199 cases of LADG.

Patients and Methods

Patient Characteristics

Between March 2005 and December 2007, 199 patients with early gastric cancer underwent LADG with B-I reconstruction in the Department of Gastrointestinal Surgery at the Cancer Institute, Tokyo, Japan. Histologically, all of the tumors were classified as adenocarcinomas that had invaded only the mucosa, submucosa, or muscle layer of the stomach without lymph node metastasis (cT1, cN0 or cT2, cN0). Clinical classification of tumor depth (cT) and nodal involvement (cN) was determined by preoperative and intraoperative evaluations, including barium radiography, upper gastrointestinal tract endoscopy, abdominal ultrasonography, computed tomography (CT), and endoscopic ultrasonography. Intramucosal, submucosal, or muscle layer invasive carcinoma without lymph node metastasis (cT1, cN0 or cT2, cN0) was the indication for these operative procedures. Gender, age, body mass index (BMI), comorbidities, and clinical staging were documented for all patients.

Exclusion Criteria

Patients were excluded if they had cardiac (greater than New York Heart Association II), pulmonary (greater than Hugh–Jones II), hepatic (Child classes B and C), or renal insufficiency.

Lymphadenectomy for Gastric Cancer

The scope of the lymph node dissection was as described previously.[6] Lymphadenectomy of the modified D2 dissection (D1+alpha or D1+beta) or D2 dissection was performed for all gastric cancers.

Indication of Billroth I Anastomosis

B-I anastomosis was indicated if cancer located in the distal stomach was less than 5 cm proximal to the pyloric ring. When this distance was greater than 5 cm, the pylorus-preserving gastrectomy (PPG) method of anastomosis was indicated.[7,8]

Ports Settings

The pneumoperitoneum was created by injection of carbon dioxide (10–12 mmHg) and the laparoscope was inserted through the umbilical port. While viewing the laparoscopic image, a total of four ports (each 5–12 mm) were inserted into the left upper, left lower, right upper and right lower quadrants.

Duodenal Bulb Mobilization in the Ventral Direction

The assistant stood at the right side of the patient and lifted the epiploic arcade using dual-grasper forceps. The anterior sheet of the omentum (gastrocolic ligament) was divided using AutoSonix™ ULTRA SHEARS™ (Tyco Healthcare, Tokyo, Japan) to allow access to the lesser peritoneal cavity. The greater omentum is comprised of four sheets, two anterior and two posterior (Fig. 1a). The anterior sheet of the greater omentum was dissected from the transverse colon and the anterior sheet of the transverse mesocolon (Fig. 1b). In this procedure, the end point of dissection was at the lower edge of the second part of the duodenum. The two posterior sheets of the greater omentum were dissected to expose the pancreatic head and the origin of the right gastroepiploic vein and the anterior superior pancreatic duodenal vein. At this stage of the procedure, the end point of the dissection was similar to that of the anterior sheet dissection (Fig. 1c). Completion of this procedure allowed full mobilization of the duodenum bulb in the ventral direction.

Lymph node dissection of station 6 commenced after division of the origin of the right gastroepiploic vein, continued in the upper direction, and carefully exposed the surface of the pancreatic head. The right epiploic artery was divided using a clip (Lapro-Clip™ [single absorbable ligating clip cartridge], Tyco Healthcare, Tokyo, Japan) and Ligasure (Tyco Healthcare) at station 6.

Procedure for B-I Anastomosis

A 4- to 5-cm midline incision was made and the hemidouble stapling technique using circular stapler was performed for the B-I anastomosis. A purse-string suture was placed at the transaction line of the duodenum, just distal to the pylorus, using purse-string forceps and a 2-0

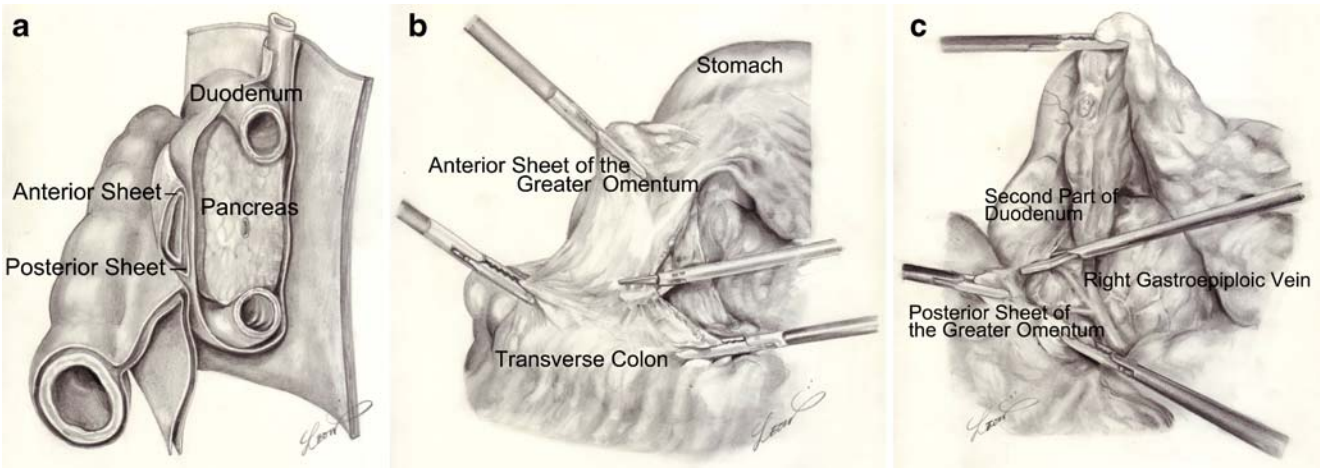

Figure 1 Duodenal bulb mobilization in the ventral direction. **a** The greater omentum is comprised of four sheets, two anterior and two posterior. **b** The anterior sheet of the greater omentum was dissected from the transverse colon and the anterior sheet of the transverse mesocolon. **c** In this procedure, the end point of dissection was at the lower edge of the second part of the duodenum. The two posterior sheets of the greater omentum were dissected to expose the pancreatic head and the origin of the right gastroepiploic vein and the anterior superior pancreatic duodenal vein. At this stage of the procedure, the end point of the dissection was similar to that of the anterior sheet dissection. Completion of this procedure allowed full mobilization of the duodenum bulb in the ventral direction.

polypylene (Prolene; Ethicon, Inc Japan) suture. After transecting the duodenum, 25 or 28 mm of the detachable anvil head of the circular stapler was inserted into the duodenal stump. The purse-string suture was tied over the anvil shaft. These procedures were performed in an extracorporeal manner as the duodenum was fully mobilized.

The proximal stomach was transected at the appropriate line (1–2 cm proximal to the bifurcation of the gastro-epiploic trunk) using a linear stapler (80 mm) from the greater curvature halfway (5 cm) to the lesser curvature. The anterior gastric wall of the remnant stomach was opened partially and the circular stapler was inserted into the stomach. The trocar was extended to penetrate the corner of the staple line at the greater curvature and then connected to the detachable anvil shaft placed in the duodenum (Fig. 2a). The instrument was gently closed so that the anastomotic line appeared on the ventral surface beyond the midline incision (Fig. 2b). After confirmation of the continuity of the anastomotic line, the circular stapler was fired to complete the end-to-end gastroduodenostomy.

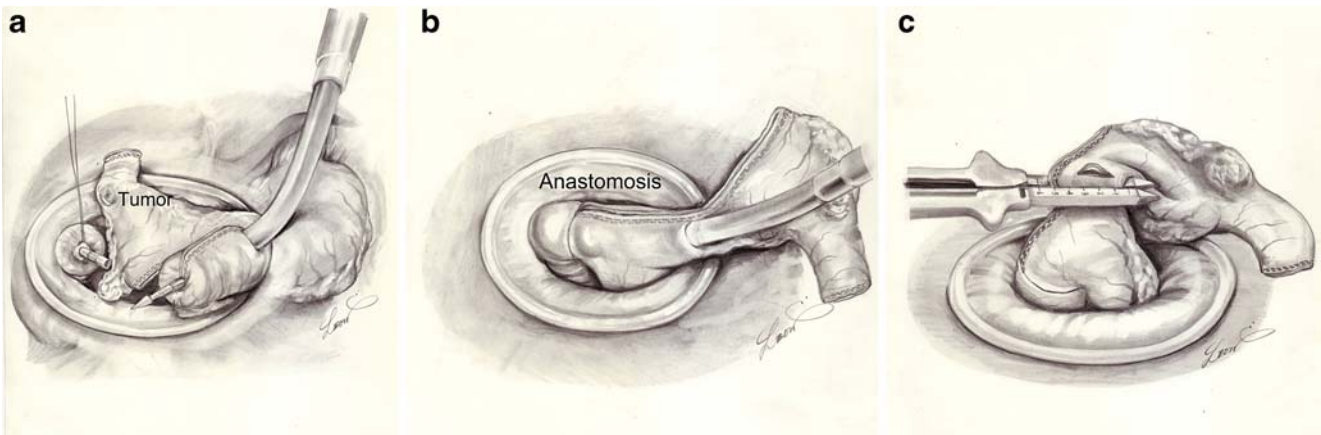

Figure 2 Procedure for B-I anastomosis. **a** A 4- to 5-cm midline incision was made and the hemidouble stapling technique using circular stapler was performed for the B-I anastomosis. After transecting the duodenum, 25 or 28 mm of the detachable anvil head of the circular stapler was inserted into the duodenal stump. The proximal stomach was transected using a linear stapler (80 mm) from the greater curvature halfway (5 cm) to the lesser curvature. The anterior gastric wall of the remnant stomach was opened partially and the circular stapler was inserted into the stomach. The trocar was extended to penetrate the corner of the staple line at the greater curvature and then connected to the detachable anvil shaft placed in the duodenum. **b** The instrument was gently closed so that the anastomotic line appeared on the ventral surface beyond the midline incision. **c** The remaining upper gastric segment was divided using an 80-mm linear stapler to complete the distal gastrectomy.

The instrument was opened, disengaged from the anastomosis, and gently withdrawn. The anastomosis was examined using direct vision through the opening in the anterior wall of the stomach and homeostasis was made by direct suture of the stapler line. The remaining upper gastric segment was divided using an 80-mm linear stapler to complete the distal gastrectomy (Fig. 2c). The entry hole of the circular stapler was included in the resection specimen.

Clinical Data

The following parameters were recorded: operation time, intraoperative estimated blood loss, and success rate of the anastomosis. All resected stomachs were opened immediately after the operation and tumor size, tumor location, the proximal resection margin, and the distal resection margin were recorded. The depth of wall invasion was determined histologically from hematoxylin–eosin-stained sections of formalin-fixed specimens.

Postoperative data was recorded for the overall complication rate, anastomosis-related complications (anastomotic leakage, stenosis, bleeding, and ulcer), ileus, early dumping syndrome, the presence of an intraabdominal abscess of unknown origin, pancreatitis and pancreatic juice leakage, the presence of a subcutaneous abscess, and intraoperative enteric injury. The time until the start of oral intake, the length of the postoperative hospital stay, the postoperative reexploration rate, and the rate of mortality were recorded.

Table 1 Characteristics of Patients Undergoing LADG with B-I Anastomosis

Characteristics of the patients	
Number of cases	199
Sex	
Male/female	114/85
Age	
Average (years)	64±1
Range (years)	34–80
BMI (kg/m^2)	22.8±0.2
25 kg/m^2<BMI (%)	24
BMI<25 kg/m^2 (%)	76
Comorbidities, *n* (%)	
Diabetes	12 (6)
Ischemic heart disease	5 (3)
Asthma	9 (5)
Hypertension	62 (31)
Clinical staging, *n* (%)	
IA	183 (92)
IB	15 (8)
II	1 (0.5)

Data are presented as the means±SE. Body mass index=body weight/height^2 (kg/m^2)

Table 2 Operative Data of Patients Undergoing LADG with B-I Anastomosis

Operative data of the patients	
Operation time (min)	229±4
Intraoperative blood loss (mL)	63±12
Number of retrieved lymph nodes	34±1
Success rate of anastomosis	199/199 (100%)
No. of cases with conversion to open surgery	2 (1%)
Conversion for further lymph node dissection	2 (1%)

Data are presented as the means±SE

Data Expression

All data are presented as the means±standard error (SE).

Results

The clinical characteristics and the operative data of patients who underwent LADG are summarized in Tables 1 and 2, respectively. The mean operation time for the LADG procedures was 229±4 min, and the estimated blood loss during LADG was 63±12 mL. The mean number of retrieved lymph nodes was 34±1. The success rate of the extracorporeal B-I anastomosis was 100%. The ratio of conversion to open surgery was 1%, and the reason for the conversion of these two cases was the necessity for further lymph node dissection (Table 2).

Tumor characteristics are summarized in Table 3. Tumor location was equally distributed in the middle (45%) or lower third (55%) of the stomach. The tumor size was 36.2±1.5 mm and a sufficient resection margin (proximal, 59.4±2.3 mm; distal, 52.7±2.0 mm) was maintained for the distal gastrectomy. Further histological analysis of the depth of cancer invasion revealed that 27%, 66%, and 7% of patients had mucosal, submucosal, and muscle invasion of tumors, respectively.

Table 3 Tumor Characteristic

Characteristics of the tumor	
Tumor location, *n* (%)	
Middle	90 (45)
Lower third	109 (55)
Size (mm)	36.2±1.5
Proximal resection margin (mm)	59.4±2.3
Distal resection margin (mm)	52.7±2.0
Depth of cancer invasion, *n* (%)	
Mucosa	54 (27)
Submucosa	132 (66)
Muscle	13 (7)

Data are presented as the means±SE

The overall incidence of postoperative complications was 7% after LADG (Table 4). The rate of postoperative complications involving anastomosis was 2%. Anastomotic leakage was not observed during this study. Anastomotic stenosis was observed in 2 (1%) patients, and these cases were treated with endoscopic balloon dilation. Anastomotic bleeding was observed in 1 (0.5%) patient, and homeostasis was easily performed by endoscopic clipping of the bleeding points in the anastomotic staple line. One patient was diagnosed with an anastomotic ulcer and was cured by treatment with an antiacid drug (Proton Pomp Inhibitor). Postoperative ileus and early dumping syndrome were not observed in any of the patients. Intraabdominal abscess formation was observed in 2% of patients but the site of the abscess was distant to the anastomosis. Pancreatic juice leakage was observed in 2% of patients and subcutaneous abscess formation was observed in 1% of patients. Postoperative enteric injury observed in one case resulted in reexploration on postoperative day 1. There was no mortality in this study. The time to the start of oral intake was 2.3±0.1 days, and the mean postoperative hospital stay was 11.4±0.7 days.

Discussion

The performance of B-I anastomosis after distal partial gastrectomy is simple and rapid and requires only a single anastomotic site. A further advantage of B-I anastomosis is the maintenance of physiological conditions as food can pass through the duodenal root. Disadvantages of B-I anastomosis include postoperative gastritis of the remnant stomach and gastroesophageal regurgitation due to duodenal juice. For this reason, we prefer to perform PPG or B-I anastomosis without the Kocher maneuver and use B-I anastomosis only for laparoscopic gastrectomy.

Table 4 Postoperative Outcomes

Outcomes of the patients	
Postoperative complications (overall), *n* (%)	13 (7)
Anastomosis-related complications, *n* (%)	4 (2)
Anastomotic leakage	0 (0)
Anastomotic stenosis	2 (1)
Anastomotic bleeding	1 (0.5)
Anastomotic ulcer	1 (0.5)
Ileus	0 (0)
Early dumping syndrome	0 (0)
Intraabdominal abscess unknown origin	2 (1)
Pancreatic juice leakage	3 (2)
Subcutaneous abscess	2 (1)
Enteric injury	1 (0.5)
Time until start of oral intake (days)	2.3±0.1
Postoperative hospital stay (days)	11.4±0.7
Reexploration, *n* (%)	1 (1)
Mortality, *n* (%)	0 (0)

Data are presented as the means±SE

The circular stapling technique has been used for B-I anastomosis and applied to LADG.[2–5] The performance of B-I anastomosis for LADG is problematic for patients with obesity and a large body shape as full retraction of the duodenal stump from the small laparoscopic wound is necessary for insertion of the anvil head into the duodenal cavity for further anastomosis. Although the Kocher maneuver is effective for mobilization of the second part of duodenum for LADG,[2,3] it is not always effective for lifting the duodenum bulb in the ventral direction. Instead of using the Kocher maneuver, we achieved effective mobilization of the duodenal bulb by complete dissection of the greater omentum of the anterior and posterior lobes. This procedure allows the duodenum to be easily drawn out beyond the midline of the wound and greatly increases the ease with which extracorporeal B-I gastroduodenostomy can be performed in patients with obesity and a large body shape. We demonstrated that our approach to mobilize the duodenum for B-I anastomosis achieved an equally successful outcome for all patients, including the 24% patients with a BMI greater than 25.

Duodenal mobilization has the advantage of reducing the traction force of anastomosis, a crucial factor for reducing postoperative anastomotic complications, such as anastomotic leakage. In the present study, there was no excessive tension postoperatively, despite the maintenance of an appropriate resection margin. Furthermore, among the 199 cases, anastomosis-related complications were only 2% and anastomotic leakage was not observed. It is possible that dissection of the posterior lobe of the greater omentum on the pancreatic head surface may lead to pancreatic injury; however, pancreatic juice leakage was observed in only 2% of cases and fluid correction was only observed around the celiac axis and thought to be related to lymph node dissection. There was no mortality in the present study and anastomosis-related reexploration was unnecessary. LADG with B-I anastomosis was performed with a success rate of 100% with 70 mL of estimated blood loss and without anastomotic procedures related to conversion to open surgery. Our results indicate that B-I anastomosis for LADG is safe and stable. This study included only patients with serosal-negative gastric cancer, therefore, we applied gastroduodenostomy for gastric cancer.

In summary, effective duodenal bulb mobilization by complete dissection of the greater omentum allowed extracorporeal B-I anastomosis to be easily performed and minimized anastomosis-related complications in LADG. All complications related to the anastomosis were managed conservatively. There was no postoperative mortality and

no reexploration related to the anastomosis. A further prospective study with a large sample size of patients is required to confirm and explore the findings of this study.

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ORIGINAL ARTICLE

Percutaneous Endoscopic Gastrostomy Tube Placement Is Safe in Patients Undergoing Corticosteroid Therapy

Nora Meenaghan · Kimberly Lumpkins · J. Scott Roth

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Abstract
Background Percutaneous endoscopic gastrostomy tube placement is performed commonly in patients unable to eat. Corticosteroids have been shown to increase the incidence of infections in patients undergoing surgical gastrostomy. The safety of percutaneous endoscopic gastrostomy in patients receiving corticosteroids has not been demonstrated.
Methods A retrospective review of 746 patients undergoing percutaneous endoscopic gastrostomy at a single institution between January 2002 and June 2007 was performed. Patients receiving corticosteroid therapy either acutely or chronically were identified. Charts were reviewed for demographic information, diagnoses, comorbidities, complications, and death.
Results Seven hundred forty-six patients underwent percutaneous endoscopic gastrostomy tube placement of which only 745 charts were complete and available for review. Ninety-four patients (12.6%) were receiving steroids at the time of the procedure. Fifty-nine patients (7.9%) received steroids for two or less weeks (acute), and 35 patients (4.5%) received steroids for more than 2 weeks (chronic). The overall incidence of complications was 98/745 (13.3%). No significant difference in post-procedural complications occurred in patients not receiving steroids 83/651 (12.7%) and steroid recipients 15/94 (16.0%). There was no difference in complications between the acute steroid group 10/59 (16.9%) and the chronic steroid group 5/35 (14.3%).
Conclusions Percutaneous endoscopic gastrostomy tube placement may be safely performed in patients receiving corticosteroids both acutely and chronically with complication rates comparable to those patients not receiving steroid medications.

Keywords Corticosteroids · Steroids · Percutaneous endoscopic gastrostomy · PEG

Introduction

Percutaneous endoscopic gastrostomy (PEG) tube placement is a commonly performed procedure to aid in the administration of enteral feeding in patients who are unable to eat. This has been established as a safe and effective technique.[1,2] Patients who require PEG for enteral nutrition often are being treated for multiple medical problems. A subset of these patients requires corticosteroids for comorbid conditions such as autoimmune disease, pulmonary disease, or post-transplant immunosuppression. As steroids are known to impair wound healing,[3,4] it may be speculated that patients taking steroids might be more prone to PEG site complications. The effect of steroid use in patients undergoing PEG has not been investigated in prior studies of PEG outcomes, thus little is known about the safety of PEG placement in patients who are receiving corticosteroid therapy. We hypothesize that PEG placement in patients on steroids therapy does not result in increased rates of complication. Data from PEG procedures performed at one institution were examined to determine if an association existed between steroid use and PEG complications.

N. Meenaghan · K. Lumpkins
University of Maryland Medical Center,
Baltimore, MD, USA

J. Scott Roth (✉)
Department of Surgery, University of Maryland School of Medicine,
22 South Greene Street,
Baltimore, MD 21201, USA
e-mail: sroth@smail.umaryland.edu

Table 1 Demographic Characteristics

	Steroid group, n=94 (%)	No steroid group, n=651 (%)
Diagnosis		
Neurologic	50 (53.2)	277 (42.5)
Head/neck cancer	15 (16.0)	187 (28.7)
Esophageal disease	4 (4.3)	36 (5.5)
Failure to thrive	2 (2.1)	1 (0.2)
Cardiac	7 (7.4)	67 (10.3)
ESRD/transplant	11 (11.7)	4 (0.6)
Pulmonary	3 (3.2)	23 (3.5)
Vascular	0 (–)	11 (1.7)
Gastrointestinal	1 (1.1)	27 (4.1)
Other	1 (1.1)	18 (2.8)
	p=0.00	
Gender		
Male	49 (52.1)	412 (63.3)
Female	45 (47.9)	239 (36.7)
	p=0.04	
Race/ethnicity		
White	51 (54.2)	379 (58.2)
Black	40 (42.6)	240 (36.9)
Asian	3 (3.2)	23 (3.5)
Hispanic	0 (–)	7 (1.1)
Other	0 (–)	1 (0.2)
	p=0.81	
Age		
Mean	61	62
Minimum	22	18
Maximum	92	97
	SD=0.04	

Methods

A retrospective review was performed of 746 patients who underwent a PEG procedure between January 2002 and June 2007 at a single institution. Medical records for each patient were examined. Demographic data were recorded along with primary diagnosis, indication for PEG, current and recent medications, recent lab values, history of prior abdominal surgery, endoscopic findings, and 30-day complications. In particular, steroid use was documented. Steroid use was defined as acute or chronic based on length of duration of treatment with chronic use defined as patients receiving steroids for greater than 2 weeks prior to PEG placement and acute steroid use as those who received steroids for two or less weeks. Complications were categorized as hemorrhage, infection, tube dislodgement, abdominal complaints, inability to tolerate gastric feeding, hypoxia, hypovolemia, and death. Complications were further characterized as minor or serious. Minor complications are defined as those requiring no treatment or intervention, a bedside procedure, or antibiotic administration alone. Serious complications required transfusion of blood or blood products, operative intervention, endoscopy, or resulted in patient death. Data were analyzed using chi-square analysis.

Table 2 Complications in Steroid and Non-steroid Groups

	Steroid group, n=94 (%)	No steroid group, n=651 (%)
Complications	15 (16.0)	83 (12.7)
Serious	8 (8.5)	35 (5.8)
Minor	7 (7.4)	47 (7.2)
	p=0.47	

Table 3 Complications in Acute and Chronic Steroid Groups

	Acute steroid group, n=59 (%)	Chronic steroid group, n=35 (%)
Complications	10 (16.9)	5 (14.3)
Serious	6 (10.2)	2 (5.7)
Minor	4 (6.8)	3 (8.6)
	p=0.67	

Results

Seven hundred forty-six patients underwent successful PEG placement between January 2002 and June 2007. One patient's medical record was incomplete and information about steroid use was not obtained; the patient's data were omitted from further analysis. Ninety-four of 745 patients (12.6%) were receiving steroids at the time of their PEG procedure. Thirty-five of 745 (4.7%) had been on chronic steroids. Fifty-nine of 745 (7.9%) had received steroids acutely.

Characteristics of patients in the steroid and no steroid groups are shown in Table 1. The overall number of complications in patients undergoing PEG was 98 of 745 (13.3%). There was no significant difference in complication rates of patients who were treated with steroids (15/94, 16.0%) and those who were not (83/651, 12.7%; Table 2). Additionally, no difference in complication rates is noted between acute and chronic steroid users (Table 3).

Rates of infectious complications are noted in Table 4. Overall, the rate of infectious complications was 2.7%.

Table 4 Infectious Complications

No steroids	19/651 (2.9%)
Steroids	1/94 (1.1%)
	p=0.30
Acute steroid use	1/59 (1.7%)
Chronic steroid use	0/35 (–)
	p=0.52

There were no significant differences in the rates of infectious complications between patients taking and not taking steroids, or between acute and chronic steroid users.

Discussion

Steroid use is generally not considered to be a contraindication to PEG placement. However, the potential for impaired healing and increased infection rates are a concern whenever a patient is taking corticosteroids. It is well known that steroids inhibit healing of epidermal wounds and there is equivocal evidence as to whether they also impair gastrointestinal tract healing.[5] Although PEG placement involves both of these systems, our investigation suggests that the use of steroids does not impair healing of the gastrostomy tract to an extent which increases the rates of complication in these patients.

Previous studies have demonstrated fewer complications in patients undergoing PEG than surgical gastrostomy.[2,6] In one study of open surgical gastrostomy tube placement, the rate of infection in patients receiving steroids was considerably higher than those not receiving steroids (17% vs. 0.9%).[7] Taken together, this suggests that PEG is the best choice for patients who require both steroid therapy and gastrostomy.

Examination of our demographic data does show some differences between the two groups. The steroid group contained a larger number of transplant patients and patients with neurologic disorders. This likely is a result of the increased utilization of steroid medications in patients with these conditions. A separate analysis was performed which showed no statistical significance in complication rates between the steroid and no steroid groups within those populations. There also appears to be a larger proportion of men in the no steroid group. The reason for this is unclear but, again, no differences in complication rates are seen between genders.

Our study is limited by its retrospective nature and single source of data; however, it does show similar rates of complications in similar populations of patients as have been noted in other studies.[8–10] Additionally, a post hoc power analysis shows that our study is sufficiently powered to have detected small differences between complication rates in the steroid and no steroid groups. Although the study is limited by its retrospective nature, our findings may be reassuring to practitioners who perform PEGs in patients requiring steroids either acutely or chronically but otherwise have no contraindications to the procedure.

Conclusion

PEG is a known to be a safe and effective method of gaining enteral feeding access in patients unable to take adequate nutrition by mouth. Often these patients have chronic medical conditions, some requiring treatment with corticosteroids. The incidence of procedural complications following PEG is similar between those patients that are taking steroids and those that are not. This holds true for patients who have received acute and chronic steroid regimens. We conclude that PEG is a safe procedure in patients being treated with corticosteroids.

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ORIGINAL ARTICLE

Complications Requiring Reoperation after Gastrectomy for Gastric Cancer: 17 Years Experience in a Single Institute

Sung Jin Oh · Won Beom Choi · Jyewon Song · Woo Jin Hyung · Seung Ho Choi · Sung Hoon Noh · Yonsei Gastric Cancer Clinic

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Abstract
Introduction Morbidity and mortality rates following gastric cancer surgery are still high. The present study documented complications requiring reoperation after gastrectomy for gastric cancer and described surgical management for each complication.
Materials and Methods Between 1987 and 2004, 8,033 patients underwent gastrectomy at the Department of Surgery, College of Medicine, Yonsei University, and the records were reviewed.
Results and discussion The most frequent complication was intestinal obstruction (88 patients, 54.3%), followed by intraabdominal bleeding (15, 9.3%), wound dehiscence or evisceration (15, 9.3%), incisional hernia (15, 9.3%), anastomotic leakage (seven, 4.2%), acalculous cholecystitis (five, 3.1%), duodenal stump leakage (five, 3.1%), intraabdominal abscess without leakage (five, 3.1%), bowel perforation (five, 3.1%), bile peritonitis due to hepatic duct injury (one, 0.6%), and biliary stricture (one, 0.6%). There were ten cases of hospital mortality (6.2%) from intraabdominal bleeding (four patients), intestinal obstruction (four patients), and anastomotic leakage (two patients). The most common long-term complication requiring reoperation was intestinal obstruction (69, 75.8%) due to adhesive formation rather than technical failure, while short-term complications were surgery-related and associated with high hospital mortality (14.1%).
Conclusion Proper preoperative preparation and faultless surgical skills are required during initial surgery to reduce complications and the need for reoperation.

Keywords Gastric cancer · Complication · Reoperation · Mortality

This work was done through the Yonsei Gastric Cancer Clinic, Severance Hospital, College of Medicine, Yonsei University, Seoul, South Korea.

S. J. Oh · W. B. Choi · J. Song · W. J. Hyung · S. H. Choi · S. H. Noh (✉)
Department of Surgery, College of Medicine, Yonsei University,
134 Shinchon-dong Seodaemun-gu,
Seoul 120-752, South Korea
e-mail: sunghoonn@yuhs.ac

S. J. Oh · W. B. Choi · W. J. Hyung · S. H. Noh
Cancer Metastasis Research Center, College of Medicine,
Yonsei University,
Seoul 120-752, South Korea

S. H. Noh
Brain Korea 21 Project for Medical Science, College of Medicine,
Yonsei University,
Seoul 120-752, South Korea

Introduction

Gastric cancer is the second most common cause of cancer death worldwide, and surgical resection with lymphadenectomy is the only curative treatment.[1] Although surgical skills, anesthesiology, antibiotics, nutritional support, and radiological intervention have improved remarkably in recent years, significant morbidity and mortality still occur following gastric cancer surgery. Western countries have reported morbidity and mortality rates of 35–46% and 4–16%, respectively, after D2 lymph node dissection.[2–4] Major complications include anastomotic leakage, intraabdominal bleeding, intraabdominal abscess, intestinal obstruction, pancreatitis, and wound dehiscence. Indeed, the reoperation rate for these complications ranges from 2.8% to 10%.[4–6] However, a study of a large series of complications requiring reoperation has not been reported in the literature.

The present study reviewed our experience with patients who experienced complications requiring reoperation fol-

lowing gastrectomy for gastric cancer over a 17-year period. The study assessed the frequency of the major complications, surgical outcomes, and surgical management. Longer life expectancy and better quality of life are expected outcomes of optimal management of complications following gastric cancer surgery.

Materials and Methods

The records of 8,033 patients who had undergone gastrectomy for pathologically confirmed gastric adenocarcinoma from January 1987 to December 2004 at the Department of Surgery, College of Medicine, Yonsei University were reviewed retrospectively, and 162 patients with complications requiring reoperation were identified for this study. Patients who underwent reoperation due to recurrence or complications related to recurrence, positive resection margin, and patients with chronic (>1 month) gallbladder disease after gastrectomy were excluded because the focus of this study was on surgery-related complications requiring reoperation.

Complications were categorized as either short-term or long-term according to the time of reoperation, and then further subdivided into three groups: group A, within 1 week; group B, from 1 week to 1 month; and group C, after 1 month. Hospital mortality was defined as death within 30 days or during the same hospitalization. All patients in the study underwent the following standard operations: (1) total or distal subtotal gastrectomy, depending on the location and macroscopic appearance of the primary tumor, and (2) D2 or higher than D2 lymphadenectomy according to the rules of The Japanese Research Society for Gastric Cancer.[7] All statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 13.0 for Windows (SPSS, Chicago, IL, USA). The clinicopathological variables were analyzed using the chi-square test for discrete variables or the one-way analysis of variance for continuous variables. A P value of <0.05 was considered to indicate a significant difference.

Results

Of the 8,033 gastrectomy patients, 162 (2.0%) underwent reoperation because of postoperative complications. Of those, 129 (79.6%) were male and 33 (20.4%) were female, and the mean patient age was 57.7 years (range, 30–77 years). The clinicopathological characteristics are shown in Table 1. There were significant differences between the reoperation and nonreoperation groups in terms of age and gender.

Comparison of Incidence, Mortality, Time to Reoperation

The most frequent complication requiring reoperation after gastrectomy for gastric cancer was intestinal obstruction in 88 patients (54.3%), followed by intraabdominal bleeding in 15 patients (9.3%), incisional hernia in 15 (9.3%), and wound dehiscence or evisceration in 15 (9.3%). Other complications requiring reoperation were anastomotic leakage in seven (4.2%), acalculous cholecystitis in five (3.1%), duodenal stump leakage in five (3.1%), bowel perforation in five (3.1%), intraabdominal abscess without leakage in five (3.1%), bile peritonitis due to hepatic duct injury in one (0.6%), and biliary stricture in one (0.6%) (Table 2). The mean interval to reoperation for each complication is shown in Table 2. Hospital mortality occurred in ten of the 162 patients (6.2%), and these occurred in patients who underwent reoperation due to intraabdominal bleeding (four patients), intestinal obstruction (three patients), anastomotic leakage (two patients), and wound evisceration (one patient) (Table 3). The main cause of reoperation in the immediate short-term (group A) was intraabdominal bleeding (13 patients, 54.2%), while intestinal obstruction was the main reason for reoperation in the long-term (69 patients, 75.0%; group C, Table 4).

Treatment

Reoperative management according to each complication is summarized in Table 5. Of 88 patients with intestinal obstruction, 40 (45.5%) were treated for bandlysis, 31 (35.2%) with bowel strangulation were treated using segmental resection of small bowel, and 17 (19.3%) underwent bypass surgery.

Postoperative bleeding developed in 15 patients (9.3%). The most common bleeding site was branch of the splenic artery (six patients, 40%). The mean decrease in hemoglobin was 4.1 g/dL (from 12.9 to 8.8 g/dL) before reoperation. The mean blood loss in the abdominal cavity was 1,673 mL and the mean perioperative packed red blood cell transfusion volume was 8.3 U. The source of bleeding was identified at reoperation and a bleeder ligation was created, except for one patient with in whom the bleeding source had an unknown focus. Total gastrectomies with Roux-en-Y esophagojejunostomy were performed in two patients with bleeding at the gastrojejunostomy site after subtotal gastrectomy. One patient who was bleeding due to a spleen laceration was treated with a splenectomy.

Wound disruption occurred in 15 patients with a mean onset of 8 days (range, 4–12 days). Wound evisceration which protruded into the small bowel through the wound occurred in ten patients and was managed using primary closure of the wounds, while wound dehiscence (separation of the fascial layer) developed in five patients and was cured by secondary closure.

Table 1 Patient Characteristics

Variables	Reoperation group (n=162) (%)	Nonreoperation group (n=7,871) (%)	P value
Mean age (years)±SD	57.7±11.6	55.5±11.9	0.024
Gender			<0.001
Male	129 (79.6)	5,225 (66.4)	
Female	33 (20.4)	2,646 (33.6)	
Mean size (cm)±SD	4.3±2.8	4.5±3.0	0.589
Tumor location			0.346
Upper	23 (14.2)	1,195 (15.2)	
Middle	41 (25.3)	2,409 (30.6)	
Lower	94 (58.0)	4,146 (52.7)	
Diffuse	4 (2.5)	121 (1.5)	
Gross appearance			0.389
Borrmann type I	9 (5.6)	307 (3.9)	
II	24 (14.8)	1,293 (16.4)	
III	65 (40.1)	2,747 (34.9)	
IV	10 (6.2)	689 (8.8)	
EGC	54 (33.3)	2,835 (36.0)	
Histologic type			0.192
Differentiated	73 (45.1)	3,147 (40.0)	
Undifferentiated	89 (54.9)	4,724 (60.0)	
Depth of invasion			0.561
T1	54 (33.3)	2,835 (36.0)	
T2	32 (19.8)	1,320 (16.8)	
T3	68 (42.0)	3,182 (40.4)	
T4	8 (4.9)	534 (6.8)	
Lymph node metastasis			0.652
Negative	85 (52.5)	3,989 (50.7)	
Positive	77 (47.5)	3,882 (49.3)	
Combined resection			0.609
No	126 (77.8)	6,251 (79.4)	
Yes	36 (22.2)	1,620 (20.6)	
Type of operation			0.210
Total	38 (23.5)	2,197 (27.9)	
Subtotal	124 (76.5)	5,674 (72.1)	

Incisional hernias developed in 15 patients (9.3%) and were treated with hernioplasties. Two of those patients had incisional hernias with intestinal obstruction. One was treated with a hernioplasty plus segmental resection due to a strangulated bowel. The other was treated with a hernioplasty alone.

Of 80 patients with postoperative intraabdominal abscess (0.9%), 63 were treated using ultrasono-guided aspiration

Table 2 Incidence and Mean Interval to Reoperation After Gastrectomy

Causes	Number (n=162) (%)	Mean interval to reoperation, range (days)	Mortality (n=10)
Intestinal obstruction	88 (54.3)	592 (4–3,957)	3
Intraabdominal bleeding	15 (9.3)	4 (0–17)	4
Wound dehiscence or evisceration	15 (9.3)	9 (4–17)	1
Incisional hernia	15 (9.3)	457 (57–1,267)	0
Anastomotic leakage	7 (4.2)	12 (1–27)	2
Duodenal stump leakage	5 (3.1)	18 (10–28)	0
Acalculous cholecystitis	5 (3.1)	14 (2–31)	0
Intraabdominal abscess without leakage	5 (3.1)	46 (10–77)	0
Bowel perforation	5 (3.1)	213 (10–460)	0
Bile peritonitis due to hepatic duct injury	1 (0.6)	2	0
Biliary stricture	1 (0.6)	534	0

Table 3 Details of the Ten Patients Who Died within 30 Days of Reoperation

Procedure	Age (years)/sex	Stage	Cause of reoperation	Cause of death	Time to death (days)
TG, Sp	65/M	IV	A-loop obstruction	Sepsis	11
STG B II	46/F	II	E-loop obstruction	Sepsis	17
STG B II	64/M	IIIa	E-loop obstruction	Sepsis	25
STG B I	70/F	I	Gastroduodenal a. bleeding	DIC	2
STG B II	70/M	IIIa	Anastomosis site bleeding	DIC	5
STG B I	49/M	I	Splenic a. bleeding	DIC	14
STG B II	72/M	II	Mesentery bleeding	DIC	17
TG, Sp	60/M	IV	Anastomotic leakage	Sepsis	2
STG B II	62/M	IV	Anastomotic leakage	Sepsis	6
STG B II	72/M	IIIb	Wound evisceration	Aspiration pneumonia	1

TG total gastrectomy, *STG* subtotal gastrectomy, *B* Billroth, *A* afferent, *E* efferent, *Sp* splenectomy, *DIC* disseminated intravascular coagulation

drainage (78.8%). Seven patients with anastomotic leakage were treated with primary closure and feeding jejunostomy, revision of anastomosis site, and total gastrectomy with uncut Roux-en-Y esophagojejunostomy. Five patients with duodenal stump leakage who were clinically septic were not cured by the interventional procedure and underwent reoperation for primary closure of the duodenal stump and tube duodenostomy. Five patients with intraabdominal abscesses without leakage were treated using irrigation and drainage.

Acalculous cholecystitis requiring reoperation occurred in six patients (3.7%). Cholecystectomy was performed in four patients. One underwent a tube cholecystostomy and a diverting ileostomy on postoperative day 24 due to an enterocutaneous fistula.

Bile peritonitis due to an intrahepatic duct injury developed on postoperative day 2 due to a liver biopsy at the first operation, and suture ligation was performed at the reoperation. A biliary stricture occurred in one patient at 17.8 months postoperatively due to iatrogenic transection of the common bile duct during lymph node dissection around the hepatoduodenal ligament. This was treated with a choledochoduodenostomy and T-tube insertion.

The incidence of bleeding were not significantly different between total and subtotal gastrectomy (10.5% vs. 8.9%) while the reoperative rate for anastomotic leakage in total gastrectomy was higher than that of subtotal gastrectomy (10.5% vs. 2.4%), although it was only marginally significant (P=0.053).

Discussion

Postoperative complications requiring reoperation after gastric cancer surgery are stressful to both patient and surgeon. Such complications can affect both quality of life and patient survival. The rate of complication rate follow-

Table 4 Causes According to the Time to Reoperation

	Time to reoperation		
	Short-term		Long-term
	Group A (n=25) (within 1 week)	Group B (n=46) (1 week–1 month)	Group C (n=91) (after 1 month)
Intraabdominal bleeding	13 (52.0)	2 (2.2)	0
Wound dehiscence or evisceration	5 (20.0)	10 (21.7)	0
Acalculous cholecystitis	3 (12.0)	2 (2.2)	0
Anastomotic leakage	2 (8.0)	5 (10.9)	0
Intestinal obstruction	1 (4.0)	18 (39.1)	69 (75.8)
Intraabdominal abscess without leakage	0	2 (2.2)	3 (3.3)
Duodenal stump leakage	0	5 (10.9)	0
Bowel perforation	0	2 (2.2)	3 (3.3)
Incisional hernia	0	0	15 (16.5)
Bile peritonitis due to hepatic duct injury	1(4.0)	0	0
Biliary stricture	0	0	1 (1.1)

Values in parentheses are percentages

Table 5 Name of operation according to postoperative complication

Complications	Name of operation	No.
Intestinal obstruction	Bandlysis	40
	Segmental resection of bowel	31
	Bypass surgery	17
Intraabdominal bleeding	Bleeder ligation	12
	Total gastrectomy with Roux-en-Y	2
	esophagojejunostomy	1
	Splenectomy	
Wound evisceration	Primary closure	10
Wound dehiscence	Secondary closure	5
Incisional hernia	Hernioplasty	9
	Hernioplasty with prolene mesh	5
	Segmental resection of small bowel with hernioplasty	1
Anastomotic leakage	Primary closure and feeding jejunostomy	4
	Revision of anastomosis site	2
	Total gastrectomy with uncut Roux-en-Y esophagojejunostomy	1
Duodenal stump leakage	Primary closure of duodenal stump and tube duodenostomy	5
Acalculous cholecystitis	Cholecystectomy	4
	Tube cholecystostomy	1
Intraabdominal abscess without leakage	Irrigation and drainage	5
Bowel perforation	Primary closure and bypass surgery	2
	Segmental resection of small bowel	2
	Transverse loop colostomy	1
Bile peritonitis due to hepatic duct injury	Ligation of bile duct	1
Biliary stricture	Choledochoduodenostomy with T-tube insertion	1

ing reoperation was lower in the present study compared to previous studies.[2,4–6] However, short-term complications requiring reoperation were associated with a high mortality. In this study, we believe that the total of 162 patients who required reoperation in our hospital is a conservative estimate because there could have been some patients who underwent resurgery due to late complications in other hospital. Although this is a limitation of our study, our major goal was to describe the types of complications requiring reoperation, time to reoperation, and surgical treatment according to each complication.

The overall incidence of adhesions, regardless of abdominal surgery type, is nearly 95%, and the postoperative severe consequence of adhesions is intestinal obstruction.[8] The present study found that the most frequent complication was intestinal obstruction. Patients underwent surgical management for intestinal obstruction after gastrectomy at a rate of 25.6% during the same hospitalization, 55.6% during the first readmission, and 16.7% during the second readmission (data not shown). Exploratory laparotomy has traditionally been the treatment of choice for patients with recurrent small bowel obstruction. However, a major concern is that patients who are managed surgically may develop more adhesions and obstructions of the small bowel, and this possibility must be minimized. Recently, we have performed gastrectomy through a small abdominal incision (15 cm) and sought to decrease the operation time to reduce the incidence of small bowel adhesions. Moreover, laparoscopic adhesiolysis has been reported to be safe and feasible for assessment and management of recurrent small bowel obstruction.[9,10] We also have applied laparoscopic adhesiolysis safely and effectively for recurrent small bowel obstruction after radical gastrectomy since 2005.[11]

Although most postoperative bleeding is minor, uncontrolled bleeding requiring reoperation which is not responsive to conservative management is associated with high mortality. In carcinoma of the esophagus or cardia of the stomach, reported rates of emergency reoperation and mortality are 0.3–10% and 17–75%, respectively.[12,13] In the current study, a high mortality rate (26.7%) was observed among reoperation patients with postoperative bleeding. However, most postoperative bleeding is preventable and can be controlled by careful and attentive surgical manipulation. Therefore, it is important that precise anatomical lymph node dissection be applied to reduce the bleeding in curative gastrectomy for gastric cancer. Moreover, suture ligation is more effective than cauterization at the site of active bleeding.[13] Recently, if possible, radiological embolization has been an alternative to surgical

management of postoperative bleeding to reduce the surgical stress of reoperation.[14]

The incidence of wound dehiscence has been reported to vary from 0.2% to 10%.[15,16] Wound dehiscence is usually associated with old age, coexisting disease (diabetes mellitus, chronic lung disease, malignancy, chronic renal insufficiency), increased pressure or tension on the closure, malnutrition, drug exposure (chronic steroid use, chemotherapy), or inadequate surgical techniques. For patients at risk of wound dehiscence, the fascial layer of the abdomen should be closed more carefully and retention sutures should be used if necessary.

In general, incisional hernias are associated with old age, male gender, obesity, type of suture, chest infection, abdominal distension, wound infection, and surgical skill.[17,18] The true incidence after abdominal surgery is not clear because data from thorough long-term follow-up studies are not available. The incisional hernia rate is reported to be 2–11% in abdominal surgery patients.[17,19] We could not determine the exact time of incisional hernia development after the first operation. However, attention should be paid to minimize incisional hernias because such patients complain of abdominal discomfort and cosmetic problems.

It is difficult to decide whether to surgically treat intraabdominal abscess after gastric cancer surgery. Clinically, a prolonged ileus, pain, and/or wound infection (i.e., the most important positive peritoneal signs) suggest an intraabdominal abscess[20] and should lead to abdominal cavity evaluation using computed tomographic scans or ultrasonography, which would also show whether there is anastomotic leakage or bowel perforation. Image-guided (computed tomography, ultrasonography) percutaneous drainage of intraabdominal abscesses effectively controls sepsis in 53–64% of intensive care patients.[21,22] In the present study, computed tomography or ultrasonography was performed to identify intraabdominal abscesses in clinically septic patients, and ultrasono-guided percutaneous drainage of such fluid was performed. On follow-up ultrasonography, which showed multiple localized abscess pockets, patients underwent reoperation to remove the abscess effectively. We, therefore, suggest that patients with intraabdominal abscesses be treated with optimal drainage (nonsurgical or surgical) and antibiotics to prevent multiple organ failure.

Conclusion

The present study found that most long-term complications were intestinal obstruction (69, 75.8%) due to adhesive formation rather than technical failure, while most short-term complications requiring reoperation were surgery-related complications and associated with high hospital mortality (14.1%). Proper preoperative preparation and faultless surgical skills are required during the initial surgery to reduce complications and the need for reoperation.

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ORIGINAL ARTICLE

Frequency, Pattern, and Risk Factors of Postoperative Recurrence of Crohn's Disease After Resection Different from Ileo-Colonic

Sara Onali · Carmelina Petruzziello · Emma Calabrese · Giovanna Condino · Francesca Zorzi · Giuseppe Sigismondo Sica · Francesco Pallone · Livia Biancone

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Abstract
Background The frequency of recurrence in Crohn's disease (CD) patients after curative resection different from the ileo-colonic is undefined. We aimed to assess the frequency, pattern, outcome, and risk factors of postoperative recurrence in CD patients under regular follow-up after anastomosis different from ileo-colonic.
Materials and Methods In a retrospective study, clinical records of 537 CD patients under regular follow-up from January 2001 to August 2007 were reviewed. The outcome after surgery was assessed on the basis of clinical records prospectively recorded.
Results Previous resection was observed in 183 of 537 (34%) patients, including the ileo-colon in 145 (79%) and other gastrointestinal (GI) segments in 38 (21%). Recurrence was detected in 16 of 38 (42%) patients (all symptomatic) including five of 14 (35%) with ileostomy, five of five (100%) with ileo-rectal, three of 11 (27%) with ileo-ileal, one or four (25%) with colorectal, and two of three (33%) with duodenum-jejunal anastomosis. Ileo-colonic resection was reported in 145 of 183 (79%) patients, showing recurrence in 128 (88.3%) and symptomatic in 47 (36.7%) patients. The frequency of recurrence was higher in patients with ileo-colonic resection than in patients with other types of resection (128/145, 88% vs 16/38, 42%, $p<0.001$). The frequency of symptomatic recurrence was lower in patients with ileo-colonic resection than in those with other resections (47/128, 37% vs 16/16, 100%; $p<0.001$). Risk factors for recurrence were comparable in the two subgroups (smoke, odds ratio, OR 1.5 vs 1.4; appendectomy, OR 0.32 vs 0.33; familial inflammatory bowel disease, OR 0.43 vs 1.26).
Conclusions Postoperative recurrence is observed in a high proportion of CD patients after resection different from ileo-colon (including ileostomy), although at a lower frequency than observed after ileo-colonic resection.

Keywords Crohn's disease · Postoperative recurrence · Ileo-colonic resection · Ileo-rectal anastomosis

S. Onali · C. Petruzziello · E. Calabrese · G. Condino · F. Zorzi · F. Pallone · L. Biancone (✉)
Cattedra di Gastroenterologia, Dipartimento di Medicina Interna, Università "Tor Vergata" di Roma,
Via Montepellier,
1 00133 Rome, Italy
e-mail: biancone@med.uniroma2.it

G. S. Sica
Cattedra di Chirurgia Generale, Dipartimento di Chirurgia, Università "Tor Vergata" di Roma,
Rome, Italy

Introduction

Postoperative recurrence after ileo-colonic resection is a feature of Crohn's disease (CD). Almost two thirds of patients show endoscopic recurrence at 1 year, rising to 90% of patients 3 years after curative ileo-colonic resection.[1–4] The natural history of recurrence after ileo-colonic resection has been extensively investigated.[1] However, the outcome of CD patients after "curative" resection different from the ileo-colonic is less well defined. The prevalence pattern and the site of CD lesions has been reported to be comparable before and after ileo-colonic resection.[3] Several studies have looked for the potential role of risk factors for

CD recurrence after ileo-colonic resection, but only active smoking, especially in women, and location of disease (ileocolitis) appears significant risk factors.[5–8] "In vivo" studies showed that the fecal stream is required for the development of recurrence after ileo-colonic resection,[9] almost invariably including neo-terminal ileum.[2] In CD patients with curative resection different from the ileo-colonic, recurrence may involve other segments of the gastrointestinal (GI) tract.[2] However, very few studies investigated the natural history of recurrence after curative resection for CD involving GI segments different from the ileo-colon. In a small retrospective study, 92% of patients with jejuno-colonic anastomosis showed endoscopic recurrence, suggesting that the proximity to colonic contents also predisposes to recurrence.[10] The few retrospective studies investigating this issue suggest that the recurrence rate in CD patients with colo-colonic anastomosis is lower than in patients with ileo-colonic anastomosis, while the natural history of jejunal CD after surgery appears to run a more aggressive course when compared with patients resected for ileo-cecal CD.[11–12]

As upper GI lesions related to CD appears more frequently in younger patients[12] and a lower age at disease onset is being observed during the last few years,[11] the knowledge of the natural history of CD after "curative" resection of the upper small intestine (jejunum or proximal ileum) may add clues for proper indication for surgery, including timing and type of surgical approach. In this retrospective analysis, we aimed to identify the frequency, pattern, and risk factors associated with postoperative disease recurrence in patients with CD during regular clinical follow-up following "curative" resection different from ileo-colonic, including permanent ileostomy.

Materials and Methods

Study protocol In a retrospective study, clinical records of all CD patients under regular follow-up in our Gastroenterology Unit from January 2001 to August 2007 were reviewed. Diagnosis of CD was made according to conventional clinical, endoscopic, and radiological criteria, confirmed by the histological analysis of the surgical specimen.[1–2] Clinical records, including demographic and detailed clinical characteristics, were prospectively recorded for each patient. The following parameters were collected on a computer datasheet for each patient: sex, age, smoking habits, previous appendectomy, familial history of inflammatory bowel disease (IBD), and previous intestinal resection(s) for CD. All patients with one or more previous intestinal resection for CD were included in the analysis. Patients were subgrouped according to the type of resection (ileo-colonic vs other anastomosis) on the basis of the last surgical resection for CD. The following parameters were recorded when considering the last resection: localization, extent, and prevalence pattern of the lesions before surgery, type of resection (ileo-colonic vs all other GI resections for CD), type of anastomosis, time from surgery to diagnosis of recurrence, time from surgery to clinical recurrence, and prevalent pattern of the recurrent lesions. In all patients, indication for surgery was made according to conventional clinical criteria.[2–3] In particular, clinical characteristics of patients with previous curative resection for CD different from the ileo-colonic resection were recorded and considered for the analysis. Indication for surgery in the subgroup of patients with ileo-colonic vs other types of resection included recurrent sub/occlusions (n=108 vs n=18), abdominal abscess and/or fistulae (recto-vaginal or entero-vesical; n=25 *vs* n=5), and refractory disease (n=12 vs n=15).

The two patients subgroups (i.e. with ileo-colonic resection vs other resections) were treated similarly in terms of both treatment and follow-up. All patients received medical treatment after resection. In particular, all clinically inactive patients were treated with oral mesalazine (2.4 g/day) after resection, with the exclusion of patients with permanent ileostomy. Differently, all clinically active patients with recurrence (including those with permanent ileostomy) were treated with corticosteroids or immunomodulators (azathioprine, 6-mercaptopurine, or biologic therapies).[14]

In both subgroups, routine timing of clinical follow-up and extent evaluation at the referral center was performed every 3 months, according to conventional criteria.[14] Endoscopy or radiographic imaging was performed in case of new symptoms, suggesting either the development of recurrence or changes of the pattern/extent of the lesions (low hemoglobin and altered bowel habits).[14] The assessment of CD recurrence was made according to conventional criteria, including different approaches in relation to the type of anastomosis. In particular, endoscopic assessment was performed in patients with permanent ileostomy, ileo-rectal, or colorectal anastomosis, while radiological assessment, including small bowel follow through (SBFT) was used for assessing recurrence in patients with ileo-ileal, duodenum-jejunal, or jejunum-jejunal anastomosis. The development of radiologic or endoscopic recurrence at any time from surgery and the possible need of subsequent surgery were reported. The prevalent pattern of the lesions related to CD recurrence was assessed according to the Roma classification.[13] In patients with ileo-colonic anastomosis, endoscopic recurrence was assessed according to Rutgeerts et al.[1] Risk factors for CD recurrence, including smoking habits, previous appendectomy, and familial history of IBD, were considered.

Statistical Analysis

All data were expressed as median and range in all figures, tables, and along the text. Differences in terms of frequency of postoperative recurrence between CD patients with ileo-colonic vs other intestinal anastomoses were searched by using the χ^2 test.

The odds ratio (OR) for known risk factors of CD recurrence were calculated.

Results

Clinical records showed that among 537 CD patients under regular follow-up in our GI Unit from January 2001 to August 2007, 183 (34%) had at least one previous curative resection for the disease. Among these 183 patients, 145 (79%) had at least one previous ileo-colonic resection, while 38 (21%) patients had other types of intestinal resection for CD. When considering the whole group of 537 patients, a higher percentage of patients had a previous ileo-colonic resection (145/537; 27%) when compared with other types of resections for the disease (38/537; 7%; $p<0.0001$; Fig. 1). Among the subgroup of 145 patients with ileo-colonic resection, there were 72 men and 73 women, with a median age of 47.5 (range, 18–82 years), including 47 (32%) smokers, 67 (46%) no smokers and 31 (21%) ex-smokers, 17 (12%) patients with familial history of IBD, and 47 (32%) patients with previous appendectomy. When considering the group of 145 patients with ileo-colonic resection, 33 (22.7%) patients had at least one previous resection for the disease. In particular, the ileo-colonic resection represented the second resection for 21 (64%) patients and the third resection for 12 (36%) patients.

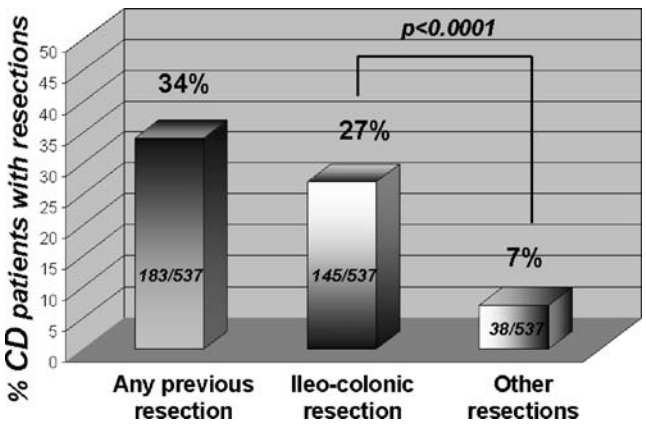

Figure 1 Histograms showing the percentage of CD patients with any previous intestinal resection for CD. The percentage of patients with ileo-colonic or other types of anastomoses are also indicated. As shown, a higher percentage of patients had a previous ileo-colonic resection (145/537; 27%) when compared with other types of resection for the disease (38/537; **7%**; $p<0.0001$).

Previous intestinal resection different from ileo-colonic was observed in 38 CD patients (18 men, 20 women; median age, 45 years; range, 23–8; Table 1). Among these 38 patients, two patients had two anastomoses different from the ileo-colonic (CL, jejunum-jejunal, and ileostomy; EM, duodenum-jejunal, and ileo-ileal), while 2 additional patients (DIA, DAD) had a two sequential resections different from the ileo-colonic. When considering the group of 38 patients with previous intestinal resection different from ileo-colonic, 13 (34%) patients had at least one previous resection for the disease. In particular, resection different from ileo-colonic represented the second resection for eight (61%), the third resection for four (31%), and the fourth resection for one (8%) patient. Therefore, a comparable percentage of patients from the two subgroups underwent more than one intestinal resection for CD before the last resection considered in the study (ileo-colonic resection vs other resections, 22.7% vs 34%; p=n.s.).

Recurrence in Patients with Curative Resection for CD Different from Ileo-Colonic

Table 1 summarizes, for each of the 38 patients with previous curative resection for CD different from ileo-colonic, the clinical characteristics (age, gender, and type of anastomosis) and risk factors for recurrence (smoking habits, familial history of IBD, and appendectomy).

The median follow-up of patients after surgery was 8 years (range, 1–26). Recurrence was assessed by endoscopy in 22 of 38 (57.8%) patients and by SBFT in 15 of 38 (39%) patients, while in one of the two patients with two anastomoses different from ileo-colon (jejunum-jejunal and ileostomy), CD recurrence was assessed by both techniques.

Endoscopic or radiological recurrence was detected in 16 of 38 (42%) patients. Among the 22 patients with recurrence assessed by endoscopy, recurrence was detected in 11 (50%) patients, while among the 16 patients with recurrence assessed by radiology, recurrence was detected in five (31%; including patients studied using both techniques). All the 16 patients with endoscopic or radiological recurrence also showed clinical recurrence at time of assessment. The median follow up from surgery to the last clinical assessment was 78 months (range 12–240), the median time from the diagnosis of recurrence to the last clinical assessment was 12 months (range 0–84) and the median time from the ileo-colonic resection to the diagnosis of endoscopic/radiological recurrence was 12 months (range, 3–384).

When the frequency of CD recurrence was considered in relation to the type of anastomosis, recurrence was observed in five of 14 (35%) patients with permanent ileostomy, in five of five (100%) patients with ileo-rectal anastomosis, in three of 11 (27%) patients with ileo-ileal

Table 1 Patients with Previous Curative Resection for CD Different from Ileo-Colonic: Demographic Characteristics and Risk Factors for Recurrence

Patient	Age	Sex	Type of anastomosis	Smoking habits	Familial history of IBD	Previous Appendectomy
1. EC	64	F	Colorectal	Y	N	N
2. BG	41	F	Colorectal	Y	Y	Y
3. CR	60	M	Colorectal	Ex	N	Y
4. ADI	61	F	Colorectal	Y	Y	Y
5. MDS	23	M	Colo-rectal	Y	N	Y
6. ML	45	M	Ileo-rectal	Y	Y	Y
7. PC	53	F	Ileo-rectal	Y	N	N
8. RC	61	F	Ileo-rectal	Y	N	Y
9. DDA	37	F	Ileo-rectal	Y	N	N
10.LVDL	24	M	Ileo-rectal	N	N	N
11. DC	38	M	Duodenum-jejunum	N	N	N
12. EM	38	M	Duodenum-jejunum+ Ileo-ileal (T-T)	Ex	N	Y
13. AA	63	F	Duodenum-jejunum	N	N	Y
14. MLP	37	F	Jejunum-jejunum	N	N	N
15. PT	40	M	Jejunum-jejunum	Ex	N	N
16. LC	60	F	Jejunum-jejunum+ileostomy	Y	N	N
17. SP	33	M	Ileo-Ileal (T-T)	N	N	N
18. ES	61	M	Ileo-Ileal (T-T)	N	N	N
19. AP	62	F	Ileo-Ileal (T-T)	Ex	N	Y
20. DF	70	M	Ileo-Ileal (S-S)	N	N	N
21. RP	35	M	Ileo-Ileal (S-S)	N	N	N
22. FS	63	M	Ileo-Ileal (S-S)	Ex	N	Y
23. OS	45	F	Ileo-Ileal (S-S)	Y	N	N
24. CV	41	M	Ileo-Ileal (S-S)	Y	N	N
25. AS	58	F	Ileo-Ileal (S-S)	N	Y	Y
26. FP	65	F	Ileo-Ileal (S-S)	N	N	Y
27. RB	53	M	Permanent ileostomy	N	N	N
28. SC	43	F	Permanent ileostomy	N	N	N
29. GB	48	F	Permanent ileostomy	N	N	N
30. GD	60	F	Permanent ileostomy	Y	N	N
31. LC	76	F	Permanent ileostomy	N	N	N
32. GV	60	F	Permanent ileostomy	N	N	N
33. AP	47	M	Permanent ileostomy	N	N	Y
34. MB	76	M	Permanent ileostomy	Ex	N	N
35. LI	76	M	Permanent ileostomy	Ex	N	N
36. SF	36	F	Permanent ileostomy	N	N	Y
37. MS	73	M	Permanent ileostomy	Ex	N	N
38. CC	48	F	Permanent ileostomy	N	N	Y

F female, *M* male, *Y* yes, *N* no, *IBD* inflammatory bowel disease, *T-T* termino-terminal, *S-S* side-to-side

anastomosis, in one of four (25%) patients with colorectal anastomosis and in two of six (33%) patients with duodenum-jejunal or jejunum-jejunal anastomosis (total 40 anastomoses, as two patients had two concomitant anastomoses at time if the study; Fig. 2). Figure 3 shows endoscopic CD recurrence in three patients with permanent ileostomy (panel a) and with colorectal (panel b) or ileo-rectal (panel c) anastomosis. The site of recurrence included both the anastomosis and the neo-terminal ileum in all the five patients with ileo-rectal anastomoses and in the three patients with ileo-ileal anastomoses showing recurrence. Recurrence involved both the anastomosis and the neo-terminal jejunum or ileum in the two patients with duodenum-jejunal or jejunum-jejunal anastomoses, while recurrence involved the anastomosis only in both patients with colorectal anastomoses.

The prevalent pattern of CD recurrence was fibrostricturing in eight of 18 (44%) and inflammatory in 10 of 18 (56%) anastomoses.

Among the group of 14 patients with permanent ileostomy, three had a previous recurrence in the ileum.

When analyzing risk factors for CD recurrence, previous appendectomy was observed in 15 of 38 (39%) patients, familial history of IBD in four of 38 (10%) patients, and smoking in 12 of 38 (31%) patients. Among patients with symptomatic recurrence, four of 16 (25%) had a previous appendectomy, two of 16 (12.5%) had a familial history of IBD, and seven of 16 (43.7%) were smokers.

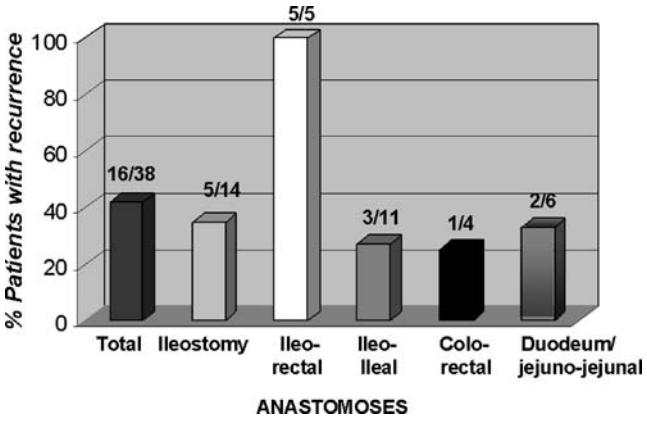

Figure 2 Histograms showing the frequency of endoscopical and/or radiological recurrence observed when considering the 38 patients with anastomoses different from ileo-colonic, subgrouped according to the type of anastomoses (ileostomy n=14, ileo-rectal n=5, ileo-ileal n=11, colorectal n=4, duodenum-jejunal or jejunum-jejunal anastomosis n=6: duodenum-jejunal n=3, jejunum-jejunal n=3).

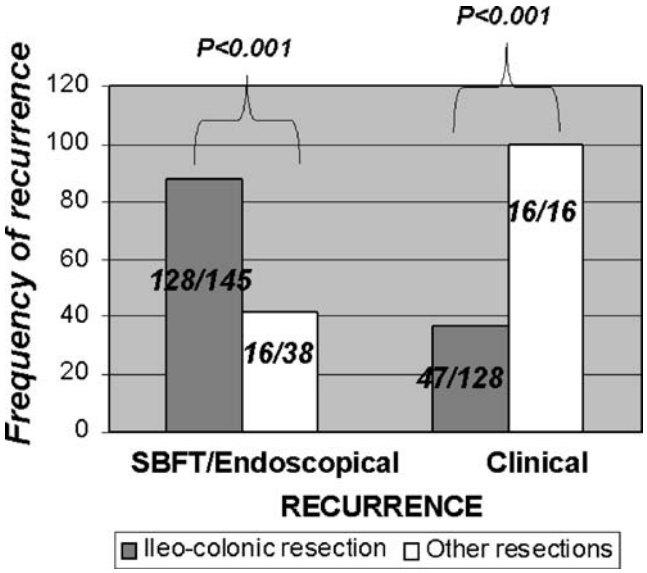

Figure 4 Histograms showing the frequency of endoscopical/radiological and clinical recurrence in patients with ileo-colonic vs other types of curative intestinal resections for CD. As shown, the frequency of recurrence was significantly higher in patients with previous ileo-colonic resection when compared with patients with other curative resections for CD (p<0.0001). The frequency of clinical recurrence was higher in patients with curative resection different from the ileo-colonic (16 out of 16 patients, 100%) than in patients with ileo-colonic resection (47 out of 128 patients, 37%; p<0.001).

Frequency of Recurrence Considering the 42 Anastomoses

In a subgroup analysis, the frequency of recurrence was investigated among the 38 patients, the 42 anastomoses different from ileo-colonic (two patients had two anastomoses different from ileo-colonic and two other patients had a second resection different from ileo-colonic). These 42 anastomoses included ileostomy (n=14), ileo-rectal (n=6), ileo-ileal (n=11, end-to-end n=4, side-to-side n=7), colorectal (n=5), duodenum-jejunal or jejunum-jejunal anastomosis (n=6, duodenum-jejunal (n=3), and jejunum-jejunal n=3). Among the 42 anastomoses, recurrence was assessed by endoscopy in 25 of 42 (59.5%) and by SBFT in 17 of 42 (40.4%) patients. Peri-anastomotic recurrence was detected in 18 of 42 (43%) patients by using endoscopy in 11 of 25 (44%) or SBFT in seven of 17 (41%) patients.

When CD recurrence was considered in relation to the type of anastomosis, it was observed in five of 14 (35%) patients with ileostomy, in six of six (100%) patients with ileo-rectal anastomosis, in three of 11 (27%) patients with ileo-ileal anastomosis, in two of five (40%) patients with colorectal anastomosis and in two of six (33%) patients with duodenum-jejunal or jejunum-jejunal anastomosis. The site of recurrence included both the anastomosis and the neo-terminal ileum in all six patients with ileo-rectal anastomosis, three patients with recurrence involving the ileo-ileal anastomoses, and two patients with duodenum-jejunal or jejunum-jejunal anastomoses, while recurrence involved the anastomosis only in both colorectal anastomoses.

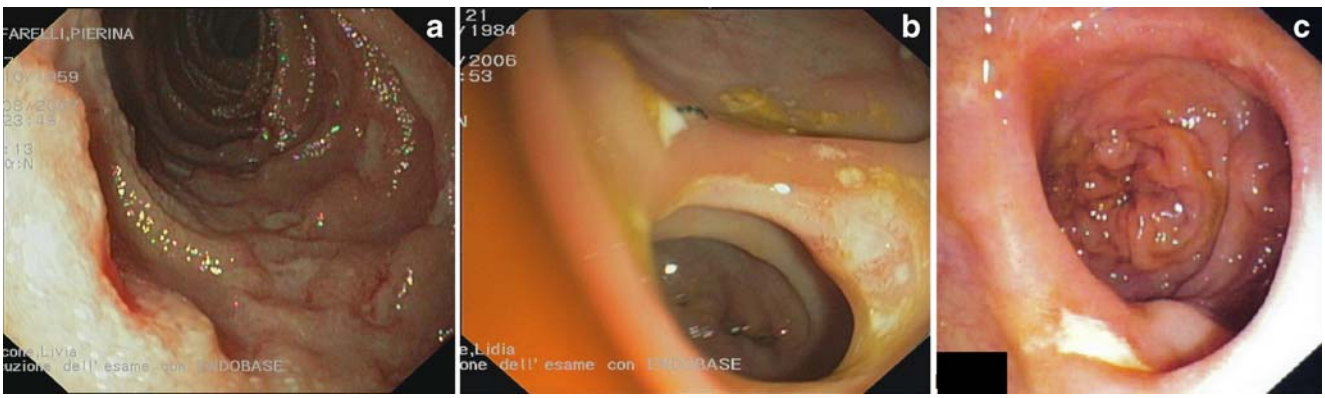

Figure 3 Endoscopic CD recurrence in 3 patients with permanent ileostomoy (**a**) and with colorectal (**b**) or ileo-rectal (**c**) anastomosis.

Recurrence in Patients with Ileo-Colonic Curative Resection for CD

Among the 183 patients enrolled, 145 (79%) patients had a previous ileo-colonic resection.

In this subgroup of patients, endoscopic or radiological recurrence was observed in 128 out of 145 (88.3%) patients, assessed by endoscopy in 95 of 128 (74%) and by SBFT in 33 of 128 (26%) of patients. At time of endoscopical/radiological recurrence, 47 out of 128 (36.7%) patients were clinically active. The prevalent pattern of the lesions related to recurrence was fibrostricturing in 57 of 128 (44.5%) and inflammatory in 71 of 128 (55.5%). The median follow-up from surgery to the last clinical assessment was 72 months (range, 3–408), the median time from the diagnosis of recurrence to the last clinical assessment was 12 months (range, 0–84), and the median time from the ileo-colonic resection to the diagnosis of endoscopical/radiological recurrence was 12 months (range, 3–384).

When comparing the timing of recurrence between patients with ileo-colonic vs other GI resections, both the median follow-up from surgery to the last clinical assessment and the median time from surgery to the diagnosis of recurrence were comparable between the two subgroups ($p=0.4$ and $p=0.83$, respectively). Differently, the median time from the diagnosis of recurrence to the last clinical assessment was higher in the subgroup of patients with other types of anastomoses ($p=0.002$).

Recurrence: Comparison between Patients with Ileo-Colonic vs Other Types of Curative Intestinal Resections for CD

In our cohort of patients, the frequency of radiological/endoscopical recurrence was significantly higher in patients with ileo-colonic resection when compared with patients with other types of curative intestinal resections for CD (128/145, 88% vs 16/38, 42%, $p<0.001$)(Fig. 4). At time of endoscopical/radiological recurrence, the frequency of symptomatic recurrence was significantly higher in patients with curative resection different from the ileo-colonic resection (16 out of 16 patients, 100%) than in patients with ileo-colonic resection (47 out of 128 patients, 37%; $p<0.001$) (Fig. 4).

When considering the known risk factors for CD recurrence, comparable findings were observed when comparing patients with ileo-colonic vs other types of anastomoses (smoke: OR 1.5 vs 1.4; previous appendectomy: OR 0.32 vs 0.33; familial history of IBD: OR 0.43 vs 1.26).

Discussion

Despite the growing knowledge regarding the pathogenesis of CD, no treatments are currently available in order to avoid the postoperative recurrence of CD after ileo-colonic resection. Although ileo-colonic resection represents the most frequent surgical procedure for CD,[1–3] other surgical resections may be required in these patients. Differently from patients with previous ileo-colonic resection, the outcome and the natural history of CD after other surgical procedures is not clearly defined. To our knowledge, only few retrospective studies including a limited number of patients investigated this issue, with conflicting results.[10–13] The knowledge of the natural history of the postoperative course of CD patients after surgical resection different from the ileo-colonic may be useful for proper clinical management and surgical indications. In order to address this issue, we aimed to assess, in a retrospective analysis, the frequency and pattern of CD recurrence in a cohort of CD patients under regular follow-up. Present findings further indicate that CD recurrence may also develop in patients with anastomosis different form the ileo-colon, including patients with permanent ileostomy. Although the limited number of enrolled patients and the different type of anastomoses do not allow conclusive statements, present findings also suggest a high frequency of symptomatic recurrence in other types of anastomoses, particularly including the ileo-rectum. Comparisons with previous studies in this regard are limited by the observed wide range of frequency of recurrence in different series. Our findings from a retrospective analysis of data recorded prospectively indicate that CD recurrence above the anastomosis is observed also in patients with previous resections different from ileo-colonic, including permanent ileostomy. However, this frequency appeared to be lower than after ileo-colonic resection. Prospective longitudinal studies are ongoing in order to address this issue.

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Conflict of interest All authors declare no conflict of interest.

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ORIGINAL ARTICLE

*Notch*1 Expression in Colorectal Carcinoma Determines Tumor Differentiation Status

Dake Chu · Weizhong Wang · Huahong Xie · Yunming Li · Guanglong Dong · Chunsheng Xu · Dongli Chen · Jianyong Zheng · Mengbin Li · Zifan Lu · Gang Ji

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Abstract
Introduction The significance of Notch1 expression in colorectal cancer has not been clearly described. We investigated the expression of Notch1 and its relationship with differentiation status and tumor (Union Internationale Contre le Cancer, UICC) stage using a series of 237 colorectal cancer samples with matched adjacent normal tissues and a series of 46 normal colorectal specimens.
Materials and Methods Immunohistochemistry, real-time polymerase chain reaction, and Western blot analysis were performed to assess the expression of Notch1.
Results It was found that Notch1 was overexpressed in cancer tissues as compared with adjacent normal tissue and normal control tissues. Also, a tendency for increased expression was observed when going from well to poorly differentiated carcinomas, as well as going from UICC stage I to stage IV. With the differentiation of colon cancer cells, the expression of Notch1 decreased. To support this observation, colon cancer cell lines HT29 and SW620 were induced to differentiate in culture, and expression of Notch1 was investigated. A clear reduction of Notch1 expression was observed.
Conclusion These results suggest that Notch1 expression correlated closely with colorectal cancer and may play an oncogenic role during colonic carcinogenesis.

D. Chu · W. Wang · G. Dong · C. Xu · D. Chen · J. Zheng · M. Li · G. Ji
The State Key Laboratory of Cancer Biology, Department of Gastrointestinal Surgery, Xijing Hospital, The Fourth Military Medical University, Xi'an 710032, China

H. Xie
Institute of Digestive Diseases, The State Key Laboratory of Cancer Biology, Xijing Hospital, The Fourth Military Medical University, Xi'an 710032, China

Y. Li
Department of Health Statistics, The Fourth Military Medical University, Xi'an 710032, China

Z. Lu
Department of Biochemistry and Molecular Biology, The Fourth Military Medical University, Xi'an 710032, China

G. Ji (✉)
Department of Gastrointestinal Surgery, Xijing Hospital, The Fourth Military Medical University, Xi'an 710032, People's Republic of China
e-mail: jigang@fmmu.edu.cn

Keywords Notch1 · Colorectal carcinoma · Differentiation · Stage

Introduction

Colorectal cancer is a tumor type with 1,020,000 new cases and 530,000 deaths worldwide per year.[1,2] It is the fourth most common non-cutaneous malignancy in China and is the fifth most frequent cause of cancer-related death.[3] In 2007, 153,760 cases of colorectal cancer were diagnosed, and 78,700 people died from the disease in China. Over the past several years, therapeutic options for patients with colorectal cancer have increased substantially due to earlier diagnosis, progressions in radical surgery, radiotherapy, and neoadjuvant chemotherapy. However, despite these improvements, many colorectal cancers remain incurable. Efforts to better understand the biological basis for colorectal cancer progression may provide important, clinically relevant insights into disease management.

Colorectal cancer initiation and progression are associated with stepwise genetic alterations. There is a wealth of evidence that the Wnt pathway plays a central role in the pathogenesis of colorectal cancers. Colorectal cancers almost invariably carry activating mutations in the Wnt pathway, which target the tumor suppressors APC or Axin2 or the oncogene b-catenin.[4] Allelic loss and somatic mutations of the APC tumor suppressor genes represent the most frequent molecular events in colorectal cancer.[5] The common denominator of the Wnt pathway tumors is the formation of nuclear Tcf/b-catenin complexes and the subsequent uncontrolled Tcf4 target gene transcription, leading to benign adenomas or polyps. A considerable amount of evidence indicates the Wnt cascade as the major driving force behind the proliferative potential of adenomas and adenocarcinomas of the colon. Recent data indicated that active Notch signaling may play an equally important role in the maintenance of the undifferentiated state of Apc-mutant neoplastic cells. It will be extremely valuable to investigate changes of Notch-related signals in clinical samples.

The receptors of the Notch family are large transmembrane epidermal growth factor-like repeat-containing proteins, important in regulating cell proliferation and differentiation processes closely related with cancer formation.[6,7] Depending on the cell type, Notch signaling can positively or negatively affect cell proliferation, differentiation, and apoptosis.[7,8] To date, four Notch receptors have been identified in mammals, i.e., Notch1, -2, -3, and -4. Five types of Notch binding ligands have been identified, namely, Delta-like-1, -3, -4, Jagged-1, and -2.[9,10] These ligands are all transmembrane proteins containing multiple epidermal-growth-factor-like repeats (known as DSL ligands) and can activate Notch receptors in most contexts.[11,12] The Notch1 protein consists of an extracellular domain with 36 epidermal-growth-factor-like repeats, a single transmembrane domain, and an intracellular domain containing a RBP-JK-associated molecule (RAM) region, ankyrin domains, and a proline/glutamate/serine/threonine-rich (PEST) region. Notch1 has been shown to play an essential role in the differentiation of the lung and gastrointestinal tract.[13–16] Notch1 activity is necessary to maintain a cancerous phenotype in Ras-transformed human cells.[17] However, Notch1 signaling plays a paradoxical role, either as a tumor suppressor or oncogene, depending on the tissue type. Its signaling has a tumor-suppressive effect on murine skin tumors and in non-small cell lung cancer.[18,19] Activation of the Notch1 signaling pathway was reported to inhibit cancer cell growth and induce apoptosis of B cells and other hematopoietic lineages in vitro. In contrast to its tumor-suppressive role, Notch1 has been shown to be upregulated in prostate cancer, small cell lung cancer, and pancreatic carcinoid.[20,21] It has also been reported that Notch1 expression inhibits apoptosis,[22–24] suggesting a possible role of Notch as an oncogene in many cancers. These findings indicated a variable role for Notch1 signaling in cancers. To date, there is no direct evidence of Notch1 expression in colorectal carcinomas.

In the current study, we determined and compared the expression level of Notch1 in colorectal carcinoma specimens with corresponding normal tissues and other normal control colorectal tissues. In addition, the association of Notch1 expression with different tumor staging and level of differentiation was investigated. Our results provide the first direct evidence of Notch1 expression in colorectal cancer tissues and cell lines, indicating that Notch1 may have an oncogenic role in colorectal formation.

Materials and Methods

Tissue Specimens

This study was approved by the ethics committee of the Fourth Military Medical University. Fresh colorectal carcinoma specimens and patient-matched normal tissues were obtained from 237 patients who underwent surgery at the Department of Gastrointestinal Surgery of Xijing Hospital, the Fourth Military Medical University (Xi'an, China) between October 2005 and November 2007. None of the patients received chemotherapy or radiotherapy prior to surgery. Forty-six control colorectal tissues were obtained from patients without malignant disease that underwent surgery. Histomorphology of all specimens was confirmed by the Department of Pathology, Xijing Hospital. Based on histology of colorectal cancer, we have divided all colorectal carcinoma specimens into three groups: poorly differentiated (n=43), moderately differentiated (n=95), and well-differentiated (n=99). Additionally, tumors were also staged according to the Union Internationale Contre le Cancer (UICC) classification system. Other clinical parameters such as gender, age, differentiation, and UICC stage were collected and stored in a database. Parts of the specimens were put into liquid nitrogen for 10 min, then into a −70°C ultra-freezer for messenger RNA (mRNA) and protein isolation. Other parts were fixed in 10% formaldehyde and embedded in paraffin for histological sections.

Cell Culture and Differentiation Induction

The human colon carcinoma cell lines HT29 and SW620 were obtained from the Chinese Type Culture Collection. HT29 cells were cultured in 1640 medium (Sigma-Aldrich), while SW620 cells were cultured in L-15 medium (Sigma-Aldrich). Media was supplemented with 10% fetal bovine serum (Atlanta Biologicals), and cells were cultured at 37°

C in 5% CO_2. Differentiation was induced by treatment with 2 mM sodium butyrate (Sigma Chemical) for 7 days, and cells were harvested each day from the beginning of treatment to the sixth day. The differentiation stage was assessed by transmission electron microscopy (for changes in cell structure and architecture) and alkaline phosphatase activity (AP) as a marker of differentiation. After removal of the culture medium, the attached cells were scraped into ice-cold phosphate-buffered saline (PBS), centrifuged at 4,000×*g*, resuspended in PBS, and sonicated with an ultrasonic cell disrupter. Cellular debris was pelleted by centrifugation, and supernatants were transferred to new tubes and stored at −70°C until assayed. AP activity was measured according to the manufacturer's instructions using *p*-nitrophenylphosphate as substrate (Merck, Darmstadt, Germany) and calculated in units per milligram protein (U/mg prot). Protein content was determined using a BCA™ protein assay kit.

Immunohistochemistry

Immunohistochemistry involved the use of the avidin–biotin–peroxidase method on all the 237 colorectal cancer tissue specimens. All sections were deparaffinized in xylene and dehydrated through a graduated alcohol series before endogenous peroxidase activity was blocked with 0.5% H_2O_2 in methanol for 10 min. Nonspecific binding was blocked by incubating sections with 10% normal goat serum in PBS for 1 h at room temperature. Without washing, sections were incubated with anti-Notch1 (1:300) in PBS at 4°C overnight in a moist box. Biotinylated goat anti-rabbit IgG (1:400, Sigma) was incubated with the sections for 1 h at room temperature and detected with a streptavidin–peroxidase complex. The brown color indicative of peroxidase activity was obtained by incubating with 0.1% 3,3-diaminobenzidine (Sigma) in PBS with 0.05% H_2O_2 for 5 min at room temperature. The tissue specimens were viewed separately by two pathologists under double-blind conditions. An immunoreactivity score system was applied as described earlier.[25]

Quantitative Real-Time RT-PCR

Total RNA from all the 237 colorectal cancer tissue and matched normal tissue specimens together with 46 control colorectal tissues was purified from tissues and cells as recommended by the manufacturer using Trizol reagent (Invitrogen, Carlsbad, CA, USA). Complementary DNA (cDNA) synthesis was performed using approximately 5 μg RNA per 20 μl using a cDNA reverse transcription kit (Fermentas). Real-time PCR was performed on an ABI 7500 system (Applied Biosystems) using SYBR Green I (TAKARA). Primers were designed using Primer Express v3.0 Software. Notch1 primers were: forward 5′-TCAGC GGGATCCACTGTGAG-3′ and reverse 5′-ACACAGGCA GGTGAACGAGTTG-3′. The internal control 18S ribosomal RNA (rRNA) primers were: forward 5′-CGCCG CTAGAGGTGAAATTC-3′ and reverse 5′-TTGGCAAA TGCTTTCGCTC-3′. After first strand synthesis, an equivalent of 50 ng of starting total cellular RNA (1/10 of the cDNA reaction) was added to two duplicate PCR reactions containing 12.5 μl SybrGreen mix, 0.5 μl SybrGreen rox, 100 nmol/l forward primer, and 100 nmol/l reverse primer in a final volume of 25 μl. Each sample was used in a single reaction that cycled at 95°C for 10 min (to activate enzyme), followed by 45 cycles of 95°C for 10 s and 60°C for 34 s on an ABI SDS 7500 system (Applied Biosystems). The expression of Notch1 was analyzed using the $2^{-\Delta\Delta Ct}$ method. Fluorescent data were converted into RQ measurements, which stand for relative expression automatically by the SDS system software and exported to Microsoft Excel. Notch1 mRNA levels were compared to 18S rRNA. Thermal dissociation plots were examined for biphasic melting curves, indicative of whether primer–dimers or other nonspecific products could be contributing to the amplification signal.

Western Blot Analysis

Total tissue proteins from 86 colorectal cancer tissues and matched normal tissues were purified in lysis buffer and then centrifuged at 12,000×*g* for 5 min at 4°C. The supernatants were collected and protein concentrations determined using Bio-Rad protein assay dye reagent (Bio-Rad). Aliquots (50 μg) of whole protein lysates were loaded onto sodium dodecyl sulfate polyacrylamide (10%) gels for electrophoresis. For Western blot analysis, proteins were transferred to Hybond electrochemiluminescence (ECL) nitrocellulose membranes (Amersham Biosciences). The membranes were blocked with 5% nonfat milk in Tris-buffered saline containing 0.1% Tween-20 and incubated with each primary antibody (Notch1 or actin) overnight at 4°C. Finally, blots were incubated with horseradish peroxidase-conjugated secondary antibodies (Promega) for at least 1 h at room temperature and detected using the ECL method (Amersham Biosciences).

Statistical Analysis

The rank sum test was used to analyze the ranked data using the statistical package SPSS (version 11.0). The ranked data were analyzed by the Mann–Whitney *U* test and the Kruskal–Wallis test. Data were analyzed using one-way analysis of variance (ANOVA). Randomized complete block design ANOVA was used to analyze the statistical difference among different tissue types, differentiation

levels, and UICC stages. A value of $P<0.05$ was considered statistically significant.

Results

Overexpression of Notch1 in Colorectal Cancer Tissues and Relationship with Stage and Level of Differentiation

The biological function of Notch1 in cancer is complex and dependent on the tissue type. However, it has not been systematically investigated in colorectal cancer. We collected 237 colorectal cancer samples and patient matching adjacent normal tissues to analyze the expression of Notch1 by immunohistochemistry. We detected a higher expression of Notch1 in colorectal cancer tissues as compared to the normal tissues. Notch1 was mainly localized in the cytoplasm and cell membrane, suggesting the active status of the protein. In addition, its expression level increased from well-differentiated to poorly differentiated tumors. A similar trend was observed from UICC stage I to stage IV. Based on the hierarchical scores of the staining, statistical analysis revealed that the increase of Notch1 expression in colorectal cancers compared with normal region, which was statistically significant. Most importantly, the higher expression of Notch 1 was closely related with poor differentiation status and tumor stage (Table 1). The increased expression of Notch1 from well-differentiated to poorly differentiated tumors was found to be statistically significant ($P<0.05$). Moreover, the increase of Notch1 from UICC stage I to stage IV was also significant ($P<0.001$). These observations indicated that increased Notch1 expression is associated with cancer malignancy.

Quantitative Analysis of Notch1 Expression in Clinical Samples by Western Blot and Real-Time PCR

In order to accurately quantify Notch1 expression level changes in colorectal carcinomas, we performed Western blot analysis in 86 colorectal cancer tissues and matched normal tissues. Among the 86 samples of clinical specimens, as expected, 67 samples of colorectal cancer tissues showed higher expression than that in adjacent normal tissues; 15 samples of colorectal cancer tissues showed lower expression than that in adjacent normal tissues; four samples of colorectal cancer tissues showed no expression.

Table 1 Statistical Results of Immunohistochemistry Assay

	Number	Notch-1				*P*
		–	+	++	+++	
Total	237	12	41	60	124	
Gender						0.88[a]
Men	139	7	25	33	74	
Women	98	5	16	27	50	
Age						0.74[a]
<60	90	4	15	23	48	
≥60	147	8	26	37	76	
Family history						0.836[a]
Positive	23	1	3	7	12	
Negative	214	11	38	53	112	
Tumor location						0.799[b]
Right colon	54	2	10	16	26	
Left colon	61	4	12	13	32	
Rectum	122	6	19	31	66	
Histology						<0.05[b]
Poorly Differentiated	43	1	1	9	32	
Moderately differentiated	95	3	21	24	47	
Well-differentiated	99	8	19	27	45	
UICC stage						<0.001[b]
I	36	6	11	11	8	
II	97	4	20	23	50	
III	55	1	8	14	32	
IV	49	1	2	12	34	

[a] *P* value when expression levels were compared using Mann–Whitney test
[b] *P* value when expression levels were compared using Kruskal–Wallis test

Based on these results, we confirmed that Notch1 protein expression was higher in carcinomas as compared with adjacent normal tissues (Fig. 1a). This was consistent with the immunohistochemistry results. We subsequently investigated whether the expression of Notch1 correlated with the differentiation status and UICC stage. The collected colorectal cancer specimens were classified into three different grades by pathological diagnosis and into four grades based on UICC stage. Notch1 expression was found to be decreased in more differentiated tumors (Fig. 1b). Furthermore, Notch1 expression increased gradually with increasing stage (Fig. 1c). To investigate if differences in Notch1 expression are based on transcriptional regulation, we determined the mRNA levels of Notch1 by quantitative real-time reverse transcription polymerase chain reaction (RT-PCR). As shown in Table 2, there was a clear increase of approximately 500% in Notch1 mRNA in colorectal cancer as compared to adjacent normal tissues and normal colorectal tissues. The increased expression of Notch1 in colorectal cancer as compared to adjacent normal tissues and control normal tissues was statistically significant in both comparisons ($P<0.001$), while no statistical significance was discovered between adjacent normal tissues and control normal tissues ($P=0.989$).

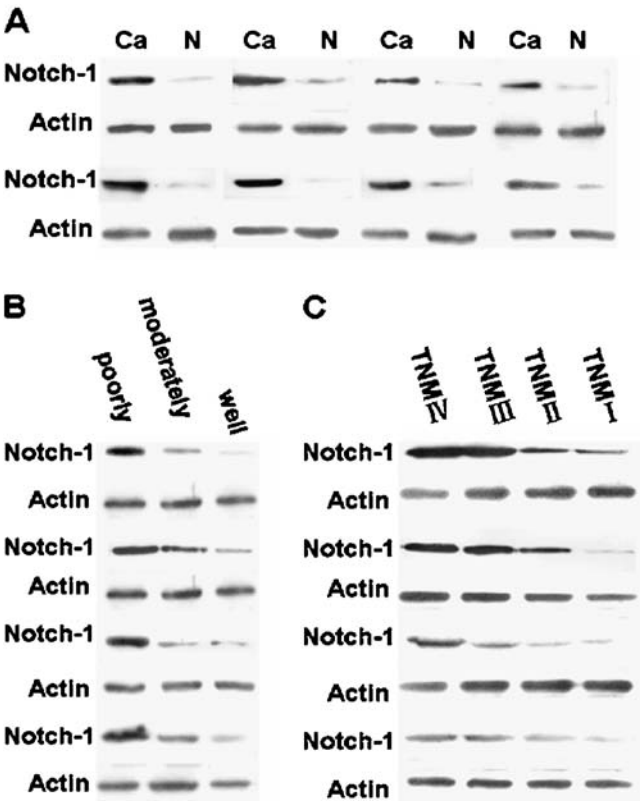

Figure 1 Expression of Notch1 protein in cancerous tissues and adjacent normal tissues by Western blot. **a** Notch1 expression level in cancerous and adjacent normal tissues of the same patients. **b** Notch1 expression level in poorly, moderately, and well-differentiated cancer tissues. **c** Notch1 expression in cancer tissues with different UICC stages. β-actin staining was used as a control for equal protein loading.

Table 2 Statistics of NOTCH-1 mRNA Levels in Colorectal Cancer

	Number	NOTCH-1	*P*
		Mean (SD)	
Tissue type			<0.001[a]
Control	46	1.037 (0.269)	0.989[b]/ <0.001[c]
Adjacent	237	1.041 (0.323)	<0.001[d]
carcinoma	237	5.148 (0.616)	
Histology			<0.001[a]
Poorly differentiated	43	6.392 (0.742)	
Moderately differentiated	95	5.311 (0.685)	
Well-differentiated	99	4.451 (0.573)	
UICC stage			<0.001[a]
I	36	3.613 (0.456)	
II	97	4.765 (0.578)	
III	55	5.536 (0.629)	
IV	49	6.598 (0.713)	

[a] *P* value when expression levels were compared using complete block design ANOVA test
[b] *P* value of difference between adjacent tissues and the control group of healthy individuals using the one-way ANOVA test
[c] *P* value of difference between carcinoma tissues and the control group of healthy individuals using the one-way ANOVA test
[d] *P* value of difference between the carcinoma group and the group of adjacent tissues using one-way ANOVA test

Table 3 Statistical Results of Patient Data Correlated to NOTCH-1 mRNA Levels in Colorectal Cancer

	Number	Notch-1	*P*
		Mean (SD)	
Gender			0.789[a]
Men	139	5.157 (0.624)	
Women	98	5.135 (0.618)	
Age			0.835[a]
<60	90	5.159 (0.623)	
≥60	147	5.141 (0.657)	
Family history			0.838[a]
Positive	23	5.174 (0.655)	
Negative	214	5.145 (0.646)	
Tumor location			0.947[b]
Right colon	54	5.167 (0.618)	
Left colon	61	5.155 (0.623)	
Rectum	122	5.136 (0.589)	

[a] *P* value when expression levels were compared using Student's *t* test
[b] *P* value when expression levels were compared using complete block design ANOVA test

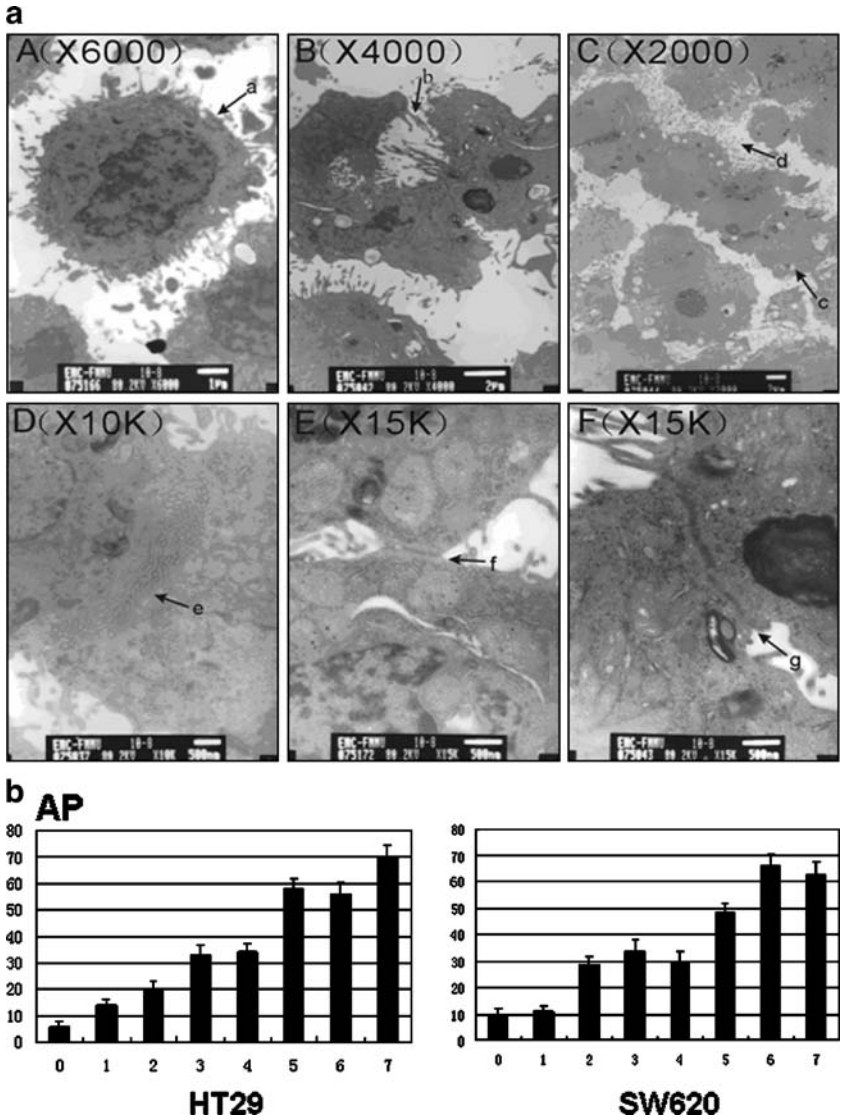

Figure 2 **a** Electron microscopy of colon cancer cells during the process of induced differentiation. *A* undifferentiated colon cells; *B–F* changes in ultramicrostructure during colon cell differentiation. undifferentiated cell **(***A***)**, cryptae structure **(***B***)**, disciplinary conjunction between cell **(***C***)**, polarization of microvilli **(***D***)**, cryptae structure between cells **(***E***)**, macula adherens in cell **(***F***)**, tight junction and macula adherens between cells **(***G***)**. **b** Alkaline phosphatase (*AP*) level during induced cell differentiation in three different colon cancer cell lines. AP levels in cell lines HT29 and SW620 were measured from day 1 to day 7 during the induced differentiation process compared with untreated cells (day 0).

We further analyzed the expression of Notch1 mRNA from all the 237 colorectal cancer tissues based on level of differentiation and UICC stages and that in matched normal tissues together with 46 control colorectal tissues were analyzed too. Interestingly, Notch1 mRNA expression was found to be increased with decreasing levels of differentiation, as well as with increasing UICC stage (Table 2). The increase of Notch1 from well-differentiated to poorly differentiated tumors as well as from UICC stage I to stage IV was of statistical significance ($P<0.001$). We also analyzed whether the expression of Notch1 mRNA was associated with other patient-related factors. However, no significant associations between Notch1 expression and gender, age, family history, or tumor location were observed (Table 3).

Notch1 Expression Increases with Differentiation in Cultured Colorectal Carcinoma Cell Lines

Aberrant Notch1 expression in colon cancer most likely affects the balance between colonic epithelial cell growth and differentiation. Therefore, we set out to investigate the expression of Notch1 during colonic cell differentiation. HT-29 and SW620 colon carcinoma cell line cultures were treated with 2 mM sodium butyrate to induce differentiation. Following the treatment, the differentiation profile was

confirmed by examining the presence of regular brush borders and tight junctions by use of transmission electron microscopy (Fig. 2a). In addition, measurement of AP activity in cell lysates was performed to confirm cell differentiation (Fig. 2b). Notch1 protein and mRNA expression were examined in these cell lines at the indicated time points after butyrate treatment. Incubation with butyrate resulted in a time-dependent decrease of Notch1 expression (Fig. 3a). Quantitative real-time PCR analysis confirmed the results by indicating a seven to ninefold suppression of the mRNA expression (Fig. 3b).

Discussion

Notch signaling is an important factor in epithelial cell differentiation and proliferation. In colon cancer formation, aberrant Wnt signaling increases aggravated cell proliferation, accompanying failure of normal cell differentiation. It has been reported that signaling through Notch1 is important for maintaining an undifferentiated state of colon epithelia cells.[7] Until now, it was still unclear whether a similar increase of Notch-related factors is present in clinical samples.

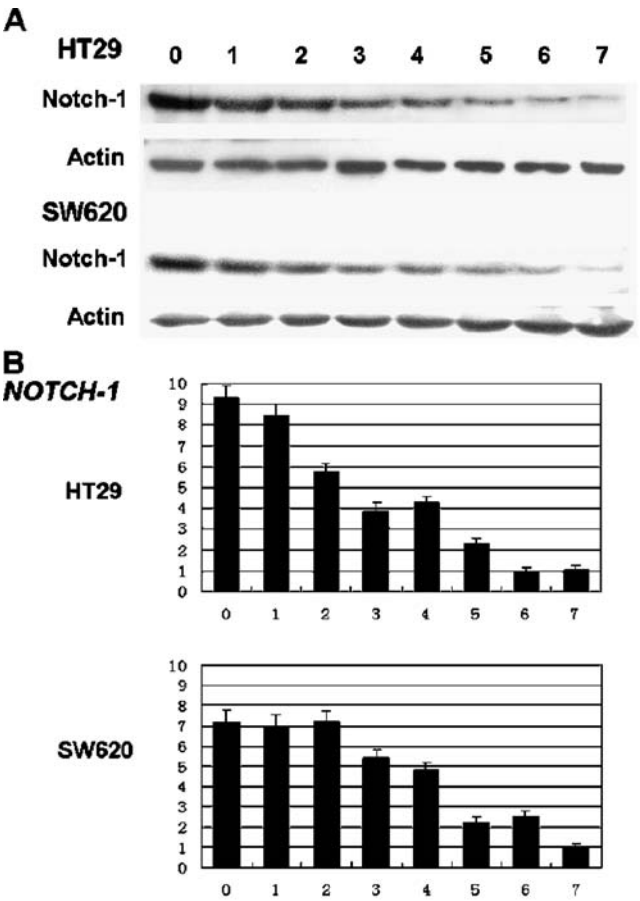

Figure 3 Notch1 protein level by Western blot and Notch1 mRNA level by real-time PCR during induced cell differentiation. The differentiation of HT-29 and SW620 colon cancer cells was induced as described in "Materials and Methods". **a** Notch1 protein level from day 1 to day 7 compared with untreated cells (day 0). β-actin staining was used as a control for equal protein loading. **b** Notch1 mRNA level by real-time PCR from day 1 to day 7 of induced differentiation compared with untreated cells (day 0), normalized to 18s rRNA.

To date, four types of Notch receptors in mammals have been identified (Notch1 to Notch4). Notch1 is a multifunctional transmembrane receptor that was found to play an important role in tumor cell proliferation and differentiation.[6,7] However, the role of Notch1 in cancer remains controversial. Recent studies on Notch1 signaling reported that it may act either as a tumor suppressor or a tumor activator, suggesting that the effects of Notch1 signaling are cell-context-specific.[26] The tumor-promoting role of Notch1 was first recognized in human T cell neoplasia.[27] It was discovered that in many types of cancer, including pancreatic cancer, cervical cancer, renal cell carcinoma, and several lymphomas, Notch1 was overregulated. The higher level of Notch1 prevents normal differentiation leading to malignancy and transformation, highly denoting an oncogenic role of Notch1 in these cancers.[28–30] Downregulation of Notch1, either by siRNA targeting or by treatment with a small molecule compound such as genistein and curcumin in pancreatic cancer cells, led to growth inhibition and apoptosis. It was also reported that activation of Notch1 signaling may promote human melanoma formation.[22] These apparent paradoxical functions in carcinogenesis indicated that the role of Notch1 signaling is cell-context-dependent. However, the precise role and mechanism of Notch1 in colorectal carcinomas remains unclear.

In this study, we investigated the expression patterns of Notch1 mRNA by real-time PCR in 237 cases of human colorectal cancer samples. Our data showed for the first time that Notch1 mRNA expression was increased in colorectal cancers compared with adjacent normal colorectal tissue from the same individual ($P<0.001$). However, the expression of Notch1 may vary across primary tumor. Among the 86 samples of clinical specimens investigated by Western blot, 67 samples of colorectal cancer tissues showed higher expression, while 15 samples showed lower expression and four samples showed no expression. Notch1 mRNA levels were decreased from poorly differentiated to well-differentiated carcinomas and from UICC stage IV to I ($P<0.001$). Similar results were observed at the protein level by Western blot and immunohistochemistry studies. Whether Notch1 is related to invasion and metastasis is still unknown. The staging method in our assay is according to clinical standards, which means that the higher staging value stands for the poor outcome and higher malignancy of the tumor associated to higher Notch1 expression levels. In this regard, Notch1 may have an oncogenic effect in colorectal cancers. Our data at least showed the potential

involvement of Notch1 in invasion and metastasis. These results highly suggest that Notch1 plays an oncogenic role in colon tissue. This was supported by in vitro assays using colon carcinoma cell lines. Notch1 mRNA and protein levels declined gradually during the induced differentiation process.

It is currently widely accepted that Wnt signaling plays a major role in the colon cancer formation.[31] Our results support the findings that Notch1 expression correlated closely with colorectal cancer as well as colon epithelial differentiation and growth and that abnormal upregulation of Notch1 may contribute to colorectal cancer formation.

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ORIGINAL ARTICLE

Functional Outcome After Restorative Proctocolectomy in Pigs: Comparing a Novel Transverse Ileal Pouch to the J-Pouch and Straight Ileoanal Anastomosis

F. H. Schmitz-Winnenthal · M. Kadmon · E. Schwab · L. V. Galindo · K. Bläuer · A. Niethammer · U. Hinz · F. Thomas · B. M. Schmied · R. Nobiling · J. Weitz · M. W. Büchler · K. Z'graggen

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Abstract
Background Restorative proctocolectomy followed by an ileoanal J-pouch procedure is the therapy of choice for patients with familial adenomatous polyposis and ulcerative colitis. After low anterior rectal resection, the authors have reported on a novel, less complex pouch configuration, a transverse coloplasty pouch. The aim of the present work was to apply this new design to the ileal pouch construction, to evaluate feasibility, and to measure functional results in comparison with the J-pouch and the straight ileoanal anastomosis using the pig as an animal model.
Methods Twenty-three pigs underwent restorative proctocolectomy followed by reconstruction with straight ileoanal anastomosis (IAA; $n=5$), J-pouch ($n=7$), and a transverse ileal pouch (TIP; $n=11$). Pigs were followed for 6 days postoperatively. Peristaltic function was assessed by manometry proximal to the pouch, in the reservoir, and at the level of the ileoanal anastomosis. Functional outcome was monitored by semiquantitative assessment of the general condition of the animals, postoperative feeding habits, and stool frequency and consistency. A Fourier analysis was performed in order to compare peristalsis in the ileal reservoirs. The reservoir volume was measured in situ by triple contrast computed tomography scan with 3D reconstruction.
Results Seventeen animals survived for 1 week. There was no difference in the general condition or the feeding habits of the groups. A significant number of pigs with the TIP pouch (7/10) had semisolid or formed stools as opposed to liquid stools after J-pouch (6/6) and IAA (4/5; $p=0.01$). TIP animals had a lower stool frequency (3.2±1.14 per day) on day 6 after the operation than pigs with J-pouch, 5.33±1,03, and IAA, 4.6±1.82 ($p=0.0036$). The in situ volume of the pouches did not differ significantly. The Fourier analysis demonstrated a disruption of peristalsis by the J-pouch and the TIP reconstruction but not after IAA.
Conclusion The function of ileoanal reservoirs after proctocolectomy may result from the disruption of properistaltic waves after pouch formation. The mechanism of peristalsis disruption is independent of the in situ volume of the pouch.

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F. H. Schmitz-Winnenthal and M. Kadmon contributed equally to this work.

F. H. Schmitz-Winnenthal · M. Kadmon · E. Schwab · L. V. Galindo · K. Bläuer · A. Niethammer · U. Hinz · F. Thomas · B. M. Schmied · J. Weitz · M. W. Büchler
Department of Surgery, Ruprecht-Karls University, Heidelberg, Germany

R. Nobiling
Physiologie, Ruprecht-Karls University, Heidelberg, Germany

K. Z'graggen (✉)
Berner Viszeralchirurgie, Klinik Beau-Site Hirslanden, Bern, Switzerland
e-mail: kaspar.zgraggen@hirslanden.ch

Keywords Ulcerative colitis · Familial colon polyposis · Restorative proctocolectomy · Ileoanal pouch

Introduction

Restorative proctocolectomy with an ileal pouch anal anastomosis (IPAA) with or without a diverting ileostomy has become the procedure of choice for patients with ulcerative colitis and familial adenomatous polyposis. Various pouch constructions have been described, the J-pouch proving to be superior with regard to functional results. However, early and long-term results of IPAA may be impaired by pouch-related complications due to the technical procedure. Local septic complications occur in 7–32% of the cases, strictures of the IPAA in three out of 98 cases.[1–7]

A novel technique of a small-volume colon reservoir after low anterior sphincter-preserving rectal resection, the transverse coloplasty pouch, has been described in pigs.[7] In a prospective phase 1 study in human patients with rectal cancer or benign rectal disease, this operative technique was shown to produce early functional results similar to other colonic reservoirs. In randomized controlled studies, the coloplasty pouch is functionally comparable to the standard J-pouch.[8–9]

In the present study, we analyzed whether a transverse ileoplasty (TIP) can give equivalent results to the established J-pouch procedure in an animal model and how the different techniques of reconstruction compare functionally in the early postoperative course.

Methods

Animals

We report the results on 24 female domestic pigs included in this study. The pigs had a mean age of 4 to 8 weeks and a mean weight of 26.4 kg (16 to 40 kg). One pig was sacrificed intraoperatively for technical reasons leading to bowel ischemia and is not included in the study. The animals were fed with standard diet up to the day before surgery and starved on the day of the operation. Before surgery, the animals were randomly assigned to one of the three groups undergoing IAA without reservoir construction and construction of a TIP or a J-pouch (Fig. 1).

Anesthesia

The operative procedure was performed under general anesthesia using ketamine, midazolam, dipidolor, remifentanyl, and propofol or y-hydroxybutyrate. Monitoring consisted of an electrocardiogram, pulse oximetry, capnometry, and temperature detection.

Establishment of The Operative Procedure

Resection Phase of Restorative Proctocolectomy

The surgical technique of total proctocolectomy in the pig was first established in a pilot phase owing to the special anatomy of the pig's colon. After a medial laparotomy, the ascending and descending colon were mobilized from their adhesions up to the colon helix (ansa spiralis coli). After complete mobilization of the colon and sigma including the basis of the colon helix, the mesocolon was dissected after proximal and distal ligation of the bowel. The ileum was resected approximately 2 to 4 cm proximal to the cecum using a Multifire GIA 60 (Covidien, Elancourt, France). Thereafter, a rectal resection with total mesorectal excision (TME) was performed according to the method described by Z'graggen and coworkers.[8] Rectal mucosectomy was performed transanally starting 1 cm above the dentate line up to the level of the TME from the abdomen. Finally, the colon was removed.

Reconstruction Phase

Due to the anatomy of the mesenteric vessel arcades of the small bowel of the pig, a segment of about 30 cm of

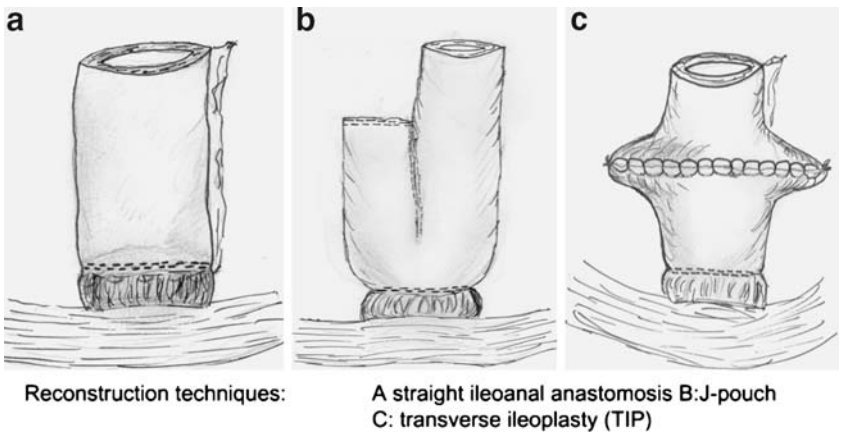

Figure 1 Reconstruction techniques: **a** straight ileoanal anastomosis, **b** J-pouch, **c** transverse ileoplasty.

terminal ileum had to be resected regularly in order to reach the anus for performing the anal anastomosis, regardless of the pouch shape.

J-pouch

The J-pouch was constructed with a limb length of 3 cm by a GIA 50 after defining the part of the ileum which reached as far down in the small pelvis as possible. An ileotomy was performed and the Multifire GIA 50 (Covidien, Elancourt, France) was placed in the two loops. The J-pouch was formed releasing the GIA on the side opposite the mesentery. The distal ileum end was closed by a GIA (Auto Suture, Elancourt, France) and the stapled anastomosis was secured by a second layer of serosa sutures using PDS 5.0.

Transverse Ileum Pouch

The ileum loop reaching furthest into the small pelvis was identified and a purse-string suture (3-0 Prolene) was placed. The anvil of a circular stapler was inserted, and the purse-string was tied. Two centimeters proximal to the rim of the anvil, a transmural 3-cm longitudinal ileum incision was performed (Fig. 2). Lateral traction by stay sutures shaped the pouch, and ileotomy was closed in two layers by transverse running sutures (5–0 PDS; Fig. 3).

Ileoanal Anastomosis

An end-to-end stapled anastomosis was performed with a 25-mm circular stapler (Covidien). The anastomosis was visible from the anus. It was controlled for leaks and transanally placed sutures where added if necessary. If a tension-free ileoanal anastomosis was not possible, the root of the mesentery was further mobilized by a Z-shaped

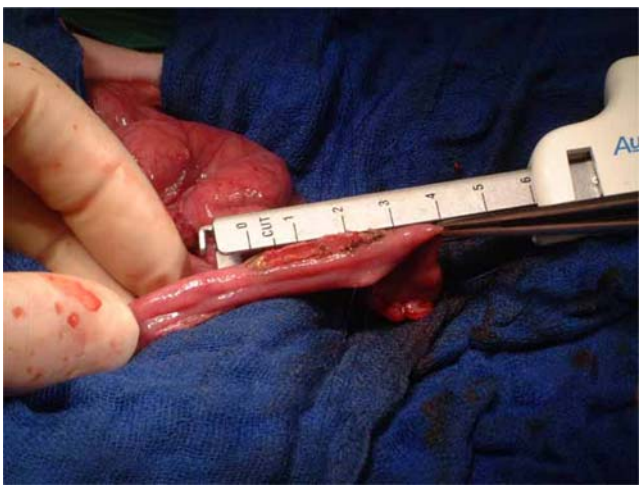

Figure 2 Two centimeters proximal to the rim of the anvil, a transmural 3-cm longitudinal ileum incision is performed.

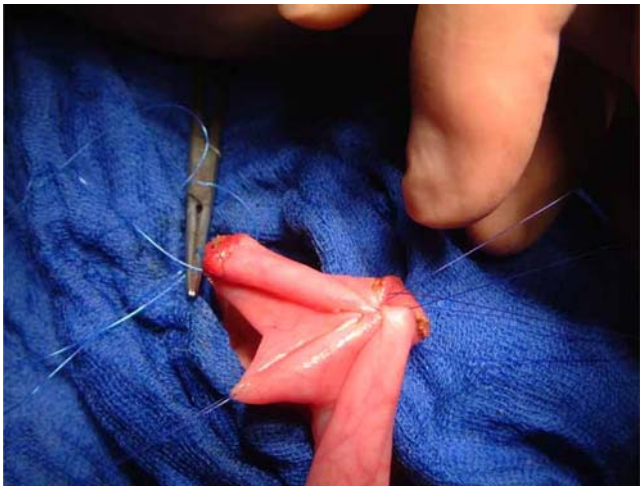

Figure 3 Under lateral traction by stay sutures, the Pouch is shaped and the ileotomy is closed in two layers by transverse running sutures (5-0 PDS).

incision cranial to the root. Following the pouch construction (as described below), the anvil was placed in the ileal reservoir and fixed by a purse-string suture. The ileum was then pulled into the pelvis and the inner shaft was guided through the anus (Fig. 4). After closure of the purse-string suture in the area of the dentate line, the Premium Plus CEEA (25 mm, Covidien, Elancourt, France) was placed and released. The anastomosis was checked by palpation and by controlling the rings for completeness and integrity. If necessary, the stapled anastomosis was secured by hand sutures from the anus.

Postoperative Management

Postoperatively, the pigs were fed starting on day 1 after surgery. For laboratory workup, the animals were anesthetized on day 3. Animals with electrolyte disturbances were infused

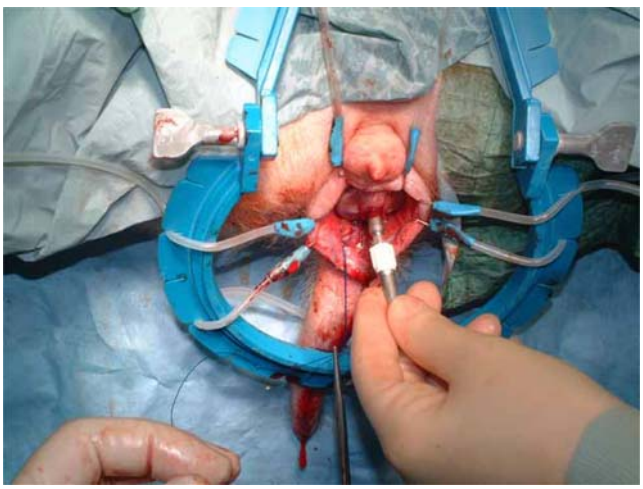

Figure 4 The ileum is closed over the anvil and the inner shaft is guided through the anus.

with 500-ml Ringer lactate and potassium or sodium as needed.

After the experiments, all animals were sacrificed and an autopsy was done to assess the condition of the pouch and the pouch anal anastomosis. Animals of deteriorating physical condition were euthanized for autopsy.

Follow-up and Functional Assessment

During the operative procedure, pressure measurements were performed with a self-devised balloon catheter consisting of three balloons for simultaneous detection of the transmural pressure. The measurement was performed before and after the pouch construction in order to facilitate comparison of pressure curves. The balloons were placed proximal to the pouch, inside the pouch, and at the level of the ileoanal anastomosis (Fig. 5). Thereafter, the pressure transducer was connected to a computer for simultaneous pressure detection over time in all three balloons. Prior to pressure measurement, the balloons were filled up to a defined pressure of 10 mmHg.

The pig model may not be ideal for long-term follow-up. The resection of the colon leads often to severe electrolyte imbalances not observed to such an extent in humans. Because of these differences, we focused on physiologic measurements, pouch volume in situ, and function during the first 6 days postoperatively.

Postoperative observations of the animals and data collection were done in a standardized way. Postoperative complications and deaths were recorded. The animals were observed twice daily and data were recorded about the general condition of the animals and their feeding habits. Stool frequency and consistency was assessed twice daily by large animal caretakers, blinded to the performed procedure. Stool was removed after count to avoid colocalization of excrements and therefore low frequencies.

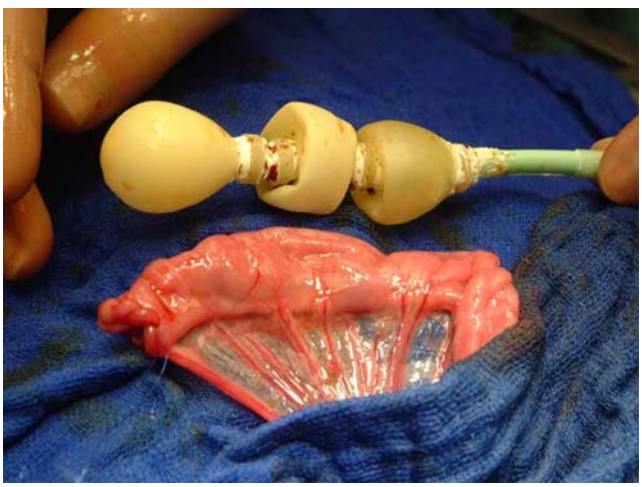

Figure 5 Balloon catheter consisting of three balloons for simultaneous detection of the transmural pressure.

Oscillation Measurements

In order to analyze the functional mechanism of pouch procedures, we measured the intraintestinal pressure at three defined points. The changes in pressure were recorded over 30 min immediately before and after pouch construction. After performing the pouch anal anastomosis, the catheter was placed with two balloons in the pouch and one balloon oral to the pouch. In the TIP, the middle balloon was placed above the transverse ileotomy, the others above and below this area. The purpose was to analyze the probability of an interdependence between pressure time curves at the different measuring locations using the Fourier analysis.[9,10]

The obtained results were compared in order to detect rhythmical changes in (J-pouch and TIP) and below the pouch (TIP).

Statistical Analysis

SAS software (release 9.1, SAS Institute, Inc., Cary, NC, USA) was used for explorative statistical analysis. Quantitative variables were expressed as mean with standard deviation. Comparisons between two and three groups were performed using the Mann–Whitney u test and the Kruskal–Wallis test, respectively. To compare categorical variables between the groups, Fisher's exact test was used. Two-sided p values were always computed and a difference was considered statistically significant at $p \leq 0.05$.

Results

We followed 23 pigs (seven with a J-pouch, five with an IAA and 11 with a TIP) for a period of 6 days. During this time span, we lost one pig with a J-pouch on day 5 and one pig with a TIP on day 4 due to leakage of the pouch anal anastomosis.

General Condition

There were no significant differences regarding their general condition between pigs with a J-pouch, an IAA, or a TIP. On day 1, only two pigs, one with a J-pouch and one with an IAA, showed a reduced general condition. All pigs were in an acceptable general condition on days 2 and 3, while, on day 4, three animals deteriorated (two with a J-pouch and one with a TIP). On day 6, six animals presented with a poor general condition (three with J-pouch, one with an IAA, and two with a TIP; Fig. 6).

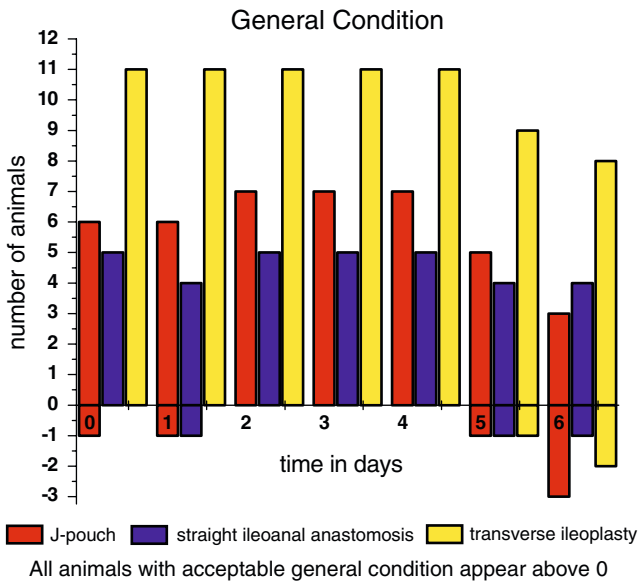

Figure 6 All animals with acceptable condition appear above 0.

Feeding Behavior and Weight

We detected no statistically significant difference in feeding habits between the three groups. In all three groups, single animals presented with a reduced food intake on different days (Fig. 7). There was also no significant difference with regard to change of weight in the postoperative period between the three groups: the mean pig weight was 28.21 kg (±5.82) in the J-pouch group, 27.2 kg (±3.75) in the IAA group, and 25.23 kg (±6.43) in the TIP group.

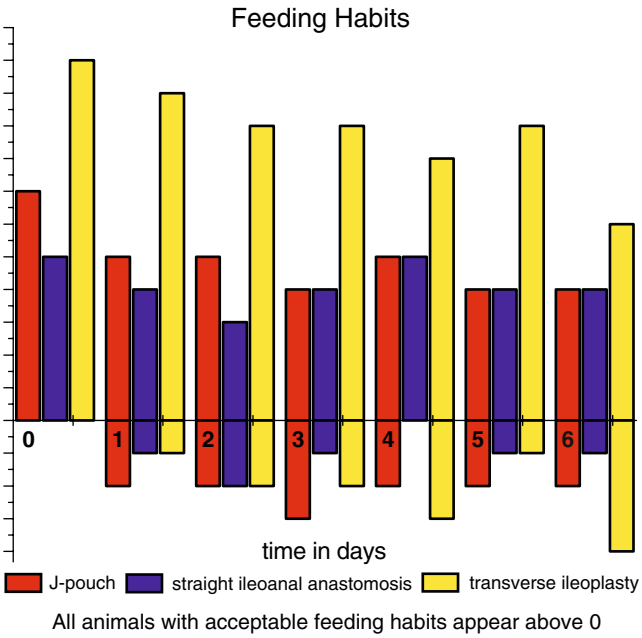

Figure 7 All animals with acceptable feeding habits appear above 0.

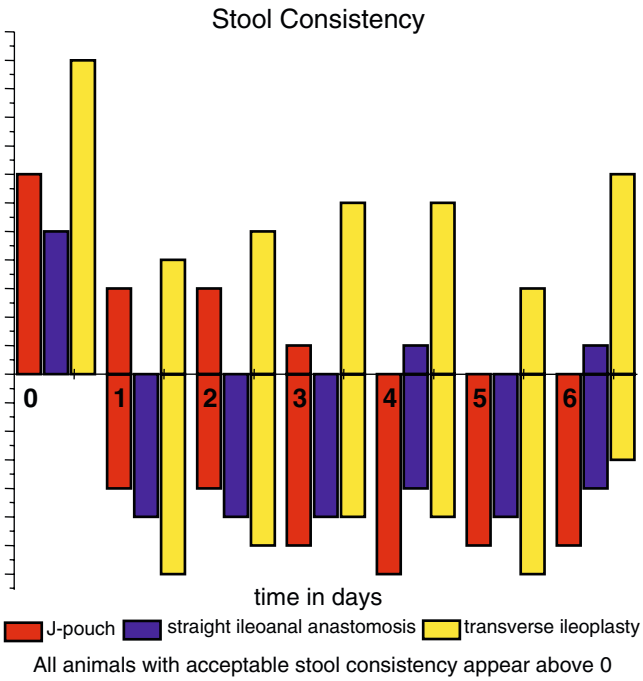

Figure 8 All animals with acceptable stool consistency appear above 0.

Stool Consistency

All pigs with an IAA suffered from severe diarrhea during the entire postoperative period, except for one pig which presented with mushy or formed feces after day 4. On days 4 and 6, the number of animals showing a mushy stool consistency was significantly higher in the TIP group than in the groups following IAA or a J-pouch procedure (p=0.0377 Fisher exact test; p=0.011 Fisher exact test; Fig. 8). During the rest of the observation period, no significant difference

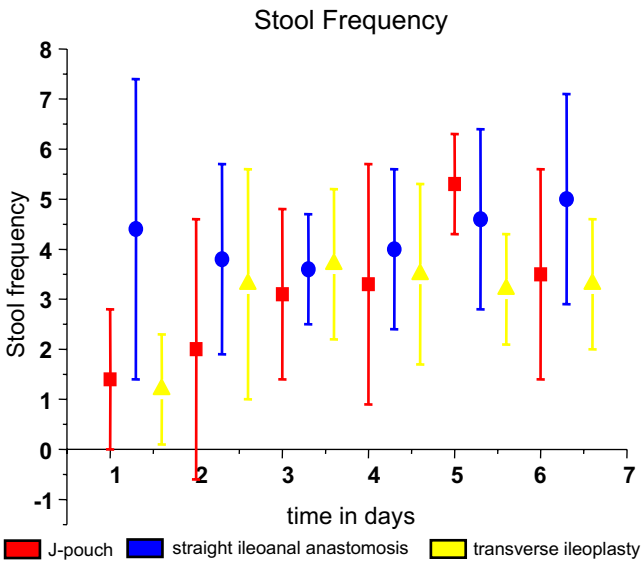

Figure 9 Stool frequency.

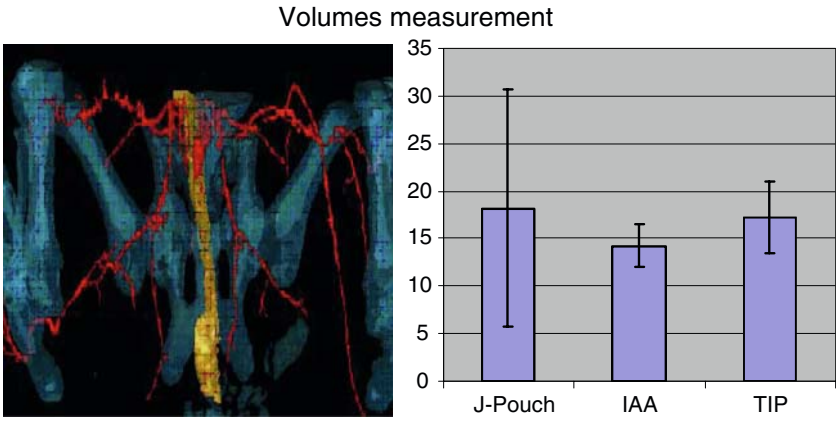

Figure 10 The in situ volume of the neorectal reservoirs was measured by triple contrast computed tomography and 3D reconstruction.

The in-situ volume of the neorectal reservoirs was measured by triple contrast computed tomography and 3D-reconstruction

was detected between the groups with respect to stool consistency.

Stool Frequency

In pigs with an IAA, the stool frequency increased to 4.4 (±2.97) on the first postoperative day. Pigs with a J-pouch, on the other hand, showed a gradual increase of stool frequency from day 1 (1.43±1.4) to day 5 (5.33±1.03). The same phenomenon was observed in the TIP group (stool frequency 1.18±1.08 on day 1 and 3.73±1.49 on day 3). The animals of both groups showed a decrease in stool frequency after the fourth (J-pouch) and the third (TIP) postoperative day, respectively. During the last 2 days of the observation period, stool frequency was significantly lower in pigs with a TIP (3.3±1.25) as compared to animals with a J-pouch (4.2±2.16) and an IAA (4.8±2.21; p=0,0036; Fig. 9).

Pouch Volume

The pouch volume was calculated from computed tomography (CT) scan after contrast rectal filling (cellulose mash) and 3D reconstruction. No difference in volumes within the three groups was detected (Fig. 10). The volume differed from 32.4 to 11.8 ml (p>0.05).

Perioperative Complications

There were no significant differences in postoperative adverse events between the groups. Anastomotic complications occurred in four (17.0%) of 23 pigs and were not significantly influenced by the pouch design [J-pouch 1/7 (14%) pigs; straight ileoanal anastomosis 1/5 (20%) pigs; TIP 2/11 (18%) pigs; p>0.05]. One postoperative death occurred in one (4%) of the 23 pigs after a TIP reconstruction due to electrolyte imbalance.

Single Series Fourier Analysis

The obtained periodograms were compared in order to detect rhythmical changes of the peristalsis related to the pouch design. The probability of a synchronous peristalsis between the three balloon locations (oral to, inside the pouch, and at the level of the ileoanal anastomosis) decreased after J-pouch and TIP reconstruction. The results of the Fourier analysis are demonstrating a dissociation of the peristalsis by the TIP, while this effect was not observed

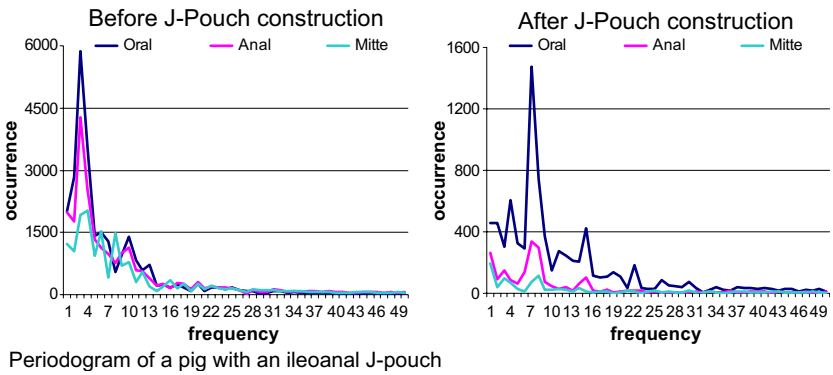

Figure 11 Periodogram of a pig with an ileoanal J-pouch.

Periodogram of a pig with an ileoanal J-pouch

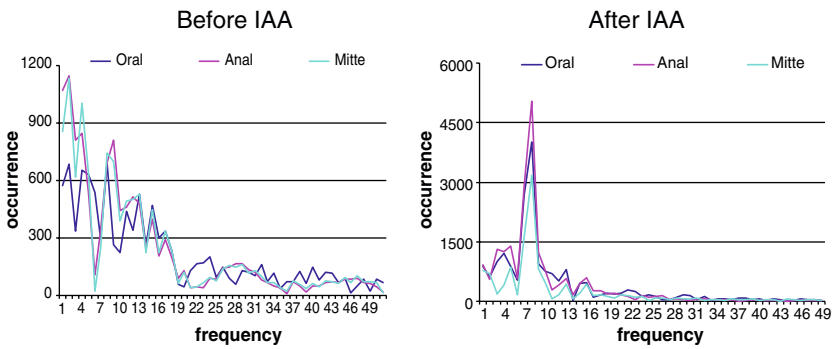

Figure 12 Periodogram of a pig with a straight ileoanal anastomosis.

Periodogram of a pig with a straight ileoanal anastomosis

in pigs with IAA and to a lesser extent in pigs with a J-pouch (Figs. 11, 12, and 13).

Discussion

Restorative proctocolectomy followed by an ileal pouch anal anastomosis is considered the therapy of choice for familial adenomatous polyposis and ulcerative colitis. Various pouch constructions (J-pouch, S-pouch, and W-pouch) have been developed and clinically assessed. The J-pouch has become the design of choice due to the convenience of construction by stapling as opposed to the S- and W-pouches requiring a more time-consuming hand-sewn construction. Recently, a meta-analysis by Lovegrove and coworkers[11] demonstrated an advantage of the W-pouch.

In the present work, early postoperative clinical and functional results after restorative proctocolectomy in pigs are described. Two different pouch designs where compared with the straight IAA. Because of resources, group sizes were not powered for statistical significance. Rather, the present study observes and generates physiologic data and hypotheses to be followed in the future. Postoperative complications did not occur at a higher frequency in animals with a TIP than after a J-pouch construction or an IAA. Anastomotic leakage occurred with a similar frequency after the different pouch constructions.

No significant differences were found in the general postoperative condition of the animals, feeding habits, or volume of the pouch reservoirs. However, pigs with a TIP showed a significantly better result with respect to stool consistency and stool frequencies at the end of the observation period, suggesting that the TIP may be a functional alternative to the J-pouch.

The stool frequency has to be addressed carefully. Pouch function can take several months to stabilize in patients and to reach optimal functionality. This short-term study will miss the long-term effects of applying the different techniques. In our experience, the model is not suited for follow-up on late effects.

The experience with the straight coloanal anastomosis procedure and the results observed with different sizes of the J-pouch indicate that function is related to the capacity of the neorectal reservoir.[12,13] The volume of the ileum pouch seems to play a major role for its function. Furthermore, the total daily volume of ileal effluent seems to influence the pouch function. This has been shown to be directly proportional to the daily stool frequency and is primarily influenced by individual dietary preferences and the absolute volume of ingested food.[14] In addition, severe diarrhea of secretory and malabsorptive origin including pouchitis may also affect clinical function in pouch patients. Certainly, mouth-to-pouch transit time is correlated inversely with stool frequency.[15,16]

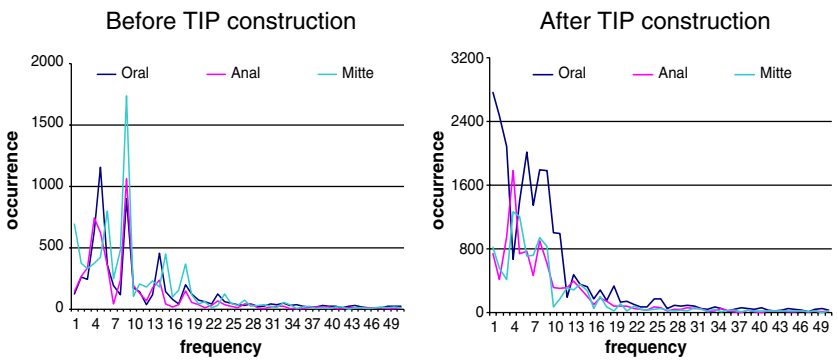

Figure 13 Periodogram of a pig with an ileoanal transverse ileoplasty pouch (*TIP*).

Periodogram of a pig with an ileoanal transverse ileoplasty pouch (TIP)

The results of the present study demonstrate that in the early period after restorative proctocolectomy in pigs stool frequency is not only a function of the reservoir size. The in situ measurement of the neoreservoir size, by 3D CT reconstruction, did not show significant differences in volume. The expandable volume of the neorectal reservoirs seems to depend on the surrounding musculoskeletal pelvis in pigs. Their pelvic cavity is indeed narrow and may not allow the pouch to expand to its maximum volume, which can be measured ex situ.[17] Still, pigs with a TIP presented with a significantly lower stool frequency at the end of the observation period.

Therefore, the disruption or redirection of pouch peristalsis may play a major role in pouch function. High pressure within the pouch reservoir despite low filling volumes may increase the stool frequency. This can be improved by the pouch design. Due to the incision of the muscular wall and neural plexus and the altered direction of peristalsis through the pouch design, the pressure in the pouch is reduced and the physiological peristaltic rhythm is disrupted. This theory is supported by the results of the Fourier analysis. The Fourier analysis was accomplished pre and post pouch formation for one animal of each group. The Fourier analysis allows detection of changes in the rhythm, the frequency of certain peristaltic patterns, and their coupling before and after the pouch formation. After J-pouch and TIP construction, the pressure time curves of the three balloons were dissociated (Fig. 11), which could be interpreted as an interruption of the peristaltic wave by the pouch. This suggests that not only the reservoir volume but also the antiperistalsis effect caused by the pouch construction is essential for the functional outcome of the neorectal reservoir.

The study further demonstrates that a TIP can be used as a functional reservoir after restorative proctocolectomy in the pig model. The operative technique is feasible and reaches similar early functional outcomes as the established J-pouch. However, the observation time of this study is short and projection of long-term functional results is not possible. In humans, the pouch function reaches its final state after 6 months to a year after surgery.[18,19] Therefore, a prolongation of the observation time to 6 months may add the information on medium-term functional outcome of the novel technique.

In conclusion, this animal study points towards the pouch design rather than the volume being the decisive factor in determining the functional results after restorative proctocolectomy. This may be caused by a disruption of the peristaltic wave.

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ORIGINAL ARTICLE

Neoadjuvant Chemoradiation for Rectal Cancer Reduces Lymph Node Harvest in Proctectomy Specimens

Sebastian G. de la Fuente · Roberto J. Manson · Kirk A. Ludwig · Christopher R. Mantyh

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Abstract
Purpose The purpose of this study was to compare the number of lymph nodes retrieved following proctectomy for rectal cancer in patients either receiving no neoadjuvant therapy versus those treated with standard preoperative chemoradiation.
Methods A retrospective review was performed of all consecutive patients that underwent proctectomy for rectal cancer from 1997–2006. Specimens from patients that received neoadjuvant therapy were compared to patients that did not receive preoperative chemoradiation.
Results Of a total of 286 patients, 188 received neoadjuvant therapy and 88 did not. More patients with stage II or higher cancers received neoadjuvant therapy. Overall, fewer neoadjuvant patients underwent an anastomotic procedure than the no neoadjuvant group (17% vs. 7% APR). Significantly fewer total lymph nodes were retrieved in the neoadjuvant therapy patients compared to those who did not receive preoperatively therapy (Neo 14.6±0.6 vs. No-Neo 17.2±1.1, $p<0.029$).
Conclusions Standard neoadjuvant therapy significantly decreases the number of lymph nodes retrieved following proctectomy for patients with rectal cancers. Quality initiatives or performance measures evaluating lymph node harvest following proctectomy should reflect the use of preoperative chemoradiation.

Keywords Rectal neoplasms · Lymph node excision · Neoadjuvant therapy · Proctectomy · Chemotherapy

Introduction

An estimated 153,760 patients were diagnosed with colorectal cancer in 2007 in the United States.[1] In these patients, accurate lymph node evaluation is crucial in the staging of the disease. Lymph node harvest following colectomy or proctectomy for colorectal cancer has been shown to be a key prognostic indicator for survival. Furthermore, data from the National Cancer Data Base (NCDB) have suggested improved survival rates in patients with stage II disease with an increased number of lymph nodes recovered at the time of surgery.[2] In the year 2000, The National Cancer Institute (NCI) sponsored a panel of experts to systematically review the available literature and to draft guidelines to standardize the practice in the surgical management of colorectal cancer patients.[3] The consensus reached from this study was that at least 12 lymph nodes should be harvested at the time of the operation.

With this background, lymph node harvest during colorectal cancer surgery has been established as an important process measure to assure quality of care. However, routinely administered preoperative chemoradiation given to patients with mid and low-lying rectal cancers may negatively affect the quantity of lymph nodes present in proctectomy specimens. The purpose of this study was to compare the total number of lymph nodes resected following surgery for rectal cancer. For analysis purposes, specimens from a group of patients that received standard neoadjuvant therapy (Neo)

Study presented at the 2007 Annual Meeting of the American Society of Colon and Rectal Surgeons in St. Louis, Missouri.

S. G. de la Fuente (✉) · R. J. Manson · C. R. Mantyh
Department of Surgery, Duke University Medical Center,
P.O. Box 3443, Durham, NC 27710, USA
e-mail: delaf002@mc.duke.edu

K. A. Ludwig
Medical College of Wisconsin,
Milwaukee, WI, USA

were compared to specimens of patients that did not undergo preoperative chemoradiation (No-Neo).

Materials and Methods

This study was approved by the Institutional Review Board for the Protection of Human Subjects in Research at Duke University Medical Center. The studied population included all consecutive patients that underwent open proctectomy for colorectal cancer at Duke University Medical Center from 1997 to 2006. Basic demographics such as age, gender, and race as well as tumor location, type of surgery, and postoperative staging were retrospectively recorded. Tumor location refers to the macroscopic distance of the tumor from the anal verge on the initial proctoscopic examination performed by the senior authors of this paper (KAL and CRM). These authors operated on all the patients included in this study.

The surgical technique in these patients has remained standardized throughout the study period. All these patients underwent a total mesorectal excision (TME). Surgery begins by inspecting the abdomen for metastasic or unresectable disease. The left colon is then mobilized along its lateral peritoneal attachments over to the midline. The omentum is taken off of the distal part of the transverse colon and we mobilize the splenic flexure along the inferior edge of the pancreas. The peritoneum is then incised to the right of the inferior mesentery artery (IMA), which is isolated from the aorta and taken down. The left colic artery is taken off of the IMA and then the inferior mesenteric vein is transected beneath the inferior edge of the pancreas. We come out through the mesentery of the sigmoid-descending colon junction and divide the marginal vessels. The distal dissection is taken behind the fascia propria of the mesorectum posteriorly, laterally on the pelvic sidewall, just outside the mesorectum, and anteriorly in front of Denonvillier's fascia exposing both of the seminal vesicles.

Patients were divided in two groups based on the administration or not of preoperative chemoradiation. The Neo group received a 6-week course of 5-FU-based chemotherapy with 5,040 cGy of fractionated radiation. Patients that presented with stage I or II tumors that were deemed not candidates for preoperative chemoradiation were used as controls. Patients with rectal cancer in our institution routinely undergo rectal examination, colonoscopy, transrectal ultrasound, and CT scanning for preoperative staging purposes. Treatment of patients with rectal cancer has been standardized at our institution during the study period. Patients are immediately referred to the oncology service for neoadjuvant therapy as soon as the colorectal surgeons diagnose the patient with a rectal cancer that needs chemoradiation. All patients included in the study completed their treatment with both chemotherapy and radiation therapy.

All electronic records containing pathology reports on proctectomy specimens were reviewed. Pathology reports included tumor size in cm, histology type, pathology stage, total number of regional lymph nodes present in the resected specimen, and number of lymph nodes with cancerous cells. For comparison purposes, subanalysis of the number of lymph nodes retrieved during surgery of patients that underwent abdominal perineal resection (APR) and low anterior resection (LAR) was also performed. A senior pathologist at our institution reviewed all specimens studied.

Statistical Analysis of the Data

Chi-square or Student *t* test was used for comparison of groups as indicated. Data were also analyzed using analysis of variance and bivariate test and generalized linear models using total nodes as outcome and all other variables as predictors (age, gender, race, surgery type, and neoadjuvant therapy). A $p<0.05$ was considered statistically significant. Results are expressed as mean±standard error of the mean (SEM) unless otherwise indicated.

Results

Two hundred eighty-six patients were identified over a 9-year period that underwent proctectomy for colorectal cancer. Of these, 188 patients were treated with standard chemoradiation while 88 patients presenting with stages I or II cancers did not receive neoadjuvant therapy. Basic demographics were similar between groups (Table 1). Patients within the No-Neo group had significantly larger tumors as compared to those treated within the Neo group (No-Neo 3.49 cm±0.2 vs. Neo 2.66 cm±0.1, $p<0.001$). In addition, initial proctoscopic examination revealed that

Table 1 Basic Demographics were Similar Between the Neo and No-Neoadjuvant Group

	Neoadjuvant therapy (n=188)	No neoadjuvant therapy (n=98)	p values
Age	Mean 56 years old	Mean 62 years old	N.S.
Gender	Males 69%	Males 58%	N.S.
Race			
Whites	78%	73%	N.S
Blacks	14%	19%	N.S.
Other	8%	8%	N.S.
Distance on proctoscopy	7.66±0.2 cm	11.05±0.3 cm	0.026
Tumor size	2.66±0.1 cm	3.49±0.2 cm	0.001

N.S. Not significant

Table 2 Postoperative Staging Between Groups

	Neoadjuvant therapy (n=188)	No neoadjuvant therapy (n=98)
Postoperative staging	No cancer 12%	No cancer 18%
	Stage I 20%	Stage I 32%
	Stage IIA 20%	Stage IIA 15%
	Stage IIB 1%	Stage IIB 1%
	Stage IIIA 9%	Stage IIIA 10%
	Stage IIIB 17%	Stage IIIB 14%
	Stage IIIC 9%	Stage IIIC 5%
	Stage IV 12%	Stage IV 5%

those patients within the No-Neo group had higher tumors compared to Neo patients (No-Neo 11.05 cm±0.3 vs. Neo 7.66 cm±0.2, p<0.026).

Table 2 illustrates postoperative staging between studied groups.

Retrospective analysis shows that more patients with postoperative stage II or higher stages received neoadjuvant therapy (Neo 68% vs. No-Neo 50%, p<0.001). Overall, fewer Neo patients underwent an anastomotic procedure than No-Neo patients (Fig. 1); the rate of APR was higher in the Neo group (Neo 17% vs. No-Neo 7% vs. p<0.01). The length of stay in days was undistinguishable between groups (Neo 8.17±0.2 vs. No-Neo 8.6±0.3)

Examination of pathology reports revealed that all patients within the Neo group that had cancerous cells in their specimens had adenocarcinoma. Adenocarcinoma was also present in all positive reports of the No-Neo group except for three patients (one gastrointestinal stromal tumor and two neuroendocrine tumors, carcinoid type). Significantly more lymph nodes were retrieved in the group that did not undergo neoadjuvant chemoradiation compared to those exposed to it (No-Neo 17.2±1.1 vs. Neo14.6±0.6, p<0.029). Patients in the Neo group had also more nodes with metastatic disease compared to the No-Neo group (Neo 1.32±0.2 vs. No-Neo 0.86±0.18, p<0.05). The number of negative lymph nodes was lower in the Neo group (Neo 13.16±0.6 vs. No-Neo 16.2±1.1, p<0.01). When comparing patients between groups that underwent APR, the total number of lymph nodes resected was similar between groups (Neo 13.3±1.1 vs. 18±3.9, p=0.14)(Fig. 2). This similarity was also noted when comparing patients that underwent a LAR (Neo 15.2± 0.8 vs. No-Neo 17±1.2, p=0.11) (Fig. 3).

Further analysis of the data using bivariate analysis and regression models to determine the association between the total number of lymph nodes and other predictors (age,

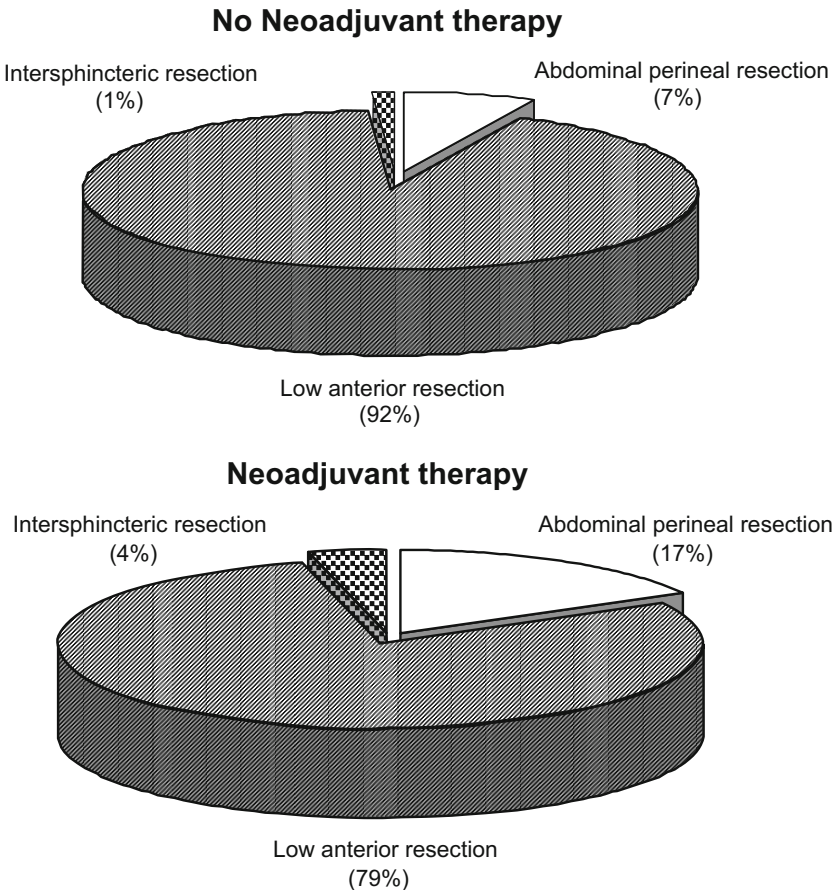

Figure 1 Patients within the Neo group had a statistical significant higher number of APR. No statistical differences were seen in the rate of LAR or intersphincteric resections.

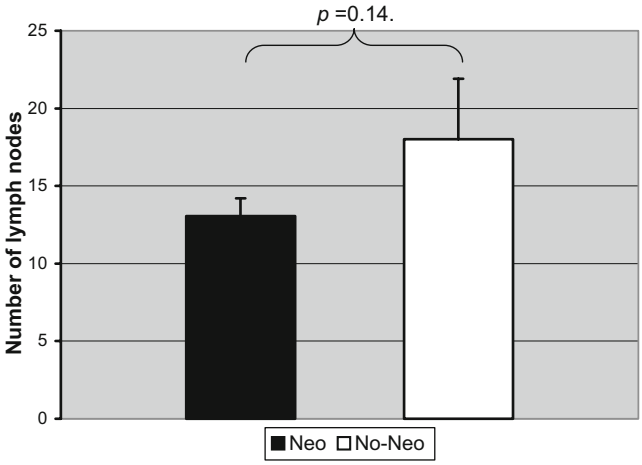

Figure 2 Subanalysis of patients that underwent APR showed no differences between groups in the total, positive or negative number of lymph nodes resected during surgery.

gender, race, surgery type, and neoadjuvant therapy) showed that neoadjuvant therapy was the only factor affecting the total number of lymph nodes (Table 3).

Discussion

Our work shows that patients exposed to preoperative standard chemoradiation for colorectal cancer have a significantly lower number of lymph nodes retrieved during surgery. Even though the average number of lymph nodes in the Neo patients in this study was above the recommended number of 12, the use of chemoradiation should be taken into consideration when standardization of surgical therapy is proposed.

Due to the significant risk of local recurrence, adjuvant chemoradiation is frequently recommended for patients

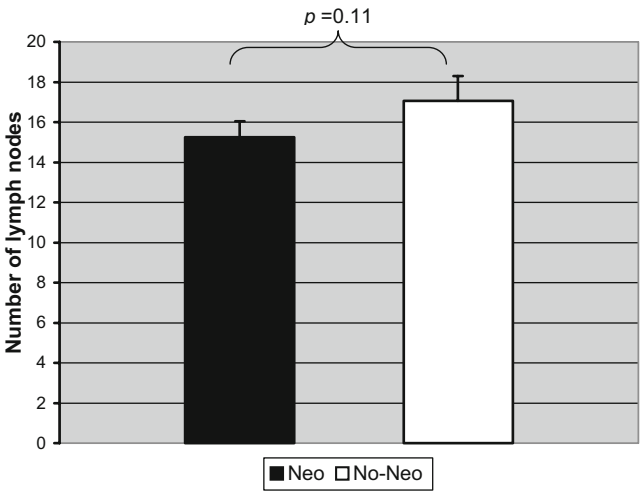

Figure 3 The of total number of lymph nodes was similar between groups in patients requiring LAR.

Table 3 Association Between Total Nodes and Predictors

Predictors variables	*p* value	Confidence interval 95%	
Race	0.76	−19,681	18.7261
Gender	0.15	−4,021	0.7993
Age	0.06	−0.165	0.0127
Surgery type	0.53	−2.520	4.1644
Neoadjuvant therapy	0.02	−4.760	0.2708

with stages II and III to increase the probability of cure.[4] Multiple trials have demonstrated that these patients are at risk of recurrence if surgery alone is performed.[5–7] Both pre- and postadjuvant therapies have shown to improve cancer-specific survivals.[8] Preoperative radiation reduces local recurrence by approximately 50% and improves survival by 15% compared with surgery alone. The absolute reduction in 5-year mortality is approximately 3.5% in these patients (95% CI, 1.1–6%).[7] Patients treated at our institution for advanced stages (stages III and IV) of colorectal cancer routinely undergo a regimen consisting of a 6-week course of 5-FU-based chemotherapy with 5,040 cGy of fractionated radiation, which has shown to be well tolerated with relatively no effects in postoperative morbidity.[9]

Despite the mounting evidence that an adequate lymphadenectomy improves survival in stage II cancers,[10] a small percentage of patients in reality meet the cutoff number of 12 lymph nodes recommended by the NCI. In an extensive population-based study of 116,995 adults in the USA with colorectal adenocarcinoma who underwent surgery and were not treated with neoadjuvant radiation, Baxter and colleagues evaluated the number of lymph nodes, the likelihood of receiving adequate lymph node evaluation (i.e., at least 12 lymph nodes examined), and the influence of tumor and patient factors on lymph node evaluation.[11] The authors found that only 37% of all patients received adequate lymph node evaluation. Before the NCI guidelines were implemented, 32% of patients had more than 12 nodes retrieved compared to 44% in 2001. In another population-based analysis in Europe, Lemmens found that adherence to these clinical guidelines was less than 22% when referred to the total number of lymph resected during surgery.[12]

Some of the factors found to be important determinants affecting lymph node harvesting include cancer location and stage, age, surgeon volume, pathologist training status, and hospital type.[13–16] Baxter found that advanced tumor stage was associated with adequate lymph node evaluation (odds ratio [OR] of receiving adequate lymph node evaluation=2.27, 95% CI=2.18–2.35), older patients were less likely to receive adequate lymph node evaluation than younger patients (greater than or equal to 71 years, OR=0.45, 95% CI=0.44–0.47), and those with left-sided (OR=

0.45, 95% CI=0.44–0.47) or rectal (OR=0.52, 95% CI=0.50–0.54) cancers were less likely to receive adequate lymph node examination than patients with right-sided tumors. Geographic location was also an important predictor of adequate lymph node evaluation in this analysis. In a retrospective review of patients operated on in a tertiary care academic institution, Johnson found that right-sided resections, high surgeon volume, and gross examination of specimens by a staff pathologist were associated with higher nodal harvests, compared to left-sided resections, low surgeon volume, and gross examination of specimens by a pathology resident/technologist, respectively.[17] There was no association with pathologist volume. Only 22% of the reviewed pathology specimens had more than 12 nodes present.

To the best of our knowledge, no study has shown that neither operative technique nor size of the tumor is associated with a higher number of lymph nodes retrieved during surgery. In our study, the type of surgical technique was found not to influence the number of total lymph nodes resected (Figs. 2 and 3). Only neoadjuvant therapy was found to do so. Even though the patients within the APR group that did undergo neoadjuvant therapy had less nodes compared with the No-Neo group, was not statistically different in our analysis. The same case was for patients exposed to LAR. Patients in this group that were subjected to neoadjuvant therapy had fewer nodes resected than those that were not treated preoperatively, but again this difference was not statistically different. None of the other factors such as age, gender, race, or tumor location were found to affect lymph node harvesting.

Even though it seems reasonable to assume that the chances of identifying positive nodes are greater when a higher number of nodes is examined, controversy exist on what is the exact number of lymph nodes that should be recovered.[18–24] Despite these controversies, in an effort led by the American College of Surgeons (ACoS) Commission on Cancer (CoC), in conjunction with the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), the National Quality Forum (NQF) endorsed that at least 12 lymph nodes should be resected in all patients undergoing surgery for colorectal cancer to assure quality of care.[25] Surgeon performance measures used in Medicare pay-for-performance programs must be evidence-based, broadly accepted, clinically relevant, and in the case of lymphadenectomy for colorectal cancer, take into consideration the factors that affect lymph node harvesting such as chemoradiation, age, location of the tumor, and geographic location.

In, conclusion, this retrospective, nonrandomized study reveals a relationship between neoadjuvant therapy and total number of lymph nodes retrieved during surgery. Quality initiatives or performance measures evaluating lymph node harvest following proctectomy should reflect the use of preoperative chemoradiation.

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ORIGINAL ARTICLE

Multidimensional Analysis of the Learning Curve for Laparoscopic Resection in Rectal cancer

In Ja Park · Gyu-Seog Choi · Kyoung Hoon Lim · Byung Mo Kang · Soo Han Jun

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Abstract
Background We attempted to assess the learning curve for laparoscopic resection for rectal cancer.
Method We included 381 patients who underwent laparoscopic resection for rectal cancer between December 2002 and December 2007. The operative experience was divided into four periods according to numbers of operations and significant changes in main surgical results.
Results Operative time decreased significantly after 90 operations. The overall anastomotic leakage rate was 3.7%; 14.6% for the first 50 patients and 5.4% for the following 40 patients. The overall conversion rate was 2.9%, 4–6% during the first and second periods, but decreasing thereafter. The number of harvested lymph nodes and distal resection margin was within an acceptable range during the entire period. For the patients with stage I–III tumors, the local recurrence rate was 4.4% and the overall recurrence rate was 22.9%. The local recurrence rate was 8.9% initially and decreasing to 1.4% after the second period. The cumulative incidence of local recurrence decreased to less than 7% after 120 patients and to less than 5% after 180 cases.
Conclusion The learning curve for laparoscopic surgery for rectal cancer changed over time. Moreover, the learning curve for oncological safety was longer than that for operative safety.

Keywords Laparoscopic · Rectal cancer · Learning curve

Introduction

Laparoscopic surgery for treatment of colon cancer has been accepted as an alternative to open surgery on the evidences from favorable results of prior randomized clinical trials. However it is still technically demanding procedure due to the limited range of motion of instruments, the loss of depth perception and decreased haptic sense.

Laparoscopic colectomy for colon cancer has been shown to be equivalent in success rate to open colectomy, as measured by recurrence and survival outcomes.[1–3] Over the past decade, laparoscopic techniques have also been used for resection of primary rectal cancers. Because of technical difficulties, however, the application of laparoscopy to rectal cancer surgery has been relatively slow. Short-term outcomes have been compared between patients who underwent open and laparoscopic approaches,[4–7] with several studies reporting positive circumferential margins[7] and increased anastomotic leakage[8] in patients who underwent laparoscopic surgery. These results suggested that inadequate laparoscopic procedures could lead to increased complication rates and poor survival.

The laparoscopic approach is not a simple procedure, requiring proper training and experience in advanced minimally invasive surgery. Studies of surgeons' learning curves in laparoscopic colectomy have shown trends

I. J. Park · G.-S. Choi · K. H. Lim · B. M. Kang · S. H. Jun
Department of Surgery, School of Medicine,
Kyungpook National University,
Daegu, Korea

G.-S. Choi (✉)
Department of Surgery, Kyungpook National University Hospital,
50, Samduk-dong 2ga, Jung-gu,
Daegu, Korea
e-mail: kyuschoi@mail.knu.ac.kr

toward declining rates of short-term complications with increasing experience.[9–12] One of the most common methods to measure the complex of difficulties in learning new procedures is figuring a "learning curve". The learning curve is usually defined as the number of cases that a surgeon needs to perform before reaching competency for a given procedure based on comparisons with the outcomes of prior standard procedures.[9,13–15] Although the operating time is the most commonly used parameter to show a learning curve in laparoscopic surgery, some reports have shown a better comprehensive learning curve by adding variables of intra- and post-operative complications, conversion to open surgery, and hospital stay in conjunction with operative time. Previous studies suggest wide range of minimum requirement of 30–70 cases to reach the first stabilization of laparoscopic surgery for colorectal diseases. However some of these studies have inhomogeneous disease entities, unclear indication for laparoscopic approach and many surgeons involved, which may affect the learning curve.

To date, studies for a learning curve in laparoscopic rectal cancer surgery are rare, despite the fact that rectal cancer surgery seems more intriguing in several aspects of considerations such as level of expertise needed, higher rate of anastomotic leak and potential risk of jeopardizing resection margins.

We believe that operative procedures might change over intervals of time, in other words, the initial stabilization of operative outcomes could change at later periods. And as a recent study mentioned that an oncologic parameter of number of harvested lymph node is of meaning, in the learning curve of surgery for malignancy can not be judged by early outcomes of procedure, but should be evaluated with oncologic results to represent the quality of surgery as a whole.

We have therefore assessed changes in operative quality according to the period during which the surgery was performed. We also determined the time interval during which the learning curve achieved a plateau and competency in laparoscopic colorectal surgery was attained.

Material and Methods

We included 381 patients who underwent laparoscopic resection for rectal cancer performed by a single surgeon between December 2002 and December 2007 at the Kyungpook National University Hospital, Daegu, Korea. All patients undergoing laparoscopic surgery gave written informed consent when the methods and risks of the procedure were explained. All laparoscopic surgery was performed by a single surgeon (GS Choi). Data on patient demographics, medical comorbidities, tumor locations, operative details, postoperative outcomes, and follow-up status were collected prospectively and entered into a database for colorectal malignancy. Anastomotic leakage was defined as any evidence of dehiscence of the anastomosis, either clinical or radiological. This definition included all patients with a localized or generalized leak in which reoperation or conservative management including intravenous antibiotics and CT-guided drainage of pelvic fluid collections was required. Postoperative limited contrast radiology was not performed routinely.

Initially, we assessed groups of 10 patients and analyzed changes in surgical procedures and results. Patients were subsequently divided into four time periods: 2002–2003, 2004, 2005, and 2006. During the first period (2002–2003), coloanal anastomosis was performed most frequently. Starting in the second period (2004), we added an intraoperative leak test procedure. This retrospective review of prospectively collected data was approved by the Institutional Review Board.

Operative Techniques

Using a four-port technique in most cases, lymph node dissection was commenced around the origin of the inferior mesenteric artery, which was divided at its origin in most cases. The sigmoid and descending colon was mobilized up to the splenic flexure, which was completely taken down. The rectum was then mobilized as far distally as required by tumor location, while attempting to keep the mesorectal fascia intact. After a routine rectal washout with betadine solution, the rectum was divided using articulating endoscopic linear staplers to achieve a distal margin $\geq$2 cm. In patients requiring a coloanal anastomosis, the rectum was cut using monopolar cautery. The specimen was delivered through a small incision using a camera port below the umbilicus or through the anus. Transection of the proximal bowel was performed extracorporeally. An anastomosis was performed intracorporeally using a standard double-stapling technique. Trans-anal intersphincteric dissection and pull-through hand-sewn coloanal anastomosis were performed in patients with very low-lying cancers, in whom sphincter preservation was desired. A diverting ileostomy or colostomy was selectively constructed according to intraoperative events, such as a positive air-leak test, incomplete doughnuts, or extreme difficulty with the pelvic dissection. For abdominoperineal resection, the sigmoid colon was divided and the total mesorectal excision was completed intracorporeally. The perineal dissection and end colostomy were constructed in the usual manner.

Radiation therapy was not given to patients when complete removal of local disease was achieved. Selected patients with fixed T4 cancer received preoperative chemoradiation. Chemotherapy was the mainstay of adjuvant

therapy; this was offered to patients with stage III disease and to those with stage II disease if other risk factors were present. This decision was made by the surgeon, the patient, and clinical oncologists, working together. The policy of adjuvant therapy did not change during the study period, with 5-fluorouracil-based regimens being employed for the majority of patients.

To represent the operation time and to construct a learning curve, we used the moving average method. Because trends in operation time are obscured by individual variations, averaging of previous values filters this variation and accentuates any trend in data collected. Creating an average of the values that "moves" with the addition of new data results in a "smoothing" of the value action on the variables being analyzed. A moving average order of 30 was used. Differences between groups were analyzed using the unpaired *t* test or one-way ANOVA method with LSD multiple comparison. Confidence intervals (CIs) were set at 95% and the significance level of the *p*-value was set at 0.05.

Results

Overall Patient Characteristics

A total of 381 patients underwent laparoscopic resection for rectal cancer. There were 226 men and 155 women with a mean age of 61±12 years and a mean body mass index of 23.4±3.3 kg/m^2. The lower edge of the tumor was a mean 6.8±3.5 cm from the anal verge. Tumors were located in the extraperitoneum in 201 patients and in the intraperitoneum in 180. According to the clinical TNM classification, there were 42 T1, 72 T2, 237 T3, and 27 T4 tumors; 168 patients had node-positive disease.

TME with sphincter preservation was achieved in 351 patients. The mean height of the anastomosis above the anal verge was 3.8±1.9 cm. There were 280 low stapled colorectal and 71 coloanal anastomoses.

The mean operating time was 227±70 min. The mean number of lymph nodes analyzed per specimen was 19±12. The median distal margin was 2.6±2.1 cm. In five patients, the circumferential resection margin was less than 2 mm. Anastomotic leakage occurred in 13 of the 351 patients (3.7%) who underwent sphincter-saving resections. Protective stoma was constructed in 15 patients (4.3%).

Operative Outcomes by Period

Operation time gradually decreased with increasing experience. The moving average learning curves are shown in Fig. 1. Mean operating time achieved a plateau after 90 patients and fluctuated thereafter, but tended to gradually decrease with increasing experience.

Intraoperative complications, including intraoperative bleeding, inadvertent bowel injury, and unintended vas or vessel injury, were noted in 1.5% (1–3.3%) of patients, with all complications controlled laparoscopically. The conversion rate in 2002–2003 was 5.6%, decreasing to 4.3% in 2004 and then to less than 2% thereafter. The sphincter preservation rate was similar during all four time periods. Protective stoma was not constructed during the initial period; but was rather selectively made after accumulation of experience.

Anastomotic leakage occurred in 10.3% of patients during the initial period (2002–2003). After 2004, the anastomotic leakage rate decreased to around 3% (Table 1), and to below 2% after 2005. When patients were subdivided into sets of 10 cases, the operation time changed significantly after 90 patients, whereas the anastomotic leakage rate was significantly reduced after 30 patients. That is, the anastomotic leakage rate was 20% for the first 30 patients, 3.7% for patients 31 to 60, and 7.1% for patients 61–90 (Fig. 2).

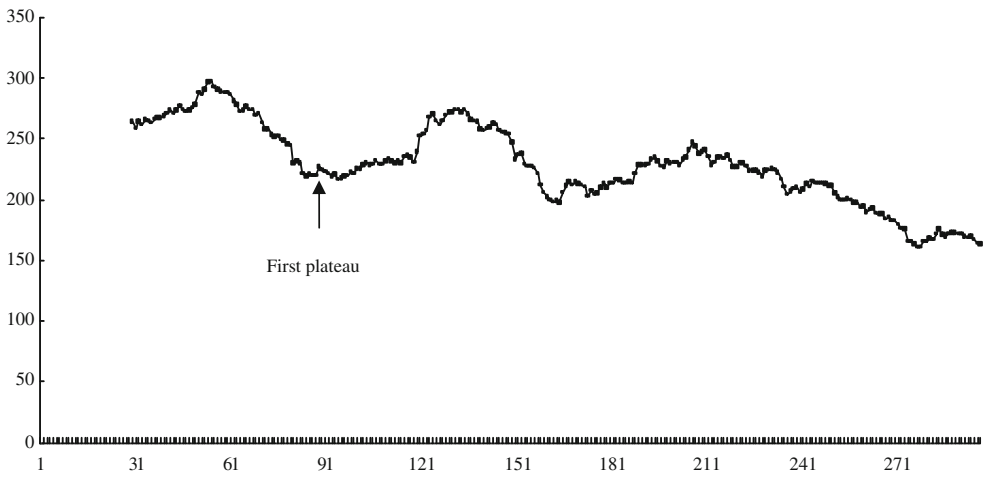

Figure 1 Changes in operating time for laparoscopic resection in rectal cancer (moving average). The first plateau was observed after 90 patients.

Table 1 Operative Outcomes Over Time

Period	1st period (2002.12–2004.2)	2nd period (2004.3–2005.2)	3rd period (2005.3–2006.2)	4th period (2006.3–2007.12)	*p* value
Age, years	60±11	60±13	60±13	62±14	0.873
BMI, kg/m^2	23.2±3.5	23.6±3.1	23.4±3.4	23.5±3.2	0.971
Male: female	48:36	35:27	46:34	70:61	0.996
Operation time, min	282.3±87	254.8±114	221.1±70	196.1±66.7	0.047
Conversion, %	5.6	4.3	1.1	1.5	0.435
Sphincter-saving, %	86.7	92.9	94.4	93.9	0.198
Protective stoma, %	0	6.2	5.9	3.3	0.058
Anastomotic leakage	10.3	3.1	1.7	1.6	0.042

Oncological Outcomes

Oncological outcomes were assessed only for patients who underwent surgery from September 2002 to December 2005, because a minimum 2-year follow-up is required for analysis of such outcomes. The mean follow-up duration was 36 months (range, 2–75 months).

The distribution of rectal cancer stage changed slightly over the course of the study. Even in the initial period, however, 30% of patients had stage III disease. The mean number of retrieved lymph nodes was within acceptable range, beginning in the initial period (2002–2003). By subdividing these patients into groups of 10, we found that fewer than 12 lymph nodes were retrieved from each of the first 20 patients. The mean length of the distal resection margin was acceptable throughout.

The local recurrence of rectal cancer was highest (9.5%) during the initial period (2002–2003), decreasing thereafter. The percentage of patients given radiotherapy was significantly higher after the second period (2004). When patients were subdivided into groups of 10 cases, the local recurrence rate was reduced below 10% after 60 patients, and was maintained thereafter (Fig. 2). During the entire period, only three stage I patients had local recurrences, all during the initial period.

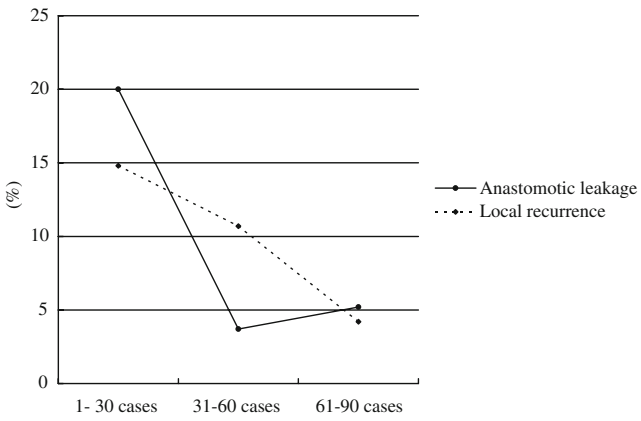

Figure 2 Changes in anastomotic leakage rate and local recurrence over time. Local recurrence decreased later than did anastomotic leakage.

Overall recurrence rate did not change over time, although it was slightly lower in patients who underwent surgery during the third period (2005), when the follow-up duration was shorter. The proportion of patients given chemotherapy was similar during all four periods (Table 2).

Discussion

Several studies have analyzed laparoscopic colon surgery "learning curves".[9,14,15] The point on the learning curve at which a surgeon is considered capable of performing laparoscopic procedures proficiently in clinical practice is referred to as the "breakpoint". Identification of the breakpoint provides valuable information on the number of patients required for adequate training. The learning curve for laparoscopic colorectal surgery has been found to plateau at 30 to 70 patients.[9–11,16,17] Moreover, operating time decreased as the learning curve improved. We hypothesized that the learning curves for laparoscopic rectal cancer surgery would be first manifest in operation time and conversion, representing surgical proficiency; second, in the rate of peri-operative complications, representing surgical safety; and finally, but most importantly, in oncological outcomes, such as rates of local recurrence and adequate lymph node dissection. We found that operating time was associated with the learning curve for the first 90 patients. It decreased continuously according to accumulation of experience, though some fluctuations intervening within period.

Laparoscopic surgery for rectal cancer has been associated with high rates of conversion and anastomotic leakage,[8,18–20] whereas some studies reporting low rates of conversion have reported anastomotic leakage rates >10%.[21,22] We found that the overall conversion rate was

Table 2 Oncologic Outcomes Over Time

Period	1st period (2002.12–2004.2)	2nd period (2004.3–2005.2)	3rd period (2005.3–2006.2)	*p* value
Stage, %				0.789
I	26.7	24.3	24.4	
II	26.7	28.6	33.3	
III	40	35.7	31.1	
Chemotherapy, %	66.7	67.7	67.5	0.998
Postoperative radiotherapy, %	8.3	32.3	27.5	<0.0001
No. of harvested lymph nodes	16.6±9.8	21.4±13.1	20.2±12.9	0.455
Length of distal resection margin, cm	2.2±1.6	2.6±1.3	2.7±1.4	0.887
Local recurrence, %	9.5	1.6	0	0.004
Overall recurrence, %	25	27.4	17.5	0.331

2.9%, 4–6% during the earlier periods (2002–2004) but <2% after the third period (2005). The conversion rates reported here were much lower than those of other studies of laparoscopic surgery for rectal cancer.[21,22] These differences may be related more to a surgeon's threshold for conversion than to a surgeon's expertise. Interestingly, around 50% of conversions happened within the first period, suggesting an association with a learning curve.

Sphincters were preserved in 92.1% of patients and the preservation rate was similar through all four subperiods of the study. A protective stoma was required in 4.3% of the patients during overall period. We constructed a stoma in cases with an incomplete doughnut, positive leak test, and severe bowel edema, regardless of the height of the anastomosis or preoperative chemoradiation. For open resection for rectal cancer during the same period, 5.3% of the patients required a protective stoma. The results of the study showed that the necessity for a protective stoma was not different between laparoscopic and open resection groups according to our protective stoma construction policy.

The overall anastomotic leakage rate observed was lower than seen in other studies[21,23] of laparoscopic surgery for rectal cancer, although one study reported an outstanding results.[4] Moreover, our results were comparable with data from other open resections.[24,25] We found that the rate of anastomotic leakage decreased significantly over time, to 3.1% during the second period (2004), although only 6.2% of these patients underwent ileostomies. The high rate of leaking during the initial period of the study was due to rectal stumps that were too thick or thin to be stapled in a linear or circular fashion. These events were caused by inappropriate trimming in the distal resection area or improper stapling due to technical inexperience. Most of the anastomotic leaks occurred during the early postoperative period; these negative events implied technical mistakes made by the surgeon. We refined the rectal denuding and stapling technique with the routine use of an air leak test. Eventually, we reduced the frequency of the leaks. Additionally, starting in 2004, we performed air leak tests intraoperatively, because early postoperative leakage (by day 3) was more frequent than expected. We performed intraoperative suture repairs or transanal repairs in patients positive for air leak tests, who required additional procedures. After this change, the rate of early leakage was decreased, but it later decreased to 2%. It is uncertain whether the frequency of anastomotic leakage decreased due to the air leak test; however, it was evident that the air leak test helped prevent early leakage. These findings suggest that such improvement can be achieved not only by implementation of a new strategy but also by the accumulation of experience.

Lymph node involvement is a major prognostic factor for colorectal carcinomas,[26] and accurate histological assessment of nodal status is important for disease staging.[27,28] Survival is linked not only to lymph node metastasis, but also to the number of retrieved lymph nodes.[29,30] Thus, it has been suggested that a minimum number of lymph nodes be examined to provide confidence that the cancer stage has been correctly identified.[31] To date, however, few studies evaluating learning curves for surgeons learning laparoscopic colorectal surgery have included data regarding the number of retrieved lymph nodes.[27] From the initial period onward, the retrieved number of lymph nodes was acceptable, based on AJCC guidelines. When subdivided into groups of 10 patients, however, the number of harvested lymph nodes for the first 20 patients did not reach the recommended level. The mean number of nodes harvested during the first and second 10 patients was 12 and 11, respectively.

Although cancer outcomes were initially a concern, particularly following early reports of port-site metastases, randomized studies of colonic and rectal cancer patients have demonstrated that oncological outcomes after laparoscopic resection are similar to those after open surgery.[2,3,6,7] We found that the proportion of patients with advanced

stage tumors was not low, even during the initial period, and did not change over time. The length of the distal resection margin was >2 cm for the entire series, with only five of 381 patients having circumferential resection margins <2 mm. Local recurrence rates decreased with accumulating experience. During the initial period (2002–2003), radiotherapy was infrequently given; this may have affected the local recurrence rates in addition to lack of surgical proficiency. During the same period, the number of retrieved lymph nodes and the length of the distal resection margin were adequate, suggesting that the high local recurrence rate seen during this period may have been because of lack of proficiency in specimen manipulation rather than inadequate dissection. Difficulty in manipulating the specimen may have caused mesorectal tearing and tumor cell spillage during surgery. Other studies of laparoscopic surgery for rectal cancer have reported local recurrence rates of 4–9.7%. In contrast, one study of open resection for rectal cancer with 8.7-years follow-up showed an overall local recurrence rate of 4.5%.[32] We therefore set the acceptable level for local recurrence as less than 7%. When subdivided into groups of 10 patients, the local recurrence rate reached an acceptable level after 60 patients, greater than the number of patients needed to stabilize the rate of anastomotic leakage. Therefore, the learning curve for safe oncologic outcomes was longer than that for surgical safety.

Chemotherapy was administered to similar proportions of patients in all four study periods. The overall recurrence rate was 25–30%, but was slightly lower during the third period (2005), which may have been because of a shorter follow-up duration. The overall recurrence rate did not differ among the four periods.

This study had several limitations. It included a heterogeneous group of patients with varying previous histories of major abdominal surgery and variations in body mass index, both of which may have influenced operative outcomes. By considering these factors for each of the intervals studied, we were able to identify sequential changes in operative outcomes. For oncological outcomes, the role of adjuvant therapy should also be considered. Chemotherapy was given to similar proportions of patients in all periods, whereas radiotherapy was less frequently given in the initial period, which may have affected local recurrence rates. Thus, the true impact of surgical competence on local recurrence could not be analyzed accurately. Because we regard changes in treatment strategy as affecting a learning curve, this difference was included in our learning curve analysis.

In conclusion, the learning curve for laparoscopic resection in rectal cancer showed gradual improvements over time. The breakpoint for the operation time occurred after 90 patients. However, this plateau was not maintained for all surgical experiences, decreasing after accumulation of experience. The breakpoint for technical safety was seen after 30 patients and for oncologic safety after 60. The learning curve for oncological outcomes was longer than that for safe surgical outcomes.

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ORIGINAL ARTICLE

Comparison of the Two Types of Bioresorbable Barriers to Prevent Intra-Abdominal Adhesions in Rats

Eren Ersoy · Vedat Ozturk · Aylin Yazgan · Mehmet Ozdogan · Haldun Gundogdu

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Abstract
Purpose The aim of this study was to evaluate the efficacy of two absorbable film barriers, polylactic acid and sodium hyaluronate–carboxymethyl cellulose, in preventing postoperative intra-abdominal adhesions, inflammation, and fibrosis in an animal model.
Methods Forty Wistar albino rats were grouped as polylactic acid, sodium hyaluronate–carboxymethyl cellulose, and control. All rats underwent laparotomy with subsequent cecal wall abrasion and abdominal wall injury. The two treatment groups received polylactic acid or sodium hyaluronate–carboxymethyl cellulose film barriers, while control group received nothing. On postoperative day 21, three observers graded the intra-abdominal adhesions and resected specimens. Fibrosis, inflammation, and adhesions were graded using quantitative scoring systems.
Results When compared to control group, polylactic acid group showed significantly less inflammation and adhesion ($p<0.005$), while there was no significant difference for fibrosis. Sodium hyaluronate–carboxymethyl cellulose group has showed significantly less adhesions ($p<0.005$), but there were no significant differences among fibrosis and inflammation when compared to control group. There were no significant differences between polylactic acid and sodium hyaluronate–carboxymethyl cellulose groups on adhesion formation, inflammation, or fibrosis.
Conclusions Placement of polylactic acid or sodium hyaluronate–carboxymethyl cellulose film barriers between injured surfaces is associated with a significantly reduced rate of postoperative adhesions. No superiority was detected between two barriers.

Keywords Adhesions · Biocompatible materials · Polylactic acid · Sodium hyaluronate–carboxymethyl cellulose animal model

E. Ersoy (✉) · V. Ozturk · M. Ozdogan · H. Gundogdu
Department of General Surgery,
Ataturk Research and Training Hospital,
Acar Beytepe Evleri, 154/27, Beytepe,
Ankara, Turkey
e-mail: perenersoy@gmail.com

A. Yazgan
Department of Pathology,
Ataturk Research and Training Hospital,
Ankara, Turkey

Introduction

Postoperative intra-abdominal adhesion is a major concern in surgery. They occur after nearly all abdominal operations. Adhesions may result from mechanical peritoneal damage, ischemia, or presence of foreign materials in the abdominal cavity. The results are a wide range of morbidities like bowel obstruction, abdominal pain, and infertility.[1–5] They are the leading cause of small bowel obstruction in the western world, accounting for approximately 75% of all cases.[1]

The role of adhesions is to protect the injured area, provide vascular support, and sequester the inflammatory cells necessary for repair of the defect.[6] It is normal for fibrinous adhesions to form during the acute phase of injury and to resolve as the peritoneum heals. With an imbalance

toward fibrin deposition, fibroblasts and capillaries invade the fibrinous adhesion, collagen is deposited, and maturation into a fibrous adhesion occurs.[6,7]

Intra-abdominal adhesions generally form in the early postoperative period, so most of the studies on this subject are focused on developing products to be used during surgery. As the formation of adhesions is the natural result of wound healing process, the researchers focused on the foreign materials surrounding the viscera. Biodegradable physical barriers have been successfully used to prevent adhesion formation by mechanically limiting tissue apposition during the critical period of mesothelial repair and healing. By minimizing the development of the fibrin matrix between serosal tissue surfaces, such membranes may prevent adhesion formation.[8]

At present, sodium hyaluronate–carboxymethyl cellulose (Seprafilm, Genzyme Corporation, Cambridge, MA, USA) is the most common adhesion prevention product that has been studied in randomized controlled clinical trials. Multiple studies have demonstrated that this barrier membrane significantly and safely decreases the incidence, extent, and severity of adhesion formation.[1,8–11] Another biodegradable material for the same purpose is the polylactic acid membrane barrier (SurgiWrap, Macropore Biosurgery, San Diego, CA, USA). Polylactic acid polymers are currently used as implants in various orthopedic, neurosurgical, and maxillofacial surgical procedures.[3,12–14] The number of studies on the use of polylactic acid in general surgery is limited, but it seems to be a promising agent to prevent intra-abdominal adhesions.

The aim of this experimental study is to assess and compare the effectiveness of sodium hyaluronate–carboxymethyl cellulose with polylactic acid in reducing intra-abdominal adhesion and their influence on fibrosis and inflammation in a rat model. As there are not enough studies on polylactic acid barrier in quality and quantity, we set our hypothesis on this material's efficacy. If it works in an animal model, then further studies about economic and medical limitations on humans would follow.

Materials and Methods

This study was performed in the experimental research laboratories of Ankara Research and Training Hospital with the approval of both Ataturk and Ankara Research and Training Hospitals' ethics committees. The tissue samples were examined for inflammation and fibrosis at the Department of Pathology in Ataturk Research and Training Hospital. All procedures were performed in accordance with the "National Institute of Health, Guide for the Care and Use of Laboratory Animals".

Forty Wistar albino female rats having median weight of 250 mg were used in this study. All rats were housed in the laboratory 2 weeks before the study and kept at 12-h-day and 12-h-night conditions at standard temperature (22°C). They were fed with standard laboratory food and tap water ad libitum.

Operative Technique

Same surgical team performed all operations and evaluations, and rats were randomly allocated to sodium hyaluronate–carboxymethyl cellulose, polylactic acid, and control groups.

All animals were anesthetized with ketamine hydrochloride and xylazine hydrochloride intramuscularly. A midline laparotomy incision of 4 cm was performed, and the cecum was identified. The ventral side of the cecum was abraded with surgical gauze until an area of 2 cm^2 was deserosalized as evidenced by punctuate bleeding without hemostasis. Then, an injury of approximately 2 cm^2 was created with scalpel in the right lateral peritoneal surface of the abdominal wall. The two injured surfaces were approximated with 3/0 Vicryl (Ethicon Endo-Surgery Inc., TR Medical Inc., Istanbul, Turkey) suture in order to induce adhesions as the cecum was too floppy in rats. Rats in the first group received 4 cm^2 polylactic acid film barriers (SurgiWrap™, Macropore Biosurgery) films, which were placed between the deserosalized surfaces, incorporating the suture. Rats in the second group received 4 cm^2 sodium hyaluronate–carboxymethyl cellulose (Seprafilm™ Genzyme Corporation) in the same manner. No additional interventions were performed to the rats belonging to the control group after the approximation of cecum and the abdominal wall. The abdominal layers and skin incisions were closed separately with running 4/0 silk suture (Dogsan, Istanbul, Turkey). All rats were allowed to receive tap water and food ad libitum 24 h later.

Macro- and Microscopic Evaluations

All animals received the same anesthetic protocol on postoperative 21st day, and a U-shaped laparotomy was performed in order to examine all adhesions clearly. Three surgeons blinded to the study (not members of the original surgical team) scored the adhesions separately, and a consensus score was obtained for each rat. Adhesions were classified according to a numerical scoring system (Table 1).[15]

Table 1 Adhesion Scoring System

Score	Adhesion grade
0	No adhesions
1	Thin, filmy adhesions
2	Definite localized adhesions
3	Dense multiple visceral adhesions
4	Dense adhesions extending abdominal wall visceral

After excising the adhesion regions for histopathological examination, all animals were sacrificed by cervical dislocation. Degree of fibrosis and inflammation was evaluated using a semi-quantitative scoring system.[16] Fibrosis and inflammation scoring systems are given in Tables 2 and 3, respectively.

Statistical Analysis

SPSS 11.0 version was used for statistical evaluation. Differences were examined by performing the Kruskal–Wallis one-way analysis of variance. Further comparisons were performed by Mann–Whitney U test. $p<0.05$ was considered as statistically significant. Correlations between the variables were analyzed by Pearson correlation test. Statistical significance limit was set at $p<0.05$.

Results

During the study, three rats died in the early postoperative period because of cecal perforation. As a result, polylactic acid, sodium hyaluronate–carboxymethyl cellulose, and control groups consisted of 13, 12, and 12 rats, respectively.

The adhesion, inflammation, and fibrosis scores for all animals are given in Table 4.

Intra-Abdominal Adhesions

Statistical analysis indicated that adhesion grades were significantly low in polylactic acid and sodium hyaluronate–carboxymethyl cellulose group when compared to the control group ($p<0.05$). On the other hand, there were no significant differences between the polylactic acid and sodium hyaluronate–carboxymethyl cellulose groups.

Fibrosis

Statistical evaluation of fibrosis scores showed no significant difference in polylactic acid and sodium hyaluronate–carboxymethyl cellulose groups when compared to the control group ($p>0.05$). Besides, the difference was not significant between polylactic acid and sodium hyaluronate–carboxymethyl cellulose groups either.

Table 2 Fibrosis Scoring System

Score	Fibrosis grade
0	None
1	Minimal, loose
2	Moderate
3	Florid dense

Table 3 Inflammation Scoring System

Score	Inflammation grade
0	None
1	Giant cells, lymphocytes, plasma cells
2	Giant cells, plasma cells, eosinophils, neutrophils
3	Many inflammatory cells, microabscess

Inflammation

Inflammation scores were significantly different in the polylactic acid group when compared with the control group. On the other hand, there were no significant differences between hyaluronate–carboxymethyl cellulose–control and polylactic acid–hyaluronate–carboxymethyl cellulose groups.

Correlations

Fibrosis and adhesion scores were significantly correlated with inflammation grades with p values 0.001 and 0.004, respectively. On the other hand, fibrosis and adhesion grades were not ($p=0.081$).

Discussion

Adhesion-related complications constitute a major cause of morbidity for the patient, a serious operative challenge for the surgeon and a significant cost for health care providers. The incidence of inadvertent enterotomy during re-operation is high, and this has a significant impact on postoperative morbidity.[17] Assessment of the postoperative incidence, severity, and location of the adhesions has not been frequently described because no noninvasive method is available.[9]

Although several methods have been studied for adhesion prevention, including the use of anti-inflammatory agents, antioxidants, anticoagulants, fibrinolytics, and mechanical barriers, the golden standard has not been stated yet.[18–22] At present, there is no pharmacological means available to prevent the formation of adhesions that has been shown to be clinically effective.[21]

Absorbable polylactic acid film barrier is composed of a co-polymer of two forms of lactic acid and is degraded in the organism by hydrolysis followed by liver metabolism. This material has been widely used in maxillofacial and neurosurgical operations but not in intra-abdominal procedures yet.[13,14] A similar material is shown to be effective in the repair of ventral herniorrhaphy against other meshes by preventing adhesion formation.[16,23] The effect of polylactic acid film on adhesion prevention is not clearly

Table 4 Adhesion, Fibrosis, and Inflammation Scores of Polylactic Acid, Sodium hyaluronate–Carboxymethyl Cellulose, and Control Groups

Rats		1	2	3	4	5	6	7	8	9	10	11	12	13
SW	Adhesion	0	2	0	0	2	0	0	1	0	0	1	0	1
	Fibrosis	1	0	1	2	2	0	1	2	1	2	1	1	1
	Inflammation	2	0	2	1	3	2	2	1	2	2	1	2	2
SF	Adhesion	0	2	0	1	1	2	1	0	0	4	0	3	
	Fibrosis	1	2	0	2	2	3	1	0	2	3	1	1	
	Inflammation	1	2	0	2	2	3	2	0	2	3	2	2	
C	Adhesion	4	3	3	4	2	3	2	4	2	3	2	3	
	Fibrosis	1	3	1	2	3	2	1	0	2	2	2	1	
	Inflammation	3	2	3	2	3	2	3	2	2	3	2	2	

SW Polylactic acid group, *SF* sodium hyaluronate–carboxymethyl cellulose group, *C* control group

understood metabolically, but the material's efficacy is supposed to be achieved by preventing the apposition of two damaged surfaces during the critical time of adhesion formation.

It is previously shown in animal models that the use of sodium hyaluronate–carboxymethyl cellulose at the damaged surfaces of peritoneum significantly reduces the incidence of adhesion formation, and it does not adversely affect postoperative inflammatory response or clinical outcomes even in cases with intra-peritoneal septic complications.[24,25] Sodium hyaluronate–carboxymethyl cellulose adheres well to tissue surfaces. After placement, it rapidly turns into a gel, and the hyalurunate component is cleared from the body within 28 days of implantation. Hyaluronate, which is naturally found in connective tissues, not only has anti-adhesive properties but also accelerates wound healing.[26] However, because of the lack of human studies, those results have to be confirmed with further studies. Especially, the behavioral of polylactic acid in human body is not clear yet. The rate and mechanism of carboxymethyl cellulose clearance is not clear either, but it diminishes in the same period.[3] Although sodium hyaluronate–carboxymethyl cellulose film barrier has been introduced with promising safe and effective clinical outcomes, there are some authors questioning that statement.[27,28] Klingler et al. reported a case that showed an extensive inflammatory response to sodium hyaluronate–carboxymethyl cellulose barrier and had negative clinical outcomes.[28]

In this study, adhesion formation and inflammation grades were significantly different between the polylactic acid and control groups; however, fibrosis grades were not. This result leads us to question the relationship between adhesion formation and fibrosis. Fibrin deposition, the primary step in the formation of post-surgical adhesions, is the result of an imbalance between the fibrin-forming and fibrin-dissolving capacities of a peritoneum.[22] Fibrin is a protein derived from fibrinogen in the presence of thrombin, and fibrosis is the cumulation and invasion of an organ or tissue by the fibrotic material. Therefore, fibrin deposition and fibrosis do not have to be parallel procedures. Given the above study results, polylactic acid barrier's fibrotic potential in the early post-surgical period may be questioned. However, the final adhesion grades were still significantly lower than the untreated group.

When we analyzed the correlations, we found that the correlations between fibrosis–inflammation and inflammation–adhesion were significant, while fibrosis–adhesion was not. This, again, leads us to question the relationship between adhesion and fibrosis.

According to our results, the inflammation, fibrosis, and adhesion scores were not significantly different between polylactic acid and sodium hyaluronate–carboxymethyl cellulose groups. However, inflammation scores were significantly different in polylactic acid group when compared to the control but not in the sodium hyaluronate–carboxymethyl cellulose group. This leads us to think that they both inhibit adhesion formation, but there might be different routes for each.

One paradox about bioresorbable film barriers is that they are foreign materials, and foreign materials are known to induce intra-abdominal adhesions. In a clinical trial, it is shown that in recent adhesions, suture gangliomas occurred in large percentage.[29] Therefore, a film barrier should not only be biocompatible but also be rapidly metabolized. In our study, we saw no remnants of polylactic acid or sodium hyaluronate film in any of the rats.

The results demonstrate that both of the products significantly reduced the incidence of intra-abdominal adhesions, and none had superiority on the other in adhesion, inflammation, and fibrosis aspects.

Many investigators are incorporating adhesion prevention barriers into their routine clinical settings. Owing to multiple demonstrations of barrier efficacy, adhesion prevention adjuvants have received widespread acceptance in appropriate surgical settings. In this aspect, polylactic acid film barrier needs to be studied further in clinical trials.

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ORIGINAL ARTICLE

Superior Mesenteric Artery Syndrome: Diagnosis and Treatment Strategies

N. D. Merrett · R. B. Wilson · P. Cosman · A. V. Biankin

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Abstract
Introduction Superior mesenteric artery (SMA) syndrome is an unusual cause of vomiting and weight loss resulting from the compression of the third part of the duodenum by the SMA. Various medical and psychiatric conditions may result in the initial rapid weight loss which causes narrowing of the aortomesenteric angle. The vomiting and obstructive syndrome is then self-perpetuated regardless of the initiating factors. The young age and nonspecific symptoms often lead to a delay in diagnosis.
Discussion A series of eight cases is presented reviewing the presentation, investigations, surgical treatment by division of duodenum and duodenojejunostomy, and outcomes.
Conclusion SMA syndrome is a well-described entity which must be considered as a cause of vomiting associated with significant weight loss in young adults. Surgical treatment should be allied with psychological assessment to treat any underlying psychosocial abnormality.

Keywords Superior mesenteric artery syndrome · Cast syndrome · Wilkie's syndrome · Duodenal obstruction · Strong's procedure · Laparoscopy · Duodenojejunal bypass

Introduction

Duodenal outlet obstruction may result from variations in the anatomical relationship between the aorta, mesenteric vessels, and duodenum. In young and otherwise healthy patients presenting with abdominal pain, nausea, anorexia, weight loss, and vomiting, the diagnosis of superior mesenteric artery (SMA) syndrome should be considered. SMA syndrome differs from conditions with similar symptoms including familial neuropathic diseases, such as megaduodenum, in that it is a true obstructive condition without any underlying myopathy. In recent years, there have been numerous case reports of this condition, but in spite of this, diagnosis of this condition is frequently delayed resulting in ineffective symptomatic therapies and inappropriate investigations. This manuscript presents a series of eight SMA syndrome patients treated at a single institution being the largest series reported in over 30 years and a literature review to raise awareness of the condition and try and redress this problem of late diagnosis.

N. D. Merrett (✉) · R. B. Wilson · P. Cosman · A. V. Biankin
Department of Upper Gastrointestinal Surgery,
Bankstown Hospital,
Suite 101/68 Eldridge Road,
Bankstown, NSW 2200, Australia
e-mail: neil.merrett@sswahs.nsw.gov.au

Patients and Methods

From January 2002 to March 2007, eight patients presented to the Upper Gastrointestinal Surgical Unit (UGI) of Bankstown and Liverpool Hospitals. The unit is a tertiary referral center with a local drainage population of 1.5 million, and two of the patients were referred from outside the normal drainage area. A prospective collated database was then retrospectively reviewed for demographic data, clinical presentation, diagnostic workup, treatment, and outcomes. Long-term follow-up was obtained from patient review for all patients.

Eight patients (one male/seven females) presented over the period (Table 1). Mean age was 27 years (range 18–32 years).

Table 1 Patient Characteristics

Patient	Age/sex	Comorbidities	Symptoms	Length symptoms (months)	Weight loss (kg)	Preoperative weight (kg)	Aortosuperior mesenteric artery angle (°)	Other radiology	Postoperative weight gain (6 months) (kg)
1	32/M	Drug use	Vomiting reflux	24	25	49	17	Ba meal: dilated to D3	9
2	18/F	Binge ETOH	Vomiting	8	30	45	12	Ba meal: obstructed D3	12
3	22/F	Intentional dieting	Vomiting	12	23	48	14	Ba meal: dilated stomach	15
4	28/F	Nil	Vomiting/reflux	18	22	42	18	CT: dilated to D4	10
5	32/F	Pancreatitis	Vomiting/reflux/ulcer/electrolyte abnormality	24	40	32	9	Ba meal: obstructed D3	10
6	32/F	Obstructive defecation	Vomiting/reflux/ulcer/electrolyte abnormality	18	30	35	15	CT dilated to D3	12
7	31/F	Domestic abuse/ social issues	Vomiting/reflux	28	32	38	12	CT dilated to D3	15
8	23/F	Drug abuse	Vomiting and reflux	18	20	35	17	CT dilated to D3	5

One patient had a previous laparoscopic cholecystectomy but no other patient had a history of abdominal surgery.

Presentation consistently involved persistent chronic vomiting, esophageal reflux, and epigastric pain. In six patients, this was associated with severe reflux, and in two patients, significant electrolyte abnormalities, particularly hypokalemia requiring intravenous replacement. The symptoms were chronic with length of symptoms ranging from between 8 to 28 months (mean 18 months) prior to diagnosis. All patients had sought medical advice during this period and had specialist gastroenterologist review and endoscopies. All had been diagnosed with reflux and treated with proton pump inhibitors. In all cases, there was a prolonged period of medical review, investigation, and treatment from the development of symptoms to final diagnosis.

Confounding the ability to accurately diagnose the condition were comorbidities including psychosocial conditions. These included drug and alcohol abuse, domestic violence, eating disorders as well other illnesses such as pancreatitis.

All patients had extreme weight loss from the development of symptoms ranging from 20 to 40 kg (mean 29 kg) with the weight loss ranging from 33% to 55% of their body weight.

Endoscopies were performed in all patients. Nonspecific findings of reflux esophagitis were described with only one endoscopist suspecting a possible obstruction of the third part of the duodenum (D3).

Suspicion of SMA syndrome occurred late in the disease course and only after the patients had a second opinion with the UGI surgical team. All patients then underwent diagnostic imaging aimed at confirming the suspected diagnosis. All patients had either formal Barium meal (Ba meal) studies (Fig. 1) or computerized axial tomography (CT) scans with oral contrast (Fig. 2) which showed a dilated stomach and duodenum with an obstructive lesion in D3.

In spite of the marked weight loss, all patients had serum albumin and serum proteins within normal limits. Two patients had electrolyte abnormalities as previously noted, and in one of these patients, we elected to give 3 weeks of total parental nutrition (TPN) prior to surgery

CT angiography was performed on all patients to assess the aortosuperior mesenteric artery angle (Figs. 3 and 4). The angle ranged from 9° to 18° with a mean of 12° (normal 38–68°). Scans also indicated reduction of the aortomesenteric distance with compression of the left renal vein seen in one case (Fig. 4).

Hence, all patients met the diagnostic criteria of SMA syndrome with radiological evidence of obstruction of D3, reduced aortosuperior mesenteric artery angle, and reduced aortomesenteric space.

Figure 1 Ba meal showing dilated stomach and cut off at third part of duodenum.

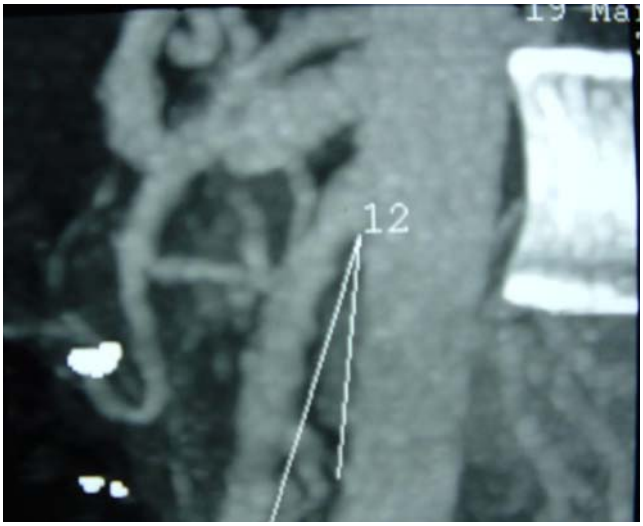

Figure 3 CT angiography showing aortoduodenal angle.

All patients were treated with mobilization and division of the fourth part of the duodenum with the end portion of the jejunum then being placed through the avascular portion of the right mesocolon and a side to side anastomosis between the third part of the duodenum and jejunum. All patients had uneventful postoperative recoveries. All patients had oral nutrition reinstated after 4 days. There were no wound infections or anastomotic breakdowns and the average length of stay was 10 days (range 7–14 days).

All patients had an excellent clinical outcome gaining between 5 and 15 kg at 6 months review. Postoperative imaging with Ba meal studies and endoscopy showed good emptying from the stomach and duodenum and no evidence of further obstruction. The patient's weight gain stabilized at the 6-month period with no patient recording any major weight gain after this period. One patient developed an incisional hernia for which she has since had a laparoscopic repair. Three of the patients continued to require long-term psychological support for their underlying psychological disorders and one patient committed suicide at 9 months. All other patients remain well (follow-up range 5–68 months).

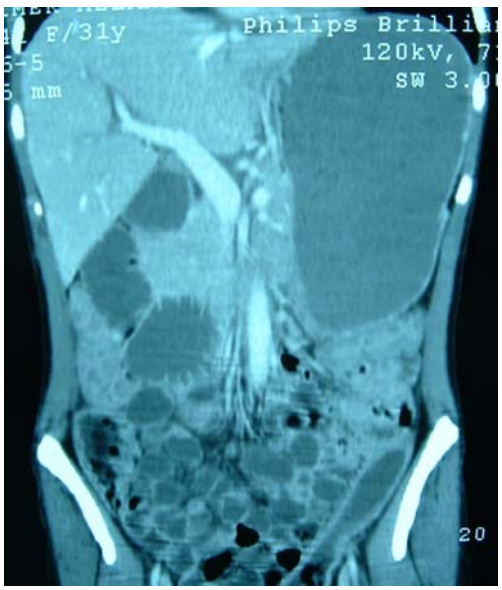

Figure 2 CT scan showing dilated stomach and duodenum with obstruction by SMA.

Discussion

The SMA syndrome was first described in 1842 in an anatomy text by Rokitansky.[1] It involves the entrapment and obstruction of the third part of the duodenum between

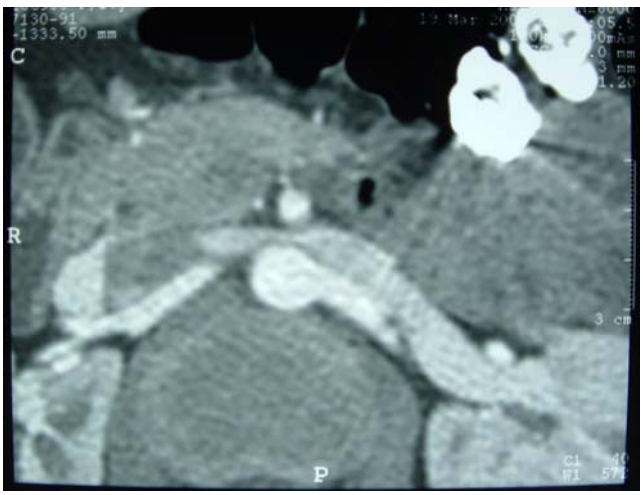

Figure 4 CT showing reduction of aortoduodenal distance with compression of left renal vein.

the SMA and the aorta. Wilkie published the first large series of 75 patients in 1927 and his name is frequently ascribed to this condition.[2] The majority of reports of this condition are limited to case reports and small series.

The main anatomical feature of this syndrome is the narrowing of the angle between the SMA and aorta, normally 38° to 65°.[3] The angles in our series were between 9° and 22°. This narrowing results in the compression of the third part of the duodenum as it crosses between the aorta and the SMA and may even result in compression of the left renal vein. The aortomesenteric distance is reduced from the normal 10–28 to 2–8 mm.[4]

The cause of this narrowing, rather than a congenital abnormality, is postulated to be related to loss of intra-abdominal adipose tissue. In the normal individual, this adipose tissue displaces the SMA anteriorly away from the aorta so avoiding duodenal compression by increasing the space for the duodenum to pass. Loss of this intraabdominal fat narrows the aortosuperior mesenteric artery angle resulting in functional obstruction. In our series, all patients had been asymptomatic until an initial significant weight loss, either related to intentional dieting or illness, followed then by a continuation and worsening of symptoms. A similar etiology is seen in patients who develop this condition following scoliosis and other surgery,[5] the condition developing from alteration of the relationship of the structure which forms the aortosuperior mesenteric artery angle with the relative lengthening of the spine following surgery increasing the tension on the mesentery and narrowing this angle.

This syndrome has been described in patients falling into two broad categories: those who develop it following surgery or compression and the second associated with severe weight loss. This first group includes those following corrective spinal surgery which traditionally has been the most frequently described cause.[6] The second includes wasting conditions such as AIDS,[6] malabsorption, cancer,[7] cerebral palsy, and other conditions associated with cachexia; catabolic conditions such burns;[8] and with eating disorders such as anorexia nervosa and drug abuse.[9,10] Similarly, it has been described following surgery-associated rapid weight loss such as bariatric surgery, esophagectomy, and abdominal trauma.[11,12] Regardless of the etiology, once the condition has become established, it becomes self-perpetuating with a cycle of vomiting leading to further weight loss and thus further vomiting.

Females and young adults (18–35 years) are more likely to be affected by the condition, though it can occur at any age.[2,7,13] This age and sex distribution may simply reflect the predisposing cause of the condition and, in particular, eating disorders.

The classical features include chronic food intolerance with nausea and vomiting, weight loss, and epigastric pain. The pain is classically described as being relieved by lying prone or in the left lateral decubitus position, maneuvers which release tension on the small bowel mesentery, and thus releasing the aortomesenteric angle. The patients are usually significantly underweight at the time of diagnosis. Patients may also complain of severe reflux and endoscopy may demonstrate severe esophagitis and gastritis associated with stasis and chronic obstruction. It usually occurs after an episode of weight loss and can manifest during puberty, possibly due to changes in lean body mass with some reduction in intraabdominal fat. Food intolerance promotes ongoing weight loss, which may further reduce intra-abdominal adipose tissue and exacerbate the problem, resulting in a vicious cycle and deterioration in clinical condition.[5,9,13,14]

Diagnosis is frequently delayed, relies on a high index of suspicion, and is often made by a process of exclusion. The differential diagnosis includes megaduodenum[15] and other more common conditions including chronic pancreatitis and peptic ulcer disease. A thorough investigative process, including gastroscopy with biopsy and contrast imaging, is recommended before arriving at the diagnosis of SMA syndrome.

The diagnosis of duodenal obstruction is made with contrast X-ray studies, either barium studies or CT imaging with oral contrast, and may demonstrate dilatation of the proximal duodenum with failure of contrast passage beyond the third part of the duodenum with a cut off.[16]

The vascular abnormalities are well-delineated by fine slice CT imaging with vascular reconstruction[17] measuring the aortosuperior mesenteric artery angle. An aortosuperior mesenteric artery angle of less than 25° is regarded as being the most sensitive measure of diagnosis, particularly if the condition is associated with diminution of the aortomesenteric distance to less than 8 mm.[4,18]

Treatment is either conservative or surgical. Fluid resuscitation, bowel rest, TPN, and enteric feeding with a nasojejunal tube inserted past the obstruction have all been advocated. In children and in adults with a short history, this may have a reasonable prospect of success, but in the chronic adult patient, conservative treatment is often a prolonged in-hospital therapy with a low success rate.[8,13] Thus, in the fit adult patient, after correction of electrolyte abnormalities and a period of refeeding, surgery is indicated.

To date, there is no data to guide as to an optimal period or indications for preoperative or postoperative nutritional support either enterically or by TPN. Although it is well-recognized that significant preoperative weight loss is associated with an increased risk of postoperative complications, all of our patients had uneventful recoveries as indicated by the length of stay and only one long-term incisional hernia. Only one patient had TPN given preoperatively and this would indicate that, in the presence

of normal serum proteins, surgery may be safely performed with the use of preoperative nutritional supplementation being used on a individualized basis. Similarly, the possibility of refeeding syndrome in the postoperative period may need to be considered, but again it did not occur in our series. We can only surmise that the prolonged period of vomiting and weight loss in the community setting differs from other situations of malnutrition in that good quality food, nutritional supplements, and vitamin supplements were frequently used by the patients and their treating clinicians in the months leading up to their eventual diagnosis, limiting the nutritional and healing effects.

Surgical options that have been proposed include mobilization of the duodenum by division of the ligament of Trietz, allowing the duodenum to fall away from the aorta (Strong's procedure);[19] duodenojejunostomy[20] with or without division of the fourth part of the duodenum; and gastrojejeunostomy.[21]. Strong's procedure has the advantage of maintaining bowel integrity, but has a failure rate of 25% presumably due to short branches of the inferior pancreaticoduodenal artery not permitting the duodenum to fall inferiorly. Gastrojejunostomy allows gastric decompression but the failure to relieve the duodenal obstruction may result in recurrent symptoms requiring a second procedure. As well, the unrelieved obstruction may result in blind loop syndromes and continuing peptic ulceration.[1,21] Duodenojejunostomy as a treatment for this condition was first described by Stavely in 1908 and is generally accepted as having superior results to both Strong's procedure and gastroenterostomy, but duodenojejunostomy without division of the fourth part of the duodenum also carries a risk of blind loop syndrome. Based on this, our preference has been for mobilization and division of the fourth part of duodenum with the proximal jejunum being passed through the right part of the mesocolon and a side to side duodenojejunostomy performed. This overcomes the obstructive problem and returns the bowel continuity to as normal as possible with minimal possibility of blind limb syndromes.

Advances in laparoscopic surgery have seen laparoscopic Strong procedures and laparoscopic duodenojejunostomy reported by several centers.[22,23] These techniques are certainly feasible and we performed a mobilization of the ligament of Trietz, division of the fourth part of the duodenum, and duodenojejunostomy laparoscopically on our last case.

Some authors have promoted resection of the abnormal duodenum in patients thought to have SMA syndrome rather than bypassing the duodenal third part, as they have postulated that it is a variant of a motility disorder rather than a true mechanical obstruction.[24] Certainly, patients with motility disorders such as intestinal neuronal dysplasia type B and familial megaduodenum may have similar clinical features of SMA syndrome. However, there is little evidence, either pathological or physiological, to support this postulate. In our cases, four patients had mechanical obstruction demonstrated on contrast studies and all six had critical narrowing of the aortomesenteric angle on CT scan. Two cases also had mechanical obstruction demonstrated at endoscopy. All patients had bypass surgery rather than resection with good improvement of their symptoms. All cases had postoperative contrast studies showing normal emptying of the duodenum which further supports a mechanical rather than motility disorder in patients with SMA syndrome. Furthermore, all of our patients have had good long-term results with weight gain and resolution of all of their preoperative symptoms of reflux and vomiting which would not be expected in a primary motility disorder. It remains somewhat puzzling, however, that our patients have not gained more weight over the period of follow-up.

There is undoubtedly a significant psychological overlay in many patients who present with this condition. Its association with anorexia nervosa, drug abuse, and other eating disorders is well-documented[9,10] and the psychological well-being of the patient must be considered in those diagnosed with this condition. It is, therefore, essential that the surgical correction is allied on a multidisciplinary basis with psychologists and dieticians to ensure optimal long-term outcomes once the physical obstruction has been relieved.

Conclusion

The SMA syndrome should be considered as a potential diagnosis in young adults who present with a history of persistent postprandial vomiting and weight loss. In its modern incarnation, it may be more commonly related to psychological and eating disorders rather than the traditional paradigm of weight loss from surgical and other physical causes and its relief includes treating of the psyche as well as surgical intervention.

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ORIGINAL ARTICLE

Laparoscopic Treatment of Celiac Artery Compression Syndrome: Case Series and Review of Current Treatment Modalities

Khashayar Vaziri · Eric S. Hungness · Erik G. Pearson · Nathaniel J. Soper

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Abstract
Introduction Compression of the celiac artery by the diaphragmatic crura, the median arcuate ligament, or the fibrous periaortic ganglionic tissue results in a rare constellation of symptoms known as celiac artery compression syndrome (CACS).
Anatomy First described in 1963 by Harjola in a patient with symptoms of mesenteric ischemia, it remains an elusive diagnosis.
Clinical Presentation Patients commonly present with a wide variety of symptoms resulting in multiple diagnostic tests.
Diagnosis A firm diagnosis is difficult to establish, and treatment is equally challenging. These challenges are illustrated by the following case series, and evidence supporting current treatment modalities is reviewed.
Treatment We describe a laparoscopic approach to decompression of the celiac artery facilitated by intraoperative ultrasound.

Keywords Celiac artery · Mesenteric ultrasound · Laparoscopy · Decompression

Introduction

Compression of the celiac artery by the diaphragmatic crura, the median arcuate ligament or fibrous periaortic ganglionic tissue results in a rare constellation of symptoms known as celiac artery compression syndrome (CACS). First described in 1963, the symptoms mimic those of mesenteric ischemia. CACS has always been and remains an elusive and controversial diagnosis. External compression of the celiac artery leads to a wide variety of symptoms frequently resulting in an exhaustive diagnostic work-up. These tests can demonstrate compression of the celiac artery, but the pathophysiology behind the syndrome remains largely unknown. A firm diagnosis is difficult to establish in the majority of patients, and treatment is equally as challenging. A variety of surgical treatment modalities have been described including endovascular and laparoscopic procedures. These challenges are illustrated by the following case series, and evidence supporting current treatment modalities is reviewed.

K. Vaziri · E. S. Hungness (✉) · N. J. Soper
Department of Surgery,
Northwestern University Feinberg School of Medicine,
201 E. Huron Street, Galter 10-105,
Chicago, IL 60611, USA
e-mail: ehungnes@nmh.org

K. Vaziri
e-mail: kvaziri7@yahoo.com

E. G. Pearson
Royal College of Surgeons Ireland,
123 St. Stephens Green,
Dublin, Ireland

N. J. Soper
Department of Surgery,
Northwestern University Feinberg School of Medicine,
251 E. Huron Street, Galter 3-150,
Chicago, IL 60611, USA

Case Series

Three patients recently presented to our clinic with symptoms of post-prandial epigastric pain, nausea, and abdominal bloating. All were female with ages of 37, 47, and 49 years. Two of the three patients experienced mild weight loss. These women had vague abdominal complaints which led to extensive investigations by primary care physicians and gastroenterologists. After multiple

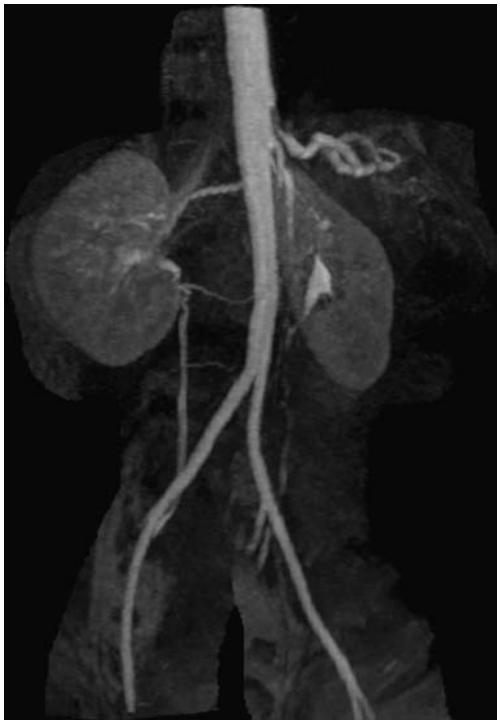

Figure 1 Narrowing at the origin of the celiac artery.

unremarkable laboratory, radiological, and endoscopic tests, a computerized tomography (CT) and magnetic resonance imaging (MRI) scan were obtained. All three of these patients had some suggestion of celiac artery compression on contrast CT or MRI. Figure 1 demonstrates narrowing at the origin of the celiac artery. With other pathology reasonably excluded, and vague symptoms centered on post-prandial epigastric pain, a mesenteric duplex ultrasound was obtained to assess the flow in the celiac artery. Results of mesenteric duplex ultrasounds on all three patients were highly suspicious for CACS. Color flow Doppler was used to identify the aorta, the celiac artery, and its branches (Fig. 2). The velocities in the celiac artery were elevated suggesting a narrowing of the lumen just distal to its origin from the aorta. Velocities in our three patients were 128, 132, and 377 cm/s during normal respiration, with a significant increase seen on deep expiration to velocities of 349, 301, and 459 cm/s, respectively. Figure 3 illustrates the increase in compression and resultant higher velocity (349 cm/s) in the celiac artery of one of the patients during deep expiration. These findings in addition to their clinical presentation and the absence of other pathology were confirmatory in the diagnosis of CACS. Catheter angiography was not felt to be necessary in any of these patients.

All of the patients underwent laparoscopic decompression of the celiac artery. This was performed with the use of general anesthetic and four to five laparoscopic ports. The patients were placed in a modified split-leg position, and an 11-mm trocar was inserted approximately 12 cm inferior to the xiphoid process and just left of the midline. This served as the camera port, and three to four additional 5-mm ports were placed across the upper abdomen in order to retract the left lateral segment of the liver and aid in dissection. Various methods were used to identify the celiac artery. One method follows the left gastric artery from the lesser curve of the stomach to its origin at the celiac artery. Alternatively, the aorta is exposed at the base of the right crus and followed caudally along its anterior surface until the celiac artery is identified. We have found the use of intraoperative ultrasound valuable in the identification of the celiac artery and its branches. Furthermore, during the dissection, intraoperative ultrasound is used to assess the adequacy of decompression by measuring velocities before and after releasing the constricting fibers. Once the celiac artery is identified, a meticulous dissection of all surrounding fibrous and periganglionic tissue is performed. These structures can be vascular in origin, and hemostasis is imperative to assure adequate visualization and to avoid inadvertent arterial injury. We prefer to perform this dissection with a combination of electrocautery and ultrasonic shears. The dissection is carried onto the aorta, and a wide decompression is performed. Once the dissection of the celiac artery is completed, the vessel should be easily visualized from its aortic origin to all of its branches. Once again, intraoperative ultrasound is used to confirm adequate decompression.

Postoperatively, all of our patients are kept overnight on the surgical ward. They are given a clear liquid diet on the night of surgery and advanced to a regular diet as tolerated. Patients are discharged home on the first postoperative day (Table 1). All of our patients were seen within 4 weeks of surgery for standard follow-up. Two of the three patients had complete resolution of their preoperative symptoms.

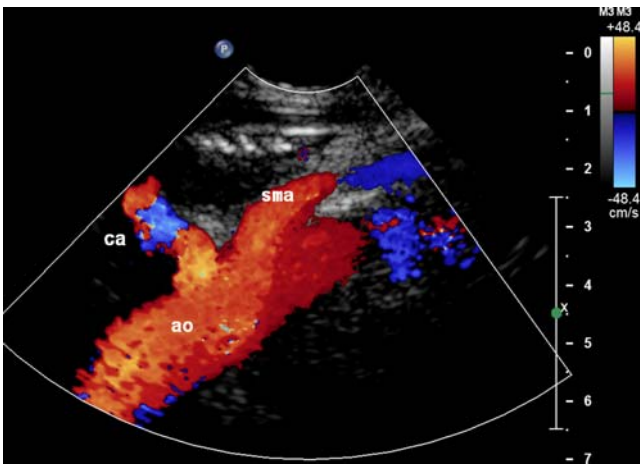

Figure 2 Color flow Doppler was used to identify the aorta, the celiac artery, and its branches.

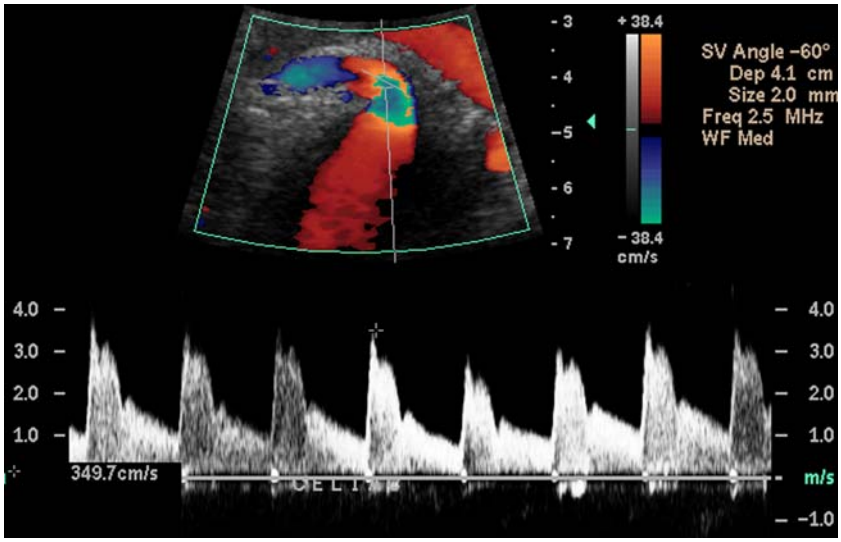

Figure 3 Increase in compression and resultant higher velocity (349 cm/s) in the celiac artery of one of the patients during deep expiration.

The third patient experienced marked improvement in her preoperative postprandial epigastric pain; however, she did continue to have vague episodes of bilateral lower abdominal discomfort. Despite her residual symptoms, she has seen an improvement in her diet and has been successfully gaining weight. Postoperative mesenteric duplex ultrasound was performed within 6 months of the operative procedure. The velocities of the celiac artery were all in the normal range (102, 172, and 217 cm/s), and there was no evidence of variation on deep expiration (Fig. 4). No morbidities or mortalities occurred.

Anatomy

Celiac artery compression syndrome was first identified by Harjola in 1963 and further described by Dunbar in 1965.[1,2] The anatomical description predated the clinical syndrome as the anatomist Lipshutz demonstrated extrinsic compression of the celiac artery by surrounding structures, such as the median arcuate ligament, as early as 1917.[3]

The posterior abdominal wall, aorta, and celiac artery have an important anatomical relationship with reference to CACS. The celiac trunk most commonly emerges from the aorta between the level of the 11th thoracic vertebrae and the first lumbar vertebrae, though some report a greater variability.[4] In close relation is the median arcuate ligament (MAL), a fibrous arch that unites the diaphragmatic crura crossing superior to the celiac axis at the level of the first lumbar vertebrae. The right crus arises from the surface of L1–L4 vertebral bodies while the left crus arises from the L1 and L2 bodies, and both are additionally anchored by the intervertebral disks and the anterior longitudinal ligament.[5] In an anatomic study, the position of the MAL was described superior to the celiac axis and was found to impinge on the celiac artery.[6] Similarly, Park et al. evaluated 29 patients with celiac artery stenosis and found that 55% of cases were caused by compression from the MAL, lending CACS the alternate description as MAL syndrome (MALS).[7] In addition, others have described impingement of the celiac artery by anomalous fibrous bands, periaortic ganglionic tissue of the celiac plexus, sympathetic neural fibers, and enlarged lymphatics.[8,9]

Table 1 Patient Information

	Patient 1	Patient 2	Patient 3
Age (year)	37	47	49
Preoperative velocity (cm/s)	349	301	459
Postoperative velocity (cm/s)	102	172	217
Ports used	4	4	5
OR time (min)	122	114	217
Estimated blood loss (cc)	<50	<50	<50
Hospital stay (day)	1	1	1

Etiology and Incidence

The incidence of CACS has been reported as high as 27% and as low as 7.3%.[7,10] It is more common in women than men by a 4:1 ratio and seen between the ages of 30 and 50.[10] The etiology of CACS remains controversial. Bron and Redman studied 717 patients and suggested that atherosclerosis was the most common etiological agent while Park et al. concluded that extrinsic compression by the MAL was responsible for 55% of the cases they encountered.[7] Additionally, several other causes have been described including pancreaticoduodenectomy, duodenal carcinoma, aortic dissection, papillary neoplasms of the pancreas, nutcracker syndrome, abdominal trauma, sarcoid-

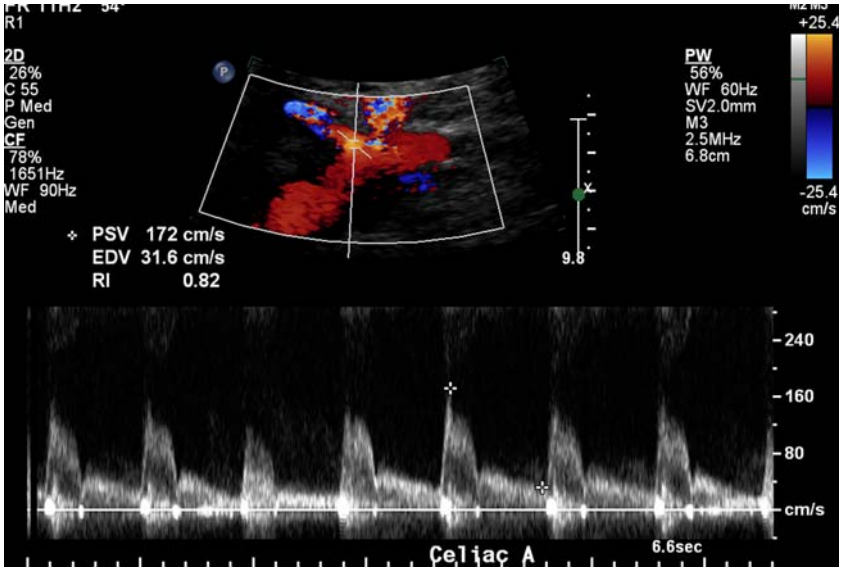

Figure 4 The velocities of the celiac artery were all in the normal range (102, 172, and 217 cm/s), and there was no evidence of variation on deep expiration.

osis, aneurysms of small pancreatic arteries, and celiac plexus neuromas.[4,11,12] A consensus on the pathophysiological basis of this clinical syndrome has not been found; however, several theories have been proposed including: mesenteric ischemia from celiac axis compression, vascular steal from collateral vessels, and neurogenic stimulation from celiac ganglion compression.[13]

Clinical Presentation

This syndrome is characterized by chronic postprandial abdominal pain, weight loss, nausea, vomiting, diarrhea, and the presence of an epigastric bruit. Some patients experience pain that radiates to the left flank or back. The abdominal pain can be intensified by deep expiration and alleviated by inspiration. Deep inspiration moves the celiac artery and the aorta caudally and the MAL ventrally, thus, minimizing compression and decreasing the intensity of the epigastric bruit.[8] Movement and exercise can influence the abdominal pain. Some have found certain movements to alleviate pain,[14] while others have observed exacerbation of pain with exercise.[13]

Diagnosis

Invasive and noninvasive diagnostic studies can illustrate CACS. Traditionally, catheter angiography was used to show the characteristic superior indentation of the celiac axis approximately 5 mm from its origin at the abdominal aorta.[5] Modern technology has allowed noninvasive approaches to the diagnosis through duplex ultrasonography, three-dimensional CT angiography, multidetector CT, and magnetic resonance angiography.[5,15–18] Lateral aortographies at inspiration and expiration can also aid in the diagnosis. Although CT or MRI may suggest the diagnosis, some recommend that mesenteric duplex scanning, to assess the celiac, superior mesenteric artery, and inferior mesenteric artery, should be performed in all suspected patients.[14] Intra-arterial velocities can be measured and a marked increase in flow velocity during deep expiration is known as the "Doppler Duplex Sign of CACS."[19] Similarly, obtaining MRI images at inspiration and expiration can increase the specificity of this diagnostic test.[20]

In addition to imaging studies, recent investigations into the use of gastric tonometry to aid in the diagnosis and follow-up of patients have shown promising results. Gastric tonometry is a monitoring modality which measures variations in gastric mucosal pCO_2 which correlates to the perfusion of the gastric mucosa. Faries et al. demonstrated significant relief of gastric mucosal ischemia in a patient with CACS after surgical decompression.[21] Others have found a postoperative normalization of gastric exercise tonometry in symptom-free patients and suggest that gastric exercise tonometry is 86% accurate in diagnosis of gastric ischemia.[22]

Despite the multitude of tests available to the clinician, the diagnosis remains elusive. Recently, a clinical algorithm was proposed to aid in the evaluation of CACS.[10] This algorithm calls for a full gastrointestinal workup with esophagogastroduodenography, upper GI imaging, right upper quadrant ultrasound, CT, and MRI in patients with a history suggestive of mesenteric ischemia. If any abnormalities are identified, causes other than CACS should be pursued. However, if these tests are normal, a gastric emptying time should be determined. If abnormally prolonged, a duplex ultrasound of the celiac and superior

mesenteric arteries should be obtained to confirm the diagnosis of CACS. If this diagnostic study is normal, then a biplanar mesenteric aortogram may be helpful.

Treatment

Similar to the diagnosis of CACS, the optimal treatment is challenging and also an area of controversy. The two main treatment modalities described in the literature are endovascular and surgical therapy. Descriptions of endovascular therapy with balloon dilatation and stent deployment arise from similar interventions for chronic mesenteric ischemia. Multiple studies have shown that endovascular treatment of celiac and mesenteric occlusive disease is a safe and successful treatment for chronic mesenteric ischemia.[23,24] However, these studies also show a lower success rate for single vessel intervention and a higher mechanical and long-term failure rate for endovascular treatment of extrinsic celiac artery compression. This suggests that endovascular modalities are not successful in the treatment of CACS. This is highlighted in a report by Delis et al. where open celiac artery decompression and reconstruction was required after failed endovascular therapy for CACS.[25] Theories underlying failure of endovascular treatment stem from the proposed anatomical relationships of CACS. Unlike atherosclerotic disease, celiac artery compression is an extrinsic phenomenon and a dynamic process as evidenced by the change in arterial flow during the respiratory cycle. This dynamic compression is theorized to lead to repetitive arterial trauma and resultant mechanical stent failure. Endovascular therapy of CACS has not been successful and is unlikely to be the best therapeutic modality.

A variety of surgical treatments have been reported, all of which involve either decompression of the constricting fibers or reconstruction with bypass of the compressed arterial segment. Decompression can be further accompanied by dilatation of the celiac artery. The largest study to date by Reilly et al. described 51 patients who underwent either open surgical decompression, decompression with dilatation, or decompression with reconstruction. Eighty-six percent of these patients were followed for a mean postoperative period of 9 years. They found sustained symptom relief in 53% with decompression alone, 79% with decompression and dilatation, and 73% with decompression and reconstruction.[26] Furthermore, patients that presented with classic symptoms of postprandial pain and weight loss enjoyed the best postoperative results, reinforcing the importance of proper patient selection.

Recently, celiac artery decompression has been performed through a laparoscopic approach with and without the aid of intraoperative ultrasound.[9,13,27] This procedure has also been described with the use of a robotic surgical system.[28] Laparoscopic celiac artery decompression is the approach used in our patients, and we find intraoperative ultrasound essential in the clarification of vascular anatomy and in ensuring the adequacy of arterial decompression. Laparoscopic visualization and exposure is superior to open surgery, avoids the morbidity of an upper-midline laparotomy, shortens hospital stay, and eliminates the confounding factor of incisional pain on postoperative follow-up. We report the largest laparoscopic series with successful outcomes in a short-term follow-up period. No long-term follow-up studies of laparoscopic approach are available.

In our experience, laparoscopic celiac artery decompression with intraoperative ultrasound is a safe and effective treatment of CACS. This procedure, as with any other laparoscopic procedure, has some relative contraindications. Patients should be evaluated on an individual basis for the laparoscopic approach. Relative contraindications to laparoscopic celiac artery decompression include all contraindications to laparoscopic surgery, such as: inability to tolerate pneumoperitoneum, multiple previous abdominal operations, previous aortic or mesenteric reconstruction or bypass, and patients who have undergone surgical decompression of the celiac artery. In light of the difficulty in diagnosis and the multitude of vague abdominal complaints encountered, these patients are best served with the least invasive approach. Long-term follow-up studies need to be performed to assess the durability of this technique, but one can extrapolate from the open surgical experience as the arterial release is performed in a similar manner. Celiac artery dilatation or a more invasive arterial reconstruction can be reserved for refractory cases. Although laparoscopic celiac artery decompression can be performed with good short-term results, proper patient selection remains the key to successful long term postoperative outcomes.

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ORIGINAL ARTICLE

Biliogastric Diversion for the Management of High-Output Duodenal Fistula: Report of Two Cases and Literature Review

Konstantinos Milias · Nikolaos Deligiannidis · Theodossis S. Papavramidis · Konstantinos Ioannidis · Nikolaos Xiros · Spiros Papavramidis

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Abstract High-output duodenal fistula occurs as a result of a duodenal wall defect caused by gastroduodenal surgery, endoscopic sphincterotomy, duodenal injury, and tumors with high morbidity and mortality rate. A new technique for its management is reported along with literature review. This procedure consists of transection of the duodenum 2 cm distally to the pylorus, transection of the common bile duct, and end duodenostomy with or without suturing the duodenal wall defect. The continuity of the alimentary tract is reinstated by an end-to-end duodenojejunostomy, end-to-side choledochojejunostomy, and end-to-side Roux-en-Y jejunojejunostomy, obtaining biliogastric diversion from the duodenum and closure of the fistula. This technique was performed in two patients with excellent results.

Keywords Duodenal fistula · Duodenal perforation · Duodenal wall defect · Endoscopic sphincterotomy · Biliogastric diversion · Pylorus preservation

Introduction

High-output duodenal fistulas constitute a surgical challenge with high morbidity and mortality rate. They occur as a result of a duodenal wall defect caused by gastroduodenal surgery, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic sphincterotomy, duodenal injury, and tumor and usually need surgery for definitive solution.[1] Multiple procedures with controversial results have been introduced to manage them.[2] Our suggested operation is a novel approach on this problem and was performed in two cases. We report the new technique along with review of the literature concerning the various modes of surgical treatment.

K. Milias (✉)
2nd Surgical Department, 424 General Military Hospital, Thessaloniki, Greece
e-mail: konmil@med.auth.gr

N. Deligiannidis · T. S. Papavramidis · S. Papavramidis
3rd Surgical Department, AHEPA University Hospital, Thessaloniki, Greece

K. Ioannidis
1st Surgical Department, 424 General Military Hospital, Thessaloniki, Greece

N. Xiros
Surgical Department, 404 General Military Hospital, Larisa, Greece

Materials and Methods

A male patient was admitted to our department with acute abdomen and sepsis after perforation on the posterior wall of the duodenum's second part due to an erosion by clips from a previous nephrectomy for hypernephroma 10 years ago. Initially, he was treated with suturing of the duodenal wall in two layers. During the primary postoperative period, a high-output duodenal fistula was developed (>1,000 mL/day) and an unsuccessful nonsurgical management with antibiotics, total parenteral nutrition (TPN), and octreotide was applied, following the existing protocol of our department concerning the upper gastrointestinal high-output fistulas.[3]

A female patient was admitted after perforation of the duodenal wall, sepsis, and severe pancreatitis caused by an ERCP and endoscopic sphincterotomy for choledocholithiasis. She was treated with surgical lavage and draining of the periampullary area. A high-output duodenal fistula was

developed later (>1,000 mL/day) and the aforementioned conservative protocol was also applied unsuccessfully.

Both patients underwent transection of the duodenum 2 cm distally to the pylorus, transection of the common bile duct, and end duodenostomy. The continuity of the alimentary tract was reinstated by an end-to-end duodenojejunostomy, end-to-side choledochojejunostomy, and end-to-side Roux-en-Y jejunojejunostomy (Fig. 1a,b). In the first patient, the duodenal wall defect was sutured, while in the second one, suturing was impossible due to pancreatitis. A drain was placed in both patients adjacent to the duodenojejunostomy and the choledochojejunostomy.

Results

Sepsis was easily controlled after surgery. Both patients had an untroubled recovery and were discharged after 28 and 45 days, respectively. The high-output duodenal fistula in the female patient transformed immediately into a low-output pancreatic one (30–100 mL/day), which progressively closed within 8 months after surgery. Today, the overall functionality of the gastrointestinal tract in both cases is excellent.

Discussion

Duodenal fistula is a rather rare entity in the total amount of enterocutaneous fistulas, representing 3% to 14% of them. In medical literature, we found only a few cases of high-output duodenal fistulas between 1974 and 2006 (Table 1). The vast majority of them are reported to arise after surgery for duodenal ulcer.[1,4] Other recorded causes include injuries, especially after endoscopic operations (e.g., sphincterotomy or polypectomy); tumors originating from neighboring organs; cholecystoduodenal fistulas; and rarely, Crohn's disease.[1,5–8] Lateral fistulas are the most difficult to manage, while those deriving from duodenal stumps usually tend more frequently to close spontaneously. Morbidity and mortality rates are high; morbidity ranges from 38% to 75%[9] and is associated with the high output from the fistula (over 500 cc/day), poor nutritional status of the patient, and development of peritonitis and sepsis. Mortality is also significant (from 7% to 40%) with an average of 32% according to Sitges-Serra et al.,[10] while lots of different outcomes related to the initial cause of the fistula and the therapeutic method provided are reported in the literature.[1,2] Factors associated with mortality are advanced age (greater than 65 years), uncontrolled sepsis and multiple organ failure, high-output fistula, malnutrition, defect >1 cm, transferrin <200 mg/dL, delay in diagnosis (more than 3 days), and multiple reoperations to treat the fistula or complications.[11]

Once a duodenal fistula is recognized, the patient has to be stabilized. This includes fluid resuscitation, correction of electrolytes, control of infection and sepsis, optimal nutrition, and treatment of acidosis.[3,12] Then, the investigation of the fistula is performed. Fistulography is the most common method including traditional fluoroscopic and roentgenographic tests or modern computed tomography imaging.[13] In late years, fistuloscopy is an alternative and requires special training and tools.[14]

Conservative treatment with TPN alone or with somatostatin and its analogs (e.g., octreotide), although associated with serious complications,[15] is advocated by many authors and achieves spontaneous fistula closure in 70% to 92% of cases.[3,16–19] TPN improves the nutritional status of patients

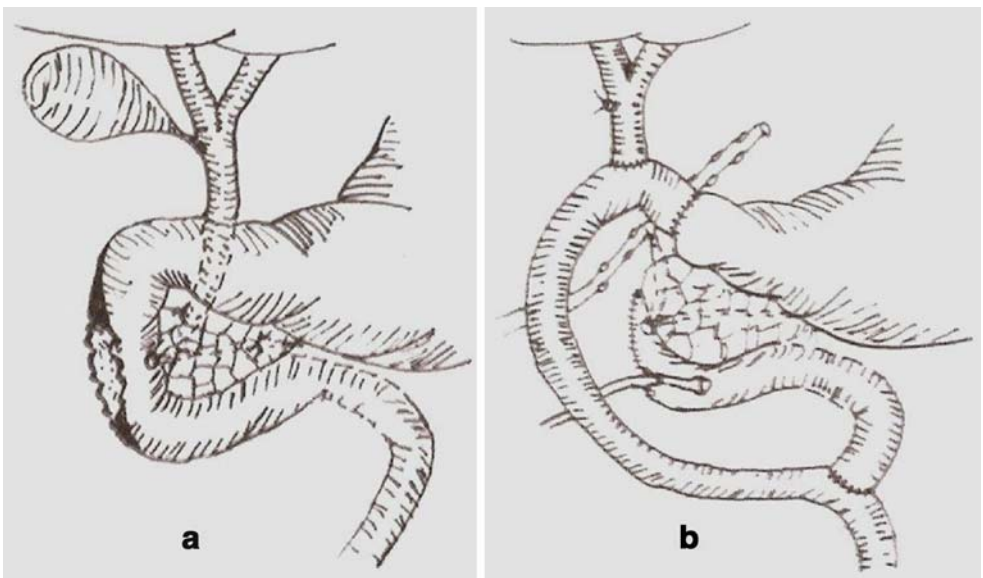

Figure 1 **a** Schematic representation of the duodenal wall defect causing the formation of a high-output duodenal fistula. **b** The technique for the management of the duodenal fistula.

Table 1 High-Output Duodenal Fistula: Literature Review

Author	Year	Main topic of series and number of patients	Number and percentage of patients with external duodenal fistula	Conservative treatment and spontaneous closure, *n* (%)	Mortality (%)	Surgical treatment
Corley et al.[34]	1975	Duodenal injuries (98)	10 (10.2)	None	40	Primary repair or repair+ decompression or triple ostomies
Reber et al.[19]	1978	Enterocutaneous fistula (186)	19 (10.2)	7 (36.8)	10.5	Primary repair or bypass
Ivatury et al.[31]	1985	Penetrating duodenal injuries (100)	4 (4)	None	25	Primary repair+enterostomies
Feliciano et al.[41]	1987	Management of combined pancreatoduodenal injuries (129)	7 (5.4)	5 (71.4)	0	Pyloric exclusion+ gastrojejunostomy
Schein et al.[3]	1991	Postoperative external alimentary tract fistulas (117)	15 (12.8)	2 (13.3)	13	Exteriorization+enterostomies
Yamamoto et al.[7]	1998	Gastroduodenal fistulas in Crohn's disease (14)	2 (14)	None	–	Debridement and closure of the defect or excision and duodenojejunostomy
Hollington et al.[48]	2004	An 11-year experience of enterocutaneous fistula (277)	53 (19.1) (including jejunal fistulas)	Not stated	10.8	Resection or defunctionalization
Talving et al.[50]	2006	Civilian duodenal gunshot wounds (75)	2 (3)	–	–	Percutaneous drainage+ feeding jejunostomy or omental patch+feeding jejunostomy
Draus et al.[18]	2006	Enterocutaneous fistula: are treatments improving? (106)	5 (5.3)	1 (20)	7	Not stated

and, thus, the prognosis of gastrointestinal fistula is substantially improved in late years.[20,21] Somatostatin and its analogs potentially accelerate the fistula closure process due to the decrease of the alimentary tract's fluid production. Recent randomized controlled trials comparing the use of octreotide with nonoperative therapy failed to demonstrate decrease in fistula output, time to closure, or closure rate.[22,23] Few reports of obliteration of duodenal fistula using various sealant factors are found in the literature.[3,24–27] Verna et al. report management of duodenal fistula using only nasojejunal feeding tube as early as possible.[28] Vacuum-assisted closure (VAC) is helpful in terms of reducing the fluid outflow and for better wound healing.[29,30] The recently reported percutaneous transhepatic duodenal diversion seems to have good results in the management of duodenal fistulas, but needs further evaluation.[31]

If a duodenal fistula does not heal after 4–6 weeks of optimum medical management, it is unlikely to close without surgical intervention. There is a significant number of patients requiring one or more surgical operations to get released from the fistula. Suturing of the duodenum wall in one or two layers, with or without serosal patch, is performed by many surgeons as the primary operation,[32,33] unfortunately with poor results in many cases due to the formation of a duodenal wall defect followed by sepsis and high-output duodenal fistula.[20] Numerous surgical procedures have been described with varietal results for the management of the high-output fistulas: triple ostomies,[34,35] various grafts (small bowel, gastric wall, rectus and transversalis muscle),[2,7,36] pyloric exclusion,[37,38] clips,[39] and even radical procedures like Billroth II, Roux-en-Y gastrojejunostomy, Longmire's, and Whipple's.[40–43] Continuous intraluminal aspiration and infusion with feeding jejunostomy gave good results in the past.[44] Experimental use of expanded polytetrafluoroethylene patch seems promising.[45] Primary repair with debridement of the area and pyloric exclusion seem to have better results in low-output fistula originating from up to grade III duodenal injuries in children.[46,47] Proximal duodenojejunostomy is advised for the management of difficult duodenal stumps.[48] It is recommended to delay surgery for a few weeks up to 6 months to control sepsis and improve nutritional status.[49]

The suggested procedure of biliogastric diversion is based on the same principles to the duodenal exclusion

procedure. The bypass of the duodenum has the advantage of the diversion of the gastric and biliary fluids from the duodenal wall defect area, allowing only the pancreatic fluid to enter the duodenal lumen, offering a more complete exclusion. Moreover, the biliogastric diversion overcomes a main difficulty of the duodenal exclusion, since there is no need for restoration of the gastroduodenal continuity. It also has the advantage that does not require complete mobilization of the duodenum and can be performed with or without suturing of the duodenal wall defect. In cases where suturing of the duodenal wall defect is hazardous and cannot be performed, this technique converts eventually the high-output duodenal fistula into a low-output pancreatic one, leading to easier control of the sepsis and faster closure of the fistula. It is obvious that the technique is safer if the duodenal fistula is stabilized. The duodenojejunal and choledochojejunal anastomoses should be carried out with special care, so they are out of the septic field. Otherwise, the likelihood of undesirable outcome is high.

In two cases where we performed this procedure, the results are very encouraging and both patients are easily released from their problem. In the first patient, the duodenal wall defect was sutured, while in the second one, it remained untouched, leaving a low-output pancreatic fistula (30–100 mL/day) which closed spontaneously. It is easy to understand that all patients with persisting high-output duodenal fistula are candidates for the biliogastric diversion. The site of the duodenal fistula does not dictate who would benefit, since the reduction of the fluids reaching the traumatized area improves the condition and promotes the closure of the fistula and, eventually, healing. In a theoretical basis, biliogastric diversion may have potential long-term sequelae in patients' nutritional status, but no such complication was observed in our cases.

Despite the advances in intensive care, nutritional support, antimicrobial therapy, wound care, and operating techniques, high-output duodenal fistulas continue to have a high mortality rate whether they are postoperative, posttraumatic, or secondary to a disease process.[11,50–52] The prolonged hospitalization for TPN provision, its high cost, especially in developing countries, and its complications, preserve surgery for the management of duodenal fistula still a challenge.[28]

We believe that the abovementioned procedure is a considerable option for patients with high-output duodenal fistula with the limitation that must be performed by very experienced personnel.

Conclusion

External high-output duodenal fistula is still a challenge, leading, in some cases, to surgical intervention. Various surgical procedures have been reported in the medical literature with controversial results. Our new technique of biliogastric diversion seems to be a good solution in the management of these fistulas.

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ORIGINAL ARTICLE

Prospective 6 Weeks Follow-up Post-cholecystectomy: The Predictive Value of Pre-Operative Symptoms

M. C. Mertens · J. De Vries · V. P. W. Scholtes · P. Jansen · J. A. Roukema

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Abstract
Objective Many patients with symptomatic cholelithiasis report persisting symptoms after elective cholecystectomy. The current prospective follow-up study aims at the identification and valuation of risk factors for negative symptomatic outcome at 6 weeks.
Methods Consecutive patients (n=183), age 18–65 years, indicated for elective cholecystectomy due to symptomatic cholelithiasis, completed a self-report questionnaire. At 6 weeks post-operatively, the same self-report questionnaires were completed (n=129). Predictors of the persistence and emergence of biliary and dyspeptic symptoms at 6 weeks post-cholecystectomy were investigated using univariate and multivariate logistic regression.
Results At 6 weeks post-operatively, the report of post-operative biliary symptoms was independently predicted by pre-operative dyspeptic symptoms (OR=6.60) and bad taste (OR=3.55). Pre-operative flatulence was an independent predictor of the report of biliary and dyspeptic symptoms ((OR=3.33) and (OR=3.27), respectively) and persisting biliary symptoms (OR=4.21). Predictors of symptomatic outcome were only identified in women, not in men.
Conclusion Patients with pre-operative dyspeptic symptoms, notably bad taste and flatulence, have an increased risk of negative post-cholecystectomy outcomes at 6 weeks. A symptom-specific approach should lead to optimalization of the indication of cholecystectomy and information of patients. Known risk factors for long-term outcomes might be valuable in female patients only.

Keywords Cholecystectomy · Prediction · Symptoms

M. C. Mertens · J. De Vries (✉) · J. A. Roukema
CoRPS—Center of Research on Psychology in Somatic diseases,
Department of Medical Psychology, Tilburg University,
P.O. Box 90153, 5000 LE Tilburg, The Netherlands
e-mail: j.devries@uvt.nl
e-mail: JVries@elisabeth.nl

P. Jansen · J. A. Roukema
Department of Surgery, St. Elisabeth Hospital,
P.O. Box 90151, 5000 LC Tilburg, The Netherlands

J. De Vries
Department of Medical Psychology, St. Elisabeth Hospital,
P.O. Box 90151, 5000 LC Tilburg, The Netherlands

V. P. W. Scholtes
Department of Surgery, Diakonessenhuis Utrecht,
P.O. Box 80250, 3508 TG Utrecht, The Netherlands

Introduction

Gallstone disease (cholelithiasis) is a common condition in the Western world. In the Netherlands, 32,000 patients are yearly diagnosed with this condition.[1] The majority of patients remains asymptomatic and only 20% of patients develop clinical symptoms.[2–4] Symptomatic gallstone disease is typically diagnosed after an episode of biliary pain, which is defined as a severe steady pain, lasting more than 15–30 min, usually located in the epigastrum and/or right upper quadrant, sometimes radiating to the back,[2,5] which is often accompanied by dyspeptic symptoms.[6–9] However, some patients experience mild dyspeptic symptoms without biliary colics.[10] Additional ultrasonography is recommended,[2,9,11] as clinical symptoms are not consistently related to the presence of gallstones.[11–14] Professional guidelines propose conservative treatment (wait and see) in asymptomatic cholelithiasis[2,9,15] and cholecystectomy in symptomatic

cholelithiasis. In biliary pain without stones, cholecystectomy is occasionally indicated[10] following additional surgical consultation.[2]

Elective cholecystectomy is widely performed in 70% of the symptomatic patients.[16] In the Netherlands, cholecystectomy is performed in 19,000 patients a year.[1] The majority of patients report positive outcomes and relief rates for biliary pain (86–96%), upper abdominal pain (66–77%), and dyspepsia (46–89%)[13] are high. However, a substantial group of patients report persistence of pre-existent biliary (5.5–19.5%) and dyspeptic symptoms (27.3–43.2%).[8,17,18] Thus, recognition of patients with a high risk of negative outcomes is crucial.

In literature, pre-operative dyspeptic symptoms, the use of psychotropic medication, and a long history of pain, symptoms, and biliary attacks are mentioned as potential predictors of poor outcome and persisting pain[17–19] at 6 months post-cholecystectomy. Although clinical experience indicates that most patients experience a major reduction of symptoms at 6 weeks post-cholecystectomy,[20] no studies have explored predictors of symptomatic outcome at this time point. The present prospective follow-up study aims at the identification and the valuation of predictors of negative symptomatic outcomes at 6 weeks after cholecystectomy.

Methods

Patients

Between March 2006 and August 2007, all patients between 18 and 65 years with diagnosed cholelithiasis (diagnosis K80 from International Statistical Classification of Diseases and Related Health Problems (ICD-10)), awaiting an elective laparoscopic cholecystectomy at the department of Surgery of the St. Elisabeth Hospital in Tilburg, the Netherlands, were eligible for the study. Exclusion criteria were: patients with ASA III or IV, undergoing an emergency procedure or intended open cholecystectomy, insufficient knowledge of the Dutch language, choledocholithiasis, cholangitis, known pregnancy, known liver cirrhosis, history of abdominal malignancy, previous upper abdominal surgery (precluding laparoscopic approach), and psychiatric diseases.

Procedure

During patients' visit to the outpatient clinic, the surgeon performed a physical examination and explained the surgical and anesthetic procedures. Patients were informed about the general prognosis after cholecystectomy and the risk of complications. Furthermore, the surgeon introduced the study and asked the patients to participate. Nurses informed patients further about the operation and the study, and handed out written information and the first set of questionnaires. Patients read the information at home and signed informed consent before participation. Pre-operatively, records were checked for medical history, comorbidity, and medication use. Before admission for cholecystectomy, patients completed the first questionnaires, which could be returned by mail or delivered to the nurses at the ward. In case the questionnaires were not returned 5 to 3 days before surgery, patients received a telephone call to remind them to complete the questionnaire. Patients who returned their first set of questionnaires after surgery were excluded from the study.

Six weeks after surgery, patients were sent another self-report questionnaire. Eight weeks and 10 weeks after surgery, a phone call reminded the patients to return the post-operative questionnaire to the hospital, if necessary. The protocol of the study was approved by the local ethics committee.

Questionnaires and Medical Files

Questionnaires comprised self-reported demographic and clinical information. The demographic questionnaire asked about sex, age, marital status, educational level, and work. Furthermore, patients completed a self-constructed symptom checklist, which asked about the presence of symptoms in the past week. Symptoms were collected from biliary patients participating in focus groups. Following a study of Weinert et al.,[17] symptoms were categorized into symptom complexes, namely biliary symptoms (upper abdominal pain, nausea, vomiting), dyspeptic symptoms (bad taste, heartburn, under abdominal pain, diarrhea, and flatulence), and non-specific symptoms (general malaise, fatigue, weight change, decrease in sexual functioning, and other health complaints not mentioned in the checklist). Medical files were checked for the experience of biliary and dyspeptic symptoms ever before visiting the outpatient clinic. After surgery, surgical reports were checked for the presence of gallstones/sludge and conversion to open surgery.

Surgical and Anesthetic Procedure

Open introduction was performed in all patients regardless of previous abdominal surgery. Pneumoperitoneum was created using the subumbilical trocar with an intra-abdominal pressure up to 12 mmHg. Three trocars for instruments were inserted. The dissection of the cystic artery and cystic duct, identifying Calot's triangle, was performed using a three-point 'flag' technique. The cystic duct and artery were clipped and transsected. After

complete dissection of the gallbladder, it was removed either through the subumbilical or subxyphoidal trocar. Fascia defects as a result of the insertion of the 10 mm trocar and the open introduction of the subumbilical trocar were closed. No suction drains were left in the subhepatic space at the end of the procedure.

In principle, all patients were subjected to a standard anesthetic regime. As premedication, patients received paracetamol 1,000 mg supp. and atropine 0.5 mg i.m. Patients <60 years and >60 kg received diazepam 10 mg. p.o.; patients >60 years and <60 kg received diazepam 5 mg. p.o. Perioperative anesthesia consists of propofol 1.5–2.5 mg/kg, sufenta 0.25 μg/kg, and rocuronium 0.6 mg/kg. Standard post-operative analgetics were paracetamol 4 dd 1,000 mg supp. and morphine 6 dd 10 mg s during the first 48 h post-operatively, until patients' indicated pain was acceptable. If necessary, patients received additional diclofenac 2 dd 100 mg supp.

Statistical Analyses

Pre-operative differences between responders (patients who returned their questionnaires at 6 weeks) vs. non-responders and dropouts (patients who ended participation within 6 weeks) were investigated by chi-square tests (using Fisher's exact test when appropriate) and Student's *t* tests. Changes in symptoms were examined by the McNemar test. Analyses were performed both for specific symptoms and symptom complexes.

Furthermore, persistence and emergence rates were calculated. Therefore, the population under study was divided in two subgroups categorized by the presence (group 1) or absence (group 2) of self-reported pre-operative biliary or dyspeptic symptoms. Patients with pre-operative biliary symptoms (group 1) reported biliary symptoms only or both biliary and dyspeptic symptoms. Patients without pre-operative biliary symptoms (group 2) suffered from dyspeptic symptoms only. Likewise, patients with and without pre-operative dyspeptic symptoms were categorized into two groups. Persistence was defined as reporting the symptoms both before and after cholecystectomy. Emergence was defined as not reporting the symptoms pre-operatively, but reporting the symptoms at 6 weeks post-cholecystectomy.

To discern which pre-operative symptoms predicted the post-operative report, the persistence, and the emergence of post-operative symptoms, we used univariate logistic regression. Furthermore, significant univariate predictors of each outcome were entered in a multivariate regression model (method enter) to assess the relative strength of each predictor. In both outcome and predictors, we differentiated between symptom complexes and specific symptoms.

A p value <.050 indicated statistical significance. Statistical analyses were performed using SPSS version 14.0.1.

Results

Patient Characteristics

Figure 1 provides an overview of the population across time. Of all 241 patients visiting the outpatient clinic and being approached for participation, 211 received the first questionnaire. Statistical analyses were performed on 183 patients (response rate 86.7%). Within 6 weeks, five patients ended participation. Six weeks after cholecystectomy, data were available from 129 patients (response rate 70.5%). Because of missing values, final statistical analyses were performed on 126 patients. In 94.0% of the patients, biliary stones or sludge were demonstrated by ultrasonic tomography. Pre-operatively, endoscopic sphincterotomy had been performed in eight patients. Laparoscopic cholecystectomy was converted to an open procedure in six patients. Table 1 shows the demographic and clinical characteristics of the patient group. Pre-operatively, participants in the study did not differ from non-responders and patients who ended participation within 6 weeks. Among the participants, 74.3% were females and the mean age was 46.0±11.4 years. Female patients were younger than male

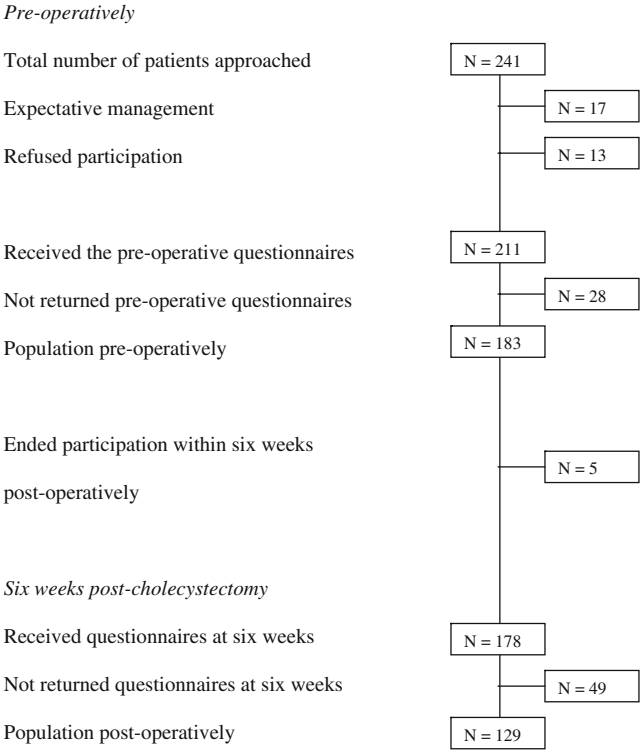

Figure 1 *Flow chart* of the population in the course of 6 weeks.

Table 1 Baseline Characteristics

	Population n=183
Demographic characteristics	
Female patients (%)	74.3
Age (M±SD)	46.0±11.4
Highest level of education	
Primary and/or lower vocational education (%)	20.6
Secondary education (%)	45.6
Higher education (%)	6.1
Higher professional education or university (%)	27.8
Working under payment (%)	72.4
Marital status	
Single (%)	6.1
Widowed or divorced (%)	6.6
Married or cohabitant (%)	87.3
Comorbidities	
Coronary arterial diseases (%)	20.3
Pneumonal diseases (%)	7.4
Abdominal diseases (%)	25.0
Kidney diseases (%)	2.0
Urogenital diseases (%)	9.5
Neurological diseases (%)	11.5
Rest category of comorbidities (%)	48.0
Self-reported medication use	
Analgesics (%)	37.8
Psychotropic medication (%)	10.1
Other medication (%)	46.7
Pre-operative symptoms (self-reported)	
Cholelithiasis-specific (%)	73.6
Dyspeptic (%)	66.7
Free of symptoms (%)	14.3
Frequency of biliary colics (M±SD)	5.47±7.68
Demonstrated gallstones (%)	94.0
Pre-operative symptoms ≤6 months (%)	68.3
Pre-operative symptoms ≥7 months (%)	31.3

patients (50.7±9.6 years vs. 44.5±11.6 years; (t=3.30, p=.001)). Male patients more often reported urogenital diseases (p=.034) than female patients.

Pre-operative Symptoms

In the week before visiting the outpatient clinic, 73.6% of the patients experienced biliary symptoms and 66.7% of the patients experienced dyspeptic symptoms (Table 1). Furthermore, 14.3% of all patients (n=27) did not report any biliary or dyspeptic symptoms. In the week before surgical consultation, female patients reported more pre-operative biliary symptoms than male patients (78.5% vs. 59.6%, p=.019), whereas male patients more often reported to be free of symptoms than female patients (25.5% vs. 10.4%, p=.021). Moreover, examination of medical files revealed that 84.7% and 73.2% of the patients had ever experienced biliary and dyspeptic symptoms. More specifically, 26.8% had experienced only biliary symptoms, 15.3% had experienced only dyspeptic symptoms, whereas 57.9% of the patients had ever experienced both biliary and dyspeptic symptoms. Patients reported a mean of 5.5±7.7 biliary attacks. Pre-operatively, upper abdominal pain was most frequently reported (66.5%), followed by nausea (39.3%) and flatulence (36.1%). Moreover, 55.2% of all patients reported non-specific symptoms. Female patients more often reported bad taste (χ^2=5.27, p=.022), upper abdominal pain (χ^2=4.25, p=.039), nausea (χ^2=9.70; p=.002), diarrhea (χ^2=4.80, p=.029), and non-specific symptoms (χ^2=6.41, p=.011) than male patients.

Course of Symptoms

In the time between the pre-operative measurement and 6 weeks after cholecystectomy, five patients received an endoscopic sphincterotomy, of which two patients already received this procedure pre-operatively. Furthermore, a general improvement was observed. The number of patients reporting biliary and dyspeptic symptoms reduced to 25.4% and 50.8%, respectively (χ^2=47.38, p<.001 and χ^2=5.56, p=.018). More specifically, the number of patients reporting bad taste, heartburn, upper abdominal pain, nausea, vomiting, and under abdominal pain reduced significantly over 6 weeks' time (see Table 2). The percentage of patients reporting to be free of symptoms increased to 44.4% (χ^2=47.38, p<.001) (see Fig. 2).

In spite of the general improvements over 6 weeks' time, biliary symptoms persisted in 27.8% of the patients with pre-operative biliary symptoms, whereas biliary symptoms emerged in 17.1% of the patients with only pre-operative dyspeptic symptoms. Persistence of dyspeptic symptoms was reported in 57.3% of the patients biliary, dyspeptic, and

Table 2 Self-reported Symptoms Pre-operatively and 6 Weeks after Cholecystectomy (Total Population)

	Baseline (n=183)	Follow-up 6 weeks (n=126)	p
Symptoms			
Bad taste (%)	24.0	12.7	.001*
Heartburn (%)	25.1	15.1	.015*
Upper abdominal pain (%)	66.5	19.8	<.001*
Nausea (%)	39.3	13.5	<.001*
Vomiting (%)	14.8	3.2	.001*
Under abdominal pain (%)	24.6	8.7	.003*
Diarrhea (%)	18.0	13.5	.839
Flatulence (%)	36.1	26.2	.082
Other health complaints (%)	55.2	46.8	.268

McNemar tests were used to analyze changes in symptoms over time
*Significance p<.050

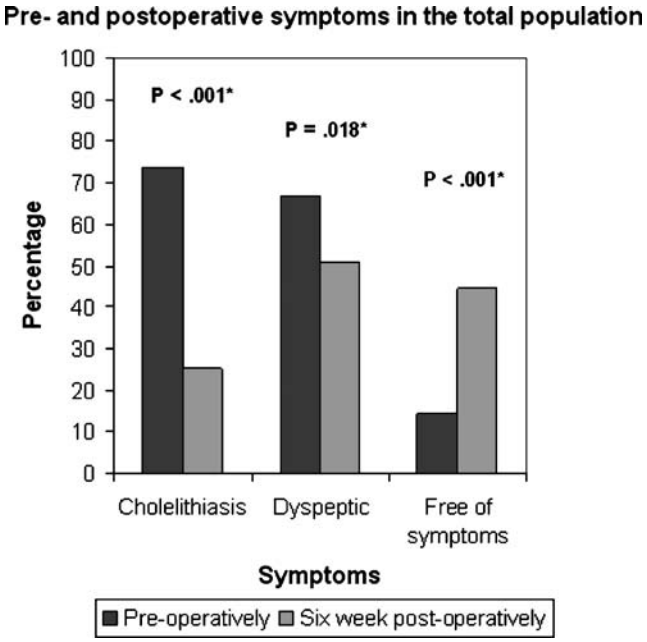

Figure 2 Report of symptoms in the total population.

non-specific symptoms. At 6 weeks, dyspeptic symptoms emerged in 38.6% of the patients who reported pre-operative biliary symptoms only.

Symptom- and Sex-specific Patterns of the Course of Symptoms

At 6 weeks post-cholecystectomy, patients with and without demonstrated biliary stones and/or sludge reported post-operative biliary and dyspeptic symptoms to the same extent. Subgroups of patients with and without pre-operative biliary symptoms experienced post-operative dyspeptic symptoms to the same extent (45.7% and 52.2%, respectively). Furthermore, patients with pre-operative dyspeptic symptoms reported post-operative biliary symptoms more often than patients without pre-operative dyspeptic symptoms (35.4% vs. 6.8%; $\chi^2=10.86$, $p=.001$).

Stratifying the self-reported improvements at 6 weeks post-cholecystectomy by sex, a different pattern of change was observed for male and female patients (see Fig. 3). Furthermore, no sex-bound patterns were found with regard to the emergence and persistence of biliary and dyspeptic symptoms after cholecystectomy.

Pre-operative Symptoms in the Prediction of Symptomatic Outcome

Univariate logistic regression analyses were used to identify the predictors of post-operative biliary and dyspeptic symptoms, and the persistence and emergence of biliary and dyspeptic symptoms (see Table 3). Duration of pre-operative symptoms and pre-operative medication use were not significant predictors. No univariate predictors could be distinguished for the emergence of dyspeptic symptoms at 6 weeks.

The differential value of the identified predictors was further explored in multivariate logistic regression analyses, inserting the univariate predictors for each outcome as variables (method enter). The report of biliary symptoms at 6 weeks post-operatively was independently predicted by pre-operative dyspeptic symptoms, bad taste, and flatulence (see Table 4). Both the report of post-operative dyspeptic symptoms and the persistence of biliary symptoms were independently predicted by pre-operative flatulence. Other univariate predictors of post-operative symptomatic outcomes were non-significant.

Eligibility of Pre-operative Symptoms in the Prediction Symptomatic Outcome

First of all, sex-specific predictors were investigated by univariate logistic regression analysis (Table 5). Predictors of the post-operative report and the persistence of biliary and dyspeptic symptoms were identified in female patients only, and not in male patients. In both men and women, no predictors were distinguished for the development of biliary and dyspeptic symptoms. Moreover, the univariate predictors of each outcome were simultaneously entered in multivariate logistic regression analyses. These analyses could only be performed on the population of female patients. In female patients, the post-operative experience of biliary symptoms was independently predicted by bad taste only (OR=3.73, $p=.008$; 95% CI 1.42–9.84). At 6 weeks, the report of dyspeptic symptoms was predicted

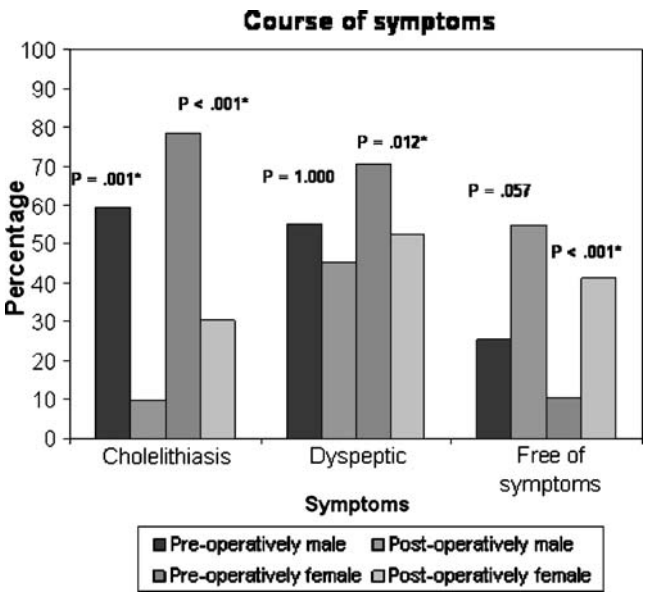

Figure 3 Course of symptoms over 6 weeks' time.

Table 3 Univariate Predictors of Post-operative Symptoms at 6 Weeks (Total Population)

Post-operative outcome	Pre-operative predictor	OR	95% CI	*p*
Report of biliary symptoms	Dyspeptic symptoms	7.48	2.13–26.27	.002*
	Sex	4.10	1.15–14.58	.029*
	Bad taste	4.00	1.67–9.55	.002*
	Heartburn	2.38	1.01–5.60	.047*
	Nausea	2.38	1.05–5.38	.038*
	Flatulence	3.36	1.46–7.73	.004*
Report of dyspeptic symptoms	Dyspeptic symptoms	2.13	1.01–4.51	.047*
	Heartburn	2.60	1.14–5.95	.024*
	Flatulence	3.54	1.62–7.75	.002*
Persistent biliary symptoms	Dyspeptic symptoms	6.73	1.46–31.09	.015*
	Bad taste	3.69	1.37–9.96	.010*
	Flatulence	2.83	1.09–7.35	.033*
Emergent biliary symptoms	Flatulence	13.13	1.32–130.24	.028*
Persistent dyspeptic symptoms	Flatulence	3.28	1.32–8.17	.011*

Univariate logistic regression analysis was used to investigate the prediction of post-operative outcomes at 6 weeks post-cholecystectomy
*Significance $p<.050$

by heartburn and flatulence (OR=2.70, $p=.040$; 95% CI 1.04–6.96 and OR=2.91, $p=.020$; 95% CI 1.19–7.13, respectively). For the prediction of persisting biliary symptoms, no independent predictors could be identified.

Discussion

Most people with gallbladder stones never become patients, as they remain asymptomatic. Elective cholecystectomy is performed in 70% of patients with symptomatic cholelithiasis[16] aiming at a release from pain and symptoms and preventing complications. Post-operatively, a significant group of patients report persisting symptoms.[17–19,21–23] Furthermore, cholecystectomy entails the risk of common bile duct injury and mortality in 0.5% and 0.2% of the patients, respectively.[24] Therefore, performance of elective cholecystectomy should be considered critically and recognition of patients with a high risk of negative outcomes is crucial. In this prospective follow-up study, we investigated the role of pre-operative symptoms in the prediction of negative symptomatic outcome. The results of this study show that pre-operative dyspeptic symptoms, or more specifically bad taste and flatulence, are independent predictors for the experience of biliary and dyspeptic symptoms and the persistence of biliary symptoms. Although sex does not predict post-operative outcome, predictors are only identified in female patients.

In the current study, all abdominal symptoms decrease after cholecystectomy (with the exception of diarrhea), which is also reported in studies with follow-up at 6 months[17,25] or more than 1 year.[23,26] In line with other studies,[13,17] greatest improvement was found for biliary symptoms, whereas dyspeptic symptoms more often persisted and emerged. At 6 months after cholecystectomy or later, biliary symptoms are found to be persistent in 5.6–20.0% of the patients[17] and dyspeptic symptoms are persistent in 10.0–40.2% of the patients.[17,23,27] In the current study, we found higher percentages of 27.8% and 57.3% for persistent biliary and dyspeptic symptoms, which may be attributed to the timeframe of 6 weeks before follow-up. Approximately one third of the patients with biliary or dyspeptic symptoms only developed another type of symptoms at 6 weeks post-operatively. Although one

Table 4 Differential Value of Predictors of Post-operative Symptomatic Outcome (Total Population)

Post-operative outcome	Pre-operative predictor	OR	95% CI	*p*
Report of biliary symptoms	Dyspeptic symptoms	6.60	1.86–23.45	.005*
	Bad taste	3.55	1.38–9.17	.009*
	Flatulence	3.33	1.48–7.26	.004*
Report of dyspeptic symptoms	Flatulence	3.27	1.48–7.26	.004*
Persistent biliary symptoms	Flatulence	4.21	1.46–12.19	.008*

Multivariate logistic regression analysis was used to investigate the prediction of post-operative outcomes at 6 weeks post-cholecystectomy
*Significance $p<.050$

Table 5 Univariate Predictors of the Report of Post-operative Symptoms at 6 Weeks (Female Patients)

Post-operative outcome	Pre-operative predictor	OR	95% CI	*p*
Report of biliary symptoms	Dyspeptic symptoms	5.29	1.45–19.28	.012*
	Bad taste	3.81	1.48–9.82	.006*
	Under abdominal pain	2.75	1.04–7.30	.042*
Report of dyspeptic symptoms	Heartburn	2.90	1.15–7.28	.024*
	Flatulence	3.09	1.29–7.43	.012*
Persistent biliary symptoms	Heartburn	2.94	1.08–8.05	.036*
	Flatulence	2.94	1.08–8.05	.036*
Persistent dyspeptic symptoms	Flatulence	3.15	1.15–8.60	.025*

Univariate logistic regression analysis was used to investigate the prediction of post-operative outcomes at 6 weeks post-cholecystectomy
*Significance $p<.050$

study[17] reports a one-directional shift from pre-operative biliary to post-operative dyspeptic symptoms, the findings from the current study suggest a bidirectional shift from pre-operative biliary symptoms to post-operative dyspeptic symptoms and vice versa.

As cholecystectomy is not beneficial to all patients, distinguishing patients with a heightened risk of persisting and emerging symptoms at 6 weeks is important. Literature mentions pre-operative dyspeptic symptoms, pre-operative flatulence, and experiencing over three symptoms of flatulent dyspepsia as predictors of negative post-cholecystectomy outcomes, such as post-cholecystectomy syndrome and persistence of a bothersome symptom.[17,25,28] In addition, the current study asserts that pre-operative dyspeptic symptoms, bad taste, and flatulence are associated with a three to seven times greater risk of post-operative biliary and dyspeptic symptoms. Furthermore, pre-operative flatulence is associated with a four times greater risk of persisting biliary symptoms after cholecystectomy. Awareness of these risk factors might have strong implications for clinical practice. Surgeons should be alert on the recognition of these patients during anamnesis and patients should be informed about their symptom-specific risk of negative post-cholecystectomy outcome. Furthermore, the existing knowledge on risk factors for negative symptomatic outcome should be integrated in clinical decision making, with regard to guidelines for the indication of cholecystectomy and consideration of alternative treatment options.

Sex has an ambiguous position as a predictor of post-cholecystectomy symptomatic outcome. Although male sex is found to be a predictor of a 'not very successful' outcome[17] in literature, the current study indicates that sex is no predictor of self-reported symptoms or the persistence or emergence of these symptoms. However, predictors are only identifiable in female patients and not in male patients. The latter point has implications for knowledge from the existing literature on predictors of post-cholecystectomy outcome. As the bulk of studies do not differentiate between male and female patients, we recommend a careful interpretation of results and the inclusion of the variable 'sex' in the design of future studies on cholecystectomy.

This study has several limitations. As this is a single-institution study, generalization of the results to other health care centers might be limited. We investigated the predictive value of pre-operative symptoms, taking biliary or dyspeptic symptoms as feature of a clinical representation of cholelithiasis. Coinciding with biliary stones, dyspeptic symptoms are easily interpreted as a clinical feature of cholelithiasis. However, dyspeptic symptoms are quite common in the general population and may still be an isolated condition, even in the context of biliary stones. Therefore, although our results imply a relation between dyspeptic symptoms and post-operative outcome at 6 weeks, results should be interpreted with care. Unfortunately, we did not specifically investigate the combination of both biliary and dyspeptic symptoms or the interaction between biliary and dyspeptic symptoms on the prediction of 6 weeks symptomatic outcome. We recommend that this issue will be addressed in future research. Furthermore, this study investigated pre-operative symptoms as predictors of negative symptomatic outcome at 6 weeks post-cholecystectomy. Future studies should investigate the relation between symptomatic outcome at 6 weeks and long-term outcomes, or the post-cholecystectomy syndrome. Despite the small sample of male patients ($n=46$), we found a sex difference in terms of the impossibility to identify predictors of negative symptomatic outcome in male patients, in contrast to several predictors in female patients. Extensive exploration of predictors should be aimed at a bigger sample of male patients and studies on predictors of long-term post-cholecystectomy outcomes should integrate sex as a potential variable. Another shortcoming in this study is the fact that symptomatic outcome is a one-dimensional outcome, indicating the presence of symptoms only. Within this measure, differentiation should be sought by investigating severity and duration, implications for all day living, and psychosocial consequences.

In summary, at 6 weeks post-cholecystectomy, 27.8% and 57.3% of the patients reported the persistence of pre-operative

biliary and dyspeptic symptoms, respectively. Furthermore, 17.1% and 38.6% of the patients with only dyspeptic or only biliary symptoms developed another type of symptoms after cholecystectomy. Sex is no predictor of post-operative outcome, whereas pre-operative symptomatology is. Patients reporting pre-operative dyspeptic symptoms, bad taste, or flatulence have a heightened risk of experiencing post-operative biliary symptoms. Besides, patients with pre-operative flatulence are at risk for the experience of post-operative dyspeptic symptoms and the persistence of pre-existing biliary symptoms. Management of cholelithiasis should be patient tailored, thereby considering the prognosis after cholecystectomy differentially, based on the clinical presentation of pre-operative symptoms. So far, predictors of post-operative symptomatic outcome have only been identified in female patients and not in male patients.

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ORIGINAL ARTICLE

Is Complicated Gallstone Disease Preceded by Biliary Colic?

Marc G. Besselink · Niels G. Venneman · Peter M. Go · Ivo A. Broeders · Peter D. Siersema · Hein G. Gooszen · Karel J. van Erpecum

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Abstract
Introduction Cholecystectomy in cases of "warning" episodes of biliary colic may prevent biliary pancreatitis. We aimed to determine which proportion of patients with biliary pancreatitis, compared to other complicated and uncomplicated symptomatic gallstone disease, experienced "warning" episodes of colic and why these episodes did not lead to early cholecystectomy.
Patients and methods One hundred seventy-five patients with complicated gallstone disease [pancreatitis (n=53), symptomatic common bile duct (CBD) stones (n=64), and acute cholecystitis (n=58)] and 175 patients with symptomatic uncomplicated gallstones were interviewed at admission.
Results Fifty-seven percent (100 of 175) of patients with complicated disease (95% confidence interval=50–65%) experienced "warning" episodes of biliary colic (pancreatitis 58%, CBD stones 67%, cholecystitis 45%) vs 96% (164 of 175) in uncomplicated disease. Eighty-seven percent of patients with "warning" episodes and complicated disease experienced patient's and general practitioner's delays. General practitioner's delay was more frequent if pain was located in the epigastric region compared to the right upper quadrant (51% vs 38%, P=0.03).
Conclusions Half of patients with biliary pancreatitis experience "warning" episodes of biliary colic, similar to other gallstone complications. In symptomatic patients, complications are often not prevented because of significant delays in diagnosis and treatment.

Keywords Acute pancreatitis · Cholecystectomy · Cholecystitis · Symptoms · Gallstone

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MGHB, NGV, and KJvE participated in the design of the study, analysis, and interpretation of data. MGHB drafted the manuscript. All authors participated in revising the article for important intellectual content. All authors approved the final version.

M. G. Besselink · I. A. Broeders · H. G. Gooszen
Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

M. G. Besselink
e-mail: m.besselink@umcutrecht.nl

N. G. Venneman · P. D. Siersema · K. J. van Erpecum
Department of Gastroenterology, University Medical Center Utrecht, Utrecht, The Netherlands

P. M. Go
Department of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands

K. J. van Erpecum (✉)
Gastrointestinal Research Unit, F.02.618, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands
e-mail: k.j.vanerpecum@umcutrecht.nl

Introduction

Acute biliary pancreatitis is associated with significant morbidity and a mortality rate of 5%.[1] The incidence of biliary pancreatitis is increasing with 5% per year.[2,3] It is estimated that, in developed countries, at least one in every ten adults carries gallstones.[4–6] In asymptomatic gallstone carriers, the annual risk of developing biliary pancreatitis is up to 0.2%.[7–9] Furthermore, there is a 0.2% annual risk of developing common bile duct (CBD) stones and a 0.3% risk of acute cholecystitis.[10,11] In symptomatic gallstone carriers, the risks of developing complications are much higher.[12]

Although cholecystectomy in asymptomatic gallstone carriers would prevent symptoms and complicated gallstone disease, (laparoscopic) cholecystectomy is also associated with morbidity and even mortality.[13] In a decision analysis study using a Markov model and Monte Carlo simulations, we found that, in most health care situations, prophylactic cholecystectomy in asymptomatic gallstone carriers did not improve outcome.[14,15] Strategies to prevent biliary pancreatitis should, therefore, rather focus on the early cholecystectomy in symptomatic carriers.[16–18] Surprisingly, it is virtually unknown what proportion of patients with biliary pancreatitis is symptomatic prior to the onset of the complication. Also, it is unknown to what extent patient's and doctor's delay due to poor recognition of gallstone-related symptoms in symptomatic patients are present.[19]

The aims of the current study were to investigate in a large group of patients with biliary pancreatitis and other complicated as well as uncomplicated symptomatic gallstone disease: (1) the occurrence of "warning" episodes of biliary colic and (2) patient's and doctor's delays in symptomatic patients.

Patients and Methods

Patients

All consecutive patients admitted with a first episode of biliary pancreatitis or CBD obstruction or acute cholecystitis in a university medical center and an affiliated large teaching hospital in the period 2003–2005 were eligible for inclusion. A parallel consecutive cohort of patients who visited the outpatient clinic because of uncomplicated symptomatic gallstone disease served as a disease–control group. Patients who refused informed consent, were under 18 years of age, with previous cholecystectomy, with a history of complicated gallstone disease, or with gallbladder carcinoma were excluded. Patients were also excluded if adequate history taking was not possible (due to inability to speak Dutch, German, or English or mental disability). All patients gave informed consent.

Data Collection

From all enrolled patients, a detailed history was taken at admission by one of two investigators (MGHB, NGV). When patients were considered to be too ill or painful for adequate history taking, they were visited again after their condition had improved. The following data were collected: age, sex, date of first biliary colic, visit to general practitioner for episodes of biliary colic, referral for ultrasound or specialist evaluation by general practitioner, numbers of episodes of biliary colic. Results of upper gastrointestinal endoscopy and presence on the waiting list for cholecystectomy at the time of the complication were retrieved from hospital records. Hospital stay, potential complicated course of the disease, and in-hospital mortality were obtained from hospital records.

Definitions

For the purpose of this study, complicated gallstone disease was restricted to acute biliary pancreatitis, symptomatic CBD stones, and acute cholecystitis. Acute pancreatitis was defined as severe abdominal pain of acute onset and elevated serum amylase or lipase level at least three times the upper limit of normal. A biliary genesis was assumed when, in the absence of alcohol abuse or other factors known to predispose to pancreatitis, gallbladder/CBD stones or sludge were detected by abdominal ultrasonography or endoscopic retrograde cholangiopancreatography (ERCP), serum liver enzymes and/or bilirubin were elevated, or when the CBD was dilated (>8 mm).[14] Symptomatic CBD stones were defined as the presence of abdominal symptoms, fever, or jaundice in combination with CBD/gallbladder stones or sludge detected by ultrasonography in combination with dilation of the CBD (>8 mm) or an elevation of serum liver enzymes and bilirubin with the result that ERCP was required. Serum amylase and lipase values had to be normal. Acute cholecystitis was defined as biliary pain of at least 2-h duration with fever and upper abdominal pain in the presence of stones or sludge in the gallbladder detected on abdominal ultrasonography with normal serum amylase and lipase levels. The diagnosis "acute cholecystitis" was always confirmed during surgery. A biliary colic was defined as one or more episodes of upper abdominal pain, lasting at least 30 min but less than 6 h.[20] Uncomplicated symptomatic gallstone disease was defined as one or more episodes of biliary colic in the absence of complicated gallstone disease as defined above. Radiating pain and urge to move were not considered mandatory.

Since biliary pain may also occur at the onset of a complication, the patient was required to have had a symptom-free interval of at least 7 days between the first colic and the complication before classification in the group

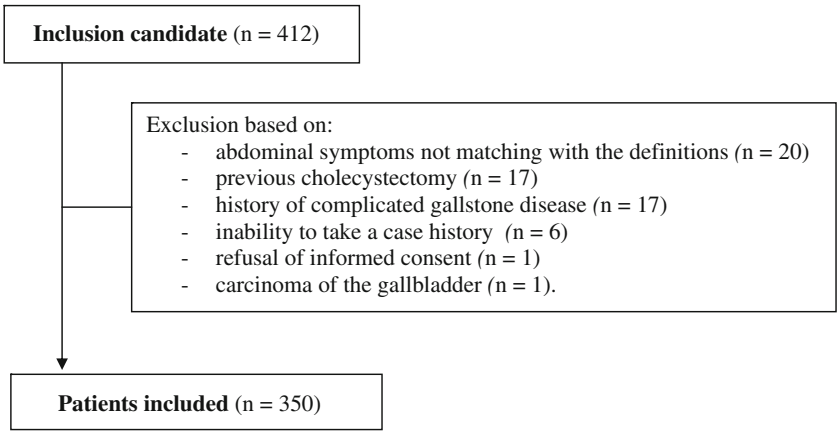

Figure 1 Flow diagram of gallstone patients referred for pain of potentially biliary origin.

complicated disease with "warning" episodes of colic was allowed. General practitioner delay was defined as at least one visit to a general practitioner because of a biliary colic without referral for ultrasound or to a specialist for further evaluation or, in case of previous diagnosis of gallbladder stones, for cholecystectomy. Patient delay was defined as at least one biliary colic without subsequent visit within 7 days to a general practitioner or emergency department.

Statistical Analysis

Categorical data were compared using Pearson's chi square or Fisher's exact test as appropriate. If appropriate, odds ratios (OR) and 95% confidence intervals (95%CI) are provided. All continuous data are expressed as medians with range. Continuous variables were compared using the Mann–Whitney *U* test, Kruskal–Wallis, or analysis of variance (ANOVA), as appropriate. No correction for multiple testing was applied. When probability was <0.05 for the Kruskal–Wallis test, the Mann–Whitney *U* test was used as a post hoc test to compare the three groups of patients with complicated gallstone disease with the symptomatic group. For the ANOVA test, the Fisher's least significant difference test was used as a post hoc test in cases of probability of <0.05 with ANOVA. In cases of positively skewed, non-Gaussian data, the 75th percentile (P75) is represented as upper range. Statistical significance was defined as two-tailed P value< 0.05. All statistical analyses were performed using SPSS version 12.01 (SPSS, Chicago, IL, USA).

Results

Patients

A total of 412 patients were screened for inclusion. Reasons for nonenrollment are summarized in Fig. 1. Finally, 350 consecutive patients were included; 175 consecutive patients with first clinical presentation of gallstone complications: acute biliary pancreatitis (n=53), symptomatic CBD stones (n=64), and acute cholecystitis (n=58) and 175 consecutive patients scheduled for elective cholecystectomy because of uncomplicated symptomatic gallstone disease. Patient characteristics are shown in Table 1. Patients with complicated gallstone disease were more often males, were older, and had less often a family history of gallstone disease compared to patients with uncomplicated symptomatic gallstone disease. Eight patients (5%) in

Table 1 Characteristics of Patients with Complicated and Uncomplicated, Symptomatic Gallstone Disease

	Biliary pancreatitis (n=53)	Symptomatic CBD stones (n=64)	Acute cholecystitis (n=58)	Uncomplicated disease (n=175)	P value
Age, years (range)	50 (24–82)	56 (19–92)	62 (24–90)	48 (20–86)	<0.01[a]
Males, n (%)	26 (49)	22 (34)	31 (53)	40 (23)	<0.01[b]
Body mass index, kg/m^2 (range)	28 (17–45)	25 (18–58)	25 (20–49)	27 (18–43)	<0.01[c]
Biliary colics prior to diagnosis, n (%)	31 (58)	43 (67)	26 (45)	164 (94)	<0.01[d]

[a] Difference between patients with CBD stones and acute cholecystitis vs uncomplicated disease
[b] Difference between patients with acute pancreatitis and acute cholecystitis vs uncomplicated disease
[c] Difference between patients with CBD stones vs uncomplicated disease
[d] Difference between patients with acute biliary pancreatitis, CBD stones, and acute cholecystitis vs uncomplicated disease

Table 2 Characteristics of Biliary Pain in Patients with "Warning" Biliary Symptoms

	Biliary pancreatitis (*n*=53)	Symptomatic CBD stones (*n*=64)	Acute cholecystitis (*n*=58)	Uncomplicated disease (*n*=175)	*P* value
No of colics (min-P75)	5 (1–18)	5 (1–10)	5 (1–16)	5 (1–13)	0.64
With urge to move (min-P75)	2 (1–10)	2 (1–8)	3 (1–10)	3 (1–10)	0.91
Maximum point of pain					
Right upper quadrant	30	33	54	50	0.15
Epigastric region	67	63	42	49	
Other	3	3	4	1	
Radiation of pain					
Only right flank	7	10	15	14	0.28
Circular band	63	63	66	72	
No radiation of pain	30	27	19	14	
Nausea during colic	65	78	58	76	0.31
Vomiting during colic	48	60	46	48	0.41
Taking pain medication for colics	48	50	65	66	0.12

Values are percentages unless mentioned otherwise

the complicated gallstone disease groups had developed a complication while awaiting elective cholecystectomy for a median of 24 days (range 3–75 days).

"Warning" Episodes of Biliary Colic

Of the patients with complicated gallstone disease, 57% (100 of 175, 95%CI=50–65%) experienced "warning" episodes of biliary colic (biliary pancreatitis 58%, symptomatic CBD stones 67%, and cholecystitis 45%, P=0.04; Table 1). Patients with symptomatic CBD stones had "warning" episodes more often than patients with cholecystitis (P=0.01). Patients with biliary pancreatitis did not differ in the incidence of "warning" episodes of biliary colic from patients with CBD stones and/or cholecystitis. As expected, patients with uncomplicated symptomatic disease more often experienced "warning" episodes of biliary colic (94%, 164 of 175) than patients with complicated disease (Table 1).

"Warning" episodes of colic were experienced in the epigastric region by 53% of patients. Although patients with pancreatitis and symptomatic CBD stones predominantly experienced epigastric pain (rather than pain in the right upper quadrant), the difference with acute cholecystitis and symptomatic uncomplicated gallstones was not statistically significant (Table 2).

Delays in Patients with "Warning" Episodes of Colic

Of the patients with complicated gallstone disease and "warning" episodes of colic, 87% of patients (87 of 100) experienced patient's and/or general practitioner's delays (Table 3). Patients with a "warning" colic experienced more doctor's delay if the maximum pain was located in the epigastric region (51%, 70 of 136) compared to the right upper quadrant (38%, 45 of 118, P=0.03). Patient delay was not associated with the location of pain (P=0.39).

Table 3 Delays in Diagnosis and Treatment of Gallstone Patients with "Warning" Colics

	Biliary pancreatitis (*n*=53)	Symptomatic CBD stones (*n*=64)	Acute cholecystitis (*n*=58)	Uncomplicated disease (*n*=175)	*P* value
Days between first colic and diagnosis (min-P75)	243 (9–709)	93 (7–305)	197 (7–885)	176 (7–568)	0.15
Delay	84	91	85	70	0.03[a]
Patient delay[b]	42	42	31	40	0.80
Doctor delay[b]	48	58	58	40	0.11
Known gallstone carrier for at least 1 month	32	29	29	55	0.002[c]
Awaiting cholecystectomy at time of complication	13	7	4	–	0.45

Values are percentages unless mentioned otherwise
[a] Difference between patients with CBD stones vs uncomplicated disease
[b] Patients may experience both patient and doctor delay
[c] Difference between patients with acute pancreatitis, CBD stones, and acute cholecystitis vs uncomplicated disease

Upper Gastrointestinal Endoscopy

Fifty-one patients (15%) underwent endoscopy of the upper gastrointestinal tract because of upper abdominal pain prior to the diagnosis of (un)complicated gallstone disease. In eight patients (16%), minor abnormalities (gastritis or esophagitis grade A) were detected during endoscopy.

Outcome

Ten out of 53 (19%) patients with biliary pancreatitis developed necrotizing pancreatitis requiring a median hospital stay of 40 days (range 8–143 days). Six patients developed (multi)organ failure and were admitted to the intensive care unit. Five of these six and one other patient ultimately underwent surgical necrosectomy for infected necrotizing pancreatitis, albeit without mortality. Four of the ten patients with necrotizing pancreatitis had experienced a "warning" colic, and all four developed infected necrotizing pancreatitis requiring surgical intervention (median hospital stay 130 days). None of these patients died. One patient died after elective cholecystectomy for uncomplicated, symptomatic gallstone disease. Total in-hospital mortality was 0.3% (1 of 350).

Discussion

This study is the first to evaluate the incidence of "warning" biliary colic and the extent of patient and general practitioner delay in patients admitted for biliary pancreatitis and other forms of complicated gallstone disease. The most important findings were that approximately half of patients with pancreatitis had experienced (a median of 5) "warning" episodes of biliary colic during a period of 5 months prior to onset of pancreatitis, very similar to other complicated gallstone diseases. In the majority of these patients, various delays had occurred, which were slightly but significantly more often observed in patients with complicated than with uncomplicated gallstone disease. Up to 40% of patients did not visit their general practitioner after a biliary colic. In addition, patients who visited the general practitioner because of biliary symptoms were often not referred for ultrasound, further specialist evaluation, or surgery. Particularly, epigastric localization of pain, as experienced by over half of gallstone patients in the present series, was associated with general practitioner delay. In patients with epigastric localization of clear episodes of biliary colic, general practitioners frequently consider gastric conditions as the underlying cause. In contrast, patients apparently exhibit no higher frequency of visits to their general practitioners for gallstone-related right upper quadrant pains vs epigastric pains since, in the current study, location of the pain was not associated with patient delays.

This study presents data on a large group of patients collected over a relatively short period of time, which minimizes potential effects of shifts in treatment protocols. The optimal study design would have been a prospective cohort series in asymptomatic gallstone carriers. However, due to the low annual incidence of complicated gallstone disease in asymptomatic gallstone carriers (approximately 0.7%), some 25,000 gallstone carriers would have to be followed up for a year in order to identify 175 patients with complicated gallstone disease as included in the present series. Although a prospective study design would minimize "recall bias," the authors feel that such bias is not likely to have played a major role in this series due to the generally vivid recollection of the intense experience of a biliary colic in our patients.

The purpose of including in the present study a group of symptomatic uncomplicated gallstone patients was not to compare them with the complicated patients for frequency of preceding colics (a priori approaching 100% in the symptomatic uncomplicated group). Rather, we aimed to compare patient's and doctor's delays in these groups. In line with the present findings, previous screening studies demonstrated that mid-upper abdominal pain occurs with equal frequency as right upper abdominal pain in patients with symptomatic gallstones.[17,21] We are aware of one other study that had addressed "warning" episodes of colic in patients with complicated gallstone disease in a retrospective survey of a state-wide database in California. Similar to our findings, approximately half of the patients with complicated gallstone disease in that study had experienced episodes of biliary colic during a period of 142 days prior to cholecystectomy.[22] The authors did not assess the reasons for delayed surgery in these patients. In line with the current data, advanced age and male gender were previously found to be associated with complicated gallstone disease.[14].

Several conclusions and recommendations can be drawn from the present study. First, approximately half the patients with biliary pancreatitis and other complicated gallstone disease do not experience "warning" episodes of biliary colic. In these patients, complications cannot be prevented by a policy of "early cholecystectomy in cases of preceding episodes of colic." Second, patient delay is common and may be reduced by increasing the awareness of the general public for the "warning" aspect of abdominal colicky pain. Third, general practitioner delay is common and may be reduced by increasing awareness of the relation between epigastric pain and gallstone disease. Fourth, the waiting time for elective cholecystectomy should be kept to a minimum in order to guarantee early intervention after diagnosis of "warning" episodes of colic in patients who are fit enough to undergo cholecystectomy.

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ORIGINAL ARTICLE

Percutaneous Microwave Ablation of Liver Cancer Adjacent to the Gastrointestinal Tract

Pei Zhou · Ping Liang · Xiaoling Yu · Yang Wang · Baowei Dong

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Abstract
Purpose The purpose of the study was to prospectively evaluate safety and effectiveness of percutaneous microwave ablation under temperature monitoring assisted with ethanol injection for liver cancer abutting gastrointestinal tract.
Materials and Methods One hundred seventy-nine hepatic tumors that underwent percutaneous microwave ablation with curative intention were included. Fifty-three lesions located less than 5 mm from gastrointestinal tract were in gastrointestinal group. One hundred twenty-six lesions located more than 5 mm from hepatic surface and first or second branch of hepatic vessels were in control group. The temperature of marginal ablation tissue proximal to gastrointestinal tract was monitored and controlled to fluctuating between 45°C and 58°C for more than 10 min for tumors in the gastrointestinal group. Ethanol (2–27 ml) was injected into marginal tissue in 33 of 53 lesions of the GI group.
Results Forty-seven of 53 tumors (88.7%) in the gastrointestinal group and 116 of 126 tumors (92.1%) in the control group achieved complete ablation ($p>0.05$). There were neither immediate nor periprocedural complications in both groups. Tumor seeding happened in one of the gastrointestinal group and two of the control group. There was no delayed complication of bile ducts injury.
Conclusion Under strict temperature monitoring, microwave ablation assisted with ethanol injection is safe and achieves a high complete ablation rate for hepatic tumors adjacent to gastrointestinal tract.

Keywords Hepatic tumor · Ablation · Gastrointestinal tract

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world, causing more than 500,000 deaths every year.[1] Its incidence has been increasing worldwide due to the spread of hepatitis B and C virus (HBV and HCV) infection. The majority of patients with HCC have cirrhosis.[2] Impaired liver function as well as multiplicity of lesions may contraindicate curative surgical resection. Although orthotopic liver transplantation offers the chance for therapeutic success,[3] its performance is limited by a shortage of donor organs. Furthermore, HBV or HCV infection recurs after transplantation, leading to severe liver damage.[4] In the meantime, non-surgical treatment modalities have been developed for hepatic tumors for more than 10 years.[5] Percutaneous ethanol injection therapy (PEIT), once accepted widely as an effective, less invasive, treatment for small HCC,[6,7] is now almost being replaced by imaging-guided thermal ablation with use of different energy sources, such as radiofrequency, microwave, high-intensity-focused ultrasound (HIFU), or laser.[8–24] Thermal ablation has also been reported to play a valuable role against hepatic metastases.[25,26]

The thermal energy, when not insulated by the visceral peritoneum covering the liver, may spread into surrounding organs. Perforation of the gastrointestinal tract has been reported as a serious complication of thermal ablation, with a overall incidence of 0.1–0.3%.[27,28] Some authors have recommended that percutaneous thermal ablation should be avoided when treating liver tumors adjacent to the

P. Zhou · P. Liang (✉) · X. Yu · Y. Wang · B. Dong
Department of Ultrasound, Chinese PLA General Hospital,
28 Fuxing Road,
Beijing 100853, China
e-mail: liangping301@hotmail.com

gastrointestinal tract,[27] whereas others have maintained that RFA is safe for such tumors.[29,30]

Thermal injury may be prevented by strict temperature monitoring of hepatic marginal tissue adjacent to the gastrointestinal tract. This prospective study was undertaken to assess the safety and effectiveness of microwave ablation with temperature monitoring assisted with small dose of ethanol infusion for such tumors.

Materials and Methods

Study Population

From May 2005 to December 2007, 382 patients with HCC or metastatic liver cancer underwent percutaneous microwave ablation (PMWA) with curative intention at the authors` institution. Inclusion criteria for PMWA were nonresectable cancer or patients' refusal to undergo surgery, tumor accessible via a percutaneous approach, single nodular HCC lesions of 6 cm or smaller, three or fewer multiple nodular hepatic lesions with a maximum dimension of 4 cm or less in each nodule, absence of portal vein thrombosis or extrahepatic metastases, prothrombin time of less than 25 s, prothrombin activity higher than 40%, and platelet count higher than 40 cells$\times 10^9$/l. Based upon the situation of China, no patients considered transplantation, and 108 patients refused resection in our groups because of economic reason. Sixty-one hepatic lesions in 59 patients located less than 5 mm from the gastrointestinal tract as shown by contrast-enhanced CT or MRI and contrast-enhanced ultrasound (CEUS) were included in GI group. One hundred forty-five hepatic lesions in 116 patients located more than 5 mm from hepatic surface and the first or second branch of the hepatic vessels as shown by contrast-enhanced CT or MRI and CEUS were included in control group. Hepatic tumors treated after TACE were excluded. Eight of the 59 patients in the GI group and 15 of the 116 patients in the control group were lost to follow-up and were excluded from this study. This investigation was approved by our institutional human research review committee. Written informed consent was obtained from all patients.

Totally, 179 lesions in 152 patients were included in our study. One hundred forty-four lesions in 124 patients were hepatocellular carcinoma. Thirty-five lesions in 28 patients were hepatic metastases. Among 144 lesions of hepatocellular carcinoma, 68 were recurrent lesions, and 76 were new lesions. Among 53 tumors of 51 patients in the GI group, 42 were hepatocellular carcinoma, and 11 were hepatic metastases. Among 126 tumors of 101 patients in the control group, 102 were hepatocellular carcinoma, and 24 were hepatic metastases.

There were 39 males and 12 females in the GI group and 74 males and 27 females in the control group. Age range was 32–79 years (mean 56.6±10.9 years) in the GI group and 34–79 years (mean 56.1±10.3 years) in the control group. The size of lesion ranged from 8 to 60 mm (mean maximum diameter 27±12 mm) in the GI group and from 10 to 60 mm (mean maximum diameter 24±9 mm) in the control group. The lesions were adjacent to stomach in 21, colon in 19, and small bowel in 13.

Child-Turcotte-Pugh score was 5–10 (median 5), and Child-Pugh stratification was A in 118 patients, B in four patients, and C in five patients in patients with hepatocellular carcinoma. The end-stage liver disease (MELD) score was 6.4–16.7 (median 8.2) and lower than 10 in 99 and lower than 20 in other 28 in 127 patients with hepatocellular carcinoma. Ten patients in the GI group and 16 patients in the control group had history of laparotomy.

Preablation Imaging Work-Up and Histological Diagnosis

Pretreatment investigation included ultrasound (US), CEUS, contrast-enhanced CT and/or contrast-enhanced MR, and tumor marker assay in all subjects. The maximum diameters of the index tumors were measured on CEUS. US and CEUS were performed using Sequoia US system (Acuson, Mountain View, CA, USA) with 3.5–5.0-MHz curved-array multifrequency transducers. Ultrasound contrast agent was Sonovue (Bracco Company, Italy). All CT studies were carried out with the same multi-detector row CT (Lightspeed 16; GE Medical Systems, Milwaukee, WI, USA) and contrast medium (iopromide, Ultravist 300; Schering, Berlin, Germany). All MR studies were carried out with the same 1.5-T unit (Signa Echo-Speed, GE Medical Systems), contrast medium (Magnevist, Schering; 0.1 mmol/kg body weight) and sequences. The distance between the edge of the lesion and the gastrointestinal tract was measured on CT or MRI images reconstructed at 5-mm intervals and on CEUS.

Histological diagnosis was obtained by ultrasound-guided tumor biopsy using an 18-gauge needle in all patients. In patients with multiple nodules, at least one biopsy was performed.

Microwave Ablation Technique and Equipment

All treatments were performed at our institution and were carried out under US guidance with the patient under intravenous anesthesia in the operating room. The microwave unit (KY-2000, Kangyou Medical, China) consists of three independent microwave generators, three flexible coaxial cables, and three water-pumping machines, which

can drive three cool-tip needle antennae. The generator is capable of producing 100 W of power at 2,450 MHz.[31] A detailed protocol was worked out for each patient on an individual basis before treatment, which included the placement of the antennae, power output setting, emission time, and appropriate approach. In general, for tumors less than 1.7 cm in diameter, a single antenna was used; for tumors 1.7 cm or larger, multiple antennae were required. An output setting between 40 and 60 W was used during ablations. During ablation, the region of ablation was monitored with US. The treatment session was ended if the hyperechoic region on gray-scale US covered the entire target region. For tumors larger than 30 mm, antennae were first inserted into the deeper region of lesions. If the hyperechoic region covered the deeper region of lesion on US after a series of microwave emission, antennae were withdrawn gradually, and microwave emission was restarted and stopped until the hyperechoic region covered the lesion along the axis of antennae. A total of three to five antennae insertions in one or two sessions were needed for tumors larger than 30 mm. Within 1 week after ablation, every patient received CEUS to evaluate treatment response. All CEUS were performed by one doctor. Possible residual tumor was doubted if abnormal nodular hypervascular region existed at the peripheral region of ablation. If residual tumor was considered, additional treatment session was performed.

Thermal Monitoring Procedure

A thermal monitoring system attached to the microwave unit was used during treatment. The threshold of coagulation necrosis for thermal ablation is 60°C or 54°C for 3 min. To avoid thermal injury to gastrointestinal tract during ablation for the tumors in the GI group, the temperature of marginal tissue of tumor or liver proximal to the gastrointestinal tract was monitored throughout the ablation procedure with one or two 21-G microwave tissue thermal monitoring needles (Kangyou Medical, China) placed with US guidance. According to our clinical experience, the temperature cut off of ablation therapy was set at 54°C in the patients without laparotomy history or 50°C in the patients with laparotomy history. If the measured temperature reached 54°C in the patients without laparotomy history or 50°C in the patients with laparotomy history, emission of microwave was stopped immediately, which was activated again after the temperature decrease to 45°C (Fig. 1). By the end of treatment session, the measured temperature fluctuated between 45°C and 58°C for more than 10 min (624–1,860 s) and did not exceed 54°C for more than 3 min in the patients without laparotomy history or fluctuated between 45°C and 53°C for more than 10 min (840–1,250 s) and did not exceed 50°C for more than 3 min in the patients with laparotomy history. For the nine tumors near the third branch of bile ducts (distance less than 5 mm on CEUS), the temperature of tissue proximal to the third branches of bile ducts was monitored with one thermal monitoring needles placed with US guidance and controlled between 45°C and 53°C throughout the ablation procedure.

Adjuvant Therapy with Small Dose of Ethanol Injection

Among 53 lesions in the GI group, 33 lesions were protruding or in contact with the gastrointestinal tract. For those 33 lesions, one to two 21-G PTC needles were placed into marginal tissue of tumor proximal to the gastrointestinal tract with US guidance. Dehydrated, sterile, 99.5%

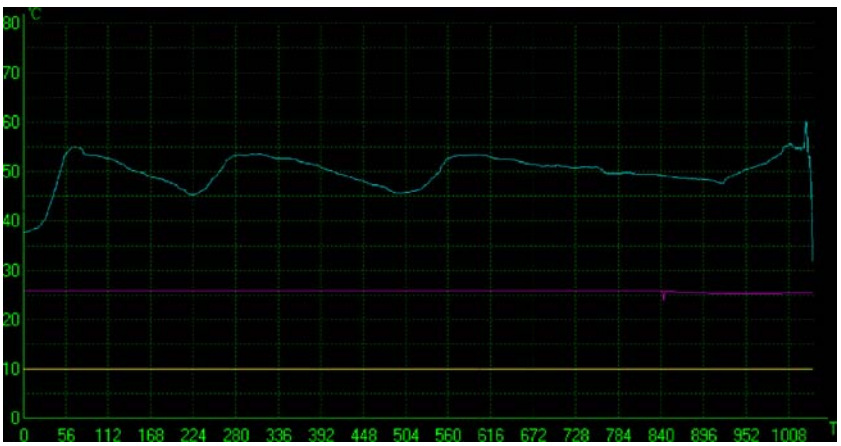

Figure 1 The curve of temperature monitoring during microwave ablation for tumor adjacent to gastrointestinal tract. The temperature of marginal tissue of tumor adjacent to gastrointestinal tract was monitored and controlled to fluctuating between 45°C and 55°C for 972 s during the whole treatment procedure.

ethanol was slowly injected into marginal tissue of tumor during the process of ablation treatment, with total sessions of 1.2±0.5 and total dose of 8.4±5.8 ml (2–27 ml) by the end of ablation procedures. For nine tumors near the third branch of bile ducts, 7.1±3.4 ml (4–13 ml) ethanol was injected into the tissue proximal to bile duct. All ethanol injections were planned beforehand.

Follow-up

The follow-up period was calculated starting from the beginning of microwave ablation for all patients. Therapeutic effectiveness was assessed on the basis of the result of contrast-enhanced imaging and serum tumor marker levels. Contrast-enhanced CT or MRI and CEUS were repeated at 1 month and at 3-month intervals within 1 year after microwave ablation treatment and then at 6-month intervals after treatment. The median follow-up time was 11 months (range 3–32 months) in the GI group and 12 months (range 3–30 months) in the control group ($p>0.05$).

Statistical Analysis

Data analysis was done using SPSS for windows (Version 10.0), and the data were expressed as means±standard deviation (SD). Independent-samples t test was used to compare the means between the groups, and Chi-square test was undertaken to compare the proportions. $p<0.05$ was considered statistically significant.

Results

Outcome of Microwave Ablation

All patients were successfully treated. Forty-seven of 53 tumors (88.7%) in the GI group and 116 of 126 tumors (92.1%) in the control group achieved complete ablation confirmed by follow-up imaging of 3–32 months. Among the tumors with more than 6 months follow-up after ablation, 42 of 48 tumors (87.5%) in the GI group and 96 of 106 tumors (90.6%) in the control group were completely ablated (Figs. 2 and 3). No significant statistical difference in the rate of complete ablation was found between GI group and control group ($p>0.05$). Total treatment duration for one nodule was 624–1,860 s in the GI group and 180–1,620 s in the control group. Although the size of tumors in the GI group had no significant difference with that in the control group, nodules in the GI group required longer duration of ablation than those in the control group; however, it did not require large number of treatment sessions (Table 1).

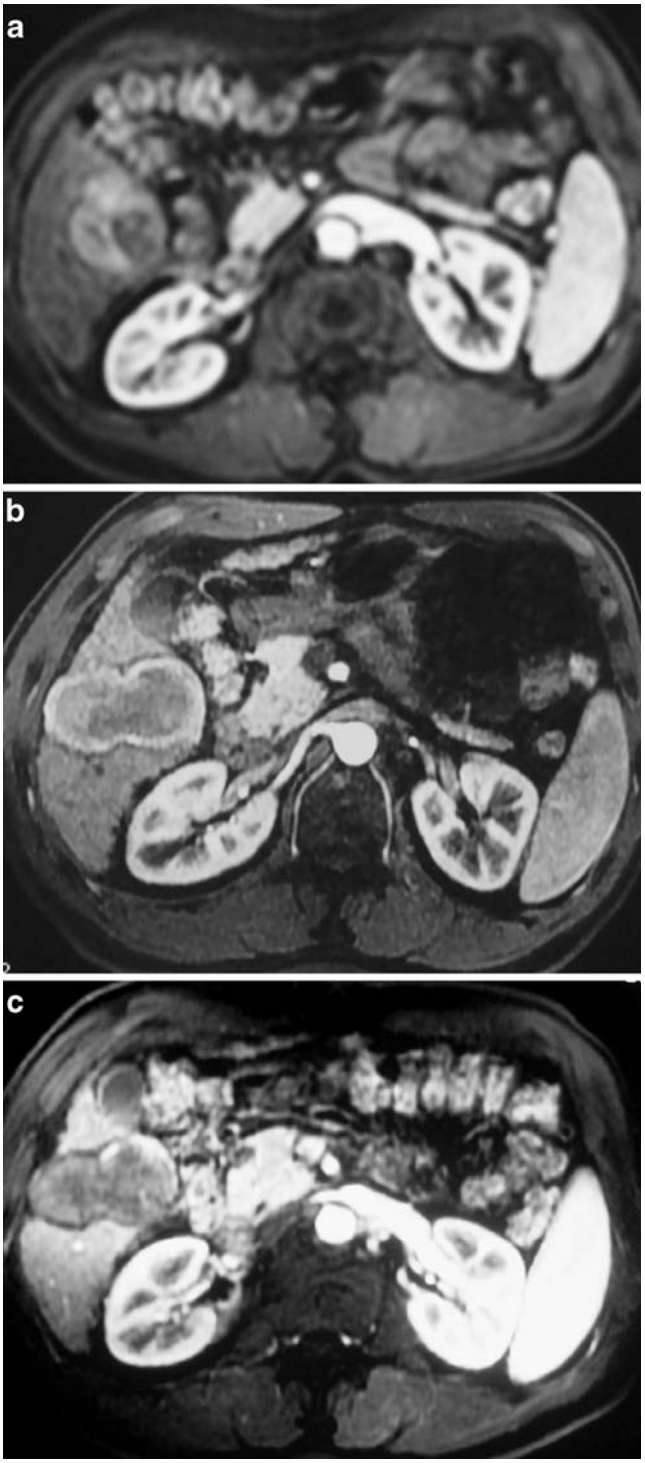

Figure 2 Microwave ablation under the temperature monitoring assisted with ethanol injection for a 58 mm HCC mass close to the bowl loop. **a** MRI showed a protruding hypervascular mass in segment 8 abutting the bowl loop. **b** One month after two sessions of microwave ablation under the temperature monitoring and adjuvant 9-ml ethanol injection, the nodule was completely ablated and showed on contrast-enhanced MRI. The patient suffered no complications. **c** Twelve months after microwave ablation, the nodule had no local tumor progression on contrast-enhanced MRI.

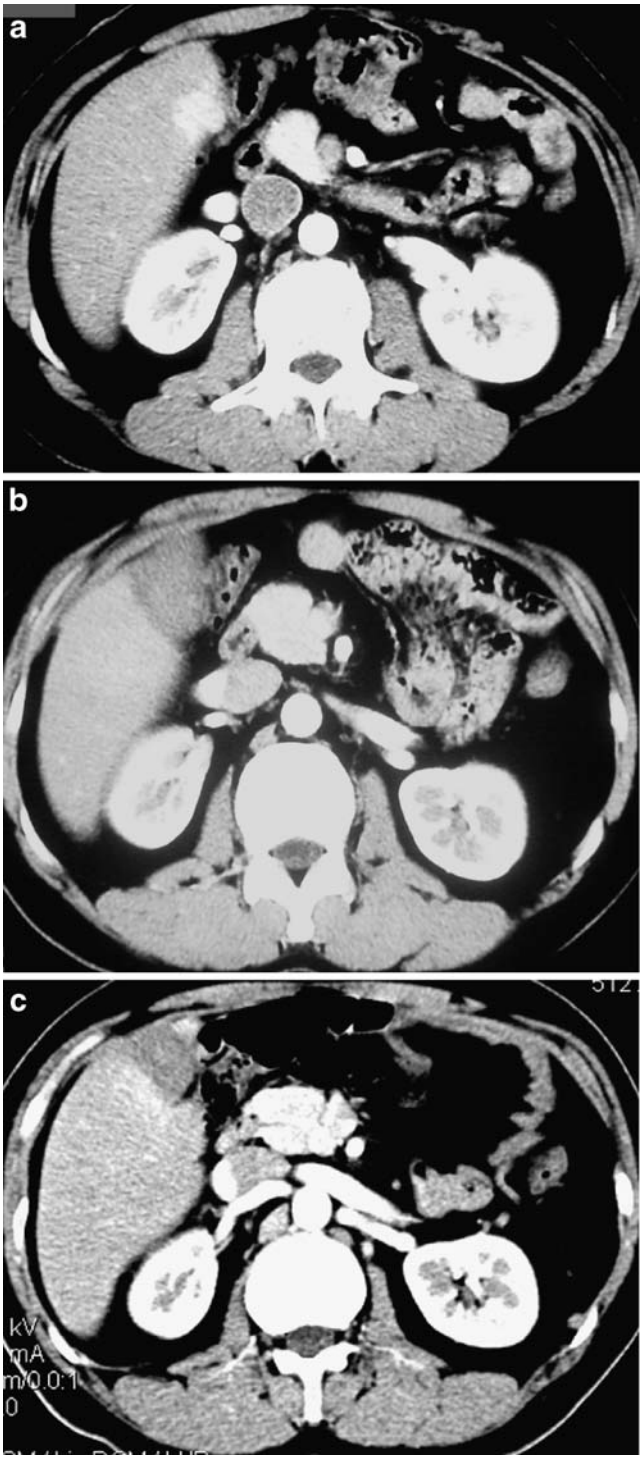

Figure 3 Microwave ablation under the temperature monitoring assisted with ethanol injection for a 25-mm metastatic nodule in contact with the intestinal tract. **a** CT revealed a protruding hypervascular metastatic nodule in segment 6 in contact with the intestinal tract originating from malignant islet cell tumor. **b** One month after one session of microwave ablation under the temperature monitoring and adjuvant 10-ml ethanol injection for the marginal tissue of the tumor proximal to the intestinal tract, the nodule was completely ablated and showed on contrast-enhanced CT. The patient suffered no complications. **c** Twelve months after microwave ablation, the nodule had no local tumor progression on contrast-enhanced CT.

Table 1 Comparison of Therapeutic Data in the GI and Control Groups

	GI group (n=53)	Control group (n=126)	p
Size (mean±SD, mm)	27±12	24±9	>0.05
Number of sessions (mean±SD)	1.2±0.4	1.1±0.3	>0.05
Total duration (s)	955±282	497±242	<0.05

Complications

There were neither immediate nor periprocedural complications in both GI and control groups. There was no gastrointestinal perforation in the GI group. Tumor seeding happened in one case (1.9%) of the GI group at 9 months and in two cases (1.6%) of the control group at 6 and 9 months after ablation. Tumor seeding located at pleura, abdominal wall, as well as hepatic surface received PMWA, HIFU, and TACE separately. No delayed complication of bile ducts injury was found.

Local Tumor Progression

Local tumor progression was found in six of 53 tumors (11.3%) of the GI group at 1–9 months (5.0±3.8 months) follow-up and in ten of 126 tumors (7.9%) of the control group at 1–9 months (4.2±3.3 months) follow-up on contrast-enhanced imagings (p>0.05). The six tumors of recurrence in the GI group abutted the stomach (n=1) and colon (n=5). The site of local tumor progressions located in the vicinity of bowel loop in two cases received PMWA and TACE, respectively, and away from bowel loop in four cases, of which three received PMWA and one received TACE. The maximum diameters of the six tumors were 1.7–5.3 cm (mean 3.3±1.4 cm). No significant statistical difference in the size of tumor was found between completely ablated lesions (range 0.6–6 cm, mean 2.6±1.2 cm) and local tumor progression lesions (p>0.05) in the GI group.

Discussion

In our study, we found no significant difference either in the complication or in the local tumor progression rate between the GI group and control group. Complete ablation was achieved 88.7% in the GI group and 92.1% in the control group on follow-up imaging. The treatment success rate was similar with those reported by others.[10,32] Although the size of tumors in the GI group had no significant difference with that in the control group, nodules in the GI group

required longer duration of ablation than those in the control group because of intermittent emission of microwave antenna to avoid thermal damage to adjacent bowel loops. That result was similar with previous report of radiofrequency ablation (RFA) for such tumors with other adjuvant techniques such as artificial ascites and a balloon interposed between the tumor and gastrointestinal tract.[33–35] However, the number of treatment sessions was not increased in our research, which profit from detailed treatment protocol design and accurate placement of antenna, tissue thermal monitoring needle, and PTC needle.

The major concern for thermal ablation for tumors adjacent to the gastrointestinal tract other than for tumors in other sites was gastrointestinal perforation. Many factors can influence the size of ablation, such as the condition of blood flow and the background of cirrhotic or non-cirrhotic liver, which influence the conductivity of heat to surrounding tissues. However, the main factor of thermal damage in tissue is temperature over the threshold of coagulation. Temperature can be used as a reliable indicator to reflect the pathologic changes of microwave ablation in liver cancers. Thus, we monitored the temperature of marginal tissue of tumor or liver proximal to the gastrointestinal tract to obtain two goals: the first is to avoid thermal damage of adjacent bowel loop and the second is to ensure treatment efficacy of the marginal tissue of tumor. We intended to control the temperature of marginal tissue of tumor lower than 60°C, the threshold temperature of coagulation, to avoid thermal damage of adjacent bowel loop, but higher than 45°C to ensure microwave thermal field covering the marginal field of tumor. We controlled the monitoring temperature in patients with laparotomy history lower than those in patients without laparotomy history. That is because bowel peristalsis in patients without laparotomy history would help to avoid persistent heating of the same area. Adhesion may occur and decrease bowel peristalsis, thus increasing the risk of thermal injure of bowel loop in patients with laparotomy history. Our results—0% immediate and periprocedural complications—show that our modality is safe for the treatment of hepatic tumor adjacent to the gastrointestinal tract.

For those tumors protruding or in contact with the gastrointestinal tract, temperature control of marginal tissue of tumor lower than the threshold temperature of coagulation, we added adjuvant therapy with small dose of ethanol injection in the vicinity of the adjacent bowel loop to achieve complete necrosis of the marginal tissue of tumor. Ethanol injection has two effects: one, procuring chemical ablation for marginal cells of tumor; two, obtaining synergistic necrotizing effect under combining use of ethanol and microwave ablation. Experimental and clinical reports show that combined use of ethanol and radiofrequency or microwave ablation causes a synergistic necrotizing effect, with coagulation volumes clearly larger than those usually obtained with PEI or RFA, MWA alone.[36–38] Our local tumor progression rate was 11.3% in GI group had no statistic significance with control group and are similar to those reported by other investigators.[15,30]

This study had some limitations. First, these data were obtained from a single center at which there was much experience with microwave ablation procedures. Therefore, there was lower local tumor progression. A multicenter study with a larger number of patients and a prolonged observation time is required. Second, at present, a thermal monitoring can get only one-point temperature. The research of multiple-points temperature monitoring with one thermal monitoring needle may be more objective for the monitoring of ablation in the future. Third, this study was our experience with microwave ablation. It may need to be further confirmed whether it can be used in radiofrequency ablation or not.

Conclusion

In conclusion, under the circumstance of strict temperature monitoring, microwave ablation assisted with small dose of ethanol injection for hepatic tumors adjacent to the gastrointestinal tract is safe and can achieve high complete ablation rate. This modality may provide a new way for the treatment of liver cancer adjacent to the gastrointestinal tract.

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ORIGINAL ARTICLE

Prognostic Impact of Surgical Complications and Preoperative Serum Hepatocyte Growth Factor in Hepatocellular Carcinoma Patients After Initial Hepatectomy

Toru Mizuguchi · Minoru Nagayama · Makoto Meguro · Toshihito Shibata · Shinsuke Kaji · Takayuki Nobuoka · Yasutoshi Kimura · Tomohisa Furuhata · Koichi Hirata

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Abstract
Introduction The relationship between postoperative complications and survival after hepatectomy is not completely understood. The purpose of this study was to determine if surgical complications would have a prognostic impact and to identify any difference of the prognostic factors between a complication group and complication-free group for hepatocellular carcinoma (HCC) patients after initial hepatectomy.
Patients and Methods One hundred consecutive HCC patients were analyzed in this study. Operative variables and liver functional markers were compared between the complication group and complication-free group. The diagnostic accuracy for predicting complications was evaluated by the receiver operating characteristic (ROC) curve. The Kaplan–Meier method with log-rank test was employed for survival analysis. Univariate and multivariate analyses were performed to identify the prognostic factors in each group.
Results and discussion A total of 45 complications in 32 patients were observed according to the modified Clavien classification. The albumin, γ-glutamyl transferase, choline esterase, indocyanine green retention rate at 15 min ($ICGR_{15}$), hyaluronic acid, prealbumin, hepatocyte growth factor (HGF), HH15, and LHL15 levels before hepatectomy, operative time, and blood loss were significantly different between the two groups. Multivariate analysis revealed that γ-glutamyl transferase, $ICGR_{15}$, and HGF were independent risk factors for postoperative complications. The values of the areas under the ROC curve for predicting complications proved the significance of the predictions. Although the recurrence-free survival rates were not significantly different, the overall survival rates were significantly different between the two groups. Univariate and multivariate analyses for the overall survival rate showed that the stage of the HCC and HGF for the complication group and tumor size for the complication-free group were independent prognostic factors for overall survival.
Conclusion Postoperative surgical complications could have a prognostic impact on overall survival in HCC patients after initial hepatectomy. Serum HGF could be a factor connected to complications and survival in this group.

Keywords Hepatectomy · Hepatocyte growth factor · Hepatocellular carcinoma · Complication · Prognosis

T. Mizuguchi (✉) · M. Nagayama · M. Meguro · T. Shibata · S. Kaji · T. Nobuoka · Y. Kimura · T. Furuhata · K. Hirata
Department of Surgery I, School of Medicine,
Sapporo Medical University,
S-1, W-16, Chuo-Ku,
Sapporo, Hokkaido 060-8543, Japan
e-mail: tmizu@sapmed.ac.jp

Introduction

The incidence of hepatocellular carcinoma (HCC) has been increasing internationally due to epidemic viral hepatitis.[1,2] Liver resection is one of the best curative therapies for HCC patients who maintain good liver function,[1,2] and assessment of liver functions before surgery is important to avoid liver dysfunction or liver failure.[3–5] Many indicators have been used for the assessment of liver function such as the Child–Pugh score,[3] indocyanine green retention rate at

15 min ($ICGR_{15}$),[3] ^{99m}Tc-galactosyl serum albumin (GSA),[4] and serum hyaluronic acid (HA) levels.[5] Knowledge of these preoperative evaluations, in addition to the improvement of surgical techniques and devices, helps surgeons to perform safe hepatectomy in modern surgery. The mortality in the 1980s was reported to be approximately 10% for major hepatectomy, but has now been reduced to only a few percent.[6,7]

Although the mortality rate in liver surgery has decreased, surgical complications may be inevitable to some degree. If the operative procedure and perioperative management with an appropriate surgical plan are completed without errors, surgical complications should become minimal. In this circumstance, surgical complications could be mostly related to the host condition. Viral-associated HCC develops in the process of disease progression such as chronic hepatitis and liver cirrhosis[8,9] when liver function deteriorates in parallel. Therefore, HCC patients are vulnerable to complications associated with surgical stress.

Many perioperative variables, such as tumor factors (tumor size, number of tumors, extension of the tumor, and vascular invasion), clinical factors (age, liver damage, and α-fetoprotein [AFP]), and operative factors (surgical curability and margin), are related to recurrence and the survival rate after hepatectomy.[10] The cause of death in HCC patients is usually either cancer-related or liver failure-related. Good liver function has the potential to prolong survival due to more chances to receive additional salvage therapy.[11] Therefore, liver function may play an important role in predicting not only postoperative complications but also survival after hepatectomy. However, the relation between postoperative complications and survival after hepatectomy is not completely understood.

Hepatocyte growth factor (HGF) is found in the sera of patients with fulminant liver failure[12] and promotes hepatocyte proliferation, including that of hepatocellular carcinoma cells.[13] Clinically, HGF levels are well-correlated with the worsening of liver disease.[8,9] High HGF levels in the cirrhotic liver correlate with the presence of hepatocellular carcinoma and overall prognosis.[9] We have also reported that the preoperative HGF level correlates with postoperative liver dysfunction.[5] Therefore, HGF is very important not only for mitogenic activity but also as a clinical indicator to predict cancer development, the severity of liver disease, and liver dysfunction after hepatectomy. However, the significance of HGF in predicting postoperative complications in liver surgery has not been clarified yet.

We surveyed patients who had complications after initial hepatectomy and compared them to patients who were discharged on schedule to identify risks for complications after hepatectomy. Furthermore, we hypothesized that the deteriorated patient condition might be a major reason for complications and result in a different clinical prognosis. The aim of this study was to identify prognostic factors among patients who had complications and those who were complication-free after initial hepatectomy in 100 consecutive HCC patients.

Patients and Methods

Patients

Between January 2001 and December 2005, 100 hepatocellular carcinoma patients who underwent hepatectomy were enrolled in this study with informed consent. Mortality was defined as any death in the hospital within 90 days after operation. Postoperative complications were defined and classified by the modified Clavien classification system.[14] Briefly, grade I was any deviation from the normal postoperative course without any special treatment. Grade II was requiring pharmacological treatment with drugs. Grade III was requiring surgical or radiological intervention with (IIIb) or without (IIIa) general anesthesia. Grade IV was a life-threatening complication involving single (IVa) or multiple (IVb) organ dysfunction. Grade V was the death of the patient. Of the complications ranked grade IV or higher, liver failure/insufficiency was defined as a serum bilirubin concentration of more than 10 mg/dL for more than 2 days. Portal vein thrombosis and pulmonary effusion were diagnosed either by ultrasound sonography or computed tomography with enhancement. Pneumonia was diagnosed either by respiratory symptoms with X-ray examination or proof of bacteria. Venous thrombosis was defined by a sudden respiratory distress symptom with decreased peripheral oxygen saturation regardless of proof of a thrombus. Angina pectoris/acute myocardial infarction was defined as chest pain and by electrocardiographic examination. Renal insufficiency was defined by oliguria (less than 400 mL/day) with sustained serum creatine elevation of more than 1.1 mg/dL. Although no mechanical ileus that required nasointestinal tube drainage occurred, paralytic ileus was observed with oral intake of less than 500 mL/day for more than 3 days. Gastrointestinal bleeding was diagnosed by endoscopic examination. Wound infection/dehiscence was defined as any wound that split open regardless of proof of bacteria. Ascites was defined as fluid discharge of more than 300 mL/day for more than 3 days.

We divided the patients into two groups. The complication group consisted of 32 patients who had complications of any grade during the hospital stay. The complication-free group consisted of 68 patients who were discharged within 14 days after hepatectomy. The study design conformed to

the ethical guidelines of the Declaration of Helsinki and obtained informed consent with individual signature prior to registry.

Assessment of Clinical and Operative Variables

Routine laboratory tests conducted before hepatectomy included those for $ICGR_{15}$, hyaluronic acid as a liver fibrotic marker, prealbumin as a rapid turnover protein, HGF, AFP, PIVKAII, and GSA (HH15, LHL15). Intraoperative data and any complications during hospital stays were recorded. Tumor size, number, and vascular invasion were recorded by pathological examinations. All laboratory tests were conducted in the early morning on the day of assessment.

Surgical Procedure

All liver resections were basically performed with Pringle maneuver techniques after more than 300 mL of intraoperative bleeding. No hepatic flow was controlled if intraoperative bleeding was less than 300 mL. A Cavitron ultrasonic aspirator (CUSA) was used for liver parenchymal dissection. Either an argon laser beam coagulator or a saline-linked monopolar electric cautery was used to achieve hemostasis. Antibiotics were administered at 30 min before laparotomy and every 3 h during the operation. Absorbable sutures (Vicryl or PDS, Johnson & Johnson Gateway, Piscataway, NJ, USA) were used for all sutures and ties except for skin closure. Skin was closed with either nylon sutures or a skin stapler. Periwound skin was washed with 500 mL of warm saline before skin closure. Either a closed-type subphrenic or hepatoduodenal drain was placed after hepatectomy and removed 2 or 3 days later.

Statistical Analysis

For statistical analyses, demographic and perioperative laboratory tests were extracted from the database and the differences between the groups were compared using the chi-square test followed by a post hoc 2×2 Fisher exact test, when needed. Logistic regression analysis was used to identify the most relevant risks of complication. Factors determining overall survival were assessed using the Kaplan–Meier method with comparison of the log-rank test and univariate or multivariate analysis using the Cox proportional hazards regression model. The calculations were performed using the StatView 5.0 software package (Abacus Concepts, Berkeley, CA, USA) or SPSS 15.0 (SPSS, Chicago, IL, USA). The receiver operating characteristic (ROC) curve for calculating the area under the ROC curve (AUC) was determined using the MedCalc software package (Version 8.0.1.0, Mariakerke, Belgium). All results are expressed as the mean values± standard deviations (SD). $p<0.05$ was considered to be statistically significant.

Results

In our 100 consecutive hepatectomies for HCC, 45 complications were observed in 32 patients, although 38 of the complications in 26 patients were minor ones (Table 1). Serious grade V complications consisted of two liver failures, one myocardial infarction, and one gastrointestinal hemorrhage. Although one patient recovered after intensive care, he was classified as having grade IVb liver failure and renal failure. Clinical and operative variables were compared between the two groups (Table 2). Although age, sex, the type of virus, pathological background, stage of the HCC, bilirubin, prothrombin time, tumor markers, tumor size, number of tumors, vascular invasion, and type of hepatectomy were not significantly different between the groups, the albumin ($p=0.010$), γ-glutamyl transferase ($p=0.002$), choline esterase ($p=0.008$), $ICGR_{15}$ ($p=0.007$), HA ($p=0.003$), prealbumin ($p=0.004$), HGF ($p=0.005$), HH15 ($p=0.001$), and LHL15 ($p=0.021$) levels before hepatectomy, operative time ($p=0.003$), and blood loss ($p=0.001$) were significantly different. Multivariate analysis revealed that γ-glutamyl transferase ($p=0.002$), $ICGR_{15}$ ($p=0.047$), and HGF ($p=0.003$) were independent risk factors for postoperative complications in our series (Table 3). The area under the ROC curve (AUC) was calculated for three factors (Fig. 1) and all of them were significantly different (γ-glutamyl transferase: $p=0.005$; $ICGR_{15}$: $p=0.002$; HGF: $p<0.001$).

The recurrence-free survival curve and overall survival curve are shown in Fig. 2. Although the recurrence-free survival was not significantly different between the two groups ($p=0.108$), the overall survival probability was significantly different ($p=0.036$). Mean overall survival times were 58.94±4.14 months in the complication-free group and 39.07±5.75 months in the complication group. Univariate (Table 4) and multivariate (Table 5) analyses were performed to identify significant impacts on overall survival among clinical and operative variables in each group independently. Univariate analysis using the Cox proportional hazards model in the complication group revealed that the pathological background ($p=0.031$), stage of the HCC ($p=0.004$), HGF ($p=0.015$), AFP ($p=0.004$), PIVKAII ($p=0.005$), tumor size ($p=0.004$), vascular invasion ($p=0.041$), and blood loss ($p=0.006$) were significant risk factors in this group. On the other hand, in the complication-free group, albumin ($p=0.024$), $ICGR_{15}$ ($p=0.001$), prealbumin ($p=0.001$), tumor size ($p=0.001$), and blood loss ($p=0.018$) were significant risk factors. Multivariate analysis of these factors in the complication group showed that the stage of

Table 1 Postoperative Complications in 32 Patients

Complications	Total number	Grade of surgical complication						
		I	II	IIIa	IIIb	IVa	IVb	V
Liver/biliary								
Liver failure/insufficiency	4					1	1	2
Bile leak	2			2				
Portal vein thrombosis	2		2					
Pulmonary								
Pleural effusion (symptomatic)	6	2	2	2				
Pneumonia	2		2					
Cardiovascular								
Venous thrombosis	2		2					
Angina pectoris/myocardial infarction	1							1
Genitourinary								
Renal insufficiency/failure	2		1				1	
Gastrointestinal								
Ileus	3			3				
Gastrointestinal hemorrhage	2			1				1
Miscellaneous								
Wound infection/dehiscence	8	6	2					
Ascites	11	4	5	2				
Total number (complications/patients)	45/32	38/26				7/6		

Grades of surgical complications are according to modified Clavien classification

Table 2 Clinical and Operative Variables in HCC Patients After Initial Curative Hepatectomy

Variables	Complication (n=32)	Complication-free (n=68)	p value
Age (years)	64.69±8.65	61.87±10.45	0.189
Sex (male/female)	26:6	50:18	0.391
Etiology (B/C/NBNC)	18:13:1	43:19:6	0.101
Background (CH/LC/N)	9:21:2	27:32:9	0.199
Stage (I/II/III/IV)	5:10:12:5	17:22:20:9	0.707
Albumin (g/dL)	3.73±0.43	3.95±0.44	0.010*
Bilirubin (mg/dL)	0.92±0.39	0.84±0.36	0.243
Prothrombin time (%)	93.19±17.44	98.59±12.15	0.081
γ-Glutamyl transferase (IU/L)	140.05±108.36	87.54±81.15	0.002*
Choline esterase (IU/L)	193.74±71.13	233.25±79.97	0.008*
$ICGR_{15}$ (%)	18.32±9.14	13.73±8.73	0.007*
Hyaluronic acid (ng/mL)	264.25±251.65	162.12±142.61	0.003*
Prealbumin (mg/dL)	13.96±6.79	18.75±7.76	0.004*
HGF (ng/mL)	0.43±0.22	0.33±0.14	0.005*
AFP (ng/mL)	5,254.56±17,866.77	2,164.15±11,688.14	0.236
PIVKAII (mAU/mL)	4,718.72±16,174.82	4,955.79±19,361.02	0.947
HH15	0.652±0.095	0.593±0.074	0.001*
LHL15	0.902±0.055	0.924±0.037	0.021*
Tumor size (cm)	4.69±3.31	4.54±3.44	0.820
Tumor number	1.97±1.44	1.69±1.21	0.267
Vascular invasion (negative/positive)	16:16	36:32	0.783
Type of resection (Hr0 or HrS/Hr1/Hr2/Hr3)	19:4:6:3	42:15:9:2	0.063
Operation time (min)	425.91±279.06	298.23±96.01	0.003*
Blood loss (mL)	1,308.78±1,474.34	562.17±503.54	0.001*

HCC: hepatocellular carcinoma, *B*: HBV, *C*: HCV, *NBNC*: non-B and non-C hepatitis, *CH*: chronic hepatitis, *LC*: liver cirrhosis, *N*: normal liver, $ICGR_{15}$: indocyanine green retention rate at 15 min, *AFP*: alpha fetoprotein, *PIVKAII*: protein induced by vitamin K absence or antagonist II, *HH15*: clearance index, *LHL15*: receptor index, *Hr0*: partial resection, *HrS*: subsectionectomy, *Hr1*: sectionectomy, *Hr2*: hemihepatectomy, *Hr3*: trisectionectomy

*$p<0.05$

Table 3 Logistic Regression Analysis for Contributing to Risk of Complications After Liver Resection in HCC Patients

Variables		Odds ratio	95%CI	*p* value
Albumin (g/dL)	>4.0	1	0.245–5.929	0.819
	≤4.0	1.204		
γ-Glutamyl transferase (IU/L)	<100	1	2.216–33.278	0.002*
	≥100	8.587		
Choline esterase	≥200	1	0.092–2.736	0.425
	<200	0.502		
$ICGR_{15}$ (%)	<10	1	1.026–35.500	0.047*
	≥10	6.034		
Hyaluronic acid (ng/mL)	<130	1	0.026–1.097	0.062
	≥130	0.168		
Prealbumin (mg/dL)	≥15	1	0.591–11.788	0.204
	<15	2.639		
HGF (ng/mL)	<0.35	1	2.392–65.979	0.003*
	≥0.35	12.562		
HH15	<0.60	1	0.210–4.315	0.951
	≥0.06	0.953		
LHL15	≥0.9	1	0.665–16.331	0.144
	<0.9	3.295		
Operation time (min)	<300	1	0.704–11.218	0.143
	≥300	2.810		
Blood loss (mL)	<600	1	0.125–2.437	0.432
	≥600	0.551		

HCC: hepatocellular carcinoma, *$ICGR_{15}$*: indocyanine green retention rate at 15 min, *HGF*: hepatocyte growth factor, *HH15*: clearance index, *LHL15*: receptor index
*$p<0.05$

the HCC ($p=0.036$) and HGF ($p=0.006$) were significant independent risk factors for overall survival, but in the complication-free group, tumor size ($p=0.015$) was the only significant independent risk factor for overall survival.

Discussion

We showed in this study that perioperative complications could be risk factors indicative of overall prognosis. Among

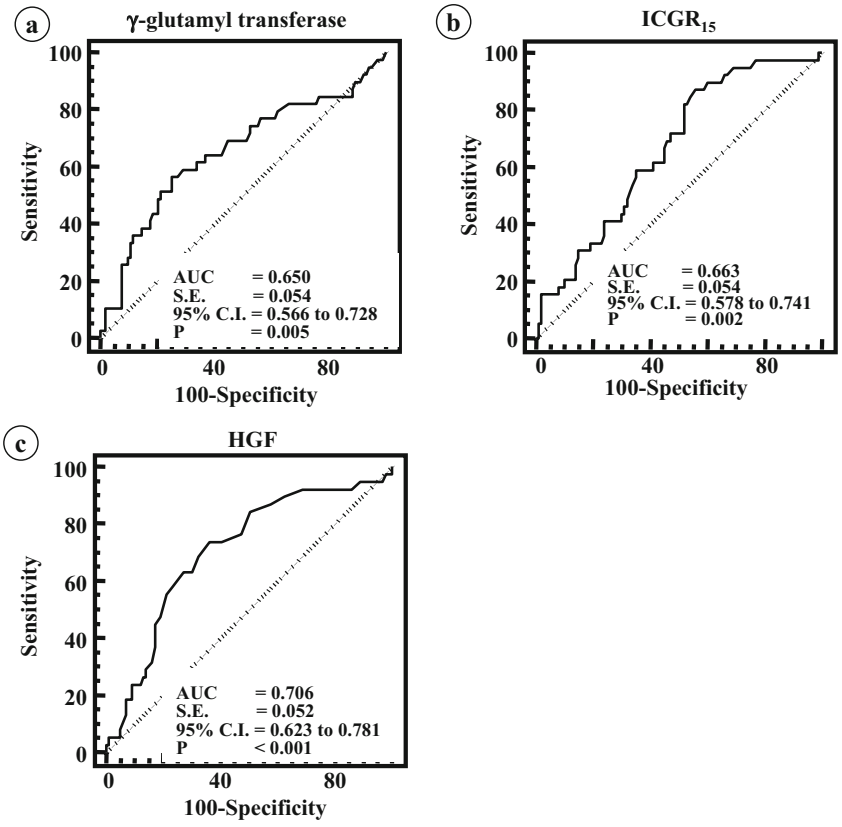

Figure 1 ROC curves of γ-glutamyl transferase (**a**), $ICGR_{15}$ (**b**), and HGF (**c**) for predicting complications after initial hepatectomy for HCC patients. *AUC* area under the ROC curve, *S.E.* standard error, *C.I.* confidence interval. $p<0.05$ was considered to be significant.

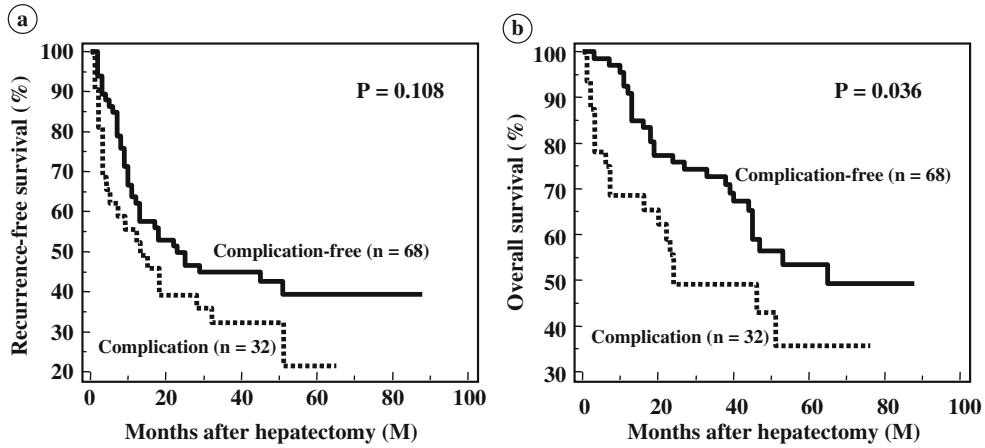

Figure 2 Recurrence-free survival curve (**a**) and overall survival curve (**b**) after initial hepatectomy for 100 HCC patients in the complication group (n=32, *dotted line*) and complication-free group (n=68, *solid line*). Mean recurrence-free times in the complication group and the complication-free group were 25.64±4.69 and 43.26±4.74 months, respectively (p=0.108). Mean overall survival times in the complication group and the complication-free group were 39.07±5.75 and 58.94±4.14 months, respectively (p=0.036).

the clinical and operative variables, γ-glutamyl transferase, $ICGR_{15}$, and HGF were independent risk factors for postoperative complications. Furthermore, HGF was an independent prognostic factor in the complication group in addition to the stage of the HCC. On the other hand, tumor size was the only independent prognostic factor in the complication-free group. Our study indicated a close relation between postoperative complications and overall survival in HCC patients after initial hepatectomy.

Morbidity and mortality after hepatectomy have been reduced by recent surgical procedures.[6,11,15] However, the quality of postoperative complications is still being debated. In fact, morbidity due to hepatectomy varied from 10% to 50% in a past study.[16] The variability of the morbidity in the literature was due to a lack of proper definition of surgical complications.[17] Recently, a definition of surgical complications has been proposed with a clear classification. The modified Clavien classification of surgical complications is a well-organized system in which any deviation from the normal perioperative course can be recorded.[14] Based on this classification, bias with regard to surgical complications in our study could be minimized.

Under minimal bias of surgical complications, morbidity reflects the balance between the patient's condition and surgical skill or management. The large case study of Blumgart and colleagues found that the number of resected segments and estimated blood loss were high risk factors for morbidity and mortality after hepatectomy.[18] Another study of 100 major hepatic resections also showed that blood transfusion, which was associated with blood loss, was a risk factor for morbidity after surgery.[19] These reports indicated that there was more bleeding and longer operation time in more severe cases in which the patient's condition might deteriorate and become vulnerable to surgical complications. Although our results showed that operation time and blood loss lost significance in multivariate analysis, in univariate analysis they were significantly different, which was partly consistent with previous reports. Furthermore, the hepatic background in the complication-free group tended to be less cirrhotic, which could make it easier control bleeding than in the complication group, although there was no significant difference between the groups. We, however, could not rule out the possibility that we employed less-invasive hepatic resection in cirrhotic cases and more aggressive hepatic resection in normal cases. As long as we conducted our routine liver resection for HCC patients, the intrinsic patient condition was a more significant risk factor for postoperative complications in our 100-case series than operative variables. Therefore, it is possible that we could not have prevented most postoperative complications in our series even if our surgical approach were reconsidered to reduce morbidity. In other words, postoperative complications are dependent on the patient's condition and cannot be totally avoided.

Furthermore, our study showed the prognostic impact of postoperative complications for HCC patients, although disease-free survival was not significantly different. The prognosis of the HCC patient after hepatectomy partially depends on the liver function,[11] which is associated with increased opportunities for various treatments. The longer overall survival in the complication-free group indicated that fundamental liver function in this group was better than that in the complication group. In fact, comparison of clinical variables between the two groups indicated that liver function in the complication-free group was much better than that of the complication group. Therefore, the survival difference between the groups was most likely due to the difference of fundamental liver function. If surgical complications randomly occurred due to technical errors, liver functions should have been similar between the

Table 4 Univariate Analysis for Clinical Factors Contributing to Overall Survival After Liver Resection in HCC Patients

Variables		Complication (n=32)				Complication-free (n=68)			
		n	Hazard ratio	95%CI	p value	n	Hazard ratio	95%CI	p value
Age (years)	<65	13	1	0.634–4.828	0.280	35	1	0.438–2.294	0.994
	≥65	19	1.749			33	1.003		
Sex	Men	26	1	0.466–4.567	0.516	50	1	0.262–2.273	0.638
	Women	6	1.459			18	0.772		
Etiology (NBNC, B/C)	N, B	19	1	0.460–3.284	0.681	49	1	0.279–1.801	0.469
	C	13	1.229			19	0.709		
Background (N, CH/LC)	N, CH	11	1	1.085–5.552	0.031*	36	1	0.593–3.870	0.386
	LC	21	2.455			32	1.514		
Stage (I, II/III, IV)	I, II	15	1	1.801–22.972	0.004*	39	1	0.990–6.181	0.052
	III, IV	17	6.433			29	2.474		
Albumin (g/dL)	≥4.0	9	1	0.412–4.086	0.656	34	1	1.143–6.850	0.024*
	<4.0	24	1.297			34	2.798		
Bilirubin (mg/dL)	<1.0	24	1	0.559–4.705	0.373	51	1	0.738–4.128	0.205
	≥1.0	8	1.622			17	1.745		
Prothrombin time (%)	≥90	20	1	0.590–4.273	0.360	52	1	0.560–3.390	0.485
	<90	12	1.588			16	1.378		
γ-Glutamyl transferase (IU/L)	<100	12	1	0.799–7.845	0.115	52	1	0.615–3.447	0.392
	≥100	20	2.504			16	1.457		
Choline esterase (IU/L)	≥200	17	1	0.519–3.761	0.508	46	1	1.933–10.418	0.001*
	<200	15	1.397			22	4.488		
$ICGR_{15}$ (%)	<10	5	1	0.491–28.439	0.203	42	1	0.957–6.314	0.062
	≥10	27	3.736			26	2.457		
Hyaluronic acid (ng/mL)	<130	11	1	0.712–8.786	0.152	39	1	1.868–11.168	0.001*
	≥130	21	2.501			29	4.568		
Prealbumin (mg/dL)	≥15	12	1	0.856–10.588	0.585	45	1	2.075–12.015	0.001*
	<15	20	3.011			23	4.993		
HGF (ng/mL)	<0.35	20	1	1.424–29.258	0.015*	50	1	0.937–5.288	0.069
	≥0.35	12	6.456			18	2.226		
AFP (ng/mL)	<100	20	1	1.615–12.671	0.004*	47	1	0.499–2.786	0.707
	≥100	12	4.524			21	1.179		
PIVKAII (mAU/mL)	<100	16	1	1.766–24.099	0.005*	39	1	0.657–3.384	0.339
	≥100	16	6.524			29	1.491		
HH15	<0.60	13	1	0.335–5.063	0.703	35	1	0.336–3.028	0.987
	≥0.06	19	1.301			33	1.009		
LHL15	≥0.9	13	1	0.134–2.106	0.368	54	1	0.398–5.317	0.571
	<0.9	19	0.532			14	1.454		
Tumor size (cm)	<5	19	1	1.645–15.717	0.004*	53	1	2.137–12.790	0.001*
	≥5	13	5.085			13	5.228		
Tumor number	Single	18	1	0.834–7.505	0.101	40	1	0.900–5.267	0.084
	Multiple	14	2.502			28	2.177		
Vascular invasion	Negative	16	1	1.052–10.804	0.041*	36	1	0.831–4.892	0.122
	Positive	16	3.371			32	2.016		
Type of resection (Hr0,S/Hr1–3)	Hr0,S	19	1	0.545–3.974	0.446	42	1	0.369–2.726	0.995
	Hr1–3	13	1.471			26	1.003		
Operation time (min)	<300	12	1	0.764–7.516	0.134	40	1	0.198–2.107	0.468
	≥300	20	2.396			28	0.645		
Blood loss (mL)	<600	13	1	1.795–35.245	0.006*	44	1	1.146–10.853	0.018*
	≥600	19	7.953			24	3.526		

HCC: hepatocellular carcinoma, *B*: HBV, *C*: HCV, *NBNC*: non-B and non-C hepatitis, *CH*: chronic hepatitis, *LC*: liver cirrhosis, *N*: normal liver, $ICGR_{15}$: indocyanine green retention rate at 15 min, *HGF*: hepatocyte growth factor, *AFP*: alpha fetoprotein, *PIVKAII*: protein induced by vitamin K absence or antagonist II, *HH15*: clearance index, *LHL15*: receptor index, *Hr0*: partial resection, *HrS*: subsectionectomy, *Hr1*: sectionectomy, *Hr2*: hemihepatectomy, *Hr3*: trisectionectomy

*p<0.05

Table 5 Multivariate Analysis for Contributing to Overall Survival After Liver Resection in HCC Patients

Variables		Hazard ratio	95%CI	*p* value
Complication (n=32)				
Stage (I, II/III, IV)	I, II	1	1.301–3896.771	0.036*
	III, IV	72.212		
HGF (ng/mL)	<0.35	1	4.146–5421.990	0.006*
	≥0.35	149.935		
AFP (ng/mL)	<100	1	0.119–157.582	0.423
	≥100	4.335		
PIVKAII (mAU/mL)	<100	1	0.252–18.559	0.482
	≥100	2.161		
Tumor size (cm)	<5	1	0.009–2.414	0.179
	≥5	0.147		
Blood loss (mL)	<600	1	0.650–106.304	0.103
	≥600	8.312		
Complication-free (n=68)				
Albumin (g/dL)	≥4.0	1	0.278–10.507	0.562
	<4.0	1.710		
Choline esterase (IU/L)	≥200	1	0.074–6.846	0.766
	<200	0.710		
Hyaluronic acid (ng/mL)	<130	1	0.745–18.819	0.109
	≥130	3.744		
Prealbumin (mg/dL)	≥15	1	0.412–38.993	0.232
	<15	4.008		
Tumor size (cm)	<5	1	1.377–21.299	0.015*
	≥5	5.416		
Blood loss (mL)	<600	1	0.255–6.916	0.736
	≥600	1.328		

HCC: hepatocellular carcinoma, *CI*: confidence interval, *HGF*: hepatocyte growth factor, *AFP*: alpha fetoprotein, *PIVKAII*: protein induced by vitamin K absence or antagonist II
*$p<0.05$

groups. In such a case, no survival impact would be observed and our results could not have been obtained. Therefore, complications could become a prognostic factor as long as the surgical technique and management are properly conducted.

In the complication group, HGF was one of the independent prognostic factors besides the stage of the disease. The serum HGF level represents the severity of clinical liver disease.[8,9] HGF is correlated with pathological fibrosis and the presence of hepatocellular carcinoma.[9] Severe pathological fibrosis could be a cause of perioperative complications and the presence of HCC leading to a poor prognosis. In the complication group, high HGF indicated disease deterioration with poor liver function. Additional therapy for recurrence in this group was difficult due to poor liver function. Basically, HGF function in the normal liver could play an important role for hepatocyte survival and tissue remodeling.[20] However, our study and others seem to show controversial results in the clinical setting. This indicates that the liver is desensitized to HGF signals for some reason when liver disease deteriorates. Therefore, a high HGF level in a diseased patient does not have a biological effect on the diseased liver. This suggests that the function of c-*met*, as an HGF receptor, may decrease or the activity of HGF itself may be reduced. Receptor abnormality[21] and the inactive form of HGF[22] are considered to be potential mechanisms of the HGF elevation in liver disease, including HCC. In some way, the mechanism quenching HGF from the serum fails and the signals never go through the hepatocytes. On the other hand, cancer cells, apart from the normal hepatocytes, might respond to mitogenic activity of HGF, which might promote disease progression and affect overall survival.

Conclusion

We surveyed 100 consecutive HCC patients who had initial hepatectomy. Postoperative complications were recorded with the modified Clavien classification. We have shown that postoperative surgical complications could be a prognostic factor for overall survival in our study. Furthermore, a high serum HGF level could be a risk factor for complications and overall survival in this group, although we observed no difference of recurrence-free time between the groups due to the small number of subjects on this study. A large number of multiple center trials should be designed to clarify the prognostic value of the preoperative HGF level in the future.

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ORIGINAL ARTICLE

Ultrasound Monitoring of a Novel Microwave Ablation (MWA) Device in Porcine Liver: Lessons Learned and Phenomena Observed on Ablative Effects Near Major Intrahepatic Vessels

S. Garrean · J. Hering · A. Saied · P. J. Hoopes · W. S. Helton · T. P. Ryan · N. J. Espat

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Abstract
Background Microwave ablation (MWA) is postulated to have several advantages over other thermoablative modalities in the treatment of hepatic tumors. Herein, we use an in vivo porcine model to determine the effect of hepatic blood flow on a novel MWA applicator.
Methods Four 100-kg pigs underwent hepatic MWA (2,450 MHz, 100 W, 4 min) using a 5.7-mm diameter applicator (Microsulis Americas, Sulis™ V) inserted near large intrahepatic blood vessels. Real-time monitoring was performed using 3, 5, and 12 MHz diagnostic ultrasound transducers. The ablated zones were sectioned for gross and histological processing.
Results Ablation zones were uniform in shape and size (3–4 cm) and related to power deliver only. Gross and microscopic examination revealed direct extension of ablation zones to the margin of major hepatic blood vessels and occasionally beyond the intended target. Of note, a momentary acoustic white-out occurred around the probe at 25±−1 s in every ablation.
Discussion The Sulis V^{TM} MWA applicator produced uniform zones of ablation that remain unaffected by convective heat loss. The applicator induced a reproducible but temporary event as seen by ultrasound. Further study is warranted to define the physics, benefits, limits, and clinical safety of this new MWA technology.

S. Garrean · J. Hering · A. Saied
Department of Surgery, University of Illinois at Chicago, Chicago, IL, USA

P. J. Hoopes
Department of Pathology, Dartmouth Medical School, Hanover, NH, USA

W. S. Helton
Chair of Surgery, Hospital of Saint Rafael, New Haven, CT, USA

T. P. Ryan
Freefall Consulting, Marrero, LA, USA

N. J. Espat (✉)
Hepatobiliary and Oncologic Surgery, Roger Williams Cancer Center, 825 Chalstone Ave. Prior 4, Providence, RI 02908, USA
e-mail: espat@hepaticsurgery.com

Keywords Microwave ablation · Microwave coagulation · Convective heat loss · Hepatic tumor · 2,450 MHz

Introduction

Surgical resection remains the optimal treatment strategy for hepatic malignancy; however, most patients with hepatic tumors are not amenable to resection. Consequently, liver-directed ablative technologies have been developed for the treatment of patients with unresectable hepatic tumors. Several technologies for hepatic tumor ablation are available, including laser, cryotherapy, radiofrequency, and microwave-based energy sources. However, radiofrequency ablation (RFA) and microwave ablation (MWA) are the two dominant modalities currently in the algorithms of hepatic tumor management.

Both RFA and MWA employ electromagnetic radiation to thermally ablate hepatic tumor. In RFA, various configurations of needle arrays (i.e., one to three needle electrodes) are inserted into the tumor, and a high-frequency (20–1,200 Hz) alternating current is passed back and forth through the tissue to grounding pads. Rapid ionic agitation ensues, leading to frictional heating. The needles deposit power to a depth of 1–2 mm, and thermal conduction carries the heat to greater depths over time, causing coagulation necrosis of the tumor tissue. Similarly, in MWA, an applicator is inserted into tissue and acts as microwave antenna, launching a wave into the hepatic tumor. Single or multiple antennas (arrays) are used to transmit microwave energy at a frequency of 915 or 2,450 MHz into the tumor tissue. The microwave antennas induce rotation of dipoles found in water molecules, causing them to rotate with changes in the electromagnetic field. Due to internal friction in the cells, each dipole becomes a heating source; thus, microwaves heat in the near and far fields simultaneously, immediately affecting tissue temperature at a radius of 10–20 mm. Rapid frictional heating from dipole rotation results in coagulation necrosis of tissue.[1–3]

Both RFA and MWA are safe, effective, and easy to use. However, RFA has several disadvantages when compared to MWA. RFA is poorly visualized on ultrasound due to artifact caused by the activation of RF power, making the procedure difficult to monitor.[4] RFA is also prone to tissue charring; applicators typically must be kept below a source temperature of 100°C to avoid sticking to tissue and to avoid buildup of crusted tissue that will insulate the source needle from the tissue causing the system to halt ablation. Additionally, due to shallow tissue penetration, convective heat loss from the heat-sink effect of local blood flow represents a challenge to RFA heating, necessitating longer heating times.[5–7] Both tissue charring and convective heat loss result in residual tumor cells at the tumor periphery and blood vessel margins.[8,9]

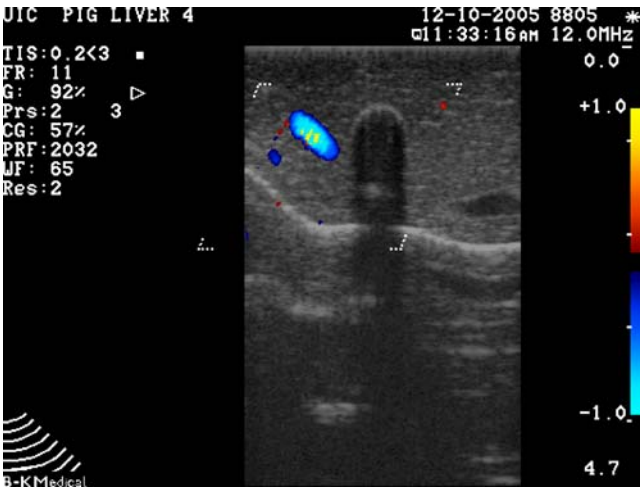

Figure 1 MWA probe is adjacent to portal vein branch.

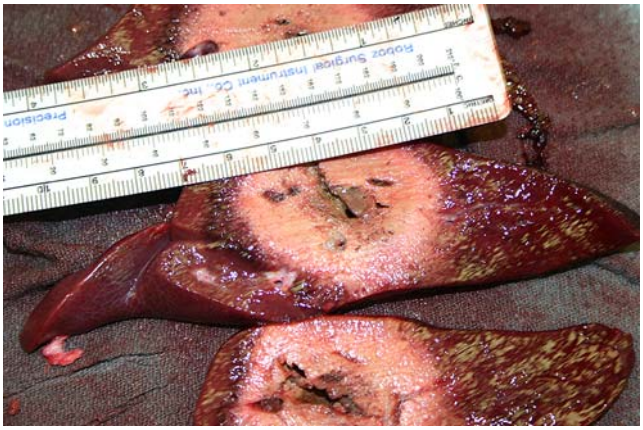

Figure 2 Concentric ablation.

Though used less frequently than RFA in clinical practice, MWA may be a superior ablation modality due to its greater penetration of energy into tissue with the potential to overcome the limitations faced by RFA. MWA has better visibility on ultrasound, with no visible artifact, and does not produce tissue charring.[10] In addition, unlike RFA applicators that require direct electrical contact with tissue (i.e., bare metal), MWA applicators are coated with nonstick plastic, as microwaves easily penetrate this material. It is also presumed that due to the penetration of microwaves, the technology may be less susceptible to convective heat loss from hepatic blood flow, though this presumption has yet to be systematically studied.

In this study, the authors used an *in vivo* porcine model to evaluate the effect of hepatic blood flow on a novel MWA device.

Methods

Four 100-kg pigs underwent laparotomy under general anesthesia. Using ultrasound (US) guidance, a 5.7-mm diameter MWA applicator (MicroSulis Americas, Sulis™ V) was inserted into the liver to a depth of 5 cm; the tip was positioned so that it was in close proximity (within 2 cm) to major hepatic vessels (Fig. 1). A 2,450-MHz generator was then used to deliver 70–100 W for 4 min in four separate areas of the liver. MWA was monitored using real-time US with 3, 5, and 12 MHz transducers (B&K Medical). During some ablations, hepatic blood flow was interrupted by a Pringle maneuver. One heating was done after expiration of the pig. After completion of MWA, livers were explanted and the ablated zones multiply sectioned (in a bread loaf fashion) from above the ablation zone to below the zone for gross inspection and measurements prior to formalin fixation.

Results

The Sulis™ V MWA applicator (Microsulis) produced rapid, repeatable, and uniform ablation of porcine liver tissue, even around large blood vessels. With standard power settings between 70 and 100 W, ablation diameters of 3 to 6.54 cm were consistently achieved within 4 min. Despite being in close proximity to large blood vessels, ablation zones remained uniform in size (3–4 cm) and related to power delivery only. While the presence of local blood flow did not significantly attenuate ablation zone size, reduction of blood flow by the Pringle maneuver resulted in a 70% increase in gross diameter of ablation zones.

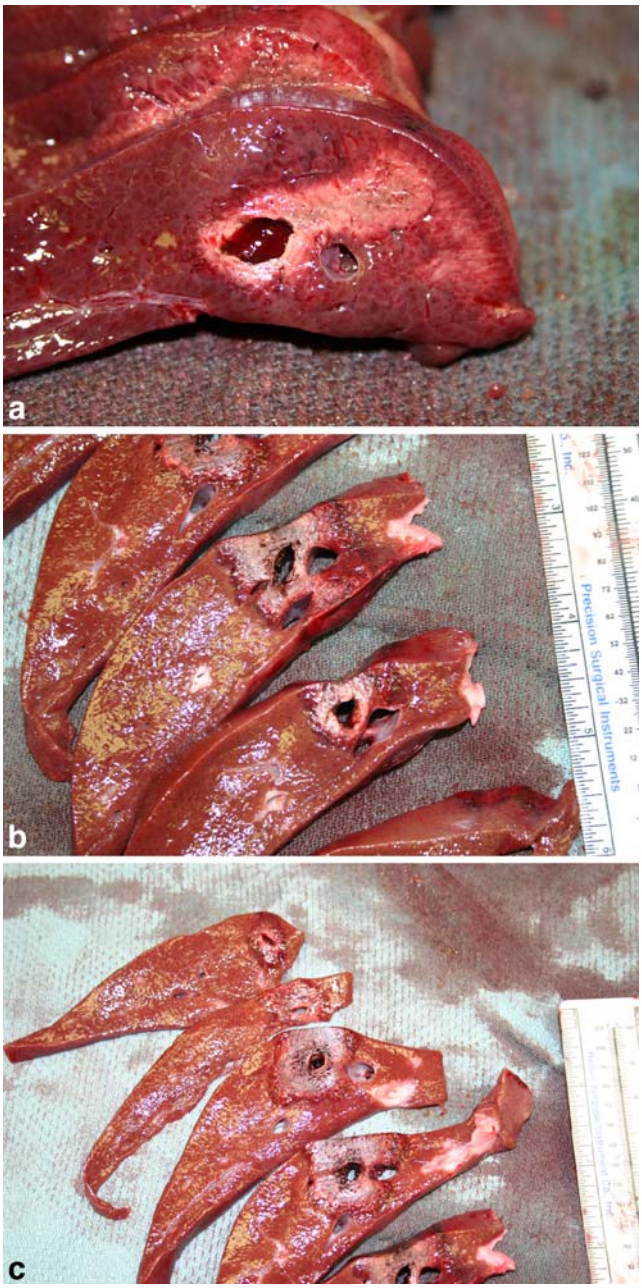

Figure 3 The shape of ablation was marginalized by the blood vessel in (**a**) but minimally affected by large hepatic veins in (**b**) and (**c**).

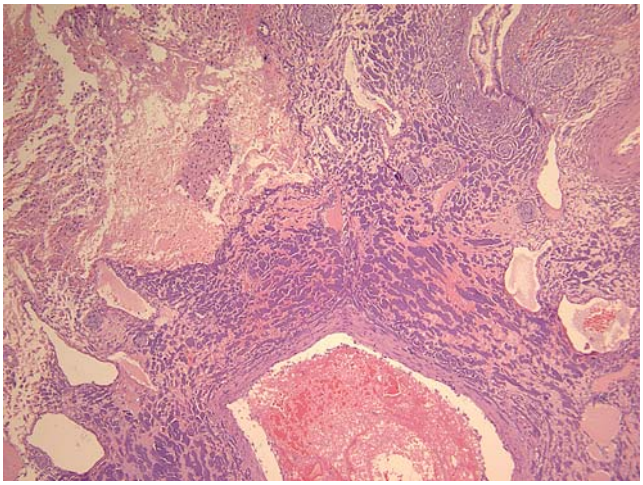

Figure 4 Coagulative necrosis is noted surrounding the hepatic artery branch. (H&E×16).

The shape of ablation zones also appeared unaffected by hepatic blood flow. Ablation zones were nearly always concentric (Fig. 2), though they were occasionally "indented" by large blood vessels (Fig. 3). This suggests that some degree of convective heat loss may have occurred. However, microscopic examination revealed uniform coagulative necrosis circumferentially around both arteries and veins (Figs. 4 (H&E×16) and 5, (H&E×16, 200)), indicating that ablation was not impaired by heat-sink from local blood flow.

Real-time monitoring of MWA was performed using 12, 5, and 3 MHz US transducers. Unlike the 3 and 5 MHz transducers, the 12 MHz probe provided excellent resolution to the submillimeter level. The 12 MHz probe also demonstrated three distinct concentric zones of injury (Fig. 6): edema, hemorrhagic rim, and dessicated zone (outside to inside, respectively). These zones of injury were present both on US as well as gross and histological examination (Fig. 7). In addition to clearly delineating the zones of injury, 12 MHz US was also able to show evidence of "thermal tracking." Thermal-induced injury could be observed by US along small hepatic veins emanating from the core ablation zone and extending centripetally far from the central zone of ablation. In some cases, this "tracking of heat" was associated with the formation of venous thrombus in the small vessels. Cell viability was confirmed around the desiccation zones, surrounding the major vessels, using reduced NADH-diaphorase staining (figure not shown).

Another important observation made during MWA was the phenomenon of "steam popping." In every ablation, a highly reproducible event occurred around the probe at 25±1 s. The explosion was heard as a "pop" and was accompanied by

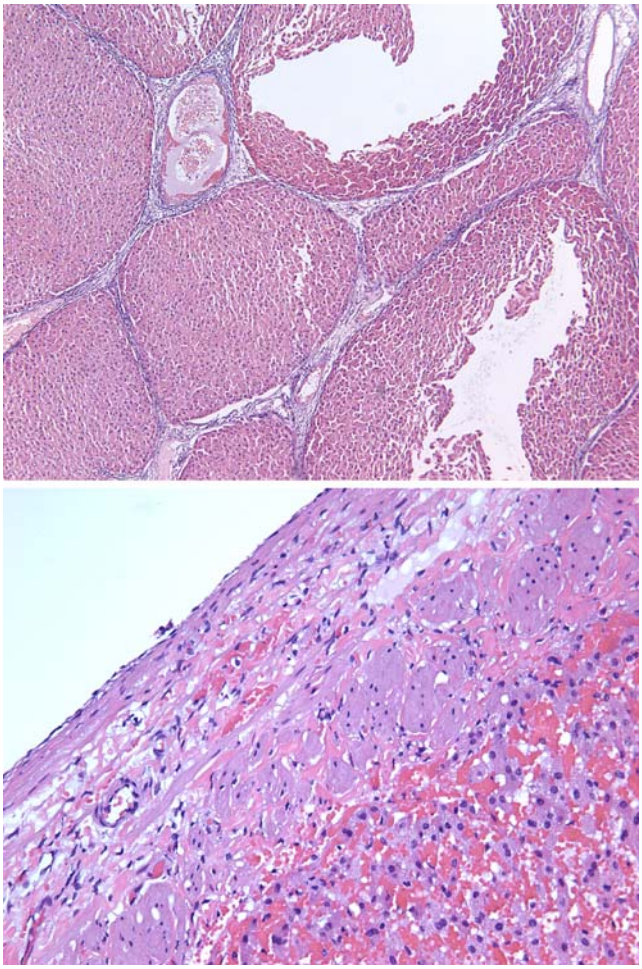

Figure 5 Necrosis extends through and around the vessel; no sparing of tissue from "heat sink" is observed. (H&E×16, 200).

momentary acoustical white-out on real-time US. In one ablation, this event was associated with cracking and hemorrhage of the liver parenchyma; application of 100-W microwave energy for an extra 30 s resulted in complete

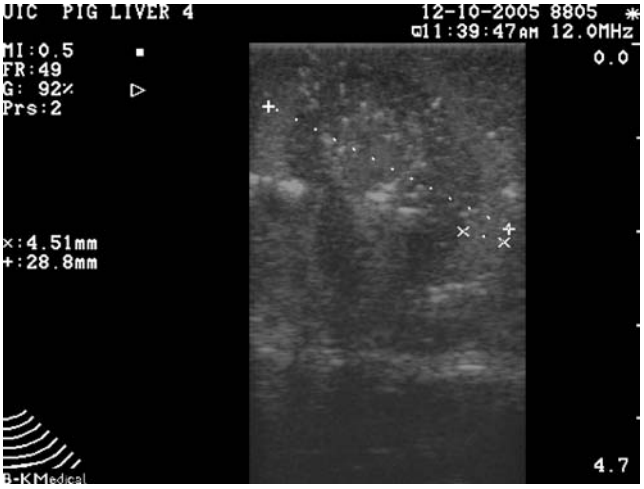

Figure 6 Distinct zones of injury seen by 12 MHz transducer.

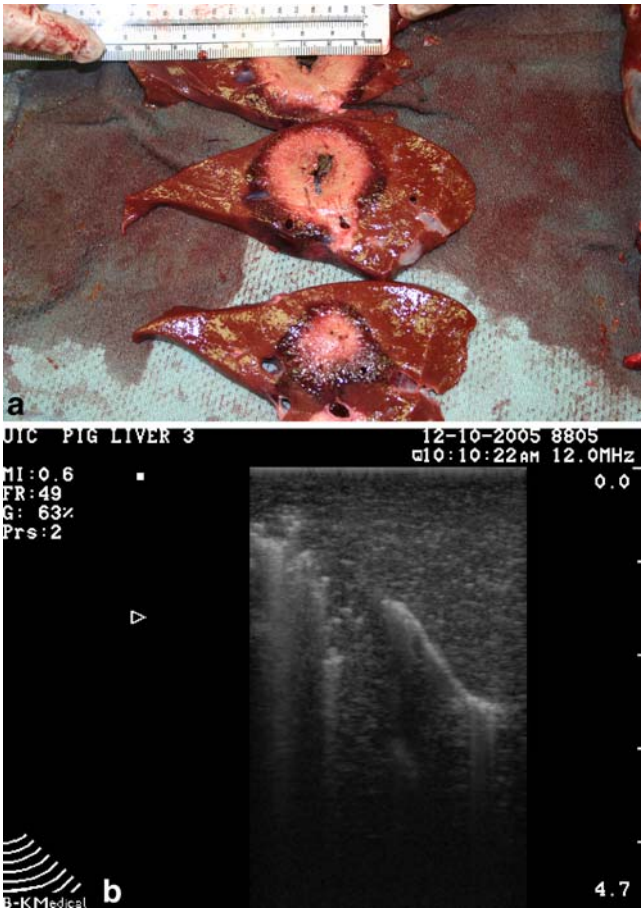

Figure 7 Zone of injury seen along afferent hepatic vein (**a**) which was observed in real time by US (**b**).

cessation of bleeding. Of note, the timing of this phenomenon was independent of hepatic blood flow and, hence, was not affected by convective heat loss. In most cases (15 of 16 ablations), the large applicator was removed from the liver with no bleeding along the track. The applicator was easily cleaned due to the coating of the nonstick surface.

Discussion

Microwave coagulation was first developed in the 1980s as a tool to facilitate hemostasis during hepatic parenchymal transection.[11] While it proved not to be useful in this regard, microwave coagulation was later adapted for the ablation of hepatic malignancies.[12] MWA of hepatic tumors is now considered a safe and effective treatment strategy for unresectable hepatic tumors. Compared to the more widely used thermal ablation device RFA, MWA possesses several theoretical and practical advantages.

Unlike RFA, MWA is not dependent upon the conduction of electricity by water and as such is not limited by tissue charring. In RFA, ablation is accomplished by the passage of

high-frequency alternating current via water in the tumor tissue. As temperatures rise above 100 C, tissue water evaporates, increasing resistance and inhibiting conduction of current. Increased tissue resistance, coupled with loss of the heat sink from tissue water, results in rapid temperature increase, leading to tissue charring and impaired distribution of thermal energy to the lesion periphery.[5,10]

Because it does not involve conduction of electricity but rather direct application of microwave energy, MWA is not detrimentally affected by tissue desiccation and, therefore, can achieve higher intratumoral temperatures, faster ablation times, and larger ablation volumes. In fact, dessicated tissue in the near field of the applicator is actually more transparent to microwaves, thus, providing deeper penetration during ablation.[13] In our study, we observed markedly faster ablation times with the Microsulis MWA device compared to conventional RFA. Ablation diameters of 3 to 4 cm were readily achieved between 1.5 and 4 min with MWA, whereas conventional RFA devices are known to take as long as 10 to 20 min to create comparable ablation diameters.[5] Furthermore, the Microsulis MWA probe produced uniformly large spheres of ablation with only a single applicator deployment. This is in contrast to traditional MWA devices that have been limited to low power operation necessitating short applications of power and multiple needle deployments, as well as conventional RFA which often requires multiple overlapping deployments to achieve ablation diameters of greater than 3 cm.[10,14,15]

Another significant advantage of MWA compared to RFA is improved visualization by ultrasound. In RFA, ultrasound often fails to delineate the border between normal and ablated liver and is commonly obscured by artifacts from gas bubble formation and the lower frequency of RF generators.[4] MWA, by contrast, may be accurately and easily monitored using transabdominal or intraoperative ultrasound. In this study, the 12 MHz US transducer provided excellent visualization of the interface between normal and ablated liver, with resolution to the submillimeter level. The 12-MHz probe was also able to demonstrate three distinct zones of injury that correlated precisely with gross and microscopic examination.

Perhaps the most significant theoretical advantage of MWA over RFA is its decreased susceptibility to the heat-

Table 1 Power Level Listed is the Power Set on the Generator

Applicator	Pig #/ lesion #	Time (min)	Power (W)	NFP (W)	Ablation diameter (cm)	Track bleeding	Comments (ultrasound = US)
5.6 mm surgical 17	1/1	4	100	98	4.5	No	
5.6 mm surgical 17	1/2	4	100			No	At 20 s, US outgassing; tracking seen 3 cm away from ablation
5.6 mm surgical 17	2/1	4	100	99 90 (at end)	4.0		Surrounded by portal and hepaic vein; at 24 s, pop then outgassing
5.6 mm surgical 17	2/2	4	100	98 90 (at end)	5.0		At 24 s, pop then outgassing
5.6 mm surgical 17	2/3	4	100				
5.6 mm surgical 17	2/4	4	100		7.0		Liver removed then ablation made
Deep surface	3/1	1 1	60 100				Pop cracked liver, bleeding; 100 W, 30 s stopped the bleeding
Deep surface	3/2	3	100		13 mm depth		Moving applicator as aid to resection
5.6 mm surgical 17	3/3	4	70	68	3.0	Yes	9 mm hepatic vein
5.6 mm surgical 17	3/4				2.5	No	Near portal vein pedicle; track heating used
5.6 mm surgical 17	3/5						Interlobar heating (adjacent lobe of liver heated)
Shallow surface	4/1	3	100		13 mm depth		More friction than deep surface applicator
Shallow surface	4/2	1.5	100		10 mm depth		Fracture to liver surface by scalpel, applicator use for hemostasis
5.6 mm surgical 17	4/3	4	100	89 at end	3.4	No	Pop at 26 s, outgassing; hepatic arteries on both sides of applicator
5.6 mm surgical 17	4/4	4	100		5.6	No	Pringle maneuver; pop at 25 s
5.6 mm surgical 17	4/5	4	100	81 at 3 min 77 at 4 min	6.0	No	Pringle maneuver; pop at 27 s

NFP is the actual power delivered, which is the set power minus any reflected power. This characterizes the match with tissue
NPF net forward power

sink effect of local blood flow. In RFA, ionic agitation creates a relatively small zone of active heating (only a few millimeters in diameter). The majority of tissue heating occurs via thermal conduction from the active zone of heating.[10,16] Power falloff from RF applicators is proportional to $1/r^2$, where r is the radius from the applicator. MW applicators have power falloff proportional to $1/r$, thus, arguing for deeper penetration of significant power capable of ablation tissue. Thermal conduction is an inefficient process; not only does it decrease exponentially away from its source but it is also very susceptible to heat-sink from local blood flow.[10,17] MWA, by contrast, has a much larger active zone of heating and, hence, does not rely solely on thermal conduction for ablation.[18] Thus, in theory, MWA is less prone to convective heat loss from blood flow. One study assessed this by comparing a new 915-MHz MWA device with a conventional RFA system.[10] Both MWA and RFA produced elliptical zones of ablation in porcine liver, with MWA creating longer ablation zones than RFA. MWA also showed less heat-sink effect than RFA, as measured by the ratio of ablation zone diameters near large blood vessels to diameters across the same blood vessel. It must be noted that there was no direct comparison between MWA and RFA in this study.

In this study, we deliberately inserted the MWA probe within 2 cm of large blood vessels in order to evaluate the effect of heat-sink on MWA. The Microsulis MWA probe produced uniformly spherical ablation zones of consistent diameter (3 to 4 cm) around large blood vessels. Pathological analysis revealed complete circumferential necrosis of hepatic tissue around all arteries and veins that were examined (six specimens). These results are compelling and suggest that the Microsulis MWA probe may be potentially superior to conventional RFA in terms of treating tumor blood vessel margins and limiting recurrence at these locations; however, further clinical trials are necessary to determine this.

While the Microsulis MWA device performed well both in general and around large blood vessels, it was associated with two potentially detrimental phenomena: "thermal-tracking" and "popping." Real-time US demonstrated tracking of thermal injury along small hepatic veins beyond the extent of the core ablation zone. In some cases, this thermal tracking was associated with the formation of venous thrombus in the small hepatic vessels. This same phenomenon was observed by Wright et al.[19], who noted thermal tracking along small hepatic vessels (<5 mm) extending as far as 1 cm from the main body of the lesion. The authors postulated that this preferential tracking may be due to creation of high-temperature water vapor that follows blood vessels along the path of least resistance in a direction away from the ablation site; alternatively, differences in the permittivity of perivascular tissue may cause preferential tracking of microwave energy along these vessels. Regardless of the etiology, this phenomenon is of some concern as it poses the risk of venous coagulation and hepatic infarction. Further study is needed to ascertain this.

In addition to thermal tracking, use of the Microsulis MWA device was invariably associated with a "popping" at 25±1 s. This explosion was presumed to be related to the sudden liberation of steam as tissue is heated beyond the boiling point. While unrelated to hepatic blood flow, it was associated with parenchymal cracking and hemorrhage in one instance. A similar phenomenon called "steam popping" has also been observed during RFA of surface hepatic lesions.[20] Increases in subsurface temperature above 100°C may lead to steam formation, expansion, and small explosions of the surface parenchyma. Factors related to this phenomenon include power level and inflow occlusion, with lesion diameter inversely correlated with the propensity for this phenomenon Table 1.

In summary, the Microsulis MWA probe provides effective and uniform ablation of hepatic tissue, while remaining unaffected by the heat-sink effect of hepatic blood flow. The technology is still in its infancy, however. Further study of the safety and potential risks of the Microsulis MWA probe is needed before the device is widely adopted for use in human trials.

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ORIGINAL ARTICLE

Do not Deny Pancreatic Resection to Elderly Patients

Roberto Ballarin · Mario Spaggiari · Fabrizio Di Benedetto · Roberto Montalti · Michele Masetti · Nicola De Ruvo · Antonio Romano · Gian Piero Guerrini · Maria Grazia De Blasiis · Giorgio Enrico Gerunda

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Abstract
Introduction Radical resection is the only potential cure for pancreatic malignancies and a useful treatment for other benign diseases, such as pancreatitis. Over the last two decades, medical and surgical improvements have drastically changed the postoperative outcome of elderly patients undergoing pancreatic resection, and appropriate treatment for elderly potential candidates for pancreatic resection has become an important issue.
Materials and Methods Ninety-eight consecutive patients undergoing radical pancreatic resection between 2003 and 2006 at the Surgery Unit of the University of Modena, Italy, were considered and divided into two age groups, i.e., over 75-year-olds (group 1, 23 patients) and under 75-year-olds (group 2, 75 patients). The two groups were compared as regards demographic features, American Society of Anesthesiologists scores, comorbidities, previous major surgery, surgical procedure, postoperative mortality, and morbidity.
Results There were no significant differences between the two groups concerning postoperative mortality, and the duration of hospital stay and days in the postoperative intensive care unit were also similar. Complications such as pancreatic fistulas, wound infections, and pneumonia were more frequent in the older group, but the differences were not statistically significant. The overall median survival was 29.4 months and did not differ significantly between the two groups when calculated using the log-rank test ($p=0.961$).
Discussion In the light of these findings and as reported for other series, old age is probably not directly related with any increase in the rate of postoperative complications, but comorbidities (which are naturally related to the patients' previous life) may have a key role in the postoperative course.

Keywords Pancreas · Pancreatic resection · Elderly

Introduction

Pancreatic cancer is the third most frequent neoplasm of the gastrointestinal tract and usually has an unfavorable prognosis.[1–3] Radical resection represents the only chance of cure for pancreatic malignancies and is also useful for other benign pathologies, such as pancreatitis. The incidence of pancreatic cancer is strongly age-related: People over 65 years of age are at the highest risk of developing this kind of tumor, representing 60% of all cases diagnosed[4], and considering the general increase in average life expectancy, the incidence of pancreatic cancer is likely to increase. The appropriate treatment of elderly potential candidates for pancreatic resection is thus becoming an important issue. Over the last two decades, medical and surgical improvements have drastically changed the postoperative outcome of elderly patients undergoing pancreatic resection, and studies have reported that age is no longer a contraindication for major pancreatic resection in survival terms.[5–7] Some preexisting comorbidities, such as chronic obstructive pulmonary disease or heart disease, can nega-

R. Ballarin (✉) · M. Spaggiari · F. Di Benedetto · R. Montalti · M. Masetti · N. De Ruvo · A. Romano · G. P. Guerrini · M. G. De Blasiis · G. E. Gerunda
Center for Liver and Multivisceral Transplants and HPB Surgery, University of Modena and Reggio Emilia,
#71, Via del Pozzo,
41100 Modena, Italy
e-mail: ballarinroberto@hotmail.com

tively influence the outcome in the elderly[8]; therefore, the surgeon's efforts must focus on proper patient selection and treatment before surgery.

This study compares a group of elderly patients with a group of younger patients undergoing major pancreatic resection with a view of analyzing the different factors that might influence postoperative outcome in the more elderly.

Materials and Methods

Data were collected on 98 consecutive patients undergoing radical resection between 2003 and 2006 at the Surgery Unit of the University of Modena, Italy, divided into two groups, i.e., 23 patients over 75 years old (elderly patients, group 1) and 75 patients under 75 years of age (younger patients, group 2). Patients over 75 were considered "elderly" because the frequency of pancreatic cancer shows a marked increase in this age group[9,10] and several authors have consequently preferred to adopt this cutoff to identify elderly patients.[11–13]

The two groups of patients were compared in terms of demographic features (age, sex), American Society of Anesthesiologists (ASA) score, comorbidities (hypertension, arrhythmia, cardiac valve disease, coronary artery disease, peripheral vascular disease, chronic obstructive pulmonary disease [COPD], diabetes mellitus, nephrolithiasis, cerebrovascular disease, hepatitis C, hyperlipoproteinemia, and pulmonary embolism), previous major surgery (major biliary or gastric surgery, nephrectomy), surgical procedure, postoperative mortality, and morbidity.

Comorbidities were defined as follows: hypertension—treatment with antihypertensive drugs at the time of admission; arrhythmia—rhythm other than sinus or sinus plus atrial premature beats; cardiac valve disease—evidence of significant valvular heart disease from history or physical examination; coronary artery disease, e.g.—history of myocardial infarction, history of a positive exercise test, current complaints of chest pain considered secondary to myocardial ischemia, use of nitrate therapy, or electrocardiogram with pathological Q waves[14]; COPD—cough, sputum production, or shortness of breath in cases where spirometry showed a forced expiratory volume in 1 s (FEV_1) lower than 80% or a FEV_1/forced vital capacity< 70%[15]; diabetes mellitus—treatment with oral hypoglycemic agents or insulin at the time of admission, a fasting plasma glucose≥7.0 mmol/l (126 mg/dl), or a 2-h plasma glucose≥11.1 mmol/l (200 mg/dl) during an oral glucose tolerance test[16]; cerebrovascular disease—history of transient ischemic attack or stroke; nephrolithiasis and pulmonary embolism—history of two or more events before hospitalization; hyperlipoproteinemia—the use of specific treatments (fibrates and nicotinic acid) for high triglyceride and low high-density lipoprotein cholesterol levels at the time of admission; peripheral vascular disease—history of intermittent claudication.

Patients underwent standardized preoperative assessment consisting of: general medical examination, blood tests, chest X-ray, endoscopic retrograde cholangiopancreatography, color Doppler ultrasonography, and abdominal computed tomography scan. Pancreatic resection was performed in the absence of peritoneal or hepatic metastases and providing the tumor was not locally advanced. Limited invasion of the portal or superior mesenteric vein (less than 2 cm in length and less than 50% of circumferential involvement)[17] was not considered a contraindication for resection. As for surgical risk, all patients were classified according to the ASA. Pancreatic resection was not performed in patients in poor general conditions (Karnofsky performance status<50%) or with significant comorbidities (ASA 4–5). Major pancreatic resection includes pancreaticoduodenectomy (PD; the Whipple procedure or pylorus-preserving PD) and left (LP) or total (TP) pancreatectomy. The surgical techniques were standardized with systematic lymph node dissection. Briefly, our policy was as follows: (1) We preferred to perform a pylorus-preserving resection in periampullary and pancreatic head cancer, reserving distal gastric resection for lesions involving the first portion of the duodenum; (2) in PD, we preferred to restore pancreatic-enteric continuity via a pancreaticojejunostomy; (3) in LP, 60–85% of the whole pancreatic parenchyma was resected. Postoperative mortality and morbidity were recorded prospectively. The mortality rate included all deaths within 30 days after surgery. The morbidity rate included all complications after surgery up until discharge from hospital. Postoperative complications were classified as surgical complications (gastric atony, pancreatic fistula, portal thrombosis, wound infection, line sepsis, gastrointestinal bleeding, chylous ascites, hemoperitoneum) and nonsurgical complications (respiratory insufficiency, pneumonia, symptomatic pleural effusion, cardiovascular conditions, multiple organ failure, pulmonary embolism, cerebrovascular disorders). A pancreatic fistula was defined as the drainage of more than 50 ml of amylase-rich fluid (a greater than threefold rise above the upper normal limit in the serum) on or after postoperative day 10 or radiographically demonstrated pancreatic anastomotic disruption.[18] Gastric atony was defined as the inability to eat a normal diet by postoperative day 10 and the need for a nasogastric probe on or beyond day 10. Pneumonia, line sepsis, and wound infection required positive cultures from the specified site, fever, and radiographic evidence of an infiltrate in the case of pneumonia. Symptomatic pleural effusion was defined as the onset of postoperative dyspnea associated with the need

for oxygen therapy and confirmation on chest X-ray. Cardiovascular complications included myocardial infarction, atrial fibrillation, arrhythmia, and hypertensive crises. Cerebrovascular complications included ischemic stroke and transient ischemic attack.

The total hospital stay (in days) was defined as the period from admission to discharge; the duration of the postoperative period was defined as the period from the day of surgery to discharge. The survival after surgery includes all patients with malignancies discharged from the hospital; all deaths within 30 days after surgery were excluded.

Statistical Analysis

Continuous data are expressed as mean±standard deviation (SD) and were compared using Student's two-tailed *t*-test. Comparisons between groups were drawn using Pearson's chi-square test with Yates' continuity correction or Fisher's exact test, as appropriate. Patient overall survival and disease-free survival (DSF) were evaluated using the Kaplan–Meier method and compared with the log-rank test. Statistical significance was set at $p<0.05$. The statistical analysis was performed using the SPSS© for Windows rel. 15.0.

Results

The most frequent symptoms were jaundice (41.8%), abdominal pain (42.9%), weight loss (31.3%), anorexia (29.6%), diarrhea (16.3%), nausea/vomiting (11.2%), and pruritus (10.2%).

The sample included 44 (44.9%) women and 54 (55.1%) men; the ASA score was 1–2 in 85 (86.7%) cases and 3 in 13 (13.3%). The most frequent comorbidity was hypertension (32 cases, 32.7%), followed by diabetes mellitus (21 cases, 21.4%), hyperlipoproteinemia (13 cases, 13.3%), coronary artery disease (8 cases, 8.2%), and COPD (six cases, 6.1%). The comparison between the two groups is shown in Table 1. There were no significant differences regarding gender or prior major surgery. As for comorbidities, hypertension and coronary artery disease were significantly more frequent in the elderly patients ($p=0.011$ and $p=0.002$, respectively), as was an ASA score of 3 ($p=0.002$).

PD was the surgical procedure performed in the majority of cases (60, 61.2%), while TP and LP were used less frequently (23 cases, 23.5%, and 15 cases, 15.3%, respectively). The superior mesenteric vein (SMV) was resected in three patients and the portal vein (PV) in four due to signs of tumor involvement. Table 2 compares the surgical procedures in the

Table 1 Characteristics of Patients Who Underwent Major Pancreatic Resections

Parameter	Group 1 ≥75 years ($n=23$)	Group 2 <75 years ($n=75$)	p value
Age, years, mean (SD) [range]	76.9 (2.5) [75–84]	56.9 (11.4) [20–71]	0.000
Sex			
Female	11 (47.8%)	33 (44%)	0.813
Male	12 (52.2%)	42 (56%)	
Comorbidities			
Hypertension	13 (56.5%)	19 (25.3%)	0.011
Arrhythmia	0 (0%)	1 (1.3%)	1.000
Cardiac valve disease	0 (0%)	2 (2.7%)	1.000
Coronary artery disease	6 (26.1%)	2 (2.7%)	0.002
Peripheral vascular disease	2 (8.7%)	3 (4%)	0.334
COPD	0 (0%)	6 (8%)	0.331
Nephrolithiasis	1 (4.3%)	5 (6.7%)	1.000
Diabetes mellitus	4 (17.4%)	17 (22.7%)	0.774
Cerebrovascular disease	3 (13%)	2 (2.7%)	0.083
Hepatitis C	1 (4.3%)	1 (1.3%)	0.416
Hyperlipoproteinemia	4 (17.4%)	9 (12%)	0.496
Pulmonary embolism	1 (4.3%)	2 (2.7%)	0.556
Previous major surgery			
Major biliary surgery	0 (0%)	2 (2.7%)	1.000
Nephrectomy	1 (4.3%)	1 (1.3%)	0.416
Major gastric surgery	1 (4.3%)	3 (4%)	1.000
ASA score[a]			
1+2	15 (65.2%)	70 (93.3%)	0.002
3	8 (34.8%)	5 (6.7%)	

[a] Patients with an ASA score of 4 or 5 were not operated on

Table 2 Procedures and Operative Factors

Parameter	Group 1 ≥75 years (n=23)	Group 2 <75 years (n=75)	p value
Procedures[a]			
PD	13 (56.5%)	47 (62.7%)	0.776
LP	2 (8.7%)	13 (17.3%)	0.509
TP	8 (34.8%)	15 (20%)	0.237
Additional resection of SMV or PV	1 (4.3%)	6 (8%)	1.000
Length of surgery, min, mean (SD) [range]	440 (118) [130–695]	444 (121) [200–635]	0.892
Intraoperative blood loss, ml, mean (SD) [range]	495 (212) [200–1000]	482 (282) [0–1500]	0.831
Reoperation	3 (13%)	4 (5.3%)	0.350

[a] Patients with an ASA score of 4 or 5 were not operated on

two groups: Blood loss, operating time, and types of procedure were much the same in both groups.

Seven patients required re-operation during the same hospital stay. In the group of elderly subjects, two patients underwent re-laparatomy for pancreatic fistulas (grade C fistulas according to the International Study Group on Pancreatic Fistulas)[19]; one for portal thrombosis, and two for wound infections, which led to evisceration. In the younger group, one patient underwent re-laparotomy for grade C pancreatic fistula and one for bladder repair.

Postoperative mortality and morbidity, duration of hospital stay, and days in postoperative intensive care are summarized in Table 3. There were no significant differences between the two groups in terms of postoperative mortality. The causes of death included myocardial infarction (n=1) and multiple organ failure (n=1). Both the patients who died had

Table 3 Complications Following Radical Resection

Complication[a]	Group 1 ≥75 years (n=23)	Group 2 <75 years (n=75)	p value
Hospital stay, days, mean (SD) [range]	15.2 (9.6) [7–54]	16.3 (11.9) [1–60]	0.695
Stay in ICU, days, mean (SD) [range]	1.6 (0.7) [1–3]	1.3 (0.8) [0–7]	0.141
Complications			
Surgical	14	38	NA
Gastric atony	1 (4.3%)	5 (6.7%)	1.000
Pancreatic fistula	4 (17.4%)	8 (10.7%)	0.468
Biliary fistula	0 (0%)	2 (2.7%)	1.000
Portal thrombosis	1 (4.3%)	0 (0%)	0.235
Wound infection	5 (21.7%)	11 (14.7%)	0.519
Line sepsis	0 (0%)	2 (2.7%)	1.000
Gastrointestinal bleeding	2 (8.7%)	3 (4%)	0.334
Chylous ascites	1 (4.3%)	6 (8%)	1.000
Hemoperitoneum	0 (0%)	1 (1.3%)	1.000
Nonsurgical	35	45	NA
Respiratory insufficiency	1 (4.3%)	2 (2.7%)	0.556
Pneumonia	10 (43.5%)	17 (22.7%)	0.091
Symptomatic pleural effusion	12 (52.2%)	15 (20%)	0.006
Cardiovascular	8 (34.8%)	7 (9.3%)	0.008
Multiple organ failure	0 (0%)	1 (1.3%)	1.000
Pulmonary embolism	0 (0%)	3 (4%)	1.000
Cerebrovascular	3 (13%)	0 (0%)	0.012
Overall complications	49	83	NA
Number of complications			
0	4 (17.4%)	33 (44%)	0.040
1	5 (21.7%)	24 (32%)	0.495
≥2	14 (60.9%)	18 (24%)	0.002
In-hospital mortality	1 (4.3%)	1 (1.3%)	0.416

[a] Patients with an ASA score of 4 or 5 were not operated on

Table 4 Pathologic Diagnoses and Histologic Type

Diagnosis	Group 1 ≥75 years (n=23)	Group 2 <75 years (n=75)	p value
Benign disease			
Chronic pancreatitis	1 (4.3%)	17 (22.7%)	0.064
Pancreatic microcystic cystadenoma	1 (4.3%)	0 (0%)	0.235
Schwannoma	0 (0%)	1 (1.3%)	1.000
Total benign disease	2 (8.7%)	18 (24%)	0.194
Malignant tumors			
Pancreatic cancers (solid and cystic)	15 (65.2%)	37 (49.3%)	0.273
Ampullary cancers	3 (13%)	6 (8%)	0.434
Neuroendocrine tumors	0 (0%)	7 (9.3%)	0.194
Distal bile duct adenocarcinoma	1 (4.3%)	2 (2.7%)	0.556
Duodenal cancers	1 (4.3%)	1 (1.3%)	0.416
Metastases	1 (4.3%)	4 (5.3%)	1.000
Total malignant tumors	21 (91.3%)	57 (76%)	0.145

significant and multiple prior comorbidities, including coronary artery disease and peripheral vascular disease (one patient in group 1), and cerebrovascular disease and hypertension (one in group 2). None of the patients who underwent resection and reconstruction of the SMV or PV died postoperatively. The total hospital stay and postoperative intensive care unit (ICU) stay were similar in the two groups. As for morbidity, symptomatic pleural effusion, cardiovascular and cerebrovascular complications, these were significantly more frequent in the older patients (p=0.006, p=0.008, and p=0.012, respectively). Complications such as pancreatic fistula, wound infection, and pneumonia were also more frequent in the older group, but the differences were not statistically significant. However, an analysis of the number of complications per subject showed a statistically significant (p=0.002) higher incidence in the older group (Table 3).

The histological diagnoses are summarized in Table 4: Overall, there was no difference in the distribution of the final diagnoses between the two age groups.

As regards malignancies (n=78), the overall median survival was 29.4 months; the 1-, 2-, and 3-year survival rates were 73.7%, 51.1%, and 51.1%, respectively, in the older group (n=21) and 76.6%, 52.6%, and 43.8%, respectively, in the younger group (n=57): There was no statistically significant difference between the two groups using the log-rank test (p=0.961). Overall survival and survival of patients in groups 1 and 2 are shown in Fig. 1.

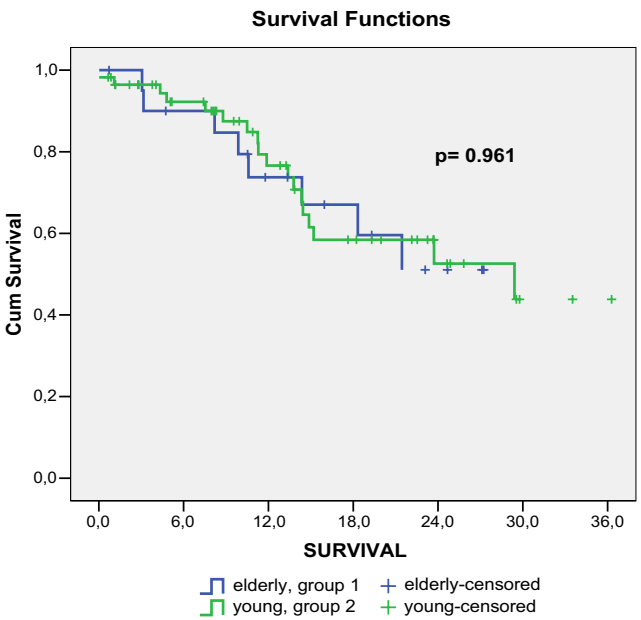

Figure 1 Overall survival and survival of patients in groups 1 and 2.

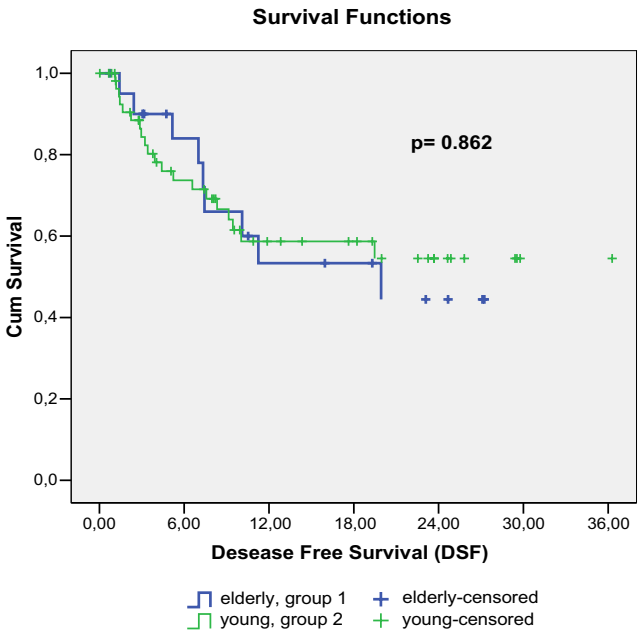

Figure 2 DFS of patients in groups 1 and 2.

The median DFS for both groups was 19.9 months. This did not differ significantly between the two age groups when calculated with the log-rank test (p=0.862). The DFS of patients in groups 1 and 2 is shown in Fig. 2.

Table 5 shows postoperative morbidity in relation to various prognostic factors. Only the ASA score, age, and histotype correlated significantly with postoperative morbidity (p=0.036, p=0.040 and p=0.011, respectively).

The postoperative morbidity in relation to putative prognostic factors in the two age groups is summarized in Table 6. No prognostic factors significantly increased the postoperative morbidity rate in the younger group, while in the elderly group, only the type of surgical procedure correlated significantly with the postoperative morbidity rate (TP+PD: 90.5% vs LP: 0%, p=0.024).

Discussion

Until recently, the consensus of opinion on major pancreatic resection for the elderly was that this age group was at greater risk of postoperative mortality and morbidity. Reports dating from the early 1980s confirmed this opinion,[20,21] showing a 25–41% higher mortality rate in over 60-year-olds. Improvements in surgical technique and postoperative care in the last two decades have lately enabled surgeons to broaden the selection criteria for major pancreatic resection, progressively enrolling more and more elderly patients.

As the general population's life expectancy continues to increase and pancreatic resection represents the only chance of cure for pancreatic malignancies, this new approach

Table 5 Overall Postoperative Morbidity According to Putative Prognostic Factors

Prognostic factors	No. cases	p value
Age		
≥75 years	19/23 (82.6%)	0.040
<75 years	42/75 (56%)	
ASA[a]		
1+2	49/85 (57.6%)	0.036
3	12/13 (92.3%)	
Hypertension		
Present	20/32 (62.5%)	0.853
Absent	41/66 (62.1%)	
Hyperlipoproteinemia		
Present	11/13 (84.6%)	0.139
Absent	50/85 (58.8%)	
Diabetes mellitus		
Present	9/21 (42.9%)	0.070
Absent	52/77 (67.5%)	
Coronary artery disease		
Present	7/8 (87.5%)	0.247
Absent	54/90 (60%)	
Comorbidities		
0 or 1	33/56 (58.9%)	0.568
≥2	28/42 (66.7%)	
Surgical procedure		
TP+PD	54/83 (65.1%)	0.288
LP	7/15 (46.7%)	
Intraoperative blood loss		
<750 ml	54/88 (61.4%)	0.850
≥750 ml	7/10 (70%)	
Length of surgery		
≤420 min	24/42 (57.1%)	0.489
>420 min	37/56 (66.1%)	
Additional resection of SMV or PV		
Present	5/7 (71.4%)	0.908
Absent	56/91 (61.5%)	
Histologic type		
Benign disease	7/20 (35%)	0.011
Malignant tumors	54/78 (69.2%)	

[a] Patients with an ASA score of 4 or 5 were not operated on

Table 6 Postoperative Morbidity in Relation to Putative Prognostic Factors According to Age

Prognostic factors	Gruppo 1 (≥75 years)			Gruppo 2 (<75 years)		
	Factor present	Factor absent	*p* value	Factor present	Factor absent	*p* value
ASA 3[a]	8/8 (100%)	11/15 (73.3%)	0.303	4/5 (80%)	38/70 (54.3%)	0.514
Hypertension	9/13 (69.2%)	10/10 (100%)	0.169	11/19 (57.9%)	31/56 (55.4%)	0.940
Hyperlipoproteinemia	4/4 (100%)	15/19 (78.9%)	0.776	7/9 (77.8%)	35/66 (53%)	0.296
Diabetes	4/4 (100%)	15/19 (78.9%)	0.776	5/17 (29.4%)	37/58 (63.8%)	0.026
Coronary artery diseases	6/6 (100%)	13/17 (76.5%)	0.496	1/2 (50%)	41/73 (56.2%)	1.000
Comorbidities≥2	13/16 (81.2%)	6/7 (85.7%)	0.735	15/26 (57.7%)	27/49 (55.1%)	0.977
Intraoperative blood loss≤ 750 ml	1/2 (50%)	18/21 (85.7%)	0.324	6/8 (75%)	36/67 (53.7%)	0.442
Length of surgery>420 min	11/13 (84.6%)	8/10 (80%)	0.791	26/43 (60.5%)	16/32 (50%)	0.504
Surgical procedure						
TP+PD	19/21(90.5%)	0/2 (0%)	0.024	35/62 (56.5%)	7/13 (53.8%)	0.892
Additional resection	2/2 (100%)	17/21 (81%)	1.000	3/5 (60%)	39/70 (55.7%)	1.000

[a] Patients with an ASA score of 4 or 5 were not operated

seems to be justified, although the related morbidity is high and long-term survival is poor, amounting to a mean 11–20 months.[22–24]

The debate consequently remains open, and recent publications, like ours, are striving to identify the correct approach.

The most recent data show a marked decrease in the postoperative mortality rate in elderly patients. In Karl's series of 14 elderly patients, the mortality rate was 0%, as it was in Cameron's cohort of 37 cases.[5,25] Fong reported on 138 patients aged 70 or over, recording a 6% incidence of postoperative mortality, statistically no different from their younger counterparts.[10] Similar results have been reported in several other recent studies.[8,26–28]

As for postoperative morbidity, the results are less uniform. In Fong's recent report,[10] there was no significant difference in hospital stay, complication rate, or ICU admission rate between the elderly and the younger groups. Other studies published in the last decade have recorded an incidence ranging from 30% to 45% of postoperative medical and surgical morbidity in elderly patients, similar to the situation in younger groups.[8,13,29] Conflicting evidence emerges from other recent studies, however, such as Lightner's[11] on 3,331 older and younger patients undergoing major pancreatic resection, reporting a higher rate among the older group of morbidities such as major cardiac complications, the need for intensive care, and poor nutritional and functional status. Sohn et al.[30] performed pancreatic resection in octogenarians and found these patients had a higher complication rate and longer postoperative hospital stay than their younger counterparts. Such variable data can probably be explained by the different criteria used by each study group to select elderly candidates for major resection. If the groups of elderly and younger candidates are similar in terms of presurgical comorbidities (e.g., cardiopulmonary disease, diabetes, hypertension, and ASA score), we can probably conclude that age has only a chronological and not a biological value.

In our experience, the group of over 75-year-olds had a significantly higher incidence of hypertension, coronary disease, and ASA score of 3 than in the younger group. No significant difference emerged in postoperative mortality rate (4.3% vs 1.3%; $p=0.416$). After surgery, complications such as pneumonia, symptomatic pleural effusion, and cardiovascular and cerebrovascular accidents were significantly more frequent among the elderly patients. Analyzing the overall morbidity in relation to prognostic factors, older age, an ASA score of 3, and histotype were linked to a significant increase in morbidity. When we analyzed age-related morbidity, only the type of surgical procedure was a significant prognostic factor, probably because of the limited number of patients considered. On more in-depth analysis, however, we found that all the older patients with an ASA score of 3, hyperlipoproteinemia, diabetes, and coronary artery disease experienced postoperative complications.

Long-term survival and DSF did not differ statistically between the two groups.

As reported in other series,[8,26–28] therefore, old age per se is probably unrelated with any increase in the rate of postoperative complications, but comorbidities (that are naturally related to the patient's previous life) could have a key role in the postoperative course.

In conclusion, we believe that elderly patients should not be denied pancreatic surgery, especially if it represents the only chance of cure, as in the case of malignancies.

The surgeon's efforts must focus, however, on a meticulous preoperative diagnosis and prophylaxis of any comorbidities and an earlier postoperative rehabilitation. Preoperative anti-aggregation prophylaxis in elderly

patients with diabetes, arterial disease, and hyperlipoproteinemia, combined with early postoperative mobilization, respiratory rehabilitation, and enteral/parenteral nutrition, could prove valuable in improving the outcome for elderly patients.

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ORIGINAL ARTICLE

CA 19-9 Velocity Predicts Disease-Free Survival and Overall Survival After Pancreatectomy of Curative Intent

Jonathan M. Hernandez · Sarah M. Cowgill · Sam Al-Saadi · Amy Collins · Sharona B. Ross · Jennifer Cooper · Desireé Villadolid · Emmanuel Zervos · Alexander Rosemurgy

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Abstract
Introduction This study was undertaken to correlate serum CA 19-9 levels and CA 19-9 velocity with disease-free and overall survival after pancreatectomy for adenocarcinoma.
Methods From 1997 to 2002, 96 patients underwent pancreatectomy without adjuvant chemotherapy as the control arm of a large randomized prospective adjuvant therapy trial. After resection, CA 19-9 levels were drawn at baseline, 4 weeks, and 12-week intervals thereafter. CA 19-9 velocity denotes rate of change in CA 19-9 levels over a 4-week period. Postoperative baseline CA 19-9 levels and CA 19-9 velocity were correlated with disease-free and overall survival. Data are presented as median (mean±SD).
Results Disease-free survival was 7 months (14±13.7), and overall survival was 12 months (19±14.3) with 24 (25%) patients alive at 41 months (39±7.8). Baseline CA 19-9 levels and CA 19-9 velocity predicted disease-free ($p<0.01$) and overall survival ($p<0.01$). CA 19-9 velocity was a better predictor of overall survival than baseline CA 19-9 ($p<0.001$). CA 19-9 velocity at disease progression was 131 U/ml/4-weeks (1,684±4,474.8) vs. 1 U/ml/4-weeks (1±3.8) at 22 months for patients without disease progression ($p<0.001$).
Conclusions CA 19-9 velocity predicts imminent disease progression after resection of pancreatic adenocarcinoma and is a better predictor of overall survival than baseline CA 19-9 levels. CA 19-9 velocity is a reliable and relatively inexpensive means of monitoring patients after resection of pancreatic cancer and should be considered in all patients enrolled in clinical trials as well as patients receiving adjuvant therapy.

Keywords CA 19-9 velocity · Pancreatic cancer · Survival

J. M. Hernandez · S. M. Cowgill · S. Al-Saadi · A. Collins · S. B. Ross · J. Cooper · D. Villadolid · E. Zervos · A. Rosemurgy
Department of Surgery,
University of South Florida College of Medicine,
Tampa General Hospital,
P. O. Box 1289, Room F145,
Tampa, FL 33601, USA

A. Rosemurgy (✉)
University of South Florida, C/O Tampa General Hospital,
P. O. Box 1289, Room F-145,
Tampa, FL 33601, USA
e-mail: arosemur@health.usf.edu

Introduction

Pancreatic cancer is a deadly disease. In 2007, death due to pancreatic cancer is projected to approximate the incidence of the disease, with about 34,000 patients being diagnosed with pancreatic cancer in the United States.[1] Advances in operative technique and patient care have limited perioperative morbidity and mortality for those fortunate enough to undergo resection. Nonetheless, surgical therapy (i.e., pancreatectomy) despite curative intent results in high rates of recurrence and disappointing median survivals of about 12 months.[2] Although generally encouraged, the use of adjuvant therapy that is inconsistently applied has historically been relatively ineffective. Recent advances in immunotherapy and chemotherapy may offer hopes of improved survival.[3]

With the increasing use of, efficacy of, and options for adjuvant therapy, it will become increasingly important to monitor disease recurrence and progression, as well as response to treatment. Furthermore, patients and families may demand close monitoring of disease recurrence, disease progression, and response to treatment, so they may investigate other options and prepare for their course ahead. The most appropriate method by which patients with pancreatic adenocarcinoma should be monitored is a subject of debate. Currently, follow-up after resection of pancreatic adenocarcinomas is based upon measurement of serologic markers and radiologic studies, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans. The most widely used and accessible serum marker for pancreatic cancer is carbohydrate antigen 19-9 (CA 19-9). However, current recommendations from the American Society of Clinical Oncology state that CA 19-9 cannot provide definitive evidence for cancer recurrence without additional confirmatory studies, such as radiological studies.[4] Sufficient data is also lacking to recommend CA 19-9 as a means of monitoring response to treatment. Unfortunately, radiological studies are limited by their sensitivity in detecting recurrent disease, often requiring a cancerous mass measuring more than 1 cm in diameter and in a discrete location. Clearly, radiologically apparent disease is not biologically subtle or occult and radiologically recurrent disease, thereby, does not represent "early" recurrence. Given national interest in pancreatic cancer and its treatment and therapies, new and better modalities are needed for monitoring of cancer recurrence, disease progression, and response to treatment, or new and improved ways to utilize existing modalities are needed to accomplish the same.

Because of our interest in pancreatic cancer, we seek better ways to monitor disease recurrence, disease progression, and response to treatment. Radiological evaluations of patients following resections for pancreatic cancer fail us in their ability to detect occult or preclinical disease, when persistent or recurrent disease is most amenable to treatment. Therefore, we have undertaken this study to determine if an alternate use of CA 19-9 levels, specifically rate of change of CA 19-9 levels over 4-week periods (i.e., CA 19–9 velocity), can serve to denote early, subtle disease recurrence following pancreatectomy of curative intent for pancreatic cancer. In undertaking this study, we sought to correlate postoperative baseline serum CA 19-9 levels and CA 19-9 velocity with disease-free and overall survival after resections of curative intent for pancreatic adenocarcinoma. Our hypotheses in undertaking this study were that baseline CA 19-9 levels and CA 19-9 velocity would correlate with disease-free and overall survival after pancreatectomy for cancer and that CA 19-9 velocity would be best in detecting disease recurrence.

Methods

Four years after completion of a double-blind placebo-controlled adjuvant therapy trial evaluating a novel oral antitumor agent, patients receiving placebo were unblinded revealing a cohort of closely monitored patients undergoing pancreatic resections without adjuvant treatment. The control arm of the trial, our study population, consisted of 96 patients with pancreatic adenocarcinoma who underwent pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy with curative intent. Stage was determined using the AJCC classification system (sixth edition). Patients with stage III or IV disease and those undergoing palliative bypass were excluded. No patients had gross residual disease; only patients undergoing R0 or R1 resections were included. Pancreatic ductal adenocarcinoma was confirmed histologically for each patient. By protocol, patients did not receive adjuvant chemotherapy during the study period, though they were able to choose to receive postoperative radiation therapy, administered over 6 weeks with radiosensitizing 5-FU prior to enrollment. All patients were enrolled in the study by 6 weeks from the date of their operation.

Survival, including disease-free survival and overall survival, was determined utilizing the date of resection as baseline. Tumor stage and margin status were noted. Tumors were staged according to the American Joint Committee on Cancer (AJCC) guidelines. Margin status was codified as R0 (microscopically negative/macroscopically negative) or R1 (microscopically positive/macroscopically negative). Recurrence was determined radiologically (e.g., by CT scan, MRI, and/or PET scan) or by clinical criteria, and disease-free survival was determined. Clinical criteria for recurrence were prospectively defined as the absence of radiological recurrence in the presence of unexplained weight loss, intractable pain, jaundice, or ascites. Patients dying of or with cancer prior to declaration of disease progression were considered to have experienced disease progression at the time of death. Overall survival was measured at the time of death.

By protocol, CA 19-9 levels were drawn at the time of enrollment (after convalescence from surgery or radiation therapy) to establish a baseline value, 4 weeks after baseline, and at 12-week intervals thereafter until disease recurrence. CA 19-9 velocity denotes rate of change in CA 19-9 levels (reported as U/ml/4 weeks). Four-week velocity was obtained by dividing the change in CA 19-9 levels over the 120-week period by three.

Data were stored, analyzed, and plotted utilizing Microsoft Excel (Microsoft Corp, Redmond, WA, USA) files. Statistical analysis utilized Graphpad Instat version 3.06 (Graphpad Software Inc., San Diego, CA, USA). Where appropriate, data are presented as median (mean±standard deviation). Postoperative baseline CA 19-9 levels and CA 19-9 4-week velocity were correlated with disease-free and

overall survival utilizing Spearman nonparametric regression analyses. Spearman coefficients were compared utilizing a Fisher transformation test. Comparison of CA 19-9 baseline medians stratified by stage was undertaken using Mann–Whitney *U* test. When comparing survival data, a Log-rank test was undertaken for survival analysis.

Results

Of the 96 patients with pancreatic adenocarcinoma undergoing resection, 46 (48%) were male and 50 (52%) were female. Of the 96 patients undergoing resection, 84 patients underwent pancreaticoduodenectomy, eight patients underwent distal pancreatectomy, and four patients underwent total pancreatectomy. Patient demographics are depicted in Table 1. Adjuvant radiation therapy was utilized in 35 patients. Median disease-free survival for all patients undergoing resection of pancreatic adenocarcinoma was 7 months (14±13.7). Recurrence is shown in Fig. 1. Overall median survival was 12 months (19±14.3).

The median baseline CA 19-9 level was 23 u/ml (200±1032.4). Baseline CA 19-9 levels correlated significantly with disease-free survival ($p<0.01$, $r=-0.35$; Fig. 2) and overall survival ($p<0.01$, $r=-0.35$; Fig. 3). CA 19-9 velocity predicted disease-free survival ($p<0.01$, $r=-0.40$; Fig. 2) and overall survival ($p<0.01$, $r=-0.58$; Fig. 3). Thirteen patients experienced disease recurrence, while serum CA 19-9 levels remained very low. Median CA 19-9 velocity at disease recurrence was 104 U/ml/4 weeks (1,663±4,474.8) vs. 1 U/ml/4 weeks (1±3.8) at 22 months for 26 patients without disease recurrence ($p<0.001$, Mann–Whitney *U* test).

Utilizing nonparametric Spearman correlation, CA 19-9 velocity and baseline CA 19-9 levels correlated significantly with overall survival; the correlation coefficient was higher for CA 19-9 velocity than for baseline CA 19-9 levels ($p=0.04$, Fisher transformation). Again, utilizing nonparametric Spearman correlation, CA 19-9 velocity and baseline CA 19-9 levels correlated with disease-free survival, though the nonparametric Spearman correlation coefficient was not significantly different with CA 19-9 velocity than with baseline CA 19-9 levels. With 100% certainty, a CA 19-9 velocity of 95 U/ml/4 weeks denoted disease recurrence documented by radiographic confirmation.

Table 1 Demographic Data

Characteristic	Value
Age [median (mean + SD)]	65 years (64 years±9.9)
Gender	48% males, 52% females
Post-op 5-FU/XRT	36%
AJCC stage	
IA ($n=9$)	9% (4 without recurrence)
IB ($n=20$)	21% (4 without recurrence)
IIA ($n=11$)	11% (3 without recurrence)
IIB ($n=54$)	56% (7 without recurrence)
Indeterminable ($n=2$)	2% (1 without recurrence)
Margin status	
Negative (R0) ($n=62$)	65% (16 without recurrence)
Positive (R1) ($n=32$)	33% (3 without recurrence)
Indeterminable ($n=2$)	2% (0 without recurrence)

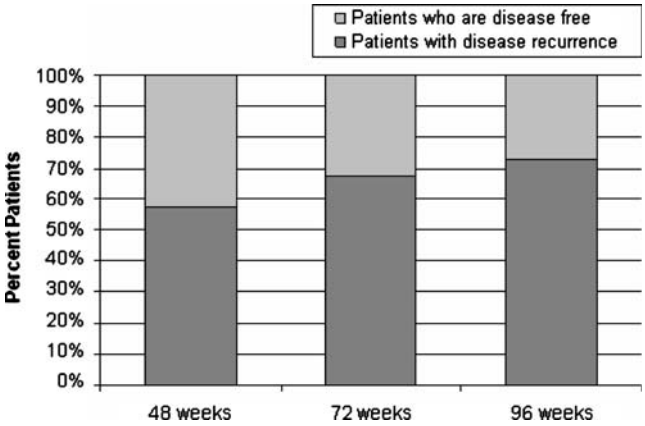

Figure 1 Percentage of patients with disease recurrence after resection.

Discussion

The treatment of pancreatic cancer is changing with further understanding of the disease, more aggressive and widespread application of pancreatectomy, and evolving novel neoadjuvant and adjuvant therapies. Based on survival data, pancreatic adenocarcinoma is generally a systemic malignancy at the time of diagnosis, and resection as a sole source of therapy is, or at least seems, insufficient. The opportunity for improved survival therefore primarily lies in application of improved neoadjuvant or adjuvant systemic therapy. The importance of monitoring disease recurrence, disease progression, response to treatment, and treatment failure is paramount and provides a means to identify patients who may benefit from treatment continuation, intensification, or adjustment. Serum CA 19-9 is the most commonly employed nonradiological proxy or surrogate marker to monitor pancreatic cancer; however, consensus regarding its validity as a marker is lacking. In the present study, we have shown that CA 19-9 velocity predicts disease-free and overall survival, with elevated velocities being highly predictive of imminent radiological disease progression. Furthermore, this report documents that relative to baseline CA 19-9 levels, CA 19-9 velocity is a more accurate predictor of overall survival. Notably, CA 19-9 velocity can be determined and will be of value when

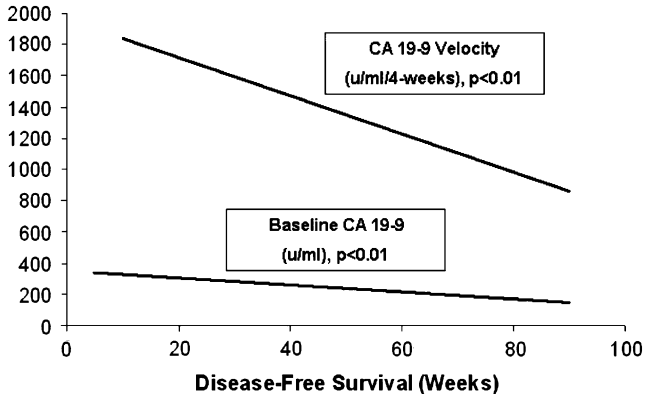

Figure 2 Both baseline CA 19-9 levels and CA 19-9 velocity had significant relationships with disease-free survival by Spearman regression analyses.

baseline CA 19-9 levels were not drawn or are not available.

CA 19-9 is a tumor-associated antigen that was first isolated from a colorectal cancer cell line in 1979.[5] Detection became commercially possibly in 1983 with the introduction of a quantifying radioimmunometric assay. CA 19-9 is a sialylated lacto-*N*-fucopentose II antigen related to the Lewis blood group antigens.[6] Patients who lack the *Le* gene (i.e., patients that have Lewis $a^{-}b^{-}$ phenotype) are either unable to synthesize CA 19-9 or will have falsely low levels. Therefore, approximately 5–15% of the population will have very low levels of CA 19-9, irrespective of the presence or stage of pancreatic malignancy. Thirteen patients (13%) in our study experienced disease recurrence with very low serum levels of CA 19-9. Although the status of their Lewis blood group antigens is not available, the number of patients with levels of CA 19-9 not representative of disease burden lies within the anticipated range. We recommend blood typing all patients prior to utilizing serum CA 19-9 after pancreatic resection.

Clearly, CA 19-9 levels can understate issues with pancreatic cancer. Furthermore, CA 19-9 levels can overstate issues with pancreatic cancer. CA 19-9 levels can be elevated in the setting of biliary obstruction, for whatever reason, and altered bilirubin excretion. Biliary obstruction, commonly seen with pancreatic cancer, can elevate CA 19-9 levels beyond what would be appropriate for the extent or behavior of the cancer. Nonetheless, the sensitivity and specificity of CA 19-9 in the diagnosis of pancreatic cancer has been reported to be as high as 90% and 97%, respectively.[7,8]

CA 19-9 as a surrogate marker of disease recurrence, progression, and response to treatment is attractive because of cost and availability. Furthermore, it has been extensively utilized with pancreatic cancer in many different scenarios, and years of clinical application support its use. For example, Ferrone et al. and Montgomery et al. have shown that postoperative baseline CA 19-9 levels less than 200 or 180 U/ml, respectively, were strong predictors of survival after resection of pancreatic adenocarcinoma.[9,10] We agree that baseline CA 19-9 levels inversely correlate with survival. Not surprisingly, Safi et al. observed that normalization of CA 19-9 after resection conferred increased survival and that 88% of patients with disease recurrence had obvious coincident increases in CA 19-9 levels.[11] As well, Ko et al., Maisey et al., Rosemurgy et al., and Ziske et al. have each shown that a decrease from baseline CA 19-9 greater than 20–25% was an independent predictor of improved survival in patients with advanced pancreatic adenocarcinoma treated with chemotherapy.[12–15]

Postoperative baseline CA 19-9 levels likely correlate with tumor burden and therefore, not surprisingly, with recurrence and survival. Likewise, CA 19-9 velocity is likely related to tumor growth and would intuitively correlate with recurrence and survival, as demonstrated in this report. Most notably, we documented that CA 19-9 velocity does predict disease-free and overall survival and predicts the latter with better accuracy than do baseline CA 19-9 levels. Furthermore, in this study, we identified a CA 19-9 velocity that predicts imminent radiological recurrence (i.e., 95 U/ml/4 weeks). In the future, such a number may not require radiological confirmation so as to promote the concept of detecting occult recurrence. At present, there is, however, a conundrum. CA 19-9 velocity predicts disease recurrence with radiological confirmation. Without radiological confirmation, occult recurrence would go unconfirmed, and CA 19-9 velocity would be designated as "false positive". With such methodology, CA 19-9 velocity cannot be utilized to detect truly occult disease, and the implications of a critical CA 19-9 velocity beyond radiological

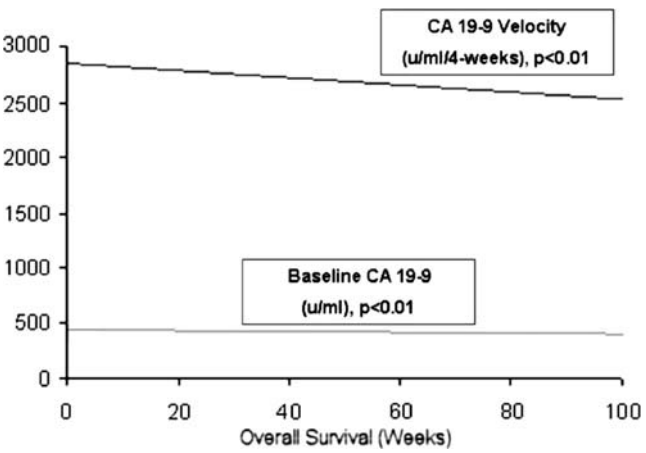

Figure 3 Both baseline CA 19-9 levels and CA 19-9 velocity had significant relationships with overall survival by Spearman regression analyses. CA 19-9 velocity had a significantly higher correlation with overall survival than baseline CA 19-9 levels (p=0.04, Fisher transformation test).

imaging need to be considered. With further clinical use and refinement, and without the encumberment of radiological confirmation, we anticipate a significantly lower critical CA 19-9 velocity which denotes recurrent disease and therefore earlier detection.

This report has established the concept of utilizing CA 19-9 velocity to follow patients after resection of pancreatic adenocarcinoma for disease recurrence. Questions remain, however, regarding the development of guidelines for the frequency of monitoring CA 19-9, the establishment of a velocity that denotes occult recurrence, and clinical application. We recommend determining CA 19-9 levels at monthly intervals. This may improve the accuracy of 4-week velocity without being overly cumbersome to patients and their families. Certainly, these suggestions need confirmation prior to ratification as guidelines. The ability to determine early occult recurrence will likely be defined with the clinical application of CA 19-9 velocity. We recommend the application of monthly CA 19-9 levels to determine velocity in all patients enrolled in adjuvant therapy trials, all patients receiving adjuvant therapy, and patients requesting close monitoring of their disease. An exception applies to those patients who lack Lewis blood group antigens given the unreliability of serum CA 19-9 in these patients. The most appropriate means of monitor for this subgroup remains unresolved and herein, unaddressed

Resection remains the only chance for cure with pancreatic adenocarcinoma. Preoperative diagnosis and staging and postoperative morbidity and mortality rates have improved significantly over the past 20 years. Long-term survival however remains elusive, but seems to be improving, in general, with many reports across the United States offering encouraging results. Given the nature of pancreatic adenocarcinoma, adjuvant therapy seems essential, and new therapies offer hope for improved survival beyond current norms. We have shown that CA 19-9 velocity is an accurate predictor of disease-free and overall survival. In addition, CA 19-9 velocity can predict imminent radiological evidence of disease progression and provides a means of continuous monitoring of treatment response. We recommend that CA 19-9 velocity be utilized in surveillance of patients with pancreatic cancer to monitor for disease recurrence, disease progression, response to treatment, and treatment efficacy to provide a means of identification for patients who may benefit from treatment initiation, continuation, intensification, or adjustment. After resection of pancreatic cancer, CA 19-9 velocity should be included in treatment algorithms.

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ORIGINAL ARTICLE

Pleuropancreatic Fistulae: Specialist Center Management

A. Z. Khan · R. Ching · G. Morris-Stiff · R. England · M. B. Sherridan · A. M. Smith

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Abstract
Background and Aims Internal pancreatic fistulae are uncommon sequelae of severe acute pancreatitis. Due to their low prevalence, experience in the management of this condition remains sparse outside specialist centers and management remains controversial. We report our experience with pleuropancreatic fistulae (PPF).
Patients Six patients (three males, median age 34 years [range, 32–74 years]) with PPF were managed in our unit over a 24-month period from April 2006 to April 2008. The etiology of pancreatitis was alcohol (four), gallstones (one), and unknown cause (one). All patients had documented pleural effusions with amylase content >1,000 iu/dl.
Results All patients underwent computerized tomography (CT) and magnetic resonance imaging (MRI) cross-sectional scanning to identify the site of ductal disruption. CT alone was able to identify the disruption in four cases and a combination of CT and MRI localized the ductal disruption in all patients. Five of six patients required ERCP and placement of a pancreatic duct (PD) stent. No patient required pancreatic surgery and all patients remain well at a median follow up of 39 weeks.
Conclusion Pleuropancreatic fistulae can present a challenging diagnostic dilemma. A multi-disciplinary approach addressing nutritional support and endotherapy allows successful non-operative resolution within specialist units.

Keywords Pancreatopleural fistula · Duct disruption · Pancreatitis · Plueropancreatic fistula

Introduction

Internal pancreatic fistulae are a consequence of pancreatic inflammatory disease and remain an uncommon pathology. A pleuropancreatic fistula (PPF) may present with isolated pleural effusion or in conjunction with pancreatic ascites or other symptoms of pancreatic disease. A posterior disruption of the pancreatic duct remains the underlying pathology with tracking of secretions up into the chest and eventual erosion into the pleural cavity. Although pancreatitis from any cause can lead to duct disruption, certain patterns of ductal injury are recognized. Pancreatitis from alcohol excess can lead to duct disruption anywhere along the course of the pancreatic duct whereas disruption in gallstone pancreatitis is usually located in the head of the gland, where the duct angulates backward this being the area with where the blood supply is the most tenuous.[1]

As PPF are rare, many centers do not have experience in the multi-modal management of this condition which embraces: correcting the electrolyte imbalance and malnutrition, identification of ductal anatomy, and finally definitive management in most cases by means of specialist endotherapy. In this paper we present our management with our series of pleuropancreatic fistulae.

Materials and Methods

Six patients were treated for PPF in our unit between April 2006 and April 2008. All patients included in the study had a radiologically supported diagnosis of pancreatic inflam-

A. Z. Khan
Royal Marsden Hospital,
London, UK

R. Ching · G. Morris-Stiff · R. England · M. B. Sherridan · A. M. Smith (✉)
Pancreatic Service, St James University Hospital,
Leeds LS9 7TF, UK
e-mail: Andrewm.smith@leedsth.nhs.uk

matory disease resulting in loss of mid pancreatic duct (MPD) integrity, producing an exudative fluid evidence of a pleural effusion with an amylase content in excess of 1,000 iu/l and an albumin content >3 g/dl. All patients underwent cross-sectional imaging with computerized tomography (CT) scans and magnetic resonance cholangio-pancreatography (MRCP) to delineate pancreatic duct morphology and localize the ductal disruption. Clinical end points were complete resolution of the pleural effusion and treatment failure was defined as non-resolution of the effusion. Conservative management consisted of correction of electrolyte abnormalities, early institution of postpyloric fine bore nasojejunal tube enteral feeding alongside somatostatin analogue (octreotide) therapy at 600 mcg daily.

CT

CT scans were performed using a standard pancreatic protocol with two breath hold acquisitions. Sequences were extended up into the chest taking sections of 2.5-mm thickness in order to follow any fistulous tracks up into the thorax. Initial non-contrast images were obtained to outline pancreatic calcification. This was followed by intravenous contrast administration and images obtained at scan delays of 20 s (arterial phase) and 60 s (venous phase). Complications of acute pancreatitis including pseudocysts were best outlined in the arterial phase where 1-mm cuts were taken and collimated (Fig. 1). Diluted oral contrast was used to outline the gastrointestinal tract.

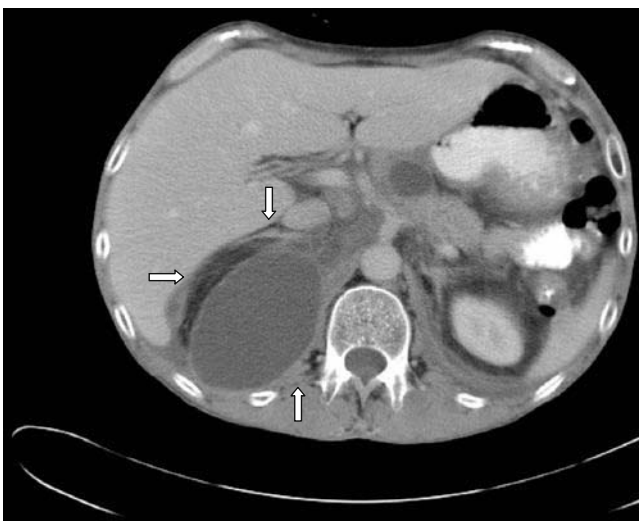

Fig. 1 CT scan showing location of pancreatic pseudocyst. Such images allow prediction of the site of ductal disruption.

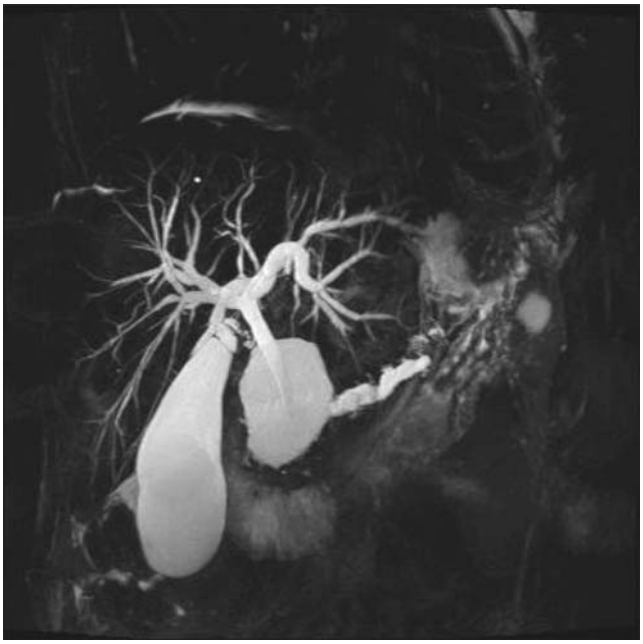

Fig. 2 MRI Scan T2 image showing proximal ductal disruption in the region of the neck of the pancreas leading to pseudocyst formation.

MRI

All magnetic resonance (MR) Scans were performed using a phased array coil obtaining both T1 and T2 images. Heavy T2 images were useful for outlining pancreatic ductal pathology including ductal dilatation and disruption (Figs. 2 and 3).

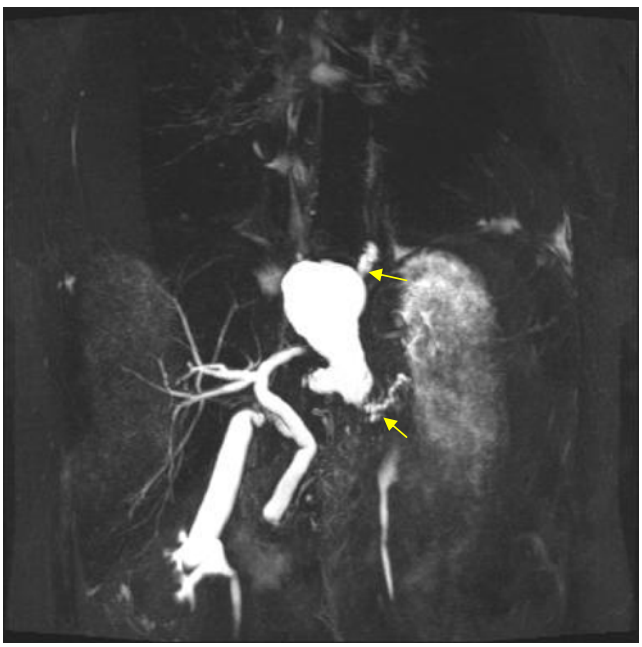

Fig. 3 PPF demonstrated on MRI T2-weighted image with disruption of the mid pancreatic duct (MPD) in the tail with fistula tracking up into the mediastium. The origin of the fistula from the pancreatic duct can be seen clearly.

Results

Three males and three female patients with a median age of 34 years were treated for PPF in our unit. Four patients were known to suffer from alcohol-related chronic pancreatitis, one patient had gallstone-induced acute pancreatitis, and in the final patient, the aetiology of the pancreatitis was unknown.

Results of CT and MRI/MRCP

CT scanning demonstrated pancreatic parenchymal changes associated with chronic pancreatitis in four patients. A combination of CT and MRCP was accurate in diagnosing the site of disruption in five of six patients (83%) (three in the body, one at the junction of the body and tail, and two in the tail (one patient had dual site disruption). In one patient the ductal disruption had healed over by the time an MRCP was obtained but the site of the initial CT suggested disruption in the neck (Table 1).

Results of Endoscopic Treatment

Five patients required endoscopic retrograde pancreatography (ERCP) with PD stent placement. PD stents were placed at the initial endoscopy and changed at 3–6-month intervals. All patients had successful resolution of the PPF at 1 year as suggested by follow-up CT or MRI. This approach was used alongside conservative treatment mentioned above.

Other Interventions

Only one patient required surgical intervention in the form of a rib resection to allow dependent drainage for intrathoracic sepsis.

Discussion

Internal pancreatic fistulae occur as a result of ductal disruption with leakage of pancreatic fluid not contained by the inflammatory response of the surrounding tissues in the retroperitoneum or the lesser sac. Most pleuropancreatic fistulae occur on a background of chronic pancreatitis when the fragility of the surrounding fibrotic tissue is unable to contain the inflammatory response. When the ductal disruption occurs posteriorly, the pancreatic fluid may track through the retroperitoneum via the aortic hiatus into the mediastinum and eventually into the pleural space, typically on the left side, although both sides can be affected. The end result of this process is a pleuropancreatic fistula. Such fistulae are uncommon, and the published literature on pleuropancreatic fistulae is limited.[2–6] The negative intrathoracic pressure and dynamics of respiration help to keep the fistula track open. These patients may give a previous history of previous episodes of pancreatitis within the 12 months preceeding this admission (up to 50%).[7–9]

Patients with pancreatic pleural effusions usually present with shortness of breath. Often, they have undergone multiple pleural taps with recurrence of the effusion before the diagnosis is considered. Thoracentesis reveals fluid with clearly elevated amylase (greater than 1,000 U/dL) and albumin (greater than 3 g/dL).[10]

Cross-sectional imaging is mandatory in these patients and a CT scan helps in identifying peripancreatic or distant fluid collections and may be used as a guide for non-operative drainage. The location of fluid collections can indicate the site of duct disruption.[11,12] A CT scan can also help to differentiate small duct chronic pancreatitis from large duct disease (7-mm main pancreatic duct), and therefore define appropriate operative intervention. Additional information from CT scanning sheds light on the extent of the underlying chronic pancreatic disease as shown in Fig. 4. Magnetic

Table 1 Details of Patients with Pleuropancreatic Fistulae

Patient details	Aetiology	Presentation	Imaging	Chronic pancreatitis on index CT	Site of ductal disruption	Management
34 F	Alcohol	Malnutrition, pancreatic insufficiency	CT MRCP	Yes	Dual site disruption (body+tail)	ERCP+PD stent
42 F	Alcohol	Shoulder pain, pancreatic insufficiency	CT MRCP	Yes	Tail	ERCP+ stent
74 F	Gallstones	Respiratory distress, malnutrition	CT MRCP	No	Neck	Conservative Mx (Rib resection and drainage for thoracic sepsis)
34 M	Alcohol	Asymptomatic pleural effusion	CT MRCP	Yes	Body	ERCP+PD stent
42 F	Alcohol	Nausea+vomiting, malnutrition	CT MRCP	Yes	Neck-body junction	ERCP+PD stent
43 M	Alcohol	Abdominal pain	CT MRCP	Yes	Body	ERCP+PD stent

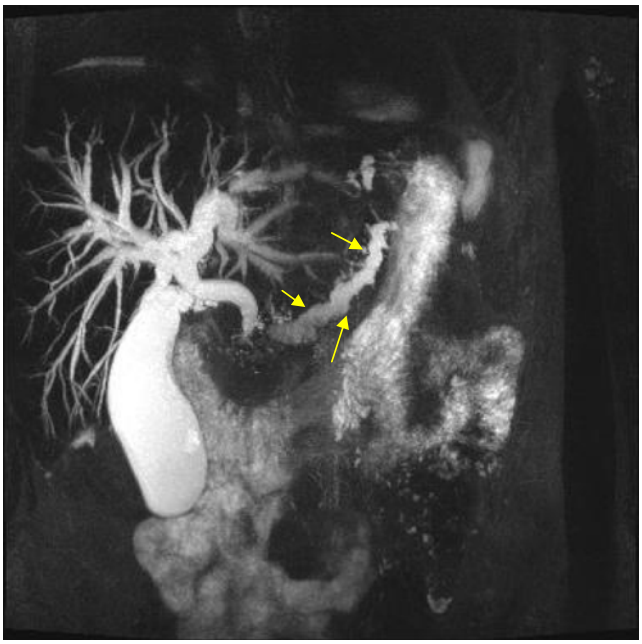

Fig. 4 MRCP images of patient 4. Note the state of the mid pancreatic duct (MPD), with the dilatation and irregular outline as shown.

resonance cholangiopancreatography can more precisely image the pancreatic duct. The addition of secretin stimulation increases pancreatic exocrine secretion, and therefore enhances the quality of duct imaging.[13] Often, the duct injury is identified with MRCP and the remainder of the duct can also be evaluated for associated strictures or stones, guiding definitive management.

Endoscopic retrograde pancreatography is the most sensitive and specific modality to identify pancreatic duct anatomy and the site of disruption.[14] It also offers the opportunity for definitive therapy with endoscopic stenting, sphincterotomy, or nasobiliary drainage. Access to ERCP is essential in both diagnosing and managing pancreatic fistulae. In addition to identifying the site of disruption, other findings include: identification of factors precluding response to conservative therapy, such as obstructing proximal calculi, strictures, or frank ductal discontinuity. Lack of preoperative identification of the point of leakage can lead to a 50% surgical failure rate due to inadequate surgical planning while the failure rates fall to 12–18% in patients in whom the rupture site was diagnosed preoperatively at ERCP.[2] Endotherapy with intraductal stenting functions by bypassing a proximal stricture and partially occluding the leaking duct. PD stents work by bypassing the pancreatic sphincter, thereby converting the normally high-pressure pancreatic ducts to a low pressure system with preferential flow through the stent, and thus facilitating spontaneous healing of the disruption site.[15–17]

Management of PPF in the initial stages relies on optimization of fluid and electrolyte imbalance at presentation and is of paramount importance. These patients are usually malnourished at presentation and may have additional sodium bicarbonate deficiency due to large volume loss of pancreatic exocrine secretions. Traditionally the initial management of PPF involves a period of TPN for 2–3 weeks which is thought to contribute to minimizing pancreatic secretions, there by aiding initial stabilization. We have adopted the approach in our institution of using postpyloric feeding from an early stage in the illness alongside octreotide infusional therapy to minimize basal pancreatic secretion. Using the enteral route in these patients maintains enteral mucosal integrity, preventing bacterial translocation, and stimulating lymphoid tissue within the gut, thus enhancing immune system protection. In addition, drainage of pleural effusions should be obtained early in the illness. Pancreatic fistulae result in loss of exocrine secretions compromising fat and protein absorptive capacity thereby adding to the nutritional compromise. Synthetic pancreatic supplements may offset this and should be administered from an early stage to enhance gut absorptive capacity.[1,18–25] Most authors recommend using somatostatin analogues (Octretoide) although there is no direct evidence to suggest that octreotide helps a fistula to close that would not have otherwise done so. It may, however, expedite closure and at least limits protein and electrolyte losses during fistula management.[25]

Surgical intervention in these patients should be reserved for patients such as those in whom there is an inability to cannulate the duct at ERP, a ductal stricture or large defect not amenable to endoscopic therapy is present, or there is a disconnected pancreatic duct. The type of the operation is dictated by the nature of the ductal anatomy and ideally should treat the underlying pancreatic pathology. Patients with large duct disease may be offered a lateral pancreto-jejunostomy and patients with fistulas in the body or tail can be managed with subtotal or distal pancreatectomy. Kaman et al. reported on six patients two of whom eventually underwent operative intervention following a trial of conservative management.[15] However, in their series, in only two of six patients was the pancreatic ductal disruption successfully crossed with a nasopancreatic tube, allowing ongoing leakage of pancreatic juice and contributing to ongoing ascites or pleural effusion. We feel that early successful bridging of the pancreatic ductal disruption is an important aspect in managing these conservatively and is a policy we have adopted.

In conclusion, pleuropancreatic fistulae remain rare complications of pancreatitis. Although the presentation of these patients can vary, ductal disruption remains the consistent underlying pathology. Cross-sectional imaging with CT and MRI should be used to outline the anatomy in these patients. Enteral feeding should be established early on, and endotherapy with ERCP can lead to satisfactory outcomes.

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HOW I DO IT

'How I Do It': TEM for Tumors of the Rectum

Rowan J. Collinson · Neil J. McC. Mortensen

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Abstract
Introduction Transanal endoscopic microsurgery (TEM) has an established role in the management of benign rectal tumors. It also has an expanding role in the management of malignant tumors, which is more demanding for the clinician. It requires accurate histological and radiological assessment and draws on an expert understanding of the nature of local recurrence, metastasis, and the place of adjuvant therapies.
Discussion A multidisciplinary approach is recommended. This paper discusses our institutional approach to TEM for benign and malignant tumors and covers some of the current management controversies.

Keywords Rectal adenoma · Rectal cancer · TEM · Transanal endoscopic microsurgery

It is almost a quarter of a century since transanal endoscopic microsurgery (TEM) was first reported by Buess and colleagues from Cologne for the management of tumors of the mid to lower rectum.[1] It now has an established role in the management of benign tumors and an expanding role in the management of malignant tumors. This demands an expert understanding of the nature of local recurrence and metastasis and the place of adjuvant therapies.

The ideal lesion for TEM surgery is an adenoma within 20 cm of the anal verge. More specifically, the lesion must be below the peritoneal reflection to avoid incursion into the peritoneal cavity in a full thickness excision. Therefore, 12 cm is the approximate limit anteriorly (Fig. 1). Adenomas of this description are typically large, sessile lesions not amenable to colonoscopic polypectomy and may even be circumferential. As the operating surgeon, we find it useful and necessary to repeat the endoscopy on any patient referred by another physician, prior to bringing them forward for TEM, to verify the tumor location, appearance, and suitability for TEM. Repeat biopsies are also taken.

In general, following macroscopic assessment and histological confirmation, adenomata can move straight to TEM excision. In the case of early rectal cancer (ERC), however, the tumor must be imaged, as the T-stage is crucial. Endorectal ultrasound (ERUS) is our preferred imaging modality. It is particularly suited to the important distinction between T1 and T2 cancers, with an accuracy of 82–93% in the published literature.[2] While less useful for early T-staging, magnetic resonance imaging (MRI) can provide valuable information about the status of mesorectal lymph nodes. The accuracy of MRI in detecting lymph node metastasis ranges from 72% to 92%, compared to 65% to 81% for ERUS.[3] Therefore, in practical terms, our patients with ERC undergo both ERUS and MRI to assess the suitability of their tumor for TEM excision.

All of our ERC cases are discussed in a multidisciplinary meeting, with representation from surgery, pathology, oncology, and radiology. In particular, the histology is examined for features of ERC (i.e., cancer invasion limited to the submucosa) that may preclude TEM. We are guided by the histological criteria of Hermanek and Gall,[4] and the

R. J. Collinson (✉) · N. J. McC. Mortensen
Department of Colorectal Surgery, The John Radcliffe Hospital,
Headley Way, Headington,
Oxford OX3 9DU, UK
e-mail: rowan.collinson@ntlworld.com

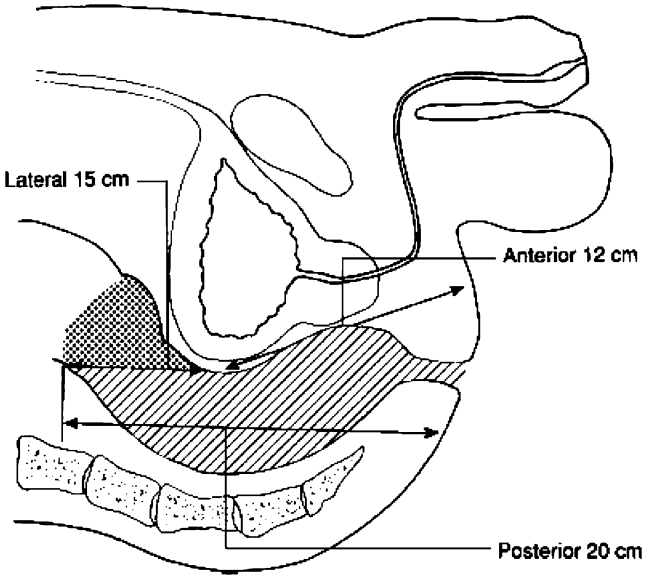

Figure 1 The 'safe' area for resection of rectal lesions (with permission from Cook and Mortensen[15]): Hatched area: all tumors. Stippled area: care should be taken anteriorly and laterally beyond 12 cm.

depth of invasion as defined by Kikuchi et al.[5] Using this approach, we restrict curative TEM cancer operations to small (<3 cm), well- to moderately differentiated adenocarcinomas with no lymphovascular space invasion and minimal (sm1) invasion of the submucosa (Table 1). This is in accordance with current consensus practice guidelines.[6]

Preoperatively, our patients receive full bowel preparation and intravenous antibiotics. Bladder catheterization is performed. The TEM procedure is performed under general anesthesia, preferably with muscle relaxation to avoid respiratory excursions. Patient positioning is crucial, as the tumor must always be orientated inferiorly. Therefore, for anterior tumors, the patient is placed in prone jack-knife position with legs apart (surgeon stands or sits between the legs). For posterior tumors, the lithotomy position is used.

We use the Richard Wolf (Knittlingen, Germany) TEM equipment. This has a 4-cm diameter operating rectoscope which comes in 12-cm and 20-cm lengths, with a bevelled end and a gas-tight face plate (Figs. 2 and 3). Balanced carbon dioxide insufflation and suction is used. The

Table 1 T1 Tumors and Risk Factors for Lymph Node Metastases

	'Low risk'	'High risk'
Degree of differentiation	Well/moderate	Poor
Histological grade	1 and 2	3
Histological subtype		Mucinous adenocarcinoma
Lymphovascular space invasion	−	+
Kikuchi level	sm1	sm2 and sm3
Tumor diameter	<3 cm	≥3 cm

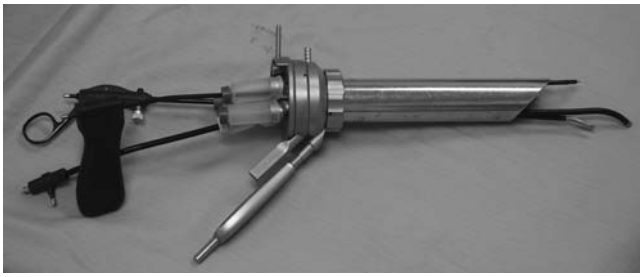

Figure 2 Assembled TEM rectoscope.

instruments used include a suction/irrigation unit, graspers, a needle-point diathermy knife, and needle holders for suturing. The rectoscope is held in fixed position by the Martin arm clamp. The binocular optical system with ×6 magnification is used, with a concurrent camera feed to television monitors within the operating room.

Following establishment of pneumorectum, a margin of at least 5 mm for adenomata and 10 mm for cancers is scored around the tumor with diathermy. The resection is usually performed with a diathermy knife, but we have also used ultrasonic shears (Ultracision®, Johnson and Johnson, Amersfoot, The Netherlands) with good effect. A submucosal resection is adequate for proven small adenomata (especially high or anteriorly situated), but for T1 cancers or larger adenomata (larger than 1.5 cm), full thickness resection is performed. In doing so, progress into the mesorectal fat is minimized to avoid compromising any subsequent transabdominal total mesorectal excision if found to be necessary on postoperative histology review. The tumor is removed and pinned out on a cork board for orientation. The wound is irrigated with chlorhexidine acetate and cetrimide solution (Travasept 100®, Baxter, UK). The defect can be closed with a running absorbable suture secured with silver clips if it is in the anterior or upper rectum; otherwise, it is left open.

Figure 3 Face plate with entry ports.

Intraoperative technical difficulties can be challenging due to the sometimes restricted access down the rectoscope. A bulky adenoma can be preoperatively 'decapitated' with colonoscopy to make its size more manageable, or it can be removed piecemeal at TEM; obviously, both of these strategies are contraindicated in the case of cancer. The peritoneum may be unintentionally opened, and if small enough, the defect can be sutured closed and the peritoneal gas vented with a needle. A large defect may require conversion to a laparotomy. Hemostasis must be meticulous as intraoperative bleeding can rapidly obscure the view; therefore, a blend of coagulation/cut is usually set on the diathermy machine. Care must be taken anteriorly in female patients to avoid entry into the vagina.

Postoperatively, the patient is returned to the surgical ward. Early mobilization is encouraged, and diet is commenced on day 1 postoperatively. The patient is discharged from hospital once they have passed a bowel motion. Postoperative fever is investigated in a standard manner, with exclusion of other foci such as urine, IV site, and chest prior to pelvic imaging. If there is a suspicion of pelvic sepsis, then computed tomography scan of the pelvis is the investigation of choice.

Compared with conventional surgery, an obvious benefit of TEM is decreased operative morbidity and mortality. In our own recently published experience of 200 cases,[7] these were 14% and 0.5%, respectively, which mirrors that of others.[8] The most common complications were bleeding requiring readmission to hospital (5%), pelvic sepsis (2%), urinary tract infection (2%), chest infection (1.5%), rectal stenosis (1.5%), and urinary retention (1%). In the case of cancer, it is self-evident that these levels of morbidity and mortality are far more acceptable than those of the traditional surgical approaches, such as low anterior resection (LAR) and abdominoperineal excision (APE). However, even in the case of benign lesions of the low rectum where the alternative operation would be a standard transanal resection, TEM also has benefits, such as a decreased rate of local recurrence,[8] most likely due to the increased operative precision.

While it is a concern, it is evident that there is little clinically relevant impact upon sphincter function, despite the prolonged operative anal sphincter dilatation. Preoperative incontinence and long operative time (>2 h) have been implicated as risk factors for postoperative incontinence,[9,10] highlighting the need for adequate preoperative assessment, particularly in the elderly. However, we do not routinely perform preoperative anal physiology studies. Furthermore, it is suggested that any iatrogenic sphincter impairment may have recovered by 6 months postoperatively.[11]

An issue which causes us concern is the approach to a patient with unfavorable tumor characteristics following TEM excision. This generally means 'high-risk' tumors (Table 1), fragmented excisions, or those with excision margins ≤1 mm. These patients are again discussed in the multidisciplinary meeting, but as a general rule, our first-line approach is immediate rescue surgery (i.e., LAR or APE). This takes place within 6 weeks of the original TEM and results in a lower rate of local recurrence than observation alone. While this approach has not been shown to affect overall disease-free survival when compared with TEM alone, it carries a greater likelihood of 5-year disease-free survival than delaying the reoperation until local recurrence occurs.[3,12] The exception to this would be elderly or unfit patients, where the consensus decision may be to avoid further surgery. These patients are offered postoperative radiotherapy, although they are counseled that this is a compromise situation.

Some centers have begun to explore the option of neoadjuvant chemoradiotherapy to downsize high T-stage (T2/T3) tumors in unfit patients in an attempt to render them suitable for transanal excision.[13,14] While we have made use of this technique in isolated cases, it has not been employed in a systematic study at our center. We have, however, occasionally carried out palliative or compromise resection of T2–T3 tumors where the patient was unfit for a major resection.

Nearly a quarter of a century on, TEM is now an established and acceptable modality for dealing with benign tumors of the mid to lower rectum. It offers a low morbidity approach that is cost effective and surgically precise. TEM also has a growing role for malignant tumors of the rectum. Accurate histological analysis is central to this approach. The risk of lymph node metastasis dictates whether TEM excision alone is adequate or whether salvage surgery or adjuvant therapy is required. Neoadjuvant techniques show promise but rely on accurate preoperative radiological staging. It is important, however, that standards achieved with this minimally invasive approach are benchmarked against the recent progress made in the more radical approaches such as total mesorectal excision.

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HOW I DO IT

Adult Type I Choledochal Cyst Resection

John B. Ammori · Michael W. Mulholland

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Abstract Type I choledochal cysts are characterized by fusiform dilatation of the common bile duct, commonly associated with an anomalous pancreatobiliary duct junction. Most are diagnosed in childhood, but the diagnosis may be delayed until adulthood. All type I choledochal cysts should be resected because of the risk of malignant degeneration. The steps for resecting a type I choledochal cyst are described. Through a right subcostal incision, the cyst is exposed and transected distally as it narrows within the pancreatic parenchyma. A total transmural excision of the extrahepatic biliary tree is performed. A retrocolic Roux-en-Y hepaticojejunostomy restores biliary-enteric continuity. Thirty-day mortality is low and long-term outcomes are excellent.

Keywords Choledochal cyst

Choledochal cysts are congenital cystic dilatations of the biliary tract that occur with an estimated incidence of 1:150,000 live births.[1] More than 80% of choledochal cysts are characterized by fusiform dilatation of the common bile duct referred to as type I. A type II cyst is a true diverticulum of the extrahepatic bile duct located proximal to the duodenum. A type III cyst, or choledochocele, is a dilatation limited to the intraduodenal portion of the distal common bile duct. Type IV includes cases of multiple cysts, whether intra- and extrahepatic (type IV-A) or extrahepatic alone (type IV-B). Type V, known as Caroli's disease, includes isolated or multiple cystic dilatations of the intrahepatic ducts without extrahepatic duct involvement. We will focus on type I choledochal cysts.

The diagnosis is delayed until adulthood in 20–50% of patients.[2–4] Adults may present with non-specific right upper quadrant pain, jaundice, pancreatitis, or cholangitis. Initial diagnostic studies include ultrasound and computed tomography. Detailed information about ductal anatomy can be obtained with cholangiography. Contemporary practice utilizes magnetic resonance cholangiopancreatography preferentially with endoscopic retrograde cholangiopancreatography, or percutaneous transhepatic cholangiography as secondary methods. Information on ductal anatomy is crucial since an anomalous pancreatobiliary duct junction is documented in more than 90% of patients. In this anatomic variant, the pancreatic duct joins the common bile duct more than 1 cm proximal to the ampulla of Vater, resulting in a long intrapancreatic common channel. The anomaly may permit free reflux of pancreatic secretions into the biliary tract. Reflux of pancreatic juice into the biliary tract may be etiologically important in the formation of choledochal cysts by increasing biliary pressures or by causing inflammatory changes in the biliary epithelium.

Operative therapy should be recommended to symptomatic patients, and also to asymptomatic patients due to the risk of malignant cyst degeneration. Cyst enterostomy, formerly employed for this condition, is no longer recommended due to high rates of anastomotic stricture and to the development of cancer in approximately 25% of patients.[5] The currently recommended surgical procedure for type I choledochal cysts is cyst excision with Roux-en-Y hepaticojejunostomy reconstruction.

Technique

A right subcostal incision is used to enter and explore the abdomen. The Omni-tract self-retaining retractor (Omni-Tract Surgical, St. Paul, MN) is placed, and the cyst exposed within the hepatoduodenal ligament (Fig. 1). With

J. B. Ammori · M. W. Mulholland (✉)
Department of Surgery,
The University of Michigan Medical Center,
2101 Taubman Center, 1500 East Medical Center Drive,
Ann Arbor, MI 48109-0346, USA
e-mail: micham@med.umich.edu

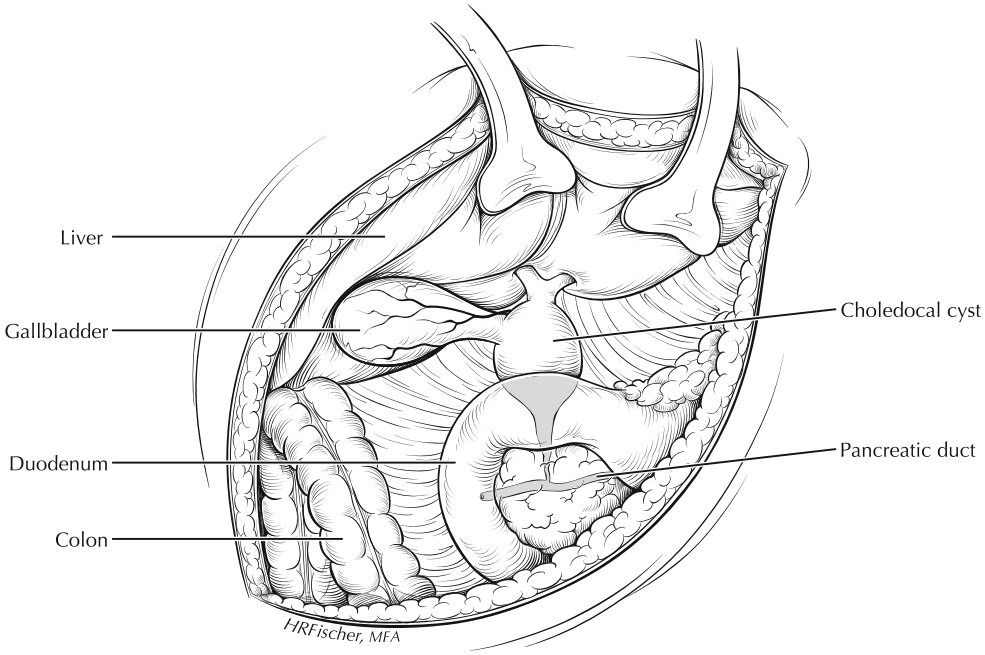

Figure 1 Type I choledochal cyst after retractor placement.

appropriate preoperative cross-sectional imaging, cholangiography is not usually necessary. The cystic artery is divided and ligated. The gallbladder is mobilized from the liver bed.

Excision of Common Bile Duct

The hepatic flexure of the colon is mobilized and retracted inferiorly to provide exposure of the duodenal sweep. A wide Kocher maneuver is performed as the cyst extends posterior to the first and second portions of the duodenum. Dissection on the anterior cyst wall is carried inferiorly toward the pancreas, with the plane of dissection extending posterior to the duodenum and pancreatic head. The dissection proceeds until the common bile duct narrows, at which point the common bile duct is circumferentially mobilized. The narrowed cyst is transected and the distal bile duct is ligated (Fig. 2). Elevation of the gallbladder and reflection of the cyst cephalad facilitate identification of the portal vein and hepatic artery. Dissection is carried proximally in a plane anterior to the portal vein to the level of the hepatic duct bifurcation. The dissection can usually

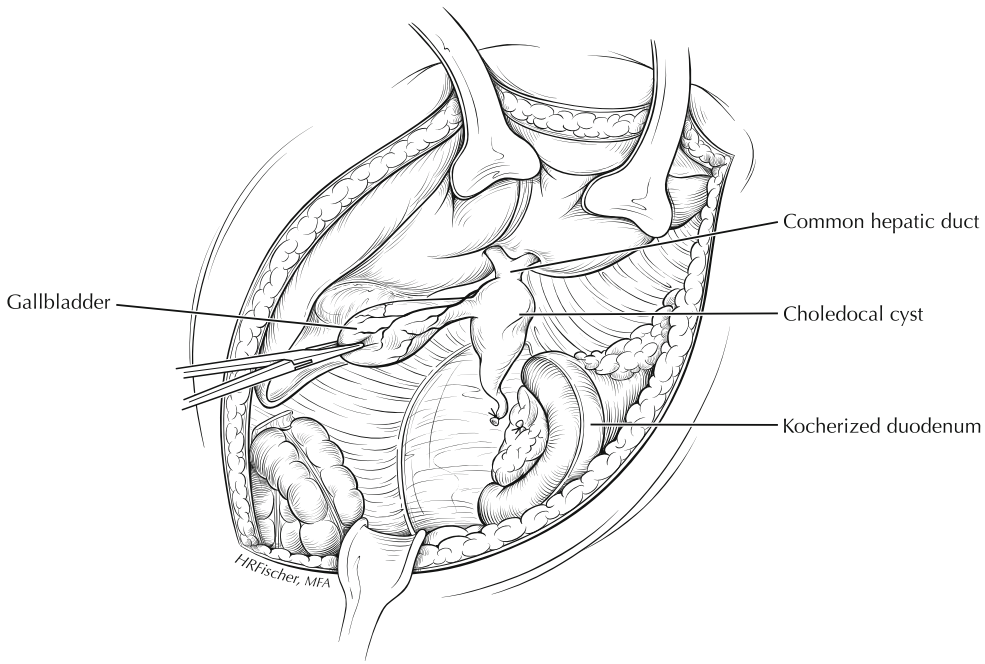

Figure 2 Transected choledochal cyst and oversewn distal bile duct.

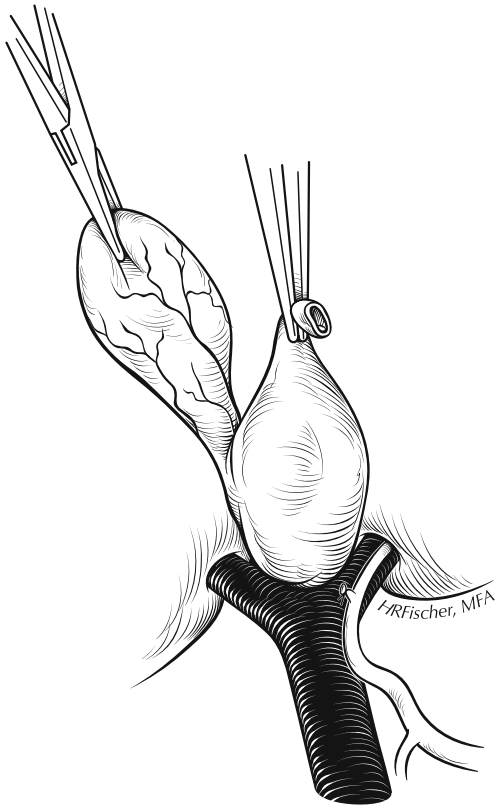

Figure 3 Cephalad retraction of the choledochal cyst allows identification and safe dissection of the cyst wall from the portal vein and hepatic artery.

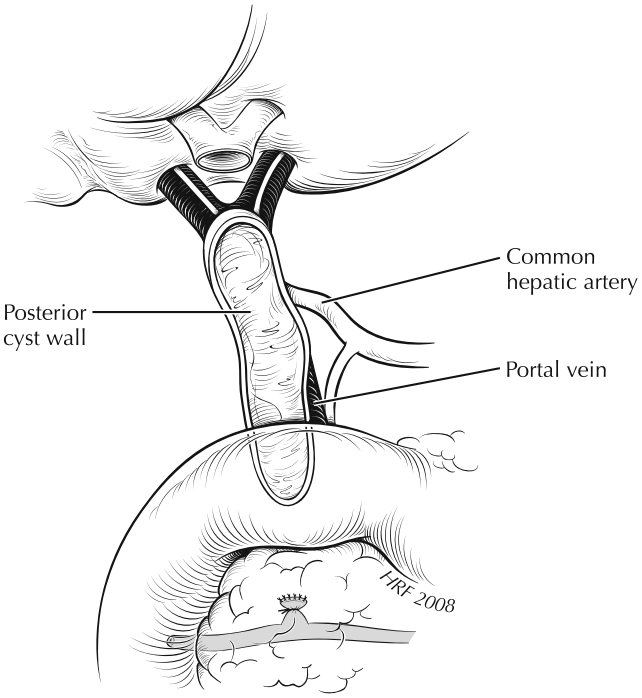

Figure 4 The choledochal cyst has been resected with the posterior wall left behind.

be performed bloodlessly in a plane of areolar tissue immediately adjacent to the cyst wall (Fig. 3). The cyst is transected at the hepatic duct bifurcation.

Preferably, primary cyst resection is performed as total transmural excision. In patients with severe inflammation and fibrosis, total resection may be difficult owing to adhesion of the cyst wall to the portal vein or hepatic artery. An alternative approach in this situation is intramural cyst dissection through a longitudinal incision on the cyst wall and removal of the cyst wall epithelium, leaving the posteromedial outer cyst wall adjacent to the portal vein and hepatic artery intact (Fig. 4). In this circumstance, it is critical to excise all cyst mucosa to reduce the risk of development of cholangiocarcinoma.

Roux-en-Y Enteroenterostomy

A Roux-en-Y jejunal loop 50 cm in length is constructed. A side-to-side hand-sewn enteroenterostomy establishes bowel continuity. A posterior row of Lembert 3-0 silk sutures is placed followed by enterotomies along the anti-mesenteric border in each limb of the jejunum. The inner layer uses a double armed 3-0 absorbable suture in a continuous non-locking fashion for the posterior layer and continuous

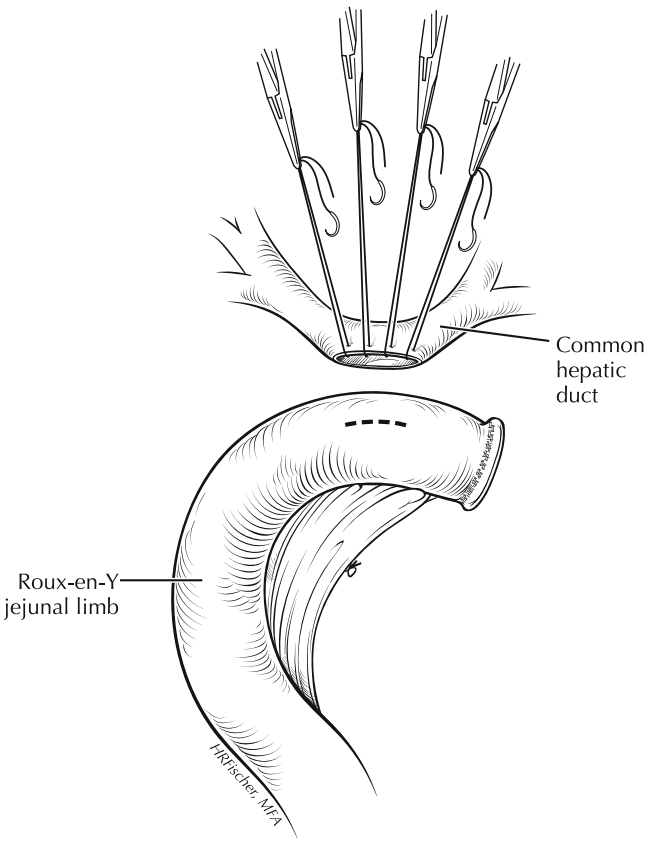

Figure 5 Retraction of the anterior bile duct sutures tilts the transected bile duct in a cephalad direction improving exposure.

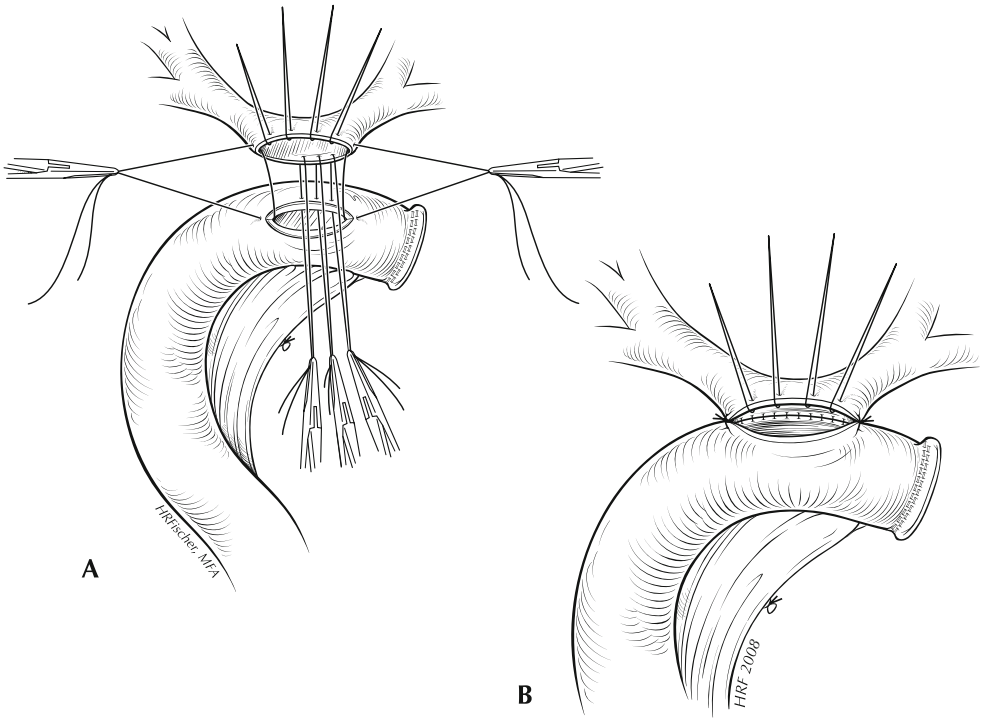

Figure 6 A: Corner and posterior wall sutures are placed. B: The completed posterior wall.

Connell suture for the anterior layer. The outer wall is completed with a row of Lembert 3-0 silk sutures. The defect in the small bowel mesentery is closed with interrupted 3-0 silk sutures.

Biliary-enteric Anastomosis

The Roux limb is brought to the right upper quadrant in a retrocolic position through the transverse mesocolon. The limb should easily reach the hepatic duct bifurcation without tension. Using interrupted 5-0 absorbable suture, a single-layer end-to-side hepaticojejunostomy is constructed with the bile duct to jejunum mucosal apposition.

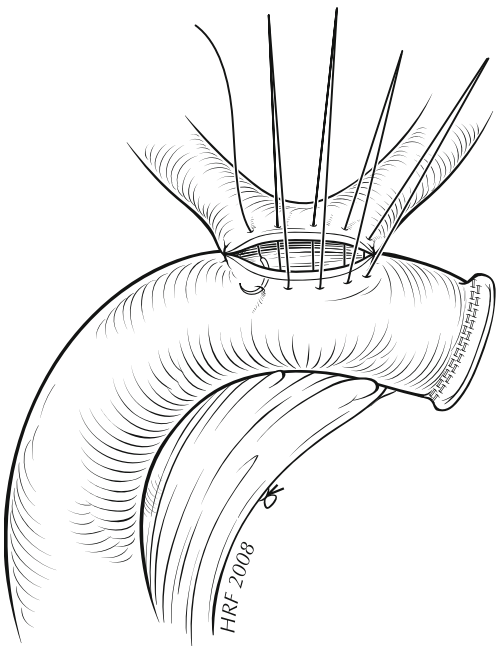

Figure 7 Placement of anterior jejunal stitches.

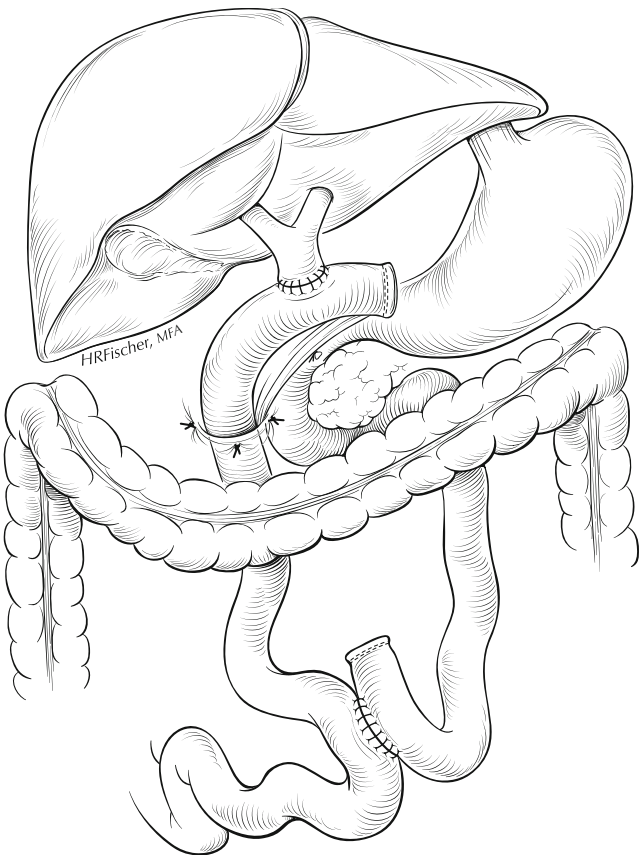

Figure 8 Configuration at the conclusion of the operation.

Placement of the anterior bile duct sutures first is a useful maneuver to improve exposure. The sutures are placed, with needles attached, and secured with fine hemostats. Retraction of the tagged sutures tilts the transected bile duct in a cephalad direction (Fig. 5). The enterostomy is made smaller than the opening of the bile duct as the incision tends to enlarge during suture placement. Sutures pass through all layers of bowel, taking approximately 4- to 5-mm bites of the seromuscular layer, smaller bites of the mucosa, and 3-mm bites of the bile duct. Corner and posterior wall stitches are placed and tied initially (Fig. 6). Anterior jejunal stitches are then placed, using the previously tagged sutures (Fig. 7). We do not routinely stent or drain the anastomosis. The Roux limb is secured to the transverse mesocolon with interrupted 3-0 silk sutures. Figure 8 shows the final operative configuration.

If the situation arises in which the cyst extends into the hepatic duct bifurcation, we resect all diseased portions of the duct including the bifurcation. Each hepatic duct is then separately anastomosed to the jejunal limb over a stent, such as a pediatric feeding tube.

Postoperative Management

Postoperatively, patients leave the operating room with a nasogastric tube and urinary catheter in place. Postoperative pain is controlled with epidural anesthesia, which is transitioned to oral analgesics. Typically, inpatient length of stay averages 5–7 days while the patient regains bowel function and advances to a regular diet. Thirty-day operative mortality is less than 2%. Specific complications related to the procedure include biliary leak and anastomotic stricture presenting with acute cholangitis, which may occur in 10–20% of patients followed long term. Stricture can be managed with a revision hepaticojejunostomy once cholangitis has resolved. Development of cancer after resection occurs in less than 1%. Overall, long-term outcomes are excellent.

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HOW I DO IT

Esophageal Extension Encountered During Transhiatal Resection of Gastric or Gastroesophageal Tumors: Attaining a Negative Margin

Diego Avella · Luis Garcia · Brett Hartman · Eric Kimchi · Kevin Staveley-O'Carroll

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Abstract
Introduction Over the last several decades, the incidence of gastroesophageal junction tumors has been increasing. Often, patients present late in the course of their disease. However, if the disease is localized, then complete surgical resection remains the standard of cure and the best chance for cure. On occasion, these tumors involve a significant portion of both the distal esophagus and proximal stomach.
Materials and Methods In order to completely remove these tumors with an adequate surgical margin and lymph node dissection, a total gastrectomy and total esophagectomy with colonic interposition may be required. We have utilized this approach on six patients with excellent clinical results. In this manuscript, we discuss the technical considerations involved in this approach and present our results.

Keywords Gastroesophageal junction tumors · Esophageal cancer · Colon interposition

Introduction

Over the last several decades, the incidence of gastroesophageal junction (GEJ) tumors has been increasing. Unfortunately, adenocarcinoma of the GEJ continues to be one of the most difficult malignancies to treat. Often, patients present late in the course of their disease, at which time spread to adjacent organs and distant lymph nodes has occurred.[1] However, if the disease is localized at the time of diagnosis, then complete surgical resection remains the standard of care and the best chance for cure.

To better understand the etiology and clinical course that these malignancies will follow, Siewert et al. devised a classification system based on the topographic-anatomic location of the tumor in relation to the gastric cardia. Tumors arising in the distal esophagus are type I, tumors at the true gastric cardia are type II, and those that are subcardial are type III.[2] A general consensus for the treatment of these tumors has been formed: Patients with type I tumors usually receive a radical en bloc esophagectomy with a resection of the proximal stomach; type III tumors are often treated with an extended total gastrectomy and a distal esophagectomy.[3]

The management of type II tumors is somewhat controversial: Some advocate an extended total gastrectomy and a distal esophagectomy, while others suggest that the treatment of choice is a radical en bloc esophagectomy with resection of the proximal stomach.[3] On occasion, when type II tumors involve a significant portion of both the distal esophagus and proximal stomach, a total esophagectomy and gastrectomy may be required for adequate resection and lymphadenectomy. This surgical approach is sometimes avoided as it leads to a reconstructive challenge in order to reestablish gastrointestinal continuity. While colonic interposition is well described for esophageal reconstruction, its use in the setting of a total esophagectomy and gastrectomy is not well documented. Here, we propose a solution to these difficult but potentially curable tumors, with a total esophagectomy, total gastrectomy, a substernal colonic interposition graft, and a Roux-en-Y

D. Avella · L. Garcia · B. Hartman · E. Kimchi · K. Staveley-O'Carroll (✉)
Penn State University,
500 University Dr.,
Hershey, PA 17033, USA
e-mail: ksoc@hmc.psu.edu

jejunocolostomy. In addition to describing the technique, we report a small series of patients in whom we have had excellent functional outcomes. This retrospective review was performed with Institutional Review Board approval. All patients were informed that there was a potential for a total gastrectomy and esophagectomy with a colon interposition prior to surgery and consented to this surgical plan.

Operative Selection/Technique

Patients with tumors originating at the GEJ, which are demonstrated by esophagogastrodudenoscopy and endoscopic ultrasound to extend proximally up the esophagus and distally into the stomach, are subsequently considered for a total gastrectomy and total esophagectomy with colonic interposition. A colonoscopy is always obtained preoperatively to rule out colonic pathology. A visceral angiogram, although helpful, is not essential in the preoperative workup.

The patient is placed in the supine position, and the head is turned to the right. The left arm is tucked, and the shoulder blades are elevated with blankets. The neck, chest, and abdomen are prepped and draped. A midline incision is made and carried down to the peritoneal cavity (Fig. 1). The peritoneal cavity is entered and thoroughly explored. Typically, the xiphoid process is removed. The splenic flexure is mobilized, and the colon is thoroughly inspected. At this point, the remaining greater omentum is dissected away from the transverse colon, and an omental bursectomy is performed. Next, the vascular supply of the colon is evaluated; palpable pulses should be present in the marginal artery of Drummond, the ascending branch of the inferior mesenteric artery, and the middle colic artery. The

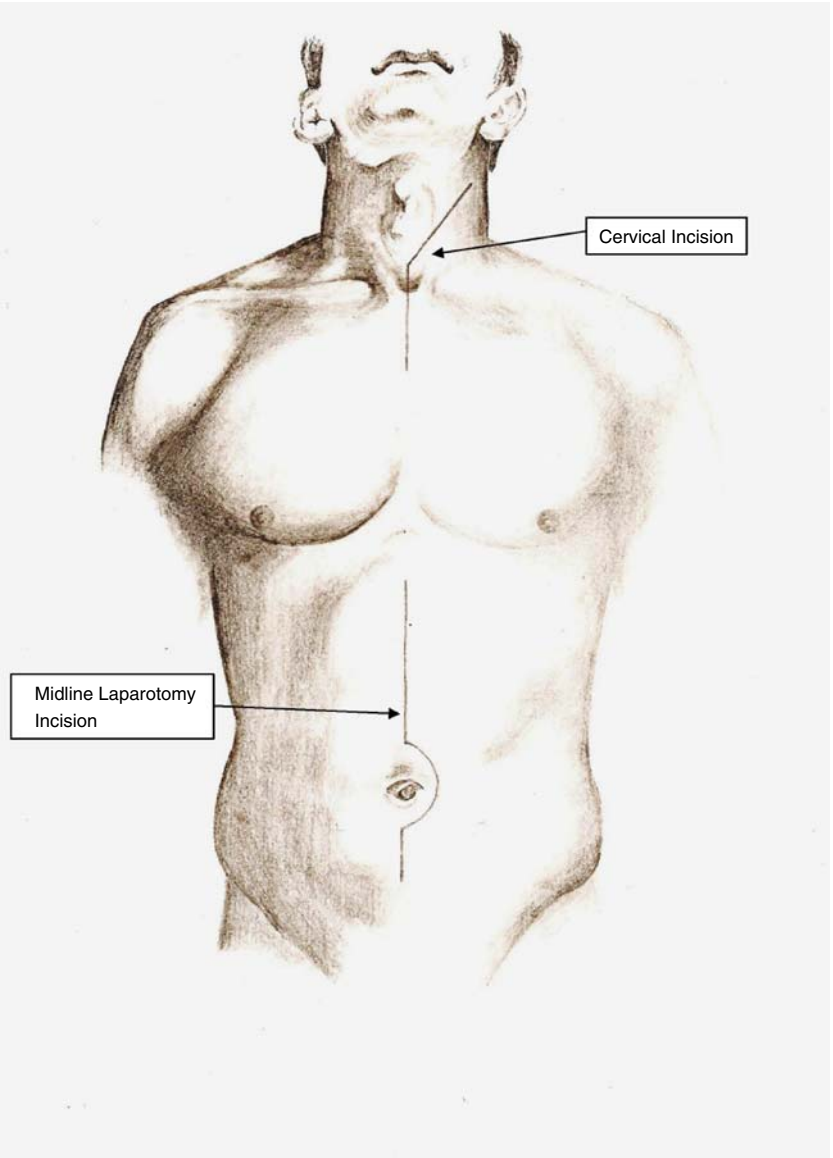

Figure 1 Schematic representing the midline laparotomy incision and the cervical incision.

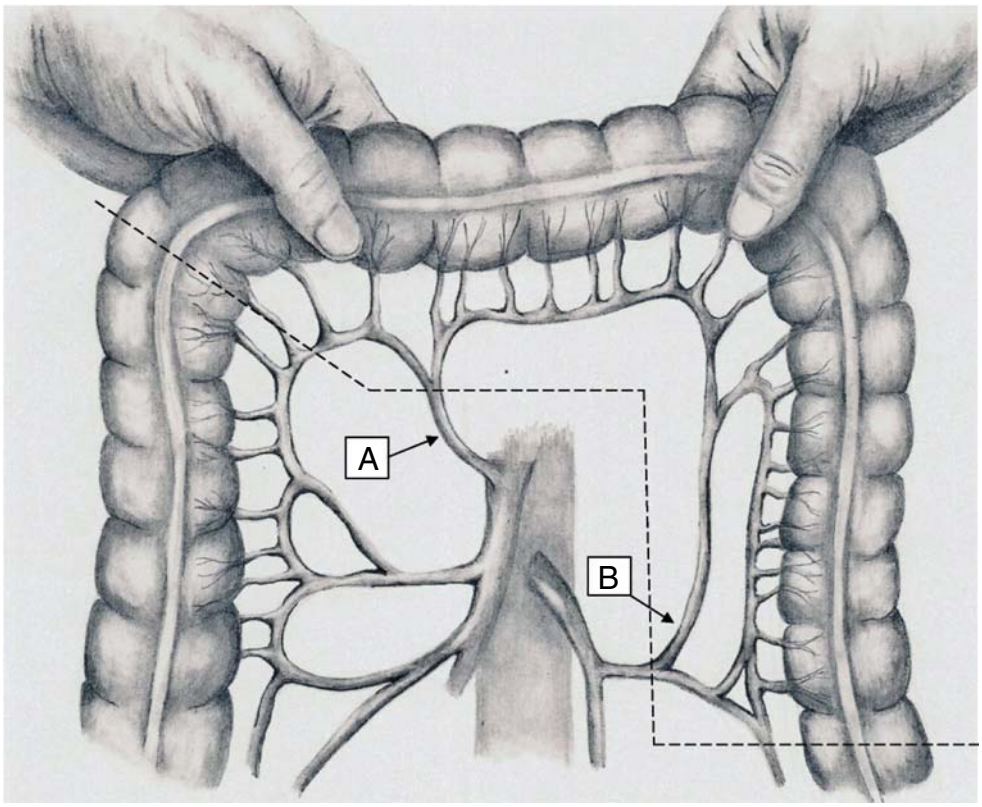

Figure 2 The two vascular pedicles that may be used for the graft. If the middle colic artery is selected (*arrow A*), then the ascending branch of the IMA (*arrow B*) is ligated; this will result in an anti-peristaltic graft. If the ascending branch of the IMA is selected (*arrow B*), then the middle colic artery (*arrow A*) is ligated; this will result in an iso-peristaltic graft. The *hatched line* represents the transection line for the colon conduit based on either pedicle.

ascending branch of the inferior mesenteric artery (IMA) is now occluded, and the pulse in the marginal artery of Drummond is evaluated. Subsequently, the middle colic artery is occluded, and the pulse is once again palpated in the marginal artery of Drummond. Based on this examination, the splenic flexure is used as a conduit based on the vessel which provides the best blood supply through the marginal artery. An interposition supplied by the ascending branch of the IMA will provide an isoperistaltic interposition, with the transverse colon being brought up to the cervical esophagus and the descending colon brought to the jejunum. An interposition supplied by the middle colic artery will result in an anti-peristaltic conduit, with the descending colon being brought up to the cervical esophagus and the transverse colon brought to the jejunum (Fig. 2). In our experience, the orientation of peristalsis does not have any appreciable effect on the length of the colon interposition or the function of the neoesophagus.

After selecting the conduit, a total gastrectomy and transhiatal esophagectomy is performed in a standard fashion. This includes the previously mentioned omental bursectomy and a complete skeletonization of the celiac axis and a ligation of the left gastric, right gastric artery, and gastroepiploic arteries at their origin. A splenectomy may be considered if the tumor involves the fundus of the stomach to a significant degree. A ring of diaphragmatic hiatus is taken en bloc with the specimen. The hiatus is then further widened anteriorly, behind the heart, after ligation of the left phrenic vein. Through this widened hiatus under direct vision, the pleura surrounding the distal esophagus is routinely removed. Above the tumor, the vagus nerves are divided; this brings the plane of the dissection onto the muscular layer of the esophagus. At this level, a transhiatal thoracic anastamosis may be considered; otherwise, more proximal dissection may be continued bluntly, performing a total thoracic esophagectomy.

A neck incision (Fig. 1) is then created, and the sternocleidomastoid muscle is retracted laterally. The omohyoid muscle is divided and the esophagus identified just anterior to the cervical spine. A rib cutter is used to transect the clavicle and a sternal saw used to make a cut in the midline of the manubrium. Subsequently, the medial part of the clavicle, left side of the manubrium, and the adjacent portion of the left first rib are removed en bloc (Fig. 3). This technique is utilized to allow for ease of passage of the colonic segment and its mesentery.

The chosen segment of colon is then divided proximally and distally and brought up to the neck in a substernal fashion. A substernal route (Fig. 4) is chosen over the posterior mediastinum because of its larger diameter, avoiding possible damage or kinking of the colonic mesentery. In addition, placing the colonic conduit in the anterior mediastinum allows for postoperative radiation of the posterior mediastinum without radiation injury to the colonic conduit. An esophagocolostomy is performed in the neck, and a Roux-en-Y reconstruction is fashioned with a

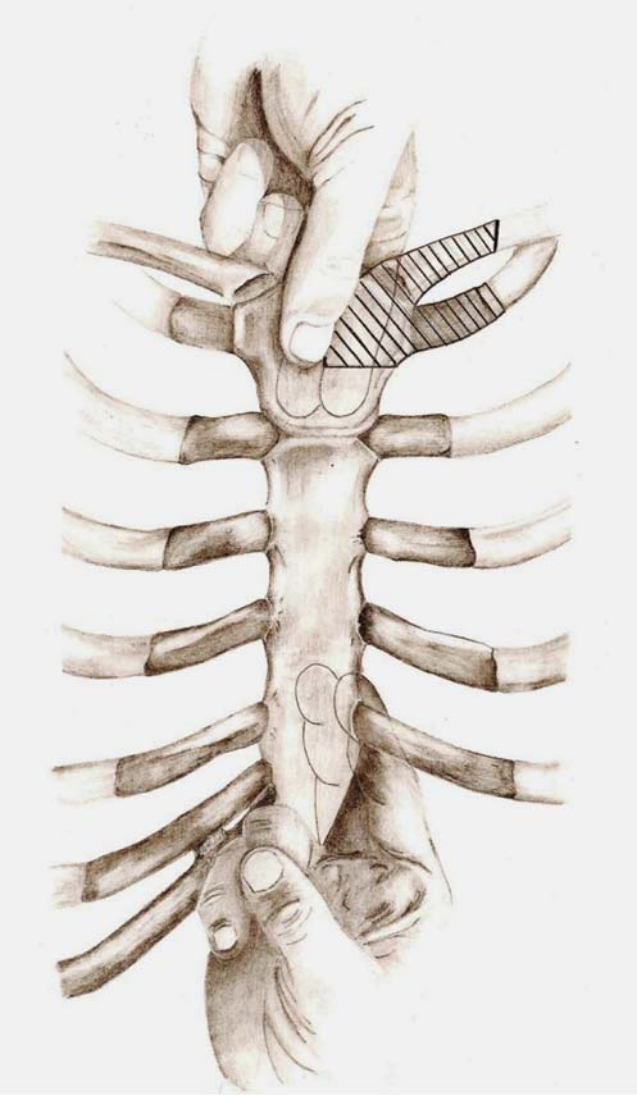

Figure 3 The technique for the creation of the substernal tunnel. The *shaded area* indicates the portion of manubrium, clavicle, and first rib that are removed.

proximal jejunal pouch anastomosed to the interposed colon (Fig. 5). A jejunal feeding tube is also placed. A tube thoracostomy is not routinely required. The abdominal fascia is reapproximated and the skin closed. The neck incision is closed by reapproximating the platysmus and the skin edges.

Results

We have utilized this approach on six patients with excellent clinical results (Table 1). Follow-up gastrograffin swallow studies were obtained in all patients, and all demonstrated no evidence of anastomotic leak or stricture. All four patients were discharged home on clear liquid diets with jejunal feed supplementation. Over the 2 weeks following discharge, all patients had their diets advanced and were able to be weaned from their supplemental jejunal feeds. Patients tolerated the procedure well and were discharged after an average hospital stay of 9 days (with a range of 7–12 days). Five patients were able to be discharged to home directly from the hospital. One patient required a short stay at a rehabilitation facility prior to discharge home.

Discussion

Over the past several decades, there has been a change in the epidemiology of esophageal cancer. Once rare, adenocarcinoma of the esophagus and GEJ is now the most common esophageal cancer, and its incidence continues to increase.[4] Though there have been significant advances in adjuvant medical therapies, complete surgical resection remains the mainstay of therapy.

GEJ tumors may be approached through transhiatal and thoracoabdominal exposures. A thoracoabdominal incision, which offers excellent visualization of the tumor, provides a straight-forward approach to removal of these tumors with a distal esophagectomy, proximal gastrectomy, and an intrathoracic esophagogastrostomy.[5] We do not advocate this approach as it often is an inadequate cancer operation and removes the GEJ resulting in debilitating reflux. If a thoracoabdominal approach is selected, we prefer a total gastrectomy and distal esophagectomy with an intrathoracic Roux-en-Y esophagojejunostomy as a reconstructive option.

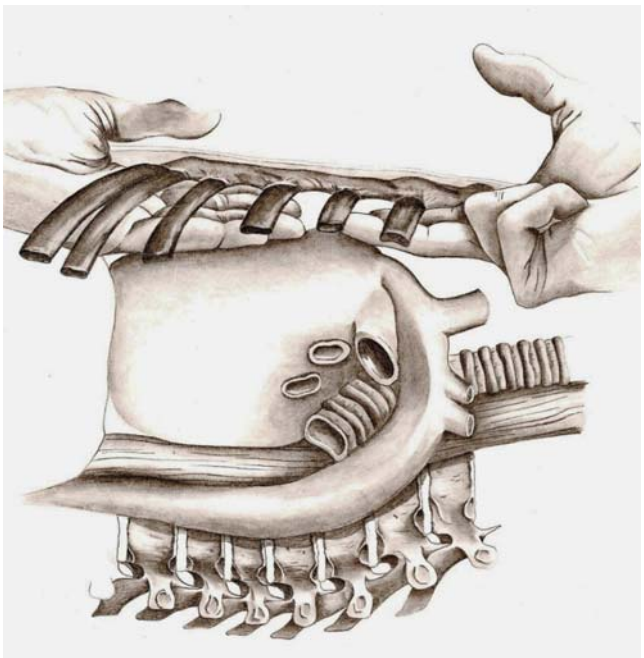

Figure 4 Sagittal section depicting the creation of the substernal tunnel.

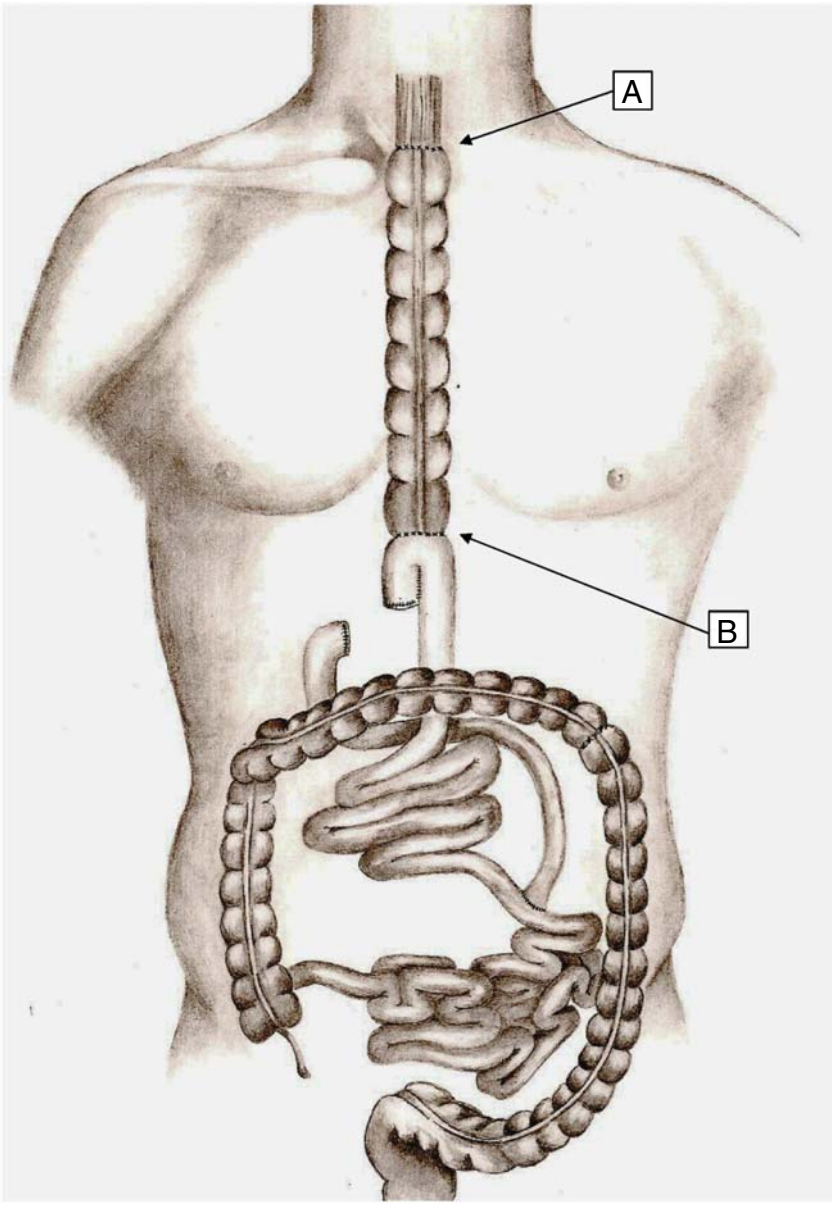

Figure 5 *Arrow A* points to the esophagocolostomy, and *arrow B* points to the Roux-en-Y esophagojejunostomy.

Table 1 Outcomes of Four Patients with Total Esophagectomy and Total Gastrectomy with Colonic Interposition Reconstruction

Patient Age (year)/Gender	Diagnosis	Intervention	Outcome
65/male	Adenocarcinoma of the GEJ	Transhiatal esophagectomy, total gastrectomy, splenectomy, colon interposition	Enjoying a regular diet, 34 months postop
80/female	Adenocarcinoma of the GEJ	Transhiatal esophagectomy, total gastrectomy, colon interposition	Died of recurrence 6 months postop
61/male	Hemorrhaging tumor of the GEJ (adenocarcinoma)	Transhiatal esophagectomy, total gastrectomy, splenectomy, colon interposition	Enjoying a regular diet, 18 months postop
49/male	Adenocarcinoma of the GEJ	Transhiatal esophagectomy, total gastrectomy, colon interposition	Died of recurrence 6 months postop
79/male	Adenocarcinoma of the GEJ	Transhiatal esophagectomy, total gastrectomy, colon interposition	Enjoying a regular diet, 4 months postop
37/male	Adenocarcinoma of the GEJ	Transhiatal esophagectomy, total gastrectomy, colon interposition	Enjoying a regular diet, 2 months postop

With this resection and reconstruction, tumors extending to the aortic arch can be adequately treated.

More recently, the transhiatal approach to GEJ tumors has become the preferred operative method by many surgeons for several reasons: (1) shorter operative time, (2) less intraoperative blood loss, (3) fewer days spent in the intensive care unit, and (4) equivalent margins and number of lymph nodes obtained.[6] Through this approach, total gastrectomy and distal esophagectomy with an esophagojejunostomy is now a standard operation for Siewert types II and III tumors. Unfortunately, during this procedure, the esophageal margin may be found grossly or by frozen section to be positive for tumor. This presents a difficult situation in which the surgeon may be tempted to accept a positive margin for a number of reasons: (1) further attempts at resection through a transhiatal approach are limited due to suboptimal exposure for the esophagojejunostomy as visualization is eventually obscured by the heart; (2) a thoracoabdominal approach in the supine position (a lateral extension of a midline incision across the costochondral margin at the level of the xiphoid process) is of little value as it does not improve exposure to the posterior mediastinum since the heart continues to obscure the operative field; and (3) while repositioning the patient and entering the thoracic cavity in the lateral position is a straightforward option that provides better access to mediastinal dissection and still permits an intrathoracic or cervical anastomosis; it extends operative time and adds the potential morbidity of an additional incision. In these difficult situations when gastrectomy and distal esophagectomy are necessary but the tumor is found to extend to the proximal margin, completing the transhiatal esophagectomy and reconstructing with colonic interposition and cervical anastamosis is a safe technique that provides excellent oncologic and functional outcomes.

Neoadjuvant chemoradiation therapy is many surgeons' preferred method of treatment for esophageal tumors which have been demonstrated by endoscopic ultrasound to have transmural or nodal involvement. Ideally, neoadjuvant chemoradiation is followed by a total esophagectomy, in which the cervical esophagus is anastamosed to the fundus of the stomach as neither of these is in the preoperative radiation field (carina to the gastric cardia). On the other hand, when neoadjuvant radiation is used and a total gastrectomy with distal esophagectomy is required, this can be problematic as one is forced to anastamose jejunum to an irradiated esophagus. The technique we describe is most useful in achieving a negative proximal esophageal margin after an extended gastrectomy for a Siewert type II lesion. In such circumstances, neoadjuvant radiation is usually not used, and post-operative radiation is sometimes given for more aggressive tumors with nodal involvement.

One added benefit of the anterior reconstruction is that it allows for post-operative radiation without damaging the neo-esophagus. However, we reconstruct through the anterior mediastinum resecting the manubrium, first rib, and proximal clavicle primarily for the following reason: In our experience, more space is available for the conduit and its appropriate mesentery; this prevents vascular kinking and mesenteric injury.

We have not found the anterior substernal reconstruction to require any additional length of colonic conduit; in fact, we routinely must trim a portion of excess colon after bringing the conduit to the neck to prevent redundancy. We have also not found any cardiopulmonary dysfunction, although this is a potential concern in patients with inadequate cardiopulmonary reserve.

The technique described above allows for a complete resection of extensive tumors involving both the stomach and esophagus, while avoiding difficulties with surgical margins, repositioning, reflux, and an intrathoracic esophageal anastomosis. The substernal colon interposition provides a reliable conduit in an easily accessible space, allows for postoperative radiotherapy to be given to the posterior mediastinum without compromising the colonic conduit, and provides excellent clinical results.

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REVIEW ARTICLE

Quantitative Assessment of Hepatic Function and its Relevance to the Liver Surgeon

G. Morris-Stiff · D. Gomez · R. Prasad

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Abstract
Background Standard evaluation of patients undergoing hepatic surgery has been through radiological and quantitative determination of liver function. As more complex and extensive surgery is now being performed, often in the presence of cirrhosis/fibrosis or following administration of chemotherapy, it is questioned whether additional assessment may be required prior to embarking on such surgery. The aim of this review was to determine the current knowledge base in relation to the performance of quantitative assessment of hepatic function both pre- and post-operatively in patients undergoing hepatic resectional surgery and liver transplantation.
Methods An electronic search was performed of the medical literature using the MEDLINE database to identify relevant articles with cross-referencing of all identified papers to ensure full literature capture.
Results and Conclusions The review has identified a number of different methods of dynamically assessing hepatic function, the most frequently performed being through the use of indocyanine green clearance. With the recent and further anticipated developments in hepatic resectional surgery, it is likely that quantitative assessment will become more widely practiced in order to reduce post-operative hepatic failure and improve outcome.

Keywords Hepatic neoplasms · Hepatocellular carcinoma · Liver metastasis · Hepatic failure · Hepatectomy · Liver transplantation

Introduction

Whilst conventional liver function tests provide information on the integrity of hepatocytes and biliary epithelium, dynamic assessment of hepatic function using quantitative tests represents and provides the significant advance of allowing an estimation of functional reserve of the liver parenchyma. Such tests are useful for a surgeon during pre-operative workup of patients in many clinical scenarios including: determining the extent of safe liver resection that will provide adequate hepatic reserve; allowing prioritisation of transplant waiting lists; and in selection of optimal living donor livers. Dynamic assessment of liver function is also important following surgery in a number of settings including: evaluating hepatic function and predicting complications during the early post-operative period following transplantation or resection; assessing the regeneration of residual parenchyma after resection; the evaluation of graft function following transplantation; and the monitoring of residual function of remnant livers of living-related donors.

The purpose of this review is to describe the nature and results of the various dynamic function tests currently performed and to consider the evidence for their use by liver surgeons during the pre-operative assessment and post-operative management of patients.

G. Morris-Stiff · D. Gomez · R. Prasad
Department of Hepatobiliary and Transplant Surgery,
St. James's Hospital,
Leeds, UK

R. Prasad (✉)
The Leeds Teaching Hospitals NHS Trust,
St. James's University Hospital,
Beckett Street,
Leeds LS9 7TF, UK
e-mail: raj.prasad@leedsth.nhs.uk

Methods

The English language literature was searched using Medline for all studies published using text searches for quantitative assessment of liver function. In addition, the following MeSH headings were searched: hepatic neoplasms; hepatocellular carcinoma; liver metastasis; hepatic failure; hepatectomy; and liver transplantation. The abstracts of all identified articles were reviewed to determine their relevance and all appropriate papers were obtained and analysed.

Assessment of Hepatic Reserve

It has been suggested by some authors that routine biochemical liver function tests are adequate for the prediction of post-operative liver failure.[1] In particular, a high alkaline phosphatase in the presence of a normal bilirubin has been suggested as being of prognostic value.[2] However, these views are not widely held and many investigators believe that such tests are of no predictive value.[3,4]

In patients with fibrosis and/or cirrhosis, the Child–Pugh score[5] is a reliable semi-quantitative means of classifying patients into risk based on presence or absence of ascites and encephalopathy, and measurement of albumin, bilirubin and prothrombin time (Table 1). For patients classified Child–Pugh A, the mortality is minimal at <5% whereas for Child–Pugh B cirrhotics the 1-year liver failure-related mortality is in the order of 20% and for patients with Child–Pugh C cirrhosis the mortality is in the order of 55%.[6] Whereas it might be expected that the Child–Pugh score would be of use in the prediction of mortality following resection in cirrhotic patients, the results have shown it to be unreliable and it has not been shown to be of any use in non-cirrhotic resection patients.[7,8]

The model for end-stage liver disease (MELD) score is now in common use in predicting deterioration in hepatic failure in patients with end-stage liver disease and is used to prioritise liver transplant waiting lists.[9] The MELD score has recently been shown to predict the development of post-operative liver failure after hepatectomy for patients with cirrhosis undergoing resection of hepatocellular carcinoma (HCC), with a pre-operative score of ≥11 being associated with a poor outcome.[10–12] Furthermore, Cucchetti et al. demonstrated that an increase of MELD during the post-operative period between days 3 and 5 was associated with a high risk of developing hepatic failure.[13]

Balzan et al. have recently reported on the value of the '50–50' criteria on day 5 following resection, as a predictor of both hepatic failure and mortality.[14] The criteria were a prothrombin time <50% of the normal prothrombin index and a bilirubin >50 μmol l^{-1} and when present together were associated with a >50% chance of mortality in a series of 775 liver resection cases.

Bruix and colleagues[15] evaluated assessment of both wedged and free hepatic venous pressure and the hepatic venous pressure gradient (HVPG) as a means of predicting outcome in cirrhotic patients undergoing resection of HCC. They studied 29 patients, 11 of which had unresolved decompensation 3 months following surgery, and found pre-operative HVPG to be significantly higher in the subgroup with decompensation and on multivariate analysis identified HVPG as the only factor predictive of the development of hepatic failure.

Dynamic Liver Function Tests

There are many different tests available for the determination of dynamic function with several distinct methodologies utilised as summarised in Table 2. The ideal test would be: easy to perform; reproducible; cost efficient; accurately predict outcome; and be widely accepted thus allowing widespread use and comparative audit.

Clearance Tests

Quantitative estimation of liver function by clearance tests are based on one of two principles: assessment of synthetic capacity of the liver through administration of a substrate and measuring the formation of a known product or clearance of an exogenous compound which is primarily handled by the liver. Hepatic clearance of the exogenous

Table 1 Child–Pugh Classification of Hepatic Failure

Points	1	2	3
Ascites	None	Diuretic-controlled	Tense
Encephalopathy	Absent	I–II	III–IV
Albumin (g l^{-1})	3.5	2.8–3.5	<2.8
Bilirubin (mg dl^{-1})	<2	2–3	>3
Prothrombin time (seconds>control) or INR	<4	4–6	>6
	<1.7	1.7–2.3	>2.3

Child–Pugh A=5–6 points; B=7–9 points; C=10–15 points

Table 2 Quantitative Assessment of Hepatic Function

Assessment	
I Clearance/retention tests	
A	Indocyanine green (ICG)
B	Lidocaine/monoethylglycinexylidide (MEGX)
C	Galactose elimination capacity
D	Aminopyrine breath test
E	Hippurate ratio
F	Trimethadione/dimethadione (TMO/DMO)
G	Amino acid
H	Caffeine
I	Antipyrine
II Redox chemistry	
A	Arterial ketone body ratio (AKBR)
B	Redox tolerance index (RTI)
III Volumetry	
A	Computed tomography (CT)
B	Magnetic resonance imaging (MRI)
IV Scintigraphy	
A	99m technetium galactosyl human serum albumin (99m Tc-GSA)

substance approaches systemic clearance if it is primarily handled by the liver alone. The hepatic clearance then depends upon three factors namely: hepatic perfusion; exchange across the blood–hepatocyte barrier; and functional hepatocyte mass.

Clearance of substrates such as indocyanine green (ICG) which is highly extracted depends predominantly on blood flow, whereas substrates such as aminopyrine and caffeine are dependent upon microsomal function and thus on the functioning hepatocyte mass. However, for many substances, the clearance is dependent on concentration of agent administered and many agents will show characteristics of being both flow and mass dependent. This review will concentrate on the three most commonly performed tests: indocyanine green elimination; lidocaine elimination; and galactose elimination capacity tests.

Indocyanine Green (ICG)

ICG is a highly protein-bound, water-soluble anionic organic dye which is bound in plasma to albumin and β-lipoproteins. It is selectively taken up by hepatocytes with a plasma extraction of 70–90% and is excreted unchanged in the bile via a carrier-mediated mechanism. The hepatic clearance of this compound approaches that of the plasma flow and when higher doses of ICG are administered, the uptake process is saturated and the maximal removal of ICG, which is then calculated, reflects the functioning hepatocyte mass. It can therefore be used both as a measure of hepatic blood flow and of functional hepatocyte mass. Its importance was first recognised by Caesar et al. in 1961 although it is only relatively recently been widely used.[16]

The standard procedure involves a bolus injection of 0.5 mg kg^{-1} of ICG following an overnight fast, and blood samples are collected at 5-min intervals for 20 min. ICG concentrations are measured using a spectrophotometer. The various parameters that can be evaluated and their normal values are as shown in Table 3.[17] The ICGR-15 is the most commonly determined value.[1]

The recommended safety limit for a major hepatic resection does vary in the literature. Lau et al. prospectively evaluated the ICG test, together with the aminopyrine breath test and the amino acid clearance test in 127 patients with HCC undergoing hepatectomy, and found that a safety limit of 14% for ICG retention at 15 min was the best discriminating test for evaluating the functional hepatic reserve pre-operatively.[1] Fan et al.[4] also recommended an ICGR-15 of 14% in their initial reports although a more recent paper from their unit has upped the safe limit to 20% in patients with Child–Pugh grade A, although they do stress extra vigilance in those with ICGR-15 of 14–20%.[5] A number of other studies looking at ICGR-15 have shown it to be of prognostic significance in this setting.[7–14,16–22]

The ICG test has also been used to provide an algorithm for treatment, with differing modalities being preferred according to the pre-operative test results as illustrated in Fig. 1. If a patient has a normal bilirubin and an ICGR-15 less than 10%, then an extended resection is safe whereas if the ICGR-15 is ≥40%, then the only safe option is enucleation. For intermediate ICGR-15 values, varying degrees of resection are possible. Using this algorithm, 0% mortality was reported in a series of 107 consecutive patients.[23]

The usefulness of the ICG test was elegantly confirmed by Imamura et al. in a follow-up of the original work in a series of 1,056 hepatic resections for HCC associated with cirrhosis.[24] Using the pathway outlined above, they managed to maintain 0% mortality over an 8-year period.

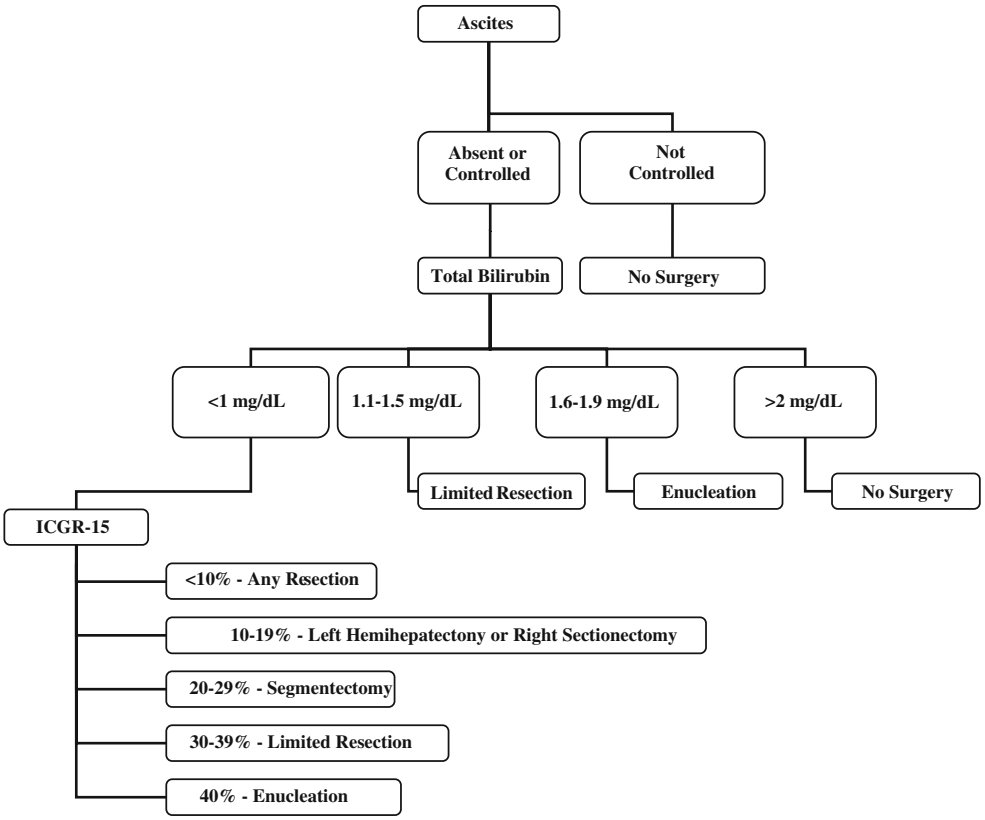
Others have preferred ICGR-Max as it relates to the volume of liver remaining after hepatectomy. Noguchi et al.

Table 3 Measurement Criteria in Relation to Indocyanine Green Clearance

Parameters	Definition	Normal values
ICGR-15	ICG retention at 15 min	3.5–10%
ICGR-20	ICG retention at 20 min	4%
ICGR max	Max removal rate	0.4 mg kg^{-1} min^{-1}
ICG cl	ICG clearance	>5 ml kg^{-1} min^{-1}
ICG t1/2	Half life	4 min
ICG PD	Plasma disappearance rate	18–30%
ICG-K	Elimination constant	0.06 min

Modified from Prasad[17] with permission

Figure 1 Algorithm.



reported that an ICGR-Max of >0.8 μg kg^{-1} cm^{-3} predicted fair morphological regeneration but no functional recovery but a value <0.5 μg kg^{-1} cm^{-3} predicted functional deterioration of the remnant liver. They also noted a 100% accuracy in predicting outcome using this methodology.[25]

Ohwada et al. recently reported a study of 75 patients undergoing resection for hepatocellular carcinoma using peri-operative real-time monitoring of ICG using ICG clearance as the parameter of choice.[26] They found the test beneficial in evaluating for hepatic reserve prior to, during and after liver resection.

However, not all hepatic surgeons are in agreement with the benefit of ICG. Bennett and Blumgart point out that it has never been proven to be superior to clinical scoring systems such as Child–Pugh and Okuda classifications and also note the overlap in ICG parameters between patients and healthy controls.[27] They also point to the experience of only six deaths in 1,800 liver resections at their institution as evidence not to rely on dynamic function tests.[28]

The role of ICG has also been extensively investigated in the setting of liver transplantation.[29–37] Clements and colleagues noted impaired ICG clearance during episodes of rejection and noted that clearance improved as the rejection was successfully treated.[29] Tsubono et al. prospectively evaluated ICG-K in 50 orthotopic liver transplants and found that the day 1 ICG-K was a better predictor of graft outcome than any of the other conventional liver functional tests.[30] ICG-K also correlated with the length of intensive therapy unit (ITU) stay, preservation injury and septic complications. Oellerich et al. compared ICG with conventional liver function tests and Child–Pugh scores and found it to be superior in predicting short term prognosis of potential transplantation candidates.[31]

Jochum et al. compared three different systems—ICG, galactose elimination capacity (GEC) and lidocaine half-life in 22 living donors and their recipients.[32] They noticed a 42.6% decrease in GEC and a 50.6% increase in ICG in the donors. These changes persisted over a 3-month follow-up period although the parameters did improve. In the recipient group, there were significant improvements, with the ICG decreasing by 63.7% and the GEC increasing by 16.3% during the course of the study. The lidocaine half-life remained unchanged throughout both groups. The patterns of ICG, lidocaine and GEC metabolism seen in Jochum et al.'s recipients are identical to those reported in previous studies of cadaveric transplant recipients.[33]

More recently, the use of non-invasive methods of determining ICG-K has been reported for both resection and transplantation settings using pulse spectrophotometry.[14,38–42] Using this methodology, Okochi et al. found that ICG-K decreased significantly after surgery and that the fall correlated with the extent of resection.[38] They also noted that the low ICG-K persisted for 7 days and that the effect was most evident in patients with cirrhosis. Furthermore,

the results correlate well with a pre-operatively calculated post-operative ICG-K based upon volumetric assessment. Sugimoto and colleagues examined serial changes in ICG-K using pulse-dye densiometry in 51 patients undergoing resection of HCCs and found that the day 1 ICG-K accurately predicted the subsequent development of liver failure, with a significantly lower value than for patients not developing hepatic insufficiency.[39]

Several studies have now compared both utilities. Purcell et al. compared non-invasive monitoring with standard blood estimations and found a strong correlation between the two methods and advocated into its incorporation into a scoring system to determine respectability.[41] Hsieh and colleagues compared the two modalities in 13 patients undergoing liver transplantation and found an excellent correlation between the standard and densiometry methods with a correlation coefficient r^2 of 0.977.[42] Hori and colleagues monitored 30 adult living donor recipients for 28 days following surgery using ICG-K as determined non-invasively by spectrophotometry and compared their results to results of liver scintigraphy and histological changes. They found that measuring ICG in this way accurately predicted clinical outcomes.[43]

Lidocaine/Monoethylglycinexylidide (MEGX)

The metabolism of lidocaine to monoethylglycinexylidide (MEGX) through oxidative *N* dealkylation by the hepatic microsomal cytochrome P450 system is the basis of the MEGX test. Serum MEGX concentrations are measured following slow intravenous infusion of 1 mg kg^{-1} of 2% lidocaine hydrochloride over 1–2 min. MEGX appears rapidly in the blood and a steady state is achieved in 15 min. Serum samples are obtained from the contralateral arm just before the injection and after 15 min, with MEGX concentrations measured by fluorescence polarisation immunoassay. The normal value ranges between 60 and 96 ng ml^{-1}.

In a prospective study of 56 patients with chronic liver disease evaluated for transplantation, death occurred only in patients with MEGX values of <10 ng ml^{-1}.[44] Lee and Chen opted for a higher value of 30 ng ml^{-1} as a predictor of outcome, noting hospital stay to be significantly reduced in patients with a MEGX concentration >30 ng ml^{-1}.[45]

Studies using MEGX as a predictor of donor liver suitability have yielded contrasting findings. Oellerich and Armstrong, while evaluating MEGX for donor liver function, found a significantly better graft function at 120 days if the donor MEGX value was >90 ng ml^{-1}.[44] However, Reding et al. did not manage to identify any relationship between MEGX and graft outcome or early functional parameters using a cut-off value of 80 ng ml^{-1}.[46] It has been suggested the variability of the test may be due inter-patient variability in cytochrome P450 activity and thus MEGX may be more useful when assessed serially over a period of time in individual patients.

MEGX has also been used in the post transplant period to evaluate early graft function.[47,48] Potter et al. undertook serial MEGX estimations in 155 transplant recipients and found a low initial MEGX value in patients who ultimately required re-transplantation or died in the first 8 weeks.[47] MEGX levels were noted to be influenced by graft ischemia, cholestasis, rejection, cardiac output and sepsis.

Ercolani et al. investigated the role of MEGX in liver resection and identified that the finding of low MEGX levels in cirrhotic patients correlated with the development of complications, with a cut-off level of 25 ng ml^{-1} below which they did not recommended extensive resections.[49]

Galactose Elimination Capacity (GEC)

Galactose is a pharmacologically safe and non-protein bound with up to 95% hepatic extraction. The test is performed through the intravenous administration of 50% galactose (0.5 g kg^{-1}) and its elimination is estimated using serial blood samples from 20 to 50 min post-injection. A recently developed breath test utilising GEC may prove easier to perform. The normal GEC is said to be >6 mg kg^{-1} min^{-1}; however, galactose is subject to a variable amount of renal clearance and hence due caution must be exercised in interpreting the results. There is also a genetic variation in galactokinase activity which must be taken into consideration.

Zoedler et al. used GEC, MEGX and ICG in patients undergoing hepatic resection and found that GEC and ICE were best at predicting the development of liver failure.[50] Similarly, Redaelli et al. found that a low GEC (<6 mg kg^{-1} min^{-1}) combined with patient ASA (>2) was associated with an increased risk of mortality following liver resection.[51]

There is little data on the role of GEC in liver transplantation. A decrease in GEC has been noted in living-related donors and their recipients, and in cadaveric organ recipients. Nadalin et al. looked at GEC in combination with MRI volumetry in 27 right lobe living donors at baseline, 30, 60, 60, 180 and 360 days.[52] They found that the GEC decreased 25% by day 30 then increased to 125% of the pre-operative level by day 180 and returned to normal after 1 year.

Redox Chemistry

Regulation of hepatic mitochondrial adenosine triphosphate (ATP) synthesis is the key determinant of major metabolic reactions that take place in the hepatocyte. The oxidation–reduction theory is based on the hypothesis that the ATP production determines the energy charge of the liver and is reflected by the balance of oxidised and reduced nicotin-

amide adenine dinucleotide (NAD/NADH). Under aerobic conditions, the energy charge of the cells is maintained at a high level and in this reduced state NADH accumulates in the mitochondria. NADH in turn inhibits the citric acid cycle thereby resulting in fall in ATP production.

Arterial Ketone Body Ratio (AKBR)

The mitochondrial NAD/NADH ratio was shown to correlate with the concentration of acetoacetate/β hydroxybutyrate (ketone body ratio) within the mitochondria which in turn is reflected by the ratio of the two metabolites in the hepatic venous blood. Subsequently, it has further been shown that the arterial ketone body ratio (AKBR) correlates with that seen in the hepatic venous blood. AKBR is measured in 1 ml of heparinised arterial blood using a commercially available assay.

Yamaoka et al.[53] evaluated the usefulness of pre-operative donor liver AKBR estimation along with other parameters such as age, dopamine requirements and clinical laboratory findings in predicting the graft outcome following transplantation following cadaveric and living-related liver transplantation. They found that an AKBR of <0.7 was found to be the only predictor of increased risk of early non-function.

Asonuma et al. used sequential AKBR measurements in a prospective study of 84 patients undergoing liver transplantation.[54] The patients were divided into three groups based on outcome: group A survived longer than 1 month and had good graft function; group B had a successful transplant but with a prolonged ITU stay; and group C had failed grafts. The AKBR were further stratified as: state I—AKBR >1.0; state II—AKBR 1.0–0.7; and state III—AKBR <0.7. The AKBR was significantly suppressed in groups B and C when compared to group A. The AKBR state of the majority of group A patients had elevated to state I by day 2 and all had done so by day 5. All the patients in group B had AKBR level at state II during the first 2 days. The 12 patients in group C had AKBR level persistently in state III at day 2. Hence, an AKBR of <0.7 represents an indication for re-transplantation and conversely an AKBR of >1.0 should discourage from re-transplantation in spite of other doubts with regards graft viability.

Likewise, Egawa et al. reported similar correlates of AKBR in a paediatric transplant programme. In addition, they observed uncoupling of AKBR and prothrombin time in pathologies such as hepatic artery thrombosis and hyperacute rejection and that information gained from the AKBR could be used to detect early liver injury that was amenable to reversal by surgical or pharmacological intervention.[55]

The value of AKBR has also been assessed in relation to hepatic resection. The detection of an AKBR <0.4 at the end of a hepatic resection has been associated in some series with a poor outcome and a reported mortality of 50–100%.[56,57] However, others dispute the finding and claim that there is no correlation between outcome and morbidity or mortality.[58]

Redox Tolerance Index

Workers at Kyoto, Japan who had championed the AKBR further developed the test and introduced the concept of the redox tolerance index (RTI) in an attempt to quantify the deterioration of hepatic mitochondrial energy metabolism by measuring changes in AKBR in response to oral glucose loading. The glucose intolerance seen in jaundiced rats and in humans after massive liver resection closely correlates with the decrease in hepatic energy charge.[59] The group demonstrated in laboratory studies that the NAD/NADH ratio and AKBR change in proportion to the blood glucose levels after an oral glucose tolerance test.

Mori et al. defined RTI by the following equation: RTI= $100 \times \mathrm{AKBR}/\mathrm{Glucose}$.[60] In an evaluation of 127 hepatic resections, they found that RTI of <0.5 was associated with a significantly higher post-operative morbidity and mortality.[60]

Volumetry

Volumetric assessment of the liver using non-invasive techniques has been made possible using computed tomography (CT) and more recently magnetic resonance imaging (MRI). Pre-operative volumetric assessment prior to liver resection should take into account the amount of parenchyma replaced by the tumour tissue which does not contribute to the functioning liver mass. Okamoto et al. proposed the concept of calculating a parenchymal hepatic resection rate (PHRR) thus excluding the tumour mass in the planning resection limits.[61]

PHRR by itself cannot accurately predict post-hepatectomy complications, especially in the presence of liver fibrosis because of the obvious pitfall of non-uniform function within the remaining parenchyma. The predictive value can be improved by combining the results of such volumetric estimations with functional tests such as ICG. However, when used in the absence of chronic liver disease, volumetric studies are invaluable to the surgeon in several scenarios including the assessment of contralateral liver hypertrophy following portal vein embolisation (PVE) prior to hepatic resection.

Computed Tomography

CT volumetry is widely practiced as a means of determining the volume of functional parenchyma that will remain following liver resection and pre-operative estimations have been shown to correlate well with actual volumes resected.

Kubota and colleagues suggested that resections of 60% of non-tumorous liver was possible in patients with normal livers and that patients with ICGR-15 scores of 10–20% could tolerate resections of 50%.[62] In cases where a resection of ≥60% was to be performed in the presence of an ICGR-15 score of 10–20%, pre-operative PVE was recommended. Shirabe et al. found that, when resections are to be performed in the presence of chronic liver disease such as hepatitis B/C, a post-operative liver volume of <250 ml m^{-2} was found to correlate with the development of post-resection hepatic failure.[63]

Shoup et al. reported that, for non-cirrhotic patients undergoing extensive resections for colorectal metastases, among those with a ≤25% remaining volume, 90% developed hepatic dysfunction compared with 0% when the residual volume was >25%.[64] However, Yigitler et al. in an assessment of liver remnant volume in a similar patient cohort found no such correlation, but they did identify a longer ITU stay and higher complication rate in the low volume group.[65] Similar findings of safe liver volumes for non-cirrhotics have since been reported, with Schindl et al. reporting results that were consistent with the previous studies noting a safe cut-off of 26.6% below which there was a risk of severe hepatic dysfunction.[66]

Hsieh et al. assessed CT volumetry in comparison to ICGR-15 in 40 patients with HCCs invading the portal vein and found that having an estimated CT volume less than the estimated ICG volume was a significant predictor of hepatic dysfunction.[67]

Akaki et al. compared CT with radionucleotide scanning and found that CT sometimes overestimated the resection volume in patients with impaired portal venous flow as its calculates values for lobes that may be hypo-functioning. This may be beneficial in terms of reducing post-resection failure; however, it does mean that a few borderline candidates may miss out on resection if CT alone is used in making a decision on respectability.[68]

In patients with cirrhosis or when extended resections are planned, volumetric assessment becomes even more crucial in determining the extent of safe resection that can be performed without leading to liver failure. Vauthey and colleagues investigated the role of PVE in 20 patients with hepatic tumours but no underlying liver disease after performing CT volumetry. They noted an increase in complications for liver remnants <25%[69] and also noted that performance of PVE in cases where liver remnants were predicted to be small led to a 10% increase in size thus making resection safer. Azoulay et al. proposed that in the presence of cirrhosis, a resection of >2 segments should only be performed if the estimated remnant functional liver was >40%, whilst in cases with <40% remnant functioning liver a pre-resection PVE was advised.[70] Hemming et al. further evaluated the role of PVE prior to resection and was in agreement with both the <40% cut-off for PVE in cirrhotics and the minimal anticipated remnant size of <25% in those with otherwise normal livers.[71]

Volumetric assessment with CT has also proved useful in the pre-operative assessment of living donors for liver transplantation. CT volumetry may be used to assess the size of the proposed graft to ensure that the modified liver weight ratio, namely the ratio of graft weight to that of the donor's expected liver weight based on body weight, is more than 0.35.[72] Paluszkiewicz and colleagues used CT to evaluate liver volumes pre-operatively and to examine the process of regeneration of the donor liver after living-related liver transplantation.[73] They found that the CT predicted the actual graft weight, and also noted there was a variation in regeneration according to the segments donated with a higher regenerative rate amongst donors of segments II, III and IV compared to II and III alone.

Magnetic Resonance Imaging (MRI)

Nadalin et al. used MRI in conjunction with GEC to evaluate dysfunction in relation to residual volume in living donor transplantation.[52] The volume of liver was outlined and the volume calculated using specifically deigned software. Following right donor hepatectomy and 61% volume loss, the liver had regained a volume necessary for its function within 10 days of hepatectomy; however, this represented only 74% of its initial size. The GEC tests showed that, despite the rapid increase in volume, hepatic function was regained much slower.

Marcos et al. looked at donor and recipient liver regeneration a 7, 14, 30 and 60 days post-resection and noted that the donor mass increased at a slightly different rate and pattern—101% vs. 87% at 7 days; 110% vs. 101% at 14 days; 115% vs. 119% at 30 days; and 144% vs. 99% at 60 days.[75] Furthermore in their series, steatosis did not appear to affect regeneration and there was no difference for grafts of >1% graft to recipient body weight, or those with a ratio <1%.

Scintigraphy

Radionuclide investigations of the liver provide information on both hepatic haemodynamics and cellular function and these investigations will be discussed. In addition to contributing to the understanding of the pathophysiology of various liver disorders, scintigraphic investigations have also been used for quantitative estimation of hepatic function. Measurement of the relative contributions to perfusion by the portal vein and hepatic artery allows estimation of the hepatic artery perfusion index and this has been found to be reliable in the diagnosis of cirrhosis and liver metastasis.

Technetium-Labelled GSA Scintigraphy

Asialoglycoprotein receptor (ASGP-R) is a hepatocyte-specific receptor for galactose-terminated glycoproteins and is believed to play a role in glycoprotein metabolism. Receptor numbers are reduced in patients with chronic liver disease and these are absent on HCC cells. Scintigraphy using a radiolabelled ligand—technetium-99m-galactosyl human serum albumin (99mTc-GSA) identifies the presence of these receptors and allows diagnosis of chronic liver disease.[75]

Several series have now evaluated scintigraphy using 99mTc-GSA in patients undergoing liver resection, much of which has originated from Osaka.[67–81] Kwon et al. were the first to evaluate 99mTc-GSA scintigraphy in relation to evaluation of pre- and post-operative hepatic reserve.[76] They evaluated 36 patients with HCC undergoing resection and calculated a modified receptor index which they related to ICGR-15. They found a significant correlation between the two parameters. Discrepancies were seen in eight cases, in all of which scintigraphy correlated with histology but the IGC did not. Fujioka et al. assessed 99mTc-GSA uptake at 15 min and found it to correlate with the development of post-operative complications, hepatic regeneration and ICGR-15 clearance.[78]

Hwang et al. used 99mTc-GSA with single photon emission computed tomography (SPECT) to study 114 consecutive patients including 55 undergoing hepatectomy.[79] They found a good correlation between the SPECT results and both ICGR-15 and ICG-K, and also between predicted and actual post-operative 99mTc-GSA clearance. All five patients with major complications due to hepatic insufficiency, including two deaths had significantly lower 99mTc-GSA clearance than those without complications. Satoh et al. used similar techniques to study 57 patients with underlying liver disease undergoing resection. They calculated a predictive residual index and found that no patients with an index >0.38 developed hepatic failure whereas five patients with an index <0.37 developed post-operative complications.[80]

It has been suggested that scintigraphy may provide a more accurate reflection of functional volume than other volumetric studies as the ASGP-R is absent from fibrous and stromal tissue.[81] Kwon and colleagues studied the maximal removal of 99mTc-GSA which they termed GSA-RMax in remnant 187 livers following resection and related their findings to CT-predicted residual liver volumes and ICGR-15. They found a good correlation between the CT and GSA-RMax for normal livers but no correlation for livers with background hepatitis or cirrhosis.[82] They identified seven patients with hepatic insufficiency all of which had GSA of <0.15 in their predicted residual liver. In addition, both patients that died had a poor correlation between GSA-RMax and CT-predicted residual volume.

Two studies have evaluated 99mTc-GSA in relation to PVE prior to resection.[83,84] Hirai et al. examined liver volume and function using CT and 99mTc-GSA, and found scintigraphy to be useful, demonstrating a rapid increase in uptake during the first week following PVE but little in the second.[83] They also noted that the functional increase in 99mTc-GSA uptake was more pronounced than the morphologic changes identified on CT, and that uptake was poorer in patients with evidence of post-operative hepatic insufficiency. Nanashima and colleagues explored the relationship between CT and 99mTc-GSA, and found that scintigraphy was better at identifying changes in functional volume and that it was a more dynamic test than CT which identified the morphologic changes.[84]

There is limited literature on the use of 99mTc-GSA in the assessment of graft parenchymal function after liver transplantation.[43,85,86] Hori et al. examined the relationship between 99mTc-GSA and ICG clearance using spectrophotometry in 30 adult recipients up to 28 days following living donor liver transplantation.[43] They demonstrated significant correlations between the two functional tests but found in favour of the new ICG test as it was portable, quick, easily repeated and did not involve administration of radioactive injections.

Future Developments

Future developments in the pre-operative prediction of post-operative liver failure are, in common with most areas of medicine, likely to be centred on developments in molecular biological techniques.

Over the course of recent years, investigators have gained a better understanding of the mechanism of impaired hepatic regeneration following hepatic surgery, in particular in relation to the importance of cytokines such as: hepatocyte growth factor; epidermal growth factor; transforming growth factor α; interleukin 6 and tumour necrosis factor α.[87] Whilst much knowledge has been gained, the precise interaction of these growth factors is not currently understood and it is not clear what triggers their release. However, given that these cytokines may now be easily measured using commercially available assays, once the mechanism has been confirmed they are likely to move rapidly into clinical practice.

Possibly more interesting is the potential of the new 'omics' technologies—genomics, proteomics and metabonomics to help further elucidate the pathophysiology and also provide a profile of patients undergoing hepatic resection thus identifying individuals most at risk. The former two sciences have been much in use in the laboratory setting and are starting to generate clinically relevant and useable data. Metabonomics, the newest of the

'omics', is concerned with the dynamic metabolic response and may indeed be the most useful when fully exploited.

A number of studies, all emanating from the same Chinese, have utilised microarray technology to examine gene expression in relation to hepatic regeneration in a rat model of liver resection/regeneration. These have looked at expression of: lipid metabolism-associated genes[88]; genes associated with cellular immune response[89] and blood coagulation[90]; cell junction-associated genes[91]; and genes associated with the metabolism and transport of amino acids.[92] Each study identified a large number of genes which are up- or down-regulated during liver regeneration but unfortunately the studies did not determine whether the genes altered protein expression nor did they assess for polymorphisms of the genes concerned. Furthermore, no study has thus far has been conducted in humans.

There is a little data published on the role of proteomics in the assessment of regeneration following liver resection. Sun et al. studied the immediate effect changes of the proteome in the rat immediately following liver resection.[93] They identified significant up-regulation of 24 proteins, the most notable of which were: pyruvate dehydrogenase complex; paraoxonase 1; thyroid hormone receptor β; growth-associated protein 43; and interleukin-2, the up-regulation being validated by Western blotting. Whilst the relevance of certain protein to metabolic activity was evident, the importance of up-regulation of other proteins was less clear and so further studies in this field are ongoing.

A further development in relation to proteomics and the liver was the launch of the human liver proteome project in 2002, which to-date has identified in excess of 5,000 proteins in normal hepatic tissue.[94] This resource will undoubtedly be of benefit in terms of relating changes in protein expression seen in physiological/pathological states to those of healthy parenchyma.

There is currently no data relating metabolomics to the development of impaired hepatic function following resection; however, as this science advances it is likely to profile and able to predict the development of hepatic dysfunction following liver resection.

Conclusions

Despite the existence of a number of dynamic tests of liver function, there is no high grade evidence for the use of one test over any other.

We would suggest that when operating on a non-cirrhotic liver that CT volumetry is probably adequate for all but extended resections. In such a cohort, quantification of liver function is advised to minimise the risk of post-operative hepatic failure. Since ICG clearance has the largest clinical experience, and it can now be performed quickly and non-invasively, it is likely to be the standard mode of dynamic functional assessment. As cross-sectional imaging improves and chemotherapy-associated hepatic toxicity is diagnosed by MRI and CT, it is likely that this cohort will also benefit from a quantitative assessment of hepatic function.

For patients undergoing resection on the background of cirrhosis, functional assessment by ICG clearance is advisable in all cases in order to achieve optimal outcome without compromising patients in terms of morbidity or mortality.

For resections of cholangiocarcinomas, in addition to assessment of hepatic reserve, it is important to relieve cholestasis and cholangitis as both the factors are associated with a high risk of post-operative hepatic dysfunction.

It is likely with the advent of new molecular biological techniques that the prediction of the risk of hepatic failure will be based on genetic, proteomic and metabolic profiles. These will provide a simple, rapid, non-invasive means of sequentially assessing liver function and may well aid in the reduction in the prevalence of post-operative hepatic insufficiency.

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GASTROINTESTINAL IMAGE

Duodenoduodenal Intussusception

Manphool Singhal · Mandeep Kang · Srikala Narayanan · Rajesh Gupta · Jai D. Wig · Amanjit Bal

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Abstract Duodenoduodenal intussusception is a rare event which is usually caused by the presence of a tumor. We present a case of duodenoduodenal intussusception secondary to a large tubulovillous adenoma causing gastric outlet and biliary obstruction in a 50-year-old female. The imaging features on ultrasonography, CT, and MRI are described.

Keywords Gastric outlet obstruction · Duodenum · Intussusception · Tubulovillous adenoma

Case Report

A 50-year-old woman presented with the complaints of dull aching pain localized to the upper abdomen, insidious in onset and intermittent in nature. For the last 3 months, the pain had increased in severity and was associated with nonbilious vomiting and progressive distension of the abdomen. There was history of loss of appetite; however, no significant loss of weight was recorded. There was no significant past history.

On examination at the time of admission, she was conscious, oriented, moderately built, and nourished. General examination was unremarkable except for pallor. Abdominal examination revealed mild distension with visible peristalsis; however, there was no tenderness, free fluid, or any organomegaly. Other systemic examination was within normal limits.

Laboratory investigations revealed mild anemia (fhemoglobin −10.5 gm%) with normal leukocyte counts, normal serum bilirubin but slightly elevated alkaline phosphatase levels (62 IU), normal serum electrolytes, blood sugar, and urea. Ultrasonography showed hepatomegaly with dilated intrahepatic biliary radicals and patent confluence. The common bile duct was dilated (maximum diameter 18 mm) with a smooth tapering end. The main pancreatic duct (8 mm) was also dilated. A well-defined, oval, hypoechoic lesion with central bright echoes having multiple layers and a concentric ring-like appearance giving a "pseudokidney" appearance on longitudinal and "target" configuration on transverse images was seen in the right upper abdomen suggestive of an intussusception (Fig. 1a). Minimal fluid was seen in between the intussuscepting loops. In addition, the stomach was grossly distended. A diagnosis of duodenoduodenal intussusception causing gastric outlet obstruction was offered. Thereafter, an upper gastrointestinal endoscopy was performed which revealed lax lower esophageal sphincter, dilated stomach with food residue, gaping pylorus with hyperemic mucosa, and dilated first and proximal second part of the duodenum. The endoscope could not be negotiated beyond the second part of duodenum. A subsequent contrast-enhanced computed tomography (CT) of the abdomen showed a "target" appearance in the region of the duodenum confirming the diagnosis of duodenoduodenal intussusception; however, no definite cause for the intussusception was discernable (Fig. 1b). In addition, the stomach was grossly distended with dilated common bile and pancreatic ducts (Fig. 1c). In an attempt to delineate a lead point of the intussusception, if any, a magnetic resonance imaging (MRI) examination was carried out which revealed the classical multilayered, concentric appearance of intussusception. A pedunculated 5.8×5.0 cm mass lesion was seen protruding into the junction of the second and third

M. Singhal · M. Kang (✉) · S. Narayanan · R. Gupta · J. D. Wig · A. Bal
Postgraduate Institute of Medical Education and Research, Chandigarh, India
e-mail: mandykang2005@yahoo.com

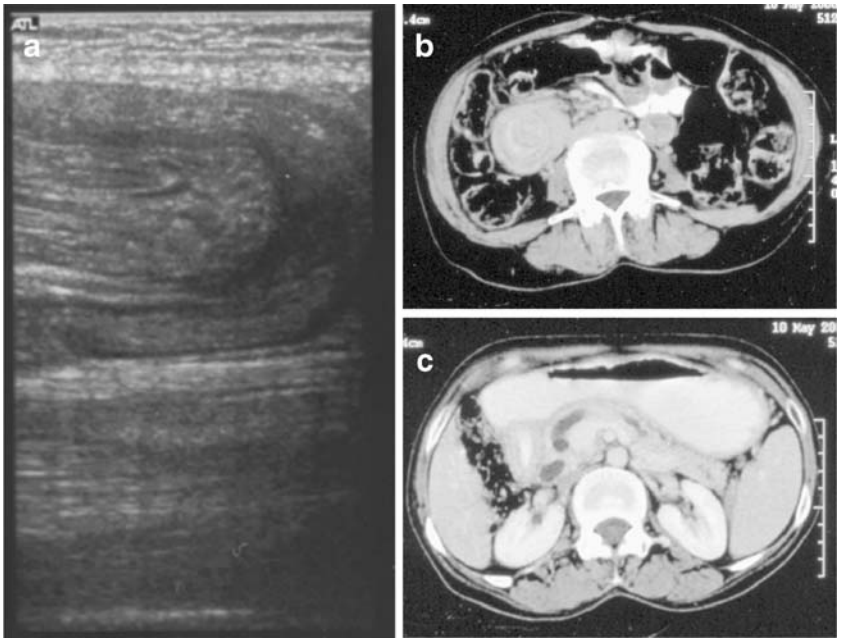

Figure 1 **a** A well-defined, oval, hypoechoic lesion with central bright echoes having multiple layers and a concentric ring-like appearance giving a "pseudokidney" appearance on longitudinal and "target" configuration on transverse images was seen in the right upper abdomen suggestive of an intussusception. **b** A subsequent contrast-enhanced CT of the abdomen showed a "target" appearance in the region of the duodenum confirming the diagnosis of duodenoduodenal intussusception. **c** The stomach was grossly distended with dilated common bile and pancreatic ducts.

part of the duodenum which was acting as a lead point for the intussusception (Fig. 2).

The patient underwent laparotomy which confirmed the duodenoduodenal intussusception and distended stomach. A pedunculated polypoidal mass measuring about 6×5 cm was seen involving the medial wall of the second part of the duodenum near the ampulla; however, the ampulla was free from tumor. The operative procedure consisted of excision of the polypoidal mass, duodenotomy with primary duodenal repair, and drainage of common bile duct. The postoperative period remained uneventful. The patient is asymptomatic on follow-up.

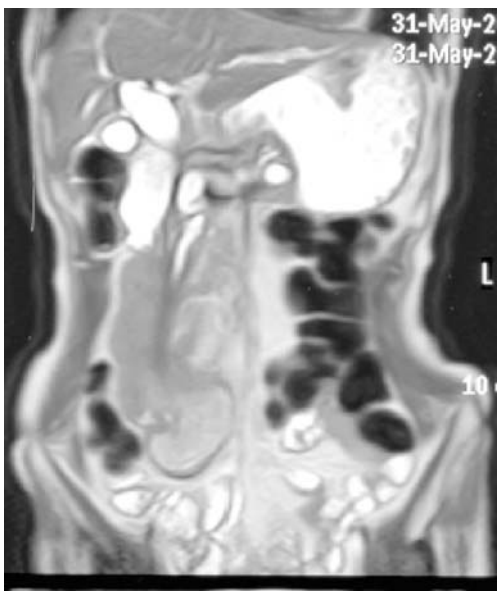

Figure 2 A pedunculated 5.8×5.0 cm mass lesion was seen protruding into the junction of the second and third part of the duodenum which was acting as a lead point for the intussusception.

Gross examination of the pedunculated polypoidal mass revealed a 1.5-cm stalk with irregular outer surface. Cut surface showed a homogenous grayish white appearance. Histopathology demonstrated villous and tubular pattern arrangement of dysplastic tall columnar cells. The glands were separated by edematous stroma and infiltrated by lymphocytes, consistent with tubulovillous adenoma.

Discussion

Intussusception is an uncommon cause of intestinal obstruction in adults, accounting for only 1–5% of adult bowel obstructions.[1,2] Ileocolic intussusceptions are the most common followed by ileoileocolic, ileoileal, and colocolic. It is well-documented that 80–90% of all adult intussusceptions have an underlying cause with neoplasms being the lead point in approximately 65% of cases.[2,3]

Intussusceptions originating in the duodenum are rare probably because mass lesions in this location are infrequent.[4]

In various case reports, the causes of duodenoduodenal intussusceptions have been described as Brunner's gland hamartoma, papillary adenoma, hyperplastic polyp, carcinoid, and rarely a duodenal duplication cyst.[4–7] The cause in the index case was a tubulovillous adenoma which forms less than 20% of all small bowel tumors. When occurring in the duodenum, they are commonly found in or near the ampulla of Vater. The most common clinical presentation of duodenoduodenal intussusception is with gastric outlet obstruction. But if the mass acting as the lead point of the intussusception is located close to the ampulla, then the common bile duct and the pancreatic duct may be dragged along with the intussusceptum leading to the dilatation of these ducts which may or may be clinically manifested.[5,6]

On ultrasound, intussusception appears as an oval hypoechoic mass with central bright echoes giving a doughnut or target configuration on transverse scans. The hypoechoic rim represents the edematous wall of the intussusceptum, and the central echogenicity represents the compressed mesentery, mucosa, and intestinal contents. Sometimes the cause of intussusceptions can be identified as a mass, a polyp, or a lymph node.[2,3]

CT demonstrates the collapsed intussusceptum lying within the opacified lumen of the distal intussuscipiens. A trace of oral contrast within the lumen of the intussusceptum forms a high-density center. This is surrounded, in turn, by the swollen wall of the intussusceptum, a low-density layer of mesenteric fat, and contrast material within the lumen of the intussuscipiens forming the outermost layer. Sometimes a tumor can be seen as a discrete intraluminal soft tissue without surrounding mesenteric fat at the leading point of the intussusceptum.[2,3] MRI confirms the diagnosis and can better delineate the cause of intussusceptions and, more so, better demonstrate the relationships with the surrounding organs because of its multiplanar facility. This is important because if the lead point of intussusception is caused by a malignancy, this will alter the management.

In conclusion, although duodenoduodenal intussusception is uncommon, it should be considered in the differential diagnosis of gastric outlet obstruction and can rarely cause biliary and pancreatic drainage obstruction also. The imaging features on CT and MRI are characteristic, and the identification of a lead point for the intussusception should always be attempted as this has great implication on the management.

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GASTROINTESTINAL IMAGE

Perivascular Epithelioid Cell Tumor of the Retroperitoneum in a Young Woman Resulting in an Abdominal Chyloma

T. E. Lans · G. H. van Ramshorst · J. J. Hermans · M. A. den Bakker · T. C. K. Tran · G. Kazemier

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Abstract Perivascular epithelioid cell tumor (PEComa) is an extremely rare neoplasm which appears to have predominancy for young, frequently Asian, women. The neoplasm is composed chiefly of HMB-45-positive epithelioid cells with clear to granular cytoplasm and usually showing a perivascular distribution. These tumors have been reported in various organs under a variety of designations. Malignant PEComas exist but are very rare. The difficulty in determining optimal therapy, owing to the sparse literature available, led us to present this case. We report a retroperitoneal PEComa discovered during emergency surgery for abdominal pain in a 28-year-old Asian woman. The postoperative period was complicated by chylous ascites that was initially controlled by a wait-and-see policy with total parenteral nutrition. However, the chyle production gradually increased to more than 4 l per day. The development of a bacterial peritonitis resulted in cessation of production of abdominal fluid permitting normal nutrition without chylous leakage. Effective treatment for this rare complication of PEComa is not yet known; therefore, we have chosen to engage in long-term clinical follow-up.

Keywords PEComa · Chylous · Retroperitoneum

Introduction

Perivascular epithelioid cell tumors (PEComas) are extremely rare mesenchymal neoplasms. They are characterized by immunoreactivity for both smooth muscle and melanocytic markers, such as smooth muscle actin, HMB-45, and melan-A. Histologically, PEComas are composed of cells with copious clear-to-eosinophilic cytoplasm that frequently shows perinuclear condensation.[1] PEComas are a family of related mesenchymal neoplasms that including angiomyolipoma, lymphangioleiomatosis, clear cell "sugar" tumor of the lung, and another group of rare, morphologically and immunophenotypically similar lesions arising at a various visceral and soft tissue sites.[2] Over the past decade, perivascular epithelioid cells (PECs) and tumors composed of these have engendered significant discussions and controversies with respect to their very existence as a clinico-pathological entity, their histogenesis, pathogenesis, and nomenclature. It appears now that these tumors may potentially arise in any anatomic location, as PECs do not have a normal anatomic homologue. Despite considerable advances in the recognition of these unusual lesions, the origin of these tumors remains elusive, and additional cases with longer clinical follow-up must be evaluated before their behavior can be predicted accurately.

In this case study, we describe a patient with a PEComa presenting with localized intra-abdominal chylous pockets probably caused by obstruction of lymphatic vessels. This combination and presentation has not been described before.

T. E. Lans (✉) · G. H. van Ramshorst · T. C. K. Tran · G. Kazemier
Department of Surgery, Erasmus MC-University Medical Center, 'sGravendijkwal 230,
3015 GD Rotterdam, The Netherlands
e-mail: T.Lans@ErasmusMC.NL

J. J. Hermans
Department of Radiology,
ErasmusMC-University Medical Center,
Rotterdam, The Netherlands

M. A. den Bakker
Department of Pathology,
ErasmusMC-University Medical Center,
Rotterdam, The Netherlands

Clinical History and Histological Findings

A 28-year-old Korean woman presented with left lower abdominal quadrant pain that had been present for 1 day. Her previous medical history was unremarkable, and laboratory investigations showed no abnormalities except for a high C-reactive protein in the absence of fever. She initially underwent a laparoscopy in a community hospital after a transvaginal ultrasound revealed a mass in the lower left abdominal quadrant, which was interpreted as a strangulated left ovary.

Intraoperatively, a rubbery gray mass measuring 15 cm in diameter was found. This mass was located in the retroperitoneum, posterior to the left broad ligament. During biopsy, murky white fluid was released. The left ovary, uterus, and other intra-abdominal organs appeared normal. Postoperatively, she developed pain in the left groin. A computer tomography (CT) scan revealed an encapsulated fluid collection in the left lower abdominal quadrant, which was considered to be an abscess (Fig. 1). This collection was drained under ultrasonographic guidance. During the following days, progressive leakage of white fatty fluid emerged through the drain. This white fluid was diagnosed as chyle.

She was placed on a high-protein and low-fat diet containing exclusively medium-chain triglycerides. As she did not respond to the above measures, she was referred to our hospital. Soon after her admission, the drain became obstructed, after which, she developed acute abdominal pain and a high fever. An emergency laparotomy was performed. Remains of the earlier described mass were identified, and an attempt was made to remove the lesion completely. The previous operation and the ongoing inflammation prohibited complete removal, and again, a drain was placed. Postoperatively, there was persistent chylous leakage. Attempts to manage this by total parenteral nutrition and fasting were again unsuccessful.

The biopsy taken at the initial laparoscopy revealed nonspecific chronic inflammation. The surgical specimen taken at the laparotomy was routinely processed for histology. This biopsy contained tumor predominantly composed of spindle-shaped cells arranged in fascicles. These spindled cells, with eosinophilic cytoplasm, resembled smooth muscle cells (Fig. 2). There was mild pleomorphism, and focal necrosis was noted. Mitoses were sparse (two per 2 mm^2). Lymph node metastases were not found. Immunohistochemically, the cells strongly expressed Vimentin, Desmin, smooth muscle actin, BCL-2, and HMB-45 and were negative for cytokeratin, S-100, and Melan-A. A diagnosis of PEComa was established.

Extensive examination revealed neither a different primary site of the tumor nor metastatic lesions. Despite optimal conservative measures, chylous leakage persisted, progressing to more than 2 l per day.

A second laparotomy was performed aimed at controlling the chylous discharge. During this procedure, the origin of the chylous leakage was identified after provocation with an extensive amount of double cream through the nasogastric tube. Macroscopically, no tumor was present, and only extensive chylous leakage was noted from the retroperitoneum (Fig. 3). An attempt was made to occlude all lymphatic vessels from the left groin to the diaphragm

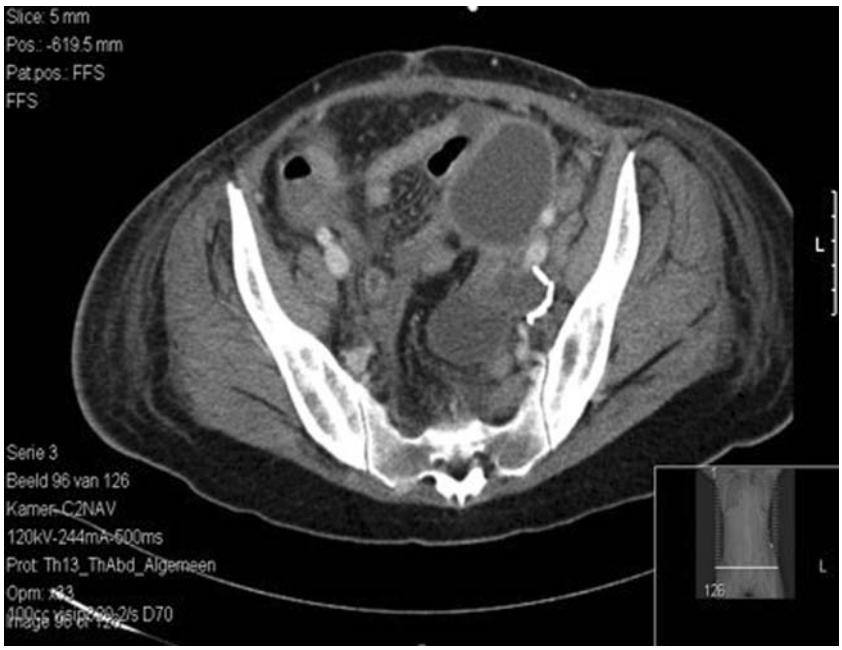

Figure 1 CT-scan abdomen with chyloma. Drain in situ in lower left abdomen.

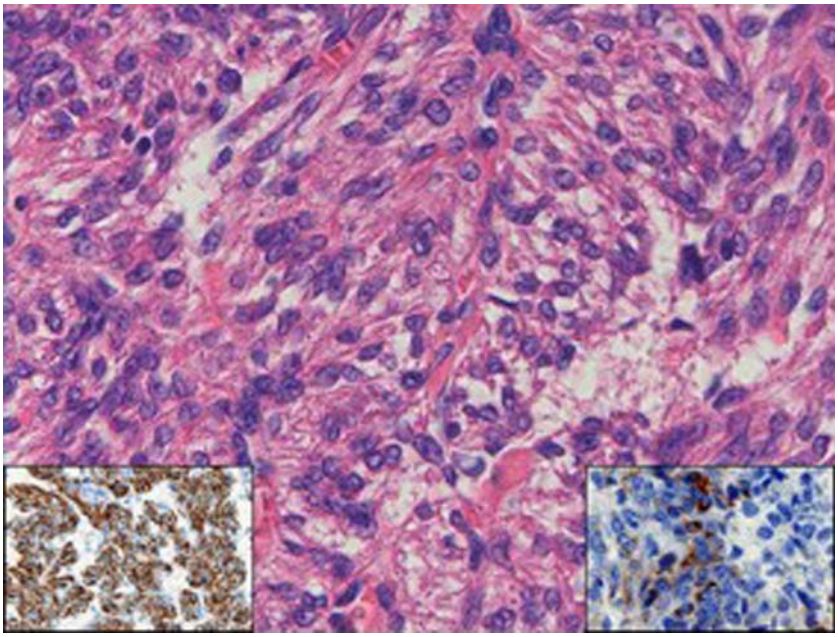

Figure 2 Histology. Photomicrograph of HE stained slide showing plump spindle cells with fibrillar eosinophilic cytoplasm with focal vacuolation. The nuclei are regular with small nucleoli. Insets: *left*, desmin immunoperoxidase stain showing intense generalized staining; *right*, HMB45 immunoperoxidase stain showing focal cytoplasmic reactivity.

with sutures and titanium clips, as the leakage extended proximally after every clip. Finally, no leakage was noted; therefore, no drain was placed in this procedure.

Postoperatively, she developed peritonitis and septicaemia within 24 h, necessitating re-operation. At relaparotomy, there was still chylous leakage but no additional pathology. A drain was placed which produced more than 1 l of chyle per 24 h. She developed another episode of peritonitis and sepsis after the drain became blocked, and further surgery was not considered effective. The drain was removed. She was treated with intravenous antibiotics (Vancomycin and Tazobactam). After 3 weeks, the chylous leakage had finally ceased. Her diet was carefully brought back to normal, and she was discharged from the hospital 5 months after admittance. On the CT scan, there was no evidence of tumor recurrence, and there is still no evidence of tumor 1 year postoperatively. Annual CT scans will not be performed regarding the young age of this patient.

Discussion

As relatively few malignant PEComas have been reported, firm criteria for malignancy have yet to be established.

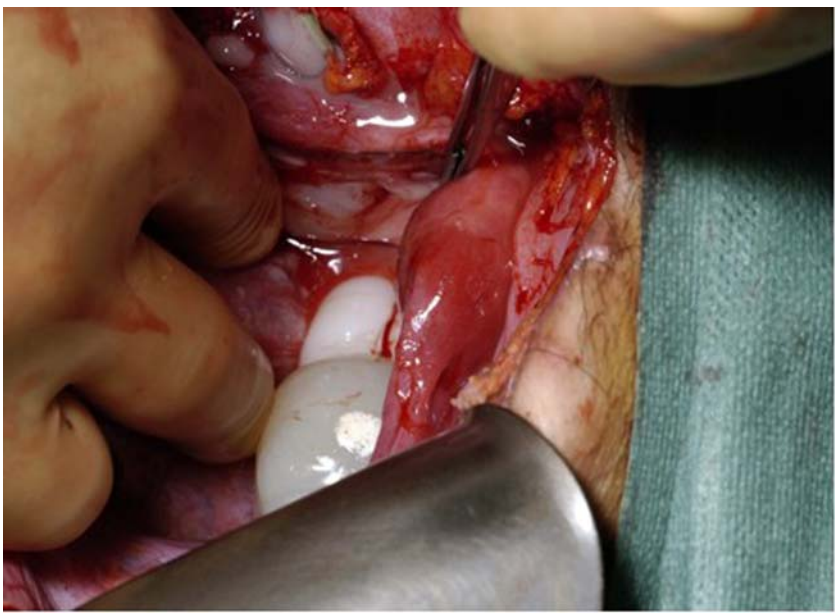

Figure 3 Intraoperative findings (head is positioned on *left side*). Chyloma can be seen as white structures behind the uterus.

However, in a recent study published in abstract form (presented at the United States and Canadian Academy of Pathology conference in 2005), Folpe et al.[3] evaluated criteria for malignancy in 24 PEComas arising at a variety of visceral and somatic soft tissue sites. The authors found that local recurrence and/or metastasis were associated with large tumor size, more than 70 mm in diameter, necrosis, and a mitotic index exceeding 1 per 50 high-power fields. Infiltrative growth and marked hypercellularity are other features that have been reported to be suggestive of malignancy in other cases. In addition, marked pleomorphism and nuclear atypia may indicate malignant behavior. Thus far, PEComas are considered tumors of uncertain malignant potential.[4] Spread of this tumor to other sites might become evident even several years after primary manifestation.[5]

Chylous ascites is a rare form of ascites resulting from an accumulation of lymph in the abdominal cavity. It is caused by an interruption in the lymphatic system. The diagnosis is established when the concentration of triglycerides in the ascitic fluid exceeds 200 mg/dl.[6] Chylous ascites may occur due to different mechanisms, including (a) obstruction of the lymph flow caused by external pressure (i.e., compression by a mass) causing leakage from dilated subserosal lymphatics into the peritoneal cavity; (b) exudation of lymph through the walls of dilated retroperitoneal vessels lacking valves, which leak fluid through a fistula into the peritoneal cavity as in congenital lymphangiectasia; or (c) traumatic thoracic duct damage causing direct leakage of chyle through a lymphoid-peritoneal fistula. An underlying malignancy is a common cause of chylous ascites in adults.

Computed tomography of the abdomen is useful in identifying pathologic intra-abdominal lymph nodes and masses and is also helpful in determining the extent and localization of fluid, particularly if there is a suspicion of thoracic duct injury. Other diagnostic studies, such as lymphangiography and lymphoscintigraphy, can assist in detecting abnormal retroperitoneal nodes, leakage from dilated lymphatics, fistulization, and patency of the thoracic duct. Lymphangiography is the gold standard in defining cases of obstruction, although several complications have been described, including tissue necrosis, fat embolism, and hypersensitivity, all related to the volume and type of contrast used. In our patient, the primary lesion was found on an ultrasound. When she developed the chylous leakage, neither a CT scan nor lymphangiography contributed to either the diagnosis or the treatment.

Whilst having taken notion of the discussion in 2002,[7] regarding the nomenclature of the "PEC" family of tumors, we still would like to refer to this tumor as a PEComa A subset of PEComas behave in a malignant fashion; a high mitotic index and the presence of necrosis, marked cytological atypia, and/or an infiltrative growth pattern appear to be associated with malignant behavior. Several of these features, including focal necrosis, a large size, and an elevated mitotic rate, were present in this case.

Because of the rarity of cases, effective treatment for malignant PEComa besides surgery is not yet known. Sporadic cases have been treated with chemotherapy with hardly any effect.[8–10]

In this patient, we had to deal with an additional clinical problem: in addition to the rare pathology, chyle was leaking until 2 months postoperatively. With our conservative treatment, this problem was adequately solved; however, the possible malignant fashion of the tumor has no further been explored.

Acknowledgments The authors thank Prof. C.D. Fletcher (Department of Pathology, Harvard Medical School, Boston) for reviewing the histology.

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LETTER TO THE EDITOR

Vagotomy During Hiatal Hernia Repair: Anatomic Observations

Fernando A. Herbella

Received: 25 July 2008 / Accepted: 24 September 2008 / Published online: 15 October 2008

Dear Editor:

We read with great interest the recent paper by Dr. Oelschlager and colleagues.[1] They propose vagotomy as an esophageal-lengthening procedure when extensive mobilization of the esophagus fails to provide adequate esophageal length during reoperative hiatal hernia repair. We went back to the anatomy laboratory to study the technical aspects of this procedure.

Our first hypothesis was that vagectomy would provide a superior esophageal length gain compared to vagotomy. We supposed that the connective tissue between the nerves and the esophagus could prevent further elongation of the esophagus. We first dissected the esophagus from the hiatus up to the carina level and measured the length of the abdominal esophagus after the dissection, as previously described.[2] Afterwards, both vagi nerves were divided close to the esophagogastric junction and the length of the abdominal esophagus was measured again (Fig. 1a). Elongation of the esophagus was clearly noticed (abdominal esophagus length=3.4 cm). Then, the vagi nerves were dissected free of the esophagus and divided proximally (Fig. 1b). Surprisingly, no further elongation of the esophagus was achieved, denoting that the connections between the nerves and the esophagus are loose enough to allow vagal retraction and esophageal elongation.

The second hypothesis was that vagal dissection would provide the same esophageal length gain compared to the vagotomy. Once more, we dissected the esophagus from the hiatus to the carina level and measured the length of the abdominal esophagus (length=3.2 cm). Digital vagal dissection was performed following the vagal-sparing esophagectomy technique[3] (Fig. 2a) and a significant length gain was obtained after the dissection (abdominal esophagus length=4.0 cm; Fig. 2b). Subsequently, bilateral vagotomy was performed and a more discrete additional length gain was obtained (abdominal esophagus length= 4.2 cm; Fig. 2c).

Based on these dissections, we can make two observations: (1) vagectomy is not necessary to obtain adequate esophageal lengthening; punctual vagotomy is sufficient; and (2) vagal dissection achieves a significant esophageal lengthening. Obviously, these findings apply to cadavers without hiatal hernia or previous operations; however, we

F. A. Herbella
Department of Surgery, Division of Esophagus and Stomach,
Federal University of Sao Paulo,
Sao Paulo, Brazil

F. A. Herbella (✉)
Division of Esophagus and Stomach, Hospital Sao Paulo,
Surgical Gastroenterology,
Rua Diogo de Faria 1087 cj 301,
Sao Paulo, Sao Paolo, Brazil 04037-003
e-mail: herbella.dcir@unifesp.epm.br

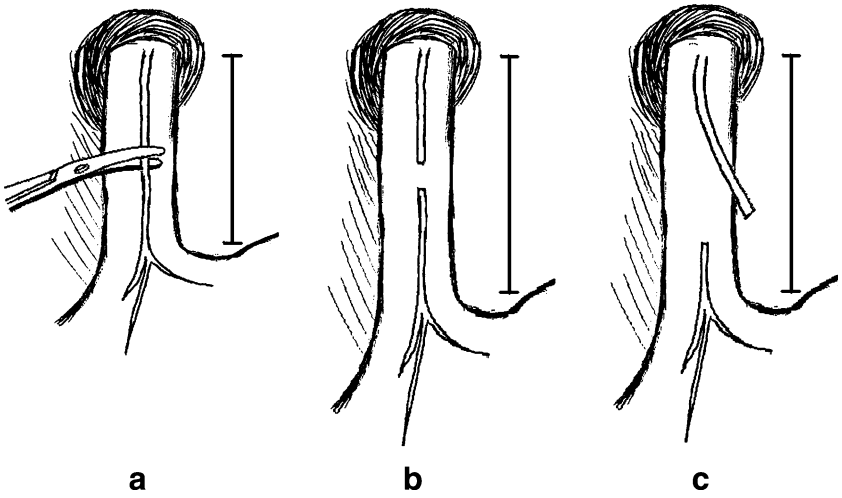

Figure 1 **a**–**c** Vagectomy versus vagotomy for esophageal elongation. Vagi nerves are divided after dissection of the esophagus up to the carina (**a**) and then dissected free of the esophagus and divided proximally (**b**). No esophageal length gain is achieved. Note that only the anterior vagus is depicted.

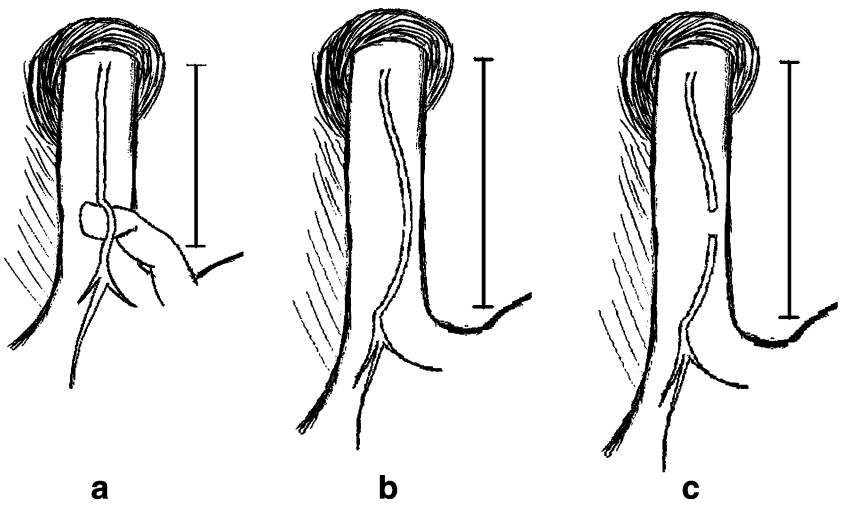

Figure 2 Vagal dissection versus vagotomy for esophageal elongation. Vagi nerves are digitally dissected up to the carina following the vagal-sparing esophagectomy technique (**a**). A significant length gain was obtained after the dissection (**b**). Extra elongation was obtained after bilateral vagotomy (**c**). Note that only the anterior vagus is depicted.

believe that vagal dissection should be tried before vagotomy during hiatal hernia repair.

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LETTER TO THE EDITOR

Re: Oelschlager BK, Yamamoto K, Woltman T, Pellegrini C. Vagotomy During Hiatal Hernia Repair: a Benign Esophageal Lengthening Procedure. J Gastrointest Surg. 2008;12(7):1155–62.

Brant Oelschlager · Kyle Yamamoto · Todd Woltman · Carlos Pellegrini

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Response to Dr. Herbella

We would like to thank Dr. Herbella for his response to our recent article published in this journal concerning the use of vagotomy as an esophageal lengthening procedure.[1] In this letter, he describes his experience with vagotomy, vagectomy, and vagal dissection in cadavers. His findings provide further evidence for what we have observed: that vagotomy increases the length of the esophagus after mediastinal esophageal mobilization. This is a phenomenon well known to us and many surgeons who deal with complex upper gastrointestinal diseases who encounter a foreshortened esophagus. This finding has not been well described in the literature, which is why we felt compelled to report this benefit, as well as the potential detriment (or in the case of our findings the lack there of), of vagotomy. Therefore, Dr. Herbella's findings are an important confirmation of our study and addition to the literature.

We are intrigued by Dr. Herbella's finding that vagal dissection away from the esophagus (as done in a vagal sparing esophagectomy) provides as much length as vagotomy. These finding by Herbella should be reproduced in patients, especially those with short esophagi. Vagal dissection is clearly more difficult and he did not show a difference in the increased esophageal length. Therefore, we prefer the ease of a unilateral vagotomy in the rare cases of short esophagi and are comforted by the lack of negative consequences reported in our study. We appreciate the opportunity to comment.

B. Oelschlager (✉) · K. Yamamoto · T. Woltman · C. Pellegrini
University of Washington,
Seattle, WA, USA
e-mail: brant@u.washington.edu

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LETTER TO THE EDITOR

Intrapancreatic Accessory Spleen: Deficiency in Diagnosis or Therapeutic Success?

Stephen M. Kavic · Adrian Park

Received: 28 August 2008 / Accepted: 12 November 2008 / Published online: 5 December 2008

To the Editor:

We read with interest the article by Drs. Uchiyama et al. on intrapancreatic accessory spleen (IPAS).[1] They provide a review of the literature of a "rare" condition, and we would like to add our case and our comments.

Our patient was a 46-year-old woman who presented with documented hypoglycemia and a 2-cm mass in the distal pancreatic body. Although the complete workup for insulinoma was negative, we performed a laparoscopic distal pancreatectomy for this solid lesion. During the procedure, we confirmed the location of the lesion using laparoscopic ultrasound. The procedure was completed in minimally invasive fashion, and the patient recovered uneventfully. However, our back table dissection revealing splenic tissue brought the operating team more disappointment than joy.

The question is one of whether we should be removing IPAS. If the diagnosis is established conclusively, then the answer is likely no. Unfortunately, current CT, MR, and ultrasound technologies do not necessarily distinguish between splenic tissue and pancreatic endocrine neoplasms. As the mere suspicion for a pancreatic neoplasm is considered to warrant resection, we may be fooled into operations with known morbidity but questionable clinical benefit.

Recently, three cases of IPAS have been described by diagnosis using endoscopic ultrasound with fine needle aspirate.[2] CD8 staining confirmed the diagnosis of splenic tissue, and provided the patients and physicians with reassurance in a truly minimally invasive fashion.

Accessory spleens are common at an estimated prevalence of 10%, which may be on the low side, which would be 400 million people worldwide with an accessory spleen. Autopsy studies suggest that 17% of accessory spleens were located in the pancreatic tail, again translating to a number approaching 75 million people. As our static imaging resolution improves, we may detect increasing numbers of these "patients."

A few cases may be reported in the literature as it is an admission that we are lacking in our diagnostic ability rather than displaying our technical prowess.

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S. M. Kavic (✉) · A. Park
University of Maryland,
Baltimore, MD, USA
e-mail: skavic@smail.umaryland.edu

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LETTER TO THE EDITOR

Reply to JGSU-D-08-00664: Intrapancreatic Accessory Spleen: Deficiency in Diagnosis or Therapeutic Success?

Shuichiro Uchiyama · Kazuo Chijiiwa

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We wish to express our appreciation for Dr. Kavic's and Dr. Park's interests in our article "Intrapancreatic accessory spleen (IPAS) mimicking endocrine tumor of the pancreas: case report and review of the literature." Their comment on differential diagnosis between the pancreatic neoplasms and IPAS is attractive. We confirmed that splenic endothelial cells were strongly positive for CD8 in our resected specimen.

We did not perform endoscopic ultrasound (EUS)-guided fine needle aspiration biopsy (FNAB) for the tumor of the pancreas tail in our case because IPAS was not considered as the differential diagnosis and we undoubtedly considered the tumor in our case was neuroendocrine tumor. Even if we considered the possibility of IPAS and EUS-guided FNAB was employed preoperatively, surgical treatment would be selected as long as conclusive diagnosis could not be obtained.

Accuracy of EUS-guided fine needle aspiration (FNA) in the diagnosis of pancreatic neuroendocrine tumor is reported as more than 80%, and EUS-guided FNA is necessary for the diagnosis of hypervascular tumors of the pancreas. As suggested, there is no doubt that we can avoid unnecessary surgery if conclusive diagnosis as IPAS is obtained. This newly reported way for the conclusive diagnosis of IPAS by using immunohistochemical technique of CD8 staining should be widely known, leading to conclusive diagnosis without surgical resection.

S. Uchiyama · K. Chijiiwa (✉)
Department of Surgical Oncology and Regulation of Organ Function, School of Medicine, Miyazaki University, Miyazaki, Japan
e-mail: kazuochi@med.miyazaki-u.ac.jp