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Prolonged Chemotherapy for Localised Squamous Carcinoma of the Oesophagus

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We evaluated the feasibility of six courses of chemotherapy in 34 consecutive patients with localised squamous cell carcinoma of the oesophagus. All 32 evaluable patients first received at least two courses of chemotherapy. There were 18 patients with resectable carcinomas who underwent surgery and 14 patients with unresectable carcinomas who received definitive chemoradiotherapy. After two courses of 5-fluorouracil and cisplatin 21 (66%) of 32 patients had either a complete or major response. A median of five courses (range, 1–6 courses) was administered. 17 out of 18 (94%) patients with resectable carcinoma had a 'curative' resection (negative proximal, distal, and radial margins by histopathology in an en-block resection specimen) and 2 patients had a complete pathological response. The median survival duration of all patients was 28 months (range, 2–46+ months). The median survival duration of 14 patients with unresectable carcinoma was 23 months (range, 8–36+ months), and the median survival duration of 18 patients with resectable carcinoma has not been reached at a median follow-up of 24+ months (range, 10+ to 46+ months). No deaths occurred because of chemotherapy or chemoradiation therapy. Our data suggest that prolonged chemotherapy is feasible in patients with locoregional squamous carcinoma of the oesophagus. An ongoing controlled trial will determine the contribution of chemotherapy to patients' survival.
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INTRODUCTION

CARCINOMA OF the oesophagus results in 5-year survival rates less than 6% which have not changed over the past 4 decades [1]. At the time of diagnosis, only 48% of patients have carcinoma confined to the oesophagus or regional lymph nodes [1]. Unless adequately controlled, the primary carcinoma is the common cause of morbidity and mortality.

The results of treatments to control the primary carcinoma have been dismal producing median survival rates well below 18 months [2, 3]. The 5-year survival rates following surgery have ranged from 1% to less than 20%, and the median survival duration has been 12 months or less [2, 4–6]. Similarly, treatments with definitive or palliative radiotherapy have resulted in poor 5-year survival rates as well [3, 7, 8]. The increased sensitivity with potential radiocurability of squamous cell carcinoma of the oesophagus to radiotherapy has long been known [9]; similarly, its sensitivity to many chemotherapy agents has been noted [10, 11]. More recently, the introduction of chemotherapy in the treatment of localised carcinoma has led to several newer approaches.

Chemotherapy has been employed in two common strategies. First, one or two courses of combination chemotherapy have been administered before surgery [12–14]. Second, combination chemotherapy and concurrent radiotherapy (chemoradiation therapy) have been administered [15–19] prior to surgery or chemoradiation therapy has been used as a definite method to eradicate localised carcinoma [20–22].

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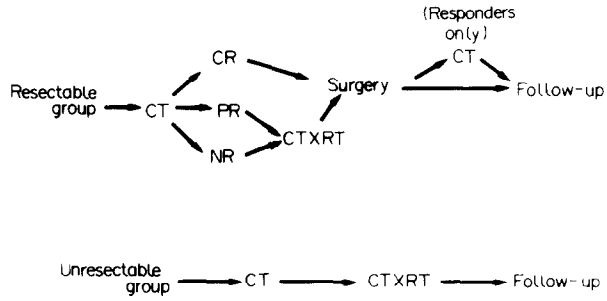

Fig. 1. Study design. CT, chemotherapy; CTXRT, chemoradiation therapy.

Evidence suggests that occult metastases exist frequently in patients with localised carcinoma [23, 24]; thus, the strategies that emphasise treatments of both the localised and occult metastatic carcinomas would be desirable. Our hypothesis was that the drug sensitivity of the primary carcinoma partially or fully represented that of metastatic carcinoma. Therefore, our goal was to administer prolonged chemotherapy (six courses) to patients whose primary carcinomas regressed after the first two courses and their primary carcinomas were also treated aggressively with a locoregional modality.

Previously described single-agent activity of 5-fluorouracil (5-FU) and cisplatin [25, 26] and the evidence of preclinical synergism [27, 28] were the basis for combining these two drugs and selecting the schedule that promoted synergism.

PATIENTS AND METHODS

Patient selection

Patients with histological proof of non-metastatic squamous cell carcinoma of the oesophagus were eligible. Patients were required to have a performance status of 2 or less (Zubrod scale; 29), serum creatinine <1.5 mg/dl, serum bilirubin <1.6 mg/dl, an absolute granulocyte count $<1\,500$ cells/μl, platelet count $>100\,000/\mu$l. All patients gave informed consent.

Based on tumour characteristics and associated medical conditions, patients were considered: potential resectable or unresectable. Characteristics that rendered tumours unresectable included histological evidence of tracheobronchial invasion, celiac adenopathy >5 cm in diameter as evidenced by computerised tomography; and a tumour length >10 cm by barium swallow or endoscopy. Characteristics that rendered a patient inoperable included, forced vital capacity in the first second (FEV_1) less than 1 l, and cardiac disability class III or IV according to the New York Heart Association.

Study design

The objective was to administer six courses of chemotherapy. Figure 1 demonstrates the schema used for all patients. Patients with resectable tumours first received two courses of chemotherapy and tumour responses were judged; if no carcinoma cells were found in the endoscopic biopsy and cytological brushings, patients underwent surgery. However, if the endoscopy revealed carcinoma cells; patients received chemoradiation therapy (30 Gy) and were re-evaluated by endoscopy prior to surgery. Patients responding to preoperative chemotherapy received four additional courses postoperatively.

Patients with unresectable carcinoma received up to six courses of chemotherapy, followed by definitive radiotherapy (up to 60 Gy) with concurrent 5-FU.

Patients were followed every 3 months for the first year and then every 6 months for additional 4 years, or until death.

Chemotherapy

Chemotherapy consisted of a combination of 5-FU and cisplatin, 5-FU was administered at a starting dosage of 1000 mg/m^2 continuously over 20 h on days 1–5 and cisplatin was administered at a starting dosage of 20 mg/m^2 over 1 h on days 1–5. The 5-FU infusion was limited to 20 h to allow cisplatin administration. Patients routinely received hydration and antiemetic therapy. Chemotherapy courses were repeated every 21–25 days, provided patients recovered from all toxic effects. Based on the predetermined criteria of toxicity grades, the dose of chemotherapy drugs was increased or decreased by 25%. Complete blood counts, serum creatinine, electrolytes, blood urea nitrogen, and magnesium levels were monitored. Toxicities were graded according to the previously described criteria [30].

Chemoradiation therapy

The daily radiotherapy fraction was 1.8–2.0 Gy five times each week. A total radiation dose of 30 Gy was given preoperatively, and it was up to 60 Gy in the unresectable group. 5-FU was administered at a dosage of 300 mg/m^2/24 h given daily during radiotherapy [31, 32]. For grade 2 diarrhoea, mucositis, or 'hand and foot' skin reactions [33], the 5-fluorouracil dose was reduced by 20%, whereas 5-FU was stopped for 7 days for grade 3 toxicities and resumed at a 20% reduced dose.

Surgery

Oesophagogastrectomy through combined abdominal and thoracic incisions [34] was performed in patients in the resectable group. During surgery, a feeding jejunostomy tube was placed in all patients.

Nutritional support

Attempts were made to meet caloric and protein requirements in all patients throughout the treatment and follow up duration which also included the use of prolonged nasogastric or jejunostomy tube feedings. Long-term intravenous alimentation was avoided.

Evaluations and response criteria

Barium swallow was repeated after the first course. Oesophagoscopy and barium swallow were repeated after the second course of chemotherapy, after the last course of chemotherapy, and after chemoradiation therapy.

Because of the lack of bidimensional tumour mass in these patients, some conventional criteria for response could not be applied. Modifications of the standard response criteria have been recently described [35].

RESULTS

Among the 34 patients registered, 2 patients were not evaluable; 1 refused to complete his first course of chemotherapy and was lost to follow-up and the second patient was lost to follow-up after the second course of chemotherapy. Patients' characteristics are shown in Table 1. 18 patients were considered to have potentially resectable carcinoma whereas 14 had unresectable tumours. A total of 136 courses were delivered, with a median of 5 (range 1–6). 19 patients received either five (8 patients) or six (11 patients) courses of chemotherapy. 3 patients who had tumour regression refused further chemotherapy due predominantly to the development of severe mucositis (after one, two, and four courses). 3 responding patients (2 in the unresectable group) had progressive carcimona after four courses (1 patient) and two courses (2 patients). A Pearson's correlation of coef-

Table 1. Patients' characteristics

Total no. of patients	34
No. evaluable	32
Resectable	18
Unresectable	14
Male:female	18:14
Median age, years (range)	65 (51–77)
Median performance status	1 (0–2)
Median length of tumour in cm (range)	6 (2*–14)
Histology	
Well differentiated	1
Moderately differentiated	17
Poorly differentiated	14
Dysphagia to	
Liquids	18
Solids	11
None	3

*Accurate determination not possible in 2 patients because of malignant stricture formation.

ficient between the number of chemotherapy courses and patients' age was not significant ($r = -0.3255$; $P = 0.69$).

The response to chemotherapy was evident after one course of chemotherapy in all but 2 patients. 13 of 32 patients had no carcinoma cells in the endoscopic biopsy and cytological specimens, in addition, 8 patients had a major response (one example is shown in Fig. 2). Thus, 21 (66%) of 32 patients had a response (clinical complete and major response). In addition, 4 patients had minor responses and 7 patients had no response to chemotherapy.

The median duration of survival for all patients was 28 months (range, 2 to 46+ months). 16 of 32 patients were alive at a minimum follow-up of 10 months and a maximum follow-up of 46+ months (Fig. 3). The median duration of survival of 21 patients with responses was 31 months (range, 8–46+ months), whereas that for patients with no response (no change and minor regressions) was 11 months (range, 2–35 months).

Patients with resectable carcinoma

Among the 18 patients with resectable carcinoma, clinical complete response occurred in 7 patients and major response occurred in 4 patients. 7 patients with complete clinical response did not receive preoperative chemoradiation therapy. Curative resection (proximal, distal, and radial margins negative for malignant cells in the enblock resection specimen) of carcinomas was accomplished in 17 out of 18 (94%) patients and only 1 patient had positive microscopic margins. The pathological responses were as follows; two complete pathological responses, two specimens with no carcinoma cells in the oesophagus but microscopic carcinoma in the lymph nodes, three additional specimens with only microscopic carcinomas and 13 out of 18 (72%) specimens contained no metastases in the lymph nodes.

12 of the 18 patients remain alive and the duration of median survival has not been reached at a median follow up time of 24 months (range, 10–46+ months).

In this group, the following patterns have been observed: 8 patients remain without any evidence of carcinoma; 3 developed distant metastases; 3 had locoregional recurrence (none had received chemoradiation therapy prior to recurrence); 1 died immediately following complete resection of the primary carcinoma; 1 died of chronic aspiration pneumonia 3 months after surgery (considered a long-term surgical complication) but had no carcinoma at an autopsy examination, 1 developed both local and metastatic carcinoma, 1 had lung carcinoma as a second primary which was discovered at surgery, and died of pulmonary failure 6 months later.

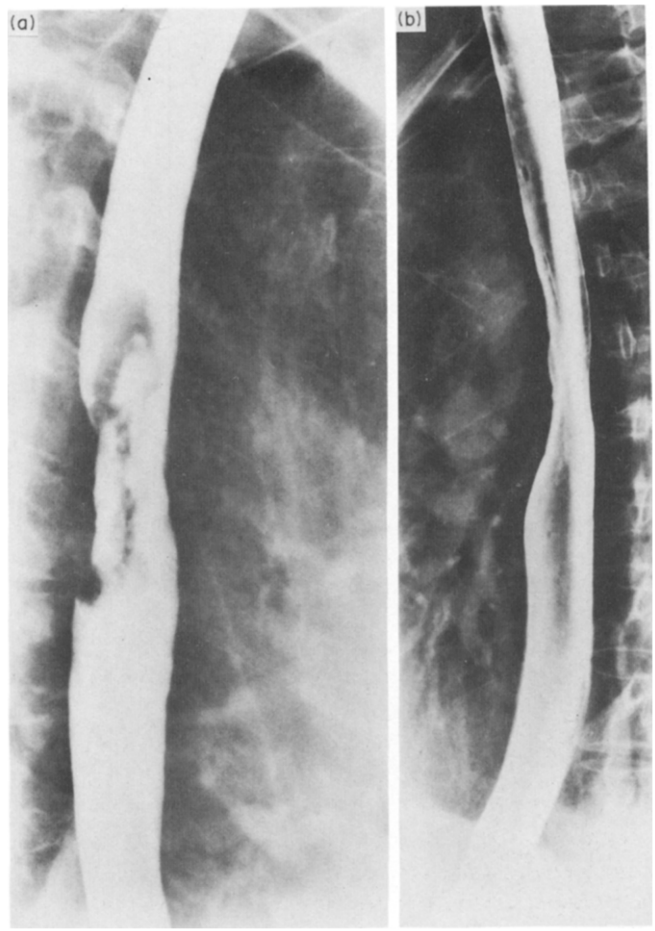

Fig. 2. Examples of major response to chemotherapy in 1 patient. (a) Barium swallow of a patient in the resectable group showing a midoesophageal carcinoma. (b) Evidence of response by barium swallow after two courses of chemotherapy. Endoscopic evaluation revealed no carcinoma cells and the patient had a complete pathologic response.

Patients with unresectable carcinoma

Among the 14 patients with unresectable carcinomas, 6 patients achieved clinical complete responses and 4 patients achieved major responses. After the completion of chemoradiation ther-

Table 2. Treatment characteristics

Total no. of patients	32
Total no. of chemotherapy courses	136
Median no. of courses (range)	5 (1–6)
Median daily dose in mg/m^2 for	
5-FU (range)	1000 (750–1250)
Cisplatin (range)	20 (15–25)
Clinical response to chemotherapy (no. of patients)	
Clinical complete response	13
Major response	8
Minor response	4
No response	7

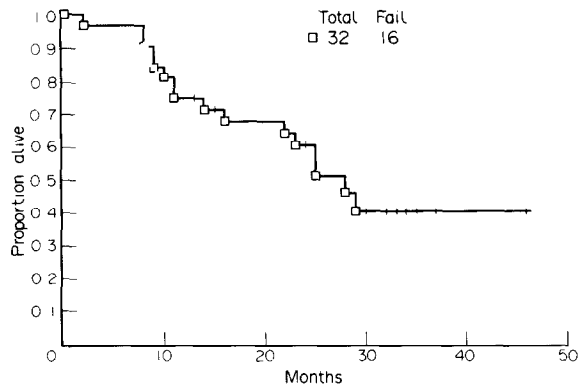

Fig. 3. Kaplan–Meir survival plot of all 32 patients. The median survival duration was 28 months (range, 2–46+ months).

apy (median radiotherapy dose, 60 Gy; range, 30 to 60 Gy), 11 out of 14 patients had clinical complete responses and a major response, which resulted in an upgrading of clinical response.

Only 4 of 14 patients remain alive in this group with a median duration of survival of 23 months (range, 8 to 36+ months). Pearson's correlation performed between the following parameters: patient survival and length of the tumour ($P = 0.02$, $r = 0.911$); age and patient survival ($P = 0.173$, $r = 0.34$); and the number of chemotherapy courses and patient survival ($r = 0.5$; $P = 0.003$).

In this group, only 2 patients remained alive with no evidence of carcinoma, 7 had only local recurrences, 3 developed distant metastases, 1 died of another cancer, and the cause of death in another patient was unknown.

Toxic effects

No deaths occurred related to chemotherapy or chemoradiation therapy. Common non-haematological toxic effects due to chemotherapy with 5-FU and cisplatin are listed in Table 3. Toxic effects were moderate and treatments were generally well tolerated. One patient developed 5-FU induced angina, which was confirmed by repeat administration of the drug.

Granulocytopenia was more frequent than thrombocytopenia; the lowest median granulocyte count was 900 cells/μl (range, 0–10 000) and the lowest median platelet count was 127 000/μl (range, 120 000–382 000).

Surgical complications included, one death due to suffocation immediately postoperatively as a result of a tracheal tear. 1 patient died 3 months following surgery as a result of chronic aspiration pneumonia. However, the common side effects included reflux oesophagitis and dumping syndrome which eventually diminished in severity. Symptomatic oesophageal anastomotic stricture requiring temporary endoscopic dilatations occurred in 4 patients. An anastomotic leak did not develop in any patient.

Chemoradiation therapy was well tolerated by patients in the resectable group; however, because of a longer therapy period, reversible grade 2 or less than grade 2 mucositis, diarrhoea, and dermatitis developed in most of the patients in the unresectable group between the 4th and 6th weeks of therapy. 1 patient had significant exacerbation of neuropathy, which diminished with time.

Table 3. Non-haematological toxic effects of 5-FU and cisplatin

	Grade* (%)		
Toxic effects	1	2	3
Mucositis	25	50	25
Nausea and vomiting	5	60	10
Diarrhoea	5	30	5
Malaise	10	20	10
Neuropathy	—	15	10
Infections	—	—	35

*See reference 30.

DISCUSSION

Because the uncontrolled primary carcinoma frequently results in complications leading to the patients' demise, adequate control of localised carcinoma has been the dominant strategy used in the treatment of carcinoma of the oesophagus. The primary carcinoma appears to respond best to chemoradiation therapy. For example, the complete pathological responses have been more frequent (up to 30%) in studies that have used preoperative chemoradiation therapy [15, 17, 18] than those that have used only preoperative chemotherapy [12–14,36]. Nonetheless, preoperative methods of treatment appear to facilitate resection and also provide effective palliation. Definitive chemoradiation therapy has been used to eliminate the need for resection with success in some patients [20–22, 37] and appears most successful in early stages of this carcinoma. The durations of median survival reported in these trials have been similar whether patients received chemoradiation or radiotherapy alone [12–22]. Similar experience exists with preoperative radiotherapy [38].

Frequent development of metastatic disease in patients who have failed to respond to preoperative chemotherapy or definitive chemoradiation therapy programs is evident [22, 36]. In a study by Leichman *et al.*, utilising definitive chemoradiation therapy for patients with potentially resectable tumours resulted in the development of metastatic disease in 10 out of 20 patients, with a median survival time of 22 months for all patients [22]. Similarly, 29 patients with resectable carcinoma received preoperative chemotherapy; 7 out of 9 patients who failed had distant metastases [36]. Therefore, it is reasonable to consider that therapeutic strategies should include adequate treatments to control both localised and metastatic carcinoma. One or two courses of chemotherapy has not resulted in substantial gains in survival rates [12, 13, 16, 17] and could be considered inadequate. Equally important is the issue of toxicities and mortality associated with prolonged therapy [16, 22, 36].

We elected to administer six courses of chemotherapy with 5-fluorouracil and cisplatin. The number of courses was limited to six in our trial design predominantly due to the anticipation of dose-limiting neurotoxicity of cisplatin in this age group after the cumulative dose of 600 mg/m^2. A response in 21 (66%) out of 32 patients was achieved after two courses of chemotherapy, which is similar to that reported previously [14, 39]. Patients could tolerate prolonged chemotherapy as was evidenced by the median number of chemotherapy courses, which was five. Complete pathologic responses in 2 patients and microscopic carcinoma in five specimens from chemotherapy alone suggests its potential usefulness in the future. Admittedly, a small number of patients are presented in our pilot study, however, curative resection rate of >90% with >70% of specimens with negative lymph nodes remains an interesting and encouraging finding. In conclusion, a strategy involving prolonged chemotherapy to

control the primary as well as the metastatic carcinomas is feasible and should be studied further in patients who present with localised squamous cell carcinoma of the oesophagus.

All trials utilising chemotherapy in the treatment of localised carcinoma of the oesophagus, including ours, are pilot in nature [12–22, 35, 36] and controlled trials are necessary to determine its impact on patient survival. A prospective randomized trial comparing surgery versus chemotherapy (5-FU plus cisplatin) and surgery is now underway in the USA to determine the value of chemotherapy on patient survival.

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