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RESEARCH ARTICLES

Long-term results of neoadjuvant chemotherapy and combined chemoradiotherapy before surgery in the management of locally advanced oesophageal cancer: a single-centre experience

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Abstract
Introduction Neoadjuvant chemoradiotherapy before surgery is an option in the treatment of locally advanced resectable oesophageal cancer (EC). However toxicity is substantial and the improvement in overall survival (OS) with this approach is controversial.
Methods This was a prospective, single-centre study of neoadjuvant chemotherapy and concomitant chemoradiotherapy with CDDP and 5-FU and 50.4 Gy of external radiotherapy before possible radical surgery in patients with locally advanced resectable EC. If surgery was not possible, a second-phase radiotherapy boost of 10 Gy and one cycle of modified dose chemotherapy were used.
Results Seventy-three patients included between 1998 and 2007: 96% males, median age 61, 83% squamous cell carcinomas, 23% lower third tumours, 36% stage II and 54% stage III and 47% local lymph node involvement. Eighty-six percent completed the combined protocol. Main grade 3–4 toxicities: mucositis (19%) and infections (8%); 4 toxic deaths. Clinical response rates: complete response 54%, partial response 27%, stable disease 8%. Twenty-five patients proceeded to surgery, with radical resection in 24. Pathological response rate: complete response 32%, partial response 52%, progression 16%. There were 7 postoperative deaths and 16 of 34 patients that did not have surgery received the second-phase RT boost. Survival analysis: Median follow-up of 64 months (range 6–134 months). Median OS of 10.33 months. 2-year and 5-year OS of 22 and 16%. The only significant prognostic factor in OS is the clinical complete response rate: 13.9 vs. 7.7 months (p=0.0049).
Conclusions Our protocol offers a high rate of clinical activity although it is relatively toxic and seems to increase the postoperative mortality, which would blunt any small improvement in survival. The achievement of a complete response is a powerful prognostic factor.

Keywords Oesophageal cancer · Adenocarcinoma · Chemotherapy · Radiotherapy

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Introduction

Oesophageal cancer (EC) remains a significant treatment challenge worldwide. Although classically squamous cell carcinoma (SCC) was the most frequent type seen, the inci-

dence of oesophageal adenocarcinoma has increased steadily in the last thirty years and has even surpassed SCC in some parts of the world [1, 2]. The pathogenesis of both subtypes is probably different and will be clarified in the future. It is a highly lethal malignancy and it is usually diagnosed at locally advanced or metastatic stages in both subtypes [1].

Treatment is largely unsatisfactory in most stages of the disease. Surgical resection alone offers good long-term results in very early presentations, a rare finding in this illness [3]. Results with exclusive radiotherapy are even poorer [4]. Due to these dismal results, different combinations of chemotherapy, radiotherapy and surgery (multimodality treatments) have been tried, with conflicting results. Neoadjuvant chemotherapy before surgery is an option, especially in adenocarcinomas of the lower oesophagus [5, 6]. Combined exclusive chemoradiotherapy offers the same long-term results as surgery alone and is an option in unresectable disease and in those unfit for surgery [7, 8]. A third attractive option is the use of neoadjuvant chemoradiotherapy followed by surgery, as there is evidence that it can improve the pathological response rate and increase the curative resection rate of the surgery; however, its benefit in improving survival is much more controversial and the toxicity of this approach can be substantial [9].

Against this background, we present our long-term results of our prospective programme of neoadjuvant chemotherapy and concomitant chemoradiotherapy before possible radical surgery in patients with locally advanced resectable EC of both histologies treated at our institution.

Material and methods

Between January 1998 and September 2007 we performed a prospective single-centre study of treatment with neoadjuvant chemotherapy and concomitant chemoradiotherapy before possible radical surgery in patients with locally advanced resectable EC. Both histologies, adenocarcinoma and SCC, were permitted. Patients had to be 18 years or older, with an adequate performance status (PS 0 or 1) and with no major cardiac, hepatic or renal comorbidity that would contraindicate combined chemoradiotherapy. Patients with stage II through to stage IVA according to the TNM criteria were eligible for inclusion in the protocol. All T1 to T3 and N1 tumours were considered potentially resectable, as well as some selected T4 tumours (pleura, pericardium and diaphragm invasion) and lower oesophageal tumours with positive coeliac lymph nodes (stage IVA). Staging was performed with endoscopy, chest X-ray, oesophagogram with double contrast, thoraco-abdominopelvic CT scan, bronchoscopy in upper and mid-oesophageal tumours, and if feasible oesophageal endoscopic ultrasound. In selected cases, laparoscopy could be performed. Pathological confirmation was mandatory in all cases.

Treatment was begun with one or, in some cases where there was a delay in the beginning of radiotherapy, two cycles of neoadjuvant chemotherapy of CDDP (100 mg/m^2 day 1) and 5-fluorouracil (1000 mg/m^2/24 h days 1–5). Twenty-one days later, radiotherapy was started with a standard fractionation regimen of once a day 1.8 Gy from Monday to Friday for a total dose of 50.4 Gy. The irradiated field included the primary tumour and if possible the proximal and distal margins up to 5–6 cm. Alongside this treatment, two cycles of modified concomitant chemotherapy every 28 days were given the first and last week of radiotherapy; the doses were CDDP 15 mg/m^2 days 1–5 for a total cycle dose of 75 mg/m^2 and 5-fluorouracil 800 mg/m^2/24 h days 1–5.

Three to four weeks after radiotherapy had finished, a new CT scan and endoscopy were done as re-staging procedures. All cases were discussed in our multidisciplinary meeting and the following part of the treatment plan was decided. If feasible, radical surgery was performed shortly afterwards. An Ivor-Lewis oesophagogastrectomy with an upper thoracic oesophagogastric anastomosis was the usual surgical technique employed. In those cases where it could not be done, a 10 Gy second-phase radiotherapy boost with a standard fractionation regimen was given alongside one cycle of modified chemotherapy, similar to the first-phase doses.

The primary objective of the study was the overall clinical response rate of the combined chemoradiotherapy protocol, according to the RECIST criteria. Other secondary objectives were the pathological response rate in the surgical specimens, the overall rate of surgical procedures performed, the toxicity of the neoadjuvant regimen and the overall survival (OS) of this group of patients. Toxicity was measured in four grades of increasing severity according to the CTC version 2 criteria. OS was measured from the date of diagnosis to the date of death or last follow-up. The product-limit method of Kaplan–Meier was used to define this measure of time. Comparisons of survival among groups were made by the log-rank test. Statistical significance was established with $p<0.05$. All statistical analyses were performed in April 2008. All calculations were done using the SPSS 11 software package (SPSS, Chicago, IL.)

Results

Descriptive analysis

Seventy-three patients were included between January 1998 and September 2007. The main patient and tumour characteristics are shown in Tables 1 and 2. Figure 1 shows a flow chart of the treatment protocol and the drop-out rate in each step of the process.

Neoadjuvant chemotherapy

All patients received this phase of the protocol. Fifty-four patients (75%) received 1 cycle of CT, while 19 (25%) received two cycles. The main toxicities observed are shown

Table 1 Patient characteristics

Clinical characteristic (*n*=73)	Frequency (%)
Age (years) [median (range)]	61 (44–80)
Male	96
Female	4
Smoking history	81
Moderate or severe alcohol intake	61
Hiatal hernia or oesophageal reflux history	10
History of Barret's oesophagus	3
Dysphagia as initial complaint	85
Constitutional symptoms	26
Weight loss >10% of previous weight	26
History of previous malignant tumours	10
Head and neck tumours	4
Breast cancer	2
Colon cancer	2
Non-small cell lung cancer	2

Table 2 Tumour characteristics

Tumour characteristic (*n*=73)	Frequency (%)
Histology	
Squamous cell carcinoma	83
Adenocarcinoma	17
Tumour location	
Upper third	27
Mid third	50
Lower third	23
Gastric involvement	13
Clinical T stage	
T1/T2/T3/T4/TX	4/13/45/30/8
Clinical N stage	
N0/N1/NX	51/47/3
M1a (positive celiac lymph nodes in lower third tumours)	4
Clinical stage*	
Stage II	36
Stage III	54
Stage IV	4
Stage X	6

*CT scan, oesophagogram and endoscopy in all patients; endoscopic ultrasound could be performed in 10% of patients

in Table 3. The most frequent grade 3–4 toxicities were mucositis and emesis (both in 9% of patients). Of note, 1 case of grade 4 renal failure and 1 case of grade 3 cerebellar ataxia were seen. Two early deaths were observed: a case of septic shock in the setting of grade 4 neutropenia and a case of early intestinal ischaemia.

Combined chemoradiotherapy

Sixty-three patients (87%) received this phase of treatment. The main reasons for not starting radiotherapy are shown in Fig. 1. The main toxicities observed are shown in Table 3. The most frequent grade 3–4 toxicities were mucositis (19% of patients) and thrombocytopenia (11% of patients). Most patients received 2 cycles (48 patients, 76%) of concomitant chemotherapy, while 12 (19%) and 3 (5%) patients were given 1 and 3 cycles respectively. The total radiotherapy dose of 50.4 Gy was reached in 56 patients (89%). Four deaths were observed in this phase: 2 deaths in the setting of infection and grade 4 mucositis and neutropenia, and 2 cardiovascular deaths (a stroke and an episode of myocardial ischaemia).

The re-staging evaluation was done with CT scan and endoscopy and oesophageal biopsy in most patients (47 patients, 75%); in the remaining patients only a CT scan was performed. The clinical response rates observed are shown in Table 4.

Surgery

Surgery with radical intent was performed in 25 patients (34% of the entire cohort) out of 59 eligible patients after the combined treatment phase. The main reasons for not proceeding to surgery are shown in Fig. 1. In 9 patients, the tumour had progressed or was deemed unresectable in the new evaluation, while in 4 patients the vicinity of the tumour to the cricho-pharyngeal muscle did not favour a surgical approach due to the high risk of leakage from the cervical anastomosis. In the rest of cases, a combination of a poor state of health and advanced biological age usually precluded the surgical intervention.

Surgery was considered radical by the operating team in 24 cases; in only one case the tumour was found to be unresectable and a palliative resection was performed. The

Table 3 Main toxicity of the preoperative combined regimen

Toxicity	Neoadjuvant CT (%)				Combined CT-RT (%)			
	G1	G2	G3	G4	G1	G2	G3	G4
Neutropenia	10	4	6	2	16	9	2	5
Anaemia	9	4	2	2	7	10	2	5
Thrombocytopenia	0	0	4	2	0	2	9	2
Nausea and vomiting	12	18	9	0	12	19	5	0
Diarrhoea	3	4	2	0	0	5	5	2
Mucositis	4	9	7	2	3	9	14	5
Infection	0	0	2	2	2	2	5	3

Table 4 Clinical response rates

Clinical response	Frequency (%)
Complete response	34 (54)
Partial response	17 (27)
Stable disease	5 (8)
Disease progression	5 (8)
Not evaluated	2 (3)

Table 5 Pathological response rates

Pathological response	Frequency (%)
Complete response	8 (32)
Microscopic partial response	8 (32)
Macroscopic partial response	5 (20)
Disease progression	4 (16)

pathological response rates are shown in Table 5. However, 7 deaths were seen in the early 30-day postoperative period, with two episodes of late anastomotic leakage; the remaining five deaths were secondary to postoperative respiratory failure in the setting of nosocomial pulmonary infection.

Second-phase combined chemoradiotherapy

In the 34 patients that did not proceed to surgery, 16 patients received the 10-Gy radiotherapy boost. Nine of those received 1 cycle of modified dose chemotherapy. The remaining patients did not receive this phase, usually due to poor general status. This phase was usually well tolerated, with only one episode of grade 3 mucositis; no other grade 3 or 4 toxicity was seen. Clinical evaluation after this phase showed a complete response in 11 of the 16 patients and a partial response in 1 patient; however 4 patients had progressed in an early fashion.

Survival analysis

All 73 patients were included in the survival analysis. Median follow-up is 64 months (range 6–134 months). Median OS is 10.33 months (Fig. 2). The 2-year and 5-year survival rates are 22% and 16% respectively. No differences in median OS were seen according to age (with a cut-off age of 70 years), sex, histology, use of one or more

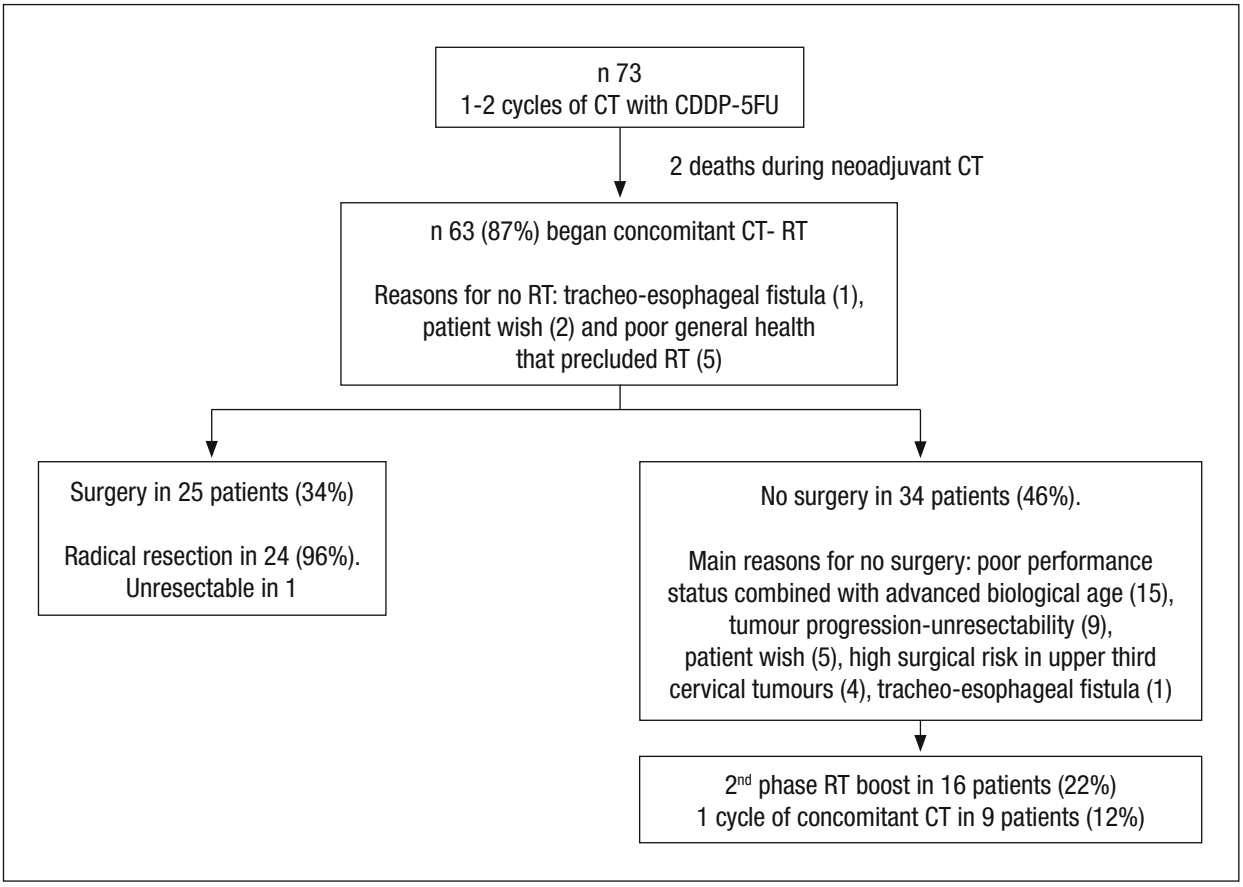

Fig. 1 Flow-chart of the treatment protocol
CT, chemotherapy

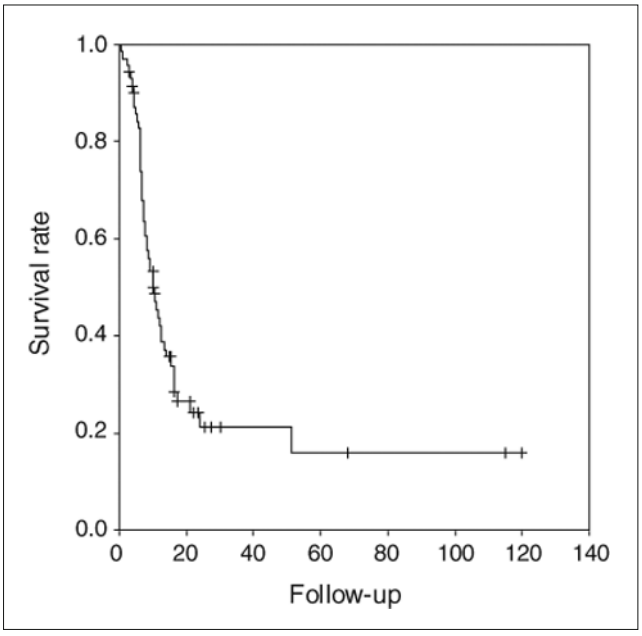

Fig. 2 Overall survival (OS) of the series (median OS of 10.3 months)

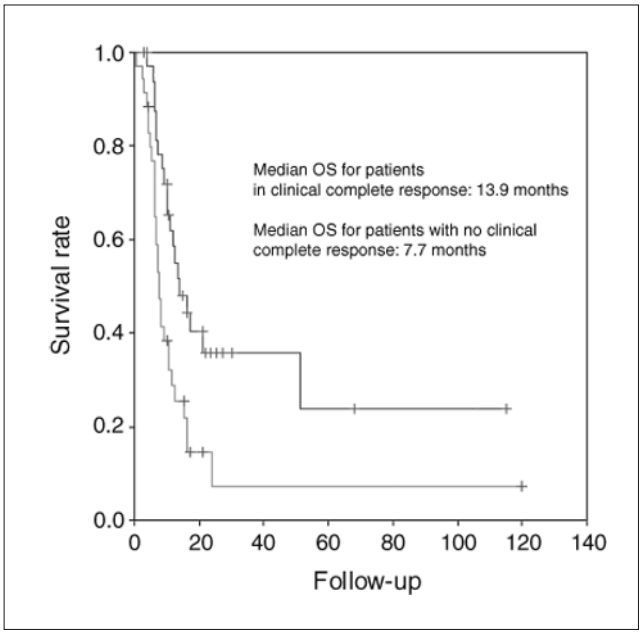

Fig. 3 OS curves according to the complete clinical response rate

cycles of neoadjuvant chemotherapy, surgical intervention, stage or tumour location. The only significant factor was the achievement of a clinical complete response (Fig. 3), with a median OS of 13.9 months for those with a complete response vs. 7.7 months for those that do not reach it (p=0.0049)

Discussion

EC is an uncommon but highly lethal malignancy, responsible for nearly 14000 deaths in the United States in 2007; almost 90% of patients diagnosed with EC will ultimately die of the disease [1]. This risk of death is clearly related to stage at presentation, with virtually no long-term survivors in those patients that present with metastatic disease. However, even in those patients with localised disease, only one-third are alive at 5 years [1]. SCC, usually of the upper and mid-oesophagus, remains the most frequent subtype worldwide, although in the western world, especially in the United States, the incidence of adenocarcinoma of the oesophagus and of the gastrooesophageal junction has increased steadily by a rate of 20% per year, surpassing the incidence of squamous carcinoma in the last few years [2]. The pathogenesis of both subtypes is probably different, with the squamous carcinomas linked to heavy alcohol and tobacco consumption, whereas the adenocarcinomas are associated rather with a previous history of oesophageal reflux disorder and Barret's oesophagus [10]. Despite these differing risk factors, most trials of EC have included both histologies, with a predominance of squamous cancers in the early trials, although more recent studies have been more balanced in accrual of both tumour types.

Our series of 73 patients was fairly representative of patients with EC in our clinical practice. There was a clear four-to-one predominance of squamous cell tumours and almost 80% of tumours were upper or midoesophageal. Most patients were male and 10% had a previous history of malignant disease, most notably head and neck squamous cell cancers. Many were or had been heavy drinkers and smokers. Staging revealed local lymph node involvement in almost half of patients and a third presented with T4 disease, typical of the usually late diagnosis of this neoplasm. However, clinical staging was usually performed with a multi-slice CT scan which, although a fair indicator of distant metastases, shows a lower sensitivity and specificity in the T and N staging, especially in the differentiation of T1-T2 vs. T3-T4 disease and most fundamentally in the diagnosis of lymph node involvement, with an accuracy of less than 70% [11, 12]. Endoscopic ultrasonography could be performed in only 10 patients of our study. Thus, staging bias cannot be excluded; of note, clinical staging was not a predictive factor in our survival analysis. Clearly, endoscopic ultrasound is the non-invasive staging procedure of choice, with an accuracy of around 85–90% [12, 13]. However, the main problem with endoscopic ultrasound is failure to pass through the stricture leading to an incomplete assessment of the tumour [14]. The poor accuracy of the clinical staging in EC remains a serious problem in the management of these patients and endoscopic ultrasonography and probably PET scanning should be included routinely in order to improve it.

As a sole treatment modality, surgical resection in T3-T4 or N positive tumours offers poor long-term results, with 5-year survivals of around 15–20% [3]. Exclusive radiotherapy results are even poorer, with virtually no 3-year survivors in different series. [4]. This low success rate of

Table 6 Phase III trials of neoadjuvant chemoradiotherapy vs. surgery in EC

Study	Number	Histology	Treatment	pCR (%)	Median OS	OS
Urba [15]	50	75% ADC	Preop CRT	28	17.6 m	32% 3 yr
	50		Surgery		16.9 m	15% 3 yr
Walsh [16]	55	100% ADC	Preop CRT	25	16 m*	32% 3 yr
	55		Surgery		11 m*	6% 3 yr
Bosset [17]	143	100% SCC	Preop CRT	26	19 m	26% 5 yr
	139		Surgery		19 m	26% 5 yr
Burmeister [18]	128	67% ADC	Preop CRT	16	22.2 m	
	128		Surgery		19.3 m	
Tepper [19]	23	75% ADC	Preop CRT	40	4.5 yr*	39% 5 yr
	23		Surgery		1.8 yr*	16% 5 yr

*Statistically significant improvement in OS

ADC, adenocarcinoma; *CRT*, chemoradiotherapy; *pCR*, pathologic complete response; *SCC,* squamous cell carcinoma

standard surgical therapy in patients with locally advanced EC has led to the development of combined-modality therapy with the incorporation of chemotherapy into surgical and radiotherapy-based treatment programmes, although the best sequence of treatments is unknown at present. Neoadjuvant chemotherapy is an option, especially in lower-third and gastrooesophageal adenocarcinomas [5, 6] and is a standard treatment in the United Kingdom and parts of Europe. The use of exclusive combined radical chemoradiotherapy, especially in SCCs, was established as a standard of care by the Radiation Therapy Oncology Group (RTOG) trial 85-01, which identified the superiority of combined chemoradiotherapy compared with radiotherapy alone, with similar long-term results to surgery alone (26% of 5-year survivors) [7]. This treatment modality should be considered standard treatment in patients with unresectable disease, or those that are unfit for or refuse surgery [7, 8].

Neoadjuvant chemoradiotherapy before surgery is another multimodality treatment option that has been evaluated in different phase III trials (Table 6) and was the subject of our study [15–19]. All trials reported have shown an increased rate of curative resection and pathologic complete response and a reduced local tumour recurrence rate with the addition of chemoradiotherapy. However, no clear-cut improvement in OS has been noted in most trials, in many cases due to a higher postoperative mortality after combined treatment. A recently published meta-analysis did show a 13% reduction at 2-year modality with preoperative chemoradiotherapy that was irrespective of histology; of note, neoadjuvant chemotherapy in this meta-analysis was linked to only a 7% reduction in 2-year mortality rates, mainly in patients with adenocarcinomas [9].

In our trial, dose intensity of the neoadjuvant regimen was quite high, with almost 85% of patients completing the protocol. The clinical response rate was also high, with only around 10% of clinical progressions. A complete clinical response was a powerful predictor of improved OS in our analysis. However, although similar to other trials, the toxicity of the preoperative regimen remained very significant, with around 20% and 10% of grade 3–4 mucositis and infectious complications, respectively, and 4 early deaths. Many patients finally did not proceed to surgery, in most cases due to a combination of poor general health and advanced age. In those patients, only half could receive the second-phase radiotherapy boost. In those patients that did proceed to surgery, a 30% pathological response rate was seen; no lymph node involvement was seen in any of the cases. Postoperative mortality was quiet high in our trial (seven deaths), although most deaths took place in the first few years of inclusion in the protocol, and may justify the poor median OS of the series. All but one of the 25 resections were radical.

In the trials mentioned previously (Table 6), the pathologic response rate has averaged 25%, although one trial reported lower pathologic response rates for adenocarcinoma (10%) compared with SCC (10%) [17]. In all the studies, superior survival is consistently achieved in patients with a pathological complete response to chemoradiotherapy. Based on the results of two recent European phase III trials [20, 21], it is those patients with SCCs in complete response after radical combined chemoradiotherapy that probably do not benefit from surgical resection, as surgery in both trials improved local control but that improvement failed to translate into a survival benefit. However, the clinical identification of those patients in pathological complete response remains problematic. Endoscopic ultrasonography cannot differentiate adequately between persistent tumour and postradiotherapy inflammation [22] and blind biopsies of the oesophageal mucosa can miss areas of persistent tumour [23]. PET scanning may play a future role in the identification of these complete responders [24].

In conclusion, the management of locally advanced EC remains controversial. Neoadjuvant chemoradiotherapy before surgery can be a useful treatment strategy as it has improved local control and rates of complete resection in several studies, although its effect on OS is much more controversial. Toxicity, as was our case, can be significant and postoperative mortality is usually increased with this approach, which could blunt any OS benefit. Clearly, we must select very carefully those patients who would benefit

from this aggressive approach in order to avoid excessive morbidity and mortality. Those patients with clinical complete response after combined chemoradiotherapy have improved prognosis. However, the identification of those patients with true pathological complete responses, in which surgery could be theoretically be avoided, is more difficult.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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