TOPIC HIGHLIGHT

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Neoadjuvant treatment of esophageal cancer

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Abstract

The management of esophageal cancer has been evolving over the past 30 years. In the United States, multimodality treatment combining chemotherapy and radiotherapy (RT) prior to surgical resection has come to be accepted by many as the standard of care, although debate about its overall effect on survival still exists, and rightfully so. Despite recent improvements in detection and treatment, the overall survival of patients with esophageal cancer remains lower than most solid tumors, which highlights why further advances are so desperately needed. The aim of this article is to provide a complete review of the history of esophageal cancer treatment with the addition of chemotherapy, RT, and more recently, targeted agents to the surgical management of resectable disease.

INTRODUCTION

Esophageal cancer is the most rapidly increasing tumor type in the Western world[1,2]. Globally, esophageal cancer is the eighth most common malignancy and sixth most fatal, with approximately 460 000 new diagnoses and > 380 000 deaths annually[3]. The lifetime risk, as well as histology of esophageal cancer varies worldwide from 1 in 200 in the United States, with more than half of new cases being adenocarcinoma (AC) to more than 10 times that risk in Iran, Northern China, India, and Southern Africa, where the histology is > 90% squamous cell carcinoma (SCC), and mirrors the growing epidemic of tobacco abuse[3-5].

Although there are multiple, rare esophageal cancer histologies (e.g. gastrointestinal stromal tumors, leiomyosarcoma, and liposarcoma), AC and SCC are the two principle variants and account for > 98% of esophageal cancer diagnoses[6]. Historically, AC and SCC have been treated as a single disease entity with many older clinical trials not differentiating between the two histologies, even in study populations[7]. Over the years, however, a great deal of evidence has been compiled to support the notion that AC and SCC represent two separate diseases based on their differing etiology, epidemiology, prognosis, and response to treatment[8-11].

AC is highly associated with obesity and gastroesophageal reflux disease (GERD). Obesity increases the risk of developing GERD by approximately twofold due to elevated intra-abdominal pressure and a resultant laxity in the lower esophageal sphincter[12]. GERD leads to chronic

irritation of the distal esophagus and can eventually cause metaplasia by the replacement of normal, squamous epithelium by columnar epithelium and the formation of what is referred to as Barrett's esophagus. The new, secretory columnar cells are thought to be better-suited to withstand the erosive contents that spill over from the gastroesophageal junction (GEJ), but unfortunately, this change also increases the risk for dysplasia by sevenfold, with Barrett's esophagus evolving to AC at a rate of approximately 1% per year[13,14].

SCC, on the other hand, is almost always linked to tobacco and alcohol abuse. Current smokers have a nine-fold increased risk of developing SCC of the esophagus, while heavy drinkers of alcohol have an increased OR of 5[15]. Combined, however, the synergistic effects of tobacco and alcohol abuse lead to a 20-fold increased risk of developing esophageal cancer[16], although more extreme abusers of the two have been reported to have an increased OR as high as 50 and even 107 in studies from Italy and South America, respectively[17,18].

Epidemiologically, there has been a dramatic shift in the two histologies[5]. In the United States between 1974 and 1994, there has been a staggering 350% increase in the number of patients with esophageal AC, which now represents 60% of all new esophageal cancer diagnoses. Prior to 1974, SCC constituted 90% of esophageal cancer in the United States, which was likely secondary to increased rates of tobacco abuse[5,19]. The median age of diagnosis for SCC is approximately one decade prior to that of AC, yet surprisingly, patients with SCC have been documented in more recent studies to fair worse[7-9,20,21]. This difference is likely to be secondary to the increased comorbidity of patients with SCC but, even more importantly, the location of the primary tumor. Compared to age and lung function, the adjusted OR for postoperative death for a tumor located in the upper third of the esophagus is 4[7,22]. SCC is usually a proximal lesion, with 75% of these cancers found to have contact with the tracheobronchial tree, while 94% of ACs are below the tracheal bifurcation[7].

With regard to location, it should be noted that the pathology, treatment and prognosis of SCC of the cervical esophagus are more closely related to that of SCC of the head and neck[23]. As such, this review instead focuses on the multimodality treatment of localized and locoregional cancer involving the thoracic esophagus and GEJ. The definition of what constitutes the GEJ is debatable in itself. Siewert and Stein have described the most accepted classification scheme for AC at the GEJ: type Ⅰ, AC arising from an area of intestinal metaplasia of the esophagus, which can infiltrate the GEJ from above; type Ⅱ, AC arising from the cardia of the stomach; type Ⅲ, subcardial gastric carcinoma that infiltrates the GEJ from below[24]. With the exception of overexpression of *COX-2* with type I GEJ AC, no known significant gene expression profile changes have been noted that differentiate the three sub-types consistently[25]. Type Ⅰ GEJ tumors tend to have lymphatic drainage toward lower mediastinal and upper gastric lymph nodes, whereas type Ⅱ and Ⅲ

GEJ tumors are more likely to drain to celiac axis nodes. As such, type Ⅰ GEJ tumors are generally treated as distal esophageal cancer, whereas type Ⅱ and Ⅲ GEJ tumors are viewed by many as gastric carcinomas[24,25].

TREATMENT

Surgery alone
Debate regarding the current standard of care for the management of esophageal cancer is ongoing[26-28]. Surgical resection alone has been the mainstay of treatment for decades[29], although its necessity has been called into question more recently for patients with SCC[30,31]. Although surgery is considered to offer the best chance of prolonged survival, alone it will only cure 15%-20% of patients with localized disease[32-35], and unfortunately, 50%-60% of patients with esophageal cancer have tumors that are considered inoperable, secondary to either tumor extension or medical comorbidity[29]. Contemporary outcome data for treatment with surgery alone report a median survival of 16 mo with a 1-, 2- and 3-year survival rate of 60%, 37% and 26%, respectively[32]. Local disease-failure rates with surgery alone are quite high at 58%, with two-thirds of those failures from lack of complete (R0) resection and one-third recurring locally despite an R0 resection[36]. Surgical approaches and techniques - transthoracic *vs* transhiatal resection with limited *vs* extended-field lymphadenectomy - are highly debated[34,35], and are beyond the scope of this review. What is clear, however, is that postoperative morbidity and mortality are decreased while overall survival (OS) is significantly improved in high-volume, expert academic centers[37,38]. Currently, National Comprehensive Cancer Network guidelines suggest surgery as a single-modality treatment option only for non-cervical T1 lesions without lymph node involvement[39].

Radiotherapy
Radiotherapy alone has been the historical treatment of choice for patients with esophageal cancer who are not surgical candidates. Radiotherapy delivered at 60-66 Gy over 6-6.5 wk has been associated with a 5-year OS ranging from 5% to 20% depending on tumor extent[40-42]. In a review by Earlam *et al*[43], 49 earlier series that involved 8489 patients with SCC treated with radiotherapy alone have been reported to yield a 1-, 2- and 5-year survival rate of 18%, 8% and 6%, respectively. Adding radiotherapy to the surgical management of esophageal cancer has the advantage of increasing local control of disease. In the adjuvant setting, radiotherapy can treat microscopic disease left behind after an incomplete surgery. In the neoadjuvant setting, radiotherapy can theoretically decrease the size of a lesion prior to surgery and potentially make that lesion more resectable. The obvious trade-off of increased local control with radiotherapy is poor wound healing in both settings and an increasingly difficult resection of previously irradiated tissue in the neoadjuvant setting.

As it stands, there have been five separate phase Ⅲ trials that have compared adjuvant radiotherapy with sur-

Table 1 Randomized controlled trials of adjuvant radiotherapy *vs* surgery alone for esophageal cancer

Studies	Histology	Treatment	n	MS (mo)	5-yr OS (%)	P	RT dose (Gy)
Kunath *et al*[44], 1984	SCC	ART	23	9		NS	50-55
		Surgery	21	6			
Ténière *et al*[45], 1991	SCC	ART	102	18	19	NS	45-55
		Surgery	119	18	19		
Fok *et al*[36], 1993	SCC	ART	42	11	10	NS	43-53
		Surgery	39	22	16		
Zieren *et al*[46], 1995	SCC	ART	33		23[1]	NS	56
		Surgery	35		22[1]		
Xiao *et al*[47], 2003	AC/SCC	ART	220		41	NS	50-60
		Surgery	275		32		

[1]3-year OS. MS: Median survival; RT: Radiotherapy; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; ART: Adjuvant radiotherapy; NS: Not significant; OS: Overall survival.

Table 2 Randomized controlled trials of neoadjuvant radiotherapy *vs* surgery alone for esophageal cancer

Studies	Histology	Treatment	n	MS (mo)	5-yr OS (%)	P	RT dose (Gy)
Launois *et al*[48], 1981	SCC	NART	77	10	10	NS	40
		Surgery	57	12	12		
Gignoux *et al*[49], 1987	SCC	NART	106	11	11	NS	33
		Surgery	102	11	10		
Arnott *et al*[50], 1992	AC/SCC	NART	90	8	9	NS	20
		Surgery	86	8	17		
Nygaard *et al*[51], 1992	SCC	NART	48[1]		21[3]	NS	35
		Surgery	41[2]		9[3]		
Wang *et al*[52], 1989	SCC	NART	104		35	NS	40
		Surgery	102		30		

[1]Group 3: NART; [2]Group 1: Surgery alone; [3]3-year OS. MS: Median survival; RT: Radiotherapy; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; NART: Neoadjuvant radiotherapy; NS: Not significant; OS: Overall survival.

gery alone[36,44-47] (Table 1), and another five phase Ⅲ trials that have compared neoadjuvant radiotherapy to surgery alone[48-52] (Table 2). Although local control of disease was improved in each of the adjuvant radiation arms, there were increased complications secondary to adhesions, scarring and fistulas, and none reported an OS advantage in their entire study population as a whole. Among these trials, however, Xiao and colleagues randomized 495 patients with SCC to surgery followed by adjuvant radiotherapy or to surgery alone. Although the 5-year OS was not statistically different for all-comers (41% *vs* 32%, *P* = 0.45), a 5-year OS advantage was noted in a subgroup analysis of patients with stage Ⅲ disease (35% *vs* 13%, *P* < 0.003), which favored the arm that received adjuvant radiotherapy[47].

Of the five phase Ⅲ trials that have evaluated neoadjuvant radiotherapy in esophageal cancer, none has demonstrated an increase in resectability or OS in those treated with preoperative radiotherapy alone[48-52]. Although Nygaard *et al*[51] have reported a 3-year OS benefit, this was only after pooling patients who had received neoadjuvant radiotherapy with those who had also received neoadjuvant chemoradiotherapy, as there was no significant difference in survival found otherwise. A meta-analysis of trials that have used neoadjuvant radiotherapy with a median follow-up of 9 years, and including data from 1147 patients who almost exclusively had SCC, has revealed a trend toward improved 5-year OS (OR: 0.89, 95% CI: 0.78-1.01, *P* = 0.062), but ultimately has failed to show a statistically significant survival advantage[53].

Chemotherapy

The theoretical advantages of adding chemotherapy to the treatment of esophageal cancer are for potential tumor down-staging prior to surgery, as well as targeting micrometastatic disease, and thus decreasing the risk of distant spread. Adjuvant chemotherapy with cisplatin-based regimens compared to surgery alone has been examined in three separate phase Ⅲ trials[54-56] (Table 3), with none of them reporting a statistically significant difference in OS, although Ando and colleagues have reported a 5-year disease-free survival (DFS) advantage (55% *vs* 45%, *P* = 0.037)[56]. In the neoadjuvant setting, there have been multiple randomized trials that have compared varying chemotherapeutic regimens to surgery alone[32,51,57-63] (Table 4). Clinical complete responses based on direct visualization and an assortment of imaging modalities have ranged from 19% to 58%, but the rate of pathological complete response (pCR) at the time of surgery was a disappointing 2.5%-13%. This is an unsurprising trend considering the relative ineffectiveness of chemotherapy alone in the treatment of esophageal cancer[32,51,57-63].

The UK Medical Research Council (MRC) trial included 802 patients of all histologies, and randomized patients

Table 3 Randomized controlled trials of adjuvant chemotherapy *vs* surgery alone for esophageal cancer

Studies	Histology	Treatment	*n*	MS (mo)	5-yr OS (%)	*P*
Pouliquen *et al*[54], 1996	SCC	CF	52	13		NS
		Surgery	68	14		
Ando *et al*[55], 1997	SCC	CV	100		45	NS
		Surgery	105		48	
Ando *et al*[56], 2003	SCC	CF	120		61	NS
		Surgery	122		52	

MS: Median survival; SCC: Squamous cell carcinoma; C: Cisplatin; F: Fluorouracil; V: Vindesine; NS: Not significant; OS: Overall survival.

Table 4 Randomized controlled trials of neoadjuvant chemotherapy *vs* surgery alone for esophageal cancer

Studies	Histology	Treatment	*n*	MS (mo)	3-yr OS (%)	*P*
Schlag *et al*[57], 1992	SCC	CF	22	7		NS
		Surgery	24	6		
Nygaard *et al*[51], 1992	SCC	BC	44	7	3	NS
		Surgery	41	7	9	
Maipang *et al*[58], 1994	SCC	BVC	24	17	31	NS
		Surgery	22	17	36	
Law *et al*[59], 1997	SCC	CF	74	17	40	NS
		Surgery	73	13	13	
Kelsen *et al*[32], 1998	AC/SCC	CF	213	15	19[1]	NS
		Surgery	227	16	20[1]	
Ancona *et al*[60], 2001	SCC	CF	47	25	34[1]	NS
		Surgery	47	24	22[1]	
MRC[61], 2002	AC/SCC	CF	400	17	43	< 0.01
		Surgery	402	13	34	

[1]5-year OS. MS: Median survival; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; C: Cisplatin; F: Fluorouracil; B: Bleomycin; V: Vindesine; NS: Not significant; OS: Overall survival.

to two cycles of neoadjuvant cisplatin 80 mg/m^2 and infusional fluorouracil 1000 mg/m^2 per d for 4 d *vs* surgery alone. A rather striking distinction of this trial compared to others was that clinicians could give their patients neoadjuvant radiotherapy (25-32.5 Gy) irrespective of randomization, and 9% of patients on each arm received radiotherapy. R0 resections were reported in 60% of assessable patients that were treated with neoadjuvant chemotherapy *vs* 54% of patients treated with surgery alone (*P* < 0.0001). OS was also improved in the neoadjuvant group (HR: 0.79, 95% CI: 0.67-0.93, *P* = 0.004), with a median OS of 16.8 mo *vs* 13.3 mo, respectively[61]. Another large trial by Kelsen *et al*[32] has evaluated neoadjuvant chemotherapy in the Intergroup (INT) 0113 study with 440 patients, however, reported no difference in OS was reported. Two large meta-analyses also have failed to demonstrate a survival advantage with neoadjuvant chemotherapy[64,65], although another meta-analysis by Gebski *et al*[66] has reported a statistically significant OS benefit with neoadjuvant chemotherapy (HR: 0.90, 95% CI: 0.81-1.00, *P* = 0.05), which corresponds to a 2-year absolute survival benefit of 7%. Caveats to this meta-analysis are that no statistically significant benefit was seen for patients with SCC treated with neoadjuvant chemotherapy (HR: 0.88, 95% CI: 0.75-1.03, *P* = 0.12) and that, although there was a benefit seen with AC (HR: 0.78, 95% CI: 0.64-0.95, *P* = 0.014), these results were based solely on the single trial whose data were available for review - the MRC trial[61,66].

At least four separate trials have compared cisplatin-based perioperative regimens (neoadjuvant and adjuvant chemotherapy) to surgery alone in esophageal cancer[32,67-69] (Table 5). Those that focused solely on esophageal cancer did not reveal survival benefits[32,67], whereas the two that included patients with AC of the stomach and GEJ did show such a benefit[68,69]. The largest of these, published by Cunningham and colleagues, randomized 503 patients with AC to three preoperative and three postoperative courses of epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 with infusional fluorouracil 200 mg/m^2 per day for 21 d *vs* surgery alone. Although the majority of patients had gastric AC, approximately 26% of the patients enrolled had AC of the GEJ or distal esophagus. Despite the fact that 58% of patients were unable to tolerate all six cycles of chemotherapy, the perioperative chemotherapy group had a statistically significant higher likelihood of OS compared to those treated with surgery alone (HR: 0.75, 95% CI: 0.60-0.93, *P* = 0.009), with an improved median OS (24 mo *vs* 20 mo) and 5-year OS (36% *vs* 23%). Although postoperative complications were not increased (46% *vs* 45%), there was also no difference in the rate of R0 resection (69% *vs* 66%) or pCR (both 0%). Importantly, there was no evidence of heterogeneity of treatment effect based on the location of the primary tumor[68].

Chemoradiotherapy
Chemotherapy in conjunction with radiotherapy was

Table 5 Randomized controlled trials of perioperative chemotherapy *vs* surgery alone for esophageal cancer

Studies	Histology	Treatment	*n*	MS (mo)	5-yr OS (%)	*P*
Roth *et al*[67], 1988	AC/SCC	BVC	19	9	25	NS
		Surgery	20	9	5	
Kelsen *et al*[32], 1998	AC/SCC	CF	213[1]	15	19	NS
		Surgery	227	16	20	
Cunningham *et al*[68], 2006	AC[2]	ECF	250	24	36	NS
		Surgery	253	20	23	
Boige *et al*[69], 2007	AC[3]	CF	113[4]		38	< 0.05
		Surgery	111		24	

[1]Of 213 patients in the perioperative arm, only 66 later received adjuvant chemotherapy; [2]26% had AC of the GEJ and lower esophagus; [3]11% had esophageal AC; [4]Of 113 patients in the perioperative arm, only 54 later received adjuvant chemotherapy. MS: Median survival; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; B: Bleomycin; C: Cisplatin; V: Vindesine; F: Fluorouracil; E: Epirubicin; NS: Not significant; OS: Overall survival.

initially evaluated as a definitive treatment for patients deemed unable to proceed with surgery[70]. In combination, chemotherapy not only compliments but augments the effect of radiotherapy in a process known as radiation sensitization, secondary to synergistic DNA damage, cell cycle synchronization, and inhibition of repair and resistance pathways[71,72]. In addition to increasing the efficacy of radiotherapy and thus controlling local tumor growth, as mentioned earlier, chemotherapy theoretically also offers the ability to eradicate micrometastatic disease and decrease the risk of distant recurrence[73].

The seminal Radiation Therapy Oncology Group (RTOG) 85-01 trial has compared radiotherapy (50.4 Gy over 5 wk) with concurrent cisplatin 75 mg/m^2 and infusional fluorouracil 1000 mg/m^2 per day for 4 d to radiotherapy alone (64 Gy over 6.4 wk). The chemotherapy arm consisted of four cycles delivered every 4 wk during radiotherapy (cycles 1 and 2) and every 3 wk for the remainder (cycles 3 and 4). The study included 134 patients with 90% having SCC and all with T1-3 N0-1 M0 disease. The trial was closed early once an interim analysis revealed that there was a statistically significant survival advantage that favored concurrent chemoradiotherapy that later amounted to a 5-year OS of 27% *vs* 0%. There was no statistically significant difference in OS based on histology[70].

Although those who received concurrent chemoradiotherapy had a decreased risk of persistent disease or local recurrence compared to those who received radiotherapy alone in the RTOG 85-01 trial, the incidence of locoregional failure was still 47%[70], and the INT 0123 trial was launched in an effort to improve upon this, with the theory that higher doses of radiotherapy would be beneficial. A total of 236 patients with T1-3 N0-1 M0 disease were enrolled (85% with SCC) and randomized to high-dose radiotherapy (64.8 Gy) *vs* low-dose radiotherapy (50.4 Gy), with both arms receiving four cycles of concurrent chemotherapy (cisplatin 75 mg/m^2 and infusional fluorouracil 1000 mg/m^2 per day for 4 d every 4 wk). The INT 0123 trial was also stopped early after an interim analysis failed to reveal a significant difference in median OS (13 mo *vs* 18.1 mo), 2-year survival (31% *vs* 40%), or locoregional persistence/recurrence of disease (56% *vs* 52%) between the high-dose and low-dose radiotherapy arms, respec-

tively[74]. With such unacceptably high locoregional failure rates with definitive chemoradiotherapy, in addition to the dismal prognosis of patients treated with surgical resection alone[32-35], numerous trials were begun to evaluate multimodality treatments that combine chemotherapy, radiotherapy, and surgical resection.

To date, at least nine randomized phase III clinical trials have compared neoadjuvant chemoradiotherapy with surgery alone[33,51,75-82] (Table 6). These trials incorporated multiple chemotherapy regimens, doses of radiotherapy used (20-50.4 Gy), and timing of radiotherapy with regard to chemotherapy (sequential *vs* concurrent), in addition to differing by surgical procedures performed and histological types of esophageal cancer enrolled (AC, SCC, or both). Only two of these trials have revealed a significant survival benefit that favored multimodality treatment, and neither was without its imperfections[77,81]. Walsh and colleagues randomized 113 patients with AC to two courses of neoadjuvant cisplatin 75 mg/m^2 and fluorouracil 15 mg/kg per day for 5 d with concurrent radiotherapy (40 Gy over 3 wk) or to surgery alone. The median OS was 16 mo *vs* 11 mo (*P* = 0.01) with a 3-year OS of 32% *vs* 6% (*P* = 0.01), which favored the multimodality treatment arm[77]. This single-institution-based trial, however, has been heavily criticized for an OS of patients with localized esophageal cancer treated with surgery alone (6%) that was far inferior to historical controls[32].

The second study, the Cancer and Leukemia Group B 9781 trial, was closed early with only 56 of an expected 500 patients enrolled, secondary to poor accrual that was reportedly due to the unwillingness of many patients and physicians to enroll in the control surgery-alone arm. Patients were randomly assigned to two cycles of cisplatin 100 mg/m^2 and fluorouracil 1000 mg/m^2 per day for 4 d with concurrent radiotherapy (50.4 Gy over 5.5 wk) prior to surgery, or to surgery alone. An impressive 5-year OS of 39% *vs* 16% was reported with a median OS of 4.48 years *vs* 1.79 years (*P* = 0.002), respectively. Although the obvious clinical significance of these findings is hard to dispute, a trial with more robust participation would have gone a long way to alleviate any uncertainties regarding the best treatment strategy for resectable esophageal cancer[81].

Table 6 Randomized controlled trials of neoadjuvant and adjuvant chemoradiotherapy *vs* surgery alone for esophageal cancer

Studies (yr)	Histology	Treatment	n	MS (mo)	5-yr OS (%)	P
Nygaard *et al*[51], 1992[1]	SCC	BC + 35 Gy	47	8	17[3]	NS
		Surgery	41	7	9[3]	
Apinop *et al*[75], 1994[1]	SCC	CF + 20 Gy	35	10	24	NS
		Surgery	34	7	10	
Le Prise *et al*[76], 1994[1]	SCC	CF + 20 Gy	41	10	19[3]	NS
		Surgery	45	11	14[3]	
Walsh *et al*[77], 1996[1]	AC	CF + 40 Gy	58	16	32[3]	< 0.05
		Surgery	55	11	6[3]	
Bosset *et al*[33], 1997[1]	SCC	C + 37 Gy	143	19	7	NS
		Surgery	139	19	9	
Urba *et al*[78], 2001[1]	AC/SCC	CFV + 45 Gy	50	17	20	NS
		Surgery	50	18	10	
Lee *et al*[79], 2004[1]	SCC	CF + 45 Gy	51	28	49[3]	NS
		Surgery	50	27	41[3]	
Burmeister *et al*[80], 2005[1]	AC/SCC	CF + 35 Gy	128	22	17	NS
		Surgery	128	19	13	
Tepper *et al*[81], 2008[1]	AC/SCC	CF + 50.4 Gy	30	54	39	< 0.01
		Surgery	26	21	16	
Macdonald *et al*[82], 2001[2]	AC[4]	F + 45 Gy	281	36	50[3]	< 0.01
		Surgery	275	27	41[3]	

[1]Neoadjuvant chemoradiotherapy; [2]Adjuvant chemoradiotherapy; [3]3-year OS; [4]20% of patients enrolled had AC of the gastroesophageal junction (GEJ). MS: Median survival; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; B: Bleomycin; C: Cisplatin; F: Fluorouracil; V: Vindesine; NS: Not significant; OS: Overall survival.

With such inconclusive and often contradictory results in trials that have evaluated neoadjuvant multimodality treatment based on disparate study populations, a myriad of regimen protocols, and more importantly, small numbers of patients, numerous meta-analyses have subsequently been performed in an effort to synthesize these data into larger pools and discover if a survival benefit exists[66,83-87]. One of the first, published by Urshel and Vasan, included nine randomized controlled trials with 1116 patients and reported a 3-year survival benefit that favored neoadjuvant chemoradiotherapy (OR: 0.66, 95% CI: 0.47-0.92, $P = 0.016$), which was most pronounced when the chemotherapy and radiotherapy were given concurrently (OR: 0.45, 95% CI: 0.26-0.79, $P = 0.005$) instead of sequentially (OR: 0.82, 95% CI: 0.54-1.25, $P = 0.36$). Although patients who received neoadjuvant chemoradiotherapy were less likely to proceed to surgery (OR: 2.50, 95% CI: 1.05-5.96, $P = 0.038$), they were still more likely to have an R0 resection (OR: 0.53, 95% CI: 0.33-0.84, $P = 0.007$) with 21% having a pCR. Although there was a decreased risk of local-regional recurrence for those who received multimodality treatment compared to those who received surgery alone (OR: 0.38, 95% CI: 0.23-0.63, $P = 0.0002$), there was no difference in risk for distant recurrence. There was a statistically insignificant but nonetheless concerning trend toward increased treatment mortality (OR: 1.63, 95% CI: 0.99-2.68, $P = 0.053$)[84]. The most recent meta-analysis published by Gebski and colleagues has evaluated 1209 patients in 10 trials, and likewise found a statistically significant benefit with neoadjuvant chemoradiotherapy compared to surgery alone, with a 19% decreased risk of death (HR: 0.81, 95% CI: 0.70-0.93, $P = 0.002$) for both AC and SCC, which corresponded to a 13% absolute difference in survival at 2 years[66].

As noted earlier, Gebski *et al*[66] also have evaluated neoadjuvant chemotherapy compared to surgery alone in a meta-analysis. These separate meta-analyses have been published at the same time in conjunction with each other. Although the two neoadjuvant chemotherapy and chemoradiotherapy data pools are not directly comparable, the absolute survival benefit of chemotherapy appears to be less than that of chemoradiotherapy (7% *vs* 13% at 2 years). This point was further supported although not confirmed by Stahl *et al*[88] who randomized 126 patients with AC of the GEJ (55% were type I GEJ tumors) to 16 wk neoadjuvant chemotherapy using cisplatin and leucovorin-modulated fluorouracil, or 12 wk of the same regimen followed by 3 wk of cisplatin and etoposide with concurrent radiotherapy (30 Gy) prior to surgical resection. Those treated with multimodality neoadjuvant chemoradiotherapy did not have a significant increase in R0 resection (72% *vs* 70%), but did have an increased probability of achieving a pCR (15.6% *vs* 2%, $P = 0.03$) and having tumor-free lymph nodes at the time of resection (64% *vs* 38%, $P = 0.01$) compared to those treated with neoadjuvant chemotherapy. There was a trend toward improved 3-year OS (47% *vs* 28%, $P = 0.07$), which favored neoadjuvant chemoradiotherapy, but with just a third of the expected 354 patients enrolled in the trial prior to its closure due to poor accrual, there was no statistically significant difference noted.

Anecdotally, patients with esophageal cancer often lack the strength to complete adjuvant chemoradiotherapy, although there are data to support its use and tolerability in patients with tumors of the GEJ[82]. The U.S. INT 0116 trial enrolled 556 patients with resected AC of the stomach and GEJ; approximately 20% of those participating had GEJ tumors. Patients were randomized to either sur-

gery alone or surgery followed by four cycles of adjuvant leucovorin-modulated fluorouracil, with the second cycle concurrent with radiotherapy (45 Gy). The median OS was 27 mo *vs* 36 mo (HR: 1.35, 95% CI: 1.09-1.66, *P* = 0.005), which favored the adjuvant chemoradiotherapy arm. Although 17% of patients were unable to finish the protocol because of treatment-related toxicity, an impressive 64% of patients were able to finish the protocol completely. There was no difference in survival based on the location of the primary tumor[82].

Targeted therapy

Despite improvements seen with the multimodality treatment of esophageal cancer, cure rates remain disappointingly low[66]. As such, targeted agents that have been found to benefit patients with head and neck, breast, lung, colon, and pancreatic cancers have generated intense interest in esophageal cancer[89-91]. Multiple pathways have been evaluated at the molecular level with potential targets in esophageal cancer including cyclin-dependent kinases, nuclear factor κB, matrix metallopreoteinases, and the inhibition of *COX-2*. The most promising targets at present, however, appear to be the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF)[89].

There are at least four types of EGFR: EGFR (human EGFR-1, HER-1), HER-2, HER-3, and HER-4. EGFR signaling plays a crucial role in modulating cell proliferation, invasion, metastasis, and resistance to cell death[89]. Overexpression of EGFR proteins has been reported in 30%-70% of AC and SCC of the esophagus, with such overexpression correlating with more aggressive disease and worse outcome[92-94]. Multiple clinical trials have been launched in an effort to target EGFR in esophageal cancer, with the most common drug used being the IgG1 monoclonal antibody cetuximab[95-99]. A trial by Gold *et al*[95] using cetuximab as a second-line monotherapy in the metastatic setting was discouraging, although regimens using cetuximab in combination with FOLFIRI[96], cisplatin and docetaxel[97], and cisplatin and fluorouracil[98] have revealed that the drug shows promise in the treatment of esophageal cancer. A phase Ⅱ trial by Safran *et al*[99] has evaluated 57 patients with esophageal cancer that were treated with weekly carboplatin, paclitaxel and cetuximab with concurrent radiotherapy (50.4 Gy). Seventy percent of patients achieved a complete clinical response and, of the 49 patients who went on to surgery, 27% had a pCR. The RTOG 0436 trial - a phase Ⅲ trial that is evaluating carboplatin, paclitaxel, and concurrent radiotherapy with or without cetuximab - is currently ongoing.

Another EGFR that is more famously associated with breast cancer, HER-2, is also overexpressed in 19%-43% of patients with esophageal cancer, and can be targeted by trastuzumab - a humanized IgG1 monoclonal antibody against the same receptor[100]. The phase Ⅲ ToGA trial randomized 594 patients with locally advanced, recurrent, or metastatic gastroesophageal cancer with HER-2 overexpression to treatment with cisplatin and fluorouracil or capecitabine, with or without trastuzumab. The median

OS was significantly improved and favored the arm that received trastuzumab (13.5 mo *vs* 11.1 mo, HR: 0.74, 95% CI: 0.60-0.91, *P* = 0.0048)[101]. How these results will affect future multimodality neoadjuvant treatment is unknown, especially considering the potential for cardiotoxicity in a patient population that is already at risk. Although there were no differences in symptomatic congestive heart failure between the two arms, the patients who received trastuzumab were more likely to experience asymptomatic decreases in their left ventricular ejection fraction (4.6% *vs* 1.1%)[101].

VEGF is a regulator of angiogenesis and is yet another potential target. Similar to EGFR, VEGF is also overexpressed in 30%-60% of esophageal cancer patients and is likewise associated with poor outcome[102]. There is even evidence to suggest that the level of VEGF expression increases during treatment with chemotherapy and radiotherapy, which makes it a particularly attractive target for multimodality neoadjuvant treatment[103,104]. Promising phase Ⅱ data with surgically unresectable AC of the GEJ combining bevacizumab - a humanized monoclonal antibody against VEGF - with cisplatin and irinotecan[105], as well as docetaxel, cisplatin and fluorouracil[106] are available, while trials that are incorporating neoadjuvant chemoradiotherapy with the addition of bevacizumab are currently ongoing[91]. As with trastuzumab, it is unknown how the potential toxicities inherent to bevacizumab - hypertension, thromboembolism, poor wound healing, bowel perforation, worsening arterial disease, and an increased risk of bleeding - will affect the treatment of esophageal cancer patients who often present with multiple comorbidities[107].

CONCLUSION

The optimal treatment strategy for resectable esophageal cancer is still a controversial topic. Multimodality neoadjuvant chemotherapy with concurrent radiotherapy has been accepted by many - although not all - as the standard of care, because such a regimen increases rates of pCR, R0 resection, and local tumor control, which all correlate with improved OS[33,66,77,78,81,84-86]. If one accepts the most recent meta-analysis, an absolute OS benefit exists but is likely to be just 13% at 2 years[66]. With such a small benefit, it is no wonder that the multiple underpowered clinical trials that have compared neoadjuvant chemoradiotherapy with surgery alone have found it difficult to demonstrate a survival difference.

Although such a survival benefit might seem small, it should be noted that it is in line with accepted treatment algorithms of other lethal malignancies, such as the addition of adjuvant chemotherapy in completely resected non-small cell lung cancer[108]. The need to treat approximately eight patients with a difficult-to-tolerate regimen to cure just one additional person is hardly ideal, yet these odds are not inconsequential when discussing them face-to-face with a patient who is at least felt to be sufficiently medically fit enough to withstand an esophagectomy.

Although neoadjuvant and perioperative chemother-

apy have also been found to be effective approaches for treating esophageal cancer, there is a reasonable amount of evidence to support the notion that such treatments are inferior to neoadjuvant chemoradiotherapy[66,88], while the data supporting adjuvant chemoradiotherapy can only be applied to patients with GEJ tumors at the present time[82]. How targeted therapy will affect our approach to resectable esophageal cancer is currently unknown as many of the trials to determine this are ongoing[91,99]. By participating in clinical trials and enrolling as many appropriate patients as we possibly can, these questions will hopefully be answered in a more timely and conclusive manner than previously seen in the history of esophageal cancer treatment.

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