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Preoperative therapy in locally advanced esophageal cancer

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Abstract

Esophageal cancer is an aggressive malignancy associated with dismal treatment outcomes. Presence of two distinct histopathological types distinguishes it from other gastrointestinal tract malignancies. Surgery is the cornerstone of treatment in locally advanced esophageal cancer (T2 or greater or node positive); however, a high rate of disease recurrence (systemic and loco-regional) and poor survival justifies a continued search for optimal therapy. Various combinations of multimodality treatment (preoperative/perioperative, or postoperative; radiotherapy, chemotherapy, or chemoradiotherapy) are being explored to lower disease recurrence and improve survival. Preoperative therapy followed by surgery is presently considered the standard of care in resectable locally advanced esophageal cancer as postoperative treatment may not be feasible for all the patients due to the morbidity of esophagectomy and prolonged recovery time limiting the tolerance of patient. There are wide variations in the preoperative therapy practiced across the centres depending upon the institutional practices, availability of facilities and personal experiences. There is paucity of literature to standardize the preoperative therapy. Broadly, chemoradiotherapy is the preferred neo-adjuvant modality in western countries whereas chemotherapy alone is considered optimal in the far East. The present review highlights the significant studies to assist in opting for the best evidence based preoperative therapy (radiotherapy, chemotherapy or chemoradiotherapy) for locally advanced esophageal cancer.

Key words: Esophageal cancer; Preoperative therapy; Multimodality treatment; Chemotherapy; Radiotherapy; Chemoradiotherapy

Core tip: The literature suggests that preoperative chemoradiotherapy followed by surgery results in optimal outcome while managing locally advanced esophageal cancer; however, there is a need to compare preoperative chemoradiotherapy with chemotherapy alone to further refine the role of preoperative therapy. The standard of care continues to be debated due to difference of opinions and practices across the world and lack of any trial with head-to-head comparison between these two established treatment protocols.

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INTRODUCTION

The eighth most common cancer in the world is esophageal cancer. Esophageal cancer, being the sixth most common cause of death from cancer, has an overall ratio of mortality to incidence of 0.88[1]. Esophageal cancer comprises of two distinct histological entities, *i.e.* squamous cell carcinoma (SCC) and adenocarcinoma. These two histological types differ in their epidemiology, etiopathogenesis, tumor biology, management and outcomes. SCC is common in Asia and Eastern Europe while adenocarcinoma is prevalent in North America and Western Europe. Unfortunately, majority of the patients present with locally advanced disease in esophageal cancer and survival is dismal regardless of histology.

Traditionally, surgical resection has been the mainstay of treatment with a potential to ensure loco-regional control as well as long-term survival. However, surgery alone fails to contend against the natural history of disease owing to the presence of occult micrometastasis and fatal distant and loco-regional disease relapse is common. Median survival after esophagectomy is 15 to 18 mo with a 5-year survival rate of 20% to 25%[2]. Therefore, clinicians now are inclined towards use of some form of multidisciplinary treatment including surgery as standard of care for locally advanced esophageal cancer. Locally advanced esophageal cancer can be defined as those restricted to the esophagus or resectable periesophageal tissue (T2-T4) and/or lymphnode involvement (N1-N3) in the absence of distant metastasis[3]. The optimal multimodality treatment is still controversial. Potential contentious issues exist regarding the (1) ideal approach-preoperative, perioperative, or postoperative and (2) ideal combination-radiotherapy, chemotherapy or concurrent chemoradiation. Though various randomized and non-randomized trials have been conducted to address these issues, no standard guidelines have been established till date. This review will highlight the significant studies to assist in opting for the best evidence based multimodality management of esophageal cancer. We limit this review to preoperative therapy followed by surgery as it is presently considered the standard of care. The objectives of preoperative treatment are to downstage the tumor to achieve R0 resection, reduce local and distant disease relapses and thus improve survival.

PREOPERATIVE RADIOTHERAPY

High rate of local failure after curative resection led to conception of many studies in the '80s and '90s to evaluate the role of preoperative radiotherapy (RT) in esophageal cancer. Preoperative RT was envisaged to increase the resectability rates with negative circumferential margins, to lower the loco-regional recurrences and to improve survival. Five randomized control trials (RCTs) addressed this issue and compared preoperative RT followed by surgery to surgery alone. Table 1 displays the salient features of these RCTs[4-8]. None of the studies reported significantly higher complete resections following preoperative RT. Only two studies reported loco-regional recurrences in the study arms: Wang *et al*[7] reported no difference whereas Gignoux *et al*[8] observed significantly lower loco-regional recurrences following preoperative RT and surgery compared to surgery alone (46% *vs* 67%). None of the RCTs reported significant improvement in survival. Nygaard *et al*[6] reported improvement in 3-year overall survival (OS) (21% *vs* 9%) among patients who underwent surgery following preoperative RT compared to patients who were operated upfront. Oesophageal Cancer Collaborative Group conducted a quantitative meta-analysis using updated data from these five RCTs comprising 1147 patients to assess whether preoperative radiotherapy improves OS and whether it is differentially effective in patients defined by age, sex and tumour location[9] (Figure 1). In a group of patients with mostly squamous cell carcinoma, who had a median follow up of 9 years, the hazard ratio (HR) was found to be 0.89 (95%CI: 0.78-1.01). This suggested an overall reduction in the risk of death by 11% and an absolute survival benefit of 3% at 2 years and 4% at 5 years. It, however, failed to achieve conventional statistical significance (P = 0.062). There was no apparent difference in the magnitude of the benefit by sex, age or tumor location. The authors concluded that there is not enough evidence to suggest that preoperative radiotherapy improves the survival of patients with potentially resectable esophageal cancer. The effect of such preoperative radiotherapy regimens is likely to be modest, even if they do improve survival. The absolute improvement in survival is not expected to be more than 3% to 4%. To detect such an improvement (from

Study or subgroup	Preoperative RT Events	Total	No preoperative RT Events	Total	O-E	Variance	Weight	Hazard ratio Exp [(O-E)/V], fixed, 95%CI
1.1.1 Preoperative RT only trials								
Launois 1981	56	61	40	46	0.22	22.60	9.3%	1.01 (0.67, 1.53)
Gignoux 1988	108	116	108	113	1.02	53.72	22.2%	1.02 (0.78, 1.33)
Wang 1989	131	195	165	223	-16.67	78.83	32.6%	0.81 (0.65, 1.01)
Arnott 1992	87	90	75	86	6.82	40.02	16.5%	1.91 (0.87, 1.62)
Nygaard 1992 (a)	52	58	50	50	-11.58	22.92	9.5%	0.60 (0.40, 0.19)
Subtotal (95%CI)		520		518			90.1%	0.91 (0.80, 1.04)
Total events	434		438					
Heterogeneity: χ^2 = 8.69, df = 4 (P = 0.07); I^2 = 54%								
Test for overall effect: Z = 1.37 (P = 0.17)								

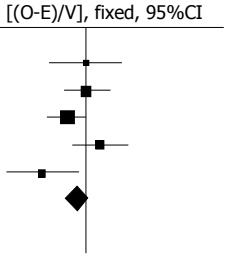

Figure 1 Forest plot comparing survival in esophageal cancer in patients who received preoperative radiotherapy followed by surgery *vs* surgery alone (Reproduced with permission from Arnott *et al*[9]).

Table 1 Salient features of randomized controlled trials addressing the role of preoperative radiotherapy followed by surgery versus surgery alone in the management of esophageal cancer

Ref.	Study period	Treatment	No. of patients	Histology	Complete resection	Local recurrence rate	Operative mortality	5-yr OS	Conclusion
Launois *et al*[5], 1981	1973-1976	40 Gy RT + Surgery	67	SCC	74%	NA	22.6%	9.5%	No significant benefit of pre-op RT
		Surgery	57	SCC	78%	NA	23.4%	11.5%	
Gignoux *et al*[8], 1987	1976-1982	33 Gy RT + Surgery	NA	SCC	43%	46%	NA	11%	No significant benefit of pre-op RT
		Surgery	NA	SCC	55%	67%	NA	10%	
Wang *et al*[7], 1989	1977-1985	40 Gy RT + Surgery	104	SCC	74%	41%	5%	5%	Higher pre-op RT dose or post-op RT required
		Surgery	102	SCC	65%	34%	6%	30%	
Arnott *et al*[4], 1993	1979-1983	20 Gy RT + Surgery	90	SCC/AC	76%	NA	NA	9%	No benefit of low dose RT
		Surgery	86	SCC/AC	72%	NA	NA	17%	
Nygaard *et al*[6], 1992	1983-1988	35 Gy RT + Surgery	NA	SCC	34%	NA	NA	21%	Beneficial effect of pre-op RT
		Surgery	NA	SCC	32%	NA	NA	9%	

SCC: Squamous cell cancer; AC: Adenocarcinoma; RT: Radiotherapy; NA: Not available; OS: Overall survival.

15% to 20%) reliably, trials or a meta-analysis of not less than 2000 patients (90% power, 5% significance level) would be needed[10].

It can be inferred, based on available RCTs, that preoperative radiation therapy is unlikely to benefit esophageal cancer patients, both in terms of significantly lowering local failure rate and improving survival.

PREOPERATIVE CHEMOTHERAPY

Distant recurrence following curative resection in localized esophageal cancer constitutes significant proportion of disease relapse and invariably limits survival. Recurrence pattern analysis of 439 patients who underwent R0 resection highlighted that almost one fifth of the patients developed distant recurrence[11]. Furthermore, autopsy study of 43 curatively resected cases of esophageal cancer revealed that 17 of the 27 patients who had disease recurrence were found to have haematogenous metastasis[12]. Two studies showed that almost 80% of the patients had disseminated tumour cells in the bone marrow samples of ribs resected during esophagectomy for localized esophageal cancer[13,14]. Presence of systemic micro-metastasis in a significant number of esophageal cancer patients and the pattern of higher rates of distant recurrence leading to failure in curatively treated patients led to exploration of role of induction preoperative chemotherapy in esophageal cancer.

The enthusiasm to use preoperative chemotherapy arose due to its potential to exterminate micro-metastasis, to down-stage the tumor, thus enhancing resectability, to improve loco-regional control and to provide relief of dysphagia. The downside of giving preoperative chemotherapy is development of chemo-resistance and progression of disease in patients who do not respond to it. It is known that almost half of the patients are unresponsive to the presently employed chemotherapy[2]. Moreover, delay in local treatment can further compromise the already marginal nutritional status of the patient when surgery is not the initial treatment.

The role of preoperative/perioperative chemo-therapy followed by surgery compared to surgery alone has been addressed by 13 RCTs (Table 2)[6,15-26]. A pooled random-effects meta-analysis of 10 RCTs comprising 2122 participants highlighted the lower risk of mortality among patients who were given preoperative chemotherapy compared to those treated with surgery alone (HR = 0.88, 95%CI: 0.80-0.96, P = 0.003)[27] (Figure 2). Another updated meta-analysis of 10 RCTs revealed that the risk of all-cause mortality

Table 2 Salient features of randomized controlled trials addressing the role of preoperative/perioperative chemotherapy followed by surgery versus surgery alone in the management of esophageal cancer

Trials	Study period	Treatment	No. of patients	Histology	R0 resection	pCR	pN+	Median follow up	LRR	OS (%)	Conclusions
Roth *et al*[21], 1988	1982-1986	Periop Cisplatin vindesine, bleomycin + S	19	SCC	35%	6%	NS	30 mo	NS	25 (3 yr)	Prolonged OS in responders in perioperative chemotherapy arm with acceptable toxicity and post-op complications
		Surgery	20	SCC	21%	-	NS	30 mo	NS	05 (3 yr)	No improvement in
Nygaard *et al*[6], 1992	1983-1988	Preop Cisplatin, Bleomycin + S	44	SCC	44%	NS	NS	NA	NS	03 (3 yr)	survival in chemotherapy arm
		Surgery	41	SCC	36%	-				09 (3 yr)	
Schlag *et al*[22], 1992	1980's	Preop FC + S	22	SCC	44%	6%	NA	NA	NS	NS	No influence on resectability or OS in chemotherapy arm.
		Surgery	24	SCC	45%	-	NA	NA	NS	NS	Rather, it results in Increase in side effects and postop mortality rate
Maipang *et al*[19], 1994	1988-1990	Preop Cisplatin Vindesine, Bleomycin + S	24	SCC	NS	0%	NS	NA	NS	31 (3 yr)	Better OS in control group. Poorly nourished patients may tolerate smaller dosages of chemotherapy
		Surgery	22	SCC		-		NA		36 (3 yr)	
Law *et al*[18], 1997	1989-1995	Preop FC + S	74	SCC	67%	6.7%	70	NA	12	44 (2 yr)	Significant downstaging and an increased
		Surgery	73	SCC	35%	-	88		30	31 (2 yr)	likelihood of R0 resection in chemotherapy arm. No survival difference but responders fared better
Ancona *et al*[15], 2001	1992-1997	Preop FC + S	47	SCC	90%	13%	NS	30 mo	32	34 (5 yr)	Significantly improved long term survival in patients
		Surgery	47	SCC	87%	-		30 mo	34	22 (5 yr)	with pathologic complete response following preoperative chemotherapy
Cunnigham *et al*[26], 2006 (Magic trial)	1994-2002	Peri-op ECF + S	37/250	AC	69.3%	NA	NS	49	14.4	36.3 (5 yr)	Peroperative chemotherapy decreased tumor size and stage, and significantly improved PFS, OS
		Surgery	36/253	AC	66.4%	-		47	20.6	23 (5 yr)	
Kelsen *et al*[17], (RTOG 8911, US Intergroup 113) 2007	1990-1995	Preop FC + S	213	SCC - 98, AC - 115	63%	2.5%	NS	8.8 yr	25	23 (3 yr)	No improvement in OS in chemotheray arm.Only R0 resection results in long-term survival, regardless of pre-op chemotherapy
		Surgery	227	SCC - 106, AC - 121	59%	-			19	26 (3 yr)	
MRC OEO2 trial, 2009 Allum *et al*[25]	1992-1998	Preop FC + S	400	SCC - 123, AC - 265, Others - 12	60%	4%	58	5.9 yr	11.5	23 (5 yr)	Preop chemotherapy improves survival and should be considered as a standard of care
		Surgery	402	SCC - 124, AC - 268, Others - 10	54%	-	68	6.1 yr	12.2	17 (5 yr)	
Ychou *et al*[23], 2011	1995-2003	Peri-op FC + S	113	AC	84%	3%	67	8.8 yr	12	38 (5 yr)	Peri-op chemotherapy significantly increased R0 resection rate, DFS, and OS
		Surgery	111	AC	73%	-	80		8	24 (5 yr)	
Boonstra *et al*[16], 2011	1989-1996	Preop Cisplatin, Etoposide + S	85	SCC	71%	7%	43	15 mo	19	26 (5 yr)	Significant improvement in OS in chemotherapy arm
		Surgery	84	SCC	57%	-	46	14 mo	25	17 (5 yr)	
Ando *et al*[24], 2012- JCOG 9907	2000-2006	Preop FC + S	164	SCC	96%	2%	65	62 mo	25	55 (5 yr)	Pre-op chemotherapy can be regarded as standard treatment
		Surgery	166	SCC	91%	-	76	NA	31	43 (5 yr)	

Periop: Perioperative; SCC: Squamoous cell cancer; AC: Adenocarcinoma; RT: Radiotherapy; NA: Not available; OS: Overall survival; NS: Not stated; ECF: Epirubicin, cisplatin, 5-FU; S: Surgery.

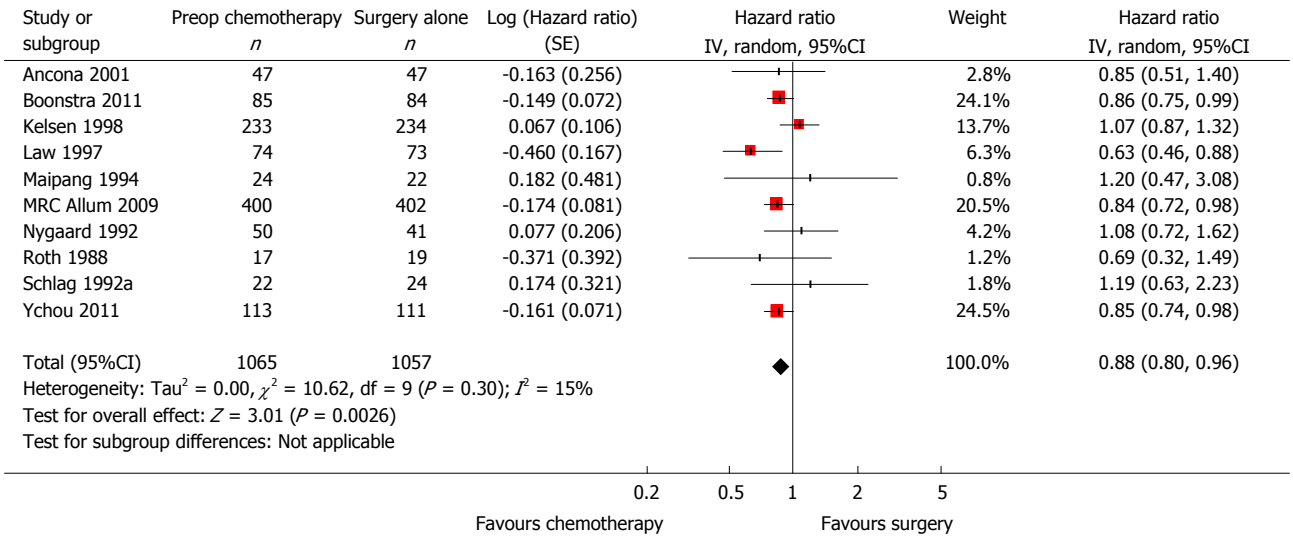

Figure 2 Forest plot comparing survival in esophageal cancer in patients who received preoperative chemotherapy followed by surgery *vs* surgery alone (Reproduced with permission from Kidane *et al*[27]).

was significantly less for preoperative chemotherapy followed by surgery compared to surgery alone (pooled HR = 0.87, 95%CI: 0.79-0.96, P = 0.005). The absolute survival difference at 2 years was calculated as 5.1% (number needed to treat = 19). A subgroup analysis by histological type for these studies showed that the preoperative chemotherapy proved beneficial in adenocarcinoma (HR = 0.83, 95%CI: 0.71-0.95, P = 0.01) and not in squamous-cell carcinoma (HR = 0.92, 95%CI: 0.81-1.04, P = 0.18)[28].

Though the objective of the present review is to analyze the role of preoperative therapy, it is worthwhile to discuss perioperative chemotherapy here as well. The role of perioperative chemotherapy (before and after the surgery) has been evaluated in lower esophageal adenocarcinoma in two RCTs. The British Medical Research Council conducted a phase Ⅲ trial (MAGIC trial) to evaluate perioperative chemotherapy in the management of resectable gastro-esophageal adenocarcinoma. Though the proportion of patients with esophageal cancers was less (lower esophagus 14% and esophagogastric junction 11%), results of this trial definitely indicated benefit of perioperative chemotherapy. OS significantly improved from 23% to 36%. Only 104 of 250 patients (41.6%) randomized to perioperative chemotherapy arm in this study could complete all six cycles of chemotherapy, due to disease progression or early death, patient choice, postoperative complications, prior toxicity, lack of response to preoperative treatment, and worsening coexisting disease, thus acting as a limitation[26]. Another recent FNCLCC/FFCD trial reported that perioperative chemotherapy improved 5-year OS from 24% to 38%. It must be noted that 75% of tumors in this trial were lower esophageal or junctional and among the 109 patients who received at least one cycle of preoperative chemotherapy, 54 patients (50%) received postoperative chemotherapy[23]. These two trials suggest that the approach of perioperative chemotherapy may be beneficial for patients with lower esophagus or junctional adenocarcinoma but only half of the patients are able to complete the planned treatment after surgery.

PREOPERATIVE CHEMORADIATION

High risk of both loco-regional and systemic failures following curative treatment, led to integration of all three treatment modalities namely surgery, chemotherapy and radiation in the management of esophageal cancer. As preoperative RT failed to meet the high expectations of providing additional loco-regional control compared to surgery alone in esophageal cancer, attempts were made to use chemo-radiotherapy (CRT) as a double-edged sword. While RT was expected to improve loco-regional control, simultaneously, chemotherapy was thought to eradicate the micrometastasis. Chemotherapy adds several benefits with its use along with preoperative RT by (1) containing micrometastasis and lowering systemic failure; (2) providing additive effect to radiation by acting against the different tumor cell populations; and (3) providing assistance to radiotherapy for control of loco-regional disease (spatial cooperation)[29]. Spatial cooperation may exist at different levels: (1) with altered DNA repair or modification of the lesions induced by chemotherapy or radiation at the molecular level; (2) through cytokinetic cooperation arising from differential sensitivity of the various compartments of the cell cycle to the drug or radiation at the cellular level, notably; and (3) including re-oxygenation, increased drug uptake or inhibition of repopulation or angiogenesis at the tissue level[30].

Table 3 displays the RCTs which compared preoperative CRT followed by surgery to surgery alone[31-39]. The most promising trials which have

Table 3 Salient features of randomized controlled trials addressing the role of preoperative chemoradiotherapy followed by surgery *vs* surgery alone in the management of esophageal cancer

Trial	Study period	Treatment	No. of patients	Histology	Completed treatment	R0	pCR	pN+	LRR	Median survival (mo)	OS	Treatment related mortality	DFS median/ proportions	Conclusion
Apinop *et al*[31], 1994	1986-1992	FC + 40 Gy RT + Surgery	35	SCC	26	NA	26.9%	NA	NA	NA	NS	NS	NA	No statistically significant difference in OS, complication rate, mortality
		Surgery	34	SCC	-	NA	-	NA	NA	NA	NS	NS	NA	
Le Prise *et al*[32], 1994	1988-1991	Sequential FC-20 Gy RT-FC + Surgery	41	SCC	39	51.0%		NA	17.9%	10	19.2 (3 yr)	8.5%	7.6 mo	No change in operative mortality or survival time
		Surgery	45	SCC	42	36.0%	-	NA	21.4%	10	13.8 (3 yr)	7%	5 mo	
Walsh *et al*[33], 1996	1990-1995	FC + 40 Gy RT + Surgery	58	AC	53	NA	25%	42	NA	32	37 (3 yr)	3%	NA	Multimodal treatment superior to surgery alone
		Surgery	55	AC	54	NA	-	82	NA	11	07 (3 yr)	2%	NA	
Lee *et al*[34], 2004	1999-2002	FC + 45.6 Gy RT + Surgery	51	SCC	35	100%	43%	37	22.8%	28.2	55 (2 yr)	8.5%	49% (2 yr)	CRT induced high clinical and pathological response, but no statistically significant benefit in OS and DFS
		Surgery	50	SCC	48	87.5%	-	78	10.8%	27.3	57 (2 yr)		51%(2 yr)	
Burmeister *et al*[35], 2005	1994-2000	FC + 35 Gy RT + Surgery	128	45 SCC + 80 AC + 3 others	105	80.0%	16%	43	11%	22.2	NS	4.7%	16 mo	No significant improvement in PFS or OS
		Surgery	128	50 SCC+ 78 AC	110	59.0%	-	67	14%	19.3	NS	5.4%	12 mo	
Tepper *et al*[36], 2008 (CALGB 9781)	1997-2000	FC+ 50.4 Gy RT + Surgery	30	7 SCC + 23 AC	29	84.6%	40%	12	13.7%	53.7	39 (5 yr)	5 yr	28% (5 yr)	Long-term survival advantage supports trimodality therapy as a standard of care
		Surgery	26	7 SCC+ 19 AC	26	88.4%	-	NA	15.3%	21.4	16 (5 yr)	3.8%	15% (5 yr)	
Lv *et al*[37], 2010	1997-2004	2 Cis, Pacli+ 40 gy + Surgery	80	SCC	80	97.4%	NA	NA	11.3%	53	24.5 (10 yr)	3.4%	61.3% (3 yr)	Rational application of pre-op or post-op CRT can improve PFS, OS
		Surgery	80	SCC	80	80.0%	-	NA	35%	36	12.5 (10 yr)	0%	49.3% (3 yr)	
Van Hagen *et al*[38], 2012 (CROSS trials)	2004-2008	5 Pacli, Carbo + 41.4 Gy + Surgery	178	41 SCC + 134 AC + 3 other	168	92.0%	29%	13	3.3%	49.4	47 (5 yr)	5.9%	not reached	Improved survival with acceptable adverse-event rates
		Surgery	188	43 SCC + 141 AC + 4 other	186	69.0%	-	75	9.3%	24	34	6.9%	24.2 mo	
Mariette *et al*[39], 2014	2000-2009	2 Cis, 5FU + Surgery	98	67 SCC + 30 AC+ 1 other	84	93.8%	33.3%	30.8	22.1%	31.8	41 (5 yr)	11.1%	35.6% (5 yr)	No effect on R0 resection rate or survival but enhanced postoperative mortality
		Surgery	97	70 SCC + 27 AC	91	92.1%	-	52.8	28.9%	41.2	33.8	3.4%	27.7% (5 yr)	

Periop: Perioperative; SCC: Squamous cell cancer; AC: Adenocarcinoma; RT: Radiotherapy; NA: Not available; OS: Overall survival; NS: Not stated; ECF: Epirubicin, cisplatin, 5-FU; S: Surgery.

almost established the role of preoperative CRT are the Dutch chemoradiotherapy in Oesophageal Cancer and the Surgery Study (CROSS) trials[29,38]. The investigators randomly assigned 368 patients with resectable esophageal cancers to either preoperative CRT followed by surgery or to surgery alone. The patients in preoperative CRT arm received weekly carboplatin and paclitaxel for 5 wk and concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy each, with 5 fractions administered per week, starting on the first day of the first chemotherapy cycle) followed by surgery. The histopathological types were adenocarcinoma (75%), SCC (23%), and large-cell undifferentiated carcinoma (2%). R0 resection rates were significantly better in preoperative CRT arm compared to surgery alone (92% *vs* 69%, $P < 0.001$). More than one fourth of patients (29%) achieved pathological complete response following preoperative CRT. Though postoperative complications and in-hospital mortality were similar in the two groups, median OS was significantly better in preoperative CRT group (49.4 mo *vs* 24.0 mo, HR for survival, 0.657, 95%CI: 0.495-0.871, $P = 0.003$). However, the HR for esophageal adenocarcinoma was only marginally statistically significant (adjusted HR = 0.74, 95%CI: 0.54-1.02, $P = 0.07$). Long- term results of the study were recently published. These revealed that the survival advantage for preoperative CRT persisted after a median follow up of 84.1 mo for surviving patients (range 61.1-116.8, IQR: 70.7-96.6). Median OS was 48.6 mo (95%CI 32.1-65.1) in the preoperative chemoradiotherapy plus surgery group and 24.0 mo (14.2-33.7) in the surgery alone group (HR = 0.68, 95%CI: 0.53-0.88, log-rank $P = 0.003$). The improvement in survival was evident for both histological subtypes - median OS for patients with squamous cell carcinomas and adenocarcinoma were 81.6 mo (95%CI: 47.2-116.0) and 43.2 mo (95%CI: 24.9-61.4) respectively in the preoperative CRT group compared to 21.1 mo (95%CI: 15.4-26.7) and 27.1 mo (95%CI: 13.0-41.2) in the surgery alone group[40]. Preoperative CRT led to significantly lower loco-regional recurrences (14% *vs* 34%, $P < 0.001$) and peritoneal carcinomatosis (4% *vs* 14%, $P < 0.001$)[41].

In sharp contrast to the findings of the CROSS trial, the French trial (FFCD 9901) could not find any significant benefit of preoperative CRT. FFCD 9901 was a multicentre RCT which was conducted to assess improvement in outcomes for patients with stage Ⅰ or Ⅱ esophageal cancer with use of preoperative CRT. The investigators randomized 195 patients (in 30 centres) to either preoperative CRT followed by surgery ($n = 98$) or surgery alone ($n = 97$). CRT protocol was 45 Gy in 25 fractions over 5 wk with two courses of concomitant chemotherapy composed of fluorouracil 800 mg/m^2 and cisplatin 75 mg/m^2. Preoperative CRT did not improve R0 resection rates (93.8% *vs* 92.1%, $P = 0.749$); there was no difference in 3-year OS either (47.5% *vs* 53.0%, HR = 0.99, 95%CI: 0.69-1.40, $P = 0.94$). Moreover, significantly higher postoperative mortality was seen in patients who received preoperative CRT (11.1% *vs* 3.4%, $P = 0.049$). The authors concluded that preoperative CRT does not improve R0 resection rate or survival but enhances postoperative mortality in patients with stage Ⅰ or Ⅱ esophageal cancer[39]. A number of factors can be attributed to these differences in survival outcomes between the French and Dutch studies: (1) small sample size in the FFCD 9901 trial reducing the statistical power of detecting a survival benefit; (2) different histological profiles in two studies (70% of patients in the French study were SCC compared with 23% in the Dutch study); and (3) larger number of patients with early-stage disease (fewer node-positive and T3 patients) in the French study compared to Dutch study[42]. The CROSS trial investigators cautioned against coming to the conclusion that preoperative CRT is not beneficial in early-stage esophageal cancer, as one might, from the results of the FFCD 9901 trial. They highlighted that CROSS trial findings should still be considered for stage Ⅱ cancers in view of its larger study population, more consistent inclusion rate, less toxic CRT regimen, more sophisticated radiation techniques and lower postoperative mortality rate[43].

A meta-analysis which was designed to compare the role of preoperative CRT for esophageal carcinoma including 14 RCTs ($n = 1737$) concluded that it has the potential to improve the long-term survival and reduce locoregional cancer recurrence compared to surgery alone. Five-year survival was significantly better in preoperative CRT group compared to the surgery alone group (OR = 1.64, 95%CI: 1.28-2.12). The authors further reported that a complete pathological response to CRT was observed in 10%-45.5% of patients[44].

In a meta-analysis of 12 trials which compared preoperative CRT followed by surgery versus surgery alone ($n = 1854$), the Australasian gastro-intestinal trials group reported that preoperative CRT led to significant reduction in all-cause mortality (HR = 0.78, 95%CI: 0.70-0.88, $P < 0.0001$). The beneficial effect was evident in both histological subtypes - the HR for squamous-cell carcinoma was 0.80 (95%CI: 0.68-0.93, $P = 0.004$) and for adenocarcinoma was 0.75 (95%CI: 0.59-0.95, $P = 0.02$). They further undertook the pooled analysis of two RCTs and highlighted that the preoperative CRT seemed to lower all-cause mortality compared to preoperative chemotherapy (HR for the overall indirect comparison 0.88, 95%CI: 0.76-1.01, $P = 0.07$). They concluded that there seemed to be strong evidence for survival benefit with the use of preoperative CRT or chemotherapy followed by surgery versus surgery alone in resectable esophageal cancer[28].

Another meta-analysis which included 13 RCTs ($n = 1930$, resectable esophageal cancers) addressed the issue of postoperative complications following preoperative CRT compared to surgery alone[45]. The

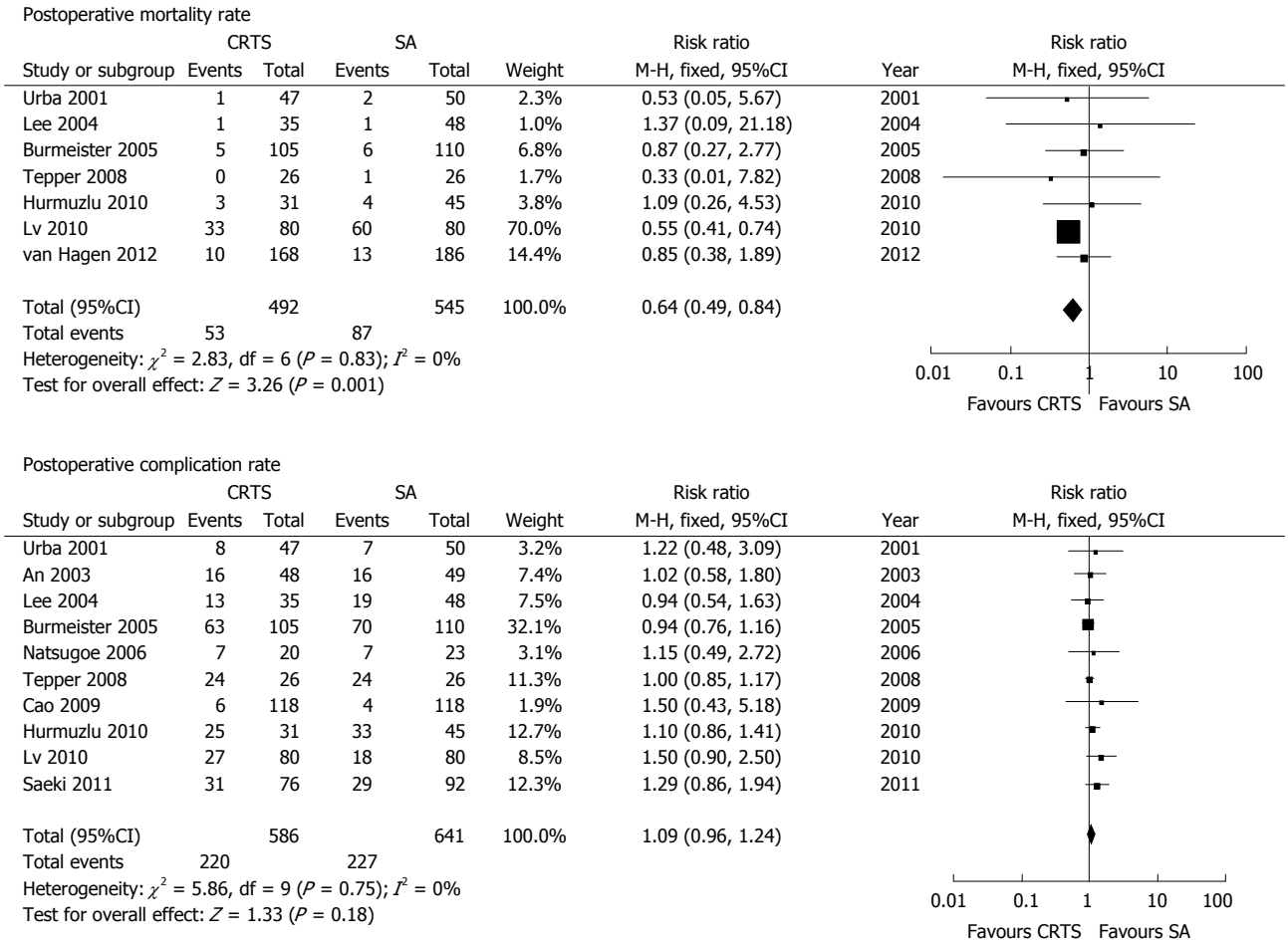

Figure 3 The forest plots of postoperative mortality and complications of chemoradiotherapy followed by surgery *vs* surgery alone using a fixed effects model (Reproduced from Deng *et al*[45]).

authors reported that preoperative CRT did not lead to significantly higher postoperative complications compared to surgery alone (RR = 1.09, 95%CI: 0.96-1.24, *P* = 0.18) (Figure 3); indeed, preoperative CRT led to reduction in postoperative mortality (RR = 0.64, 95%CI: 0.49-0.84, *P* = 0.001). Moreover, there was a significant reduction in local recurrence (RR = 0.53, 95%CI: 0.39-0.73, *P* < 0.000) and distant recurrence (RR = 0.82, 95%CI: 0.68-0.98, *P* = 0.03). These results clear the apprehension that preoperative CRT may result in higher postoperative complications.

CONCLUSION

The literature suggests that preoperative chemo-radiotherapy followed by surgery results in optimal outcome while managing locally advanced esophageal cancer; however, there is a need to compare pre-operative chemoradiotherapy with chemotherapy alone to further refine the role of preoperative therapy. The standard of care continues to be debated due to difference of opinions and practices across the world and lack of any trial with head-to-head comparison between these two established treatment protocols.

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