EUROPEAN JOURNAL OF CANCER 47 (2011) 354–360

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial

Bryan H. Burmeister [a,*], *Janine M. Thomas* [c], *Elizabeth A. Burmeister* [d], *Euan T. Walpole* [a], *Jennifer A. Harvey* [a], *Damien B. Thomson* [a], *Andrew P. Barbour* [b,c], *David C. Gotley* [b,c], *B. Mark Smithers* [b,c]

[a] *Division of Cancer Services, University of Queensland, Princess Alexandra Hospital, Australia*
[b] *Department of Surgery, University of Queensland, Australia*
[c] *Upper GI/Soft Tissue Unit, Princess Alexandra Hospital, Australia*
[d] *Nursing Practice Development Unit, Griffith University, Princess Alexandra Hospital, Australia*

ARTICLE INFO

Article history:
Received 26 July 2010
Received in revised form 27 August 2010
Accepted 2 September 2010

Keywords:
Oesophageal cancer
Adenocarcinoma
Neoadjuvant therapy
Surgery
Chemoradiation therapy

ABSTRACT

Introduction: Preoperative chemotherapy (CT) and preoperative chemoradiation therapy (CRT) for resectable oesophageal cancer have been shown to improve overall survival in meta-analyses. There are limited data comparing these preoperative therapies. We report the outcomes of a randomised phase II trial comparing preoperative CT and CRT for resectable adenocarcinoma of the oesophagus and gastro-oesophageal junction.

Methods: Patients were randomised to receive preoperative CT with cisplatin (80 mg/m^2) and infusional 5 fluorouracil (1000 mg/m^2/d) on days 1 and 21, or preoperative CRT with the same drugs accompanied by concurrent radiation therapy commencing on day 21 of chemotherapy and the 5 fluorouracil reduced to 800 mg/m^2/d. The radiation dose was 35 Gy in 15 fractions over 3 weeks. The endpoints were toxicity, response rates, resection (R) status, progression-free survival (PFS), overall survival (OS) and quality of life.

Results: Seventy-five patients were enroled on the study: 36 received preoperative CT and 39 preoperative CRT. Toxicity was similar for CT and CRT. Eight patients (11%) did not proceed to resection. The histopathological response rate (CRT 31% versus CT 8%, $p = 0.01$) and R1 resection rate (CRT 0% versus CT 11%, $p = 0.04$) favoured those receiving CRT. The median PFS was 14 and 26 months for CT and CRT respectively ($p = 0.37$). The median OS was 29 months for CT compared with 32 months for CRT ($p = 0.83$).

Conclusions: Despite no difference in survival, the improvement from preoperative CRT with respect to margin involvement makes this treatment a reasonable option for bulky, locally advanced resectable adenocarcinoma of the oesophagus.

* *Corresponding author:* Address: Division of Cancer Services, University of Queensland, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Queensland 4102, Australia. Tel.: +61 07 3176 6581; fax: +61 07 3176 5374.
E-mail address: Bryan_Burmeister@health.qld.gov.au (B.H. Burmeister).
0959-8049/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.ejca.2010.09.009

1. Introduction

Randomised trials evaluating the role of preoperative adjuvant therapy in the management of resectable oesophageal cancer have provided conflicting results[1–17] with two reporting a benefit for either preoperative chemoradiation (CRT) or preoperative chemotherapy (CT).[13,14] Most trials did not have contemporary staging methods, resulting in lower than expected survivals in the control arms. Of the meta-analyses performed,[18–23] the most comprehensive reported a benefit for both forms of therapy, but higher with CRT.[21] The subset of patients with adenocarcinoma had a magnitude of the benefit similar for preoperative CT or CRT. The quality of the meta-analyses relating to CRT has been questioned concluding that further assessment in trials is warranted.[24]

Following the report of a survival benefit in the MRC trial, OEO2, using two cycles of cisplatin and 5 fluorouracil[13] preoperatively, our oesophago-gastric multidisciplinary unit used this regimen as standard therapy for invasive adenocarcinoma of the oesophagus. An earlier study had reported a benefit for preoperative CRT for adenocarcinoma of the oesophagus.[14] However, the Australasian trial IG 9401 did not show a survival benefit for preoperative CRT but this study used only a single cycle of cisplatin with 5 fluorouracil.[16] Accepting that preoperative therapy was the standard of care, it seemed reasonable to assess the role of radiation therapy with two cycles of chemotherapy using the OEO2 protocol. Given the predominance of adenocarcinoma in our practice it was decided to confine this trial to this histology. We report the results of a randomised phase II clinical trial comparing preoperative chemotherapy with preoperative chemotherapy and concurrent radiation therapy.

2. Methods

2.1. Eligibility

Patients of all ages were required: to have histologically confirmed invasive adenocarcinoma of the thoracic oesophagus or gastro-oesophageal junction; to be candidates for the chemotherapy regimen; have disease limited to the oesophagus and oesophago-gastric junction (less than 2 cm involvement of the gastric cardia) and regional lymph nodes (cT2–3, cN0–1) and fit for resection. No prior treatment with radiation therapy or chemotherapy was allowed. A prior malignancy was allowed if there had been no recurrence for at least 5 years prior to randomisation. The ECOG (Eastern Cooperative Oncology Group) performance status had to be 0 or 1. The full blood counts and serum biochemistry results had to be within normal limits. A creatinine clearance over 1.0 ml/s calculated by the Gault and Cockcroft formula was required.

2.2. Staging

All patients underwent endoscopy, biopsy and spiral computed tomography (CT) of the neck, chest and abdomen. Lymph nodes measuring more than 1 cm were considered to be clinically involved. Endoscopic ultrasound (EUS) was not available at the time of this study. Almost half of the patients had a positron emission tomography (FDG-PET) scan as part of their staging when it became available 2 years after the trial commenced. Selected patients with disease extending into the upper stomach had a laparoscopy. Other imaging was performed if clinically indicated.

2.3. Randomisation

The trial was approved by the ethics committees in the two hospitals in which the surgery was conducted. Following written consent patients were randomly assigned to treatment groups using computer-generated permutated blocks of random sizes.

2.4. Chemotherapy

The preoperative regimen consisted of two cycles of chemotherapy in both arms, based on the OEO2 study. Cisplatin 80 mg/m^2 was given on day 1 followed by a 96 h infusion of 5 fluorouracil 1000 mg/m^2/d. The second cycle of both drugs commenced on day 21. In the CRT arm the second cycle began concurrently with the commencement of the radiation therapy with the dose of 5 fluorouracil reduced to 800 mg/m^2/d.

2.5. Radiation therapy

Radiation therapy was given using anterior and posterior fields using 6–10 MV photons. Planning was performed using a CT scanner which determined the extent of the tumour and involved lymph nodes. Where possible, confirmation of the gross tumour volume (GTV) was achieved by fusing the diagnostic PET scan with the planning CT. The recommended margins around the GTV to form the planning target volume (PTV) were 2 cm laterally and 5 cm superiorly and inferiorly. The radiation dose prescribed to the ICRU reference point was 35 Gy given in 15 fractions over 3 weeks, commencing on day 22. Lung inhomogeneity correction was used in all cases and planning was performed using three dimensional techniques.

2.6. Presurgical assessment

Patients were restaged with endoscopy, CT scan and subsequently an FDG-PET scan within 3–6 weeks after the completion of the neoadjuvant therapy to confirm there was no evidence of systemic disease. Resection was planned 4–6 weeks from completion of therapy.

2.7. Surgery

The surgical approach was standardised, requiring gross resection of the primary cancer with at least 5 cm of proximal and distal margins including the mediastinal tissue around the lower oesophagus and the subcarinal lymph nodes enbloc with the oesophagus. The thoracic duct was not routinely removed and the procedure included resection of the nodal tissue at the origin of the left gastric pedicle, and the splenic artery to the hilum of the spleen. If the cardia was not significantly involved a thoracoscopically assisted three-phase dissection with a gastric tube anastomosed to the oesophageal stump in the left neck was performed. With gastric cardia

involvement an Ivor-Lewis two-phase approach was used with the gastric tube anastomosed in the chest.

2.8. Monitoring of toxicity and response

During the preoperative therapy, all patients had weekly assessments of toxicity using the CTC (version 2.0) criteria. After completing therapy patients were assessed for response.

Histology of the resected specimen included an assessment of the response to preoperative therapy. Complete pathological response (pCR) was defined as no viable tumour seen on any of the sections of the primary lesion and within the lymph nodes. Partial response was defined as more than 90% reduction in viable tumour with fibrosis replacing the tumour. The other histological findings were assessed as poor (<50% viable tumour) or no response (>50% viable tumour). Patients considered to have a complete or partial response had their pathology reviewed to confirm the response grade. The radial margin was considered involved if there was viable tumour seen within 1 mm from the lateral aspect of the resected specimen. Patients were classified according to whether they had a complete resection (R0), complete resection with microscopic positive margins (R1) or a palliative resection (R2), where obvious disease was left in-situ at the time of the operation. Operative mortality was defined as any death within 30 days of surgery or during the episode of inpatient care following resection. Following discharge patients were assessed at 1 month and then 3 monthly intervals for 2 years and 6 monthly intervals to 4 years and then annually thereafter. Investigations were directed towards symptoms with no routine use of blood tests or scans. The site of first defined recurrence was recorded. Once recurrence was confirmed patients were assessed with a CT scan if not already performed. Further therapy was at the discretion of the treating physician.

2.9. Endpoints and statistical analysis

Because we had not previously used two cycles of chemotherapy with concurrent radiation therapy our primary end points were toxicity including surgical morbidity, pathological response rates and R0 resection rate. Patterns of failure (including sites of recurrence), overall survival, progression-free survival (calculated from the date of randomisation) and quality of life were considered secondary endpoints. Quality of life outcomes are not reported in this manuscript and will be the subject of a future publication. Loco-regional failure was defined as recurrence within a resected field or nodal disease within the typical drainage pattern of the primary lesion. For patients responding completely after neoadjuvant therapy or rendered disease-free after surgery, progression was defined as the first clinical evidence of relapse, or death. For patients not rendered macroscopically disease-free by surgery, progression was defined as occurring at the time of surgery or at the time the decision was made not to proceed to surgery. Patients who had positive margins (R1 resection) were regarded as having progressed only when there was clinical evidence of disease progression.

We chose a sample of 100 patients. This number was based on a likely accrual rate of 20 patients per year for 5 years from the participating centres. It was also deemed likely to detect any large difference (>25%) in the primary endpoints of toxicity, histopathological response and R0 resection rate. All patients were included in the analyses on an intention-to-treat basis. Differences in the major endpoints were calculated using the chi-squared method. Progression-free and overall survivals were estimated by the Kaplan–Meier method and groups were compared by using the log-rank test on an intention-to-treat basis. Determination of differences in survival between the two trial arms and the subgroup analyses also used the Cox proportional-hazards model.

3. Results

The final number of patients available for analysis was 75. This was due to ongoing problems with radiation therapy waiting lists in the last few years of the study. As a result of this, fewer patients agreed to be randomised preferring to commence neoadjuvant chemotherapy immediately. As a result of slow accrual in the last 2 years the study was ceased with 75 patients recruited from November 2000 until December 2006. We felt that this would still provide a useful outcome.

3.1. Patient characteristics

Fig. 1 outlines a summary of management of patients in each group. The 36 patients randomised to receive CT and 39 CRT had a median age of 61 years (range 36–75), with a predominance of males. The performance status, clinical stage and the number staged preoperatively with FDG-PET scanning was similar in both groups. The median follow-up in both arms was 94 months (range of 43–112 months). Details are shown in Table 1.

3.2. Treatment

Acute toxicity related to neoadjuvant therapy in the two arms was similar with no significant differences in Grade 3 or

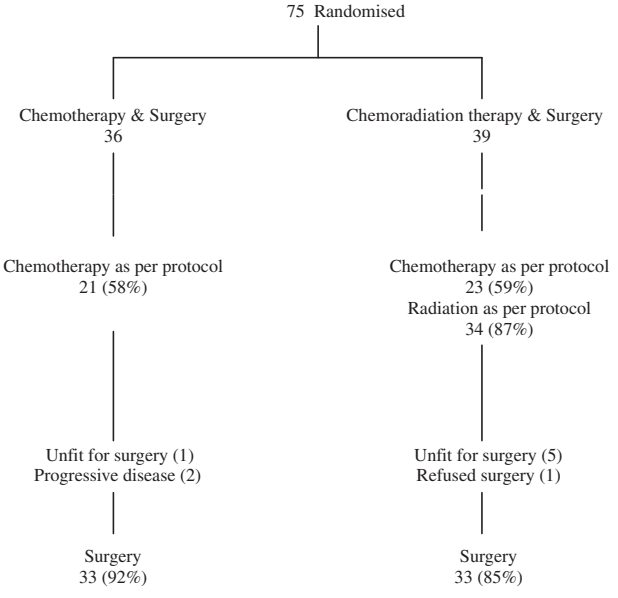

Fig. 1 – Flow diagram of patients.

Table 1 – Patient characteristics.

	CT	CRT	*p*-Value
Age years (median)	63 (36–75)	60 (41–73)	0.47
Male gender	29 (80%)	37 (95%)	0.26
ECOG			
0	33 (92%)	36 (92%)	1.00
1	3 (8%)	3 (8%)	1.00
Clinical stage			
IIA	27 (75%)	32 (82%)	0.68
IIB	4 (11%)	4 (10%)	0.89
III	5 (14%)	3 (8%)	0.91
Nodal involvement	9 (25%)	7 (18%)	0.41
PET assessment	15 (42%)	21 (54%)	0.81
Surgical approach			
Ivor-Lewis	5 (14%)	8 (20%)	0.41
Thoracoscopic 3 stage	28 (74%)	25 (64%)	0.68
Hospital stay median (days)	12 (8–86)	11 (9–43)	0.81

greater toxicity. Grade 3 oesophagitis was lower than expected in the CRT arm (Table 2). Deviations from the preoperative protocols were chiefly due to toxicity concerns. The most common variation in the radiation therapy regimen was extension of therapy beyond 3 weeks. In the CT arm three patients (6%) did not have resection, one had stage IV disease at laparotomy, one disease progression on restaging preoperatively and one became unfit for an operation and received definitive radiation therapy as an alternative treatment. In the CRT arm six patients (16%) did not have resection, five patients had deterioration in their physical status and were not fit for an operation. One refused surgery after completion of the CRT.

The approach to resection was similar in both arms. There was no difference in the rates of surgical toxicity or length of stay in hospital between the two arms. There were no treatment related deaths in either arm of the trial. Late morbidity was not available.

Table 2 – Grade 3 toxicity of neoadjuvant therapy[a] and all surgical complications.

Toxicity	CT	CRT	*p*-Value
Oesophagitis	3 (8%)	1 (3%)	0.11
Pneumonitis	0	1 (3%)	0.28
Neutropenia	5 (12%)	3 (7%)	0.37
Skin	0	0	1.00
Mucositis	1 (3%)	0	0.28
Fever	0	1 (3%)	0.28
Infection	1 (3%)	3 (8%)	0.11
Nausea/vomiting	2 (6%)	1 (3%)	0.51
Thromboembolism	1 (3%)	2 (6%)	0.51
Renal impairment	2 (6%)	1 (3%)	0.51
Cardiac	1 (3%)	0	0.28
Surgical complications	14 (39%)	9 (23%)	0.15
Chest problems	6 (17%)	7 (18%)	0.52
Cardiac problems	6 (17%)	7 (18%)	0.52
Anastomotic leak	2 (5.5%)	2 (5%)	0.69
Wound infection	1 (3%)	5 (13%)	0.08
Chyle leak	1 (3%)	1 (2.5%)	0.75
Other	4 (11%)	2 (5%)	0.21
30 d Surgical mortality	0	0	1.00

[a] No grade 4 toxicities.

Table 3 – Histopathology and post therapy staging.

	CT (36)	CRT (39)	*p*-Value
Margin status			
R0	29 (80.5%)	33 (84.6%)	0.61
R1	4 (11%)	0	0.04
AJCC stage			
0	0	5 (13%)	0.05
I	5 (14%)	1 (3%)	0.10
IIA	5 (14%)	8 (20%)	0.40
IIB	3 (8%)	7 (18%)	0.05
III	20 (56%)	12 (31%)	0.03
Not resected	3 (8%)	6 (15%)	0.27
Histological response			
pCR	0	5 (13%)	0.02
<10% viable cells	3 (8%)	7 (18%)	0.21
Macroscopic	30 (83%)	21 (54%)	0.41
Residual disease	3 (8%)	6 (15%)	0.11
Major response (pCR + <10% viable cells)	3 (8%)	12 (31%)	0.01

3.3. *Tumour response*

Following CRT, five patients (13%) had a pathological complete response but none were seen after CT. The major histological response rate (<10% viable cells) was 31% in the CRT group and 8% in the CT group ($p = 0.01$). With respect to completeness of resection (R0), there was no difference between the groups, on an intention-to-treat basis (CRT = 84.6%, CT = 80.5%). However more patients had a margin involved (R1) in the CT group (CT = 4, CRT = 0, $p = 0.04$). When the subset of patients who did not proceed to resection were excluded, analysing the resected patients revealed an R0 rate of 100% for CRT and 86% for CT. There were no patients who had an R2 resection in

Table 4 – Survival and patterns of relapse.

	CT (36)	CRT (39)	*p*-Value
Time to progression	14	26	0.37
Median (months)	95% CI 2.24–25.76	95% CI 6.805–45.848	
Overall survival	29	32	0.83
Median (months)	95% CI 13.58–44.4	95% CI 20.1–43.58	
3-year Survival	49%	52%	0.97
5-year Survival	36%	45%	0.60
Recurrence			
Nil	12 (33%)	15 (39%)	0.28
Loco-regional	4 (11%)	3 (8%)	0.52
Loco-regional and distant	6 (17%)	4 (10%)	0.39
Distant	11 (31%)	11 (28%)	0.94
No surgery	3 (8%)	6 (15%)	0.27

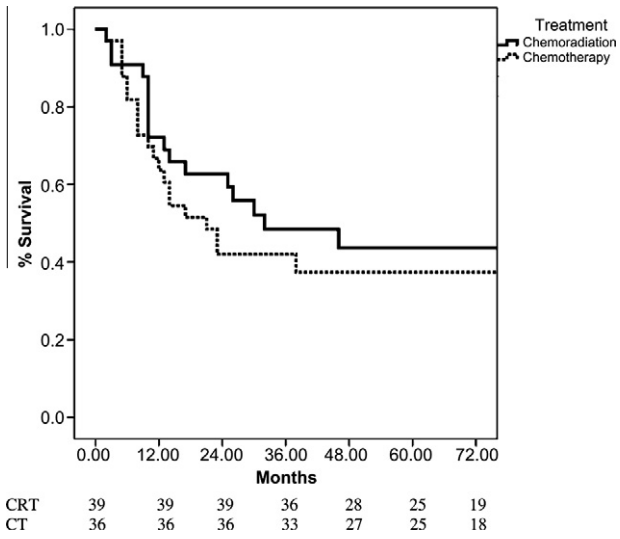

Fig. 2 – Progression free survival.

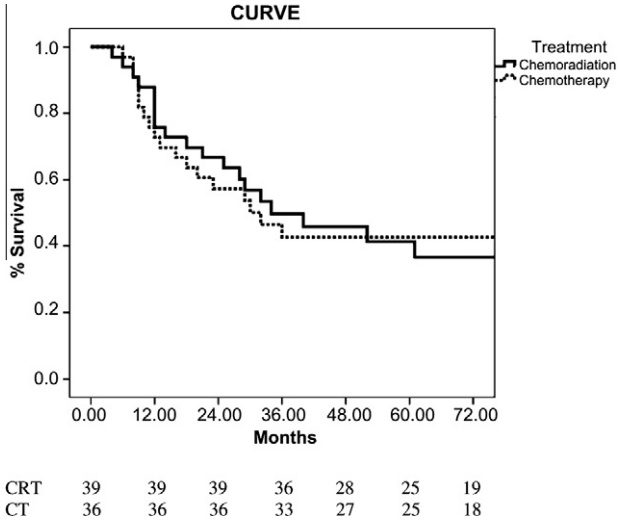

Fig. 3 – Overall survival.

either group. There was significant stage migration to lower stages in the CRT group (Table 3).

3.4. *Patterns of recurrence*

There was no difference in the site of the first recorded symptomatic recurrence between the treatment arms (Table 4). The overall loco-regional recurrence rate was 28% in the CT group compared with 18% in the CRT group ($p = 0.41$).

3.5. *Survival*

There was no difference in progression-free survival (Fig. 2) or overall survival (Fig. 3). In the CT arm the median PFS and OS were 14 and 29 months and for CRT the median PFS and OS were 26 and 32 months. The overall 5 year survival was 36% in the CT group and 45% for those having CRT (Table 4).

4. Discussion

We have compared the outcomes of patients with invasive adenocarcinoma of the oesophagus and oesophago-gastric junction that have had preoperative CT or CRT. Due to the restricted number of patients recruited definitive conclusions related to survival outcomes can only be secondary end points. However we have shown that the addition of concurrent radiation therapy at a dose of 35 Gy to preoperative CT did not add to CT toxicity or surgical morbidity. CRT provided a higher histologic tumour response with fewer patients having involved margins at the time of resection, as well as evidence of significant pathologic down-staging. Accepting the restricted size of the cohort we found that a change in disease stage in the CRT group had no influence on progression-free or overall survival.

The Australasian study, IG 9401, using the same dose of radiation therapy and a single cycle of chemotherapy as neoadjuvant therapy reported significant pathologic down-staging and complete tumour resection rates for both squamous cell and adenocarcinoma with no effect on survival when compared with surgery alone.[16] The pCR for adenocarcinoma was 8%, similar to what we have reported in this study. Although there is a low pCR rate, the addition of this dose of radiation therapy to chemotherapy still produced a high major histological response rate and less surgical margin involvement with no increase in morbidity. Studies using higher doses of preoperative radiation therapy, report pCR rates of 25%[14] and 24%.[15] In those studies the median survivals were 16 and 17.6 months, respectively, which compares with 32 months in the present study. The most recent study, using 50.4 Gy with chemotherapy, in the 30 patients, reported a pCR in 10 patients (40%) and a 5 year survival of 39%.[17] Despite a low pCR rate after CRT and nil after CT, we report comparable 5 year survivals in both arms with 45% and 36%, respectively.

pCR has been shown to be a good prognostic indicator in patients who have had CRT.[25,26] Barbour et al.[27] and others[25,26] have also shown that the addition of those patients who have <10% viable tumour cells have a similar positive outcome. Despite the improvement in both pCR and major histopathologic response in those patients having preoperative CRT compared with CT the survival outcomes were similar for both groups. One hypothesis may be that the addition of a local treatment such as radiation therapy, to appropriate surgery, in patients who have had preoperative CT may not influence the potential for the survival in a disease that has a high rate of occult systemic metastasis.

With the use of modern staging, surgical techniques, anaesthesia and intensive care support, one questions whether the local effect from radiation therapy at any dose will have a major impact on overall survival from this disease when systemic metastasis is the main cause of death. If radiation therapy is to be used with appropriate resection, what is the value of increasing radiation doses when excellent complete excision rates can be achieved at lower doses?

One recently published trial assessed patients with locally advanced adenocarcinoma of the oesophagus who received 15 weeks of preoperative chemotherapy, then resection or a

similar chemotherapy regimen with concurrent radiation therapy at a dose of 30 Gy, followed by resection.[28] There were 126 patients accrued and randomised but the analysis was performed on 116. All patients were assessed with EUS and CT scan and confirmed to have T3/4, NX disease. Three patients (2.3%) died from the neoadjuvant therapy and seven (5.5%) from the surgery. Using the information from the manuscript, and on an intention-to-treat analysis, the CT arm had a resection rate of 76% (49 of 64 patients) compared with 73% (45 of 62 patients) for CRT. Assessing the completeness of resection, the R0 and R1/2 rates for the CT and CRT groups were 64%/12.5% and 67%/3.2%, respectively. Excluding a number of randomised patients from the analysis, the median overall survival was 21 months for the CT arm and 33 months for the CRT arm. These results are comparable for the CRT arm in our study. We do however report slightly improved outcomes for the CT arm.

In this study one wonders whether the difference in the survivals between the arms of the trial was related to the number of cycles of chemotherapy adding extra weeks of therapy. Not only did this cause treatment mortality but it is possible that reduced cancer survival may relate to the lengthy chemotherapy given without the local effects of radiation therapy. There will be a group of patients receiving a treatment that has no effect on the disease thus delaying an effective treatment such as surgery. This has been postulated as one of the reasons for the null effect of the preoperative chemotherapy in a large US trial[12] which used the same drugs as the MRC trial but with three cycles and a significant percentage of the treatment group having a delay to definitive resection.

When examining survival, the MRC trial showed an advantage for CT (median survival 17 months) over surgery alone (13 months).[13] Both arms of our study report better outcomes likely related to modern staging techniques along with standardised surgery in two centres. It follows that these are likely the reasons that the outcomes in both arms of our study are better than the treatment arms in the studies analysed for the meta-analysis by Gebski et al.[21] With a meta-analysis reporting a superior outcome for survival from CRT over CT,[21] along with the French meta-analysis of CRT studies[22] and the CALGB 9781 trial,[17] CRT has become the standard of care in many units for invasive oesophageal cancer. A recent review of the meta-analyses of the CRT randomised trials highlighted their discordance and was critical of the methodology used in many of the trials analysed.[24] They highlight the heterogeneity of the histology, radiation doses, chemotherapy regimens, surgical techniques, small sample sizes and finally the staging and treatment delivery differences over a 40 year period when the trials were performed. Now that modern CT scanning along with FDG-PET scanning have become routine to exclude metastatic disease and EUS has become an essential tool to stratify the primary lesion, these imaging techniques must be used in the modern assessment of patients and trials.

There is a need for trials that will further define the role and dosage for modern radiation therapy for resectable oesophageal adenocarcinoma in the context of adequately performed surgery. From the results of our trial it is calculated that to establish equivalence or an overall survival benefit by the addition of radiation therapy to the chemotherapy regimen we used, at least 500 patients would be required to show a 6% difference at 2 years. It is unfortunate that the only two randomised trials comparing CRT and CT preoperatively are underpowered to explore overall survival as a primary endpoint. Because of the entrenched practices in most major units dealing with this cancer, it seems unlikely that an adequately powered study will be done. However, for those clinicians who believe that there is still equipoise between preoperative CT and CRT, we offer support both from the perspective of response and morbidity for the addition of radiation therapy to preoperative chemotherapy when the primary lesion is locally advanced, tailoring the neoadjuvant treatment to patient and tumour factors.

Conflict of interest statement

None declared.

REFERENCES

1. Nygaard K, Hagen S, Hansen HS, et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy—the second Scandinavian trial in esophageal cancer. *World J Surg* 1992;**16**:1104–10.
2. Schlag P. Randomized trial of preoperative chemotherapy for squamous cell carcinoma of the esophagus. *Arch Surg* 1992;**127**:1446–50.
3. Maipang T, Vasinanukorn P, Petpichetchian C, et al. Induction chemotherapy in the treatment of patients with carcinoma of the esophagus. *J Surg Oncol* 1994;**56**:191–7.
4. Kok TC, van Lanschot J, Siersma PD, et al. Neoadjuvant chemotherapy in operable esophageal squamous cell cancer: final report of a phase III multicenter randomized trial. *Proc Am Soc Oncol* 1997;**16**:227a [abstract 984].
5. Law SMB, Fok M, Chow S, et al. Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. *J Thorac Cardiovasc Surg* 1997;**114**:210–7.
6. Roth J, Pass H, Flanagan M, et al. Randomized clinical trial preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine and bleomycin for carcinoma of the esophagus. *J Thorac Cardiovasc Surg* 1998;**96**:242–8.
7. Ancona E, Ruol A, Santi S, et al. Only pathological complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma. *Cancer* 2001;**91**: 2165–74.
8. Apinop C, Puttisak P, Preecha N. A prospective study of combined therapy in esophageal cancer. *Hepato-Gastroenterology* 1994;**41**:391–3.
9. Le Prise E, Etienne PL, Meunier B, et al. A randomized study of chemotherapy, radiation therapy and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer* 1994;**73**:1779–84.
10. Bosset J, Gignoux M, Triboulet J, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous cell carcinoma of the esophagus. *New Eng J Med* 1997;**337**:161–7.
11. Lee J, Park S, Kim S, et al. A single institutional phase II trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable

esophageal squamous cell carcinoma. *Ann Oncol* 2004;**15**:947–54.
12. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *New Eng J Med* 1998;**339**:1979–84.
13. Medical Research Council Oesophageal Cancer Working Party. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002;**359**:1727–33.
14. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *New Engl J Med* 1996;**335**:462–7.
15. Urba SG, Orringer MB, Turrissi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001;**9**:305–13.
16. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus. *Lancet Oncol* 2005;**6**:659–68.
17. Tepper J, Krasna MJ, Niedziwiecki D, et al. Phase III trimodality therapy with cisplatin, fluorouracil, radiotherapy and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008;**26**:1086–92.
18. Fiorca F, Di Bona D, Schepis F, et al. Preoperative chemoradiotherapy for oesophgeal cancer: a systematic review and meta-analysis. *Gut* 2004;**53**:925–30.
19. Kaklamanos IG, Walker GR, Ferry K. Neoadjuvant treatment for resectable cancer of the esophagus and the gastroesophageal junction: a meta-analysis of randomized clinical trials. *Ann Surg Oncol* 2003;**10**:754–61.
20. Urschel JD, Vasan H. A meta-analysis of randomized trials that compare neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. *Am J Surg* 2003;**185**:538–43.
21. Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007;**8**:226–34.
22. Thirion PG, Michiels A, Le Maitre A, et al. Individual patient data-based meta-analysis assessing pre-operative chemotherapy in resectable oesophageal carcinoma. *J Clin Oncol* 2007;**25**:200s.
23. Jin HL, Zhu H, Ling TS, et al. Neoadjuvant chemoradiotherapy for resectable esophageal carinoma: a meta-analysis. *World J Gastrenterol* 2009;**15**:5983–91.
24. Wijnhoven BPL, van Lanschot JJB, Tilanus HW, et al. Neoadjuvant chemotherapy for esophageal cancer: a review of meta-analyses. *World J Surg* 2009;**33**:2606–14.
25. Brucher BL, Becker K, Lordick F, et al. The clinical impact of histopathologic response assessment by residual tumour cell quantification in esophageal squamous cell carcinoma. *Cancer* 2006;**106**:2119–27.
26. Schneider PM, Baldus SE, Metzger R, et al. Histomorphologic tumour regression and lymph node metastasis determine prognosis following neoadjuvant radiochemotherapy for oesophageal cancer: implication for response classification. *Ann Surg* 2005;**242**:684–92.
27. Barbour AP, Jones M, Gonen M, et al. Refining esophageal cancer staging after neoadjuvant therapy: importance of treatment response. *Ann Surg Oncol* 2008;**15**:2894–902.
28. Stahl M, Walz MK, Stuschke M, et al. Phase II comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009;**27**:851–6.