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Original Paper

Combined Intensive Chemoradiotherapy for Organ Preservation in Patients with Resectable and Non-resectable Oesophageal Cancer

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From January 1990 to April 1993, 60 oesophageal cancer patients were enrolled in a protocol of non-surgical treatment that consisted of induction chemotherapy followed by concurrent chemoradiotherapy. Induction chemotherapy consisted of cisplatin 40 mg/m² intravenous bolus days 1, 2, 14, 15; 24 h continous infusion of 5-fluorouracil (5-FU) 1000 mg/m² days 1 and 14; leucovorin 20 mg/m² days 1 and 14 given before and with 5-FU; bleomycin 30 UI days 1 and 14; mitomycin C 10 mg/m² day 14. Concurrent chemoradiotherapy consisted of 60 Gy (6 weeks) from day 21 and cisplatin 70 mg/m² days 28, 42 and 56; leucovorin 20 mg/m² followed by 5-FU 425 mg/m² days 28, 35, 42, 49 and 56. Complete response occurred in 44 of 55 evaluable patients (80%). The median survival is 32 months; the actuarial survival at 40 months is 35% (CI 18–53). These results appear improved over those reported with surgery or radiation alone, and suggest that organ preservation as a secondary treatment goal should be vigorously investigated.

Key words: oesophageal cancer, chemotherapy, radiotherapy
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INTRODUCTION

PROGRESS HAS been slow in the treatment of patients with oesophageal cancer. The natural history of this disease is characterised by extensive local contiguous growth and lymph node metastasis, culminating eventually in distant spread. Anatomical and biological factors determine the presence of extensive local disease at the time of diagnosis, and 20–85% incidence of local recurrence, following definitive surgery or radiotherapy [1]. The results of surgery and radiation therapy have been poor, the median survival being less than 10 months and the survival rate at 5 years being only 10% [2].

Although a prospective randomised trial of primary surgery versus primary radiotherapeutic management of oesophageal cancer has never been completed, oesophagectomy is generally considered the treatment of choice for operable patients with squamous cell carcinoma of the oesophagus [3].

Alternatively, multimodal treatment of this tumour that incorporates chemotherapy in the initial curative approach has been under investigation since the late 1970s [4–8].

The use of concurrent chemoradiotherapy before surgery or as a unique treatment shows better results than radiotherapy or chemotherapy alone, in terms of clinical and/or pathological complete response. An analysis of the data from 26 reports (811 patients) which used chemoradiation, with or without surgery, shows 2 and 5 year survival of 32 and 25%, respectively [9]. These reports indicate that organ preservation could be a major end point in the treatment of oesophageal cancer patients.

Here we submit our results of combined chemoradiotherapy without surgery in the treatment of oesophageal cancer. The purpose of this trial was to evaluate the efficacy and safety of this combined treatment by tumour response, toxicity, time to progression and overall survival.

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PATIENTS AND METHODS

Between January 1990 to April 1993, 60 patients were entered in a multicentre study. 3 patients were considered ineligible because of inaccurate pathological diagnosis, patient refusal and parallel treatment with alternative therapies; 2 patients were excluded from the analysis because treatment was discontinued as they both moved to distant cities. This protocol and the informed consent was approved by the Institutional Review Board of each Institution.

The characteristics of the 55 evaluable patients are shown in Table 1. Only 1 patient had adenocarcinoma. Males composed 69% of the population. The median age was 60 years. 29 patients (53%) were clinical stage III (UICC Staging System 1987) [10]. 15 patients (27%) were performance status 2 and weight loss was ≥10% in 31 patients (56%). Nine tumours (16%) were located in the upper third of the oesophagus, 25 tumours (46%) were located in the middle third and 21 (38%) in the lower third. 26 patients (47%) had tumours < 5 cm in length and 29 (53%) had larger tumours.

The pathological criterion of inclusion was histological evidence of squamous cell carcinoma or adenocarcinoma of the oesophagus, with no evidence of dissemination beyond the regional area.

The extent of tumour in each patient was evaluated by physical examination, thoracic and abdominal computerised tomography, chest radiography, oesophagogram and endoscopy with biopsy and measurement of tumour length, and endoscopic ultrasonsography. Bronchoscopy was only performed in patients with tumours of the superior and middle third. Complete blood cell count and multiple biochemical analyses were performed routinely. Renal and cardiac function were also evaluated to allow the use of cisplatin.

Table 1. Characteristics of patients with oesophageal carcinoma treated with chemoradiotherapy

Variable	*n*	%
Sex		
Male	38	69
Female	17	31
Stage		
I	5	9
II	21	38
III	29	53
Performance status		
0	4	7
1	36	65
2	15	27
Weight loss		
< 10%	24	44
≥ 10%	31	56
Location in oesophagus		
Upper	9	16
Middle	25	45
Lower	21	38
Largest tumour dimension (cm)		
< 5	26	47
5–10	27	49
> 10	2	4
Median age (range) (years)	60 (34–80)	

During the study, patients were interviewed and examined, and hematological and biochemical studies were conducted every other week during induction phase, and weekly in the concurrent chemoradiotherapy phase.

Evaluation 4 weeks after treatment included: barium oesophagogram, oesophagoscopy with biopsy, endoscopic ultrasonography, thoracic and abdominal computerised tomography, and at 3 month intervals endoscopic evaluation was performed during the first 2 years and then every 6 months. Endoscopic ultrasonography study after treatment was not considered for the evaluation of tumour response because this method cannot differentiate between fibrosis or residual disease.

ECOG criteria were used to determine performance status. Complete response was defined as complete disappearance of all detectable disease, without development of a new lesion and confirmed by another evaluation 4 weeks later. Partial response was defined as a greater than 50% reduction in measurable disease. Stable disease was considered as no change or a reduction less than 50% of measurable disease without the appearance of a new lesion. Progressive disease was defined as an increase in the size of initial disease by 25% or more, or the development of new lesions. Toxicity was reported using the guidelines of the National Cancer Institute common toxicity criteria.

Chemoradiotherapy

During the induction phase, cisplatin 40 mg/m^2 on days 1, 2, 14 and 15 was administered as an intravenous (i.v.) bolus; 5-fluorouracil (5-FU) 1000 mg/m^2 was given in a continuous 24 h i.v. infusion days 1 and 14; leucovorin 20 mg/m^2 was administered in a short i.v. infusion before a 5-FU infusion and 20 mg/m^2 together with 5-FU infusion. Bleomycin 30 UI was given on days 1 and 14 as an i.v. bolus and mitomycin C 10 mg/m^2 was given on day 14. During the chemoradiotherapy phase, cisplatin 70 mg/m^2 was administered as an i.v. bolus on days 28, 42 and 56; 5-FU 425 mg/m^2 was given in short infusion days 28, 35, 42, 49 and 56 after a short infusion

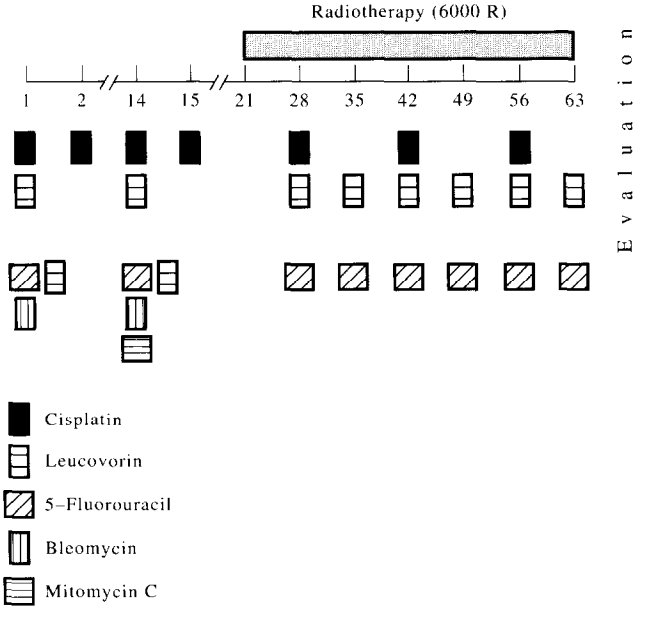

Figure 1. Treatment scheme.

of leucovorin 20 mg/m^2 (Figure 1). Chemotherapy was interrupted when the granulocyte count fell below 2.0×10^9/l and platelet count fell below 100×10^9/l. If the patient had an haemoglobin level below 9 g/l, a transfusion was performed immediately. Patients were hospitalised only on days 1 and 14, in order to perform 5-FU 24 h infusion. Radiation treatment started on day 21. Megavoltage radiation units were used (Co 60 or 6 and 10 MEV accelerator) with a minimal distance of 80 cm from the source to the axis of treatment, with one fraction per day of 1.8 Gy. The regional radiation treatment (45 Gy) extended from the supraclavicular to the coeliac lymph nodes area, including mediastinum. Radiation of the supraclavicular area was not required in the patients whose tumours originated in the lower third of the oesophagus. Radiation in the coeliac area was not performed when the primary lesion was located in the upper third of the oesophagus. In the first stage of the treatment, two anterior and posterior parallel opposed field techniques were used. A boost of 15 Gy was delivered at least 5 cm above and below the tumour in two oblique fields during the second course of radiation, in order to spare the spinal cord. All patients received a total dose of 60 Gy. Radiotherapy treatment was interrupted when granulocyte count fell below 1.0×10^9 cells/l, or the platelet count fell below 100×10^9/l.

Statistical methods

The relationship between tumour response and patient's characteristics were grouped by means of 2×2 contingency tables and examined by the chi-square test. Time to progression was measured from day of study entry to the date of relapse, or progression or death. Survival duration was measured from date of study entry to the date of death from any cause, or the date last seen. Survival was plotted using the product-limit method of Kaplan and Meier [11]. Median event times were estimated from Kaplan–Meier curves, and differences in time distributions were evaluated using the log-rank test [12]. All *P*-values are noted in the text.

RESULTS

Response

The efficacy of treatment was assessed by oesophageal endoscopy and biopsies, thoracic and abdominal computerised tomography and chest radiography, 4 weeks after the completion of concurrent chemoradiotherapy.

Complete regression of the primary tumour occurred in 44 patients (80%); partial response was observed in 5 patients (9%); stable disease in 1 (2%); initial progression in 3 (5%); and 2 patients had early deaths (4%) due to treatment toxicity.

Improvement in the ability to swallow correlated well with clinical response and was noted in the first 4 weeks of treatment.

Toxicity

Toxicity data were available on all patients (Table 2). Nausea and vomiting were noted in the majority of patients and were graded severe in 8 patients. Mucositis–oesophagitis graded 2 or 3 was observed in 7 patients and life threatening in 1. Haematological toxicity, graded 2 or 3 was reported in 33 patients and was life threatening in 2. 2 patients died due to treatment-related toxicity, 1 developed an oesophageal fistula and sepsis, and the other had respiratory failure immediately after therapy.

Table 2. Maximum toxicity in patients with oesophageal carcinoma treated with chemoradiotherapy

Toxicity	Grade 2	Grade 3	Grade 4
Nausea/vomiting	22	8	0
Mucositis/oesophagitis	5	2	1
Leucopenia	20	13	2
Infections	1	2	1
Cutaneous	2	1	0
Pain	1	1	0

Survival and pattern of failure

In the evaluation of multivariate analysis, seven variables were examined: sex, stage, performance status, weight loss, tumour localisation, tumour length and number of days of treatment interruption due to toxicity or other causes. The relationship of these variables with time to progression and survival was not statistically significant (data not shown).

23 patients remain in complete response. 21 patients developed only locoregional failure (oesophagus and regional lymph nodes), 2 patients had locoregional and distant recurrence and the rest had only distant failure.

We have also compared the relationship between the site of failure, locoregional or not, with number of days of treatment interruption, tumour length, stage, performance status, weight loss and tumour localisation. When the median of treatment interruption was more than 23 days, 92% of these relapsed patients had locoregional failure, while when it was less than 23 days, local failure was 56% ($P = 0.0483$).

Four total oesophagectomies were performed in this population. Two were carried out at the beginning of the study because of misinterpretation of partial responses. Both had pathological complete response. 1 patient was oesophagectomised because of an oesophagobronchial chronic fistulae and had pathological complete response. In the other, oesophagectomy was performed at the time of local progression, but complete resection of involved lymph nodes was not possible.

The estimated progression rate at 36 months was 34% (confidence interval, CI 19–50) and the median overall survival time was 32 months. The estimated survival at 40 months was 35% (CI 18–53) (Figure 2).

DISCUSSION

This study of non-surgical treatment of oesophageal cancer is one of several in which promising results from the use of

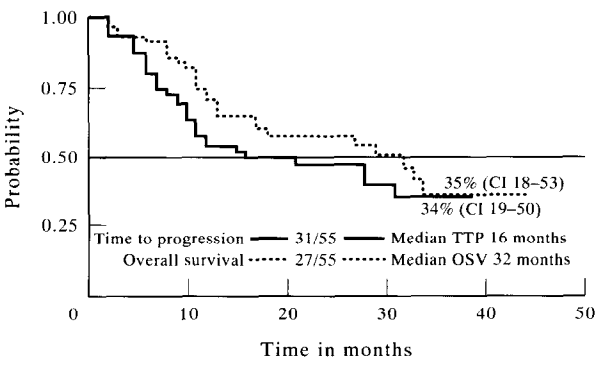

Figure 2. Overall survival and time to progression curves.

combined chemotherapy and radiotherapy without surgery have been obtained.

Radiotherapy has traditionally been considered an acceptable unique modality of treatment for cancer of the oesophagus. Herskovic [4] reported, in a well designed and well conducted trial, that chemoradiotherapy without surgery is superior in terms of survival to radiotherapy alone.

The potential benefit of using induction chemotherapy could be to administer an initial intensive dose of cisplatin in order to induce rapid tumour shrinkage with subsequent improvement of disphagia and an increase in radiotherapy efficacy.

All the drugs used in our protocol have proven activity in oesophageal cancer [12], either alone or in combined schemes. Bleomycin and mitomycin C, which were included in this study, might be related to the occurrence of pulmonary and haematological toxicity so they have been excluded in our subsequent protocol of treatment. It has been widely recognised that leucovorin modulates 5-FU activity [13], and there is some laboratory evidence that it might increase radiosensitisation of 5-FU [14–15].

We planned a short and intensive induction chemotherapy, in order to obtain rapid improvement of swallowing, followed by an outpatient treatment with concurrent radiotherapy and short infusion chemotherapy with radiosensitiser drugs: cisplatin, leucovorin and 5-FU. The use of 24 h continuous infusion of 5-FU followed by short infusions was based on the following: (1) to reduce haematological toxicity in the first phase; (2) to diminish the cost of treatment by an outpatient modality during radiotherapy, as ambulatory infusion pumps were not available; (3) there is no complete agreement about the benefit of 5-FU continuous infusion versus bolus administration in order to improve radiosensitisation; (4) the mechanism of 5-FU resistance could be via RNA when using bolus administration, and via DNA with prolonged exposure, with the potential benefit of combining both modalities to overcome resistance.

One of the best results obtained with neoadjuvant chemoradiotherapy in a selected oesophageal cancer group of patients was reported by Forastiere and associates [16–17], with a 5 year survival of 41% for curatively resected patients. All were hospitalised for several days during induction chemoradiotherapy and after surgical treatment. In our study, we discarded the surgical approach because of the high rates of perioperative mortality observed in our institutions. Our treatment was planned to be performed in an outpatient basis, and with low cost.

In the trial of Forastiere and colleagues [16], all patients were operable as an inclusion criterion and 38% had weight loss > 10%, while more than 50% of our patients were inoperable and 56% had weight loss > 10% at entry on to the study.

Several reports [17–18] have indicated that distant failure is a major problem when neoadjuvant chemoradiotherapy is used. On the contrary, we observed a higher rate of locoregional recurrence. One of the possible reasons for this may be that 98% of our patients had squamous cell carcinoma, while adenocarcinoma was more frequent in the United States trials. Another possibility could be the high tumour volume present in our patients (53% stage III).

Although surgery may have a role in the control of local disease, the good rates of survival observed in our preliminary data suggest that this role should be confirmed by randomised trials [19]. We have used a complete dose of radiotherapy (60 Gy) in order to obtain a better tumour response and have avoided surgery in our treatment plan.

In summary, this combination is an effective regimen and has moderate toxicity. The median survival in our population is 32 months, and appears better than those obtained with surgery or radiation alone and similar to other combined treatments. This suggest that organ preservation should be comprehensive investigated in future trials.

1. Roth JA, Putnam JB, Lichter AS, Forastiere AA. Cancer of the esophagus. In De Vita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology*. Philadelphia JB Lippincott, 1993, 776–817.
2. Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. *Br J Surg* 1990, 77, 845–857.
3. Haller DG. Treatments for esophageal cancer (editorial). *N Engl J Med* 1992, **326**, 1629–1631.
4. Herskovic A, Martz K, Al-Sarraf M, *et al.* Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992, **326**, 1539–1598.
5. Sischy B, Ryan L, Haller D, *et al.* Interim report of est 1282 phase III protocol for the evaluation of combined modalities in the treatment of patients with carcinoma of the oesophagus, stage I and II. *Proc Am Soc Clin Oncol* 1990, **9**, 105 (abstract 407).
6. Araújo CM, Souhami L, Hill RA, *et al.* A randomized trial comparing radiation therapy versus concomitant radiation therapy in carcinoma of the thoracic esophagus. *Cancer* 1991, **67**, 2258–2261.
7. Coia LR, Engstrom PF, Paul AR, Stafford PM, Hanks GE. Long term results of infusional 5-FU, mitomycin C and radiation as primary management of oesophageal carcinoma. *Int J Radiat Oncol Biol Phys* 1991, **20**, 29–36.
8. Leichman L, Herskovic A, Leichman CG, *et al.* Non operative therapy for squamous cell cancer of the esophagus. *J Clin Oncol* 1987, **5**, 365–370.
9. John MJ, Flam MS. Esophagus. In John MJ, Flam MS, Legha SS, Phillips TL, eds. *Chemoradiation*. Malvern, Lea and Febiger, 1993, 285–302.
10. Esophagus (CIE-O 150). In Hermanek P, Sobin LH, eds. *UICC-TNM Classification of Malignant Tumours*. Berlin, Springer-Verlag, 1987, 40–41.
11. Kaplan EL, Meyer E. Non parametric estimation for incomplete observation. *J Am Stat Assoc* 1958, **53**, 457–81.
12. Peto R, Pike M, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II Analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
13. Kelsen D. Chemotherapy of esophageal cancer. *Semin Oncol* 1984, **11**, 159–168.
14. Moran RG. Leucovorin enhancement of the effects of fluoropyrimidines on thimydilate synthase. *Cancer* 1989, Suppl 63, 1008–12.
15. Lawrence TS, Heimburger DK, Shewach DS. The effects of leucovorin and dipyridamole on fluoropyrimidine induced radiosensitization. *Int J Radiat Oncol Biol Phys* 1991, **20**, 377–381.
16. Forastiere AA, Orringer MB, Perz-Tamayo C, Urba SG, Zahurak M. Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. *J Clin Oncol* 1993, **11**, 1118–1123.
17. Forastiere AA, Orringer MB, Perez Tamayo C, *et al.* Concurrent chemotherapy and radiation therapy followed by transhiata! esophagectomy for local-regional cancer of the esophagus. *J Clin Oncol* 1990, **8**, 119–127.
18. Coia LR, Engstrom PF, Paul A. Non surgical management of esophageal cancer: report of a study of combined radiotherapy and chemotherapy. *J Clin Oncol* 1987, **5**, 1783–1790.
19. Girling DJ. Randomized trials in the treatment of cancer of the esophagus. *J Clin Oncol* 1992, **10**, 1031–1033.

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