



Dr. Edward Yu, Series Editor

## Esophageal cancer management controversies: Radiation oncology point of view

Patricia Tai, Edward Yu

Patricia Tai, Department of Oncology, Division of Radiation Oncology, Allan Blair Cancer Center, University of Saskatchewan, Regina, SK S4T 7T1, Canada

Edward Yu, Department of Oncology, Division of Radiation Oncology, Western University, London, ON N6A 4L6, Canada

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Correspondence to: Dr. Edward Yu, Department of Oncology, Division of Radiation Oncology, Western University, 790 Commissioner Road East, London, ON N6A 4L6, Canada. [edward.yu@lhsc.on.ca](mailto:edward.yu@lhsc.on.ca)

Telephone: +1-519-6858650 Fax: +1-519-6858627

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### Abstract

Esophageal cancer treatment has evolved from single modality to trimodality therapy. There are some controversies of the role, target volumes and dose of radiotherapy (RT) in the literature over decades. The present review focuses primarily on RT as part of the treatment modalities, and highlight on the RT volume and its dose in the management of esophageal cancer. The randomized adjuvant chemoradiation (CRT) trial, intergroup trial (INT 0116) enrolled 559 patients with resected adenocarcinoma of the stomach or gastroesophageal junction. They were randomly assigned to surgery plus postoperative CRT or surgery alone. Analyses show robust treatment benefit of adjuvant CRT in most subsets for postoperative CRT. The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) used a lower RT dose of 41.4 Gray in 23 fractions with newer chemotherapeutic agents carboplatin and paclitaxel to achieve an excellent result. Target volume of external beam radiation therapy and its coverage have been in debate for years among radiation oncologists. Pre-operative and post-operative target volumes are designed to optimize for

disease control. Esophageal brachytherapy is effective in the palliation of dysphagia, but should not be given concomitantly with chemotherapy or external beam RT. The role of brachytherapy in multimodality management requires further investigation. On-going studies of multidisciplinary treatment in locally advanced cancer include: ZTOG1201 trial (a phase II trial of neoadjuvant and adjuvant CRT) and QUINTETT (a phase III trial of neoadjuvant vs adjuvant therapy with quality of life analysis). These trials hopefully will shed more light on the future management of esophageal cancer.

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**Key words:** Radiotherapy; Chemotherapy; Esophagus; Cancer; Treatment

**Core tip:** Esophageal cancer treatment has evolved from single modality to trimodality therapy. There are some controversies of the role, target volumes and dose of radiotherapy (RT) in the literature over decades. Esophageal brachytherapy is effective in the palliation of dysphagia, but should not be given concomitantly with chemo or external beam RT. On-going studies include: ZTOG1201 trial (a phase II trial of neoadjuvant and adjuvant chemoradiation) and QUINTETT (a phase III trial of neoadjuvant vs adjuvant therapy). These trials hopefully will shed more light on the future management of esophageal cancer.

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### INTRODUCTION

Over the past 20 years there have been many significant

changes in the management of esophageal cancer. This disease has shown remarkable changes in histology of adenocarcinoma on the rise over squamous cell carcinoma, and in epidemiology with concentration of tumors adjacent to the gastro-esophageal junction (GEJ). Esophageal cancer has evolved from single modality treatment in the past to trimodality treatment currently. Radiotherapy (RT) has been part of the integral management of esophageal cancer for decades. Greater understanding of the natural history has influenced the approach to diagnosis and to treatment options. Appreciation of the need for multidisciplinary approach in treatment planning has reflected the important role of various treatment modalities. There are different clinical practices of combined treatments and controversies often arise. This is aggravated by the difficulty to conduct large-scale randomized trials since many patients are elderly with multiple co-morbidities. A Medline search revealed a limited number of randomized studies in the past decade. The present article reviews RT in the multimodality management of esophageal cancer, with emphasis on the controversy of RT target volume, and radiation dose. A few examples of the controversies are listed here in this section.

The challenges to treat elderly patients with esophageal cancers had been reported<sup>[1]</sup>. During recent years, the curative potential of RT *vs* surgery for esophageal cancer was investigated in randomized trials. A metaanalysis showed that overall survival (OS) was equivalent between surgery and definitive chemoradiotherapy (CRT) (HR = 0.98 95%CI: 0.8-1.2,  $P = 0.84$ )<sup>[2]</sup>. There was a trend to more cancer related deaths in the definitive RT+/-chemotherapy (chemo) arms [HR = 1.19 (0.98-1.44),  $P = 0.07$ ], predominantly due to a higher risk of loco-regional progression [HR = 1.54 (1.2-1.98),  $P = 0.0007$ ] but treatment related mortality was lower in the conservative arms [HR = 0.16 (0-0.89),  $P = 0.001$ ]. The similar outcome in survival suggests that the safer approach of CRT is a reasonable choice especially in comorbid patients with esophageal squamous cell carcinoma.

For patients with less advanced esophageal cancer patients, the benefit of neoadjuvant therapy is still unclear. However, due to the significant under staging of T2 N0 patients (50% in the Johns Hopkins series), the authors recommend neoadjuvant therapy to all cT2N0 patients before operation<sup>[3]</sup>.

## ROLE OF EXTERNAL BEAM RT

Surgery has been considered the standard of care for stage I resectable esophageal cancer with 5 year survival of 60%-70%, stage II 40%, stage III 20%<sup>[4]</sup>. RT will be discussed in the following sections including its role with chemo before surgery (abbreviated as S here), after surgery with and without chemo, and whether RT is needed in the trimodality management: (1) C + S *vs* S; (2) CRT + S *vs* S; (3) S *vs* S + RT; (4) S *vs* S + CRT; (5) CRT + S *vs* S + CRT; and (6) CRT + S *vs* CRT.

### C + S vs S: Perioperative chemo without RT

A landmark study confirmed that this treatment improves survival. The 503-patient United Kingdom National Cancer Research Institute Medical Research Council Adjuvant Gastric Infusional Chemo trial is the first randomized trial to demonstrate a conclusive survival benefit of perioperative chemo for patients with resectable adenocarcinoma of the stomach, GEJ, and lower esophagus, compared with surgery alone<sup>[5]</sup>. Epirubicin, cisplatin, and infused 5-fluorouracil (ECF) decreased tumor size and stage and hence significantly improved progression-free and overall survival. However, infusional chemo is difficult to administer<sup>[6]</sup>. In this study, RT is not required. Opinions arise regarding the relative efficacy of CRT *vs* chemo alone in the multimodality management setting. A multicenters randomized Trial of Preoperative therapy for Gastric and Esophagogastric Junction Adenocarcinoma from National Cancer Institute of Canada, European Organization for Research and Treatment of Cancer (EORTC), and Trans-Tasman Radiation Oncology Group is underway to compare preoperative CRT using 45 Gray (Gy) with preoperative chemo alone for GEJ and gastric adenocarcinoma<sup>[7]</sup>. The chemo regimen in both arms is ECF or EC Xeloda. The result of this trial may offer further insight to the above dilemma that clinicians often have.

### CRT + S vs S: Does neoadjuvant CRT improve survival?

The use of neoadjuvant CRT has become an increasingly used treatment approach<sup>[8]</sup>. Tables 1 and 2 summarizes the potential benefit of preoperative therapy<sup>[9]</sup>. A few key randomized clinical trials of preoperative CRT with surgery compared to surgery alone are discussed below. Caution to compare across studies is advised. There is great variation of RT dose schemes and the optimum treatment schedule is not clear.

Nygaard *et al*<sup>[10]</sup> showed that 3-year survival was significantly higher in the pooled groups receiving RT as compared with the pooled groups not receiving RT. Comparison of the groups having pre-operative chemotherapy with those not having chemo showed no significant difference in survival.

Walsh *et al*<sup>[11]</sup> employed two courses of 5-fluorouracil (5-FU), 15 mg/kg daily for five days, and cisplatin, 75 mg/m<sup>2</sup> on day 7. This cycle was repeated in week 6. RT of 40 Gy/15 fractions (f)/3 wk was administered.

Bosset *et al*<sup>[12]</sup> with the Fondation Française de Cancérologie Digestive and EORTC Gastrointestinal Tract Cancer cooperative Group conducted the largest study of its kind with 282 patients. They gave two courses of cisplatin, at a dose of 80 mg/m<sup>2</sup> on 0 to 2 d before each course of RT. The target of RT was the macroscopic tumor and enlarged lymph nodes, if any, surrounded by 5-cm proximal and distal margins and a 2-cm radial margin. After a median follow-up of 55.2 mo, no significant difference in OS was observed; the median survival was 18.6 mo for both groups. Although median or OS

**Table 1** Important randomized trials for preoperative chemoradiation *n* (%)

Ref.	<i>n</i>	Histology	Treatment	R0	pCR	Op mortality	MS	3 YS	Locoregional failure
Nygaard <i>et al</i> <sup>[10]</sup> , 1992		Sq	S CB → S R → S CB + R → S	37% 41% 40% 55% (Gp 4 vs 1, <i>P</i> = 0.08)	-	5 (3.4) 6 (4.0) 4 (2.7) 8 (5.4)	Approximately 0.6 yr Approximately 0.7 yr Approximately 0.9 yr Approximately 0.7 yr	Approximately 9% Approximately 2% Approximately 20% Approximately 18%	-
Walsh <i>et al</i> <sup>[11]</sup> , 1996	113	A	CF + R → S S	- -	25% 0%	5 (10.4) 2 (3.7)	16 11 mo <i>P</i> = 0.01	32% 6% <i>P</i> = 0.01	- -
Bosset <i>et al</i> <sup>[12]</sup> , 1997	282	Sq	C + R → S S	- -	26% 0%	17 (12.3) 5 (3.6)	18.6 mo 18.6 mo	36% 34%	- -
Urba <i>et al</i> <sup>[13]</sup> , 2001	100	75% A 25% Sq	CFV + R → S S	90% 90%	28% 0%	1 (2.1) 2 (4)	16.9 mo 17.6 mo NS	30% 16%	19% 42% <i>P</i> = 0.02
Burmeister <i>et al</i> <sup>[14]</sup> , 2005	256	37% Sq 62% A 1% mixed/ other	CF + R → S S	80% 59%	16% 0%	5 (4.8) 6 (5.5)	22.2 mo 19.3 mo	35% 30%	15% 19%
Tepper <i>et al</i> <sup>[15]</sup> , 2008	56	25% Sq 75% A	CF + R → S S	-	33% 0%	0 (0) 1 (3.8)	4.5 yr 1.8 yr <i>P</i> = 0.002	39% 16% 5 YS	13% 15%
Cao <i>et al</i> <sup>[9]</sup> , 2009	366	Sq	CFM → S R → S CFM + R → S S	87% 98% 98% 73%	1.7% 15% 22% 0%	0% 0% 0% 0%	Approximately 42 mo Approximately 42 mo Approximately 60 mo Approximately 42 mo	Approximately 69% 69% 74% 53% <i>P</i> = 0.013	-
van Hagen <i>et al</i> <sup>[16]</sup> , 2012	366	23% Sq T1-3 75% A N0-1 2% other M0	JT + R → S S	92% 69%	29% 0%	6 (4) 8 (4)	49.4 mo 24 mo	58% 44% <i>P</i> = 0.03	-

-. Not reported; A: Adenocarcinoma; B: Bleomycin; C: Cisplatin; F: 5-fluorouracil; Gp: Group; J: Carboplatin; M: Mitomycin; MS: Median survival; NS: Non-significant; Op: Operative mortality using number of patients actually operated as denominator; pCR: Pathological complete response; R: RT; R0: No residual tumor; S: Surgery; Sq: Squamous cell carcinoma; T: Paclitaxel; V: Vinblastine; YS: Year survival.

**Table 2** Pros and cons of pre-operative therapy for esophageal cancer

Pre-op therapy	Pros	Intact vascular supply allowing for potential improved oxygenation for radiotherapy Smaller radiotherapy volume Potential tumor downstaging Sterilization of tumor bed in preparation for surgery Improve resectability
	Cons	Treatment decision based on clinical stage, may over-treat patients Narrow window for surgical resection post CRT, may increase surgical complications with pre-op CRT Dysphagia and issue of nutrition support due to tumor and treatment

CRT: Chemoradiation therapy.

were not significantly different, there was a significant difference in the proportion of deaths that were due to esophageal cancer in the 2 groups (87 of 101 patients who had surgery alone vs 69 of 102 patients who received combined treatment CRT and surgery, *P* = 0.002). As compared with the group treated with surgery alone, the group treated preoperatively had longer disease-free survival (*P* = 0.003), a longer interval free of local disease (*P* = 0.01), and a higher frequency of curative resection (*P* = 0.017). However, there were more postoperative deaths (*P* = 0.012) in the group treated preoperatively with CRT.

In the study of Urba *et al*<sup>[13]</sup>, the preoperative CRT arm had cisplatin 20 mg/m<sup>2</sup> per day on days 1-5 and

17-21, 5-FU 300 mg/m<sup>2</sup> per day on days 1-21, and vinblastine 1 mg/m<sup>2</sup> per day on days 1-4 and 17-20. The tumor volume was treated with 5-cm cephalo-caudad margins and 2-cm radial margins by 1.5 Gy twice daily to 45 Gy. One patient had a microscopic positive margin in the surgical specimen and received postoperative RT. This study did not give postoperative RT for patients with positive nodes, but would use it for positive margins of resection.

Burmeister *et al*<sup>[14]</sup> used 80 mg/m<sup>2</sup> cisplatin intravenously on day 1 followed by 800 mg/m<sup>2</sup> per day 5-FU given intravenously on days 1-4. RT 35 Gy/15 f per 3 wk to the midplane, was started concurrently with

chemo. The results were not statistically significant. Neither progression-free survival nor OS differed between groups [HR = 0.82 95%CI: 0.61-1.10 and 0.89 (0.67-1.19), respectively]. The CRT + S group had more complete resections with clear margins than did the surgery-alone group [103 of 128 (80%) *vs* 76 of 128 (59%),  $P = 0.0002$ ], and had fewer positive lymph nodes [44 of 103 (43%) *vs* 69 of 103 (67%),  $P = 0.003$ ]. Subgroup analysis showed that patients with squamous-cell tumours had better progression-free survival with chemoradiotherapy than did those with non-squamous tumours [HR = 0.47 (0.25-0.86) *vs* 1.02 (0.72-1.44)]. However, the trial was underpowered to determine the real magnitude of benefit in this subgroup.

CALGB 9781 shows the benefit of CRT before surgery despite the closure due to poor accrual<sup>[15]</sup>. Cisplatin 100 mg/m<sup>2</sup> and 5-FU 1000 mg/m<sup>2</sup> per day for 4 d on weeks 1 and 5 concurrent with RT (50.4 Gy/28 f per 5.6 wk) was followed by esophagectomy with node dissection in the trimodality arm. The median survival was 4.48 years *vs* 1.79 years in favor of trimodality therapy over surgery alone (exact stratified log-rank,  $P = 0.002$ ).

Results from a recent multicenter phase III randomized trial, Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS study) showed that neoadjuvant CRT improved OS compared to surgery alone in patient with resectable (T2-3N0-1M0) esophageal or GEJ cancers<sup>[16]</sup>. Median survival was 49 mo in the neoadjuvant CRT arm and this seems to be the best median survival results achieved in the literature so far (Table 1). The CROSS study used a lower RT dose with newer chemo agents. The CRT consisted of weekly administration of carboplatin (doses titrated to achieve an area under the curve of 2 mg/mL per minute) and paclitaxel (50 mg/m<sup>2</sup>) for 5 wk and concurrent RT (41.4 Gy/23 f per 4.6 wk), followed by surgery. The RT volume is also modest: the planning target volume (PTV) employed a proximal and distal margin of 4 cm around the gross tumor volume (GTV), and in case of tumor extension into the stomach, a distal margin of 3 cm was used. A 1.5 cm radial margin around the GTV was provided to include the area of subclinical involvement around the GTV and to allow for tumor motion and set-up variations.

Some patients may refuse to have surgery after a clinical complete response (clinCR) to preoperative CRT. From the prospective database of MD Anderson Cancer Center, 61 of the 622 trimodality-eligible patients declined surgery after a clinCR, defined as both endoscopic biopsy showing no cancer and physiologic uptake by positron emission tomography (PET)<sup>[17]</sup>. Forty-two out of the 61 patients were alive at a median follow-up of 50.9 mo (95%CI: 39.5-62.3). The 5-year overall and relapse-free survival rates were 58.1%  $\pm$  8.4% and 35.3%  $\pm$  7.6%, respectively. Of 13 patients with local recurrence during surveillance, 12 had successful salvage resection. The authors concluded that although the outcome of 61 patients with clinCR who declined surgery appears reasonable, in the absence of a validated prediction/progno-

sis model, surgery must be encouraged for all trimodality-eligible patients.

In 2011, Kranzfelder *et al*<sup>[18]</sup> published a meta-analysis which sought to clarify the benefits of neoadjuvant treatment: there were nine randomized controlled trials involving neoadjuvant CRT *vs* surgery, eight involving neoadjuvant chemo *vs* surgery. The HR for OS was 0.81 (95%CI: 0.70-0.95,  $P = 0.008$ ) after neoadjuvant CRT and 0.93 (0.81-1.08,  $P = 0.368$ ) after neoadjuvant chemo. Morbidity (HR = 1.03,  $P = 0.638$ ) and mortality (HR = 1.04,  $P = 0.810$ ) rates after neoadjuvant chemo and surgery did not differ from those after surgery alone. However, the 30-d mortality was non-significantly higher with combined treatment.

### **S vs S + RT: Postoperative adjuvant RT without chemo**

Post-esophagectomy adjuvant RT can reduce local recurrence rate<sup>[19,20]</sup>. Several randomized trials were performed comparing surgery plus postoperative RT (PORT) with surgery alone to clarify the impact of PORT<sup>[21,22]</sup>. The majority of the evidence has revealed that PORT may improve local disease recurrence but does not confer any survival benefit over surgery alone<sup>[23,24]</sup>. These trials had limitations: (1) patients were not stratified by stage hence unlikely to detect an improvement in survival in those with high risk features (positive lymph nodes, deeply invading tumors); (2) they often include patients with positive celiac nodes; (3) they include mostly squamous cell carcinomas; and (4) no chemo were given. Adjuvant RT can theoretically treat microscopic disease left behind after surgery to increase local control, but cannot eradicate systemic spread of tumor cells.

Schreiber *et al*<sup>[25]</sup> performed a retrospective review using the American Surveillance Epidemiology and End Results (SEER) database to analyze whether there was survival benefit to adjuvant RT in stage T3-4N0M0 or T1-4N1M0 esophageal cancer who were definitively treated with esophagectomy. A total of 1046 patients met the selection criteria; 683 (65%) received surgery alone and 363 (34.7%) received PORT. For stage III esophageal carcinoma (T3N1M0 or T4N0-1M0), 346 patients underwent surgery alone and 231 patients received PORT. Use of PORT resulted in an improvement in median OS from 15 to 19 mo and an improvement in 3-year OS from 18.2% to 28.9% ( $P < 0.001$ ), respectively. This benefit was present for both squamous cell and adenocarcinoma. One limitation of the SEER data is the lack of information on use of chemo, so the benefit could be effect of CRT.

### **S vs S + CRT: Postoperative adjuvant CRT**

Some studies<sup>[26,27]</sup> addressed the impact of PORT with chemo on node-positive esophageal carcinoma, and found a survival benefit. The randomized adjuvant CRT trial, Intergroup trial (INT 0116) enrolled 559 patients with resected adenocarcinoma of the stomach or GEJ. They were randomly assigned to surgery plus postoperative CRT or surgery alone<sup>[28]</sup>. The adjuvant arm used 425



**Table 3** Pros and cons of post-operative therapy for esophageal cancer

Post-op therapy	Pros	Treatment decision based on true pathologic stage, avoid CRT in patient who may not require it Accurate assessment of disease extent to allow delineation of disease involvement Immediate relief of dysphagia due to tumor
	Cons	Difficulty to delineate RT target volume Large RT therapy volume and difficulty in RT planning Potential decrease in oxygenation to tumor bed due to postoperative tissue alteration in vascular supply Inability to assess RT or chemo tumor response May preclude the use of postoperative CRT for those patients with reduced functional status postoperatively

CRT: Chemoradiation therapy; RT: Radiotherapy.

mg/m<sup>2</sup> of 5-FU, plus 20 mg/m<sup>2</sup> of leucovorin per day, for 5 d, followed by 45 Gy/25 f per 5 wk of daily RT, with modified doses of 5-FU and leucovorin on the first 4 and the last 3 d of RT. A month after the completion of RT, two 5-d cycles of 5-FU (425 mg/m<sup>2</sup> per day) plus leucovorin (20 mg/m<sup>2</sup> per day) were given 1 mo apart. Hence a total of 4 mo cycles of adjuvant chemo was given. Twenty percent of the patients had GEJ adenocarcinoma. Subset analyses show robust adjuvant treatment benefit in most subsets.

#### **CRT + S vs S + CRT: Preoperative vs postoperative therapy**

Tables 2 and 3 compare the advantages of preoperative *vs* postoperative therapy<sup>[29,30]</sup>. There are no well performed randomized trials to compare the outcome of pre- against post-operative therapy with modern treatment staging and treatment techniques. Neoadjuvant treatments can be started immediately targeting any micro-metastatic deposits without allowing time for further cancer growth. The exact disease staging often cannot be firmly assessed at the preoperative circumstances.

Further research of the multidisciplinary management for patients with locally advanced esophageal cancer is warranted. The approach is currently being explored in two countries: China and Canada. In China the study has been carried out by investigators of the ZTOG1201 trial, a multicenter phase II trial of neoadjuvant and adjuvant CRT in locally advanced esophageal cancer (NCT01463501)<sup>[31]</sup>. In Canada, this is undertaken by investigators of the QUINTETT phase III trial (NCT00907543) of neoadjuvant *vs* adjuvant therapy in locally advanced esophageal cancer trial including quality of life<sup>[32]</sup>. Results of these trials can potentially provide further insight on the impact of trimodality therapy on the management of locally advanced esophageal cancers.

#### **CRT + S vs CRT: Does surgery add to CRT?**

The omission of surgery would leave residual disease behind and therefore surgery theoretically should contribute to treatment success. There were clinical trials comparing neoadjuvant CRT followed by esophagectomy to definitive CRT. Stahl *et al*<sup>[33]</sup> randomized 86 patients with advanced squamous cell carcinoma of the esophagus for neoadjuvant CRT of cisplatin, leucovorin, etoposide and 40 Gy RT followed by esophagectomy, compared to 86

patients treated with same chemo but 65 Gy RT and no surgery. The median survival was 16 and 15 mo with and without surgery, respectively. The 2-year survival rate was 40 and 35 mo with and without surgery, respectively. HR was 0.83 (0.54, 1.23) and was non-significant.

The other trial was performed by Bedenne *et al*<sup>[34]</sup>. Their trial randomized 129 patients with advanced squamous cell carcinoma of esophagus for neoadjuvant CRT of cisplatin, 5-FU, 46 Gy RT followed by esophagectomy, comparing with 130 patients treated with the same chemo but 66 Gy without surgery. The median survival was 18 and 19 mo with and without surgery, respectively. The 2-years survival was 34 and 40 mo with and without surgery, respectively. The HR was 0.88 (0.59, 1.31) and was non-significant.

In a Phase II trial in Radiation Therapy Oncology Group (RTOG 0246)<sup>[35]</sup>, definitive CRT employed induction 5-FU (650 mg/m<sup>2</sup> per day), cisplatin (15 mg/m<sup>2</sup> per day), and paclitaxel (200 mg/m<sup>2</sup> per day) for two cycles, followed by concurrent CRT with 50.4 Gy/28 f and daily 5-FU (300 mg/m<sup>2</sup> per day) with cisplatin (15 mg/m<sup>2</sup> per day) over the first 5 d. Salvage surgical resection was considered for patients with residual or recurrent esophageal cancer who did not have systemic disease. The study was designed to detect an improvement in 1-year survival from 60% to 77.5% ( $\alpha = 0.05$ ; power = 80%). Only 71% 1-year survival was achieved among the 43 patients enrolled from September 2003 to March 2006.

These trials had low to moderate sample size, short follow up, and the RT dose in the nonsurgical arm was above 60 Gy. This was concluded, in the meta-analysis of Kranzfelder *et al*<sup>[18]</sup> that no trials demonstrated a significant survival benefit of definitive CRT compared with neoadjuvant treatment followed by surgery, however the likelihood of R0 (no residual tumor) resection was significantly higher after neoadjuvant CRT (HR = 1.15,  $P = 0.043$ ).

In the specific scenario of T4 esophageal cancers, defined as a tumor that invades neighboring structures (*e.g.*, aorta, trachea, bronchus, and lung), are usually considered inoperable despite recent advances in surgical techniques. CRT + S is superior to CRT with respect to local control and short-term survival although CRT-S is associated with relatively higher perioperative mortality and morbidity<sup>[36]</sup>. On the other hand, it is sometimes difficult to achieve local control with CRT and the treatment often

results in fistula formation, though a complete response to CRT is often associated with better prognosis. Admittedly, the difference in the survival rate between the two modalities is marginal at long-term follow-up due to operative morbidity and inadequate control of distant metastasis in CRT-S. Randomized controlled trials involving large population samples are needed to define the standard treatment for T4 esophageal cancer.

## ROLE OF BRACHYTHERAPY

Esophageal brachytherapy alone is no longer used for curative situation because it can only effectively treat cancer within 1 cm radius, and unable to reach the adjacent lymphatic drainage at risk. If external beam RT is not possible, high dose rate (HDR) brachytherapy 6 Gy for 3 f or 8 Gy for 2 f at 1 cm from the center of the source axis can palliate dysphagia<sup>[37]</sup>. It should not be given concomitantly with chemo or external beam RT. The toxicity was reported by RTOG 92-07 study<sup>[38]</sup>. This phase I / II study planned to give 50 Gy/25 f per 5 wk of external beam RT followed 2 wk later by brachytherapy (either HDR 5 Gy during weeks 8, 9, and 10, for a total of 15 Gy, or low-dose-rate 20 Gy during week 8). Chemo was given during weeks 1, 5, 8, and 11, with cisplatin 75 mg/m<sup>2</sup> and 5-FU 1000 mg/m<sup>2</sup> per 24 h in a 96-h infusion. The final analysis showed severe toxicity, including treatment-related fistulas, occurred in 6/49 (12% patients, 14% among those starting brachytherapy) within 7 mo of brachytherapy.

HDR brachytherapy before external beam RT and chemo as a boost in the treatment of patients with esophageal cancer was reported to be safe in a single institution study<sup>[39]</sup>. Further investigation on the role of HDR brachytherapy boost treatment in multimodality management is needed. Other ways of brachytherapy for esophageal cancer palliation was studied, in the form of self expandable stent loaded with radioactive seeds of low dose rate brachytherapy. In a single institution small pilot study, 53 patients were randomized to an I-125 loaded stent or a conventional stent<sup>[40]</sup>. Systemic therapy was allowed for both the treatment and control group. The benefit for relief of dysphagia was significant after 2 mo ( $P < 0.05$ ). The stent restenosis occurred later in the RT stent group than in the control group (4.75 mo *vs* 2.00 mo) ( $P < 0.05$ ). In RT stent group, median OS was 7 mo (95%CI: 5.0-10.0) and mean OS was 8.3 mo (95%CI: 6.36-10.21). In control group, median OS was 4 mo (95%CI: 2.0-4.0) and mean OS was 3.5 mo (95%CI: 2.720-4.16) ( $P < 0.001$ , log-rank test).

## TARGET VOLUME OF EXTERNAL BEAM RT

The ERT treatment volume for esophageal cancer is controversial. For example, distal esophageal adenocarcinomas at the GEJ may be treated with esophageal cancer RT portal instead of stomach cancer RT portal. The fol-

lowing section will discuss the preoperative and postoperative RT target volumes.

### Preoperative and definitive RT

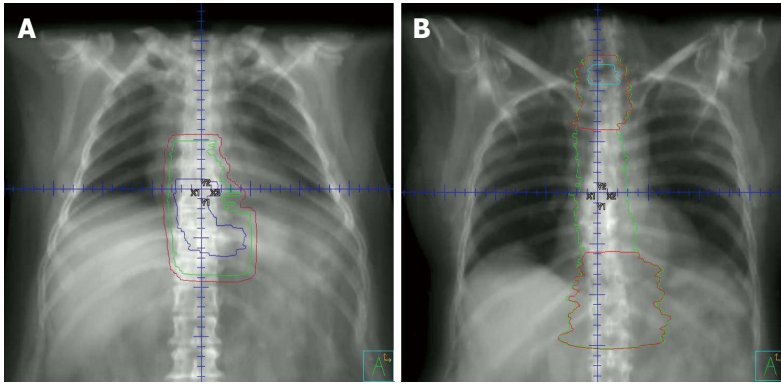
Tai *et al*<sup>[41]</sup> noted a great variability in target volume delineation. In the absence of a general consensus guideline, this could be due to practice variations among oncologists in individual cases. Esophageal cancer can extend submucosally in the longitudinal direction for a considerable distance. Miller *et al*<sup>[42]</sup> reported that in 15% of cases, microscopic longitudinal spread at greater than 6 cm from the primary lesion can occur. However, this cannot become the clinical tumor volume (CTV) since with expansion, the PTV would be very long cranio-caudally.

Recently lean management has been used in health care. A study from Loyola University Medical Center indicates the feasibility of applying the “plan-do-check-act” (PDCA) cycle to assess competence in the delineation of individual organs, and to identify areas for improvement<sup>[43]</sup>. With testing, guidance, and re-evaluation, contouring consistency can be obtained. The PDCA approach will ensure more accurate treatments and continual quality improvement.

In RTOG 9405, the initial target volume (50.4 Gy) encompassed 5 cm margin for the superior and inferior borders<sup>[44]</sup>. The lateral, anterior, and posterior borders of the field were 2 cm or more beyond the borders of the primary tumor. The tumor size was defined by endoscopic ultrasound (EUS), barium swallow, or computed tomography (CT) scan (whichever was larger). The primary and regional lymph nodes were included. For tumors of the cervical esophagus, the supraclavicular lymph nodes were included. A separate photon or electron boost to the supraclavicular lymph nodes was allowed to bring the total dose to 50.4 Gy. Patients randomized to the high-dose arm received a cone down of 14.4 Gy to attain a total dose of 64.8 Gy. The intent of the cone down was to treat the primary tumor only, not the regional primary lymph nodes. The superior and inferior borders of the field were decreased to 2 cm beyond the tumor. The lateral, anterior and posterior borders were the same as the initial target volume.

Image-guided RT is used in many North American Centers nowadays. The experience in MD Anderson Cancer Center showed large ( $> 1$  cm) inter-fractional displacements in the GEJ in the superior-inferior (especially inferior) direction was not accounted for when skeletal alignment alone was used for patient positioning<sup>[45]</sup>. Because systematic displacement in the superior-inferior direction had dosimetric impact and correlated with tidal volume, better accounting for depth of breathing is needed to reduce inter-fractional variability. Patients are also advised to be nil by mouth 3 h before planning CT or daily RT so that the stomach is empty.

To summarize (Figure 1A): (1) GTV includes visible tumor on CT, barium swallow, EUS, and PET scans; (2) CTV: GTV + 1 cm radially and 3-4 cm longitudinally. One may edit for anatomic barriers: vertebral bodies, ves-



**Figure 1 Radiation field for a lower esophageal cancer.** A: Pre-operative with minimal involvement of gastro-intestinal junction: celiac nodes are not covered. Intensity modulated radiotherapy is used. Blue: Gross tumor volume; Green: Clinical target volume; Red: Planning target volume; B: Post-operative with involvement of gastro-esophageal junction. Intensity-modulated radiotherapy treatment. Blue: Anastomosis; Green: Clinical target volume; Orange: Clinical target volume concomitant boost, planning target volume not shown.

sels and heart. Supraclavicular nodes are covered for cervical esophagus only. Coeliac nodes are covered for lower esophageal lesions; (3) PTV: CTV + 1 cm; and (4) Field borders: generally 2 cm radial, 4-5 cm longitudinal margins. For cervical esophageal tumors, the superior field border is just below larynx. If celiac nodes to be covered, the field goes down to the bottom of T12 or L1.

### Postoperative target volume

In postoperative adjuvant RT, a retrospective study of 72 high-risk patients (T3, T4, nodes positive, with or without margin involvement) treated at the London Regional Cancer Centre from 1989 to 1999 addressed the controversy whether the anastomotic site needs to be included<sup>[46,47]</sup>. Positive/close margins were found in 34 (49%) patients. Median follow-up was 30.5 mo (range 3.4-116.3 mo). Anastomosis recurrence rates were 29% with small volume and 0% with extended volume RT ( $P = 0.041$ ). Local and regional relapse occurred in 74.2% of patients treated with small volume RT compared to 15.4% in patients treated with extended volume RT ( $P < 0.001$ ). After adjusting for resection margin status, the local control benefit of extended volume RT remained significant ( $P = 0.003$ ).

To define the target volume, use of PET or PET/CT, alone or in combination with other methods, may be better to evaluate how far a tumour has spread (staging), whether it has responded to treatment (restaging), or detection of recurrences<sup>[48]</sup>. However, a German review of 48 studies found no strong evidence that PET, alone or in combination with CT, increases survival, improves quality of life, or results in fewer operations or diagnostic interventions<sup>[49]</sup>.

To summarize (Figure 1B): (1) CTV: The tumor bed and the lymphatic drainage at risk (peri-esophageal lymph nodes and regional lymph nodes). For GEJ, the celiac nodes (around T12-L1) may need to be included; (2) PTV: CTV + 1 cm radial and longitudinal margin. The superior margin of the PTV will include the surgical anastomotic site (labeled with radio-opaque clips) proximally with 2 cm margin. The inferior margin of the field

will be 5 cm beyond the previous GTV location. Lateral, anterior, and posterior borders will be 2 cm beyond the lateral borders of the tumor bed and regional lymph nodes, except if tumor bed is close to vertebral body, CTV will be on the bony surface. For the GEJ primaries, the celiac nodes (around T12-L1) may need to be included. 36-38 Gy in 28 fractions is delivered including the anastomosis. The tumor bed only should be boosted (simultaneous boost) to 50.4 Gy/28 f per 5.5 wk, together with the anastomosis if the margin is close or positive; and (3) Field borders-superiorly at about T1 to cover the anastomosis, inferiorly to L2-3 if celiac node needs to be covered.

## EXTERNAL BEAM RT DOSE FRACTIONATION

Herskovic *et al.*<sup>[50]</sup> (RTOG 85-01) randomized 121 patients to either 50 Gy with concurrent (75 mg/m<sup>2</sup>) and 5-FU (1 g/m<sup>2</sup> per 24 h  $\times$  4 d) starting with RT for 4 cycles *vs* 64 Gy alone (Table 4). At 5 years, 27% of the combined modality patients were alive *vs* none of those in the RT alone group. For the combined modality, 27% patients had persistent disease and an additional 16% developed local recurrence, compared to 40% and 24% respectively in the RT alone group ( $P < 0.01$ ). The patients who received combined treatment also had fewer distant recurrences (22% *vs* 38%,  $P < 0.005$ ). A higher RT dose, 64 Gy, cannot make up for the combined benefit of CRT. However, severe and life-threatening side effects occurred in 44 percent and 20%, respectively, of the patients who received combined therapy, as compared with 25 percent and 3 percent of those treated with RT alone.

Researchers then started to investigate if high RT dose combined with chemo can further increase survival. In the Intergroup 0123 (RTOG 94-05) trial<sup>[44]</sup> the 218 eligible patients were randomized to 64.8 Gy *vs* 50.4 Gy combined with 4 mo cycles of cisplatin and 5-FU. There was no significant difference in median survival (13.0 mo *vs* 18.1 mo), 2-year survival (31% *vs* 40%), or locoregional



**Table 4 Randomized trials for definitive chemoradiation therapy**

Ref.	n	Histology	Treatment	MS	2 yr OS	Locoregional failure
Herskovic <i>et al</i> <sup>[50]</sup> , 1992	121	88% Sq 12% A	CF + R 50 Gy R 64 Gy	12.5 m 8.9 m	38% 10%	43% 64%
Minsky <i>et al</i> <sup>[44]</sup> , 2002	218	86% Sq 14% A	CF + R 50.4 Gy CF + R 64.8 Gy	18 m 13 m	40% 31% (NS)	local recurrence + persistent primary 52% 56%

A: Adenocarcinoma; C: Cisplatin; F: 5-fluorouracil; MS: Median survival; NS: Non-significant; R: RT; Sq: Squamous cell carcinoma.

**Table 5 Complications of radiotherapy to esophagus and their management**

Acute complications
Skin erythema: 0.5% hydrocortisone, flomazine cream
Hair loss: no treatment
Mucositis, odynophagia, loss of appetite, fatigue, generalized weakness, dysphagia, dehydration, malnutrition, intestinal obstruction: intravenous hydration, xylocaine viscus, feeding tube
Pneumonitis: prednisone, oxygen
Spinal cord L'hermitte sign: no treatment
Larynx hoarseness: prednisone
Fistula/erosion of great vessels, esophageal perforation: consult thoracic surgeons
Chronic complications
Fibrosis/hyperpigmentation of skin: no treatment
Lung fibrosis: oxygen
Esophageal stricture: begins at 3-4 mo. Incidence: 50 Gy 0.8%, 60 Gy 0.6%; 60 Gy + chemo 12%. Treat by dilatation and/or stent
Peptic ulcer: proton pump inhibitor
Chronic enteritis: anti-diarrhoeal, aminosaliculates, pentoxifylline and tocopherol, cholestyramine, antibiotics, corticosteroids, hyperbaric oxygen
Spinal cord myelopathy: hyperbaric oxygen, anticoagulation

failure and locoregional persistence of disease (56% *vs* 52%) between the high-dose and standard-dose arms. Although 11 treatment-related deaths occurred in the high-dose arm compared with 2 in the standard-dose arm, 7 of the 11 deaths occurred in patients who had received 50.4 Gy or less. When comparing the high-dose arm with the low-dose arm, there was a significant prolongation of treatment time due to toxicity interruptions, and less 5-FU delivered doses.

To summarize the studies for esophageal cancer, when concurrent CRT is used without surgery, 54 Gy is recommended, although there are no firm data to support this<sup>[51]</sup>. In postoperative setting, a large elective volume (PTV1) should include the anastomosis even if the resection margins are adequate, 36-38 Gy in 28 fractions. The tumor bed should be boosted (simultaneous in field with the above mentioned PTV) to 50.4 Gy/28 f, as well as the anastomosis if the margin is close or positive<sup>[46,47]</sup>. The simultaneous integrated boost used by Yaremko *et al*<sup>[52]</sup> showed excellent result. Boost of tumor bed increases RT dose locally while a lower dose can be given to a longer clinical target volume.

## COMPLICATIONS

Table 5 summarizes the acute and chronic complica-

tions for esophageal RT. To reduce complications, RT treatment modalities used in clinical research studies include 3-dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT) and proton beam therapy (PBT)<sup>[53]</sup>. When comparing the three RT modalities in 444 esophageal cancers at different locations, there was a significant increase in postoperative pulmonary complications for 3D-CRT compared to IMRT and for 3D-CRT *vs* PBT but not for IMRT compared to PBT after adjusting for pre-RT diffusion capacity of the lung for carbon monoxide (DLCO). When mean heart dose and mean lung dose (MLD) were added to multivariate analysis after adjusting for pre-RT DLCO and RT modality, the effect of RT modality was no longer significant, whereas MLD became the only significant factor for perioperative pulmonary complications.

Another study showed that IMRT compared to 3D-CRT resulted in significantly higher OS, loco-regional control, and non-cancer related mortality rates among 676 esophageal cancer patients<sup>[54]</sup>.

PBT in treatment of esophageal cancer had few severe toxicities, with encouraging pathologic response and clinical outcomes<sup>[55]</sup>. It is difficult to justify PBT in esophageal cancers at the present time when there are other competing technologies available such as IMRT and until PBT facilities are more readily available as there are few centers currently in the world.

Another way to reduce complications is volumetric arc modulation. A study reported the comparison of RapidArc (RA) against 3DCRT and IMRT techniques for esophageal cancer<sup>[56]</sup>. CT scans of 10 patients were included in the study. Single-arc and double-arc RA plans were prepared to deliver 54 Gy to the PTV in 30 f. Target conformity improved with double-arc RA plans compared with IMRT. But RA plans resulted in a reduced low-level dose bath (15-20 Gy) in the range of 14%-16% compared with IMRT plans. The average monitor units needed to deliver the prescribed dose by RA technique was reduced by 20%-25% compared with IMRT technique. Therefore, volumetric arc modulation is also favored for shorter treatment time on the machine couch.

Similarly, tomotherapy significantly reduced dose to normal tissues<sup>[57]</sup>. Mean lung dose was respectively 7.4 and 11.8 Gy ( $P = 0.004$ ) for tomotherapy and 3D plans. Corresponding values were 12.4 and 18.3 Gy ( $P = 0.006$ ) for cardiac ventricles. Maximum spinal cord dose was respectively 31.3 and 37.4 Gy ( $P < 0.007$ ) for tomotherapy and 3D plans.



## FUTURE RESEARCH

### Chemo

An important limitation of RT is its difficulty to encompass longitudinal local extension, lymphatic and nodal drainage due to normal tissue tolerance. Future research should focus on better chemo or targeted therapy to complement RT treatment. Unfortunately, epidermal growth factor receptors-targeted agents fail to improve outcomes: Panitumumab in REAL-3 trial<sup>[58]</sup> or cetuximab in SCOPE1 trial<sup>[59]</sup>. Concomitant cetuximab, cisplatin, irinotecan, and RT were poorly tolerated in the first North American cooperative group trial (S0414) testing this regimen for locally advanced esophageal cancer as treatment-related mortality approached 10%<sup>[60]</sup>.

An on-going study RTOG 1010 examines the role of trastuzumab (Herceptin)<sup>[59]</sup>. Arm 1 uses RT (50.4 Gy), paclitaxel, carboplatin, and trastuzumab, followed by surgery 5-8 wk after completion of RT, then maintenance trastuzumab, every 3 wk for 13 treatments. Arm 2 does not have any trastuzumab nor any maintenance drug.

Single agent docetaxel was well tolerated in a phase II study in China<sup>[61]</sup>. There is an on-going multicenter study on combination docetaxel, cisplatin and 5-FU in Japan<sup>[62]</sup>.

A trimodal approach, consisting of a single cycle of induction chemo, CRT containing capecitabine and cisplatin, and surgery, was feasible and effective in patients with resectable esophageal squamous cell carcinoma<sup>[63]</sup>. In another study, neoadjuvant concurrent CRT with capecitabine and oxaliplatin was found to be well tolerated and effective in patients with locally advanced esophageal cancers<sup>[64]</sup>.

### Surgery

Improvements in perioperative management may enhance the outcome. The CRT treatment of esophageal cancer follows the example of mitomycin C and 5-FU combination in anal cancer. Recent rectal cancer research on increasing the time interval to 10-11 wk from end of neoadjuvant CRT to surgery results in the highest rate of pathological complete response for rectal cancer<sup>[65]</sup>. Similarly, future investigations of esophageal RT may pursue gradually increasing the time interval from the end of neo-adjuvant CRT to surgery to find the optimal time. Currently esophagectomy is performed 2-6 wk after completion of CRT. This will allow patients to recover from side effects of concurrent CRT by having good nutritional support prior to surgery, and to minimize any severe postoperative complications after surgery<sup>[66]</sup>. A prospective database of 266 patients in the MD Anderson Cancer Center between 2002 and 2008 showed that timing of esophagectomy after neoadjuvant CRT (within 8 wk *vs* > 8 wk) is not associated with perioperative complication, pathologic response, or OS. The authors concluded that it may be reasonable to delay esophagectomy beyond 8 wk for patients who have not yet recovered from CRT<sup>[67]</sup>.

### PET scan

Another area of on-going research is the use of PET scan

to modify therapy. In the CALGB 80803, PET scan non-responders will cross over to the other chemo regimen<sup>[68]</sup>.

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