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The use of chemoradiotherapy in oesophageal cancer

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Abstract

The results of treatment for oesophageal carcinoma remain poor and few patients are curable by surgery alone. The use of chemoradiotherapy (CRT) given as a definitive treatment or in combination with surgery may improve locoregional control and survival, when compared with radiotherapy or surgery alone. Using the keywords ''chemoradiotherapy'' and ''radiochemotherapy'', a Medline-based literature review (1980–2001) was performed. Additional literature was obtained from original papers and published meeting abstracts. Two-year survival rates of 28–72% in squamous cell carcinoma and 14–29% in adenocarcinoma from definitive CRT were reported. This is comparable to results achievable by surgery alone. The use of preoperative CRT followed by surgery may further improve survival, but current data are insufficient to justify this approach within routine clinical practice. Acute treatment-related toxicity is increased with CRT. In selected patients with localised unresectable oesophageal cancer, definitive CRT is recommended. There are uncertainties about the role of routine surgery following CRT in patients with resectable disease. For the future, the pretreatment staging of patients needs to be improved and standardised, the optimal CRT regimen needs to be defined and the role of predictive markers for CRT response needs to be developed. © 2002 Published by Elsevier Science Ltd.

Keywords: Oesophageal carcinoma; Chemoradiotherapy; Combined modality treatment

1. Introduction

Oesophageal cancer is a common cause of cancer death worldwide. In the past decade, the incidence of adenocarcinoma of the lower oesophagus and gastro-oesophageal junction has risen markedly [1,2] and it is now more common than squamous cell carcinoma in the UK and USA [3]. At least two-thirds of patients present with inoperable disease and their chances of survival are negligible [4,5]. In those who are operable, long-term survival following a 'potentially' curative resection remains poor. Pooled data from a literature-based review of 130 papers treating a total of 76 911 patients between 1980 and 1988 reported an overall 5-year survival of 20% following resection [6]. The actual results of treatment are probably even worse as these data are likely to be subject to optimistic selection and publication bias.

Although surgery remains the primary treatment of choice for oesophageal cancer, radical radiotherapy can result in long-term survival [7]. A review of 8489 patients treated by radical radiotherapy between 1954 and 1979 showed an overall 5-year survival of 6% [8]. Survival rates of patients treated by radiotherapy cannot be directly compared with those treated by resection. Firstly, patients receiving radiotherapy tend to have more unfavourable prognostic factors and, secondly, they have not been surgically staged. Three randomised trials comparing radiotherapy with surgery in patients with resectable oesophageal cancer have been attempted. The UK Medical Research Council (MRC) trial failed to accrue [9], but two subsequent small trials showed a statistically significant survival advantage in favour of surgery [10,11]. Despite receiving radiation doses which are at the limit of normal-tissue tolerance, up to 80% of patients will fail at the primary site [10,12–14].

There have been significant improvements in the selection of patients for treatment, in surgical techniques and in postoperative supportive care, but only a modest improvement in survival has been achieved. A plateau in survival following single modality treatment has been reached [6]. Other means of attempting to improve the survival of patients with oesophageal

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Table 1

Study reference	No.		Gy	F	Weeks	Gap (weeks)	Chemotherapy	Median (months)	2-year (%)	3-year (%)	5-year (%)	Notes
(a) Definitive CRT compared with RT (historical control)												
[19]								$P=0.004$				
CRT	35	SCC	45–50	20	4 or 8	0 or 4	Mito, 5-FU		28			
RT	70	SCC	50	20	4	Nil	Nil		15			
[20]								$P<0.001$				
CRT	25	Mixed	56–60	28–30	9	4	Cisplatin, 5-FU	12	37			
RT	17	Mixed	40–65	16–32	4–6	Nil	Nil	5	0			
[14]								$P<0.05$				
CRT	21	SCC	40–50	20	8	4	Mito, 5-FU	13	28			
RT	34	SCC					Nil	8	10			
[13]								$P=0.023$				
CRT + chemo	30	Mixed	41–50	28	8	2	5-FU, mito, cisplatin	15	29			
RT	35	Mixed	56–61	31–34	6–7	Nil	Nil	8	13			
[23]												
CRT	26	Adeno	50–60	28–33	6–7	Nil	Mito, cisplatin	10	14			
RT	25	Adeno	60–65	30–36	6–7	Nil	Nil	5	4			
[24]								$P=0.020$				
CRT	35	SCC	40–60	20–30			Cisplatin, 5-FU	14	30			
RT	42	SCC	60–70	30–40	6–8	Nil	Nil	8	7			
[25]												
CRT	25	SCC	60–70	30–35	6–7	Nil	5-FU PVI		32			
RT	24	SCC	60–70	30–35	6–7	Nil	Nil		21			
(b) Definitive CRT compared with surgery (±CRT)												
[20]								$P>0.05$				
CRT	25	Mixed	56–60	28–30	9	4	Cisplatin, 5-FU	12	37			
CRT + surgery	15	Mixed	30	15	3	Nil	Cisplatin, 5-FU	13	38			20% operative mortality
[23]												
CRT	26	Adeno	50–60	28–33	6–7	Nil	Mito, 5-FU	10	14			
CRT + surgery	28	Adeno	50–60	28–33	6–7	Nil	Mito, 5-FU	21	37			
[26]								$P=0.95$				
CRT	11	Adeno	60	30	6	Nil	Mito, 5-FU	19	36	36		
CRT + surgery	24	Adeno	60	30	6	Nil	Mito, 5-FU	15	41	28		
[27]								$P>0.05$				
CRT	137	Mixed	60	30	6	Nil	Cisplatin, 5-FU	26	52	43		
CRT + surgery	78	Mixed	30–35	15–20	3–4	Nil	Cisplatin, 5-FU	33	52	40		
[28]								$P>0.05$				
CRT	45	Mixed	60–64				Cisplatin, etop or 5-FU	11	26			
CRT + surgery	58	Mixed	44–46		5	Nil	Cisplatin, etop or 5-FU	15	37			
[29]												
CRT	30	SCC	50–66	43–51	8–9	2–3	Cisplatin, 5-FU	nr	72	64		
CRT + surgery	10	SCC	44	40	4	Nil	Cisplatin, 5-FU		75	38		
[30]								$P=0.96$				
CRT	82	Mixed	50–60	20–30	6 or 8	0 or 4	Mito, 5-FU	15	33		25	
Surgery	81	Mixed						16	30		23	
[31]								$P=0.008$				
CRT	74	Mixed	60–66	34–37			Cisplatin, 5-FU		31		26	
CRT + surgery	38	Mixed	40–43	20–24	5–6	2	Cisplatin, 5-FU		63		40	
(c) Definitive CRT series												
[21]												
CRT + chemo	20	SCC	50	25	16	11	Cisplatin, 5-FU	22	35			
[22]												
Chemo + CRT	13	Mixed	44–69			Nil	5-FU PVI	16		22		

(*continued on next page*)

Table 1 (*continued*)

Study reference	No.		Gy	F	Weeks	Gap (weeks)	Chemotherapy	Median (months)	2-year (%)	3-year (%)	5-year (%)	Notes
[32]												
CRT	9	Adeno	60	30	6	Nil	Mito, 5-FU	15	29	29		Stage I/II
CRT	11	Adeno	40–56	20–28	5–6	Nil	Mito, 5-FU	8	15	15		Stage III/IV
[33]												
CRT	35	SCC	40	10	5	3	Cisplatin, 5-FU	17	41			
[34]												
CRT	57	Mixed	60	30	6	Nil	Mito, 5-FU	18		29	18	
[35]												
CRT	36	Mixed	54–60				Cisplatin, 5-FU	26	65			
[36]												
Chemo + CRT	65	SCC	64	32	6–7	Nil	Cisplatin, 5-FU	18	40	37	27	
[37]												
CRT + chemo	26	Mixed	40–50	20–30	4–6	Nil	Cisplatin, 5-FU PVI	24	50			
[38]												
CRT	42	SCC	42	28	5	2	Cisplatin, vinca, ±MTX	11	29			
[39]												
Chemo + CRT	45	SCC	65	36	7	Nil	5-FU, cisplatin	20	38	30	20	
[40]												
Chemo + CRT	60	SCC	60	30	6	Nil	Cisplatin, 5-FU/FA	32	58	35		
[41]												
CRT + chemo	28	SCC	54	36	3 +	Nil	5-FU, cisplatin	26	54	39	29	Accelerated, hyper F

Gy, gray; CRT, chemoradiotherapy; RT, radiotherapy; SCC, squamous cell carcinoma; adeno, adenocarcinoma; F, fractions; mito, mitomycin-C; PVI, protracted venous infusion; nr, not reached; ns, not stated; etop, etoposide; chemo, chemotherapy; vinc, vincristine; MTX, methotrexate; FA, folinic acid.

cancer, including the use of multimodality treatments such as combinations of surgery, radiotherapy and chemotherapy, have been explored. Early work on combining chemotherapy synchronously with radiotherapy, otherwise known as chemoradiotherapy (CRT) was performed in anal cancer. Nigro and colleagues (1983) [15] reported a series of patients treated by preoperative CRT using a relatively low dose of radiation (30 Gy) with synchronous 5-fluorouracil (5-FU) and mitomycin-C. This resulted in a high pathological complete response (pCR) rate (81%), defined by the inability of the reporting pathologist to find viable tumour cells within the resection specimen. Randomised trials have since confirmed the superiority of CRT over radiotherapy alone in anal cancer [16,17], which is now predominantly treated non-surgically [18]. The use of CRT has subsequently been explored in other cancers including the oesophagus, rectum, pancreas, lung, head and neck, cervix, brain and bladder.

2. Definitive chemoradiotherapy

In an early pilot study by the Toronto group [19], 35 patients with inoperable, but localised, squamous cell carcinoma received CRT (45–50 Gy) with mitomycin-C and 5-FU. The 2-year survival was 28% compared with 15% in a historical control cohort ($P = 0.004$). Subsequent studies of CRT in patients with squamous cell carcinoma using radiation doses of 40–70 Gy with 5-FU and either mitomycin-C or cisplatin, resulted in 2-year survival rates ranging from 28 to 37% [13,14,19–22] (Table 1a–c). Although the majority of patients in these studies had unresectable disease, the 2- and 3-year survival rates achieved were similar to those achieved by surgery alone [6,30] and superior to historical controls treated by radiotherapy alone [13,14,19,20,24,25] (Table 1a). Several studies reported similar survival in patients treated by CRT with and without subsequent surgery [20,27–29] (Table 1b), however one trial which selected patients with favourable prognostic factors for resection reported better survival in the surgery group (2-year survival 63% versus 31%, $P = 0.008$) [31]. The results of CRT for patients with adenocarcinoma of the oesophagus appeared comparable to those obtained in squamous cell carcinoma, with a 2-year survival of 14–36% [23,26,32] (Table 1a–c).

Early randomised trials of combination chemotherapy (methotrexate, bleomycin or bleomycin/cisplatin) and radiotherapy given sequentially [42,43] or synchronously [44] versus radiotherapy alone showed no difference in survival (Table 2a). A further trial which randomised 31 patients to chemotherapy alone (bleomycin and doxorubicin) or CRT [45] showed an improved response rate with the combined modality treatment (60% versus 19%, $P = 0.025$).

Subsequent randomised trials comparing CRT versus radiotherapy alone have shown more encouraging results (Table 2b). Araujo and colleagues (1991) [47] reported a trial of 59 patients treated by radiotherapy alone or CRT with 5-FU, mitomycin-C and bleomycin. Although the 5-year survival appeared similar (6% versus 16% respectively; $P=0.16$), the trial was underpowered to detect any difference. The European Organization for Research and Treatment of Cancer (EORTC) trial [48] treated 221 patients with radiotherapy (20 Gy over 5 days given twice separated by a gap of 14 days) alone or with cisplatin chemotherapy (prior to each course of radiotherapy and a further four cycles afterwards). Although there was no difference in overall survival (median 7.8 months versus 10.5 months; $P=0.17$), locoregional progression-free survival was better in the combined modality arm (11.3 months versus 6.2 months; $P=0.015$). In the Eastern Cooperative Oncology Group (ECOG) trial (EST 1282), 119 patients received either radiotherapy alone or CRT with 5-FU and mitomycin-C [49]. At 40 Gy, patients in both arms of the trial could be assessed for surgery (not randomised) or for continuation of radiotherapy (additional 20 Gy). 54 patients (45%) had attempted surgical resection. The median survival of the CRT arm was better than the radiotherapy arm (14.8 months versus 9.2 months; $P=0.04$) and there was no difference between surgically and non-surgically treated patients.

Table 2

Study reference	No.	Histology		RT (Gy)	F	Weeks	Gap (weeks)	Chemotherapy	Overall survival			
		SCC	Adeno						Median (months)	2-year (%)	3-year (%)	5-year (%)
(a) Randomised trials of CRT versus radiotherapy in oesophageal cancer												
[45]												
CRT	16	12	2	36–40				Bleomycin, doxorubicin	ns	ns		
Chemotherapy	15	11	2					Nil	ns	ns		
Response rate 60% versus 19% ($P=0.025$)												
[44]									$P=0.80$			
CRT	40	40	0	55	35	10	3	Bleomycin	6.3	12		
RT	42	42	0	63	35	10	3	Nil	5.4	12		
[42]									$P=0.81$			
CRT	77	77	0	56	25	5	Nil	Methotrexate	9	14	12	
RT	73	73	0	56	25	5	Nil	Nil	8	14	6	
[43]									$P=0.19$			
CRT	46	46	0	63	36	9	3	Cisplatin, bleomycin	5.5		0	
RT	51	51	0	63	36	9	3	Nil	5.5		6	
[46]									$P=0.42$			
CRT	34	34	0	40	10	4	2	5-FU, cisplatin	6			
RT	36	36	0	40	10	4	2	Nil	5			
(b)												
[47]									$P=0.16$			
CRT	28	28	0	50	25	5	Nil	5-FU, mitomycin-C, bleomycin	15	38	22	16
Radiotherapy	31	31	0	50	25	5	Nil	Nil	15	22	12	6
[48]									$P=0.17$			
CRT	110	110	0	40	10	4	2	Cisplatin	10.5	20		8 (4-year)
RT	111	111	0	40	10	4	2	Nil	7.8	16		10 (4-year)
Locoregional progression-free survival 11.3 versus 6.2 months with CRT ($P=0.015$)												
[49]									$P=0.04$			
CRT	59	59	0	40[a] or 60	20–30	4–6	Nil	5-FU, mitomycin-C	14.8		27	9
Radiotherapy	60	60	0	40[a] or 60	20–30	4–6	Nil	Nil	9.2		12	7
[50–52]									$P<0.001$			
CRT	61	52	9	50	25	5	Nil	5-FU, cisplatin	14.1	36	30	26
Radiotherapy	62	56	6	64	32	6+	Nil	Nil	9.3	10	0	0
CRT (non-randomised)	69	55	14	50	25	5	Nil	5-FU, cisplatin	17.2	35	26	14

CRT, chemoradiotherapy; RT, radiotherapy; SCC, squamous cell carcinoma; adeno, adenocarcinoma; Gy, Gray; ns. not stated.

[a] 54 patients who proceeded to surgery were treated to 40 Gy.

An Intergroup trial (Radiation Therapy Oncology Group (RTOG) 85-01) randomised 123 patients to radiotherapy alone (64 Gy) or CRT (50 Gy) with two cycles of 5-FU and cisplatin followed by a further two cycles of adjuvant chemotherapy. On interim analysis, there was a statistically significant survival difference in favour of the CRT arm (median survival 14.1 months versus 9.3 months; $P<0.001$), which led to early closure of the trial [50]. Using the same CRT regimen, a further cohort of 73 patients was treated. The results of this, as well as more mature data on patients treated within the original randomised trial, were subsequently published [51,52]. The 3-year survival of the additional non-randomised CRT cohort was 26%, confirming that the original result obtained by the randomised trial was reproducible. The 5-year survival of patients treated in the CRT arm of the randomised trial was 26% versus 0% in the radiotherapy alone arm.

Despite the apparent survival advantage of CRT over radiotherapy alone (Table 2), achieving locoregional control remains a major problem in patients treated by definitive CRT. Although complete clinical response rates of 65–86% can be achieved by CRT [13,14,30,33,37,40], most series report a locoregional failure rate of 40% or more [13,14,20,24,30,34,40,47,50]; defined as persistent disease or subsequent locoregional recurrence. Following the results of the RTOG 85-01 trial, the Intergroup commenced a phase II trial (INT 0122) which increased the standard radiotherapy dose from 50 to 65 Gy and intensified the chemotherapy from 4 to 5 days per cycle and from a total of 4 to 5 cycles (3 neoadjuvant; 2 synchronous) [39]. Of the 45 patients entered, 4 (9%) died of treatment-related causes, which mainly occurred during the neoadjuvant chemotherapy. However, the CRT phase was well tolerated with good compliance (91% receiving the full radiotherapy dose). Disappointingly, the locoregional failure rate was 39%. The next Intergroup trial (INT 0123) randomised patients to 50.4 or 64.8 Gy (in 1.8-Gy fractions) using the same synchronous chemotherapy regimen as in the original RTOG 85-01 trial. The early results of this trial, which entered 236 patients, showed no difference in 2-year survival (33% versus 24%) or pattern of recurrence [53]. There was an unexplained excess of deaths in the 64.8-Gy arm which occurred before the dose escalation was delivered.

3. Preoperative chemoradiotherapy

Despite 'curative' resection in patients who present with localised, resectable disease, many will still die of recurrent cancer. What is the role of combined modality treatment using preoperative radiotherapy, chemotherapy or both, followed by surgery? A preoperative treatment approach may reduce the tumour extent and volume prior to surgery resulting in previously unresectable tumours being rendered resectable. Occult distant metastases will receive earlier systemic chemotherapy and may be more responsive to treatment. An early response to treatment may result in an improvement in swallowing function and in nutritional state. Finally, there is the opportunity to assess the effectiveness of the treatment regimen delivered, by histopathological examination of the resected oesophagus. However, this approach must also be balanced against the risk of disease progression if the treatment delivered is ineffective.

Five randomised trials comparing preoperative radiotherapy followed by surgery with surgery alone [54–58], as well as an individual patient data meta-analysis of these trials [59] have failed to show a survival benefit using this approach. A literature-based meta-analysis of 12 randomised trials which compared neoadjuvant or adjuvant cisplatin-based chemotherapy in combination with surgery or radiotherapy with single modality treatment (surgery or radiotherapy) also showed no survival benefit [60]. More recent and larger randomised trials comparing preoperative chemotherapy followed by surgery with surgery alone in patients with resectable disease have reported mixed results. The Intergroup trial (INT 0113) of 467 patients, which gave three cycles of 5-FU and cisplatin followed by a further two cycles postoperatively to the combined modality arm, reported no difference in the curative resection rate (62% versus 59%) or the overall survival (median 14.9 months versus 16.1 months; 2-years 35% versus 37%; $P=0.53$) between the two arms [61]. A trial from the Queen Mary Hospital, Hong Kong of 147 patients with squamous carcinoma who were given two cycles of 5-FU and cisplatin, reported a higher curative resection rate (67% versus 35%; $P<0.001$) with preoperative chemotherapy, but the difference in median survival was not statistically significant (16.8 months versus 13 months; $P=0.17$) [62]. The Rotterdam Esophageal Tumor Study Group trial of 148 patients with squamous carcinoma gave two cycles of cisplatin and etoposide initially, and a further two cycles to responding patients prior to surgery. The median survival in patients receiving chemotherapy was improved (18.5 months versus 11 months; $P=0.002$) [63]. The largest randomised trial of preoperative chemotherapy with 802 patients entered was from the UK Medical Research Council (OE 02) [64]. The combined modality treatment arm consisted of two cycles of 5-FU and cisplatin followed by surgery. An improvement in both the curative resection rate (78% versus 70%; $P<0.001$) and overall survival (median 17.2 months versus 13.3 months; 2 years 43% versus 34%; $P=0.003$) was reported in favour of preoperative chemotherapy followed by surgery.

At least 50 trials of preoperative CRT in oesophageal cancer have been published. Most were non-randomised

trials or series which included resectable and unresectable squamous cell carcinoma, adenocarcinoma or a combination of both. Early trials used low radiotherapy doses (30 Gy) combined with mitomycin-C and 5-FU, in a similar manner to Nigro and colleagues (1983) [15] for anal cancer. Later trials used escalating doses of radiotherapy (45–60 Gy) with combinations of 5-FU and cisplatin. In a recent review of this subject, the pooled data from 46 non-randomised trials treating a total of 2704 patients (squamous cell carcinoma 69%; adenocarcinoma 31%) showed that the resection rate following preoperative CRT was 74% [65]. Median survival ranged from 8 to 37 months and 3-year survival from 8 to 55%. 24% of the total number of patients treated by preoperative CRT or, 32% of those who had undergone resection achieved a pCR. Survival in patients with a pCR was significantly better than those who did not achieve a pCR [66–76]: this ranged from a median of 15–70 months and 29–92% at 3 years. Locoregional recurrence occurred in 9% of patients who had undergone resection following CRT, and 3% in those who achieved a pCR. Distant metastases accounted for the majority (80%) of recurrences, the crude overall risk being approximately 30%, but this was reduced to 15% in patients who achieved a pCR. Apart from pCR, the presence of microscopic foci only of residual disease within the resection specimen also predicted for an improved survival [77,78].

There are six published randomised trials comparing preoperative combined chemotherapy and radiotherapy followed by surgery with surgery alone in resectable oesophageal cancer [58,79–83] (Table 3). Three trials used synchronous chemotherapy with radiotherapy [80–82] and the remaining three trials used chemotherapy and radiotherapy sequentially [58,79,83]. Two trials demonstrated an improvement in overall survival in favour of the trimodality treatment [82,84], but the final results of one of these failed to reach statistical significance [81]. A third trial demonstrated an improvement in disease-free survival but not overall survival [83]: the high postoperative mortality in the CRT arm compared with the control arm (12% versus 4%) negated any overall survival benefit which may have been achieved by preoperative CRT. The other trials showed no difference in overall or disease-free survival [58,79,80]. Two further trials have since closed recruitment; the US Intergroup trial (NCCTG-C9781) failed to accrue and the Australasian trial (AGITG/TROG IG9401) reached the accrual target of 270 patients in September 2000.

4. Toxicity of CRT

By the addition of synchronous chemotherapy to radiotherapy, acute treatment-related toxicity is significantly increased [50]. Effects include myelotoxicity, oesophagitis and nausea and vomiting. In the RTOG 85-01 trial, grade 3 or 4 oesophagitis occurred in 33% of patients receiving CRT (50 Gy) compared with 18% receiving radiotherapy alone (64 Gy). In a retrospective analysis of 105 patients treated with radiotherapy for lung cancer at the Thomas Jefferson University [85], the use of synchronous chemotherapy, hyperfractionation, and especially a combination of both, were associated with the highest score for acute radiation-induced oesophagitis. The percentage increase in acute oesophagitis appears to be similar to the percentage gain in locoregional control achieved by CRT when compared with radiotherapy alone. A possible explanation is that oesophageal mucosal cells have radiobiological characteristics which are similar to malignant cells: the cell cycle time of mucosal cells is similar to the potential doubling time of oesophageal cancer cells [86] and both types of cells have an alpha–beta ratio of between 6 and 10 Gy when using the linear-quadratic model of radiation dose response [87].

Increasing the number of chemotherapy agents used or increasing the chemotherapy dose intensity of the CRT regimen given, markedly increases the risk of chemotherapy-related toxicity [38,39,88]. The scheduling of 5-FU from a 4-day to a 5-day infusion increases myelotoxicity, with no apparent improvement in the response rate [39,88]. Patients who received mitomycin-C, vinblastine, paclitaxel or etoposide in addition to 5-FU and cisplatin have reported a moderate to severe myelotoxicity rate of 36–63% [66,74,89–91]. Death from chemotherapy-related complications was reported to be more likely to occur in patients who received etoposide as part of their preoperative CRT regimen than those who did not [90]. The risk of myelosuppression also increases with age [88,92]. Patients receiving adjuvant chemotherapy following preoperative chemotherapy and surgery [61] or preoperative CRT and surgery [93] or definitive CRT [50] tolerate this poorly and compliance rates are approximately 50%.

High dose per fraction radiotherapy [83,94] is also associated with toxicity. The use of hyperfractionation or acceleration with synchronous chemotherapy enhances acute-toxicity whether combined with surgery [91,95] or not [41,85]. Late toxicity of CRT is not commonly reported. This is partly explained by the fact that there are relatively few survivors who remain at risk beyond 2 years. Jeremic and colleagues (1998) [41] reported late grade 3 oesophageal toxicity in 11% of the 28 patients treated with an accelerated hyperfractionated regimen with synchronous 5-FU and cisplatin.

When CRT is combined with surgery, the reported postoperative mortality ranged from 0 to 29% (mean 9%) [65]. Adult respiratory distress syndrome, anastomotic leak and breakdown, pneumonia and sepsis were the commonest causes of death following oeso-

Table 3
Randomised trials of preoperative CRT + surgery versus surgery in resectable oesophageal cancer

Study reference	No.	Histology		Radiotherapy			Gap (weeks)	Chemotherapy	Resection rate (%)	pCR (%)	Operative mortality (%)	Overall survival			
		SCC	Adeno	Gray	Fractions	Days						Median (months)	2-year (%)	3-year (%)	
[58]															
CRT + surgery	47	47	0	35	20	28	Nil	Cisplatin, bleomycin (sequential)	66	ns	24	7	23	17	$P=0.3$
Chemotherapy + surgery	50	50	0					Cisplatin, bleomycin	58	ns	15	6	6	3	
Radiotherapy + surgery	48	48	0	35	20	28	Nil		54	ns	11	10	25	21	
Surgery only	41	41	0						68		13	6	13	9	
[80]															
CRT + surgery	35	35	0	40	20	28	Nil	5-FU, cisplatin	74	20	12	9.7	30	26	$P=0.4$
Surgery only	34	34	0						100		15	7.4	23	20	
[79]															
CRT + surgery	41	41	0	20	10	12	Nil	5-FU, cisplatin (sequential)	85	10	8	10	27	19	$P=0.6$
Surgery only	45	45	0						84		7	11	33	14	
[82]															
CRT + surgery	58	0	58	40	15	21	Nil	5-FU, cisplatin	90	22	10	16	37	32	$P=0.01$
Surgery only	55	0	55						100		4	11	26	6	
[83]															
CRT + surgery	143	143	0	37	10	28	2	Cisplatin (sequential)	78	20	12	18.6	48	36	$P=0.8$[a]
Surgery only	139	139	0						68		4	18.6	42	34	
[81]															
CRT + Surgery	50	13	37	45	30	19	Nil	5-FU, cisplatin, vinblastine	90	28	2	16.9	40	30	$P=0.15$
Surgery only	50	12	38						90		0	17.6	34	16	

SCC, squamous cell carcinoma; adeno, adenocarcinoma; CRT, chemoradiotherapy; pCR, complete pathological response; ns, not stated.

[a] Disease-free survival 40% versus 28% at 3 years in favour of CRT + surgery arm ($P=0.003$).

phagectomy. In patients receiving preoperative CRT, increasing the radiation dose per fraction above 3 Gy significantly increases the risk of postoperative complications [94] and deaths [83]. Escalating the radiotherapy dose does not necessarily improve the pCR or survival rates and must be balanced by an increase in toxicity [91,94,96]. The risk of developing tracheobronchial fistulae may also be increased when CRT is given preoperatively [97]. Kane and colleagues (1997) [98] found that patients treated by preoperative CRT had shorter operation times and less operative blood loss when compared with a historical surgical control group, but other investigators have reported contrary findings [99,100].

In patients receiving chemotherapy (alone or with radiotherapy) preoperatively, the timing of surgery following completion of neoadjuvant treatment is important. To operate too soon would not allow sufficient bone marrow recovery [99,100] and despite careful timing, the risk of postoperative infection can remain significantly increased [100]. However, other trials of preoperative chemotherapy report no increase in risk of postoperative complications or of death [61,64,101].

5. The future of CRT in oesophageal cancer

5.1. Improving the CRT regimens

The optimum CRT regimen must be a careful balance between efficacy and toxicity. In terms of efficacy, what is the best combination of chemotherapy with radiotherapy and what means do we have of assessing response to treatment? Will increasing the pCR rate lead to further improvement in survival? If new CRT regimens could consistently achieve high pCR rates, the necessity of surgery as a primary treatment in resectable disease may be questioned. Optimising chemotherapy delivery to represent those regimens known to have an impressive track record in the palliation of advanced disease, such as using continuous infusional 5-FU [102,103] may also allow for an enhanced interaction with radiotherapy [104,105]. This approach may for the first time improve systemic disease control, which so far has remained an elusive target. A phase II trial of CRT using continuous infusional 5-FU demonstrated lower toxicity from a reduced dose-intensity, yet the pCR rate was similar when compared with intermittent infusional 5-FU [93]. Novel combinations including new drugs such as paclitaxel are known to be active and have produced encouraging results, with pCR rates approaching 70% [91,106]. By learning how high pCR rates can be achieved, we may begin to understand the reasons for our treatment failures and these lessons may be applied to other tumour sites.

Geh and colleagues (2000) [107] reported a meta-analysis of the data obtained from published preoperative CRT trials which were identified in a recent review [65]. Using pCR as an endpoint measure of response to treatment, logistic regression modelling was used to determine if a dose–response relationship for radiotherapy, 5-FU, cisplatin and mitomycin existed. The covariates analysed included total radiation dose, overall radiation treatment time, dose per fraction×dose, total 5-FU, cisplatin and mitomycin dose, and median age of patients within each trial. Increasing total radiation ($P=0.006$), cisplatin ($P=0.018$) and 5-FU ($P=0.003$) doses improved the probability of a pCR following preoperative CRT. In addition, a pCR was less likely with increasing overall radiation treatment time ($P=0.035$) and with increasing median age of patients within each trial ($P=0.019$). The radiation dose equivalent to 1 g/m^2 of 5-FU was calculated to be 2.7 Gy and 100 mg/m2 of cisplatin was 11.1 Gy. As overall radiation treatment time was found to be a significant factor, the radiation dose recovery per day of treatment was calculated to be 0.81 Gy.

This mathematical/radiobiological model clearly confirms that in addition to using the best combination of chemotherapy drugs and dose with radiotherapy, optimising the radiation dose delivery remains as important in maximising the response to CRT. Tumour cell repopulation during CRT is a likely contributing factor to treatment failure. Any gain made by the addition of synchronous chemotherapy to radiotherapy can be rapidly lost by inefficient radiotherapy fractionation. Using *in vivo* administration of bromodeoxyuridine (BrdU) and flow cytometry to obtain data on labelling index (LI) and S-phase duration (T_s), the median calculated potential doubling time (T_{pot}) of oesophageal cancer in 50 patients was 5.2 days [86]. Hyperfractionation, acceleration or both, in order to overcome tumour cell repopulation during treatment have been explored [108,109]. In a non-randomised comparison of 36 patients treated by accelerated hyperfractionated radiotherapy against 52 patients treated by conventional radiotherapy, the local control rate following accelerated radiotherapy was 45% versus 15% at 2 years [109]. Other trials of CRT using hyperfractionated or accelerated radiotherapy with [91,95,110] or without [41] subsequent surgery also report encouraging results with 2-year survival rates ranging from 49 to 61%.

5.2. Selection of patients for surgery or no surgery following CRT?

Given that with CRT alone, similar survival rates to surgery can be achieved [19,34,38,49,50], some investigators have questioned the role of surgery in the primary management of resectable oesophageal cancer [29,30,38,111]. From the data that are currently available, the benefit of trimodality treatment over surgery alone is not convincing and it is associated with increased morbidity and mortality [83,111]. There is also

evidence that patients undergoing oesophagectomy do not regain their former quality of life unless they survive 2 years or more [112]. Therefore, in order to continue recommending a surgical approach, there must be clear justification on survival and quality of life grounds. Others argue that surgery is essential because patients who do not achieve pCR following CRT and oesophagectomy have a survival rate which is similar to that of surgery or CRT alone (3-year survival 17–40%) [66,71,73,75,113,114]. The assumption is that these patients would have recurred had they not undergone surgery [32,78,98,115]. A significant cause of death following definitive CRT [39,40,50] or oesophagectomy alone [5,62,116] is due to locoregional failure, and this appears to be significantly reduced by trimodality treatment [65]. The question of surgery following induction CRT (30 Gy with cisplatin and 5-FU) is being addressed by an EORTC trial (FFCD 9102), in which patients who make a good initial response are selected to be randomised to complete their treatment with definitive CRT or with surgery.

Murakami and colleagues (1998) [29] treated 40 patients with resectable disease with CRT and then selected poor responders for resection and good responders for definitive CRT. The median survival was 45 months for the entire group with no difference between the definitive CRT or trimodality groups (2-year survival 72% versus 75%). In the ECOG randomised trial (EST 1282) [49], 45% of patients in both arms had attempted resection following 40 Gy (with or without chemotherapy). In patients receiving CRT, the overall survival was similar regardless of whether they had surgery or not. Hennequin and colleagues (2001) [31] treated 112 patients with locally advanced oesophageal cancer (T3 and/or N1) with induction CRT. Suitable patients were then selected for surgery, and patients who failed to respond adequately or were regarded as inoperable received a further cycle of CRT. The 2-year and 5-year overall survival was 42 and 29%, respectively, but patients receiving the trimodality treatment survived longer than those who only received CRT (2-year survival 63% versus 31%; $P=0.008$). There was no obvious benefit for the small number of patients treated surgically following a complete clinical response to the induction CRT.

In the event of local failure following definitive CRT, surgical salvage can lead to prolonged survival. Murakami and colleagues (1998) [29] performed salvage oesophagectomy in 4 of the 7 patients who developed local recurrence following definitive CRT, 3 of whom remained alive at 15–43 months. Algan and colleagues (1995) [26] reported a study of 11 patients treated by definitive CRT, in which 2 of the 5 patients with local recurrence were surgically salvaged and survived 20 and 100 months.

A reliable means of identifying those who are likely to achieve a pCR is required. Until high rates of locoregional control can be consistently achieved by CRT alone, surgical resection may remain an integral component of multimodality treatment in resectable oesophageal cancer. Furthermore, accurate determination of pCR rates is useful in order to compare the efficacy of the different treatment regimens.

5.3. Prediction of response to CRT

Markers of poor prognosis exist for oesophageal cancer. A high proliferative index is associated with larger tumours and lymph node involvement. Although this can be quantified by Ki-67 antigen staining, there is no consistent evidence to indicate that this is predictive of response to CRT and results have been conflicting [117–119]. The most commonly implicated gene in carcinogenesis is *TP53* [120], which is a tumour suppressor gene located on the short arm of chromosome 17. Its role is to inhibit cellular proliferation at the G1 phase of the cell cycle on recognition of DNA damage and to mediate apoptosis if this damage is not irreparable. Point mutation of the *TP53* gene is recognised to be associated with a more advanced TNM stage and a poorer prognosis in oesophageal cancer [121]. However, the presence of *TP53* gene mutation or p53 protein overexpression has been found to be associated with both a decreased response to preoperative CRT [121–124] and a better response [118], whilst other studies have found no association [125].

The role of other markers in predicting prognosis and response to treatment remains uncertain. Metallothionein expression correlates with chemotherapy drug resistance and appears to be associated with a poorer response to CRT [124]. Cyclin D1 is a protein which can shorten the G1 phase of the cell cycle and is associated with a poorer prognosis in oesophageal cancer, as well as a poorer response to CRT [118].

In the future, the discovery of a marker which can offer a consistent predictive value in terms of both prognosis and response to treatment will become an essential tool in the management decision pathway of oesophageal cancer.

5.4. Improving staging investigations

Traditional methods of staging oesophageal cancer have included the use of endoscopy, barium swallow and computer tomogram (CT) scan, but the accuracy of these methods in predicting the pathological stage have been poor. However, there have been recent improvements. Endoscopic ultrasound (EUS) has the spatial resolution to distinguish the five layers of the oesophagus (mucosal surface, muscularis mucosa, submucosa, muscularis propria and adventitia) and in experienced

hands will correctly stage (T and N) the tumour in 80–90% of cases [126]. Although EUS is the current 'gold standard' preoperative locoregional staging modality, its role in assessing response to CRT is limited. Some series report a good correlation with pathological stage [127,128], but many other series report a poor correlation [129–131]. Magnetic resonance imaging (MRI) using an endoscopic coil can produce high quality spatial resolution, but has the ability to reconstruct images in multiple planes. Its accuracy in predicting pathological locoregional stage is similar to EUS [132,133]. The use of a functional imaging modality such as [18F]fluorodeoxyglucose positron emission tomogram (PET) scan in conjunction with CT scan, will detect additional distant metastases in 14–28% of cases [134–136]. For locoregional staging, PET is unlikely to make a significant impact because of its limited spatial resolution. In the future, the use of PET to assess response to induction CRT may help to select patients for surgery or definitive CRT [137,138]. It is only by accurate pretreatment staging that many of the anomalies within the literature will be resolved.

6. Conclusions

The indications for combining chemotherapy with radiotherapy in the treatment of cancer are expanding. It has been shown to be superior to radiotherapy alone in the treatment of anal cancer [16,17], cervical cancer [139], head and neck cancer [140] and non small cell lung cancer [141], as well as oesophageal cancer [49,50]. Although surgery remains the 'gold standard' against which new approaches must be compared, there is accumulating evidence that in resectable oesophageal cancer, definitive CRT will achieve equivalent survival to surgery alone [29,30]. In patients with locally advanced disease, definitive CRT is now established as a treatment of curative intent [34,50]. The use of preoperative CRT in resectable disease is promising [81,82], but is potentially more toxic [83]. Therefore, this should only be used in the context of a clinical trial, as similar results may be achievable with preoperative chemotherapy alone [64].

Despite the impressive survival rates following definitive CRT, locoregional failure remains a major problem. There are concerns that the survival of patients with resectable disease may be compromised if they receive non-surgical treatment. Surgery alone is not without significant risks [142], but results from specialist units demonstrate that postoperative mortality rates of under 5% can be achieved [143,144]. The combination of surgery followed by adjuvant CRT may prove to be beneficial [145].

There is as much to be gained by improving the selection of patients for existing treatments as there is by developing new treatments. The means by which this might be achieved include accurate staging of patients before and after CRT and the development of reliable biological predictive tests for treatment response. For future studies, the routine use of modern imaging modalities such as EUS, spiral CT, MRI and PET scanning will be essential to help select patients for optimal treatment in order to achieve the maximum benefit at the least cost in terms of toxicity. We will then be able to select appropriate patients for organ preservation (definitive CRT), others for surgery, others for preoperative chemotherapy and others for trimodality treatment. It is likely that the pathways of care for squamous and adenocarcinoma will diverge since the two tumour types have different aetiologies, clinical behaviour and response patterns.

New CRT regimens to improve response rates without excessive toxicity need to be developed. Determining the optimal radiotherapy dose and fractionation in combination with the optimal chemotherapy drug(s) and scheduling remains an enormous challenge. The therapeutic window for the benefits of CRT in oesophageal cancer is narrow and treatment-related morbidity and mortality are serious issues. Three dimensional CT planning techniques with conformal beam shaping and intensity modulation may reduce normal-tissue toxicity and allow safer radiation dose escalation. As the survival of patients with oesophageal cancer is improved, treatment-related late normal-tissue morbidity will become a major issue to address.

As the control of locoregional disease is improved, the prevention and treatment of distant metastases needs to be tackled. A major impact on overall survival can only be made once this is achievable, as metastatic recurrence remains a significant risk in patients who achieve locoregional control. So far, trials of cisplatin-based chemotherapy have produced no convincing evidence of improved systemic disease control in oesophageal cancer. Novel chemotherapy regimens which include new drugs such as paclitaxel, gemcitabine, irinotecan and oxaliplatin may provide solutions to this elusive component of treatment.

The majority of the data on the role of CRT in oesophageal cancer are from uncontrolled series or trials, which are subject to selection and publication bias. New and larger randomised trials which incorporate quality control of patient selection, staging and treatment are needed to show the true value of CRT in oesophageal cancer. The role of surgery in resectable disease is uncertain and randomised trials comparing definitive CRT with surgery (with and without preoperative chemotherapy or CRT) are needed [111,146].

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