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Feasibility of Five Courses of Pre-operative Chemotherapy in Patients with Resectable Adenocarcinoma of the Oesophagus or Gastrooesophageal Junction

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The purpose of this study was to examine the feasibility of administering all chemotherapy pre-operatively to patients with resectable adenocarcinoma of the oesophagus or gastrooesophageal junction. 32 patients with potentially resectable adenocarcinoma of the oesophagus or gastrooesophageal junction were studied in a stepwise fashion in which combination chemotherapy with cisplatin, high-dose arabinoside and 5-fluorouracil was administered. In the first part, 15 patients were to receive three chemotherapy courses pre-operatively and two chemotherapy courses postoperatively. In the second part, the next 15 patients were to receive all five chemotherapy courses pre-operatively, provided there was an objective response after three courses. Endoscopic ultrasonography was also performed, when feasible, prior to chemotherapy and surgery, and in some patients sequentially between chemotherapy courses. All of the 14 assessable patients in the first group tolerated all three courses of pre-operative chemotherapy, and 86% of patients in this group completed all protocol chemotherapy. In the second group, 9 of 18 (50%) assessable patients tolerated all five courses of preoperative chemotherapy, and 100% of patients in this group received all protocol chemotherapy. The median number of chemotherapy courses for the entire group (32 patients) was five (range one to five). Forty-one per cent (13/32) of patients had a major response to chemotherapy. Sixty-nine per cent (or 76% of 29 patients taken to surgery) had a curative resection. One patient had a pathological complete response. The median survival time of 32 patients was 17 months (range 2–36+ months). 14 patients (37%) remain alive at a median follow-up time of 26+ months. There was a correlation between endoscopic ultrasonographic tumour and nodal stage and pathological tumour and nodal stages in 16 patients. The tumour stage correlation was higher (75%) than the nodal stage correlation (62%). Our data suggest that it is feasible to administer five courses of cisplatin-based chemotherapy to patients with potentially resectable adenocarcinoma of the oesophagus or gastrooesophageal junction. More effective chemotherapy regimens that might result in higher pathological complete response rates and acceptable toxic effects are needed.

Key words: cancer of the oesophagus, pre-operative chemotherapy
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INTRODUCTION

AN INCREASE in the incidence of adenocarcinoma of the oesophagus and gastrooesophageal junction has been reported in the U.S.A. as well as in Europe [1–6], but the reason for this is unknown. Adenocarcinoma of the oesophagus and gastrooesophageal junction afflicts younger individuals, predominantly Caucasian males, including those who do not abuse alcohol or tobacco. The prognosis of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction remains poor [7]. Most patients with local-regional carcinoma die because of the development of subsequent metastases or locally progressive carcinoma despite initial 'curative' resection or radiotherapy [8–10]. Although effective chemotherapy could prolong survival and increase cure rates, a standard has yet to be established. Recently, patients receiving definitive chemoradiotherapy were shown to have a modestly longer survival than those receiving only radiotherapy [11]. However, these results could not be generalised to all patients with the adenocarcinoma histological type as there were only a few such patients treated in that entire trial.

The clinical staging system for oesophageal and gastrooeso-

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phageal junction carcinoma has remained imprecise. However, endoscopic ultrasonography has provided new insights into the assessment of T (tumour) and N (nodal) stages [12–14]. The published data suggest a higher accuracy in predicting T penetration of the oesophageal wall than in predicting the N involvement [15]. Whether the results of endoscopic ultrasonography can influence therapeutic decisions is debatable, but continued investigation of this technology is warranted. In the current study, we evaluated patients with endoscopic ultrasonography prior to surgery as well as sequentially during chemotherapy in some patients.

We have previously speculated regarding the potential benefit of pre-operative chemotherapy [16–19]; preclinical investigations suggest that there is a benefit [20, 21]. Our goal has been to develop a pre-operative chemotherapy regimen that would result in a pathological complete response in 5–10% of specimens. The hypothesis, based on results obtained in breast and ovarian cancer, is that such a regimen could effectively prolong survival by eliminating or delaying appearance of micrometastases. Our previously studied regimens have not satisfied this objective [17, 18]. For this pilot study, we chose the combination of 5-fluorouracil, cisplatin and high-dose arabinoside. The choice of this combination was based on demonstrated preclinical synergism between cisplatin and high-dose arabinoside [22, 23]. In addition, the combination of arabinoside and cisplatin was reported to be active in patients with pancreatic carcinoma [24]. Similarly, preclinical synergism between 5-fluorouracil and cisplatin has been reported [25, 26].

Our prior experience with patients with upper gastrointestinal carcinoma suggests that postoperative chemotherapy is more toxic [16–19]. The reason for poor tolerance is unclear, but might be related to patients' poor nutritional status, weight loss, impact of a major surgical procedure, associated complications and emotional difficulties. We, therefore, studied the feasibility of administering all chemotherapy pre-operatively and omitting postoperative chemotherapy.

PATIENTS AND METHODS

Patient selection and evaluation

Patients with biopsy-proven adenocarcinoma of the oesophagus or gastrooesophageal junction with or without regional lymph node involvement were eligible. Patients were excluded if they had distant metastases. Patients had to be 18 years or older, and were required to have a performance status of 2 or less by the Zubrod scale [27], a serum creatinine level less than 1.5 mg/dl, a serum bilirubin level less than 1.6 mg/dl, an absolute granulocyte count of more than 1500 cells/μl and a platelet count of more than 100 000/μl. All patients gave informed consent. Before enrolment in the study, patients were jointly evaluated by a thoracic surgeon and medical oncologist to ensure that each patient was medically fit and that the tumour was potentially resectable.

Patients who had not had any prior surgery, chemotherapy or radiotherapy were eligible. Patients were excluded if they had a concurrent malignancy or malignancy in the previous 5 years, except for non-melanomatous skin or cervical carcinomas. The presence of malignant supraclavicular adenopathy, malignant effusions or histological evidence of tracheobronchial invasion made patients ineligible. Characteristics that rendered patients inoperable included forced vital capacity in the first second (FEV_1) less than 1.2 l and cardiac disability class III or IV as determined by criteria established by the New York Heart Association.

Prior to registration, all patients had the following tests: complete blood differential and platelet counts; electrolytes, including serum magnesium level; SMA-12; serum carcinoembryonic antigen level; chest radiograph; computed tomography of the abdomen and chest; upper gastrointestinal endoscopy; double-contrast upper gastrointestinal radiography; and, in patients with cancers at or above the carina, bronchoscopy. Sequential endoscopic oesophageal ultrasonography was performed, when feasible; patients with obstructing lesions did not undergo ultrasonography.

Study design

The objective was to administer three courses of pre-operative chemotherapy to the first 15 patients and, if well tolerated, to then administer all five courses of chemotherapy pre-operatively to the next 15 patients. There had to be stable or reduced tumour size after one course of pre-operative chemotherapy for patients to receive two additional courses. Patients who were to receive all five courses of chemotherapy pre-operatively had to show evidence of response following the first three courses. Patients who had only stable disease after three courses of chemotherapy and patients who demonstrated any evidence of progressive carcinoma at any time during the course of pre-operative chemotherapy immediately underwent an attempted surgical resection.

Pre-operative therapy

Chemotherapy consisted of 5-fluorouracil (1250 mg/m^2) over 24 h on days 1–3; cisplatin (30 mg/m^2) over 24 h on days 1–3 and arabinoside (1800 mg/m^2) every 12 h twice on day 3. Patients received continuous hydration and anti-emetic support. All patients were hospitalised for the first course of chemotherapy, but some patients received subsequent chemotherapy as outpatients. Chemotherapy courses were repeated every 28 days, provided patients had recovered from all toxic effects. For grade 3 non-haematological or grade 4 haematological toxicities, the dose was reduced by 20%, and for grade ≤ 1 non-haematological toxicities, the dose was increased by 20%.

During chemotherapy, complete blood, differential and platelet counts were monitored at least three times a week; they were monitored daily when patients developed grade 4 haematological toxic effects until recovery to at least grade 2 was documented.

Postoperative chemotherapy

Of the first 15 patients who had a maximum of three courses of pre-operative chemotherapy, any patient who demonstrated an objective response to pre-operative chemotherapy was given two cycles of postoperative chemotherapy. The postoperative chemotherapy drugs, doses and schedule were the same as for pre-operative chemotherapy.

Surgery

The method of oesophagectomy was at the discretion of the thoracic surgeon. Both intrathoracic anastomoses (Lewis-type oesophagectomy) and cervical anastomoses (transhiatal oesophagectomy, total thoracic oesophagectomy) were performed [28]. Staging was performed with node dissection. During surgery, a feeding jejunostomy tube was placed.

Endoscopic ultrasonography

Endoscopic ultrasonographic evaluations, previously described [29], were performed using the Olympus EUM-3 endoscopic ultrasound system. The ultrasonographic images were printed out as part of the permanent patient record and were saved on electromagnetic media.

Response and toxicity criteria

A barium oesophagogram was repeated after the first course (and after the third course in patients receiving all five courses of chemotherapy pre-operatively). Oesophagoscopy, barium oesophagogram, computed tomography of the chest and abdomen, chest radiograph, and all blood tests were repeated after the last course of chemotherapy prior to surgery.

An objective evidence of response to chemotherapy was used only as a guideline for continuing pre-operative chemotherapy. Because of the frequent lack of a bidimensionally measurable tumour, all standard solid tumour therapy-induced response criteria can not be applied to the primary upper gastrointestinal tumours.

Response criteria were as described previously [17, 18]. Briefly, complete pathological response was defined as an absence of carcinoma cells in the resected specimen; complete clinical response required an absence of carcinoma cells in the endoscopic biopsy and cytologic specimens, major response consisted of a marked reduction in the tumour bulk by oesophagogram as determined by two or more observers, and minor response, a minimal objective regression of carcinoma by oesophagogram or computed tomography. Thus, responses were judged by oesophagogram and the use of computer tomography as well as endoscopic findings. Chemotherapy-induced toxic reactions were graded according to the criteria developed at our institution [30]. Curative resection was defined as microscopically negative proximal, distal and radial margins.

Follow-up

Studies during follow-up visits included chest radiographs, complete blood count, SMA-12, electrolytes, magnesium level and barium swallow alternating with oesophagoscopy. A chest radiograph was obtained at every visit. Follow-up chest and abdominal computerised tomographic images were obtained 3 months following the completion of all therapy, and then only if clinically indicated (i.e. in cases of abnormal liver function studies, unexplained weight loss, rising CEA levels or specific symptoms). Patients were seen every 3 months for the first year following completion of all therapy, then every 6 months.

RESULTS

34 patients were enrolled on this study over 16 months. Patients' characteristics are listed in Table 1.

2 patients were considered not assessable. One had documented metastatic disease and had been erroneously registered; this patient was not treated according to protocol. The other was registered, but refused any chemotherapy; he is alive and disease-free following surgery (23+ months). 32 patients were treated according to the protocol. The median number of courses administered to all patients was five (range one to five) and the total number of courses was 126. In 73 (58%) of courses, the dose of all chemotherapeutic agents had to be reduced by 20% based on predefined toxicity criteria. Thus, the median doses in all patients was 80% of the starting doses. Only 1 patient tolerated a dose escalation of 20% above the starting dose for one course.

Table 1. Patients' characteristics

Total no. of patients	34	
No. assessable	32	
No. of males	32	
Median age, years (range)	59	(43–69)
Median performance status (range)	1	(0–1)
Median % weight loss (range)	2	(0–19)

Of the 14 assessable patients from the first group of 15, all received three pre-operative chemotherapy courses. 2 responding patients in this group refused postoperative chemotherapy; 4 did not receive postoperative therapy because their tumours did not respond to pre-operative chemotherapy and the remaining 8 received two postoperative chemotherapy courses. Thus, 86% of patients in this group completed therapy according to the protocol.

18 of 19 patients in the second group, who were to receive all chemotherapy pre-operatively, were assessable. 9 responding patients received all five courses of chemotherapy pre-operatively; 1 patient received only three courses of pre-operative chemotherapy because there was no change in the carcinoma; 8 patients had progressive carcinoma (2 after one course, 3 after two courses and 3 patients after three courses). None of the patients refused to continue pre-operative chemotherapy. Thus, 100% of patients in this group completed chemotherapy according to the protocol. Fifty per cent of patients in this group received all five courses pre-operatively; this being solely dictated by response to chemotherapy.

For the entire group of 32 patients, 93% received all therapy according to the protocol.

Response to chemotherapy was evaluated after the first, third and fifth (or the last) course of pre-operative chemotherapy, but it was designated only after the last course of pre-operative chemotherapy. All responses were jointly evaluated by two or more observers, and were based on barium swallow, computed tomography, and endoscopy data.

13 (41%) of 32 evaluable patients achieved a major response. 4 of 14 assessable patients in the first group achieved a major response, whereas 9 of 18 assessable patients in the second group (in which patients received all chemotherapy prior to surgery) achieved a major response. 3 (9%) of 32 patients had no malignant cells in the repeat biopsy or cytology specimens, qualifying as having a complete clinical response.

4 (13%) patients had minor objective responses, 9 had progressive disease while on chemotherapy and 6 had stable carcinoma.

Surgery results and surgical pathology

29 (91%) of 32 patients underwent surgery. 3 patients did not undergo surgery because they developed skin metastases (1 patient), supraclavicular metastases (1 patient) or rapid local progression with the development of mediastinal metastases (1 patient). 17 patients had an Ivor–Lewis procedure performed, 4 patients had intrathoracic total oesophagectomy and 5 patients had transhiatal oesophagectomy. 22 (69% of all 32 patients or 76% of 29 patients undergoing surgery) had a curative resection. Among 14 patients who had maximum of three courses of pre-operative chemotherapy, 11 had a curative resection; among 18 patients who were to receive all chemotherapy pre-operatively, 11 had a curative resection; however, 7 of 9 patients who actually received all chemotherapy pre-operatively had a curative resection. The numbers are too small in each group for a meaningful comparison. One patient who had received three courses of chemotherapy pre-operatively had a pathological complete response (3%) and 24 (75%) tumours were either T3 or T4. 7 patients had incomplete resection, among these 2 patients were found to have liver metastases at laparotomy and did not undergo resection. 5 patients had positive resection

margins and underwent postoperative radiotherapy (between 50 and 55 Gy).

Results of endoscopic ultrasonography

Since endoscopic ultrasonography was performed only when feasible, 23 patients had endosonography prior to starting chemotherapy. 16 of 29 patients who underwent surgery (55%) had endosonography prior to surgery. The endosonographic T and N stages were compared with histopathological T and N stages of the resected specimen. There was a 75% concordance between the endosonographic T stage and histopathological T stage. In 6% of cases, there was an overestimation of T stage by endosonography, whereas in 19% of cases, endosonography underestimated the pathological findings of T stage. There was a 62% concordance between the endosonographic N stage and histopathological N stage. In 25% of cases, there was an overestimation of N stage by endosonography, whereas in 13% of cases, endosonography underestimated the pathological findings of N stage. Data on sequential endosonography following pre-operative chemotherapy for evaluation of response to chemotherapy are under review and will be reported separately. One patient who had a pathological complete response had a tumour volume reduction on subsequent endosonographies, but the T stage and N stage remained unchanged, thus there was an overestimation of the pathological stage (Figure 1a,b).

Survival

The median follow-up time for the entire group of 32 patients now exceeds 24 months (range 17+ to 36+ months). 14 patients remain alive and their median follow-up is 26+ months. The median survival of the entire group is 17 months (range 2–36+ months; Figure 2). The 22 patients who had a curative resection survived longer than the 10 patients who did not have a curative resection.

Among the 14 living patients, 10 remain without any evidence of cancer (minimum follow-up time is 17+ months); 4 patients have relapsed (1 with local-regional relapse only, 1 with distant metastases and local-regional relapse and 2 with metastatic carcinoma).

Carcinoma was the cause of death in 17 patients; 1 patient died of myocardial infarction following surgery. For the entire group of 21 who experienced relapse (as 1 died postoperatively without any evidence of disease), the initial sites of relapse were local-regional in 2 patients, local-regional with metastatic carcinoma in 7 and metastatic carcinoma only in 12. The most common sites of metastases include liver, lung, bone and skin.

Toxic effects

One death was directly related to the protocol therapy, the patient died of a massive myocardial infarction following surgical resection.

Toxic effects of chemotherapy. Haematological toxicity was significant with this regimen. Thrombocytopenia dominated. The median nadir platelet count was 36000/μl (range 5000–254000/μl) and the median nadir granulocyte count was 400 cells/μl (range 0–4900 cells/μl). Thus, at least 50% of patients had grade 4 leucopenia and thrombocytopenia. Haematological toxicity peaked on day 14 and patients recovered by day 25.

Non-haematological toxicity has been summarised in Table 2. The main toxic effects were nausea and vomiting, which occurred in virtually all patients and all courses. Nausea and vomiting typically occurred following the second dose of arabinoside and tapered off in 2 or 3 days. 7 patients were hospitalised on nine occasions for the management of chemotherapy-related complications; 6 admissions were directly related to fever during neutropenia. Infrequent and minor toxic effects included skin rash, anorexia, mild hypotension, stomatitis, peripheral neuropathy and malaise.

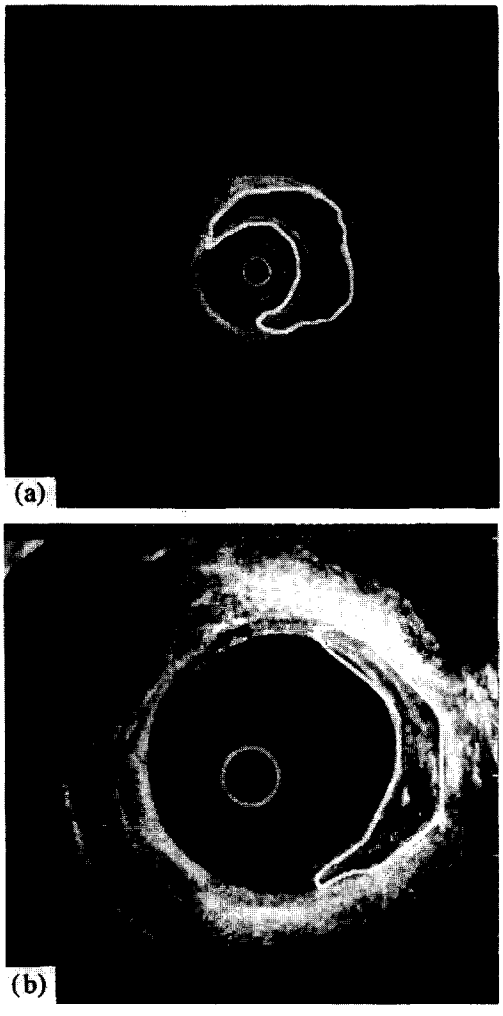

Figure 1. (a) Endoscopic ultrasonograph of patient designated as having a bulky T3N1 lesion prior to chemotherapy. (b) Endoscopic ultrasonograph of the same patient after chemotherapy and prior to surgery showing reduction in the tumour volume. However, T and N stages remained unchanged (T3). By histopathological criteria, this was a T0N0 lesion.

Complications of surgery. Complications related to surgery included the death already mentioned, which was due to a massive myocardial infarction on the 14th postoperative day, but the most common complications included dumping syndrome in 7 patients and anastomotic stricture formation requiring periodic endoscopic dilatation in 4 patients. Other complications included pneumothorax, haemorrhage, wound infection and dehiscence in 1 case each.

DISCUSSION

The administration of all chemotherapy before surgery in patients with potentially resectable upper gastrointestinal tumours has conceptual appeal. The basis for this strategy has been discussed previously [17, 18, 31]. Although the concept of pre-operative chemotherapy is strengthened by the demon-

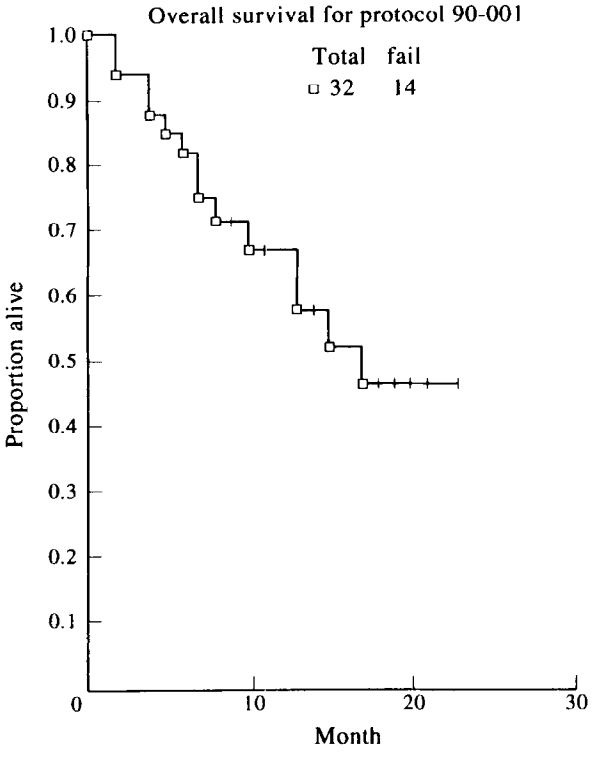

Figure 2. Kaplan–Meier survival plot of all 32 patients. The median survival duration was 17 months (range 2–36+ months).

*Table 2. Number of patients with non-haematological toxic effects**

Toxic effects	Grade 1	Grade 2	Grade 3	Grade 4
Malaise	9	12	0	0
Nausea and vomiting	8	20	4	
Infection	0	0	0	6
Mucositis	0	2	0	0
Hypotension	0	2	0	0
Dermatitis	0	5	0	0

* In some categories, toxicity data are missing in some patients.

strated benefits in the preclinical *in vivo* studies [20, 21], it is acknowledged that there is no proof of benefit to patients. Only controlled randomised trials could resolve this issue. Nevertheless, if one accepts that pre-operative therapy is worthy of further investigation, then it might be advantageous to give all systemic therapy pre-operatively. The rate of pathological complete response could conceivably increase if the responding tumours were repeatedly exposed to chemotherapy; patient compliance and tolerance might be better prior to surgery, thus allowing the administration of chemotherapy without interruption. Another potential benefit to administering all chemotherapy pre-operatively is a reduction in the size of the primary tumour that could improve the odds for curative resection.

Our data suggest that it is feasible to safely administer up to five cisplatin-based chemotherapy courses in patients with potentially resectable adenocarcinoma of the lower oesophagus or gastrooesophageal junction. We had previously found that three postoperative chemotherapy courses were associated with lower level of patient compliance and higher toxic effects for reasons that are not entirely clear [17, 18]. More recently, in patients with gastric carcinoma, we found three courses of pre-operative chemotherapy to be feasible, thus reducing the number of postoperative chemotherapy courses [19]. The ongoing Intergroup trial for carcinoma of the oesophagus also uses three pre-operative and two postoperative courses of chemotherapy. In the trial described here, one of our goals was to administer five courses of pre-operative chemotherapy. We proceeded in a stepwise fashion to administer three courses of pre-operative chemotherapy to the first 15 patients. The tolerance of three courses of chemotherapy in 14 evaluable patients in this group was satisfactory, and 86% patients completed therapy according to the protocol. Thus, in the next 19 patients, we aimed to administer all chemotherapy prior to surgery. In this group, 100% of patients received therapy according to the protocol, indicating strongly its feasibility.

If currently available systemic chemotherapy has only a modest effect on adenocarcinoma of the oesophagus and gastrooesophageal junction, then any strategy will prove ineffective. An objective clinical response to chemotherapy was used as the guideline for further pre-operative chemotherapy. We believe that the biological activity of effective chemotherapy, in this setting, will only be demonstrated by the rate of pathological complete response. In this respect, the regimen of 5-fluorouracil, cisplatin and arabinoside has only modest activity in this disease. The overall response rate was 41% which is not much different from that of other regimens we have studied [17, 18], and we observed only one pathological complete response. This regimen does not fulfil our criteria of effectiveness, that is, capable of producing a 5–10% complete pathological response. Nevertheless, except for thrombocytopenia, this regimen was generally well tolerated. Approximately 37% of patients remain alive at the median follow-up time of 26+ months. Although this observation is encouraging, further follow-up is necessary. Since the historical curative resection rate in this group of patients is approximately 55%, the curative resection rate achieved in this trial (69%) suggests that pre-operative chemotherapy strategies need to be pursued further. In our trial, there was no obvious adverse effect of pre-operative chemotherapy on patient survival and surgical morbidity, however, only controlled clinical trials can resolve this issue.

Our data on endoscopic ultrasonography suggest that it is a useful tool for pre-operative staging of carcinoma of the oesophagus or gastrooesophageal junction. It enhances clinical staging by predicting pathological staging in 67–75% of cases. With wider application of this technology, it might become useful in stratifying patients (according to T and N stages) in future randomised studies. The value of endosonography in determining resectability of the primary tumour is still questionable, and further investigation in this area is warranted. In quantifying response to therapy, the role of endosonography, namely conventional double-contrast barium studies, endoscopic observations and computerised tomographic scans, remains unclear. The studies may prove to be complementary. With endosonography, we have seen tumour volume reduction without apparent change in either T or N stage. This is exemplified by 1 patient in whom a pathological complete response was documented. By serial endosonography, a large T3 carcinoma at baseline examination appeared to be a smaller T3 carcinoma following chemotherapy (Figure 1a,b), and a histopathological examination showed the tumour to be a T0 lesion. However, one must study a larger number of patients for definitive conclusions.

Research using newer strategies and technologies continues to expand for patients with adenocarcinoma of the oesophagus and gastrooesophageal junction. Pre-operative chemotherapy, pre-

operative chemoradiotherapy, definitive chemoradiotherapy and a number of palliative methods are being investigated by various groups. Because of the systemic nature of this disease, chemotherapy is likely to play a dominant role in the treatment of these patients, but an effective chemotherapy regimen is not yet known. One of the most urgent research priorities in this disease is the development of such a regimen. New active agents are urgently needed to produce a survival benefit for patients with this cancer.

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