

# Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial

Medical Research Council Oesophageal Cancer Working Party\*

## Summary

**Background** The outlook for patients with oesophageal cancer undergoing surgical resection with curative intent is poor. We aimed to assess the effects of preoperative chemotherapy on survival, dysphagia, and performance status in this group of patients.

**Methods** 802 previously untreated patients with resectable oesophageal cancer of any cell type were randomly allocated either two 4-day cycles, 3 weeks apart, of cisplatin 80 mg/m<sup>2</sup> by infusion over 4 h plus fluorouracil 1000 mg/m<sup>2</sup> daily by continuous infusion for 4 days followed by surgical resection (CS group, n=400), or resection alone (S group, 402). Clinicians could choose to give preoperative radiotherapy to all their patients irrespective of randomisation. Primary outcome measure was survival time. Analysis was by intention to treat.

**Findings** No patients dropped out of the study. Resection was microscopically complete in 233 (60%) of 390 assessable CS patients and 215 (54%) of 397 S patients ( $p<0.0001$ ). Postoperative complications were reported in 146 (41%) CS and 161 (42%) S patients. Overall survival was better in the CS group (hazard ratio 0.79; 95% CI 0.67–0.93;  $p=0.004$ ). Median survival was 512 days (16.8 months) in the CS group compared with 405 days (13.3 months) in the S group (difference 107 days; 95% CI 30–196), and 2-year survival rates were 43% and 34% (difference 9%; 3–14).

**Interpretation** Two cycles of preoperative cisplatin and fluorouracil improve survival without additional serious adverse events in the treatment of patients with resectable oesophageal cancer.

*Lancet* 2002; **359**: 1727–33

## Introduction

The outlook for patients with oesophageal cancer who undergo surgical resection with curative intent is poor, with only about 20–30% survival at 2 years. Factors that contribute to this dismal outlook include presence of locally advanced disease and undetected metastatic cancer at diagnosis. Because of the high rates of locoregional and distant failure, there is much interest in the combination of systemic chemotherapy and local surgical treatment.

There is increasing evidence that oesophageal cancer responds to combination chemotherapy regimens based on cisplatin. Response rates before surgery of 40–60% for squamous carcinoma and 30–40% for adenocarcinoma, and 2-year survival rates of 30–40% with preoperative chemotherapy plus surgery, have been reported.<sup>1–6</sup> However, what is not clear from the results of these studies is whether these survival rates are attributable to selection of patients or whether they are an effect of chemotherapy.

We therefore did a pragmatic randomised trial in patients thought to have resectable cancer of the oesophagus, comparing surgical resection as locally practised with or without preoperative chemotherapy, to investigate whether chemotherapy first lengthens survival and second affects dysphagia and performance status. We chose the combination of cisplatin and fluorouracil since they were two of the most active single agents in both squamous carcinoma and adenocarcinoma,<sup>7</sup> and because of reported efficacy in combination.<sup>1,3,7–9</sup> We decided to give only two cycles at modest doses in view of the reported rapidity with which responses to chemotherapy arose, to keep delay of definitive surgical treatment to a minimum, to avoid excessive toxicity and morbidity before major surgery in patients who are often old and undernourished, and to encourage acceptability of the trial design by patients.

## Patients and methods

### Patients

Patients were eligible for the study if they had previously untreated cancer of the oesophagus that was judged resectable and had been microscopically confirmed as squamous carcinoma, adenocarcinoma, or undifferentiated carcinoma. Patients were invited to take part in the study by the clinician responsible for their care. We included tumours of the upper, middle, or lower third of the oesophagus and of the cardia, but not post-cricoid tumours. Patients were not eligible if they had other previous or concomitant malignant disease, apart from basal-cell carcinoma, or if there was cervical lymph-node involvement or evidence of metastases. Patients had to have no contraindication to surgery or chemotherapy, normal renal function, white-cell count  $>3.5 \times 10^9/L$ , and platelet count  $>100 \times 10^9/L$ . Local ethics committees approved the protocol, and patients' informed consent was obtained.

### Procedures

We randomly allocated eligible patients to either immediate preoperative chemotherapy followed by surgical resection (CS group) or immediate surgical resection alone (S group). Randomisation was done by telephone call to the Cancer Division of the Medical Research Council Clinical Trials Unit. We randomly assigned patients by minimisation, with

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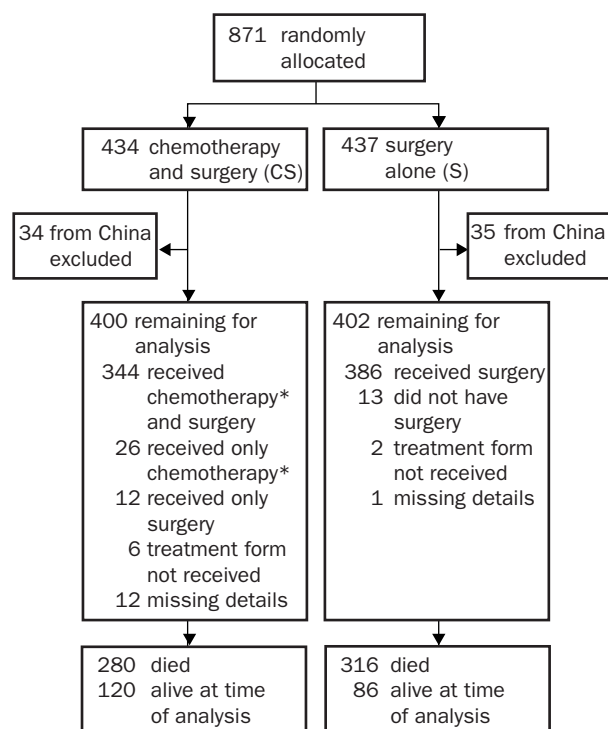


Figure 1: Trial profile

\*One or two cycles.

criteria of surgeon, site of tumour (upper, middle, lower, cardia), WHO performance status,<sup>10</sup> and histology (squamous, adenocarcinoma, undifferentiated). Because of the nature of the treatment, randomisation was not masked.

Chemotherapy comprised two 4-day cycles of cisplatin 80 mg/m<sup>2</sup> by intravenous infusion over 4 h on day 1 and fluorouracil 1000 mg/m<sup>2</sup> daily as a continuous infusion over 96 h, with an interval of 3 weeks between the first day of each cycle. We gave CS patients antiemetics and hydration intravenously before, during, and after cisplatin infusion. For patients in this group, surgical resection was done 3–5 weeks after the start of the second cycle of chemotherapy, and for patients in the S group, surgery was done as soon as possible after randomisation. The local surgeon decided the surgical procedure for patients in both treatment groups, in accordance with site of the tumour and local practice.

Clinicians chose whether to give preoperative external-beam radiotherapy, but if they did they had to use it for all their trial patients irrespective of randomisation, and the dosage and fractionation policy had to be the same in both treatment groups. If radiotherapy was given, we recommended 25 Gy in five fractions over 1 week, 32.5 Gy in ten fractions over 2 weeks, or a biologically equivalent dose.

Primary outcome measure was survival time. Secondary outcome measures were dysphagia and performance status. Patients were assessed before start of treatment, on completion of therapy, at 3, 6, 9, and 12 months from date of randomisation, and then 6-monthly until death. Assessments before treatment included chest radiography, bronchoscopy for upper-third and middle-third tumours, and liver scan by ultrasonography or computed tomography. At all assessments, the clinician recorded the patient's degree of dysphagia and WHO performance status, with the definitions in table 1. At every follow-up assessment, details of any local recurrence, metastases, and anticancer treatment were given.

### Statistical analysis

Sample-size calculations based on the log-rank test showed that we needed 800 patients to detect an increase in 2-year survival from 20% to 30%, with 90% power and two-sided  $\alpha$  of 0.05. We did analyses by intention to treat with SAS (version 6.12). Survival was calculated from date of randomisation to date of death; surviving patients were censored at the date they were last known to be alive. We calculated disease-free survival from a landmark time of 6 months after date of randomisation to allow for the difference in timing of surgery between the two treatment groups. In this analysis, events—including incomplete resection, local and distant recurrence, and death—arising within the first 6 months were regarded as events at this landmark time. We produced survival curves by the Kaplan-Meier method and made treatment comparisons with the log-rank test. To assess proportions between treatments we used the  $\chi^2$  test, and continuous data were compared with the large-scale normal approximation of the Mann-Whitney  $U$  test.  $\chi^2$  tests for interaction, trend, or both were applied to assess whether treatment effect varied according to prognostic factors.

An independent data monitoring and ethics committee monitored data and interim analyses yearly. Conventional survival analyses were supplemented by a Bayesian analysis,<sup>11</sup> which showed the probable effect our results would have on groups of clinicians with various levels of enthusiasm for chemotherapy. This analysis protected against unduly early termination of the trial, emphasising the need to continue until we obtained a convincing result for a broad range of clinicians.

### Role of the funding source

The sponsor appointed the writing committee, who interpreted data, wrote the report, and submitted it for publication.

### Results

Between March, 1992, and June, 1998, 802 patients from 42 European centres were randomly assigned either chemotherapy followed by surgery (CS group, n=400) or surgery alone (S group, 402; figure 1). 69 patients from China were also randomly allocated (34 to CS, 35 to S) but, because of changes in funding of their health-care system, recruitment ceased, and we could not obtain follow-up data. These patients were therefore excluded from the analysis.

Patients' characteristics were well balanced between the two treatment groups (table 1): over a third were younger than age 60, three-quarters were male, two-thirds had lower-third tumours, and two-thirds had adenocarcinoma. Over three-quarters of patients had dysphagia, and WHO performance status was normal in two-thirds.

Of the 400 CS patients, details of chemotherapy were available for 389, of whom 372 (96%) received chemotherapy: 350 had both cycles and 22 one. The most frequent reasons why no chemotherapy or only one cycle was given were intercurrent disease (n=9), patient's refusal (8), death (8), and progressive disease (5). 56 cycles in 53 patients were delayed or reduced dosage was given. Reasons were neutropenia (30 cycles), organisational problems (9), other toxic events (8), intercurrent disease (5), patient's refusal (3), and unknown (1). Adverse reactions to chemotherapy, other than neutropenia, were mucositis, stomatitis, or mouth ulcers (5 cycles), nausea (3), vomiting (2), and deep-vein thrombosis (1); some cycles induced more than one type of reaction.

Data on surgery were available for 392 CS and 399 S patients (table 2). The most frequent reasons for no surgery

	CS group (n=400)	S group (n=402)	Total (n=802)
<b>Age (years)</b>			
<60	160 (40%)	156 (39%)	316 (39%)
60–69	154 (39%)	167 (42%)	321 (40%)
≥70	86 (22%)	79 (20%)	165 (21%)
Median (range)	63 (36–84)	62 (30–80)	63 (30–84)
<b>Sex</b>			
Male	306 (77%)	297 (74%)	603 (75%)
Female	94 (24%)	105 (26%)	199 (25%)
<b>Site of tumour</b>			
Upper-third	3 (1%)	4 (1%)	7 (1%)
Middle-third	97 (24%)	102 (25%)	199 (25%)
Lower-third	260 (65%)	254 (63%)	514 (64%)
Cardia	40 (10%)	42 (10%)	82 (10%)
<b>Histology</b>			
Squamous	123 (31%)	124 (31%)	247 (31%)
Adenocarcinoma	265 (66%)	268 (67%)	533 (66%)
Undifferentiated	11 (3%)	10 (2%)	21 (3%)
Not known	1 (<1%)	0	1 (<1%)
<b>Degree of dysphagia</b>			
0 Able to swallow all solids without difficulty	60 (16%)	48 (13%)	108 (14%)
1 Difficulty with swallowing some hard solids or particular foods	170 (44%)	148 (40%)	318 (42%)
2 Able to swallow a semi-solid or liquid diet only	111 (29%)	123 (33%)	234 (31%)
3 Able to swallow a liquid diet only	38 (10%)	48 (13%)	86 (11%)
4 Unable to swallow liquids or saliva	4 (1%)	4 (1%)	8 (1%)
Not recorded	17	31	48
<b>WHO performance status<sup>10</sup></b>			
0 Normal activity without restriction	265 (66%)	267 (66%)	532 (66%)
1 Strenuous activity restricted, can do light work/housework	125 (31%)	122 (30%)	247 (31%)
2 Up and about ≥50% of waking hours, all self-care, no work	9 (2%)	12 (3%)	21 (3%)
3 Bed or chair >50% of waking hours, limited self-care	1 (<1%)	0	1 (<1%)
4 Confined to bed or chair, no self-care, completely disabled	0	1 (<1%)	1 (<1%)

Table 1: Pretreatment patients' characteristics

were death in the CS group and tumour unresectability in the S group. Median time from randomisation to surgery was 63 days (IQR 55–75) in the CS group and 16 days (9–27) in the S group. Resection was macroscopically and microscopically complete in more CS patients than S patients ( $p<0.0001$ ).

Preoperative radiotherapy was given to 36 (9%) CS patients and 38 (9%) S patients; all but five in each group were from one centre. The recommended regimen was given to 30 (83%) CS and 33 (87%) S patients. Of the patients who did not receive preoperative radiotherapy, microscopically complete resection was achieved in 212 (60%) CS patients and 187 (53%) S patients ( $p<0.0001$ ).

In the CS group, 13 (3%) patients died before surgery was undertaken compared with two (<1%) in the S group. Postoperative deaths (within 30 days of surgery) and non-fatal postoperative complications arose with closely similar frequency in the two groups.

Data on pathological findings of the resected specimen were available for 342 CS and 327 S patients (table 3). The main reason for missing data was incomplete resection or because resection was not attempted. Tumours in CS patients were smaller ( $p=0.0001$ ), extended less frequently into surrounding tissue, and showed less lymph node involvement, than tumours in S patients. Nodes at any site

	CS group (n=400)	S group (n=402)	Total (n=802)
<b>Surgery done</b>			
Yes	361 (92%)	386 (97%)	747 (94%)
No	31 (8%)	13 (3%)	44 (6%)
Not known	8	3	11
<b>Reason no surgery undertaken</b>			
Died before surgery	13 (3%)	2 (<1%)	15 (2%)
Tumour unresectable	11 (3%)	10 (2%)	21 (3%)
Patient refused	1 (<1%)	0	1 (<1%)
Other	5 (2%)	1 (<1%)	6 (1%)
Not known	1	0	1
<b>Extent of resection</b>			
Macroscopically complete	303 (78%)	278 (70%)	581 (74%)
Microscopically complete (R0)	233 (60%)	215 (54%)	448 (57%)
Microscopically incomplete	70 (18%)	63 (16%)	133 (17%)
Macroscopically incomplete	35 (9%)	52 (13%)	87 (11%)
Not possible	21 (5%)	54 (14%)	75 (10%)
No surgery	31 (8%)	13 (3%)	44 (6%)
Extent not recorded	2	2	4
No surgical information received	8	3	11
<b>Postoperative death*</b>			
	36 (10%)	40 (10%)	76 (10%)
<b>Non-fatal postoperative complications*</b>			
Any	146 (41%)	161 (42%)	307 (41%)
Respiratory	56 (16%)	58 (15%)	114 (15%)
Infection	21 (6%)	32 (8%)	53 (7%)
Anastomotic	23 (6%)	26 (7%)	49 (7%)
Cardiac	14 (4%)	15 (4%)	29 (4%)
Gastrointestinal	8 (2%)	9 (2%)	17 (2%)
Other	24 (7%)	21 (5%)	45 (6%)

\*Percentages based on total patients undergoing surgery.

Table 2: Surgical details

were involved in 195 (58%) CS and 216 (68%) S patients ( $p=0.009$ ). Tumour was present in the lateral resection margins of a quarter of specimens in each group; in the proximal margins, tumour was present in 19 (6%) specimens from CS patients and 20 (6%) from S patients, and in the distal margins in 21 (6%) and 13 (4%) specimens, respectively. Tumour was present in any margin in 97 (29%) CS and 98 (32%) S patients ( $p=0.549$ ).

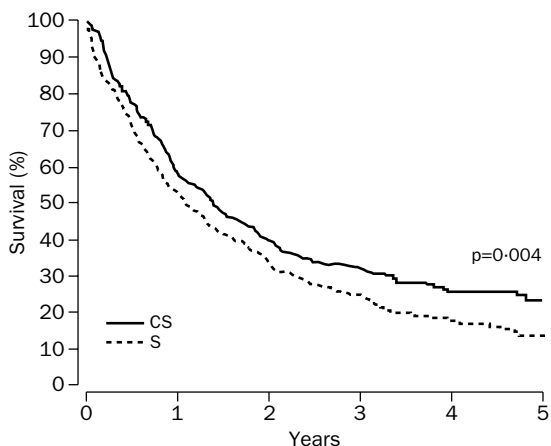
596 patients died during the study (figure 1). Median follow-up for survivors was 36.9 months in CS patients (range 14–2764 days) and 37.9 months in S patients (29–2673 days). 765 (95%) patients were followed up to death or 2 years and 707 (88%) to death or 3 years. Overall survival (figure 2) was better in the CS group than in the S group ( $p=0.004$ ; hazard ratio 0.79; 95% CI 0.67–0.93); estimated reduction in risk of death was 21%. Median survival was 512 days (16.8 months) in the CS group compared with 405 days (13.3 months) in the S group (difference 107 days; 95% CI 30–196) and survival rate at 2 years was 43% compared with 34% (9%; 3–14). Disease-free survival (figure 3) was also better in the CS group than in the S group ( $p=0.0014$ ; hazard ratio 0.75; 95% CI 0.63–0.89).

We saw no evidence that effect of chemotherapy varied in accordance with histology, age, sex, site, dysphagia, or performance status (figure 4). Of 247 patients with squamous carcinoma and 533 with adenocarcinoma (figure 5), hazard ratios for treatment effect were the same (0.78 [95% CI 0.59–1.05] and 0.78 [0.64–0.95], respectively), showing that effect of treatment was closely similar for both histologies. Estimate of treatment effect on overall survival was not altered by removal of 74 patients from the analysis who received preoperative radiotherapy; hazard ratio for the 728 patients (364 CS, 364 S) who did not receive radiotherapy was 0.78 (95% CI 0.66–0.93;  $p=0.005$ ). In the CS group compared with the S group, more patients were alive without residual or recurrent disease ( $p<0.0001$ ; table 4).

	CS group (n=342)	S group (n=327)
<b>Size of tumour (cm)</b>		
None found	14 (4%)	5 (2%)
≤4.0	184 (58%)	103 (34%)
4.1–8.0	99 (31%)	161 (52%)
8.1–12.0	15 (5%)	30 (10%)
>12.0	8 (3%)	8 (3%)
Median (range)	3.0 (0.0–40.0)	4.2 (0.0–53.0)
Not recorded	22	20
<b>Extension of tumour into surrounding tissue</b>		
Yes	155 (49%)	176 (57%)
No	163 (51%)	131 (43%)
Not recorded	24	20
<b>Tumour present in lateral resection margins</b>		
Yes	78 (25%)	83 (28%)
No	235 (75%)	217 (72%)
Not recorded	29	27
<b>Adjacent lymph nodes involved</b>		
Yes	157 (48%)	179 (58%)
No	167 (52%)	130 (42%)
Not recorded	18	18
<b>Subcarinal lymph nodes involved</b>		
Yes	25 (9%)	43 (18%)
No	243 (91%)	190 (82%)
Not sampled/recorded	74	94
<b>Left gastric/coeliac axis lymph nodes involved</b>		
Yes	79 (29%)	83 (33%)
No	194 (71%)	169 (67%)
Not sampled/recorded	69	75
<b>Number of other lymph node sites involved</b>		
0	293 (89%)	271 (86%)
1	29 (9%)	35 (11%)
2	7 (2%)	8 (3%)
3	2 (1%)	1 (<1%)
Not recorded	11	12

Table 3: Examination of resected specimen

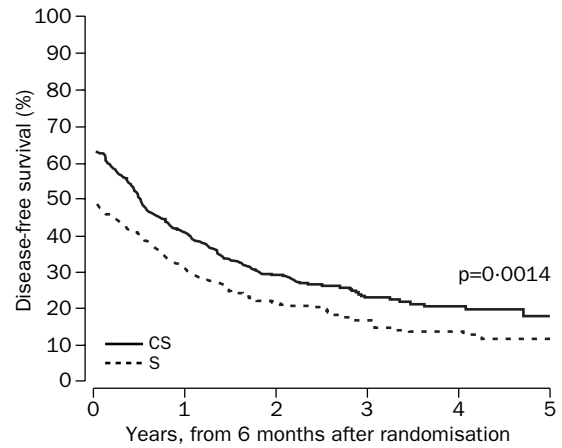
Of the 372 CS patients, data on changes in degree of dysphagia during chemotherapy were available for 319 patients, and on performance status for 317. During chemotherapy, eight (3%) patients died; dysphagia improved in 117 (37%), showed no change in 147 (46%), and deteriorated in 47 (15%). WHO performance status improved in 34 (11%), showed no change in 188 (59%), and deteriorated in 87 (27%). Dysphagia and performance status at 1 year from randomisation are shown in table 5. At 1 year, dysphagia was improved in 96 (28%) CS and 20 (27%) S patients (around half of those alive at 1 year) and was worse in only 27 (8%) and 16 (5%), respectively.



Patients at risk (events)	
CS	400 (164) 231 (73) 143 (26) 81 (13) 36 (2) 14
S	402 (185) 212 (76) 124 (32) 70 (18) 28 (5) 10

Figure 2: Kaplan-Meier curve showing survival from date of randomisation

Two CS patients died after 5 years.



Patients at risk (events)	
CS	400 (237) 156 (43) 96 (16) 48 (4) 25 (2) 9
S	402 (279) 120 (35) 74 (13) 36 (6) 17 (2) 7

Figure 3: Kaplan-Meier curve showing disease-free survival from landmark time of 6 months after date of randomisation

Performance status was improved in 13 (4%) CS and 21 (6%) S patients, and was worse in 83 (24%) and 56 (17%), respectively (45% and 36% of those alive at 1 year, respectively). Of 96 CS and 90 S patients with improved dysphagia, performance status was unchanged in 49 (51%) and 48 (53%) and worse in 39 (41%) and 27 (30%), respectively. The amounts of data missing, although substantial, were closely similar in the two treatment groups, and so it is unlikely that informative censoring has introduced substantial bias to this analysis.

**Discussion**

We have shown that two cycles of preoperative cisplatin and fluorouracil improve overall and disease-free survival compared with surgical resection alone in patients with resectable oesophageal cancer. Adherence to chemotherapy was good, and survival benefit seemed to be consistent for squamous cancers and adenocarcinomas. In patients who received chemotherapy, surgical resection was more often complete, and resection specimens showed less extension into surrounding tissue and less lymph node involvement, than in patients who had surgery alone, although the proportion of patients with involved resection margins and sites of primary failure were closely similar in the two treatment groups. Resection was more often complete after chemotherapy even though surgery was undertaken later in this group of patients, clearly showing an effect of chemotherapy on the tumour.

The chemotherapy regimen used in our trial proved to be highly acceptable to patients. It required few changes for toxic effects and substantially improved dysphagia before surgery. Carey and colleagues<sup>1</sup> also reported that patients were fitter for resection after two cycles of cisplatin 100 mg/m<sup>2</sup> on day 4 and fluorouracil 1000 mg/m<sup>2</sup> by continuous infusion for 4 days than before chemotherapy in a non-randomised study of 24 patients with squamous cancer.

Our results differ from those reported for the North American Intergroup by Kelsen and colleagues.<sup>12</sup> These investigators did a randomised trial comparing surgical resection with or without preoperative and postoperative chemotherapy in 467 patients. They reported no significant difference between the two treatment groups in overall or disease-free survival. Comparison of this trial with ours, and identification of differences between them that might help to explain the discrepant results, is important.

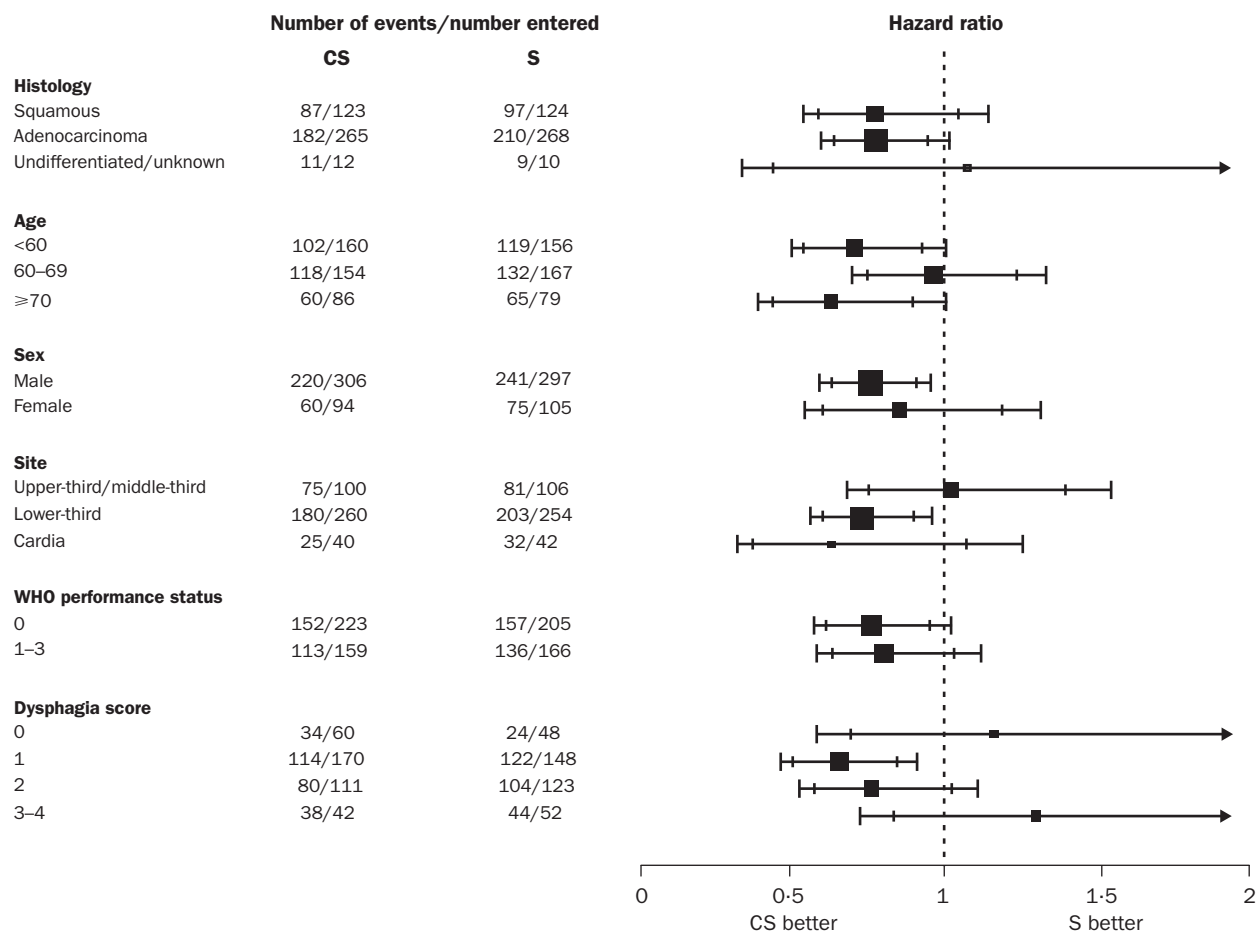


Figure 4: **Survival by characteristics at randomisation**

Centre of each square indicates hazard ratio, and area of square the amount of information. Lines on either side indicate 95% and 99% CIs.

Although comparisons across trials must be made with caution, results of surgery alone were closely similar between our trial (in which surgeons decided the surgical procedure according to local practice) and the Intergroup trial (in which surgical procedures were prescribed in the protocol). Survival differences between the two trials were seen in the CS groups: median survival was 2 months longer and 2-year survival 8% better in our trial than in the Intergroup trial.

The populations recruited to the two trials were closely similar. In the Intergroup trial compared with our trial, 84% and 75% of patients were male; 54% and 66% had adenocarcinoma; median age was 62 and 63 years; and the two treatment groups were well balanced with respect to pretreatment characteristics of patients in both trials. The small differences in patients' characteristics are unlikely to explain the different outcomes.

Although the same anticancer drugs were used in both trials, in the Intergroup trial, patients were offered three cycles of preoperative cisplatin 100 mg/m<sup>2</sup> on day 1 and fluorouracil 1000 mg/m<sup>2</sup> daily as a continuous infusion from day 1 for 5 days every 4 weeks. Patients with stable or responding disease and resection margins free of tumour were offered a further two cycles of chemotherapy postoperatively, but with the cisplatin dose reduced to 75 mg/m<sup>2</sup>. In our trial, patients were offered only two cycles of preoperative cisplatin 80 mg/m<sup>2</sup> on day 1 and fluorouracil 1000 mg/m<sup>2</sup> daily from day 1 for 4 days at an interval of 3 weeks and no postoperative chemotherapy. Thus, total prescribed preoperative doses were cisplatin 300 mg/m<sup>2</sup> and fluorouracil 15 000 mg/m<sup>2</sup> over 8 weeks in the Intergroup

trial compared with cisplatin 160 mg/m<sup>2</sup> and fluorouracil 8000 mg/m<sup>2</sup> over 3 weeks in our trial. Total postoperative doses were cisplatin 150 mg/m<sup>2</sup> and fluorouracil 10 000 mg/m<sup>2</sup> in the Intergroup trial compared with no dose in our trial.

In the Intergroup trial, 71% of patients who were assigned chemotherapy received all three preoperative cycles, 13% received two cycles, 16% one cycle, and 1% did not receive any chemotherapy. Although 100% of the planned doses were given for the first cycle, this proportion dropped to 84% for the second, and 70% for the third cycle. Of patients eligible for postoperative chemotherapy,

	CS group (n=400)	S group (n=402)
<b>Alive and without residual or recurrent disease</b>	107 (27%)	72 (18%)
<b>Nature of first failure</b>		
Residual disease	35 (9%)	52 (13%)
Resection not possible	21 (5%)	54 (13%)
Local recurrence	31 (8%)	32 (8%)
Distant metastases	49 (12%)	41 (10%)
Local recurrence and distant metastases	18 (5%)	11 (3%)
Death with cancer but site of failure not reported	88 (22%)	94 (22%)
Death from other or unspecified cause	51 (13%)	46 (11%)
<b>Total deaths</b>	280 (70%)	316 (79%)
<b>Cause of death</b>		
Cancer-related	215 (78%)	249 (80%)
Surgery-related	20 (7%)	23 (7%)
Other	41 (15%)	40 (13%)
Not known	4	4

Table 4: **Sites of first failure, survival status, and cause of death**

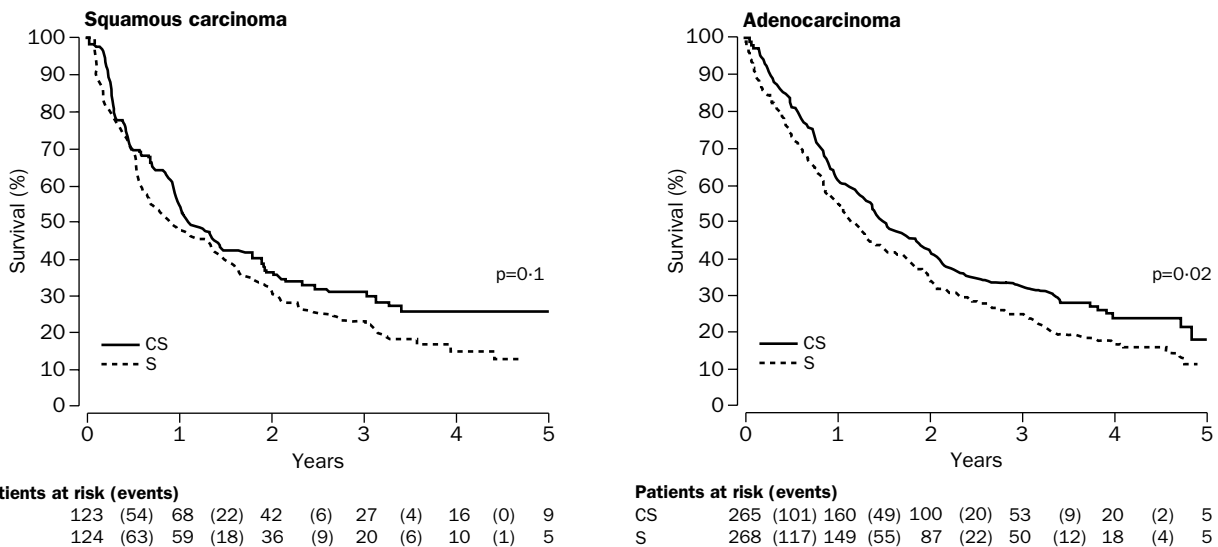


Figure 5: Survival from date of randomisation by histology  
One patient with squamous carcinoma and one with adenocarcinoma died after 5 years.

48% received none, 38% received both cycles, and the remaining 14% only one cycle. In our trial, 90% of patients received both preoperative cycles, 6% one cycle, and 4% no chemotherapy. For these differences to account for the different outcomes, if only in part, one would have to argue that any benefit from the large individual and total doses of chemotherapy given in the Intergroup trial was nullified by toxic effects, and that the benefit seen in our trial was related to choice of a less-demanding regimen in patients who are frequently undernourished.

	CS group (n=400)	S group (n=402)
<b>Degree of dysphagia</b>		
0	110 (57%)	93 (56%)
1	56 (29%)	55 (33%)
2	20 (10%)	16 (10%)
3	3 (2%)	3 (2%)
4	4 (2%)	0
Death during year	162	185
Not known	45	50
<b>WHO performance status</b>		
0	66 (34%)	64 (38%)
1	90 (47%)	78 (47%)
2	28 (15%)	21 (13%)
3	4 (2%)	4 (2%)
4	4 (2%)	0
Death during year	162	185
Not known	46	50

Table 5: Dysphagia and performance status scores at 1 year

Reference	Drugs and doses	Interval between cycles	Number of patients	Hazard ratio (95% CI)
4	Preoperative: two cycles cisplatin, vindesine, bleomycin Postoperative: four cycles cisplatin, vindesine	Not stated	39	0.79 (0.48-1.28)
14	Preoperative: two cycles cisplatin, bleomycin	2 weeks	91	1.12 (0.87-1.43)
15	Preoperative: three cycles cisplatin, fluorouracil	3 weeks	46	1.09 (0.77-1.55)
16	Preoperative: two cycles cisplatin, vinblastine, bleomycin	4 weeks	46	1.34 (0.77-2.31)
17	Preoperative: two to four cycles* cisplatin, etoposide	Not stated	160	Not possible to estimate
OESO†	Preoperative: two cycles cisplatin, vindesine, bleomycin Postoperative: three cycles cisplatin, vindesine	4 weeks 6 weeks	137	0.89 (0.65-1.21)
18	Preoperative: two cycles cisplatin, fluorouracil	3 weeks	147	0.69 (0.51-0.94)
19	Preoperative: two to three cycles* cisplatin, fluorouracil	3 weeks	94	1.00 (0.67-1.51)
12	Preoperative: three cycles cisplatin, fluorouracil Postoperative: two cycles cisplatin, fluorouracil	4 weeks	467	1.07 (0.87-1.32)
This study	Preoperative: two cycles cisplatin, fluorouracil	3 weeks	802	0.79 (0.67-0.93)

\*Only patients whose cancers showed response to chemotherapy were offered more than two cycles. †OESO=International Organisation for Statistical Studies on Diseases of the Oesophagus; Robert Giuli, personal communication.

Table 6: Chemotherapy regimens and hazard ratios for randomised trials comparing surgical resection with or without preoperative chemotherapy

1, implying a survival benefit with chemotherapy, and five had hazard ratios of 1 or greater. With the exception of our trial and the Intergroup trial, in which hazard ratios are stated, we should emphasise that these are approximate estimates. Hazard ratios range from 0.69 to 1.34, and there is substantial heterogeneity ( $p=0.02$ ).

In conclusion, our data suggest that preoperative chemotherapy with two cycles of cisplatin 80 mg/m<sup>2</sup> on day 1 and fluorouracil 1000 mg/m<sup>2</sup> daily by continuous infusion days 1–4, with an interval of 3 weeks between the first day of each cycle, should be considered for patients with resectable cancer of the oesophagus. This regimen would be appropriate as a control in further randomised trials designed to identify more beneficial regimens of preoperative chemotherapy or chemoradiotherapy.

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#### Conflict of interest statement

None declared.

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