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Original Paper

Prognostic Value of Resection-line Involvement in Patients Undergoing Curative Resections for Gastric Cancer

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Prognostic value of microscopical resection-line involvement of the proximal and distal resection lines was examined in patients undergoing potentially curative resection in a multicentre trial with strict quality control. Tumour-positive resection lines were seen in 41 of the 699 evaluable patients (5.9%). Resection-line involvement was associated with T stage ($P < 0.001$), N stage ($P = 0.003$), tumour location ($P < 0.001$) and tumour differentiation ($P < 0.001$). Presence of resection-line involvement was also associated with significantly worse survival. Together with T3 and T4 stage (relative risk (RR) 2.04), N(+) stage (RR 4.02) and tumour differentiation (RR 1.33), resection-line involvement (RR 2.28) was also an independent prognostic factor for survival. Survival in patients with resection-line involvement was comparable with patients with positive cytology. In patients undergoing potentially curative resection for gastric cancer, peri-operative frozen-section examination should be mandatory, especially in those with poorly differentiated, signet ring cell or anaplastic tumours, with tumours covering the entire stomach and T3 or T4 tumours. In case of tumour-positive margin(s) at final histology, re-laparotomy could be considered if achieving tumour-free resection lines seems realistic.

Key words: gastric cancer, resection-line involvement, cytology, prognosis

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INTRODUCTION

A CURATIVE RESECTION is the only therapy offering hope for cure in patients with gastric cancer. Presence of resection-line involvement is one of the well-known factors, together with presence of distant metastasis and free tumour cells in abdominal washing (positive cytology), associated with poor survival rate [1-3]. In order to assess whether the presence of microscopical resection-line involvement of the proximal and distal resection lines is associated with tumour related factors,

we analysed pathological findings and type of resection in patients undergoing potentially curative resection entered in the Dutch Gastric Cancer Trial [4].

PATIENTS AND METHODS

Between August 1989 and July 1993, a prospective randomised controlled multicentre trial was conducted in the Netherlands to compare the therapeutic efficacy of extended (D2) with limited lymph node dissection (D1) in gastric cancer patients operated on with curative intent. In this trial, 996 patients were entered with previously untreated primary adenocarcinoma of the stomach, without clinical evidence of distant lymphatic, peritoneal or hepatic metastasis. Of these patients, 711 underwent potentially curative resection, which was defined as macroscopic complete resection, without peritoneal, liver or distant lymph node metastasis. The latter was proven by frozen-section examination of a para-aortic lymph node biopsy (N4-tier). The type of resection (total or distal subtotal) was based on the location of the tumour [5, 6]. Peri-operative histological examination of the resection margins by

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frozen-section was not mandatory, but was performed in 226 of these 711 patients (32%).

Of the 711 patients, no resection-line information was available in 2 patients. No TNM classification was obtained in 7 patients, while tumour location and tumour differentiation was unknown in 3 patients. Therefore, the present paper is based on 699 patients for whom all relevant information was available.

For statistical analysis, the SPSS programme was used. The chi-square test (with Yates correction) was used to evaluate differences in proportions. Survival curves were drawn by the method of Kaplan and Meier, and differences between curves assessed by the Wilcoxon (Gehan) test. Logistic regression analysis was used to study the prognostic value of tumour related factors on the presence of resection-line involvement. Cox's proportional hazard analysis was used to determine important prognostic factors for survival and relative risk (RR) for each factor was calculated. Differences were considered statistically significant if $P < 0.05$.

RESULTS

Of the 699 evaluable patients, 41 patients (5.9%) had involvement of one or both resection lines; in 19 patients proximal only, in 18 distal only and in 4 patients both resection lines were involved. Resection-line involvement was seen in 5.3% of the males (21/394) and in 6.6% of the females (20/305), but this difference is not statistically significant. Resection-line involvement was also seen slightly more often in patients undergoing D2 resection (n.s.). Median age of the patients in both resection-line positive and negative patients was 64 years.

Presence of resection-line involvement was significantly associated with T3 and T4 stage, N(+) stage, tumour differentiation (poorly differentiated, signet ring cell and anaplastic), tumour location and type of resection (Table 1). By applying stepwise logistic regression analysis, T stage (T3 and T4), tumour location (tumours covering the entire stomach) and tumour differentiation (poorly differentiated, signet ring cell and anaplastic tumours) were demonstrated to

Table 1. Presence of resection-line involvement according to tumour-related factors in patients undergoing curative resections in intent for gastric cancer (n = 699)

	Total n	Present		P-value
		n	(%)	
Total	699	41	(5.9)	
Type of lymphadenectomy				
D1	373	22	(5.9)	n.s.
D2	326	19	(5.8)	
Location				
CMA	68	16	(23.5)	< 0.001
C	72	2	(2.8)	
M	191	7	(3.7)	
A	368	16	(4.3)	
Type of resection				
Distal/subtotal	462	16	(3.5)	< 0.001
Total	237	25	(10.5)	
T stage				
T1	183	0	(0)	< 0.001
T2	395	25	(6.3)	
T3 + T4	121	16	(13.2)	
N stage				
N(-)	312	9	(2.9)	0.003
N(+)	387	32	(8.3)	
TNM stage				
I	314	4	(1.3)	< 0.001
II	189	15	(7.9)	
III	166	19	(11.4)	
IV	30	3	(10.0)	
Differentiation				
Well	51	0	(0)	< 0.001
Moderate	215	2	(0.9)	
Poor	222	17	(7.7)	
Signet ring cell	127	11	(8.7)	
Anaplastic	28	7	(25.0)	
Combination	56	4	(7.1)	

CMA, entire stomach; C, proximal; M, middle; A, distal third.

Table 2. Risk factors for resection-line involvement in patients undergoing curative resections in intent for gastric cancer (n = 699)

Risk factor	n	RR	95% CI	P-value
T stage				
T1 + T2	578	1.00		
T3 + T4	121	2.33	1.12–4.81	0.02
Differentiation				
Well + moderate	266	1.00		
Other	433	10.18	2.34–44.26	0.002
Location				
C,M,A	631	1.00		
CMA	68	4.76	2.27–9.98	< 0.001

be independent prognostic factors for presence of resection-line involvement (Table 2).

Figure 1 shows the overall survival rate of resection-line positive and negative patients, median survival was 459 and 1530+ days, respectively ($P < 0.001$). Then, for each tumour related factor, the overall survival between resection-line positive and negative groups were compared (Table 3). The resection-line positive patients had a worse survival in all groups; in most cases this reached statistical significance. Median survival in patients with microscopic resection-line involvement undergoing D1 and D2 dissection was similar (405 and 495 days, respectively, $P = 0.73$).

The most important and independent prognostic factors for survival were T3 + T4 stage (RR 2.04, $P < 0.001$), N(+) stage (RR 4.02, $P < 0.001$), presence of resection-line involvement (RR 2.28, $P = 0.001$) and tumour differentiation (RR 1.33, $P = 0.04$). Tumour location (CMA) had a marginal prognostic value ($P = 0.08$).

In order to assess whether presence of resection-line involvement was associated with positive cytology, another important prognostic factor, the incidence and effect of both factors on survival was analysed. In 548 of the presently reported 699 patients cytological examination of the abdominal washing was performed. Of these 548 patients, 494 patients (90%) had no resection-line involvement and negative cytology (no free tumour cells in abdominal washing), 25

patients (4.6%) had resection-line involvement only, 23 patients (4.2%) had positive cytology only, while in 6 patients (1.1%) both resection-line and cytology were positive.

Survival in (I) patients with tumour free resection lines and negative cytology, (II) patients with positive cytology and (III) patients with positive resection line only showed that groups II and III were comparable, but different from group I.

Figure 2 shows the survival curves for the patients with negative resection-line involvement and negative cytology versus all other patients ($P < 0.001$).

DISCUSSION

Curative resection with macroscopic and microscopical clear margins (RO) is the only treatment offering hope of cure for patients with gastric cancer. Pre-operative staging of gastric cancer is notoriously difficult and reliable prognostic information is usually only obtained postoperatively. To date, only a minority of gastric cancer patients have resectable tumours at the time of diagnosis [6, 7]. Overall 5-year survival rate varies between 5 and 11% and, even after a potentially curative resection, the 5-year survival rate is still poor at around 30% [8].

In a patient care evaluation study by the American College of Surgeons, the 5-year survival rate was 35% in patients with microscopically clear margins and 13% in those with microscopically involved margins [2]. In the present study, the association of a microscopical tumour-positive resection-line with significantly worse survival was confirmed ($P < 0.001$, Figure 1). Presence of resection-line involvement was also associated with pT stage, pN stage, pTNM stage, differentiation and tumour location. The fact that resection-line involvement was seen significantly more often in total gastrectomies ($P < 0.001$) was not surprising, because the type of resection was determined by the location and extent of the tumour. Resection-line involvement was seen significantly more often in anaplastic and signet ring cell carcinoma as well as in poorly differentiated tumours. Until now, tumour differentiation had few clinical consequences, except for Borrmann type 4, where usually total gastrectomy was recommended.

Our data showed that survival in patients with resection-line involvement and in those with positive cytology of the abdominal washing is similar. The latter patients are beyond cure, while clear resection margins can be achieved and should be aimed at. Since resection-line involvement and positive cytology do not occur simultaneously (only occurring in 1.1% of the patients), both factors should be verified in order to obtain reliable prognostic information. In our study, however, no data on frozen-section examination was collected routinely, because a frozen-section examination of the resection lines was not mandatory in the DGCT. However, we do know that some patients did have clear resection lines after a re-resection based on a tumour-positive resection line in frozen-section examination. Even though the accuracy of frozen-section examination cannot be deduced from our data, frozen-section examination peri-operatively has already been demonstrated to be a reliable diagnostic tool [9]. Yokota and associates have demonstrated that intra-operative immunostaining with monoclonal antibody S202 can be useful for the detection of invasive cells in Borrmann type 4 gastric carcinoma [10]. Keighley and colleagues even suggested that all patients undergoing radical surgery for gastro-oesophageal malignancy

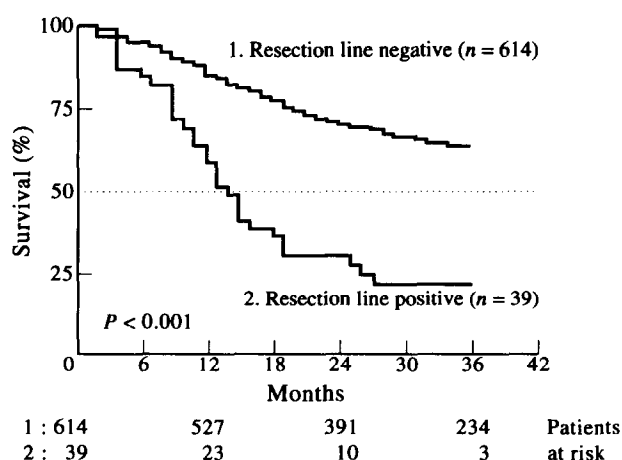


Figure 1. Survival in patients with negative and positive resection lines.

Table 3. Median survival (days), postoperative deaths (n = 46) are excluded according to tumour-related factors and absence or presence of resection-line involvement in patients undergoing curative resections in intent for gastric cancer (n = 653)

	Absent		Present		P-value
	n	Median survival (days)	n	Median survival (days)	
Total	614	1530+	39	459	< 0.001
Location					
CMA	46	696	14	428	0.21
C,M,A	568	1530+	25	483	< 0.001
T stage					
T1 + T2	515	1530+	24	450	< 0.001
T3 + T4	99	612	15	495	0.11
N stage					
N(-)	280	1530+	9	743	< 0.001
N(+)	334	867	30	428	< 0.001
TNM stage					
I + II	451	1530+	19	441	< 0.001
III + IV	163	581	20	473	0.14
Differentiation					
Well + moderate	243	1530+	2		NA
Other	371	1400	37	441	< 0.001

NA, not applicable.

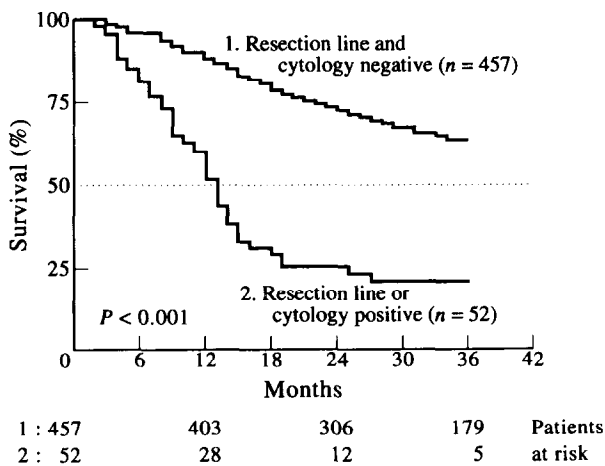


Figure 2. Survival in patients with negative resection line and cytology (1) and positive resection line and/or cytology (2).

should have frozen-section examination of the proximal margin [11].

During our search for improvement of prognosis in patients with gastric cancer, we should not lose sight of rational principles in performing RO resection. Usually, the judgement of the surgeon is very accurate in assessing resection margins. However, signet ring cell carcinoma and poorly differentiated tumours extend under the (sub)mucosal layer in the gastric wall, and therefore the actual size of the tumour cannot be assessed macroscopically: in our study, in 28 patients with microscopical resection-line involvement, no frozen-section examination was performed. Unfortunately, signet ring cells are difficult to recognise in frozen-section examination, while

these tumours have the highest rate of resection-line involvement. However, additional staining with PAS might be helpful. Since the patients with microscopically positive tumour margins with this type of tumours have an even worse prognosis compared to those without resection-line involvement, we feel that every attempt should be made to increase the chance of offering these patients an RO-resection and, since tumour differentiation can be assessed quite reliably in pre-operative biopsy specimen, extent of resection should be adjusted according to tumour type.

Performing curative resections for gastric cancer can no longer be considered the responsibility of the surgeon only. The pathologist, who can provide (microscopic) information during the operation and not only after the operation, should be committed to patient care as well. Only when gastric cancer surgery has become the territory of a surgicopathological team, can we then offer our patients the best hope for cure. Therefore, peri-operative frozen-section examination of the resection lines should be mandatory in patients undergoing potentially curative resection for gastric cancer, especially in T3 and T4 tumours and in tumours covering the entire stomach or poorly differentiated, anaplastic or signet ring cell carcinoma. If at frozen-section examination the resection line appears to be tumour-positive, re-resection should be performed, to obtain tumour-free margins. If the frozen-section examination is negative and the final histology is positive, even re-laparotomy could be considered if achieving tumour-free resection lines seems realistic.

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