Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial

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Summary

Background **Resection remains the best treatment for carcinoma of the oesophagus in terms of local control, but local recurrence and distant metastasis remain an issue after surgery. We aimed to assess whether a short preoperative chemoradiotherapy regimen improves outcomes for patients with resectable oesophageal cancer.**

Methods **128 patients were randomly assigned to surgery alone and 128 patients to surgery after 80 mg/m² cisplatin on day 1, 800 mg/m² fluorouracil on days 1–4, with concurrent radiotherapy of 35 Gy given in 15 fractions. The primary endpoint was progression-free survival. Secondary endpoints were overall survival, tumour response, toxic effects, patterns of failure, and quality of life. Analysis was done by intention to treat.**

Findings **Neither progression-free survival nor overall survival differed between groups (hazard ratio [HR] 0·82 [95% CI 0·61–1·10] and 0·89 [0·67–1·19], respectively). The chemoradiotherapy-and-surgery group had more complete resections with clear margins than did the surgery-alone group (103 of 128 [80%] *vs* 76 of 128 [59%], p=0·0002), and had fewer positive lymph nodes (44 of 103 [43%] *vs* 69 of 103 [67%], p=0·003). Subgroup analysis showed that patients with squamous-cell tumours had better progression-free survival with chemoradiotherapy than did those with non-squamous tumours (HR 0·47 [0·25–0·86] *vs* 1·02 [0·72–1·44]). However, the trial was underpowered to determine the real magnitude of benefit in this subgroup.**

Interpretation **Preoperative chemoradiotherapy with cisplatin and fluorouracil does not significantly improve progression-free or overall survival for patients with resectable oesophageal cancer compared with surgery alone. However, further assessment is warranted of the role of chemoradiotherapy in patients with squamous-cell tumours.**

Lancet Oncol 2005; 6: 659–68

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Published online August 11, 2005
DOI:10.1016/S1470-2045(05)70288-6

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Introduction

Patients with cancer of the oesophagus have a poor outlook. Resection is the best management in terms of local control, although local recurrence and distant metastases remain an issue after surgery. Postoperative radiotherapy does not improve outcomes,[1,2] and preoperative radiotherapy, chemotherapy, or both, have become the focus of adjuvant strategies. However, toxic effects and compliance with protocols have hindered the development of suitable treatments. In 1989, as part of the multicentre Trans-Tasman Radiation Oncology Group (TROG), several Australian and New Zealand centres began to collaborate in the development of a well-tolerated preoperative chemoradiotherapy regimen that would not only downstage the tumours of most patients having curative resections, but also be suitable for widespread use. Before 1989, a variant of the original Wayne State University regimen[3] had been used, consisting of two cycles of chemotherapy with cisplatin and fluorouracil and radiotherapy for 3 weeks. This regimen achieved satisfactory downstaging, but concerns remained about toxic effects.[4] Ultimately, TROG developed a well-tolerated and effective regimen of one cycle of chemotherapy with cisplatin and fluorouracil and 35 Gy radiotherapy, which was as effective as the two-cycle regimen with regard to downstaging and postsurgical outcomes, but was associated with fewer toxic effects.[5] Moreover, this regimen compared favourably in terms of effectiveness and toxic effects with other contemporary chemo-radiotherapy regimens that had been assessed.[6]

In 1994, we started a randomised controlled trial in which patients with resectable cancer of the oesophagus were randomly assigned to surgery alone or to this preoperative chemoradiotherapy regimen followed by surgery 3–6 weeks later. The trial aimed to assess whether downstaging of the tumour as a result of chemoradiotherapy improved progression-free survival and overall survival after surgery. Here, we report mature data.

Methods

Eligibility

Any patient who had histologically confirmed invasive cancer of the thoracic oesophagus was eligible. Endoscopy and CT needed to show that disease was restricted to the oesophagus and regional lymph nodes (ie, clinical T1–3, N0–1 disease), with resectable nodes

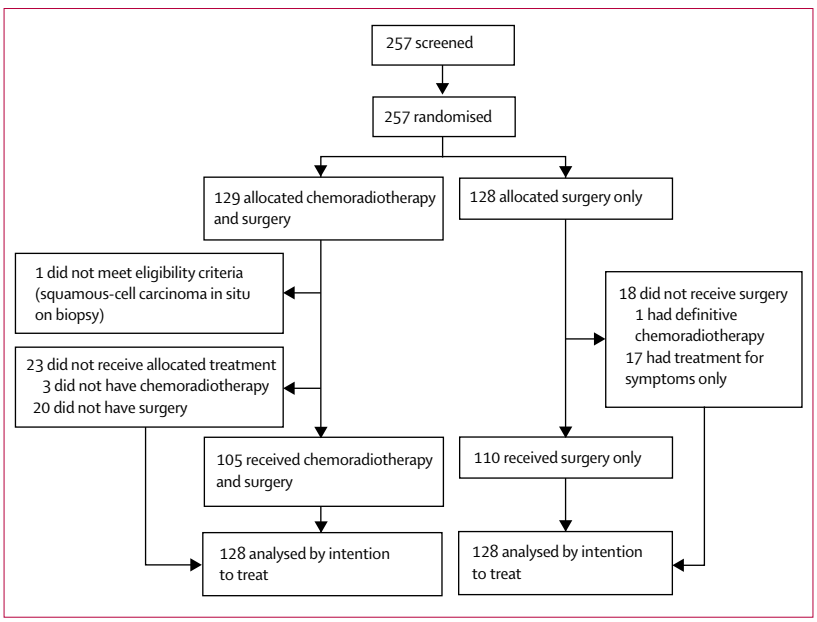

Figure 1: **Trial profile**

to be removed as part of the planned surgical procedure. Patients who had involvement of the gastric cardia that was confined to the lower third of the oesophagus were eligible, provided that the tumour was mainly in the oesophagus. Patients with tumours localised to the cervical oesophagus and those with involvement of the coeliac nodes on CT were excluded. No previous radiotherapy or chemotherapy was allowed. Patients who had had any malignant disease other than non-melanomatous skin cancer or cervical carcinoma in situ were eligible if there had been no recurrence for at least 5 years before randomisation. The ECOG (Eastern Cooperative Oncology Group) performance status of the patients had to be 0 or 1. Full blood counts, including baseline haemoglobin, and serum biochemistry results had to be within normal limits. A creatinine clearance of more than 1·0 mL/s calculated by the Gault and Cockcroft formula, or more than 0·83 mL/s by direct measurement, was required.

	Chemoradiotherapy and surgery (n=128)	Surgery alone (n=128)
Age (years)		
Median (range)	61 (41–80)	62 (28–83)
Sex		
Women	22 (17%)	28 (22%)
Men	106 (83%)	100 (78%)
Performance status		
0	40 (31%)	44 (34%)
1	88 (69%)	84 (66%)
Tumour histology		
Squamous-cell carcinoma	45 (35%)	50 (39%)
Adenocarcinoma	80 (63%)	78 (61%)
Mixed or other	3 (2%)	0
Tumour location		
Lower third	99 (77%)	104 (81%)
Middle or upper third	29 (23%)	24 (19%)
Regional nodes involved on CT		
Yes	20 (16%)	19 (15%)
No	108 (84%)	109 (85%)
Histological grade		
Poorly differentiated	60 (47%)	47 (37%)
Moderately differentiated	39 (30%)	53 (41%)
Well differentiated	6 (5%)	13 (10%)
Unknown	23 (18%)	15 (12%)

Data might not total 100% because of rounding.

Table 1: **Baseline characteristics**

Staging

All patients underwent endoscopy, biopsy, and CT of the neck, chest, and abdomen before randomisation. Lymph nodes of more than 1 cm were regarded as clinically involved. Patients with disease in the lower oesophagus had a laparoscopy if there were doubts about achieving effective resection. Other tests, such as radionuclide bone scans, were done only if indicated clinically. Endo-oesophageal ultrasonography and PET were not widely available at the time the trial was developed, and were therefore not mandatory.

Randomisation

256 patients were stratified by histological type, sex, and institution, and randomly assigned to preoperative chemoradiotherapy (n=128) or to surgery alone (n=128) by central telephone randomisation done by the trial coordinator at the NHMRC Clinical Trials Centre, Sydney, Australia. Enrolment was done by the treating clinicians and data managers of the participating institutions. The random sequence was generated by use of minimisation by the trial statistician, and blocks of four were used. The allocation sequence was concealed to all central staff. Research staff and investigators were blinded to treatment assignment before, but not after, randomisation. Patients were not blinded to treatment assignment. Patients were accrued from 25 centres, with seven centres randomising more than ten patients and one centre 90 patients. Treatment assignment was well balanced for every stratification factor. The study was approved by the ethics committees of all institutions, and all patients gave written informed consent.

Treatment regimen

The surgical requirement was for total removal of the tumour and regional lymph nodes as deemed necessary by the operating surgeon. No particular operative approach was stipulated; radical lymphadenectomy was not mandatory, and no minimum number of lymph nodes needed to be dissected. After surgery, information on the approach and extent of lymph-node dissection was obtained from the operating surgeon. Lymph-node groups were categorised by site: left gastric or coeliac; lower mediastinal; subcarinal; or superior

mediastinal. No patient had a cervical node dissection. In the chemoradiotherapy-and-surgery group, surgery was recommended 3–6 weeks after completion of radiotherapy. In the surgery-alone group, surgery was recommended as soon as possible after randomisation.

For patients assigned chemoradiotherapy, preoperative chemotherapy consisted of 80 mg/m^2 cisplatin (Cisplatin, Pfizer, Sydney, Australia, or Cisplatin DBL, Mayne Pharma, Melbourne, Australia) given intravenously on day 1 followed by 800 mg/m^2 fluorouracil (Fluorouracil, Pfizer, Sydney, Australia, or Fluorouracil DBL, Mayne Pharma, Melbourne, Australia) a day given intravenously on days 1–4. Radiotherapy at a dose of 35 Gy to the midplane, given in 15 fractions over 3 weeks, was to start concurrently with chemotherapy. This regimen was the same as that used in the phase II study that preceded this trial.[5]

Radiotherapy was given by use of anterior and posterior fields with 6–10 MeV photons. Planning was done by use of a simulator and gastrographin swallow, and with use of CT to define the extent of the tumour and involved lymph nodes. The recommended margins around the visible disease were 2 cm laterally and 5 cm superiorly and inferiorly. Customised blocks were used where shielding was required. The protocol stipulated that patients assigned chemoradiotherapy and surgery have a second endoscopy before surgery, but a follow-up CT scan was not specified. Postoperative radiotherapy was permitted for patients with residual disease after surgery if indicated clinically for patients assigned surgery alone. Radiotherapy prescriptions and simulator films of 30% of patients assigned chemoradiotherapy were reviewed centrally. On confirmation of relapse, further treatment was at the discretion of the treating physician for both groups.

Monitoring of toxic effects and response

In patients assigned preoperative chemoradiotherapy, toxic effects were assessed once a week by the Radiation Therapy Oncology Group (RTOG)/Dische scoring system.[7] Clinical response to chemoradiotherapy was assessed by endoscopy immediately before surgery. A complete response was defined as no evidence of tumour, partial response as a reduction of at least 50% in the tumour length, stable disease as a decrease of less than 50%, and progressive disease as any enlargement of the tumour as assessed by the person who did the endoscopy, usually the surgeon. Biopsies were not required for assessment of response. However, histological analysis was done for all resected samples, and reports were reviewed centrally by BMS and BHB to assess response to neoadjuvant therapy and the margin of resection. Pathological response was defined as

	Chemoradiotherapy and surgery (n=128)	Surgery alone (n =128)
Chemoradiotherapy		
Protocol regimen	106 (82%)	1 (1%)*
Alternative regimen	19 (15%)	2 (2%)†
No chemotherapy	3 (2%)	125 (98%)
Surgery		
R0	103 (80%)	76 (59%)
R1	0	27 (21%)
Nodes involved‡	44 (43%)	69 (67%)
R2	2 (2%)	7 (5%)
No resection	23 (18%)	18 (14%)

Data might not total 100% because of rounding. *Patient was randomly allocated surgery alone but elected to have preoperative chemoradiotherapy. †One patient had definitive chemoradiotherapy after exploratory surgery, and one patient elected to have definitive chemoradiotherapy after a second opinion. ‡Proportion with complete (ie, R0 or R1) resection (n=103 for both groups).

Table 2: **Treatment received by randomised group**

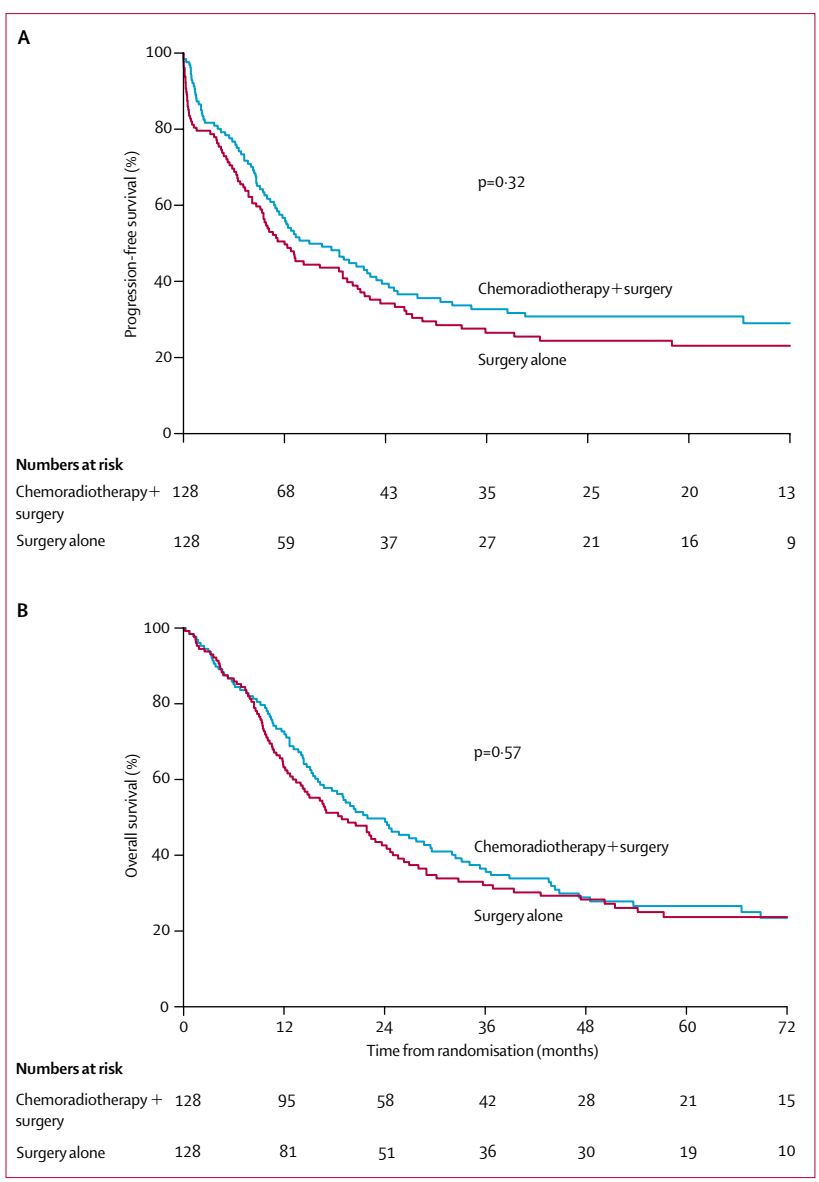

Figure 2: **Survival by treatment group**
(A) Progression-free survival. (B) Overall survival.

	n	Progression-free survival		Overall survival	
		Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Chemoradiotherapy and surgery *vs* surgery alone	128/128	0·82 (0·61–1·10)	0·18	0·89 (0·67–1·19)	0·44
Men *vs* women	206/50	1·28 (0·86–1·90)	0·22	1·36 (0·93–1·99)	0·11
Performance status 1 *vs* 0	84/172	1·24 (0·91–1·70)	0·18	1·26 (0·93–1·70)	0·14
Lower oesophageal tumour *vs* middle or upper	203/53	2·11 (1·37–3·24)	0·001	1·50 (1·03–2·18)	0·04
Squamous *vs* non-squamous	95/161	0·49 (0·35–0·69)	<0·0001	0·69 (0·51–0·94)	0·02
Tumour length >5 cm *vs* ≤5 cm	90/162*	1·35 (0·99–1·84)	0·06	1·32 (0·98–1·78)	0·07
Tumour differentiation moderate or well *vs* poor	111/107†	0·73 (0·53–1·00)	0·05	0·64 (0·47–0·88)	0·01
Age >60 years *vs* age ≤60 years	148/108	1·43 (1·06–1·99)	0·02	1·53 (1·14–2·06)	0·01

*Tumour length not recorded for four patients. †Tumour grade not assessable for 38 patients.

Table 3: **Univariate analysis of survival**

complete if there was no histological evidence of viable tumour in the resected sample, and as partial if there was any histological evidence of residual tumour. Patients were classified according to whether they had a complete resection with negative margins (R0), complete resection with positive margins (R1), or a palliative resection (R2) where obvious disease had been left in situ. Operative mortality was defined as death from any cause within 30 days of surgery or during care in hospital that was associated with resection. All operation reports and surgical complications, including hospital stay, were documented and reviewed centrally by BMS and BHB. After surgery, patients were assessed every 3 months for the first 2 years and every 6 months thereafter. Investigations to detect relapse were not done routinely, unless patients had signs of recurrence.

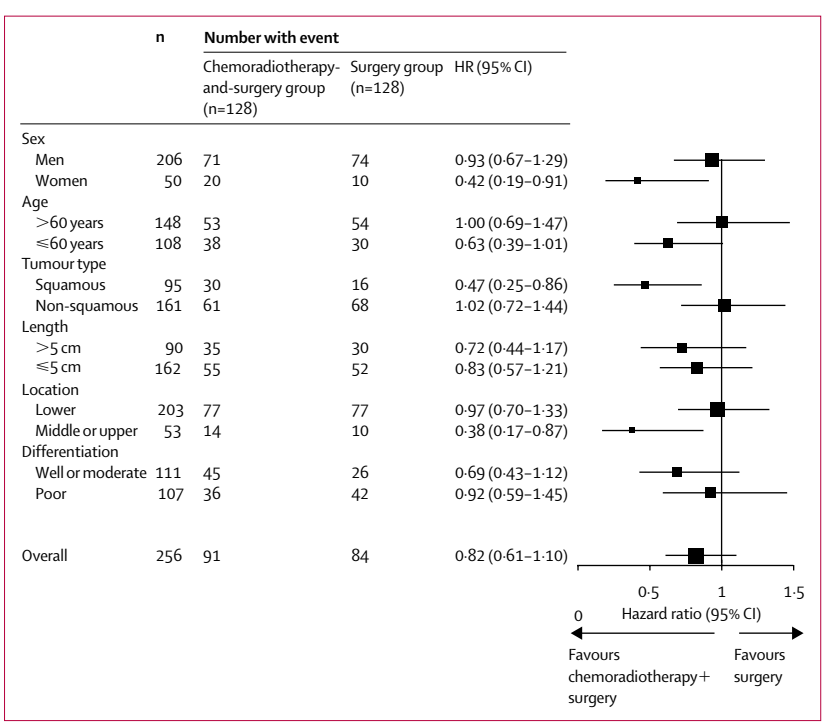

Figure 3: **Progression-free survival: subgroup analysis**

Outcome measures

The primary endpoint for the trial was progression-free survival from the date of randomisation. Progression-free survival, rather than overall survival, was chosen as the primary endpoint because the sample size, needed to measure overall survival reliably, was deemed not feasible. For patients responding completely or those free of disease after surgery, progression was defined as the first clinical (including endoscopic) evidence of relapse or death. For patients not macroscopically free of disease after 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 (ie, R1 resection) were regarded as having progressed only when there was clinical evidence of disease progression on clinical examination or radiological imaging.

Secondary endpoints were overall survival, tumour response, toxic effects, patterns of failure, and quality of life. Overall survival was defined as survival from the date of randomisation until date of death from cancer of the oesophagus or from treatment of cancer of the oesophagus; patients who died from other causes were censored. Because we were assessing the effect of local treatment, local failure was defined as recurrence within a volume that would have been covered by the radiation field had preoperative radiotherapy been given according to the protocol—a definition that applied to patients in both groups. All other failures outside a given, or proposed, radiation field were classified as distant. Assessment of all recurrences was done centrally by BHB.

Statistical analysis

Analyses were done by intention to treat. Subgroup analyses by sex, performance status, tumour site, histological subtype, tumour length, tumour grade, and age were prespecified. Sample-size calculations were made on the basis of a projected 3-year progression-free survival of 35% for patients assigned chemo-radiotherapy (estimated on the basis of previous TROG phase II data),[5] and of 20% for those assigned surgery alone.[8] With an overall two-sided significance level of

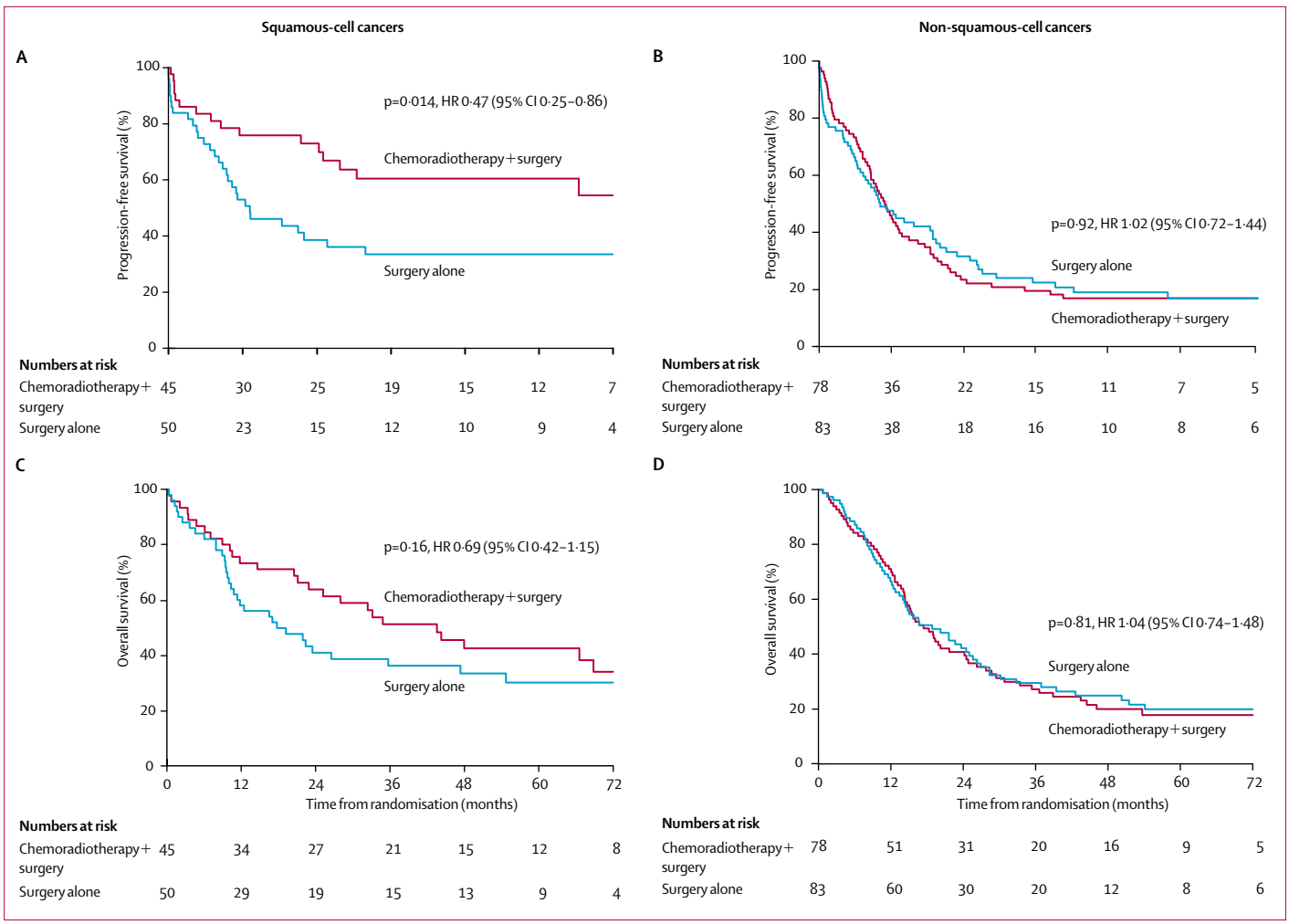

Figure 4: **Survival by histological subtype**
(A, B) Progression-free survival. (C, D) Overall survival.

5% and a statistical power of 80% to detect a difference of 15% in 3-year progression-free survival, 4 years' accrual, and 4 years' follow-up, the calculated sample size was 230 patients (or 250 patients with allowance for crossovers).

Planned interim analyses by an independent safety and data monitoring committee were done after 63 patients (25%, analysis of toxic effects only), 83 patients (32%), and 165 patients (66%) had been enrolled. The last two interim analyses were planned prospectively to exclude major differences in outcomes between groups (p=0·005 and p=0·01, respectively).

Progression-free and overall survival were estimated with the Kaplan–Meier method, and groups were compared by use of the log-rank test. Age, tumour location, and tumour grade were included in the multivariate model after the study was completed. The Cox proportional-hazards model was used to define differences in survival between groups and subgroups. Discrete data were compared by use of the χ^2 test. Statistical analyses were done with the Statistical Package for Interactive Data Analysis (SPIDA) version 3.

Quality of life

An objective linear analogue score was used to assess quality of life. Data for overall quality of life, physical wellbeing, mood, pain, nausea and vomiting, appetite, difficulty swallowing, and tiredness were recorded and will be reported elsewhere.

Role of the funding source

The sponsors of this study had no role in the study design, in the collection, analysis, or interpretation of the data, or in the writing of the report. The corresponding author had full access to all data in the study, and had the final responsibility to submit for publication.

	Grade 0	Grade 1–2	Grade 3–4
Oesophagitis	21 (16%)	82 (64%)	20 (16%)
Nausea or vomiting	45 (35%)	72 (56%)	6 (5%)
Infection	108 (84%)	12 (9%)	3 (2%)
Diarrhoea	93 (73%)	29 (23%)	1 (1%)
Mucositis	90 (70%)	31 (24%)	2 (2%)
Pneumonitis	88 (69%)	33 (26%)	2 (2%)
Neutropenia	93 (73%)	25 (20%)	5 (4%)
Raised creatinine	96 (75%)	25 (20%)	2 (2%)

Data are number of patients (%).

Table 4: **Acute toxic effects of chemoradiotherapy**

Results

From Nov 7, 1994, to Sept 6, 2000, 257 patients with localised resectable cancer of the oesophagus were randomised (figure 1). Median follow-up was 65·0 months (range 0·4–120·0), and final analysis was done on March 28, 2005.

Of the 257 patients registered on the trial, one patient was deemed ineligible. Although randomised on the basis of having invasive carcinoma, all biopsy samples showed squamous-cell carcinoma in situ, and the patient was excluded from the primary treatment comparison (figure 1).

Table 1 shows baseline characteristics. The median tumour length was 4 cm (1–9). The median interval between randomisation and start of treatment was 11 days (1–38) for patients assigned chemoradiotherapy and 12 days (3–31) for those assigned surgery alone. 28 (11%) of 253 patients who received treatment had a delay of longer than 20 days. Preoperative staging of nodal disease as assessed by CT was much the same in both groups (table 1).

Overall compliance with protocol treatment was high in both groups (table 2). Patients allocated chemoradiotherapy who received an alternative chemotherapy regimen were mainly given 20 mg/m^2 cisplatin a day for 4 days. Minor deviations in the radiotherapy protocol were noted for 15 (12%) of 125 patients, mainly because the 15 fractions were extended beyond the recommended 3 weeks because of public holidays or treatment-related delays. One patient allocated surgery alone elected to have preoperative chemoradiotherapy at an institution that did not participate in the study, but did proceed to have surgery.

In a more detailed analysis of 38 (30%) of 125 patients randomly assessed for compliance with the radiotherapy protocol, we noted one major violation, in which the spinal-cord tolerance had been exceeded by more than 10%. There were three minor violations in field sizes, in which the coverage of the tumour was 50–100% of the specified margin.

Of the 128 patients assigned preoperative chemoradiotherapy, resection was not done in 23 patients: three died before chemoradiotherapy, nine had progressive disease after chemoradiotherapy, three were medically unfit after chemoradiotherapy, seven had exploratory surgery only, and one refused surgery. Of the 128 patients assigned surgery alone, resection was not done in 18 patients: four had progressive disease, 13 had exploratory surgery only, and one refused and had definitive chemoradiotherapy only (table 2).

In patients who underwent resection, surgery was done by a formal thoracic and abdominal approach to the oesophagus with an intrathoracic or cervical anastomosis in 98 (93%) of 105 patients assigned chemoradiotherapy and in 105 (95%) of 110 patients assigned surgery alone. Other approaches such as transhiatal blunt dissection, left thoracotomy, or the abdominal approach with lower transdiaphragmatic resection were much the same in both groups. Groups did not differ in the approach or extent of nodal dissections. 93 (43%) of 215 patients had a two-field dissection, and the remaining patients had a lesser procedure. The surgery-alone group had significantly fewer R0 resections than did the chemoradiotherapy-and-surgery group (76 [59%] of 128 *vs* 103 [80%] of 128, p=0·0002). Patients allocated surgery alone who underwent complete resection had a significantly higher pathological lymph-node involvement than did those allocated chemoradiotherapy and surgery who underwent complete resection (p=0·003; table 2). Patients with residual disease after surgery were managed at the discretion of the treating physician.

Groups did not differ in progression-free survival and overall survival (hazard ration [HR] 0·82 [95% CI 0·61–1·10] and 0·89 [0·67–1·19], respectively, figure 2). Median time to disease progression for patients assigned chemoradiotherapy and surgery was 16 months (range 0–120), compared with 12 months (0–98) for those assigned surgery alone. Median overall survival was 22·2 months (0·6–120·0) for patients allocated chemoradiotherapy and surgery compared with 19·3 months (0·4–98·0) for those allocated surgery alone. Median progression-free survival in the 16 patients who had a pathological complete response after chemoradiotherapy was 26·2 months (3·9–98·0), and 3-year survival was 49%.

In univariate analyses, patients with tumours in the lower oesophagus, tumours with non-squamous histology, or poorly differentiated tumours, and those aged older than 60 years had decreased progression-free survival and overall survival compared with tumours of the middle or upper oesophagus, tumours of squamous histology, moderate or well differentiated tumours, and patients aged 60 years or younger, respectively (table 3). In a multivariate analysis of 161 patients with non-squamous tumours and 95 with squamous tumours, non-squamous tumours were associated with an increased risk of disease progression (HR 2·05 [95% CI 1·46–2·87]), as were 148 patients aged older than 60 years compared with 108 patients aged 60 years or younger (1·45 [1·07–1·97]). Independent prog-

nostic factors for decreased overall survival on multivariate analysis were non-squamous tumours (1·47 [1·06–2·05]), poorly differentiated tumours (1·50 [1·07–2·01]), and age older than 60 years (1·39 [1·01–1·92]).

The reduction in risk of progression for preoperative chemoradiotherapy compared with that for surgery alone was similar for many subgroups and, based on the width of the CIs, was consistent with the overall estimate of treatment effect (figure 3). However, patients with squamous-cell tumours showed a non-significant trend towards better outcomes with chemoradiotherapy than did those with non-squamous tumours (p=0·07), as did patients with middle-site or upper-site tumours compared with lower-site tumours (p=0·06). Moreover, women showed a non-significant trend towards better outcomes with chemoradiotherapy than did men, but this difference was not significant (p=0·08). Figure 4 shows progression-free survival and overall survival by histological subtype.

Clinical tumour response was assessed by endoscopy before surgery in 73 (57%) of 128 patients assigned chemoradiotherapy. The reasons for the poor compliance with this procedure are unclear, but could be because of concerns in delaying subsequent surgery. A complete response was recorded for 21 of 73 patients who underwent preoperative endoscopy, and 13 of 29 complete clinical responders at the time of surgery had no disease on histological analysis. Five patients had a complete endoscopic and histological response in the primary-tumour site, but had positive nodes. 49 of 73 patients had a partial response or stable disease on endoscopy, three of whom had a complete histological response; three patients had progressive disease. In the 103 patients who had chemoradiotherapy and a curative (ie, R0/R1) resection (table 2), 16 (16%) had a pathological complete response. A histological complete response was more common in patients with squamous-cell carcinoma (ten of 37) than in those with adenocarcinoma (six of 66, p=0·02). These findings are consistent with those from our pilot study.[5]

	Chemoradiotherapy and surgery (n=103)	Surgery alone (n =103)
Any failure	61 (59%)	68 (66%)
Local failure only*	11 (11%)	14 (14%)
Local failure*, nodes involved†	4 (4%)	5 (5%)
Local failure* and distant failure‡	4 (4%)	12 (12%)
Local failure* and distant failure‡, nodes involved†	2 (2%)	9 (9%)
Distant failure only‡	46 (45%)	42 (41%)
Distant failure‡, nodes involved†	26 (25%)	36 (35%)
No failure	42 (41%)	35 (34%)

*Failure within the radiation field in patients allocated chemoradiotherapy, or in a potential field in those allocated surgery alone. †Failure in patients with node involvement on histological analysis. ‡Failure outside radiation field in patients allocated chemoradiotherapy, or outside a potential field in those allocated surgery alone.

Table 5: **First failure in patients with curative (ie, R0 or R1) resection**

Chemoradiotherapy was tolerated well. No deaths were directly attributable to preoperative treatment; two patients died before receiving preoperative chemoradiotherapy because of disease progression and one died from unrelated comorbidity. Data for acute toxic effects were available for 123 (96%) of 128 patients who received chemoradiotherapy (three patients died before receiving treatment and data were not recorded for two). The most commonly reported grade 3–4 event was oesophagitis (table 4). Nausea or vomiting, infections, pneumonitis, mucositis, and diarrhoea were less common. One patient died of a cerebrovascular accident after completion of chemoradiotherapy before having surgery.

11 (5%) of 215 patients who underwent resection had a surgery-related death. The causes of death were sepsis (two in each group), respiratory complications (two in the chemoradiotherapy-and-surgery group and three in the surgery-alone group), myocardial infarction (one in the chemoradiotherapy-and-surgery group), and pulmonary embolus (one in the surgery-alone group). 63 (49%) of 128 patients assigned chemoradiotherapy and surgery and 70 (55%) of 128 patients assigned surgery alone had complications as a result of surgery. Groups did not differ in the frequency or type of complications. Major pulmonary complications occurred in 25 (20%) of 128 assigned chemoradiotherapy and surgery and in 36 (28%) of 128 assigned surgery alone, cardiac complications in 15 (12%) of 128 assigned chemoradiotherapy and surgery and 14 (11%) of 128 assigned surgery alone, and anastomotic leaks in six (5%) of 128 assigned chemoradiotherapy and surgery and six (5%) of 128 assigned surgery alone. 24 (19%) of 128 patients assigned chemoradiotherapy and surgery and 31 (24%) of 128 assigned surgery alone had anastomotic stricture formation requiring intervention. The median length of stay in hospital was 14 days in both groups (range 5–82 in the chemoradiotherapy-and-surgery group and 2–138 in the surgery-alone group), including patients who did not proceed to a radical resection.

We compared sites of first-treatment tumour failure in those who underwent a curative (ie, R0/R1) resection according to whether the treatment failure was local, distant, or both. At the time of analysis, 61 (59%) of 103 patients allocated chemoradiotherapy and surgery and 68 (66%) of 103 allocated surgery alone had evidence of treatment failure (p=0·31, table 5). The presence of nodal disease did not predict for change in the patterns of failure.

Discussion

We have shown that neoadjuvant chemoradiotherapy with cisplatin and fluorouracil did not confer a survival benefit for patients with localised resectable oesophageal cancer. However, preoperative chemoradiotherapy was tolerated well, and patients assigned

this treatment had more complete resections with clear margins and fewer positive lymph nodes than did those assigned surgery alone. Univariate exploratory analyses suggested that progression-free survival and overall survival were significantly better for patients with squamous-cell cancer who were assigned to preoperative chemoradiotherapy compared with those assigned surgery alone; however, the trial was underpowered to determine the real magnitude of benefit in this subgroup.

Outcomes after curative surgery vary substantially between treatment centres[8] because of case selection, extent of clinical staging, surgical expertise, and standards of postoperative care. Such variation might mask the benefits achieved by a moderately effective adjuvant therapy, and as such, conclusions from trials showing benefit from adjuvant therapy have been criticised because outcomes in the control (ie, surgery alone) group have been regarded as suboptimum.

The outcomes in the control group of our trial compare favourably with the results of the best groups in surgical adjuvant trials reported in the past 10 years, including assessments of postoperative radiotherapy,[1,2] preoperative radiotherapy,[9] preoperative chemotherapy,[10–13] and preoperative chemoradiotherapy.[14–19] We recognise the variation in the minimum number of lymph nodes dissected in the pragmatic design of our trial. Although two-field nodal dissections were not done for every patient, local failure was not more common in this trial compared with series from France[20] and Britain,[21] in which this technique was done. Furthermore, we accept that our clinical staging, by modern standards, was suboptimum, and that locally advanced tumours could not be distinguished. However, our finding that 69 (54%) of 128 patients in the surgery-alone group had nodes involved suggests a high proportion of patients with advanced disease, although comparison of outcomes in the control group in our trial with those from other surgical studies—such as that by Mariette and co-workers[22] where the dominant subtype was squamous-cell carcinoma—is difficult. Our trial is therefore a good test of the ability of a neoadjuvant chemoradiotherapy regimen to produce genuine improvements in outcome.

The ability of the chemoradiotherapy regimen in our trial to produce substantial downstaging cannot be refuted: a complete pathological response was seen in six patients with adenocarcinoma and in ten with squamous cancers, findings which are consistent with those from our pilot study,[5] and with the significantly increased R0 resection in the chemoradiotherapy group compared with the surgery-alone group. The inability of endoscopy to predict for pathological complete response in about 50% of patients with a clinical complete response has been described previously.[23] We think that our strict approach to the definition of local failure when using a local adjuvant therapy is justified, and the benefit of that strategy is confirmed by the local outcomes. Although assessors of the local outcomes were not blinded at the time of the assessment, we think that the measurements were without bias.

We conclude that the two main types of cancer that develop in the oesophagus (ie, squamous and non-squamous) not only have different causes, epidemiological patterns, and cellular derivations, but also have natural histories that are modified to a different extent by the preoperative regimen used in our trial. Our results also showed that tumour site is a reasonable surrogate for histological subtype. Adenocarcinoma was the commonest subtype in our trial population (62%), and chemoradiotherapy substantially downstaged this tumour subtype, but did not improve progression-free survival or overall survival. Fewer patients with adenocarcinoma of the oesophagus achieved a pathological complete response compared with previous trials,[17,19] possibly because a lower radiation dose or only one cycle of chemotherapy was used in our trial. A favourable response to chemoradiotherapy with our regimen in patients with adenocarcinoma is likely to occur preferentially in tumours with favourable biological characteristics, which could have been managed with surgery alone. Moreover, improvements in outcome in patients with adenocarcinoma are unlikely to be achieved unless adjuvant strategies are developed that eradicate microscopic metastatic disease outside the surgical sample in many patients. However, meta-analyses by Fiorca and colleagues[24] and Kaklamanos and co-workers[25] include data from the only positive trials reported to date.[11,17] Our trial has produced consistent findings with these studies and suggests that development of an adjuvant strategy that will lead to substantial improvements in postoperative outcomes for patients with adenocarcinoma is still a long way off. Such a conclusion is disappointing for a disease with increasing incidence in developed countries.

The effectiveness of the preoperative chemoradiotherapy regimen in patients with squamous-cell cancer is more encouraging. No histological evidence of tumour was found in the surgical samples of ten (22%) of 45 patients with squamous-cell cancer who were assigned chemoradiotherapy. Furthermore, those with squamous-cell tumours had substantial downstaging of tumours and improved survival on univariate analyses. The doses used in our regimen might be adequate for a benefit in patients with squamous-cell carcinoma, although we cannot conclude this possibility with certainty on the basis of the subgroup analysis. The number of patients with squamous-cell cancer recruited to this trial (95) was smaller than we expected when we designed the trial. However, long-term patterns of failure and survival data[26] for 131 patients with inoperable squamous-cell cancer given high-dose chemoradiotherapy (two sequential courses of the

preoperative chemoradiotherapy used in the present trial) suggest that chemoradiotherapy is more than twice as effective as radiotherapy alone, and leads to outcomes that compare favourably with oesophagectomy in well-selected patients.[26] Although the benefits noted for patients with squamous-cell cancer who were assigned chemoradiotherapy in our trial might be real effects, the results in this subgroup still do not differ significantly from the overall results, and a larger trial is needed to determine the real magnitude of this benefit. However, the declining incidence of squamous oesophageal cancer makes such a trial unlikely in Australia and New Zealand, but remains feasible in countries that are more heavily populated. Distant metastases are a common cause of death in patients given preoperative chemoradiotherapy who have residual cancer in the lymph nodes found in surgical samples, and suggests that adjuvant chemotherapy should be incorporated into study designs. Irrespective of histological subtype, neoadjuvant chemoradiotherapy leads to a locoregional benefit of improved resectability, reduced nodal involvement, and decreased local recurrence. However, the translation of this effect into a survival benefit might be more pronounced in patients with squamous-cell carcinoma.

Improvements in preoperative staging have, and will, continue to improve overall outcomes by the exclusion of patients with occult systemic disease. Given the poor sensitivity of CT scans in assessment of nodal disease as shown by our study and others, new techniques are urgently needed to exclude nodal metastases and allow better stage stratification preoperatively. Endoscopic ultrasonography, which improves the detection of nodal disease in patients with oesophageal cancer,[27] was not readily available at the time our study was done. This modality would have assisted in preoperative stage stratification, but would not have excluded patients who were node positive, in whom the sensitivity is only 60–70%. PET also aids detection of nodal and distant metastases, and might provide useful information regarding response to adjuvant therapy.[28] PET scanning would have excluded an extra 10% of patients with distant metastases. Future trials should include these modalities and laparoscopy for staging purposes.

In conclusion, this trial does not lend support to the routine use of preoperative chemoradiotherapy with cisplatin and fluorouracil for patients with oesophageal cancer, particularly those with adenocarcinoma, who might need more cycles of chemotherapy or increased doses of radiotherapy to show a survival benefit. Our findings lend support to further assessment of chemoradiotherapy in patients with squamous-cell cancers. The different responses of squamous-cell tumours and non-squamous-cell tumours to chemoradiotherapy suggest these subtypes should be assessed separately in future trials.

Contributions

B Burmeister was a radiation oncologist, trial chairman, TROG investigator, principal investigator at Princess Alexandra Hospital, and reviewer for radiation oncology, pathology, and failures; M Smithers was an oesophageal surgeon, trial cochairman, and reviewer for surgery; V Gebski was the trial statistician; L Fitzgerald was the principal trial coordinator; J Simes was a medical oncologist; P Devitt was an oesophageal surgeon and the principal investigator at Royal Adelaide Hospital; S Ackland was a medical oncologist, the AGITG investigator, and the principal investigator at Newcastle Mater Hospital; D Gotley was an oesophageal surgeon and had a major contribution to the trial; D Joseph was a radiation oncologist and the principal investigator at Sir Charles Gairdner Hospital; J Millar was a radiation oncologist and the principal investigator at Alfred Hospital; J North was a radiation oncologist, New Zealand representative of the trial, and principal investigator at Dunedin Hospital; E Walpole was a medical oncologist and had a major contribution to the trial; J Denham was a radiation oncologist, the phase II trial chairman, and chair of trial development committee.

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Conflict of interest

We declare no conflicts of interest.

Acknowledgments

This trial was supported by grants from the National Health and Medical Research Council of Australia (NHMRC). The funding supported central data management and statistical support in Sydney, and there was also a per-capita payment to all contributors.

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