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Original Paper

Pre-operative Sequential Chemo- and Radiochemotherapy in Locally Advanced Carcinomas of the Lower Oesophagus and Gastro-oesophageal Junction

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The purpose of this trial was to examine the feasibility of intensive, sequential chemo- and radiochemotherapy followed by surgery in patients with locally advanced carcinomas of the lower oesophagus and the gastro-oesophageal junction (GO junction). The chemotherapy consisted of two courses of 6 weekly administrations of 5-fluorouracil (5-FU) (2.0 g/m^2, 24 h infusion) and folinic acid (FA) (500 mg/m^2, 2 h infusion) combined with twice weekly cisplatin (50 mg/m^2, 1 h infusion). Irradiation of 30 Gy was given concurrently with one course of cisplatin and etoposide. 25 patients with locally advanced (T3-T4 NX M0) squamous cell or adenocarcinoma of the lower oesophagus and GO junction were included and evaluated. Toxicity was usually mild to moderate (WHO grade 1 and 2) with mucositis as the most important side-effect of the pre-operative treatment. Of the patients, 94 and 88% completed the chemo- and radiochemotherapy according to the protocol, respectively. A major response (= partial remission with subjective improvement) to chemotherapy was achieved in 6/10 patients with squamous cell carcinoma and 10/15 with adenocarcinoma. 19 patients had subsequent surgery and complete resection was achieved in 16 (3 patients had intra-abdominal metastases observed at laparotomy). The operative mortality rate was 16% (3/19). 10 of the 16 patients with tumour resection had a pathological complete response. 15 patients (43%) remain alive at a median follow-up of 20 months and the median survival exceeds 16+ months. Our data suggest that this intensive pre-operative chemoradiotherapy programme is feasible and remarkably effective in patients with locally advanced carcinomas of the lower oesophagus or GO junction. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

In the last 20 years, significant changes have been reported in the pattern of oesophageal and gastric carcinomas in Europe, as well as in the U.S.A. [1–5]. In some regions, a more than 5-fold increase in the incidence of adenocarcinomas of the oesophagus and of the gastric cardia has been observed. During the same time, the incidence of all cancers of the oesophagus remained stable and that of gastric cancer declined in these regions. In the U.S., this tumour ranks in the top 15 types of cancers among Caucasian males. The reason for this rapidly increasing rate of adenocarcinomas of the gastro-oesophageal (GO) junction is not yet clear. These tumours predominantly afflict younger Caucasian males and are not correlated with tobacco and alcohol consumption [5].

The prognosis of patients with carcinomas of the lower oesophagus or GO junction remains poor [6–9], as most of the patients are diagnosed initially with advanced disease [1, 9]. Thus, the tumours are not completely resectable or the high incidence of lymph node metastases causes tumour recurrence despite 'curative' resection in more than 70% of the patients [7–9]. Phase II trials with pre-operative chemotherapy have shown promising results in patients with oesophageal [10, 11] or gastric adenocarcinomas [12, 13]. Recently, a

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comparison of pre-operative chemoradiotherapy followed by surgery versus surgery alone showed superiority of the multimodal treatment in oesophageal adenocarcinomas [14]. We have previously reported on the high efficacy of combined pre-operative chemoradiotherapy in locally advanced oesophageal cancer, mostly squamous cell carcinomas [15] and on the high remission rates of chemotherapy in advanced gastric carcinoma [16]. The goal of the present study was to develop a pre-operative, sequential chemoradiotherapy regimen that would result in high resection rates and high pathological complete responses in locally advanced carcinomas of the lower oesophagus and the GO junction.

PATIENTS AND METHODS

Patient selection

Patients with biopsy-proven squamous cell or adenocarcinoma of the lower oesophagus (more than 32 cm from the incisors) and with adenocarcinoma of the GO junction (tumours within 5 cm of the z-line) were eligible. Patients were required to have T3 or T4 tumours (International Union against Cancer (UICC) classification) assessed by endoscopic ultrasound and computed tomography (CT), with or without lymph node metastases and without distant metastases. Moreover, eligibility criteria included age 18–75 years, World Health Organization (WHO) performance status 0–2, serum bilirubin level less than 1.5 mg/dl, serum creatinine level less than 1.3 mg/dl, leucocyte count greater than 4000/μl and platelet count greater than 100 000/μl. Patients were not allowed to have any other surgery for this disease, other than for exploration, any chemotherapy or radiotherapy, or concurrent or previous malignancy. All patients gave informed consent. Before enrolment in the study, patients were jointly evaluated by a surgeon and medical oncologist to ensure that each patient was medically fit for the treatment. Before treatment, the following tests were performed on each patient: physical examination; complete blood cell count; assessment of electrolytes, liver enzymes, bilirubin, cholinesterase, albumin, creatinine, and coagulation tests; barium oesophagogram; oesophagogastroscopy with biopsies, chest X-ray; CT of the chest and abdomen; abdominal ultrasound and endoscopic ultrasound. Surgical laparoscopy was also planned before the treatment.

Study design

The design of the study is shown in Table 1. The objective was to administer two courses of induction chemotherapy. Patients with local tumour progression during chemotherapy, defined by endoscopy and CT, were prematurely switched to chemoradiation. In the case of occurrence of distant metastases, patients were withdrawn from the study. Two weeks after the last day of chemotherapy concurrent radiochemotherapy was performed. Surgery was planned for 3–4 weeks after the end of irradiation. Patients who were thought to be inoperable after repeated functional examination were offered definitive chemoradiotherapy of 54–60 Gy.

Pre-operative chemotherapy

Each course of chemotherapy consisted of folinic acid (FA) 500 mg/m^2 over 2 h, followed by 5-fluorouracil (5-FU) 2.0 g/m^2 over 24 h, weekly times 6, combined with cisplatin 50 mg/m^2 over 1 h at weeks 1, 3, 5. This course was repeated after a 1 week's rest (Table 1). Patients received prophylactic antiemetic support and hydration when receiving cisplatin. Treatment was usually performed as outpatients with administration of 5-FU by implanted port-systems and portable pumps.

Pre-operative radiochemotherapy

Radiotherapy started 2 weeks after the last day of induction chemotherapy for 3 weeks. The clinical target volume (CTV) contained the macroscopic tumour and a margin of suspected subclinical involvement. In an oral direction, a 5 cm margin of macroscopically uninvolved normal tissues was included. Two centimetre margins of mediastinal tissues were irradiated in the transversal planes. In an aboral direction, the lower mediastinal, superior gastric, coeliac axis, common hepatic artery and splenic artery lymph nodes, as well as the gastric tumour extensions with a margin of 3 cm, were included into the CTV. The planning target volume contained the CTV and additional lateral and cranio-caudal margins of usually < 1.5 cm for the consideration of organ movements. No immobilisation device was used. The target volume was irradiated with equally weighted ap–pa 15 MV photon beams from a linear accelerator. The reference point for dose specification was at the isocentre midway between the beam entrances. A total dose of 30 Gy was given with 2 Gy per daily fraction, five fractions per week. Dose variations in the CTV should be within 95–105% relative to the reference dose. A maximum dose to the spinal cord of 105% of the dose at the reference point was allowed. Corrections for tissue inhomogeneity were not performed during dose calculation. Concurrently with radiation, chemotherapy was administered, consisting of cisplatin 50 mg/m^2, 1 h infusion, days 2 and 8 and etoposide 80 mg/m^2, 1 h infusion, days 4–6.

Surgery

Prior to surgery, a second risk analysis was performed to ensure the medical operability of the patients. The method of the resection procedure depended on the localisation of the tumour. In the case of carcinomas of the lower oesophagus, the resection of the oesophagus and the proximal stomach was performed by a combined right thoracic and abdominal

Table 1. *Study design*

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	21/22
5-FU/FA	•	•	•	•	•	•		•	•	•	•	•	•					
Cisplatin	•		•		•			•		•		•			•	•		
Etoposide															•••			
Radiation (2 Gy/day)															/////	/////	/////	
Surgery																		#

5-FU/FA, 5-fluorouracil/folinic acid.

approach, including dissection of the paraoesophageal, perigastric and coeliac lymph nodes. Tumours with their centre in the GO junction and extension to the gastric cardia were resected by transhiatal oesophagectomy and total gastrectomy with lymph node dissection of compartment I and II (D2 dissection). Independent of the results at surgery, postoperative adjunctive treatment was not planned in the study.

Criteria for response and toxicity

Complete blood tests, barium oesophagogram and endoscopy were repeated after the first 6 week cycle of chemotherapy. In addition, CT scans and endoscopic ultrasound were planned before chemoradiotherapy. The response to chemotherapy was evaluated before chemoradiotherapy. Response criteria were defined as follows: major response, reduction or relief of tumour related symptoms and greater than 50% tumour regression evaluated by CT as well as greater than 50% reduction of intra-oesophageal tumour extension assessed by barium swallow/oesophagoscopy; no change, less than 50% regression of tumour extension and no evidence of tumour progression; progression of disease, increase of tumour extension assessed by CT or oesophagoscopy or evidence of metastases. After surgery the pathohistological tumour stage, as well as the resection status, were defined according to the UICC criteria [17]. Treatment related toxicity was classified according to WHO criteria [18]. Survival times were recorded using the method of Kaplan and Meier.

Follow-up

Studies during follow-up included complete blood test, chest radiographs, abdominal ultrasound and barium swallow alternating with oesophagoscopy. CT scans were performed if clinically indicated. Patients were seen every 3 months within the first year after treatment, then every 6 months.

RESULTS

Demographic data

25 patients were enrolled in this trial from September 1994 to December 1996. All patients were eligible. Their characteristics are listed in Table 2. 16 and 9 patients had tumours of the distant oesophagus and the GO junction, respectively. At the start of treatment, 3 patients needed intravenous (i.v.) alimentation due to tumour associated stenosis. One-third of the patients (32%) had weight loss of more than 10% body weight prior to treatment. Figure 1 indicates the treatment each patient received.

Results after chemotherapy

24 of the 25 patients received two complete courses of chemotherapy. In 1 patient, chemotherapy was stopped after one course because of severe oesophagitis. 7 patients had to have an additional 1 week's rest during the second course, to resolve toxic effects from chemotherapy (stomatitis 1, hand–foot syndrome 1, diarrhoea 5). In these patients, the dose of 5-FU was reduced by 20% for subsequent treatment according to the protocol. Overall, the toxicity was usually moderate and quickly reversible and particularly haematological side-effects were negligible (Table 3). 2 patients had to be hospitalised during chemotherapy because of oesophagitis and diarrhoea. No toxic death was observed. Response evaluation after two courses revealed a major tumour response in 6 of 10 patients (60%) with squamous cell cancer and in 10 of 15 patients (67%) with adenocarcinoma. The overall remission rate was 64% (95% confidence interval: 45–83%), 8 patients (32%) had stable disease and tumour progression was observed in 1 patient during chemotherapy.

Table 2. Patient characteristics

No. of patients entered and evaluated	25
Median age, years (range)	59 (45–73)
Median performance status (range)	1 (0–2)
Males/females	21/4
Adenocarcinomas/squamous cell carcinomas	15/10
Stage T3/T4	20/5

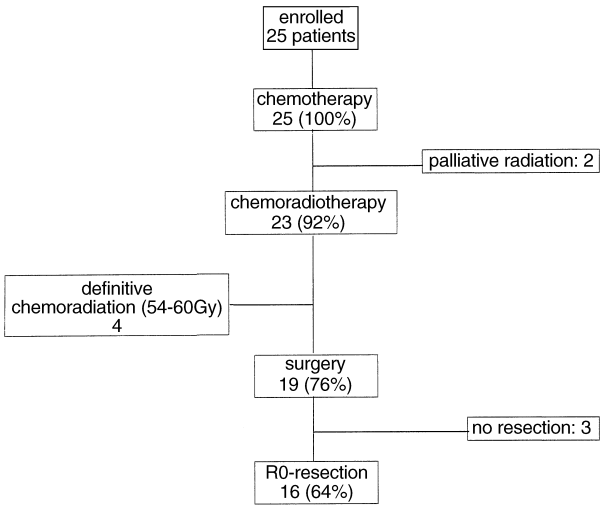

Figure 1. Flow diagram of the patients' treatment.

Results after radiochemotherapy

23 patients underwent radiochemotherapy and 2 patients received radiotherapy alone after chemotherapy because of tumour progression or worse performance status (1 patient each). Eighty-eight per cent of patients (22/25) received concurrent chemoradiation according to the protocol. 1 patient, who had suffered from severe *Candida albicans* oesophagitis during chemotherapy resulting in reduced performance status, was treated with definitive radiotherapy (60 Gy) and weekly 5-FU (bolus i.v.), instead of cisplatin/etoposide. Another 3 patients were assessed to be inoperable

Table 3. Toxic effects of chemotherapy (maximum WHO grade in % of all patients)

	WHO grade			
Toxicity	1	2	3	4
Nausea/vomiting	48	28	12	0
Diarrhoea	28	16	8	0
Mucositis	20	8	4	0
Cutaneous	48	28	0	0
Hair loss	8	0	0	0
Renal	4	0	0	0
Leucocytopenia	20	8	8	0
Thrombocytopenia	8	0	0	0
Anaemia	8	0	0	0
Infection	12	8	0	0

(medically unfit for surgery: 2 patients; distant metastases: 1 patient) and therefore were treated with definitive chemoradiation, e.g. doses of 54–60 Gy irradiation. Thus, 6 patients were treated with definitive irradiation with and without concurrent chemotherapy. 2 of these patients developed a major response, still lasting for 7 and 17 months; the other patients had progression of disease (1 patient) or no change (3 patients) and all showed local tumour progression within 8 months after treatment. The toxic effects during combined treatment were increased compared with chemotherapy alone, but were never life threatening. WHO Grade 3 and 4 leucocytopenia was observed in 38 and 9% and thrombocytopenia in 19 and 9% of patients, respectively. Other grade 3 toxicity included anaemia (22%), vomiting (17%) and oesophagitis (22%), which required a liquid diet during chemoradiation in 5 patients.

Results after surgery

19 of 25 patients (76%) underwent surgery. 6 did not because of increased operation risk (5 patients) or occurrence of metastases before surgery (1 patient). 3 patients did not undergo resection, as they were found to have liver metastases (1 patient) or peritoneal carcinomatosis (2 patients) at laparotomy. As laparoscopy was an optional staging procedure, 2 of these 3 did not have diagnostic laparoscopy prior to the study. A complete resection (R0-resection) could be performed in 16 of 19 operated patients (84%). 14 patients had transthoracic oesophagectomy and 2 patients underwent transhiatal distal oesophagectomy with gastrectomy. Careful pathohistological examination of the resected specimen revealed no viable tumour (pathohistological complete response, PCR) in 10 patients, giving a PCR rate of 53% of all patients undergoing surgery and of 40% of all patients included into the trial. PCR occurred in 4 of 6 resected squamous cell carcinomas and in 6 of 10 adenocarcinomas. In those patients with viable tumour cells in their resected specimen, histological examination revealed only a limited number of tumour cells in 1 and gross residual disease in 5 patients, respectively. 2 had metastatic disease in the liver or para-aortic lymph nodes, which were completely resected.

3 patients died within 30 days after surgery (operative mortality rate 16%) due to pneumonia, septicaemia and leakage of the anatomosis, respectively. All received complete tumour resection, with a PCR in 2 patients.

Follow-up

The median follow-up time for the entire group currently exceeds 20 months (range 6–32), with 15 patients remaining alive at the last observation. The median survival of all 25 patients is 16+ months (Figure 2). The overall 2-year survival rate was 46% and exceeds 61 and 63% for patients with tumour resection and with PCR, respectively. Prognosis was not different between squamous cell and adenocarcinomas (disease-free survival median 16+ months versus 16 months). Response to chemotherapy was predictive for prognosis with a 2-year survival rate of 57 and 25% for responders and non-responders, respectively.

Among the 16 patients with complete tumour resection, 2 distant recurrences were observed, both in patients with residual tumour within resected lymph nodes at surgery. So far, local tumour recurrence has not been observed. Long-term complications consisting of anastomotic strictures were observed in 4 patients.

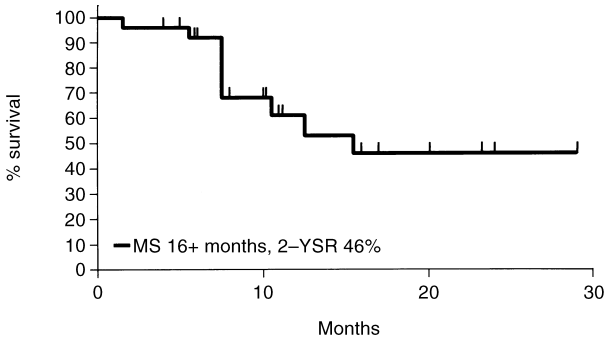

Figure 2. Kaplan–Meier survival plot of all 25 patients. The median survival duration was 16+ months and the 2-year survival rate reached 46%.

DISCUSSION

Until recently, the combination of cytostatics and radiation did not appear to have an additive effect in solid tumours in the clinic. However, this picture seems to be changing in more recent years, as more and more randomised trials have shown superiority of concurrent chemoradiation compared with chemotherapy or radiotherapy alone in different tumour types, such as lung cancer, rectal cancer and squamous cell carcinomas of the head and neck and the oesophagus [19–21]. Based on our convincing results with pre-operative chemoradiation in locally advanced (predominantly squamous cell) carcinoma of the oesophagus [15], we initiated a concept of sequential chemo- and radiochemotherapy in locally advanced cancer of the lower oesophagus and GO junction. We included squamous cell and adenocarcinoma as it has been shown that response to chemoradiotherapy may not significantly differ in these histologies and that resection rate after pretreatment depends on tumour localisation rather than on histology [15]. The choice of the chemotherapy schedule was based on our results in advanced gastric carcinoma, where low toxicity and high response rates were observed with a weekly regimen of cisplatin, high-dose infusional 5-FU and FA [16]. The high efficacy of this chemotherapy was confirmed in the present trial and was true for both histologies, with remission rates of 60 and 67% in squamous cell and adenocarcinoma, respectively. Moreover, the chemotherapy proved to be well tolerated and only 16% of patients suffered any WHO grade 3 toxicity.

In this study, we used an extended radiation field including the coeliac axis, common hepatic artery and splenic artery lymph nodes, as well as the gastric tumour extensions, with a margin of 3 cm into the CTV, which is a different approach to our former trials in oesophageal cancer. This extension of the radiation field was based on surgical data from the literature indicating that intra-abdominal lymph nodes are involved in more than 60% of patients with carcinomas of the lower oesophagus and GO junction [22, 23]. Moreover, our experience showed that these lymph node metastases cannot be destroyed by chemotherapy alone [15]. We used cisplatin/etoposide concurrently with radiotherapy as 5-FU containing regimens in combination with irradiation seem to have a higher risk of severe toxicity on the oesophago-gastric mucosa. Indeed, only 5 of 22 patients (23%) treated with concurrent chemoradiation had treatment-related mucositis that required a liquid diet and all patients were able to complete their radiochemotherapy. This fact may be due to the relatively low dose of radiotherapy (30 Gy). This was used to

ensure the tolerability of the extended target volume in terms of treatment toxicity and postoperative complications, particularly anastomotic leakage and because the dose–effect relationship of radiotherapy seems to be more linear than exponential [24]. In our trial, an insufficient anastomosis was observed in 1 patient only and we would not expect that higher doses of irradiation would have significantly improved local tumour control, as 5 of 6 patients with viable tumour cells at resection showed gross residual tumour. Our study resulted in a high complete resection rate of 84% and the 3 patients with exploratory surgery did not receive resection because distant metastases were detected; 2 of them did not have initial laparoscopy, which might have revealed metastatic disease prior to treatment. Moreover, a remarkably high PCR rate of 53% was observed after surgery. This is of particular importance as all the patients had locally advanced tumours, initially assessed by CT, endoscopic ultrasound, and, in most of the patients, also by diagnostic laparoscopy. The resection and PCR rate in our trial seems to be significantly higher than that achieved with pre-operative chemotherapy alone [10, 13] and confirms the fact, known from oesophageal cancer, that pre-operative combined chemoradiation is superior to chemotherapy alone in terms of local tumour control. Moreover, the PCR rate of the current trial seems to be better than results after pre-operative chemoradiation, with PCR rates of between 24 and 41% reported in patients with oesophageal cancer [15, 25, 26]. We do not know whether this high efficacy of pre-operative treatment will be translated into a high probability of long-term survival for these patients. However, several groups have shown that the induction of a PCR is predictive of long-term survival in squamous cell and adenocarcinoma of the oesophagus [15, 27].

It seems promising that no tumour recurrence was observed in patients with a PCR in our trial at a median observation time of 12 months after surgery. The calculated probability of survival at 2 years of this group is reaching 63%. Response to chemotherapy was predictive for prognosis, with 2-year survival rates of 57 and 25% for responders and non-responders, respectively. Our survival data (median survival time 16+ months, 2-year survival rate 46%) compare favourably with data from the literature, where median survival times of 12–16 months and survival rates at 2 years of 23–37% [13–15, 25–27] have been reported.

3 patients died postoperatively, 2 of infectious complications, resulting in a mortality rate of 16%. This is comparable to reports of other groups treating locally advanced carcinomas of the GO junction [13], but it might be higher than results with surgery alone and we cannot rule out a negative influence of our intensive combined pretreatment on postoperative mortality.

Very recently, two phase III trials predominantly treating adenocarcinomas of the oesophagus, reported a significantly improved long-term survival for patients with pre-operative chemoradiation compared with surgery alone [14, 27]. From these trials it can be concluded that patients with (adeno)-carcinoma of the oesophagus and GO junction should be treated with pre-operative chemoradiotherapy. However, there are still a number of items unsolved. What chemotherapy should be used? Cisplatin and 5-FU seem to be the standard and remission rates above 50% can be achieved if 5-FU is given by optimised schedules (24–48 h infusion (bi)weekly or protracted infusion for several weeks). However, it may be useful to add a taxane to this combination. How many cycles of chemotherapy should be given and what design should be preferred when combining chemotherapy, radiation and surgery? A number of patients do not tolerate additional treatment after surgery because of operative morbidity and toxicity from chemotherapy seems to be increased when given after surgery. Several groups have shown that it is feasible to administer three or more courses of chemotherapy before surgery [10, 15] and approximately 50% of tumours objectively respond to this treatment. These facts favour pre-operative chemotherapy, particularly in locally advanced tumours. However, it may be useful to add postoperative chemotherapy in chemotherapy-responders with viable tumour cells in the resected specimen or in the case of uncomplete resection. Do we really need combined chemoradiation when surgery is included in the treatment? It is obvious that combined radiochemotherapy is able to increase the PCR rate, but we do not know if this can be translated into an improved long-term survival and we have to consider a possible dismal influence on postoperative mortality. If pre-operative chemoradiotherapy may be used, what is the optimal way to combine it? There is little doubt that an additive effect can only be achieved by concurrent chemoradiation. Most groups used 30 Gy, as we did in our trial, but higher doses are feasible, although at the cost of increased toxicity. Nevertheless, more intensified radiation schedules, such as hyperfractionated regimens, may further improve the efficacy of radiotherapy in combined modalities.

As progress in answering these questions will come only through clinical trials, it seems to be imperative to treat patients with localised carcinomas of the GO junction within well designed prospective trials investigating combined treatment modalities. In this regard, our preliminary results may serve as the basis for future trials.

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