Esophagogastric Cancer
The Current Role of Radiation Therapy

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KEYWORDS

• Esophagogastric cancer • Radiation therapy • IMRT • Neoadjuvant

KEY POINTS

- Multimodal therapy, including radiation therapy, is superior to surgery alone for patients with operable esophageal cancer.
- Chemoradiation can be used as definitive therapy in inoperable patients.
- The role of PET-directed treatment, induction chemotherapy, and the ideal radiation dose and treatment technique are under active investigation.

INTRODUCTION

Surgery remains the primary curative therapy for patients with gastroesophageal malignancies; however, the prognosis is poor following surgery alone, with 5 year overall survival (OS) rates of about 30%.[1] As a result, multimodal treatment is warranted for most patients presenting with nonmetastatic disease. While the routine use of radiation therapy in the management of patients with gastric cancer has diminished over the years, it continues to play an important role in the management of patients with cancers of the esophagus and gastroesophageal junction (GEJ).

There are several factors which explain why radiation therapy is of particular benefit for cancers arising from the esophagus. The rich lymphatic supply of the esophagus, coupled with the absence of a serosal layer, permits early microscopic spread of tumor cells beyond the surgical field, and the location of the esophagus within the mediastinum precludes resection with wide surgical margins. Additionally, unlike gastric cancer, esophageal cancer is associated with high rates of local failure of about 20% to 30%, warranting intensified local therapy in its management.[2] Finally,

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achieving a pathologic complete response (pCR) to neoadjuvant therapy has been shown to be prognostic for improved local control and OS.[3,4]

Herein, we describe the current role of radiation therapy in the management of patients with esophageal and GEJ cancers. A summary of radiation trials in patients with esophageal cancer is shown in **Table 1**.

DISCUSSION

Operable Patients

Neoadjuvant Chemoradiation versus surgery alone

Long-term results of the landmark Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) established the superiority of multimodal therapy versus surgery alone for patients with esophageal cancer. In this phase III trial, 368 patients with nonmetastatic T1N1 or T2-3N0-1 squamous cell carcinoma (25%) or adenocarcinoma (75%) of the esophagus or esophagogastric junction were randomized to either upfront surgery or neoadjuvant chemoradiation (41.4 Gy in 23 fractions with concurrent carboplatin–paclitaxel [CP] weekly) followed by surgery.[5] The initial publication reported a significant benefit for the addition of chemoradiation, doubling the median OS from 24.0 months in the surgery group to 49.4 months in the neoadjuvant chemoradiotherapy group ($P = .003$, hazard ratio [HR] 0.657), thus establishing neoadjuvant therapy as standard of care in operable patients.[5] The pCR rates were 23% in patients with adenocarcinoma and 49% in those with squamous cell carcinomas. Ten-year outcomes revealed a persistent OS benefit to neoadjuvant chemoradiation versus surgery alone of 13% (38% vs 25%, $P < .05$). In particular, the 10 year OS was doubled for patients with squamous cell histology (46% vs 23%, $P<.05$).[6] It should be noted that neoadjuvant CRT did not have a negative impact on the postoperative complication rates as compared to patients undergoing surgery alone.[7]

The benefit of neoadjuvant CRT has been confirmed in multiple meta-analyses showing an improvement in OS, locoregional control, and R0 resection rates compared to surgery alone, without a concomitant increase in complication rates.[8,9] In an analysis of patterns of failure among patients treated on the CROSS trial, it was notable that in addition to a significant reduction in locoregional recurrence from 34% to 14%, neoadjuvant chemoradiation also significantly decreased the peritoneal and hematogenous recurrence rates from 14% to 4% and 35% to 29%, respectively. Nonetheless, distant recurrence was still the main cause of cancer mortality.

Neoadjuvant CRT ± induction chemotherapy

Owing to the high rates of distant failure for patients with esophageal cancer of approximately 50%,[10] there have been efforts to intensify neoadjuvant approaches with induction chemotherapy prior to CRT, but results have been mixed. A phase II single-institution study including 126 patients randomized to chemoradiation with or without induction chemotherapy with oxaliplatin/fluorouracil (FU) found no significant difference in median OS to the addition of induction chemotherapy (45.6 vs 43.7 months, $P = .69$).[11] A follow-up study seeking to identity any subsets of patients which might benefit found that the 5 year OS was improved in patients with well or moderately differentiated tumors when induction chemotherapy was added (74% vs 50%, $P =< 0.05$), but there was no benefit in patients with poorly differentiated tumors (31% vs 28%, $P = .04$).[12] Another phase II trial treating 85 patients with esophageal adenocarcinoma to induction chemotherapy (with oxaliplatin/capecitabine) randomized patients to receive subsequent CRT with 1 of 2 regimens (radiation therapy [RT] plus oxaliplatin/capecitabine or RT plus CP) with a primary endpoint of pCR. Only the RT arm including CP passed their predefined pCR criteria for further study.[13]

Table 1
Key trials involving radiation for esophagogastric cancer

Trial	Arms	Primary Outcome(s)	Results
Neoadjuvant CRT versus Surgery Alone			
CROSS	Arm 1: Surgery alone Arm 2: Neoadjuvant CRT (41.4 Gy + carbo/taxol)	mOS	CRT improved mOS: 24 mo vs 49.4 mOS; $P = .003$)
Neoadjuvant CRT ± Induction Chemotherapy			
Ajani et al, Phase II	Arm 1: Neoadjuvant CRT (50.4 Gy+5FU/oxaliplatin) Arm 2: IC (oxaliplatin + FU)→ the same CRT	pCR rate, mOS	No difference in (1) pCR rate: 13% (standard arm) vs 25% (exp arm) ($P = .094$) (2) or mOS 45.62 mo (standard) vs 43.68 mo (exp), $P = .69$)
NEOSCOPE	Arm 1: IC (oxaliplatin/capecitabine)→ CRT (45 Gy + carbo/taxol) Arm 2: IC (oxaliplatin/capecitabine)→ CRT (45 Gy + oxaliplatin/capecitabine)	Rate of pCR (pCR $\leq$15% would not warrant further investigation, but pCR $\geq$35% would)	Only CarPacRT passed the predefined pCR criteria for further investigation.
CALGB 80803	Arm 1: IC (FOLFOX)→ CRT (50.4+PET-response directed chemotherapy with FOLFOX for responders or carbo/taxol for nonresponders) Arm 2: IC (carbo/taxol)→ CRT (50.4+PET-response directed chemotherapy with carbo/taxol for responders or FOLFOX for non-responders)	pCR rate of PET nonresponders within each induction treatment group	pCR rates for PET nonresponders after induction FOLFOX who crossed over to CP or after induction CP who changed to FOLFOX was 18.0% (95% CI, 7.5–33.5) and 20% (95% CI, 10–33.7), respectively. Median OS: 27.4 mo for PET nonresponders vs 48.8 mo for PET responders ($P = .1$). Median OS not reached for PET responders after induction FOLFOX.
Neoadjuvant Chemotherapy vs Neoadjuvant CRT			
MAGIC	Arm 1: Surgery alone Arm 2: Perioperative ECF (epirubicin/cisplatin/FU)	5 y OS	Perioperative chemotherapy improved 5-y OS (26% vs 23%, $P = .009$)
Burmeister et al, Phase II	Arm 1: Preoperative chemo (cisplatin/FU) Arm 2: Preoperative CRT (35 Gy + cisplatin/FU)	Toxicity, pCR, R0 resection rate	Similar toxicity; improved pCR (31% vs 8%, $P = .01$) rate with CRT); higher rate of R1 resections with chemo vs CRT (11% vs 0%, respectively, $P = .04$)

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Table 1
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Trial	Arms	Primary Outcome(s)	Results
POET	Arm 1: Preoperative chemo (cisplatin/FU) Arm 2: Preoperative chemo (cisplatin/FU)→CRT (30 Gy + cisplatin/etoposide)	3 y OS	Nonstatistically significant improvement in 3 y OS with CRT (47.4% for CRT vs 27.7% for chemo alone, $P = .07$)
NeoRes	Arm 1: Preoperative chemo (cisplatin/FU) Arm 2: Preoperative chemo (cisplatin/FU)→CRT (40 Gy + cisplatin/FU)	pCR	Improved pCR rate with CRT (28% vs 9%, $P < .05$)
Neo-AEGIS	Arm 1: Perioperative chemo (MAGIC regimen or FLOT) Arm 2: CRT (41.4 Gy + carbo/taxol)	mOS	No difference between arms (mOS 48 mo chemotherapy arm vs 49.2 mo CRT arm)
Adjuvant RT			
Intergroup-0116	Arm 1: Surgery alone Arm 2: CRT (45 Gy + FU)	mOS	CRT improved mOS (36 mo for CRT vs 27 mo for surgery alone, $P = .005$)
CRITICS	Arm 1: Perioperative chemo (epirubicin/cisplatin or oxaliplatin/capecitabine) Arm 2: Preoperative chemo (as Arm 1) and postop CRT (45 Gy + cisplatin/capecitabine)	mOS	No difference in mOS between arms (43 mo in chemo alone vs 37 mo in CRT arm, $P = .90$)
CALGB 80101	Arm 1: Postoperative FU→CRT (45 Gy + FU)→FU Arm 2: Postoperative ECF (epirubicin/cisplatin/FU)→CRT (45 Gy + FU)→ECF	5 y OS	No difference in 5 y OS between arms (44% in each arm, $P = .69$)
Definitive CRT			
RTOG 85–01	Arm 1: RT alone (50 Gy) Arm 2: CRT (50 Gy + cisplatin/FU)	5 y OS	Improved 5 y OS with CRT vs RT alone (26% vs 0%, respectively, $P < .01$)
Intergroup-0112	Single Arm: FU/cisplatin→CRT (64.8 Gy + FU/cisplatin)	Toxicity	6 deaths occurred, 5 (11%) were treatment related. mOS was only 20 mo.

Intergroup-0123	Arm 1: Standard CRT (50.4 Gy + FU/cisplatin) Arm 2: Dose-escalated CRT (64.8 Gy + FU/ cisplatin)	2 y OS	No difference in 2 y OS between arms (40% vs 31% for Arm 1 vs Arm 2, respectively, $P > .05$). 11 treatment-related deaths in Arm 2, but 7 occurred before reaching 50.4 Gy
ARTDECO	Arm 1: Standard CRT (50.4 Gy + carbo/taxol) Arm 2: Dose-escalated CRT (61.6 Gy + carbo/taxol)	3 y PFS	No difference in 3 y PFS between arms (52% vs 59% for Arm 1 vs Arm 2, respectively, $P = .08$)
Xu et al	Arm 1: Standard CRT (50.4 Gy + cisplatin/ taxol) → cisplatin/ docetaxel Arm 2: Dose-escalated CRT (60 Gy + cisplatin/ taxol) → cisplatin/ docetaxel	3 y locoregional PFS	No difference in 3-y locoregional PFS between arms (48.4% vs 57.2% for Arm 1 vs Arm 2, respectively, $P = .98$)
CONCORDE	Arm 1: Standard CRT (50.4 Gy + carbo/taxol) Arm 2: Dose-escalated CRT (59.4 Gy + carbo/ taxol)	mOS	No difference in mOS between arms (26 mo vs 28.1 mo for Arm 1 vs Arms 2, respectively, $P = .054$)
SANO	Arm 1: CRT → surgery Arm 2: CRT → active surveillance if cCR	mOS	No difference in mOS between arms (HR = 0.88, 95% upper boundary 1.40, $P = .007$)

Abbreviations: carbo, carboplatin; taxol, paclitaxel; cCR, clinical complete response; CRT, chemoradiation; FOLFOX, folinic acid + fluorouracil + oxaliplatin; FU, fluorouracil; Gy, gray; IC, induction chemotherapy; mOS, median overall survival; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival.

In addition to eradicating subclinical systemic disease, induction chemotherapy prior to adding radiotherapy allows for assessment of tumor response to chemotherapy, permitting response-adapted treatment. ^{18}F-fluorodeoxyglucose PET imaging is routinely used in staging esophageal cancer, and utilizing metabolic response to therapy to guide subsequent management has been shown to improve OS in patients.[14] The randomized phase II CALGB 80803 study evaluated whether metabolic response assessment by PET imaging after induction chemotherapy could be used to direct the decision to change chemotherapy during preoperative chemoradiotherapy with the goal of improving pCR and survival outcomes among PET nonresponders.[15] Two-hundred and forty-one patients with esophageal and esophagogastric junction adenocarcinoma were randomly assigned to induction chemotherapy with either FOLFOX (modified oxaliplatin, leucovorin, and FU), or CP following baseline PET. The change in maximum standardized uptake value (SUV) from baseline after repeat PET following induction chemotherapy was used to guide subsequent management. PET nonresponders (<35% decrease in SUV from baseline) crossed over to the alternative chemotherapy during chemoradiation (50.4 Gy/28 fractions), while PET responders (≥35% decrease in SUV from baseline) continued on the same chemotherapy during chemoradiation. The primary end point was to improve pCR rates in the PET nonresponders to 20%. The pCR rates for PET nonresponders after induction FOLFOX who crossed over to CP (n = 39) or after induction CP who changed to FOLFOX (n = 50) were 18.0% (95% confidence interval [CI], 7.5–33.5) and 20% (95% CI, 10–33.7), respectively; thus, the efficacy criteria were met for both induction arms. With a median follow-up of 5.2 years, median OS was 48.8 months for PET responders and 27.4 months for nonresponders, which was not statistically significantly different, suggesting that by changing therapy based on PET response, the survival outcomes could also be improved to be closer the survival of the PET responders. For induction FOLFOX patients who were PET responders, median survival was not reached, and 5 year OS was 53%. This study demonstrated that an induction chemotherapy approach using a biomarker such as PET imaging to perform early response assessment allows for tailoring of therapy which improves outcomes in patients who are initially poor responders to induction chemotherapy. In addition, the promising 5 year OS rates suggest that selected patients who are PET responders have improved outcomes with FOLFOX induction followed by chemoradiotherapy using 5 FU and oxaliplatin.

Neoadjuvant chemotherapy versus neoadjuvant CRT

The benefit of neoadjuvant CRT versus neoadjuvant chemotherapy for cancers of the esophagus and GEJ has long been a subject of debate. Prior to the publication of the CROSS trial discussed earlier, the landmark MAGIC trial comparing perioperative chemotherapy (with epirubicin, cisplatin, and FU) with surgery alone showed an OS benefit to perioperative chemotherapy (36% vs 23% at 5 year, P = .009).[16] Unlike the CROSS study which included only cancers of the esophagus of GEJ with either squamous cell or adenocarcinoma histology, MAGIC included patients with cancers of the stomach, GEJ, or lower esophagus, thus calling into question the optimal regimen (neoadjuvant CRT vs chemotherapy alone) for patients with lower esophageal and GEJ adenocarcinomas. Subsequently, the landmark FLOT trial compared the perioperative chemotherapy used in MAGIC versus an intensified perioperative chemotherapy regimen (FU, leucovorin, oxaliplatin, docetaxel [FLOT]) in patients with gastric and GEJ adenocarcinoma. The FLOT regimen was associated with an improvement in median OS as compared to the standard arm (50 vs 35 months, respectively, P = .012), resulting in FLOT being the preferred perioperative regimen for patients with GEJ adenocarcinoma treated with perioperative chemotherapy alone.

Several randomized trials have questioned the benefit of neoadjuvant CRT versus neoadjuvant chemotherapy alone following the publication of MAGIC and CROSS. None has shown an OS benefit favoring one approach over the other, leaving this question unanswered. Two early randomized trials failed to show an OS benefit to CRT versus neoadjuvant chemotherapy alone, but both were limited by poor accrual.[17,18] While there was no improvement in OS, CRT compared to chemotherapy alone did improve the complete response rate (CRT 31% vs CT 8%, $P = .01$) and reduced R1 resection rate (CRT 0% vs CT 11%, $P = .04$).[17] Further, there were fewer locoregional recurrences among patients receiving CRT (18% vs 38%, $P = .04$) with similar rates of distant metastases (44% vs 29% for CRT vs chemotherapy, respectively, $P = .20$) and a trend toward improved OS favoring CRT (HR 0.65, 95%, CI, 0.42–1.01, $P = .055$).[19] The phase II NeoRes study randomized 180 patients with cancer of the esophagus or GEJ to neoadjuvant chemotherapy alone (cisplatin/FU) with or without concurrent radiation (40 Gy/20Fx) followed by surgery. The pCR rate was higher among patients receiving CRT (28% vs 9%), but this did not translate into an improvement in OS (42.2% vs 39.6% at 5 year for patients receiving CRT vs CT alone, respectively, $P = .60$).[20]

Two additional randomized trials sought to compare the MAGIC regimen to a neoadjuvant CRT approach. TOPGEAR is a phase III trial, which enrolled patients with adenocarcinoma of the stomach or GEJ randomizing them to perioperative chemotherapy alone (with Epirubicin, Cisplatin, 5-Fluorouracil [ECF] or FLOT) or to chemotherapy followed by preoperative CRT (45 Gy + FU).[21] While we await final publication, interim results of the first 120 enrolled patients demonstrated that CRT could be safely delivered preoperatively with an intensified perioperative chemotherapy regimen. Ninety-two percent of patients received their allocated preoperative CRT treatment and similar rates of grade 3 or higher toxicity in each arm (32% for chemotherapy alone vs 30% for CRT).

Neo-AEGIS is the only randomized study directly comparing the CROSS regimen to the MAGIC regimen (use of perioperative FLOT was permitted after publication of FLOT4 study) in patients with adenocarcinoma of the esophagus or GEJ.[22] The trial closed early following a futility analysis. There were no differences in median OS (48.0 months vs 49.2 months for chemotherapy vs CRT, respectively) or disease-free survival (32.4 months vs 24.0 months for chemotherapy vs CRT, respectively), and the patterns of failure were the same between the 2 groups. However, pCR (OR 0.33, 95% CI 0.14–0.81, $P = .012$) and R0 resection (OR = 0.21, 95% CI 0.08–0.53, $P<.05$) rates favored trimodality therapy. There were no significant differences among rates of grade 3 or higher toxicity between groups.

While there appears to be equipoise for chemotherapy or chemoradiotherapy as the optimal neoadjuvant treatment approach, the consistent improvement seen in pCR and R0 resection rates, without a concomitant increase in adverse events, highlights the continued role for neoadjuvant CRT in the management of patients with adenocarcinomas of the esophagus or GEJ. Ongoing trials, including TOPGEAR and the German ESOPEC trial (comparing preoperative chemotherapy with FLOT to CROSS chemoradiotherapy), will continue to address this question.

Adjuvant CRT

Adjunctive chemotherapy and radiation therapy in patients undergoing surgery for esophageal cancer should ideally be delivered in the neoadjuvant setting. The potential benefit of neoadjuvant as opposed to adjuvant therapy includes early treatment of micrometastatic disease, optimal selection of patients who would benefit most from surgery given the early development of metastatic disease in some patients, and to

allow for nonoperative management in patients with squamous cell cancer achieving a clinical complete response. However, for patients undergoing up front surgery who did not receive chemotherapy and radiation therapy in the neoadjuvant setting, if they were found to have more advanced disease on final pathology as compared to clinical evaluation, there is a role of adjuvant treatment.

Several trials have been conducted to elucidate the optimal adjuvant regimen. The landmark Intergroup-0116 study randomized 559 patients with adenocarcinoma of the stomach or GEJ to surgery alone or postoperative CRT (45 Gy + FU). There was a strong OS benefit to the addition of adjuvant CRT (HR 1.32, 95% CI 1.10–1.60, $P = .0046$).[23] Overall relapse and local relapse rates were significantly improved with CRT. Given the OS benefit seen with perioperative chemotherapy in the MAGIC trial discussed earlier, the CRITICS study sought to incorporate both treatment strategies (perioperative chemotherapy as in MAGIC with postoperative CRT as in 0116) to determine whether the addition of radiotherapy to postoperative chemotherapy improves survival compared to postoperative chemotherapy alone. The trial randomized 788 patients with adenocarcinoma of the stomach or GEJ all receiving preoperative chemotherapy followed by surgery, to postoperative CRT (45 Gy + capecitabine/cisplatin) or to postoperative chemotherapy (epirubicin/cisplatin/oxaliplatin/capecitabine).[24] Median OS was similar between groups (43 months in the chemotherapy group vs 37 months in the CRT group [HR = 1.01, 95% CI 0.84–1.22, $P = .90$]). Compliance with the postoperative treatment regimen was poor in both groups (59% in the chemotherapy group and 62% in the CRT group) leading the authors to conclude that future investigations should focus on optimizing preoperative regimens. CALGB 80101 sought to build upon the results of Intergroup-0116 by adding an intensified postoperative adjuvant chemotherapy regimen to CRT. The trial randomized 546 patients with gastric or GEJ adenocarcinoma who had undergone a curative resection to receive either postoperative FU/leuvovorin (LV) before and after CRT (45 Gy/FU) versus ECF before and after CRT.[25] There was no difference in 5 year OS (44% in both arms) or 5 year disease free survival (DFS) (39% in the FU/LV arm vs 37% in the ECF arm, HR = 0.96, 95% CI, 0.77–1.20, $P = .94$). There were no differences in locoregional recurrences or distant failure between treatment arms.

Inoperable Patients

Definitive CRT

Nonoperative management may be indicated in a number of clinical scenarios. Patients who are not good surgical candidates or who have inoperable disease may be treated with definitive CRT. Further, patients with squamous cell carcinoma achieving a clinical complete response to neoadjuvant therapy may be able to safely forego surgery without compromising survival outcomes. Conducted in the late 1980s, RTOG 85-01 established the superiority of CRT over RT alone for patients with either squamous cell carcinoma (SCC) or adenocarcinoma of the esophagus who do not undergo surgery.[26] Efforts are ongoing to improve upon the results of this trial for patients undergoing definitive CRT without surgery.

Randomized trials have sought to intensify both the RT and the systemic therapy used in the definitive setting. The INT-0122 phase II study sought to increase the RT dose, the chemotherapy dose, the number of chemotherapy cycles, and added induction chemotherapy to the regimen used on RTOG 85-01.[27] Treatment-related mortality was high (9%) and thought to be due to the intensified chemotherapy regimen used. The follow-up study, INT-0123, intensified only the RT. The trial enrolled 236 patients with either SCC or adenocarcinoma of the esophagus and randomized them to either standard-dose RT (50.4 Gy) or high-dose RT (64.8 Gy) with concurrent FU/cisplatin.[28]

There was no benefit in 2 year OS for dose-escalated RT (31% vs 40% for standard-dose vs high-dose RT, respectively) or locoregional failure (56% vs 52% for standard-dose vs high-dose RT, respectively, $P = .71$). There were 11 deaths in the dose-escalated arm; however, 7 of these occurred in patients who received 50.4 Gy or less, leaving the benefit of dose escalation unanswered. Moreover, the radiotherapy techniques used in this study were not as conformal as more modern treatments using intensity-modulated radiotherapy (IMRT). Thus, a criticism of this study was that the radiation therapy was potentially associated with more toxicity, especially when delivering higher doses.

There have been further attempts at dose escalation, all of which have similarly failed to show a benefit to higher doses of radiation in the definitive setting for this disease. ARTDECO randomized patients with inoperable esophageal cancer to standard (50.4 Gy) or dose-escalated (61.6 Gy) RT, using IMRT planning, with concurrent CP. The primary end point of 3 year local progression- free survival (PFS) was not improved with dose escalation (52% and 59% for the standard- vs high-dose arms, respectively, $P = .08$).[29] There was no benefit to dose escalation in either histologic subgroup (SCC or adenocarcinoma). A Chinese phase III randomized study comparing standard (50 Gy) to dose-escalated (60 Gy) radiation, with concurrent cisplatin/docetaxel, for SCC patients also failed to find a benefit to dose escalation and found higher rates of pneumonitis in the dose-escalated arm.[30] Similarly, the CONCORDE trial comparing standard- (50.4 Gy) to high-dose (59.4 Gy) RT using only an IMRT approach with concurrent CP failed to show a benefit to dose escalation in inoperable SCC of the esophagus.[31]

Despite the failure of dose escalation in patients with SCC of the esophagus, there appears to be a role for definitive CRT in the management of these patients with standard-dose RT. In the aforementioned CROSS trial, 49% of patients with SCC achieved a pCR to neoadjuvant CRT, at a dose of 41.4 Gy with concurrent carboplatin/paclitaxel.[5] Two randomized studies comparing neoadjuvant CRT followed by surgery to CRT alone found no OS benefit to surgery in patients with esophageal SCC.[32,33] The recent SANO trial, only available in abstract form, was a noninferiority trial randomizing patients with esophageal cancer (either histology) to active surveillance versus surgery if a complete clinical response to neoadjuvant CRT was achieved. At a median follow-up of 34 months, there was no difference in OS between groups (HR = 0.88, 95% upper boundary 1.40, $P = .007$), but short-term quality of life was significantly improved in the active surveillance arm.[34] The final article and long-term results of this trial will clarify the role of surgery in patients achieving a complete response to neoadjuvant CRT, in particular for patients with SCC histology.

Role of Immunotherapy

Despite the curative intent of neoadjuvant CRT followed by surgery for esophageal cancer, the rates of recurrence, particularly among patients who do not achieve a complete pathologic response, remain high. Studies have thus sought to intensify therapy with the addition of immunotherapy either prior to or following resection, with promising results.

In the neoadjuvant setting, PERFECT was a single-arm phase II feasibility study assessing the feasibility and efficacy of delivering neoadjuvant CRT (per the CROSS regimen) with concurrent atezolizumab, a programmed-death ligand-1 (PD-L1) inhibitor.[35] The pCR rate was 25%. There was no statistically significant difference in survival between the PERFECT cohort and a propensity score-matched neoadjuvant CRT cohort (29.7 vs 34.3 months, respectively, $P = .43$). On exploratory biomarker analysis, there was higher baseline expression of interferon gamma (IFNγ) among

responders to neoadjuvant CRT-atezolizumab, leading the authors to conclude that further study into an IFNγ signature and PD-L1 expression as potential biomarkers for prediction of response to neoadjuvant PD-L1 therapy is warranted. The initial safety run-in report of EA2174, a phase II/III study of perioperative nivolumab (given with neoadjuvant CRT), found that there was no increased toxicity from the addition of nivolumab to neoadjuvant CRT.[36]

Immunotherapy has also been studied in the adjuvant setting. Checkmate 577 was a phase III trial which enrolled 1085 patients with esophageal or GEJ cancer who had residual pathologic disease following neoadjuvant CRT and randomized them to receive adjuvant nivolumab versus placebo.[37] After a median follow-up of 24.4 months, the median DFS was significantly higher among patients receiving adjuvant nivolumab (22.4 vs 11.0 months, $P<.001$). Adverse events that were treatment-related were more common with nivolumab than with placebo, including grade 3 or 4 events (in 13% vs 6%, respectively).

Radiation Therapy Technique

Efforts are ongoing to optimize the radiation dose and delivery technique in patients with esophageal cancer. Patients should be simulated supine, with arms raised, on a custom immobilization device. They should be nil per os for 3 hours prior to simulation and treatment. Provided there are no contrast allergies, intravenous and oral contrast should be administered and diagnostic imaging, such as PET/CT, should be fused with the simulation CT to assist with target volume delineation. It is recommended that a motion management technique, such as 4D CT, is utilized to account for organ motion. The clinical target volume should include both gross disease and at-risk nodal volumes, which depend on the primary tumor location as per the expert consensus contouring guidelines for IMRT in esophageal cancer.[38] In addition, a generous superior and inferior anatomic margin around the esophagus is recommended due to the rich lymphatic system and absent serosal layer which allows for early subclinical tumor spread along the length of the esophagus. An analysis of the patterns of failure for patients in the CROSS trial with respect to radiation target volumes found that only 5% of locoregional recurrences occurred within the target volumes, 2% were at the border of the treatment volume, and 6% were out-of-field.[39] Of note, neoadjuvant CRT also reduced the rate of peritoneal carcinomatosis (14% with CRT vs 4% in surgery alone arm, $P<.001$) which the authors postulate was due to a reduction in microscopic residual disease following surgery in patients treated with neoadjuvant CRT.

The recommended radiation dose depends on the clinical scenario. Currently, doses in the range of 41.4 Gy (as per CROSS) to 50.4 Gy (as per CALGB 80803) are utilized in the neoadjuvant setting. For definitive treatment, 50.4 Gy is recommended given the failure of dose escalation to show an improvement in patient outcomes, as described earlier, even when utilizing highly conformal IMRT planning. For patients with cancer of the cervical esophagus, however, who are anatomically unable to undergo surgery, doses in the range of 60 to 66 Gy are considered, but this dose escalation remains a subject of active debate.[40,41]

The potential benefit of proton therapy versus photon therapy has been studied in an effort to reduce side effects from treatment. A phase IIB trial of photons using IMRT versus proton therapy in patients receiving neoadjuvant CRT to 50.4 Gy found that the total toxicity burden was significantly reduced with proton therapy (2.3 times higher with photons vs protons) with no difference in 3 year OS (44.5% in both arms).[42] A meta-analysis of 45 studies (31 of which were dosimetric comparisons) comparing proton to photon therapy found that treatment with protons resulted in reduced rates

of grade 2 or higher radiation pneumonitis and pericardial effusion and grade 4 or higher lymphocytopenia. The authors also found an improvement in OS with protons (HR, 1.31; 95% CI, 1.07 to 1.61; I^2 = 11%), but given the heterogeneity of studied included in this meta-analysis, these findings must be interpreted with caution. The ongoing phase III randomized controlled trial, NRG-GI006, is seeking to definitively answer the question of whether there is a benefit to protons therapy over IMRT in patients with esophageal cancer.

FUTURE DIRECTIONS

Trials are ongoing to determine the optimal treatment approach in patients with esophageal and GEJ cancer and to improve upon the results described heretofore. We await final survival results from TOPGEAR, discussed earlier (NCT01924819). ESOPEC is a prospective randomized phase III trial comparing perioperative chemotherapy using the FLOT regimen (FU/LV/oxaliplatin/docetaxel) to neoadjuvant CRT per CROSS in patients with adenocarcinoma of the esophagus (NCT02509286) with a primary end point of OS.[43] RACE is a randomized phase III trial investigating the role of induction chemotherapy with FLOT followed by CRT versus preoperative FLOT alone in patients with potentially resectable GEJ adenocarcinoma with the primary end point of PFS (NCT04375605).[44] POWERRANGER is a randomized phase III trial comparing neoadjuvant chemotherapy (using FLOT) versus neoadjuvant CRT with a primary outcome measure of compliance and pathologic response rates (NCT01404156). SCOPE-2 is seeking to determine whether dose escalation to 60 Gy improves survival compared to standard doses of RT and whether PET-response directed therapy with switching the chemotherapy backbone in nonresponders (similar to CALGB 80803) improves outcomes in patients with esophageal cancer (either histology).[45]

SUMMARY

Radiation therapy is an effective treatment modality in the management of patients with esophageal cancer regardless of tumor location (proximal, middle, or distal esophagus) or histology (squamous cell vs adenocarcinoma). The addition of neoadjuvant CRT to surgery in patients who are surgical candidates has consistently shown a benefit in terms of locoregional recurrence, pathologic downstaging, and OS. For patients who are not surgical candidates, CRT has a role as definitive treatment. Studies are ongoing to assess the role of PET-directed treatment, the potential benefit of proton therapy, the role of induction chemotherapy, the earlier incorporation of immunotherapy, and the ideal radiation therapy dose, as well as the role of active surveillance among patients achieving a complete clinical response to neoadjuvant therapy.

CLINICS CARE POINTS

- Neoadjuvant chemoradiation improves survival compared to surgery alone for patients with operable esophageal cancer.
- The role of induction chemotherapy remains to be elucidated but available data show promising outcomes for patients receiving induction chemotherapy followed by PET-directed CRT.
- While there remains equipoise as to the optimal neoadjuvant regimen, neoadjuvant CRT has consistently shown a benefit in pathologic downstaging of patients as compared to other neoadjuvant approaches.

- Adjuvant immunotherapy after preoperative chemoradiation and surgery has been shown to improve disease-free survival in patients who did not achieve a pathologic completer response.
- Patients with esophageal cancer who do not receive neoadjuvant therapy benefit from adjuvant treatment but the optimal regimen remains under investigation.
- Definitive CRT is a standard option for patients with esophageal cancer who are medically inoperable or have unresectable disease, and dose escalation beyond 5040 cGy has not been shown to add any benefit.
- The role of immunotherapy in the neoadjuvant setting for patients with localized esophagogastric cancer is being studied.

REFERENCES

1. Njei B, McCarty TR, Birk JW. Trends in esophageal cancer survival in United States adults from 1973 to 2009: A SEER database analysis. J Gastroenterol Hepatol 2016;31(6):1141–6.
2. Pape M, Vissers PAJ, Beerepoot L, et al. Treatment patterns and overall survival for recurrent esophageal or gastroesophageal junctional cancer: A nationwide European population-based study. J Clin Oncol 2021;39(3_suppl):186.
3. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19(2):305–13.
4. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16(9):1090–8.
5. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366(22):2074–84.
6. Eyck BM, JJBv Lanschot, Hulshof MCCM, et al. Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial. J Clin Oncol 2021;39(18):1995–2004.
7. Nederlof N, Slaman AE, van Hagen P, et al. Using the Comprehensive Complication Index to Assess the Impact of Neoadjuvant Chemoradiotherapy on Complication Severity After Esophagectomy for Cancer. Ann Surg Oncol 2016;23(12):3964–71.
8. Feng H, Zhao Y, Jing T, et al. Traditional and cumulative meta-analysis: Chemoradiotherapy followed by surgery versus surgery alone for resectable esophageal carcinoma. Mol Clin Oncol 2018;8(2):342–51.
9. Liu B, Bo Y, Wang K, et al. Concurrent neoadjuvant chemoradiotherapy could improve survival outcomes for patients with esophageal cancer: a meta-analysis based on random clinical trials. Oncotarget 2017;8(12):20410–7.
10. Kavanagh B, Anscher M, Leopold K, et al. Patterns of failure following combined modality therapy for esophageal cancer, 1984–1990. Int J Radiat Oncol Biol Phys 1992;24(4):633–42.
11. Ajani JA, Xiao L, Roth JA, et al. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. Ann Oncol 2013;24(11):2844–9.
12. Shimodaira Y, Slack RS, Harada K, et al. Influence of induction chemotherapy in trimodality therapy-eligible oesophageal cancer patients: secondary analysis of a randomised trial. Br J Cancer 2018;118(3):331–7.

13. Mukherjee S, Hurt CN, Gwynne S, et al. NEOSCOPE: A randomised phase II study of induction chemotherapy followed by oxaliplatin/capecitabine or carboplatin/paclitaxel based pre-operative chemoradiation for resectable oesophageal adenocarcinoma. Article. European Journal of Cancer 2017;74:38–46.
14. Lordick F, Ott K, Krause B-J, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol 2007;8(9):797–805.
15. Goodman KA, Ou F-S, Hall NC, et al. Randomized Phase II Study of PET Response–Adapted Combined Modality Therapy for Esophageal Cancer: Mature Results of the CALGB 80803 (Alliance) Trial. J Clin Oncol 2021;39(25):2803–15.
16. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355(1):11–20.
17. Burmeister BH, Thomas JM, Burmeister EA, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. European Journal of Cancer 2011; 47(3):354–60.
18. Stahl M, Walz MK, Stuschke M, et al. Phase III Comparison of Preoperative Chemotherapy Compared With Chemoradiotherapy in Patients With Locally Advanced Adenocarcinoma of the Esophagogastric Junction. J Clin Oncol 2009;27(6):851–6.
19. Stahl M, Walz MK, Riera-Knorrenschild J, et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. European journal of cancer (Oxford, England : 1990) 2017;81:183–90.
20. von Dobeln GA, Klevebro F, Jacobsen AB, et al. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or gastroesophageal junction: long-term results of a randomized clinical trial. Dis Esophagus 2019;32(2). https://doi.org/10.1093/dote/doy078.
21. Leong T, Smithers BM, Haustermans K, et al. TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG. Ann Surg Oncol 2017;24(8):2252–8.
22. Reynolds JV, Preston SR, O'Neill B, et al. Trimodality therapy versus perioperative chemotherapy in the management of locally advanced adenocarcinoma of the oesophagus and oesophagogastric junction (Neo-AEGIS): an open-label, randomised, phase 3 trial. The Lancet Gastroenterology & Hepatology 2023;8(11): 1015–27.
23. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012;30(19): 2327–33.
24. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018;19(5):616–28.
25. Fuchs CS, Enzinger PC, Meyerhardt J, et al. Adjuvant chemoradiotlherapy with epirubicin, cisplatin, and fluorouracil compared with adjuvant chemoradiotherapy with fluorouracil and leucovorin after curative resection of gastric cancer: Results from CALGB 80101 (Alliance). Article. J Clin Oncol 2017;35(32):3671–7.

26. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01). Article. JAMA 1999;281(17):1623–7.
27. Minsky BD, Neuberg D, Kelsen DP, et al. Neoadjuvant chemotherapy plus concurrent chemotherapy and high-dose radiation for squamous cell carcinoma of the esophagus: a preliminary analysis of the phase II intergroup trial 0122. J Clin Oncol 1996;14(1):149–55.
28. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20(5): 1167–74.
29. Hulshof M, Geijsen ED, Rozema T, et al. Randomized Study on Dose Escalation in Definitive Chemoradiation for Patients With Locally Advanced Esophageal Cancer (ARTDECO Study). J Clin Oncol 2021;39(25):2816–24.
30. Xu Y, Dong B, Zhu W, et al. A Phase III Multicenter Randomized Clinical Trial of 60 Gy versus 50 Gy Radiation Dose in Concurrent Chemoradiotherapy for Inoperable Esophageal Squamous Cell Carcinoma. Clin Cancer Res 2022;28(9): 1792–9.
31. You J, Zhu S, Li J, et al. High-Dose Versus Standard-Dose Intensity-Modulated Radiotherapy With Concurrent Paclitaxel Plus Carboplatin for Patients With Thoracic Esophageal Squamous Cell Carcinoma: A Randomized, Multicenter, Open-Label, Phase 3 Superiority Trial. Int J Radiat Oncol Biol Phys 2023; 115(5):1129–37.
32. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005;23(10):2310–7.
33. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25(10):1160–8.
34. Eyck BM, van der Wilk BJ, Noordman BJ, et al. Updated protocol of the SANO trial: a stepped-wedge cluster randomised trial comparing surgery with active surveillance after neoadjuvant chemoradiotherapy for oesophageal cancer. Trials 2021;22(1):345.
35. van den Ende T, de Clercq NC, van Berge Henegouwen MI, et al. Neoadjuvant Chemoradiotherapy Combined with Atezolizumab for Resectable Esophageal Adenocarcinoma: A Single-arm Phase II Feasibility Trial (PERFECT). Clin Cancer Res 2021;27(12):3351–9.
36. Eads JR, Weitz M, Catalano PJ, et al. A phase II/III study of perioperative nivolumab and ipilimumab in patients (pts) with locoregional esophageal (E) and gastroesophageal junction (GEJ) adenocarcinoma: Results of a safety run-in—A trial of the ECOG-ACRIN Cancer Research Group (EA2174). J Clin Oncol 2021;39(15_suppl):4064.
37. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med 2021;384(13):1191–203.
38. Wu AJ, Bosch WR, Chang DT, et al. Expert Consensus Contouring Guidelines for Intensity Modulated Radiation Therapy in Esophageal and Gastroesophageal Junction Cancer. Int J Radiat Oncol Biol Phys 2015;92(4):911–20.
39. Oppedijk V, Avd Gaast, JJBv Lanschot, et al. Patterns of Recurrence After Surgery Alone Versus Preoperative Chemoradiotherapy and Surgery in the CROSS Trials. J Clin Oncol 2014;32(5):385–91.

40. Burmeister BH, Dickie G, Smithers BM, et al. Thirty-four Patients With Carcinoma of the Cervical Esophagus Treated With Chemoradiation Therapy. Arch Otolaryngol Head Neck Surg 2000;126(2):205–8.
41. Hoeben A, Polak J, Van De Voorde L, et al. Cervical esophageal cancer: a gap in cancer knowledge. Ann Oncol 2016;27(9):1664–74.
42. Lin SH, Hobbs BP, Verma V, et al. Randomized Phase IIB Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for Locally Advanced Esophageal Cancer. J Clin Oncol 2020;38(14):1569–79.
43. Hoeppner J, Lordick F, Brunner T, et al. ESOPEC: prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286). BMC Cancer 2016; 16:503.
44. Lorenzen S, Biederstädt A, Ronellenfitsch U, et al. RACE-trial: neoadjuvant radiochemotherapy versus chemotherapy for patients with locally advanced, potentially resectable adenocarcinoma of the gastroesophageal junction - a randomized phase III joint study of the AIO, ARO and DGAV. BMC Cancer 2020;20(1):886.
45. Bridges S, Thomas B, Radhakrishna G, et al. SCOPE 2 – Still Answering the Unanswered Questions in Oesophageal Radiotherapy? SCOPE 2: a Randomised Phase II/III Trial to Study Radiotherapy Dose Escalation in Patients with Oesophageal Cancer Treated with Definitive Chemoradiation with an Embedded Phase II Trial for Patients with a Poor Early Response using Positron Emission Tomography/Computed Tomography. Clin Oncol 2022;34(7):e269–80.