Original article

Adjuvant therapy following oesophagectomy for adenocarcinoma in patients with a positive resection margin

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Background: **The role of adjuvant therapy in patients with oesophagogastric adenocarcinoma treated by neoadjuvant chemotherapy is contentious. In UK practice, surgical resection margin status is often used to classify patients for receiving adjuvant treatment. The aim of this study was to assess the survival benefit of adjuvant therapy in patients with positive (R1) resection margins.**

Methods: **Two prospectively collected UK institutional databases were combined to identify eligible patients. Adjusted Cox regression analyses were used to compare overall and recurrence-free survival according to adjuvant treatment. Recurrence patterns were assessed as a secondary outcome. Propensity score-matched analysis was also performed.**

Results: **Of 616 patients included in the combined database, 242 patients who had an R1 resection were included in the study. Of these, 112 patients (46·3 per cent) received adjuvant chemoradiotherapy, 46 (19·0 per cent) were treated with adjuvant chemotherapy and 84 (34·7 per cent) had no adjuvant treatment. In adjusted analysis, adjuvant chemoradiotherapy improved recurrence-free survival (hazard ratio (HR) 0·59, 95 per cent c.i. 0·38 to 0·94; $P = 0·026$), with a benefit in terms of both local (HR 0·48, 0·24 to 0·99; $P = 0·047$) and systemic (HR 0·56, 0·33 to 0·94; $P = 0·027$) recurrence. In analyses stratified by tumour response to neoadjuvant chemotherapy, non-responders (Mandard tumour regression grade 4–5) treated with adjuvant chemoradiotherapy had an overall survival benefit (HR 0·61, 0·38 to 0·97; $P = 0·037$). In propensity score-matched analysis, an overall survival benefit (HR 0·62, 0·39 to 0·98; $P = 0·042$) and recurrence-free survival benefit (HR 0·51, 0·30 to 0·87; $P = 0·004$) were observed for adjuvant chemoradiotherapy *versus* no adjuvant treatment.**

Conclusion: **Adjuvant therapy may improve overall survival and recurrence-free survival after margin-positive resection. This pattern seems most pronounced with adjuvant chemoradiotherapy in non-responders to neoadjuvant chemotherapy.**

Members of the Guy's and St Thomas' Oesophagogastric Research Group are co-authors of this study and can be found under the heading Collaborators

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Introduction

Although survival rates have improved, oesophageal cancer is still an important cause of cancer-related deaths worldwide[1]. Oesophageal adenocarcinoma is an aggressive disease and most patients have locally advanced or metastatic disease at presentation[2]. Despite advances in staging and oncological therapies, long-term outcomes after surgical treatment for oesophageal cancer remain relatively poor[3].

Over the past decade, UK practice has been influenced by a number of large clinical trials[4–8] that have demonstrated a significant survival benefit for patients treated with neoadjuvant therapy compared with surgery alone. The MAGIC[4] and FLOT (5-fluorouracil (5-FU), leucovorin, oxaliplatin and docetaxel)[8] trials both demonstrated a benefit for perioperative chemotherapy, but the specific gains afforded by adjuvant treatment remain unknown. In addition, only 50 per cent of patients scheduled for postoperative treatment completed chemotherapy, largely owing to the accumulation of acquired therapeutic toxicities[4].

According to the National Oesophago-Gastric Cancer Audit, most patients in the UK are offered neoadjuvant chemotherapy, rather than neoadjuvant chemoradiotherapy, although trials[9,10] comparing the two strategies are in progress. In patients with a microscopically positive resection margin (R1 resection), which occurs in 28–40 per cent of patients[11,12] when the Royal College of Pathologists (RCP) definition is used, survival is worse[13,14]. Adjuvant chemoradiotherapy is generally recommended in this group, provided that the patient is fit enough to withstand treatment[15]. However, prospective clinical trials are required to establish the benefit of adjuvant treatments in the context of neoadjuvant chemotherapy and for their role in current treatment protocols to be confirmed.

The aim of this study was to assess the survival benefit of current adjuvant treatments in patients who had margin-positive resection treated in two high-volume tertiary referral centres in the UK.

Methods

This was a retrospective cohort study of patients with oesophageal and gastro-oesophageal junctional adenocarcinoma using an ethically approved, collaborative database, from two UK-based institutions: St Thomas' Hospital and the Royal Marsden Hospital in London. Both are high-volume tertiary referral centres which provide specialist surgical and oncological care. The database combined two prospectively maintained, hospital-based operative registries of all patients undergoing oesophagogastrectomy for cancer.

Study cohort

All patients who underwent surgical resection for oesophageal adenocarcinoma between January 2006 and December 2016 were identified from the collaborative database. All included patients had at least 12 months of complete follow-up data. Patients who died in hospital or within 30 days of surgery were excluded. All patients were discussed in a specialist oesophagogastric cancer multidisciplinary team (MDT) meeting. Standard staging investigations included endoscopy, CT, endoscopic ultrasound imaging, PET–CT and staging laparoscopy in selected patients. Transthoracic and transhiatal oesophageal resections were performed, dictated by tumour location, at the discretion of the individual surgeon. All resection specimens were examined by specialist gastrointestinal pathologists and the status of the resection margin was classified according to RCP criteria[16]; an R0 resection was defined by no involvement of any margin, and an R1 resection by tumour within 1 mm of the cut margin. All patients with positive margins (R1 resection) were included in the present analysis. Some patients were also assessed using the College of American Pathologists (CAP) R1 definition of tumour at the cut resection margin[17]. All patients were allocated a tumour regression grade (TRG) according to the Mandard classification[18]. Patients with a TRG of 1–3 were considered to have had a response to neoadjuvant chemotherapy (responders) and those with a TRG of 4 and 5 were considered not to have responded (non-responders).

Treatment

The neoadjuvant chemotherapy regimens included CF (cisplatin and 5-FU), ECF (epirubicin, cisplatin, 5-FU), ECX (epirubicin, cisplatin and capecitabine) and EOX (epirubicin, oxaliplatin and capecitabine), and most patients completed the standard two to four cycles, in accordance with randomized trial evidence available at the time of treatment. Patients with positive margins (R1 resection) were subcategorized by adjuvant treatment group: adjuvant chemoradiotherapy, adjuvant chemotherapy alone or no adjuvant treatment. Tumour stage, response to neoadjuvant treatment, tolerance of chemotherapy and patient fitness were taken into account by the MDT. The adjuvant chemotherapy regimens included CF, ECF, ECX and EOX, and most patients completed three or fewer cycles. Radiotherapy in combination with chemotherapy was given as 45 Gy in 25 fractions or 50 Gy in 28 fractions.

Outcome measures

Overall survival time was the interval from the date of surgical resection until the date of death. Time to recurrence was calculated from the date of surgical resection until disease recurrence, defined as either histopathological or definitive radiological evidence of local recurrence, systemic recurrence or both. Recurrence patterns were assessed as a secondary outcome. In the absence of recurrence, survival was calculated to the last confirmed attendance at a hospital or general practitioner clinic.

Statistical analysis

Basic demographic, surgical and oncological data were evaluated using descriptive statistics. The Kaplan–Meier method with log rank test was used to calculate and compare survival. Cox proportional hazards regression analysis (crude and adjusted) was used to calculate hazard ratios (HRs) with 95 per cent confidence intervals to model the association between the study outcomes (risk of all-cause mortality and risk of recurrence) according to the study exposure (adjuvant treatment). Co-variables included in the multivariable models were: age (continuous), sex, tumour location (oesophageal, Siewert 1, Siewert 2), pathological T category (pT0–2, pT3–4), pathological N category (pN0, pN1, pN2, pN3), lymphovascular invasion, postoperative differentiation (well/moderate, poor), operative approach (Ivor Lewis oesophagectomy, transhiatal oesophagectomy, left thoracoabdominal oesophagectomy) and response to neoadjuvant chemotherapy (TRG 1–3, TRG 4 and 5). To explore whether the effects of adjuvant therapy differed according to response to neoadjuvant chemotherapy, separate analyses were undertaken for responders and non-responders. Cox regression analyses comparing overall survival and recurrence-free survival, according to different adjuvant therapies, were also conducted using data from propensity score-matched cohorts. Propensity scores for receipt of adjuvant therapies were derived using logit models based on the same variables as the Cox regression models (*Table S1*, supporting information). Matching was done using the psmatch2 module in Stata, with a caliper of 0·1 and non-replacement. $P < 0{\cdot}050$ was used to define statistical significance for all outcomes. All statistical analysis was performed using Stata version 15 (StataCorp, College Station, Texas, USA).

Results

Patient demographics, clinical characteristics and neoadjuvant treatment details are summarized in *Table 1*. The database included 616 consecutive patients with oesophageal adenocarcinoma, of whom 242 (39·3 per cent) with positive margins (R1 resection), by RCP criteria, were included in the present study. This was equivalent to a 14·9 per cent R1 resection rate according to the CAP classification. Among the 242 patients who had R1 resections, 204 (84·3 per cent) had a positive circumferential resection margin, seven (2·9 per cent) had a positive longitudinal margin, and 29 (12·0 per cent) had both. Median follow-up was 25 months among patients who survived compared with 11 months for those who died.

In total, 220 patients (90·9 per cent) received neoadjuvant chemotherapy, all of whom were scheduled for adjuvant treatment based on intention to treat; 46 patients (20·9 per cent) were deemed to be responders (TRG 1–3) and 168 (76·4 per cent) were non-responders (TRG 4 and 5). The patients were categorized into three adjuvant treatment groups; 112 patients (46·3 per cent) received adjuvant chemoradiotherapy, 46 (19·0 per cent) had adjuvant chemotherapy alone and 84 (34·7 per cent) did not have adjuvant treatment. Among those who received adjuvant chemotherapy alone, most were scheduled for chemoradiotherapy by MDT consensus, but patient fitness or inability to tolerate radiotherapy meant that they only received chemotherapy.

Deaths

The 30-day mortality rate for the whole cohort was less than 1 per cent (6 deaths among 616 patients). The in-hospital mortality rate after surgical resection was 1·6 per cent (10 deaths) and these patients were excluded from the analyses.

Overall survival

Kaplan–Meier curves for overall survival, according to adjuvant therapy type, are shown in *Fig. 1*. Survival at 3 years was improved after adjuvant treatment (39·0, 40 and 25 per cent in adjuvant chemoradiotherapy, adjuvant chemotherapy and no adjuvant treatment groups).

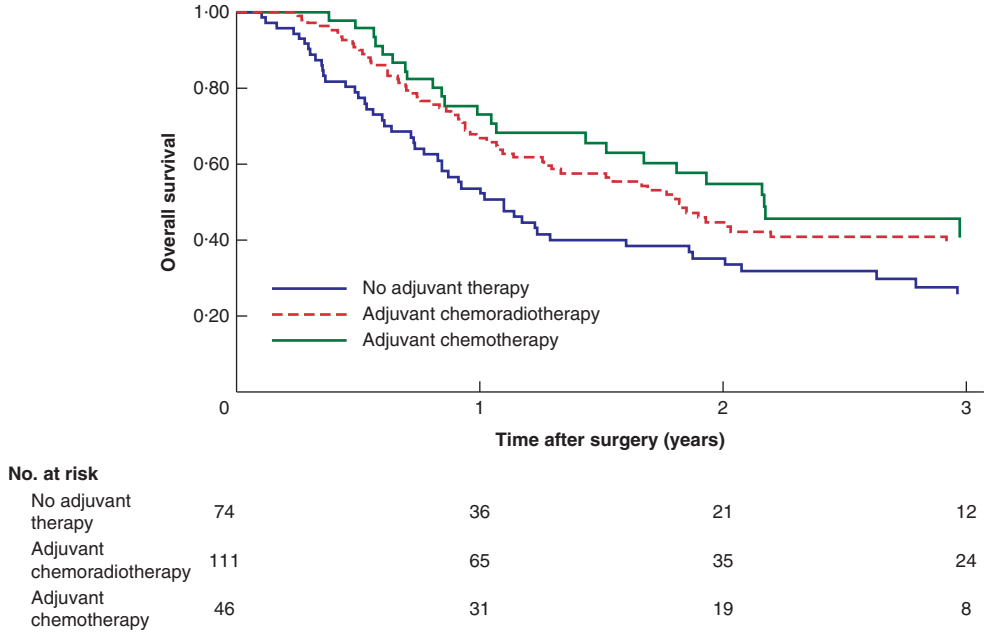
Results of crude and adjusted Cox regression analyses are shown in *Table 2* and *Table S2* (supporting information). Pathological N3 status (HR 3·03, 95 per cent c.i. 1·51 to 4·58; $P < 0{\cdot}001$) and poor differentiation (HR 1·56, 1·06 to 2·28; $P = 0{\cdot}024$) were independently associated with overall survival. For all patients who had a margin-positive resection, although the HRs favoured adjuvant treatment, these did not reach statistical significance (adjuvant chemoradiotherapy: HR 0·71, 0·47 to 1·06, $P = 0{\cdot}097$; adjuvant chemotherapy: HR 0·64, 0·39 to 1·04, $P = 0{\cdot}072$). In analyses stratified by tumour response to neoadjuvant treatment, a survival benefit was observed in non-responders (TRG 4

Table 1 Patient demographics, clinical characteristics and neoadjuvant treatment details for all patients who underwent margin-positive resection

		No adjuvant treatment ($n = 84$)	Adjuvant chemoradiotherapy ($n = 112$)	Adjuvant chemotherapy ($n = 46$)	P‡
Age (years)*		65 (58–70)	62 (54–68)	63 (56–69)	0·027§
Sex ratio (M : F)		64 : 20	93 : 19	39 : 7	0·235
Tumour location	Oesophageal – mid–low	13 (15)	38 (33·9)	12 (26)	0·001
	GOJ – Siewert 1	26 (31)	34 (30·4)	16 (35)	
	GOJ – Siewert 2	45 (54)	34 (30·4)	17 (37)	
	Not recorded	0 (0)	6 (5·4)	1 (2)	
Operative approach	THO	23 (27)	43 (38·4)	16 (35)	0·068
	LTA	23 (27)	36 (32·1)	8 (17)	
	ILO	37 (44)	29 (25·9)	21 (46)	
	McKeown/3-stage	1 (1)	4 (3·6)	1 (2)	
Clinical T category†	cT0–2	15 (18)	13 (11·6)	4 (9)	0·578
	cT3–4	69 (82)	99 (88·4)	42 (91)	
Clinical N category†	cN0	16 (19)	23 (20·5)	4 (9)	0·108
	cN1	55 (65)	63 (56·3)	30 (65)	
	cN2	12 (14)	21 (18·8)	10 (22)	
	cN3	1 (1)	5 (4·5)	2 (4)	
NAC given	Yes	71 (85)	103 (92·0)	46 (100)	0·102
	No	13 (15)	9 (8·0)	0 (0)	
NAC agent	CF	6 (8)	4 (3·9)	3 (7)	0·268
	ECF	15 (21)	14 (13·6)	8 (17)	
	ECX	33 (46)	62 (60·2)	25 (54)	
	EOX	3 (4)	7 (6·8)	4 (9)	
	Other	8 (11)	12 (11·7)	4 (9)	
	Not recorded	6 (8)	4 (3·9)	2 (4)	
Pathological T category†	pT0–2	19 (23)	9 (8·0)	6 (13)	0·032
	pT3–4	65 (77)	103 (92·0)	40 (87)	
Pathological N category†	pN0	18 (21)	24 (21·4)	8 (17)	0·406
	pN1	12 (14)	25 (22·3)	17 (37)	
	pN2	30 (36)	30 (26·8)	13 (28)	
	pN3	24 (29)	33 (29·5)	8 (17)	
Postoperative differentiation	Well/moderate	33 (39)	52 (46·4)	17 (37)	0·318
	Poor	51 (61)	60 (53·6)	29 (63)	
Mandard grade	TRG 1–3	12 (17)	18 (17·5)	16 (35)	0·923
	TRG 4–5	57 (80)	81 (78·6)	30 (65)	
	Not recorded	2 (3)	4 (3·9)	0 (0)	
Lymph node yield*		21 (16–26)	21 (15–27)	26 (20–32)	0·970§
No. of positive lymph nodes*		4 (1–9)	3 (1–7)	2 (1–4)	0·146§
Margin type	Radial only	73 (87)	92 (82·1)	39 (85)	0·989
	Longitudinal only	1 (1)	3 (2·7)	3 (7)	
	Both	9 (11)	16 (14·3)	4 (9)	
	Positive (position unknown)	1 (1)	1 (0·9)	0 (0)	
Lymphovascular invasion	Yes	63 (75)	80 (71·4)	28 (61)	0·577
	No	21 (25)	32 (28·6)	18 (39)	
Recurrence pattern	Local	8 (18)	15 (25)	5 (21)	0·486
	Systemic	24 (55)	33 (56)	14 (58)	
	Mixed	12 (27)	11 (19)	5 (21)	

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †TNM classification, 7th edition. GOJ, gastro-oesophageal junction; THO, transhiatal oesophagectomy; LTA, left thoracoabdominal oesophagectomy; ILO, Ivor Lewis oesophagectomy; NAC, neoadjuvant chemotherapy; CF, cisplatin and 5-fluorouracil; ECF, epirubicin, cisplatin and 5-fluorouracil; ECX, epirubicin, cisplatin and capecitabine; EOX, epirubicin, oxaliplatin and capecitabine; TRG, tumour regression grade. ‡Comparison of adjuvant chemoradiotherapy *versus* no adjuvant treatment; χ^2 test, except §Kruskal–Wallis test.

Fig. 1 Comparison of overall survival in patients with margin-positive (R1) resection between treatment groups (responders and non-responders)



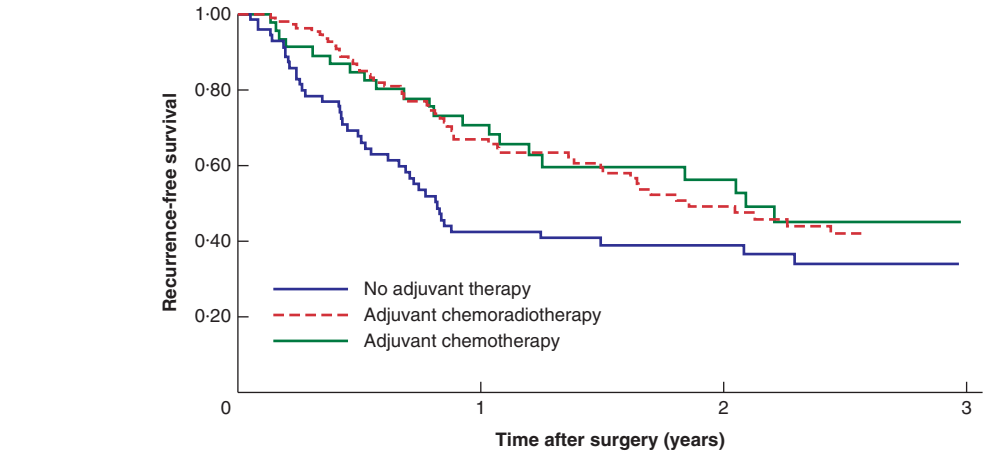
$P = 0{\cdot}154$ (log rank test).

Table 2 Crude and adjusted Cox regression analyses for overall survival in patients who underwent margin-positive resection stratified by response to neoadjuvant treatment

	Crude analysis		Adjusted analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
All patients				
No adjuvant therapy	1·00 (reference)		1·00 (reference)	
Adjuvant chemoradiotherapy	0·76 (0·53, 1·08)	0·122	0·71 (0·47, 1·06)	0·097
Adjuvant chemotherapy	0·67 (0·42, 1·06)	0·086	0·64 (0·39, 1·04)	0·072
Mandard TRG 1–3, responder				
No adjuvant therapy	1·00 (reference)		1·00 (reference)	
Adjuvant chemoradiotherapy	0·83 (0·29, 2·43)	0·739	0·64 (0·15, 2·71)	0·541
Adjuvant chemotherapy	1·66 (0·60, 4·53)	0·327		
Mandard TRG 4–5, non-responder				
No adjuvant therapy	1·00 (reference)		1·00 (reference)	
Adjuvant chemoradiotherapy	0·68 (0·45, 1·01)	0·060	0·61 (0·38, 0·97)	0·037
Adjuvant chemotherapy	0·46 (0·26, 0·80)	0·007	0·44 (0·24, 0·80)	0·008

Values in parentheses are 95 per cent confidence intervals. Stratified models were adjusted for age (continuous), sex, tumour location (oesophageal, Siewert 1, Siewert 2), pathological T category (pT0–2, pT3–4), pathological N category (pN0, pN1, pN2, pN3), lymphovascular invasion, postoperative differentiation (well/moderate, poor), and operative approach (Ivor Lewis oesophagectomy, transhiatal oesophagectomy, left thoracoabdominal oesophagectomy). TRG, tumour regression grade.

Fig. 2 Comparison of recurrence-free survival in patients with margin-positive (R1) resection between treatment groups (responders and non-responders)



No. at risk				
No adjuvant therapy	74	27	18	10
Adjuvant chemoradiotherapy	111	55	29	19
Adjuvant chemotherapy	46	28	16	6

$P = 0{\cdot}168$ (log rank test).

and 5) treated with adjuvant chemoradiotherapy *versus* no adjuvant treatment (HR 0·61, 0·38 to 0·97; $P = 0{\cdot}037$); a survival benefit was also seen with adjuvant chemotherapy (HR 0·44, 0·24 to 0·80; $P = 0{\cdot}008$).

Recurrence-free survival

Fig. 2 shows Kaplan–Meier curves for recurrence-free survival by adjuvant therapy type. Results of Cox regression analyses of recurrence-free survival are presented in *Table 3* and *Table S2* (supporting information). Pathological N3 status (HR 5·63, 95 per cent c.i. 2·82 to 11·20; $P < 0{\cdot}001$) was also independently associated with poor recurrence-free survival. Adjuvant treatment was associated with improved recurrence-free survival in adjusted analyses (adjuvant chemoradiotherapy: HR 0·59, 0·38 to 0·94, $P = 0{\cdot}026$; adjuvant chemotherapy: HR 0·57, 0·33 to 0·98, $P = 0{\cdot}044$). In analyses stratified by tumour response to neoadjuvant chemotherapy, the survival benefit from adjuvant chemoradiotherapy was observed specifically in non-responders (HR 0·53, 0·31 to 0·90; $P = 0{\cdot}014$), but not in responders (HR 0·72, 0·15 to 3·43; $P = 0{\cdot}687$).

Recurrence patterns

The association between adjuvant therapy and risk of different recurrence patterns is shown in *Table 4*. A survival benefit from adjuvant chemoradiotherapy was noted in all patients (responders and non-responders) for local (HR 0·48, 95 per cent c.i. 0·24 to 0·99; $P = 0{\cdot}047$) and systemic (HR 0·56, 0·33 to 0·94; $P = 0{\cdot}027$) recurrence.

Impact of patient fitness

Subgroup analysis of patients with available data on ASA fitness grade demonstrated an overall survival benefit (HR 0·68, 95 per cent c.i. 0·46 to 0·98; $P = 0{\cdot}041$) and a recurrence-free survival benefit (HR 0·59, 0·39 to 0·90; $P = 0{\cdot}015$) for adjuvant treatment, after adjustment for ASA grade as an additional confounder.

Impact of margin involvement definition

Among 155 patients with data available on distance to margin who underwent R1 resection by RCP criteria, 95 (61·3 per cent) had negative margins according to the CAP definition, whereas 60 (38·7 per cent) had positive margins. Survival analysis stratified by margin definition showed similar results, although the HRs for adjuvant chemoradiotherapy *versus* no treatment were lower in the CAP positive-margin group (overall survival: HR 0·58, 95 per cent c.i. 0·25 to 1·34, $P = 0{\cdot}206$; recurrence-free survival: HR 0·38, 0·12 to 1·22, $P = 0{\cdot}106$) than in the

Table 3 Crude and adjusted Cox regression analyses for recurrence-free survival in patients who underwent margin-positive resection stratified by response to neoadjuvant treatment

	Crude analysis		Adjusted analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
All patients				
No adjuvant therapy	1·00 (reference)		1·00 (reference)	
Adjuvant chemoradiotherapy	0·72 (0·49, 1·06)	0·099	0·59 (0·38, 0·94)	0·026
Adjuvant chemotherapy	0·67 (0·41, 1·11)	0·123	0·57 (0·33, 0·98)	0·044
Mandard TRG 1–3, responder				
No adjuvant therapy	1·00 (reference)		1·00 (reference)	
Adjuvant chemoradiotherapy	0·79 (0·27, 2·27)	0·655	0·72 (0·15, 3·43)	0·687
Adjuvant chemotherapy	0·71 (0·23, 2·20)	0·552	0·84 (0·12, 10·8)	0·903
Mandard TRG 4–5, non-responder				
No adjuvant therapy	1·00 (reference)		1·00 (reference)	
Adjuvant chemoradiotherapy	0·64 (0·41, 1·00)	0·051	0·53 (0·31, 0·90)	0·014
Adjuvant chemotherapy	0·63 (0·34, 1·05)	0·111	0·56 (0·30, 1·05)	0·071

Values in parentheses are 95 per cent confidence intervals. Stratified models were adjusted for age (continuous), sex, tumour location (oesophageal, Siewert 1, Siewert 2), pathological T category (pT0–2, pT3–4), pathological N category (pN0, pN1, pN2, pN3), lymphovascular invasion, postoperative differentiation (well/moderate, poor), and operative approach (Ivor Lewis oesophagectomy, transhiatal oesophagectomy, left thoracoabdominal oesophagectomy). TRG, tumour regression grade.

Table 4 Crude and adjusted Cox regression analyses by recurrence pattern in patients who underwent margin-positive resection stratified by response to neoadjuvant treatment

	Local recurrence		Systemic recurrence	
	Hazard ratio	*P*	Hazard ratio	*P*
All patients				
No adjuvant therapy	1·00 (reference)		1·00 (reference)	
Adjuvant chemoradiotherapy	0·48 (0·24, 0·99)	0·047	0·56 (0·33, 0·94)	0·027
Adjuvant chemotherapy	0·45 (0·19, 1·05)	0·064	0·62 (0·34, 1·13)	0·117
Mandard TRG 1–3, responder				
No adjuvant therapy			1·00 (reference)	
Adjuvant chemoradiotherapy			1·12 (0·20, 6·35)	0·898
Adjuvant chemotherapy			1·28 (0·15, 11·3)	0·823
Mandard TRG 4–5, non-responder				
No adjuvant therapy	1·00 (reference)		1·00 (reference)	
Adjuvant chemoradiotherapy	0·48 (0·22, 1·06)	0·069	0·48 (0·26, 0·88)	0·017
Adjuvant chemotherapy	0·53 (0·21, 1·30)	0·166	0·58 (0·28, 1·18)	0·135

Values in parentheses are 95 per cent confidence intervals. Stratified models were adjusted for age (continuous), sex, tumour location (oesophageal, Siewert 1, Siewert 2), pathological T category (pT0–2, pT3–4), pathological N category (pN0, pN1, pN2, pN3), lymphovascular invasion, postoperative differentiation (well/moderate, poor), and operative approach (Ivor Lewis oesophagectomy, transhiatal oesophagectomy, left thoracoabdominal oesophagectomy). TRG, tumour regression grade.

intermediate CAP negative-margin, RCP positive-margin group (overall survival HR 0·80, 0·36 to 1·74, $P = 0·579$; recurrence-free survival: HR 0·58, 0·23 to 1·45, $P = 0·214$).

Propensity score-matched survival analyses

Kaplan–Meier curves for overall and recurrence-free survival in the propensity score-matched subgroups are shown in *Figs S1* and *S2* (supporting information), and the results of regression analyses in *Table 5*. An overall survival benefit (HR 0·62, 95 per cent c.i. 0·39 to 0·98; $P = 0·042$) and recurrence-free survival benefit (HR 0·51, 0·30 to 0·87; $P = 0·004$) was observed for adjuvant chemoradiotherapy *versus* no adjuvant treatment. Adjuvant chemotherapy did not have a significant benefit compared with no adjuvant treatment in terms of overall survival (HR 0·64, 0·37 to 1·10; $P = 0·105$) or recurrence-free survival (HR 0·63, 0·34 to 1·15; $P = 0·130$).

Table 5 Cox proportional hazards regression analysis comparing effects of adjuvant treatments on overall survival and recurrence-free survival in propensity score-matched cohorts of patients who underwent margin-positive resection

	Death		Recurrence	
	Hazard ratio	*P*	Hazard ratio	*P*
Adjuvant chemoradiotherapy ($n = 53$) *versus* no adjuvant treatment ($n = 78$)	0·62 (0·39, 0·98)	0·042	0·51 (0·30, 0·87)	0·004
Adjuvant chemotherapy ($n = 31$) *versus* no adjuvant treatment ($n = 76$)	0·64 (0·37, 1·10)	0·105	0·63 (0·34, 1·15)	0·130

Values in parentheses are 95 per cent confidence intervals.

Discussion

The present results suggest that adjuvant chemoradiotherapy improves survival in patients with positive margins after surgical resection for oesophageal adenocarcinoma. This benefit was most pronounced in non-responders to neoadjuvant chemotherapy. A survival benefit was observed in terms of both local and systemic recurrence.

There are some methodological constraints which merit consideration. Ideally, prospective randomized data would guide therapeutic strategies in this patient group, yet few previous studies have specifically examined the role of adjuvant therapy in oesophageal cancer. Although retrospective in nature, this large cohort study combined the results of consecutive patients treated in two high-volume specialist institutions. Although this may offer a more realistic reflection of contemporaneous practice, it remains impossible to completely eliminate bias in studies of this kind, despite adjusting for confounding factors. Although data from two institutions were included, both assumed the same MDT process using very similar, evidence-based protocols for perioperative treatment decisions. The neoadjuvant and adjuvant regimens varied slightly over the course of the study, reflecting real-time working practice, and this is unlikely to have affected the overall study conclusions.

At the outset, all patients were scheduled to receive three cycles of postoperative chemotherapy according to the MAGIC regimen[4]. In UK practice, patients with a microscopically positive resection margin are generally considered for additional adjuvant radiotherapy as they have an increased risk of developing recurrence[19]. In this study, 84 patients (34·7 per cent) did not receive any postoperative treatment, despite having pathological staging that was equivalent to that in patients who did. As in other studies, this was most commonly owing to patient fitness and/or poor tolerance of neoadjuvant chemotherapy. The survival benefit seen for adjuvant chemoradiotherapy could have been a result of selection bias for patients who were medically fitter and more tolerant of perioperative treatments. This bias was mitigated by use of adjusted analyses (including patient age and ASA grade), and by using cohorts matched for a variety of patient, staging and tumour characteristics. Additional propensity score-matched analysis was included as this was considered to be the standard statistical method for comparing different treatments in retrospective populations[20]. Although overall survival may conceivably have been influenced by poorer fitness in the group that did not receive adjuvant treatment, the fact that cancer-specific survival and both locoregional and systemic recurrence rates were all improved by adjuvant treatment would suggest this to be a genuine oncological benefit. Forty-six patients (19·0 per cent) were treated with adjuvant chemotherapy alone. Chemoradiotherapy had been recommended for most of these patients but they did not receive the radiotherapy component, most commonly because of side-effects or complications of chemotherapy. This highlights an interesting area for future work, beyond the scope of the present study, to examine in greater detail which patients derive benefit from the adjuvant chemotherapy and radiotherapy components respectively.

The histological Mandard TRG was used as a marker of response to neoadjuvant chemotherapy; although this has been shown to be prognostic in patients with oesophageal cancer treated by neoadjuvant chemotherapy, it remains imperfect in identifying all true responders. Tumour downstaging[21] and lymph node regression[22] may provide important supplementary information that could be used to guide treatment decisions in these patients. Classifying patients as responders or non-responders remains logical, although to which group patients with a TRG of 3 should be allocated remains contentious[23].

Currently, there is no clear evidence from RCTs regarding the survival benefit of adjuvant treatment after surgical resection for oesophageal adenocarcinoma. Ongoing trials may help determine the role of postoperative treatment in these patients. At present, observational studies provide the available evidence to guide treatment decisions, and such studies are mostly small and from single institutions. However, there appears to be a trend towards better survival outcomes with adjuvant treatment. A number of studies have demonstrated improved survival in patients with gastro-oesophageal adenocarcinoma who continued ECF chemotherapy after surgery[24,25]. A European study[26] of 134 patients treated with ECF, EOX and FLOT showed

that the survival benefit of continuing chemotherapy after surgical resection was limited to patients with node-positive tumours and poor histological regression. This was at odds with the findings of a study[23] from the UK that demonstrated improved survival in patients with chemotherapy-responsive cancers (Mandard TRG 1–3). That study reported no clear survival benefit in patients with non-responsive tumours (Mandard TRG 4 and 5), a finding that might be considered more logical as continuation of a treatment shown to be ineffective histologically is unlikely to be of benefit to the patient. Another recent UK study[3], which also used propensity score-matched analysis, concluded that only patients with a positive margin after surgery (R1 resection) benefited from continuing chemotherapy after operation. Both overall survival and time to relapse improved in that study[3]. Two further retrospective studies[27,28] suggested a potential benefit of adjuvant chemoradiotherapy compared with no adjuvant treatment in patients with positive margins (R1 resection).

In the context of the available literature, the present study has provided evidence of a survival benefit for adjuvant chemoradiotherapy and chemotherapy in patients with positive resection margins, particularly in non-responders to neoadjuvant chemotherapy. That the addition of radiotherapy to a surgical field with an involved resection margin might improve locoregional recurrence rates would be logical, as would the idea that the patients who gain most benefit from a change in treatment strategy would be those who did not respond well to chemotherapy before surgery. Why these patients also appeared to benefit in terms of systemic recurrence remains unclear; however, there is some evidence to suggest that there may be tumour regression at non-irradiated sites in addition to the irradiated tumour site itself, the so-called abscopal effect[29,30].

Questions that remain pertinent are whether patients with clear margins should be offered adjuvant treatment, and how to individualize therapy more effectively to gain the benefit of additional treatment in suitable patients while avoiding unnecessary toxicities in those who do not respond.

Collaborators

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Supporting information

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