

# Esophageal cancer: comparative effectiveness of treatment options

Cai Xu<sup>1</sup>  
Steven H Lin<sup>2</sup>

<sup>1</sup>Department of Radiation Oncology, Cancer Hospital and Institute, Chinese Academy of Medical Sciences Peking Union Medical College, Beijing, People's Republic of China;

<sup>2</sup>Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

**Abstract:** Esophageal cancer is a lethal disease. Multimodal therapy has improved the survival and local control for locally advanced esophageal cancer compared to surgery alone. Neoadjuvant chemoradiotherapy (CRT) plus surgery is the accepted standard of care for operable esophageal cancer. Pathologic complete response is very common, ranging from 18% to 43%, and it is an independent favorable prognostic factor for survival. Salvage surgery after definitive CRT may be safe and feasible for patients with esophageal cancer who achieve pathologic complete response after neoadjuvant CRT. For inoperable cases, definitive CRT is an alternative treatment modality. Intensity-modulated radiation therapy may reduce treatment-related toxicities due to its better dose homogeneity and conformity compared to three-dimensional conformal radiotherapy. Proton therapy can further improve target conformity and normal tissue sparing when compared to photon therapy (three-dimensional conformal radiotherapy and intensity-modulated radiation therapy) and, therefore, likely to further improve the treatment outcomes of patients. This article compares the effectiveness of the various treatment approaches in the definitive or neoadjuvant setting and reviews the evidence on the benefit of utilizing advanced radiation techniques for the curative management of esophageal cancer.

**Keywords:** esophageal cancer, treatment modalities, comparative effectiveness, IMRT, proton therapy

## Introduction

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of cancer death.<sup>1</sup> It is a highly lethal disease with poor prognosis and imposes a high health burden in many societies. Esophageal cancer is mainly classified as squamous-cell carcinoma (SCC) and adenocarcinoma (AC). Traditionally, surgery alone is the standard treatment for localized SCC and AC of the esophagus, especially for patients with early-stage diseases. However, despite the remarkable improvement in surgical techniques, the survival with surgery alone in locally advanced esophageal cancer remains poor, with median 5-year overall survival (OS) of ~20%.<sup>2-4</sup> It has unacceptably high rates of locoregional recurrence (LRR), despite R0 resection, ranging from 41.5% to 49%.<sup>5-8</sup> This has prompted the introduction of multimodal therapy to improve the results, such as definitive chemoradiotherapy (CRT), pre- and postoperative CRT, pre- and postoperative chemotherapy, and pre- and postoperative radiotherapy. Over the past 3 decades, surgical advances and improvement in radiation techniques have greatly improved the disease outcomes.<sup>9-11</sup> This article focuses on integrating these approaches and tailoring the treatment strategy for individual patients, compares the effectiveness of the various treatment approaches in the definitive or neoadjuvant

Correspondence: Steven H Lin  
Department of Radiation Oncology,  
The University of Texas MD Anderson  
Cancer Center, 1515 Holcombe Blvd.,  
Unit 097, Houston, Texas 77030, USA  
Tel +1 713 563 8490  
Fax +1 713 563 2366  
Email shlin@mdanderson.org



setting, and reviews the evidence on the benefit of utilizing advanced radiation techniques for the curative management of esophageal cancer.

### Definitive treatment for esophageal cancer

Historically, surgery has been the primary treatment modality for esophageal cancer, especially for patients with early-stage disease. However, in patients with medical comorbid conditions or unresectable diseases, nonsurgery treatment modalities, such as radiotherapy, will be a cornerstone of therapy. Radiotherapy alone has historically been used as an alternative curative treatment approach for patients with these conditions. However, concurrent CRT (CCRT) has now become the standard nonsurgery treatment option for patients who could tolerate chemotherapy.

### Definitive radiotherapy alone vs definitive CRT for esophageal cancer

The prognosis is very poor when radiotherapy alone is used.<sup>12</sup> Cisplatin-based CCRT, as definitive treatment for unresectable esophageal cancer, has improved the survival compared to definitive radiotherapy alone, although at the cost of increased toxicity (Table 1).<sup>12-16</sup> An early randomized trial showed that CCRT was superior to radiotherapy alone in patients with localized esophageal cancer, in terms of survival, local control, and distant metastases.<sup>14</sup> The landmark intergroup study Radiation Therapy Oncology Group (RTOG) 85-01 demonstrated that CCRT significantly increased OS in patients with T1-3N0-1M0 SCC or AC of the esophagus compared to radiotherapy alone.<sup>12</sup> However, acute toxicity was higher in the CCRT group, yet there were no differences in the long-term toxicity.<sup>12</sup> Recently, a meta-analysis was conducted, which included nine randomized studies accounting for 1,135 patients (CCRT: 612; radiotherapy alone: 523) with 97.4% being SCC, and indicated that CCRT is the most effective approach for treating locally advanced esophageal

cancer with the improved survival and local control rates compared to radiotherapy alone.<sup>17</sup>

### Surgery vs definitive radiotherapy alone for esophageal cancer

Surgery is still considered the most effective single modality therapy for the management of esophageal cancer, while radiotherapy also plays an important role in the curative management of inoperable esophageal cancer. A few studies have demonstrated that surgery alone for esophageal cancer was superior to definitive radiotherapy. A large retrospective study from Taiwan reviewed outcomes from 12,482 patients with >90% esophageal SCC and reported that surgery significantly improves survival compared to definitive radiotherapy.<sup>18</sup> In a small randomized study of 99 patients with operable SCC of the esophagus, the results showed that surgery was superior to radiotherapy alone in improving the quality of swallowing ( $P=0.03$ ) and survival ( $P=0.002$ ).<sup>19</sup> Although surgery is the preferred option over radiation alone, radiation therapy alone is primarily a palliative option for patients who are unable to tolerate chemotherapy.

### Surgery vs definitive CRT for esophageal cancer

Phase III randomized trials comparing CCRT with radiation alone<sup>12-16</sup> have made CCRT the standard treatment for patients with inoperable esophageal cancer. However, there are only a few studies comparing the definitive CCRT with surgery alone for esophageal cancer, most of which are prospective Phases I and II clinical trials and retrospective studies,<sup>20-22</sup> and only a few of which are randomized clinical trials.<sup>23</sup> Teoh et al<sup>23</sup> reported a randomized trial of 81 patients with operable SCC of the mid- or lower thoracic esophagus with a 5-year OS favoring CRT, although it was not statistically significant (surgery 29.4% and CRT 50%;  $P=0.147$ ). It was concluded that the long-term survival of definitive CRT for SCC was at least comparable to surgery. A meta-analysis showed that OS was equivalent between surgery and defini-

**Table 1** Studies of definitive RT alone vs definitive CRT for esophageal cancer

References	N		RT dose (Gy)		Chemotherapy	Median OS (months)		5-year OS (%)		P-value
	RT	CRT	RT	CRT		RT	CRT	RT	CRT	
Cooper et al <sup>12</sup>	62	61	64	50	DDP + 5-FU	-	-	0	26	
Al-Sarraf et al <sup>13</sup>	62	61	64	50	DDP + 5-FU	9.3	14.1	0	27	<0.0001
Herskovic et al <sup>14</sup>	60	61	64	50	DDP + 5-FU	8.9	12.5	-	-	<0.001
Smith et al <sup>15</sup>	60	59	40+S; 60	40+S; 60	MMC + 5-FU	9.2	14.8	7	9	<0.05
Smit et al <sup>16</sup>	177	110	60	50.4	DDP based	-	-	-	-	0.071

**Abbreviations:** CRT, chemoradiotherapy; DDP, cisplatin; 5-FU, fluorouracil; OS, overall survival; RT, radiotherapy; S, surgery; MMC, mitomycin.

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tive CRT ( $P=0.84$ ).<sup>24</sup> The similar outcome in survival between surgery alone and CRT suggests that a nonsurgical approach of definitive CRT is a reasonable choice, especially in patients with esophageal cancer who have inoperable diseases or refuse surgery.

## Multimodal therapy for esophageal cancer

### Neoadjuvant CRT plus surgery vs surgery alone for esophageal cancer

Neoadjuvant CRT has been extensively studied in the prospective trials. The evidence to date has suggested that this approach should be integrated into the standard treatment of patients with locally advanced and operable esophageal cancer. A total of 12 randomized trials investigating preoperative CRT compared to surgery alone were identified (Table 2).<sup>11,25–36</sup> Among the 12 randomized trials, preoperative CRT improves the OS rate of patients with esophageal cancer in only five trials.<sup>11,29,30,33,35</sup> Despite some studies not showing the survival benefit, the advantages of preoperative CRT could be illustrated in certain aspects, such as improved local control rate<sup>25,29</sup> and better complete resection rate.<sup>25,28,30</sup> The Irish trial<sup>33</sup> was a small randomized trial in 113 patients with AC randomized to surgery alone vs preoperative CRT with two cycles of cisplatin/fluorouracil and 40 Gy in 15 fractions. Although the study demonstrated an improved survival with preoperative CRT, the uncharacteristic poor survival in the surgery alone group (6% vs 32% at 3 years) confounded the benefit of adding CRT. The Cancer and Leukemia Group B (CALGB) 9781 study closed early after

only 56 patients were enrolled but reported an improved OS with a median survival of 4.48 years vs 1.79 years ( $P=0.002$ ) and 5-year survival of 39% vs 16%, in favor of preoperative CRT.<sup>11</sup> The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) that compared neoadjuvant CRT vs surgery alone in patients with SCC and AC of the esophagus or esophagogastric junction (EGJ) showed a significant improved OS and complete resection rate in neoadjuvant CRT after a median of 45-month follow-up.<sup>30</sup> The updated long-term results published recently continue to show an improved OS in the neoadjuvant CRT group after a median of 84.1-month follow-up, and this improvement was clinically significant for both SCC and AC.<sup>36</sup>

Most studies published previously have also shown a reduction in LRR after preoperative CRT for esophageal cancer compared to surgery alone.<sup>26,29,37,38</sup> The LRR rates range from 5% to 14% and 34% to 42% after neoadjuvant CRT and surgery alone, respectively.<sup>26,29,37,38</sup> The recurrence outcomes in the CROSS study showed that preoperative CRT reduced the overall recurrence rate (surgery 58% vs preoperative CRT 35%) and that preoperative CRT reduced LRR from 34% to 14% ( $P<0.001$ ) and peritoneal carcinomatosis from 14% to 4% ( $P<0.001$ ). Recurrence within the radiation target volume occurred in only 5%, mostly combined with outfield failures.<sup>38</sup> Neoadjuvant CRT also reduces the risk of distant recurrence.<sup>35</sup>

The meta-analysis of randomized trials comparing neoadjuvant CRT and surgery alone for esophageal cancer also demonstrated that preoperative CRT could improve the survival and local control.<sup>39</sup> The meta-analysis by Sjoquist et al<sup>40</sup> included 12 trials that were randomized comparisons

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

References	N		RT dose	CT	pCR (%)	DFS (%)			OS (%)		
	CRT	S				CRT	S	P-value	CRT	S	P-value
Tepper et al <sup>11</sup>	30	26	50.4 Gy/1.8 Gy/28f	DDP + 5-FU	33.3	–	–	–	5 years: 39	5 years: 16	<0.05
Bosset et al <sup>25</sup>	143	139	37 Gy/3.7 Gy/10f	DPP	26	–	–	0.003	–	–	0.78
Urba et al <sup>26</sup>	50	50	45 Gy/1.5 Gy/30f	DDP + 5-FU + VCR	28	3 years: 28	3 years: 16	0.16	3 years: 30	3 years: 16	0.15
Lee et al <sup>27</sup>	51	50	45.6 Gy/1.2 Gy/38f	DDP + 5-FU	43	2 years: 49	2 years: 51	0.93	2 years: 55	2 years: 57	0.69
Burmeister et al <sup>28</sup>	128	128	35 Gy/2.33 Gy/15f	DDP + 5-FU	16	–	–	–	–	–	0.57
Lv et al <sup>29</sup>	80	80	40 Gy/2 Gy/20f	DDP + PTX	–	–	–	–	5 years: 43.5	5 years: 34	<0.05
van Hagen et al <sup>30</sup>	178	188	41.4 Gy/1.8 Gy/23f	CBP + PTX	29	5 years: 44	5 years: 27	<0.001	5 years: 47	5 years: 33	<0.05
Shapiro et al <sup>36</sup>	178	188	41.4 Gy/1.8 Gy/23f	CBP + PTX	–	–	–	–	–	–	0.003
Apinop et al <sup>31</sup>	35	34	–	DPP + 5-FU	27	–	–	–	–	–	>0.05
Le Prise et al <sup>32</sup>	41	45	20 Gy/2 Gy/10f	DPP + 5-FU	–	–	–	–	–	–	>0.05
Walsh et al <sup>33</sup>	58	55	40 Gy/2.67 Gy/15f	DPP + 5-FU	25	–	–	–	3 years: 32	3 years: 6	0.01
Natsugoe et al <sup>34</sup>	22	23	40 Gy/2 Gy/20f	DPP + 5-FU	–	–	–	–	5 years: 57	5 years: 41	>0.05
Ariga et al <sup>35</sup>	51	48	60 Gy/2 Gy/30f	DPP + 5-FU	–	–	–	–	5 years: 75.7	5 years: 51	0.0169

**Abbreviations:** CBP, carboplatin; CRT, chemoradiotherapy; CT, chemotherapy; DDP, cisplatin; DFS, disease-free survival; 5-FU, fluorouracil; OS, overall survival; pCR, pathological complete response rate; PTX, paclitaxel; RT, radiotherapy; S, surgery; VCR, vinblastine.

of neoadjuvant adjuvant CRT vs surgery alone (n=1,854) in patients with operable esophageal carcinoma and provided strong evidence for a survival benefit of neoadjuvant CRT over surgery alone in patients with SCC and AC of the esophagus.

Neoadjuvant CRT can increase the complete resection rate for esophageal cancer,<sup>25,28,30</sup> with the rate of preoperative CRT that ranges from 80% to 92% compared to the rate of surgery alone that ranges from 59% to 69%.<sup>28,30</sup> The number of positive lymph nodes could also be reduced with preoperative CRT,<sup>28</sup> which is associated with good survival.<sup>41–43</sup> Preoperative CRT significantly increases the pathologic complete response (pCR) rate, ranging from 18% to 43%.<sup>27,30,33,44–49</sup> pCR is an independent favorable prognostic factor for survival after surgery<sup>40,50–53</sup> and is also a favorable prognostic factor for both locoregional and systemic recurrences.<sup>40</sup>

Most studies report that preoperative CRT does not increase postoperative complication and mortality,<sup>25,29–32,54</sup> and a few studies report that preoperative CRT may increase postoperative complication and mortality.<sup>25</sup> Bosset et al<sup>25</sup> reported that preoperative CRT did not increase postoperative complication but increased postoperative mortality compared to surgery alone (12.3% vs 4%, respectively); however, the mortality in the preoperative group is very high, which may be associated with surgery procedure. A meta-analysis by Mungo et al<sup>55</sup> showed that preoperative therapy for esophageal cancer did not increase 30-day mortality or the overall risk of postoperative complications after esophagectomy. According to these results, preoperative CRT should not be hindered by its postoperative complication and mortality.

According to the evidence discussed earlier, especially with the results of the CROSS trial, preoperative CRT has a long-term survival benefit over surgery alone without increasing postoperative complication and mortality. Thus, neoadjuvant CRT is now considered the standard of care in many parts of the world for the treatment of resectable and locally advanced esophageal cancer, both for SCC and AC.

## Neoadjuvant chemotherapy and surgery vs surgery alone

Preoperative cisplatin-based chemotherapy is an alternative choice for locally advanced esophageal cancer, and it is widely adopted in Europe and parts of the USA, especially in patients with lower esophageal and EGJ cancers. The survival benefit of neoadjuvant chemotherapy in patients with operable esophageal cancer has been reported in a number of trials.<sup>4,56–59</sup> The randomized study in the UK demonstrated

that preoperative chemotherapy was superior to surgery alone in OS in patients with resectable esophageal cancer without increasing postoperative complications.<sup>56</sup> The updated long-term results showed maintained survival benefit of preoperative chemotherapy over surgery alone for both AC and SCC of esophagus ( $P=0.03$ ) with a 5-year survival of 23.0% for preoperative chemotherapy compared to 17.1% for surgery alone.<sup>4</sup> Some randomized trials suggest that preoperative chemotherapy has a survival benefit in resectable AC of the stomach, EGJ, or lower esophagus; however, esophageal AC only accounted for 10%–15% of the cases.<sup>10,59</sup> A meta-analysis on preoperative chemotherapy trials in esophageal cancers, including nine randomized comparisons of neoadjuvant chemotherapy vs surgery alone (n=1,981), provided the strongest evidence for a survival benefit of neoadjuvant chemotherapy over surgery alone in patients with esophageal carcinoma with a hazard ratio (HR) of 0.87 (95% confidence interval [CI], 0.79–0.96;  $P=0.005$ ).<sup>40</sup> Similarly, a Cochrane review including 14 randomized trials of AC of the stomach, EGJ, and lower esophagus also demonstrated that preoperative chemotherapy was associated with a significantly longer OS.<sup>43</sup> A meta-analysis reported by GebSKI et al<sup>39</sup> found that neoadjuvant chemotherapy did not have a survival benefit for patients with SCC (HR for mortality 0.88 [0.75–1.03];  $P=0.12$ ), whereas the survival benefit was significant for AC group (HR for mortality 0.78 [0.64–0.95];  $P=0.014$ ). On the other hand, a US Intergroup trial 0113 revealed no OS benefits for preoperative chemotherapy over surgery alone.<sup>41,60</sup>

Some series reported that preoperative chemotherapy could downstage the tumor and increase the resection rate, which may result in improved survival.<sup>4,43,61,62</sup> A retrospective study reported that patients with downstaged tumors after neoadjuvant chemotherapy experienced an improved survival compared to patients without response ( $P<0.001$ ) and the lower rates of local recurrence (6% vs 13%, respectively;  $P=0.03$ ) and systemic recurrence (19% vs 29%, respectively;  $P=0.027$ ), and downstaging was the strongest independent predictor of survival.<sup>61</sup> The updated results of the randomized trial in the UK demonstrated macroscopic residual disease from incomplete resection (R2) or no resection in 26.4% of surgery vs 14.3% of the preoperative chemotherapy ( $P<0.001$ ).<sup>4</sup> A review also revealed that preoperative chemotherapy was associated with higher rates of R0 resection and more favorable tumor stage upon resection.<sup>43</sup>

Some studies have demonstrated that preoperative chemotherapy would not increase serious postoperative complications for esophageal cancer.<sup>56,60</sup> A review and a meta-analysis also showed that preoperative chemotherapy for esophageal

carcinoma did not increase the risk of postoperative morbidity or perioperative mortality compared to surgery alone.<sup>43,63</sup> According to the evidence provided earlier, preoperative chemotherapy is a treatment option for patients with operable esophageal cancer, mainly for AC.

## Neoadjuvant CRT vs neoadjuvant chemotherapy for esophageal cancer

Theoretically, neoadjuvant CRT would be superior to neoadjuvant chemotherapy for esophageal cancer since the addition of radiation to neoadjuvant chemotherapy does increase the pathologic response and complete resection rate, both of which should result in improved treatment outcomes. There is proportionately a larger benefit for neoadjuvant CRT than for neoadjuvant chemotherapy, although both are associated with a survival benefit compared to surgery alone.<sup>39</sup> The Preoperative Chemotherapy or Radiochemotherapy in Esophago-gastric Adenocarcinoma Trial (POET) was an attempt to compare these two treatment approaches by randomizing patients with locally advanced AC of the EGJ to either neoadjuvant CRT to 30 Gy in 15 fractions or neoadjuvant chemotherapy.<sup>64</sup> Unfortunately, the trial was closed early due to poor accrual after enrolling 126 patients. The 3-year survival was 47.4% for preoperative CRT compared to 27.7% for preoperative chemotherapy, although this was not statistically significant ( $P=0.07$ ). Nevertheless, compared to preoperative chemotherapy alone, preoperative CRT significantly increased pCR and the rate of tumor-free lymph nodes (15.6% vs 2.0% and 64.4% vs 37.7%, respectively). However, a meta-analysis included only two studies: one of which is POET trial showed weak evidence in favor of neoadjuvant CRT.<sup>40</sup> Neoadjuvant CRT is accepted as the standard treatment for locally advanced esophageal cancer, both for SCC and AC, but the benefits of neoadjuvant CRT over neoadjuvant chemotherapy for AC of the esophagus remain controversial. More randomized trials are needed to compare the effectiveness of the two modalities.

## Neoadjuvant CRT vs definitive CRT for locally advanced esophageal cancer

Early nonrandomized studies with small sample sizes demonstrated that patients treated with CRT had similar survival rates with or without surgery.<sup>65,66</sup> To date, there are only two randomized trials that compared definitive CRT with neoadjuvant CRT for locally advanced esophageal cancer.<sup>67,68</sup> The Fédération Francophone de Cancérologie Digestive (FFCD) 9102 study randomized responding patients after 46 Gy with two cycles of cisplatin/fluorouracil to either surgery or

continuation of CRT to additional 20 Gy. The study reported that adding surgery after CRT brought no survival benefit for patients with locally advanced esophageal cancer, although there was a benefit in 2-year local control of 66.4% compared to 57.0% for neoadjuvant CRT vs definitive CRT, respectively.<sup>68</sup> A second multicenter randomized trial in Germany enrolled 172 patients with locally advanced SCC of the esophagus reported that definitive CRT also resulted in equivalent survival, but there was better local progression-free survival in the surgery group (64.3% vs 40.7%;  $P=0.03$ ).<sup>67</sup> Nevertheless, surgery significantly increased the local tumor control,<sup>67,68</sup> and patients who underwent surgery had a lower chance of death from cancer.<sup>67</sup> The benefits of surgery in FFCD 9102 might have been confounded by some methodological issues.<sup>69</sup> The overall lower dose of chemotherapy for patients receiving resection, the use of split radiation course, which may result in worse survival rates than conventional radiotherapy,<sup>70</sup> and the high surgical mortality<sup>25,71</sup> may have negatively impacted OS outcome. Therefore, the benefit of surgery after CRT is still an open question and may need a modern day trial using modern techniques to convincingly answer this question.

## The role of salvage surgery after CRT

Since the question of the need for additional surgery after CRT for locally advanced esophageal cancer is still not convincingly answered, an important question that is raised is which patients can surgery be spared? There are a number of studies that have shown that patients with pCR have better prognosis.<sup>40,49–53,67,68,72</sup> Berger et al<sup>53</sup> reported that the 5-year survival of patients who achieved pCR after preoperative CRT was ~50%. Furthermore, the LRR rate is also low in patients who achieved pCR after neoadjuvant CRT.<sup>51,73</sup> This suggests that if there is a clear clinical response, which likely enriches for patients with pCR, surgery can probably be avoided at the beginning, and salvage surgery can be done on the patients who have persistent diseases and local or regional recurrence. Salvage surgery after definitive CRT is appropriate and has good outcomes in responding patients.<sup>74,75</sup> A series of data on nonrandomized patients from the FFCD 9102 trial suggest that attempting surgery after early failure of CRT is beneficial and should be considered in patients who are still operable.<sup>76</sup> A retrospective propensity score-matched study included 65 patients with esophageal AC who underwent salvage esophagectomy after failed definitive CRT and compared this group to 65 matched patients who received planned esophagectomy. The study demonstrated that salvage surgery was feasible for patients with esophageal AC who failed definitive CRT and recurred locoregionally since postopera-

tive morbidity, mortality, and OS were comparable between the two groups of patients.<sup>77</sup> Recently, a large multicenter study from the modern era with propensity score matching included 308 patients in definitive CRT plus salvage surgery arm and 540 patients in neoadjuvant CRT plus surgery arm and reported that salvage surgery arm can offer acceptable short- and long-term outcomes in selected patients at experienced centers compared to neoadjuvant CRT plus surgery arm, with 3-year OS (43.3% vs 40.1%;  $P=0.542$ ), disease-free survival (39.2% vs 32.8%;  $P=0.232$ ), and similar recurrence pattern; the perioperative complication was acceptable.<sup>74</sup> Therefore, salvage surgery after definitive CRT may be safe and feasible for patients with esophageal cancer who achieve pCR after neoadjuvant CRT at experienced centers.

### CRT plus target therapy vs CRT for esophageal cancer

Epidermal growth factor receptor (EGFR) is overexpressed in 50%–80% of gastric and EGJ ACs<sup>78,79</sup> and is associated with poor prognosis.<sup>79–81</sup> Cetuximab, a monoclonal EGFR antagonist, improved outcomes when given in combination with chemotherapy in some advanced cancers, especially in squamous-cell head and neck cancer.<sup>80,81</sup> The SCOPE1 trial, a multicenter, randomized, open-label, Phase II/III trial, aimed to investigate the addition of cetuximab to definitive CRT in patients with localized esophageal SCC and ACs, and it was closed when 258 out of 600 patients were enrolled due to interim analysis for futility. The CRT plus cetuximab group had fewer patients with treatment failure free at 24 weeks than the CRT only group (66.4% and 76.9%, respectively) and also had a shorter median OS (22.1 months vs 25.4 months, respectively;  $P=0.035$ ). In addition, the toxicity was worse, and less patients completed therapy with cetuximab.<sup>82</sup> The addition of cetuximab to definitive CRT cannot be recommended for patients with esophageal cancer.

Human epidermal growth factor receptor 2 (HER2; also known as ERBB2) is an important biomarker and driver of tumorigenesis in gastric cancer, with 7%–34% of overexpression or amplification.<sup>83–86</sup> Blocking this powerful growth factor signal may improve patient's outcome. The Trastuzumab for Gastric Cancer (ToGA) study is the first multicenter randomized trial to evaluate the efficacy and safety of trastuzumab, a monoclonal antibody that targets HER2, in combination with chemotherapy for the first-line treatment of HER2-positive advanced gastric or gastroesophageal junction cancer (~80% of gastric cancer). A total of 594 patients were randomly assigned to study treatment (trastuzumab plus chemotherapy:  $n=298$ ; chemotherapy alone:  $n=296$ ). Median follow-up was 18.6 months and 17.1 months, respectively. There was a significant improvement in median OS in the trastuzumab plus

chemotherapy arm compared to chemotherapy arm alone (13.8 months and 11.1 months, respectively; HR 0.74; 95% CI 0.60–0.91;  $P=0.0046$ ). Toxicity was similar in two arms. This study established trastuzumab in combination with chemotherapy as a new standard option for patients with HER2-positive advanced gastric or gastroesophageal junction cancer. OS was longer in patients with high expression (immunohistochemistry 2+ and fluorescence in situ hybridization [FISH] positive or immunohistochemistry 3+) of HER2 protein than in patients with low expression (immunohistochemistry 0 and FISH positive or immunohistochemistry 1+ and FISH positive) in the post hoc subgroup analysis.<sup>87</sup> The addition of trastuzumab to chemotherapy substantially improved OS in patients with high expression of HER2 ( $n=446$ ; 16 months vs 11.8 months; HR =0.65) compared to those with low expression of HER2 ( $n=131$ ; 10 months vs 8.7 months; HR =1.07).<sup>87</sup> The addition of trastuzumab to CRT for esophageal cancer is currently being tested in the RTOG 1010 trial to evaluate the effectiveness of trastuzumab in combination with neoadjuvant CRT for esophageal cancer.

### Advances in radiation delivery: three-dimensional conformal radiotherapy vs intensity-modulated radiation therapy for esophageal cancer

Radiotherapy is an extremely effective treatment for esophageal cancer. The advent of three-dimensional conformal radiotherapy (3D-CRT) brought a major shift from conventional, two-dimensional techniques, and it has substituted conventional radiation gradually in clinical practice as the standard treatment for esophageal cancer. However, 3D-CRT is still associated with significant long-term toxicities because of excessive radiation dose to the lungs and heart, which may result in pneumonitis and heart failure and/or cardiac arrhythmia. Intensity-modulated radiation therapy (IMRT) is an advanced radiation technique that uses inverse planning or automated optimization to deliver a nonuniform radiation dose within the radiation field so that the dose could be concentrated within the tumor with relative sparing of the surrounding normal organs.<sup>88</sup> Therefore, IMRT has significant dosimetric advantages over 3D-CRT.

IMRT has been shown to be superior to 3D-CRT with respect to conformity and dose homogeneity to the target.<sup>89–94</sup> Most studies reported that IMRT can better spare the lungs with respect to the lung volume receiving >20 Gy ( $V_{20}$ )<sup>90,91,93,95</sup> mean lung dose (MLD),<sup>90,91</sup> and even  $V_{10}$  and  $V_5$ ;<sup>90,95</sup> however, some studies reported that IMRT resulted in larger  $V_{10}$ .<sup>96</sup> Some studies reported that IMRT can reduce the radiation dose to the heart in terms of heart volume exposed

to >30 Gy (V30),<sup>93,95–97</sup> 40 Gy (V40),<sup>93,95</sup> mean heart dose,<sup>97</sup> and even the right coronary artery.<sup>97</sup> Thus, IMRT has a much greater potential for achieving a higher degree of target conformity and/or normal tissue sparing than 3D-CRT, especially for target volumes and/or organs at risk with complex shapes and/or concave regions.

Many studies reported that lung V20 and MLD are related to radiation pneumonitis.<sup>98–103</sup> IMRT can significantly improve lung sparing in terms of the MLD and V20, and theoretically, IMRT could reduce pulmonary complications. Tsujino et al<sup>104</sup> reported that the 12-month cumulative incidences of radiation pneumonitis greater than grade 2 were 0%, 7.1%, 25%, and 42.9% in patients with a V20 of <20%, 21%–25%, 26%–30%, and >31%, respectively, for 43 patients with small-cell lung cancer receiving CRT. Lee et al demonstrated that radiotherapy techniques, which decrease the volume of lung receiving low radiation doses (V10 and V15), may also significantly reduce the risk of this potentially life-threatening complication.

It is reported that cardiac complications after radiation are related to heart V30, V40 and higher dose volumes, and mean heart dose.<sup>105,106</sup> Gayed et al<sup>106</sup> reported a 54% rate of cardiac ischemia 3 months following CRT for esophageal cancer and found that most perfusion defects were located in the region of the heart receiving  $\geq 45$  Gy. A study including 101 patients with inoperable esophageal cancer treated with CRT found that the risk of pericardial effusion increased significantly with a mean pericardial dose of >26.1 Gy (73% vs 13%;  $P=0.002$ ) and a pericardium V30 of >46% (73% vs 13%;  $P=0.001$ ).<sup>105</sup> Does the dosimetric advantage of IMRT translate to better clinical outcomes? The largest series was reported by Lin et al<sup>107</sup> that compared the long-term outcomes with 3D-CRT and IMRT and demonstrated that OS, locoregional control, and cardiac death were significantly better after IMRT than after 3D-CRT. Freilich et al<sup>108</sup> reported that compared to 3D-CRT, IMRT-based CRT resulted in comparable survival but decreased significantly grade  $\geq 3$  toxicity, which is defined as any hospitalization, feeding tube, or >20% weight loss (OR 0.51;  $P=0.050$ ).

Although IMRT is now widely adopted for esophageal cancer treatment in clinical practice, there was never a high-quality randomized trial conducted to compare the two modalities. Additional large cohort studies are needed to compare the treatment outcomes of IMRT and 3D-CRT.

## Further dosimetric and clinical advantages: proton therapy vs X-ray therapy for esophageal cancer

The defining physical characteristic of proton depth dose curves is the peak at the end of the proton range where most of the energy from the protons is deposited, beyond which

the dose is negligible. This spike in energy deposition is known as the Bragg peak. Through its characteristic Bragg peak, proton therapy has the potential to precisely deliver large and uniform dose to a tumor target while minimizing dose to surrounding healthy tissue, which may decrease the radiation-induced toxicity. The dosimetric advantages of proton therapy for esophageal cancer have been demonstrated in comparison to 3D-CRT and IMRT in several planning studies.<sup>109–111</sup> As compared to IMRT, both the two-beam and three-beam proton therapies resulted in much better lung sparing, with median lung V5, V10, V20, and MLD reduced by 35.6%, 20.5%, 5.8%, and 5.1 Gy and 17.4%, 8.4%, 5%, and 2.9 Gy, respectively.<sup>110</sup> In a dosimetric comparative study between IMRT and intensity-modulated proton therapy (IMPT), IMPT spared much more of the heart, lung, liver, and spinal cord.<sup>111</sup> The dosimetric benefits of proton therapy will need to be tailored to each patient according to their specific cardiac and pulmonary risks. In a dosimetric study comparing IMPT with IMRT in esophageal cancer, IMPT produced lower MLD, lung V5 and V20, and heart V40 than did IMRT ( $P<0.05$ ).<sup>112</sup> In another comparative planning study, proton plans showed a decreased dose to various volumes of the heart and lungs, especially lung V5, while achieving adequate target coverage when compared to both the IMRT and 3D-CRT plans.<sup>109</sup>

Furthermore, proton therapy can also improve heart sparing in terms of heart V30 and mean heart dose, which may reduce the risk of radiation-induced cardiovascular toxicity. Ling et al<sup>109</sup> reported that the proton plans delivered a significantly lower dose to the left anterior descending artery and left ventricle in comparison to both the IMRT and 3D-CRT plans. Since irradiation of left anterior descending artery and left ventricle poses a particular risk to develop coronary artery and ischemic heart disease,<sup>113</sup> proton therapy may also reduce the risk of those diseases. In a 55-patient dosimetric comparison of passive scattering proton plans to IMRT plans for the same patients, proton beam is able to significantly spare the heart, lung, and liver.<sup>114</sup>

The outcomes of proton therapy for esophageal cancer have been reported by many authors.<sup>115–121</sup> There are some studies which reported that a higher dose of irradiation delivered by proton therapy could result in improved local control and OS.<sup>115,120,121</sup> In an early Japanese retrospective study, including 15 patients with esophageal cancer treated with proton therapy with or without X-ray therapy, the mean total dose was 80.4 Gy, and the authors found that the high dose of irradiation improved not only the local control but also the long-term survival without increasing the risk of injury to normal organs.<sup>120</sup> From an update from the same

institution in 46 patients with esophageal cancer, the median total dose of combined X-ray and proton radiation for 40 patients was 76.0 Gy, and that of the remaining six patients receiving only proton therapy was 82.0 Gy. It reported that the 5-year actuarial survival, disease-specific survival, and local control rates for the 23 patients with T1 were 55%, 95%, and 83%, respectively, which was much higher than conventional radiotherapy.<sup>115</sup> The good outcome might be associated with dose escalation, with some patients receiving dose  $\geq 80$  Gy.<sup>115</sup> In another study with 30 patients with esophageal cancer (superficial: 13; locally advanced: 17) treated with proton therapy with or without photon therapy, the mean total doses were 77.7 Gy and 80.7 Gy in the superficial and locally advanced cancers, respectively.<sup>121</sup> However, all the aforementioned studies are done without chemotherapy. In a prospective study enrolling 62 patients with esophageal cancer who underwent concurrent chemotherapy (CChT) and proton beam therapy (PBT) (CChT/PBT), the preliminary outcomes demonstrated that the response rates to preoperative CChT/PBT were encouraging, with 28% of the pCR rate for the surgical cohort and 50% of the pCR and near CR rates (0%–1% residual cells).<sup>118</sup> Another recent single institutional study in 40 patients attested to the similar safety and efficacy of CChT and proton beam therapy.<sup>119</sup> Because postoperative complications are relatively common after neoadjuvant chemoradiation, particularly pulmonary complications, which relate to the radiation exposure of the heart and lungs,<sup>122</sup> proton beam therapy could potentially reduce the postoperative toxicities. Indeed, a retrospective study comparing 3D-CRT, IMRT, and proton beam therapy in patients who underwent surgery after neoadjuvant chemoradiation demonstrated significantly improved outcomes in the proton-treated patients compared to 3D-CRT and a strong trend compared to IMRT.<sup>123</sup>

Although proton therapy holds substantial promise to improve the outcomes of esophageal cancer, almost all the studies reported so far are retrospective single-institution series that may limit the reliability of the results. A prospective randomized trial comparing proton therapy and IMRT (NCT01512589) will hopefully provide definitive evidence for the value and benefit of proton therapy.

## Conclusion

Neoadjuvant CRT has been accepted as the standard treatment for esophageal cancer. pCR after CRT is associated with good survival and local control, and surgery may be spared for these patients. However, there are currently no effective mean to predict for pCR, and future efforts will be needed

to identify imaging- or blood-based methods to predict for pCR. Although it was a clinical failure to have added EGFR-targeting antibody to standard CRT in an unselected population of patients, there is a lot of hope that the addition of trastuzumab to standard backbone chemotherapy and radiation in HER2+ esophageal AC will improve pCR and clinical outcomes. There is also no high-quality evidence on comparing CRT plus salvage surgery and neoadjuvant CRT plus upfront surgery, and clinical trials may be needed to test this question. IMRT has substituted 3D-CRT as a standard treatment in clinical practice because of its dosimetric benefits. Step-and-shoot IMRT is mainly used, whereas volumetric modulated arc therapy may have some dosimetric and clinical benefits over step-and-shoot IMRT, but the former is currently being explored. Although proton therapy has many dosimetric benefits over photon therapy, but whether the dosimetric benefits could be translated into clinical benefits is still uncertain, and data on radiation therapy of esophageal cancer with protons are still relatively rare. Trials comparing proton therapy to standard photon-based radiation will be needed to answer this question.

## Disclosure

The authors report no conflicts of interest in this work.

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