Review Article

Current landscape of radiation oncology in esophageal cancer: a narrative review

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Background and Objective: Esophageal cancer is an aggressive disease that is the sixth leading cause of cancer-related death worldwide. The overall treatment paradigm for esophageal cancer has changed considerably over the past decade. This narrative review aims to summarize the current landscape of radiation oncology for esophageal cancer.

Methods: A systematic search of the MEDLINE/PubMed database and Clinicaltrials.gov was performed, focusing on studies published within the last 10 years. Our search queried "esophageal cancer [AND] neoadjuvant radiation" as well as "locally advanced esophageal cancer [AND] definitive radiation". Our search resulted in 298 total references. These were manually reviewed, and only 58 references were within our scope of interest ranging from 2012–2022.

Key Content and Findings: For resectable esophageal cancer, neoadjuvant chemoradiation followed by surgery has been defined as the standard of care over the past decade. In patients with incomplete response to neoadjuvant chemoradiation, the benefit of immunotherapy in the adjuvant setting has recently been established. Ongoing studies are examining whether perioperative chemotherapy may be equivalent to neoadjuvant chemoradiation in resectable esophageal adenocarcinoma. For locally advanced esophageal cancer, recent studies have failed to show a benefit with radiation dose escalation in an unselected population, although the use of early positron emission tomography (PET) response to guide dose escalation is currently being studied. Other ongoing studies aiming to improve outcomes in locally advanced esophageal cancer involve using proton beam therapy to reduce toxicity and combining immunotherapy or targeted therapies with chemoradiation to amplify response.

Conclusions: Recent advances in radiation oncology may continue to improve outcomes for patients with esophageal cancer.

Keywords: Radiotherapy; radiation therapy; esophageal cancer; definitive; neoadjuvant

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Introduction

Esophageal cancer is the sixth leading cause of cancer-related death and the eighth most common cancer worldwide (1). The landscape of treatment for esophageal cancer has changed dramatically over the past two decades. The Chemoradiation for Oesophageal Cancer Followed by Surgery Study (CROSS) trial first published in 2012 established a new standard of care for resectable esophageal cancer by finding an increase in overall survival (OS) with the use of chemoradiation before surgery (2). The recommended neoadjuvant chemoradiation dose is between 41.4–50.4 Gy in 1.8 Gy per fraction (3). Despite this, the optimal treatment strategy remains controversial for certain subtypes such as esophageal adenocarcinoma and gastroesophageal junction (GEJ) cancers (3-6).

Furthermore, the question of whether radiation dose escalation may improve outcomes in locally advanced esophageal cancer has been of great interest ever since the heavily critiqued Intergroup 0123 trial (7) failed to show any benefit to dose escalation. The negative results of two recently published phase III randomized trials, ARTDECO (8) and CONCORDE (9), have likely to put to rest any debate regarding the benefit of radiation dose escalation in unselected patients with locally advanced esophageal cancer. The recommended definitive chemoradiation dose remains 50.4 Gy in 1.8 Gy per fraction (3). Ongoing investigations are examining other ways to improve outcomes in these patients, such as by using early positron emission tomography (PET) response to guide dose escalation, using proton beam therapy to reduce toxicity, or combining immunotherapy or targeted therapies with chemoradiation to amplify response. The purpose of this narrative review is to summarize the current landscape of radiation oncology in the treatment of esophageal cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-939/rc).

Methods

A systematic search of the MEDLINE/PubMed database and Clinicaltrials.gov was performed, focusing on studies published within the last 10 years. Our search queried "esophageal cancer [AND] neoadjuvant radiation" as well as "locally advanced esophageal cancer [AND] definitive radiation" and was limited only to prospective studies, retrospective studies, and metanalyses, omitting abstracts, books, documents, and reviews. Our search resulted in 298 total references. These were manually reviewed, and only 58 references were within our scope of interest ranging from 2012 to 2022. Prospective randomized studies were prioritized as having the highest level of evidence, followed by prospective single-arm studies, followed by metanalyses of retrospective studies, followed by retrospective studies. A search strategy summary can be seen in *Table 1*.

Discussion

Neoadjuvant chemoradiation as standard of care for esophageal cancer

The CROSS trial established the standard of care for the treatment of esophageal and GEJ (Siewert I–II) cancer over the past decade. Prior to the CROSS trial, there was some suggestion of a survival benefit with the use of neoadjuvant therapies compared to surgery alone by a few metanalyses (10,11). CROSS was a randomized phase III trial of 368 patients with T1 N1 or T2–3 N0–1 esophageal or GEJ cancer treated with neoadjuvant chemoradiation to a dose of 41.4 Gy in 23 fractions using a 3-dimensional conformal technique (3D-CRT) with concurrent weekly carboplatin and paclitaxel *vs.* surgery alone. Ten-year outcomes from the CROSS trial were recently published in 2021 (12), which showed a persistent OS benefit with the use of neoadjuvant chemoradiation. With a median follow-up of 147 months, the 10-year OS rate was 38% in the chemoradiation arm *vs.* 25% in the surgery alone arm (P=0.004). Locoregional recurrence was reduced with neoadjuvant chemoradiation [hazard ratio (HR) 0.40, 95% confidence interval (CI): 0.26–0.72] compared to surgery, although the rate of distant recurrence was similar in both arms (27% *vs.* 28%). Patients with squamous cell carcinoma (SCC) histology appeared to have improved outcomes with this regimen compared to adenocarcinoma, with a 10-year OS rate of 46% *vs.* 36%, although this study was inadequately powered to compare OS across subgroups. From the initial publication in 2012 (2), patients with SCC histology also appeared to have higher pathological complete response (pCR) rates compared to adenocarcinoma (49% *vs.* 23%), although the study was inadequately powered to detect any difference. The addition of neoadjuvant chemoradiation did not increase the rate of postoperative complications or death, and the most common grade 3+ toxicities associated with this regimen were leukopenia (6%) and anorexia (5%). The difference in pCR seen between SCC and adenocarcinoma in the CROSS trial has led clinicians to consider offering non-operative management to patients with esophageal

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Table 1 Search strategy summary

Items	Specification
Date of search	4/1/2022
Databases and other sources searched	MEDLINE, PubMed, Clinicaltrials.gov
Search terms used	"esophageal cancer [AND] neoadjuvant radiation", "locally advanced esophageal cancer [AND] definitive radiation"
Timeframe	1/1/2012–4/1/2022
Inclusion and exclusion criteria	Inclusion criteria: prospective studies, retrospective studies, and metanalyses, English language
	Exclusion criteria: abstracts, books, documents, and reviews
Selection process	First author performed initial literature review, with feedback from principal investigator
Additional considerations	References of selected papers were also screened for additional papers that met the predetermined selection criteria

SCC who demonstrate favorable response to concurrent chemoradiation (13). The recommended neoadjuvant chemoradiation dose is between 41.4–50.4 Gy in 1.8 Gy per fraction (3). An National Cancer Database (NCDB) analysis by Haque *et al.* (14) found that the most common neoadjuvant chemoradiation dose used in the United States was 50.4 Gy (95%), although the use of 41.4 Gy has been rising over the past decade.

Despite the durable OS benefit of neoadjuvant chemoradiation, there is a lack of consensus between published guidelines regarding the optimal treatment for esophageal cancer, particularly for esophageal adenocarcinoma and GEJ cancer. The National Comprehensive Cancer Network (NCCN) guidelines (3) and the American Radium Society (ARS) Appropriate Use Criteria (6) both favor the use of neoadjuvant chemoradiation for esophageal adenocarcinoma and SCC, whereas the American Society of Clinical Oncology (ASCO) guidelines (4,5) support the use of either neoadjuvant chemoradiation or perioperative chemotherapy for esophageal adenocarcinoma and either neoadjuvant or definitive chemoradiation for esophageal SCC. Evidence to support alternative recommendations will be discussed in the following sections.

Perioperative chemotherapy in esophageal and GEJ adenocarcinoma

Although most guidelines favor the use of neoadjuvant chemoradiation over perioperative chemotherapy for esophageal and GEJ adenocarcinoma, some argue that recent advances in systemic therapy have made it so that perioperative chemotherapy is equivalent to neoadjuvant chemoradiation. The emergence of perioperative FLOT (fluorouracil plus leucovorin, oxaliplatin and docetaxel) in GEJ and gastric cancer have led some to question whether outcomes may be similar to the CROSS regimen in esophageal and GEJ adenocarcinoma. The use of FLOT in GEJ and gastric cancer was established by the FLOT4-AIO trial (15), which found an OS benefit with perioperative FLOT compared to the MAGIC (ECF; epirubicin, cisplatin, and infused fluorouracil) regimen in 716 patients with GEJ and gastric cancer (median OS of 50 *vs.* 35 months, P=0.012). FLOT differs from ECF/ECX in several features. The most important difference appears to be the use of the docetaxel instead of the epirubicin as a third drug, but also, that FLOT is a 2-week regimen, whereas ECF/ECX is a 3-week regimen, and that FLOT contains oxaliplatin instead of cisplatin. Additionally, the schedule and doses of the fluoropyrimidines differ. Therefore, it is difficult to speculate whether other docetaxel-based three-drug regimens such as the parent DCF would be associated with comparable safety and efficacy in the perioperative setting.

There are currently four ongoing trials comparing perioperative FLOT *vs.* neoadjuvant chemoradiation in esophageal and GEJ adenocarcinoma: NEO-AEGIS (16), ESOPEC (17), RACE (18), and POWERRANGER (19). A summary of these studies can be found in *Table 2*. Currently,

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Table 2 Ongoing studies comparing neoadjuvant chemoradiation *vs.* perioperative chemotherapy

Trial	Phase	Eligibility	Target accrual	Treatment arms	Primary outcome	Secondary outcome
NEO-AEGIS (16)	III	T2–3 N0–3 esophageal or GEJ adenocarcinoma	377	Perioperative MAGIC/FLOT regimen *vs.* CROSS regimen	OS	Response rate, DFS, toxicity, postop complications, QOL
ESOPEC (17)	III	T2+ or N+ esophageal or GEJ adenocarcinoma	438	Perioperative FLOT regimen *vs.* CROSS regimen	OS	PFS, patterns of failure, toxicity, postop complications, QOL
RACE (18)	III	T3+ or N+ esophageal or GEJ adenocarcinoma	340	Perioperative FLOT regimen *vs.* preoperative FLOT ×2 followed by 45 Gy with oxaliplatin/5-FU	PFS	OS, R0 resection rate, patterns of failure, QOL
POWERRANGER (19)	II	T2+ or N+ esophageal or GEJ adenocarcinoma	60	Perioperative MAGIC/FLOT regimen *vs.* preoperative 45 Gy with carboplatin/paclitaxel	Compliance, response rate	OS, PFS, QOL

GEJ, gastroesophageal; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; QOL, quality of life.

only the NEO-AEGIS trial has published interim results in abstract form (20). Of the 362 evaluable patients in NEO-AEGIS, 178 patients were treated with the CROSS regimen, and 184 were treated with perioperative chemotherapy (MAGIC/FLOT regimen). With a median follow-up of 24.5 months, the 3-year estimated survival probability was similar in both arms (56% *vs.* 57%). However, most other secondary endpoints showed an absolute improvement in the neoadjuvant chemoradiation (CROSS) arm, although statistical significance was not reported. The R0 resection rate was 95% in the CROSS arm *vs.* 82% in the MAGIC/FLOT arm, and the pCR rates were 16% *vs.* 5% respectively. The rate of grade 3 or higher neutropenia was lower in the CROSS arm *vs.* the MAGIC/FLOT arm, 3% *vs.* 14%. There was a decrease in postoperative pneumonia in the CROSS arm *vs.* MAGIC/FLOT arm (16% *vs.* 20%), but there was a higher rate of acute respiratory distress syndrome (ARDS) in the CROSS arm *vs.* MAGIC/FLOT arm (4.3% *vs.* 0.6%). There was no difference in the rate of postoperative in-hospital deaths between the two arms (3% for both arms). More mature data are needed to guide treatment decisions. A retrospective review by Ahmed *et al.* (21) found that neoadjuvant chemoradiation was associated with a higher degree of pathologically tumor regression compared to perioperative chemotherapy. Patients with major tumor regression had a better outcome than those with minimal to poor response. There was a trend toward improved time to tumor recurrence with chemoradiation but no difference in OS.

One reason to favor neoadjuvant chemoradiation over perioperative chemotherapy is that the use of adjuvant nivolumab has been shown to improve disease free survival (DFS) in patients with incomplete response to neoadjuvant chemoradiation based on the CheckMate 577 study (22). This phase III trial randomized 532 patients with completely resected stage II–III esophageal or GEJ cancer who had incomplete response to neoadjuvant chemoradiation in a 2:1 fashion to receive adjuvant nivolumab *vs.* placebo. With a median follow-up of 24.4 months, the median DFS was 22.4 months in the nivolumab arm *vs.* 11.0 in the placebo arm (P<0.001). DFS favored nivolumab across multiple prespecified subgroups independent of PD-L1 expression, HER2 status, histology, and radiotherapy dose. Grade 3 or higher toxicities occurred in 13% of patients in the nivolumab arm *vs.* 6% of patients in the placebo arm. Such data does not yet exist in the setting of perioperative chemotherapy, which further supports the use of chemoradiation in these patients in order to utilize immunotherapy as part of a multi-modality approach. Ongoing studies examining the benefit of immunotherapy with perioperative chemotherapy in GEJ and gastric cancer include EA2174 (23) (nivolumab and ipilimumab), KEYNOTE 585 (24) (pembrolizumab), and MATTERHORN (25) (durvalumab), among others.

Nonoperative approach with selective esophagectomy in esophageal SCC

Given that pCR rates were as high as 50% after neoadjuvant chemoradiation for SCC histology in the CROSS trial (26),

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there is a growing interest in a nonoperative approach for patients with esophageal SCC who have a complete clinical response (cCR) after initial therapy. A nonoperative approach is attractive for both patients and providers since these patients often have medical comorbidities that increase the risk of surgery, and morbidity tends to be higher in patients with SCC since esophageal SCC is usually located in the upper or mid esophagus and requires a higher anastomosis as part of the surgical approach (27).

The use of definitive chemoradiation for esophageal SCC was first established by two European studies, one by Stahl *et al.* (28) and the second by Bedenne *et al.* (29). The Stahl (28) trial randomized 172 patients with T3–4 esophageal SCC to receive neoadjuvant chemoradiation followed by surgery *vs.* definitive chemoradiation. There was no difference in OS between the two arms (median OS of 16 *vs.* 15 months), although the 2-year freedom from local progression (FFLP) was higher with surgery compared to chemoradiation alone (64% *vs.* 41%, P=0.003). Treatment-related mortality was significantly higher in the surgery arm compared to the chemoradiation alone arm (12.8% *vs.* 3.5%, P=0.03). The Bedenne (29) trial similarly randomized 259 patients with T3N0–1 mostly esophageal SCC (90%) to receive neoadjuvant chemoradiation followed by surgery *vs.* definitive chemoradiation. There was no difference in OS between the two arms (median OS 18 *vs.* 19 months), and the 2-year local control was higher with surgery compared to chemoradiation alone (66% *vs.* 57%, P=0.03). The 3-month mortality rate indicative of treatment-related death was significantly higher in the surgery arm compared to the chemoradiation arm (9.3% *vs.* 0.8%, P=0.002). Based on the results of these studies, the ASCO guidelines (4,5) now recommend that definitive chemoradiation with selective esophagectomy may be considered for esophageal SCC. The benefit of concurrent chemotherapy with radiation has been long established by the RTOG 8501 trial (30), which found an OS benefit and higher rates of acute toxicity with the use of chemoradiation *vs.* radiation alone.

RTOG 0246 (31) was the first prospective phase II trial to demonstrate that a nonoperative approach was feasible and effective in patients with esophageal cancer who achieved a cCR after definitive chemoradiation. A total of 43 patients with operable nonmetastatic esophageal cancer (27% SCC) received induction 5-fluorouracil, cisplatin, and paclitaxel followed by chemoradiation to a dose of 50.4 Gy in 28 fractions with concurrent 5-fluorouracil and cisplatin. Response was then evaluated using computed tomography (CT), endoscopic ultrasound (EUS), and optimal PET scan. Patients who achieved a cCR underwent observation, and those who had incomplete response underwent surgery. The cCR rate was 37% in this cohort. 51% of patients who achieved a cCR eventually underwent surgery (41% due to patient choice, 10% due to recurrent disease). The 5-year OS rate was 37% for all patients, although it was much higher for patients who achieved a cCR at 53%. Although results are favorable, OS data appears less favorable compared to the CROSS trial (12), which found a 5-year OS rate of 47% in all patients. This may be due to selection bias in this study toward those with poorer performance status. A retrospective study by Markar *et al.* (32) found much more favorable outcomes, with a 3-year OS rate of 56.2% and a 3-year DFS rate of 51.6% in 308 patients (64.9% SCC) who were observed after cCR and received esophagectomy in the salvage setting. The results of this large multicenter study suggests that a nonoperative approach can offer acceptable short- and long-term outcomes in select patients at experienced centers.

Radiation dose escalation in locally advanced esophageal cancer

The Intergroup 0123 (7) trial published over two decades ago was the first landmark dose escalation study that randomized patients with locally advanced esophageal cancer to receive high dose (64.8 Gy in 36 fractions) *vs.* standard dose (50.4 Gy in 28 fractions) chemoradiation. The study found no benefit with dose escalation. However, many of these deaths occurred prior to receiving 50.4 Gy. It has been hypothesized that the failure of the study to show any benefit with dose escalation was due to problems with patient selection from improper staging and rudimentary radiation treatment techniques, both of which may have contributed to the early deaths.

More recently, the ARTDECO (8) and CONCORDE (9) studies clearly indicate that radiation dose escalation does not provide a clinical benefit in an unselected population, even with more modern radiation therapy techniques and proper staging. ARTDECO (8) was a phase III trial that randomized 260 patients with T2–4 N0–3 inoperable esophageal cancer to receive either standard dose 50.4 Gy in 28 fractions *vs.* dose escalated 61.6 Gy in 28 fractions using a simultaneous integrated boost (SIB) technique chemoradiation with weekly carboplatin and paclitaxel. With a median follow-up of 50 months, the 3-year OS rate was 42% in the standard dose arm *vs.* 39% in the high dose arm (P=0.22). There was no difference in the 3-year local

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progression free survival (LPFS) between the two arms (52% *vs.* 59%, P=0.08). There was no difference in LPFS between the two arms when stratified by SCC or adenocarcinoma histology. The rate of grade 4 or higher toxicities was not significantly different between the two groups (17% *vs.* 24%, P=0.15). CONCORDE (9) is an ongoing phase III trial that has yet to be published, but interim results were recently published in abstract form. This study randomized 160 patients with inoperable esophageal cancer to receive 40 Gy elective nodal irradiation followed by a standard 10 Gy boost (arm A) *vs.* a dose escalated 26 Gy boost (arm B) with concurrent FOLFOX-4 for 3 cycles followed by 3 cycles of adjuvant chemotherapy. With a median follow-up of 35.3 months, there was no significant difference in OS (median 25.2 *vs.* 23.5 months, P=0.44) or LPFS (median 16.2 *vs.* 18.4 months, P=0.88) between the two arms. There was also no difference in grade 3 or higher toxicities between the two arms (29.5% *vs.* 29.3%, P=not reported).

Given the negative results of these studies, the benefit of radiation dose escalation in an unselected population is rightfully in question. However, there could be a subset of patients with poor response to neoadjuvant therapy who may still benefit from dose escalation. CALGB 80803 (33) found that making an early change in systemic therapy for PET non-responders improved pCR rates after neoadjuvant chemoradiation. It is possible that increasing the radiation dose for PET non-responders may similarly improve outcomes. The SCOPE2 (34) trial is currently underway and uses early PET response after beginning chemoradiation to guide the use of radiation dose escalation.

Using proton beam therapy to reduce toxicities

Over the past decade, there have been significant improvements in the technology used to deliver radiotherapy, particularly proton beam therapy (PBT). PBT allows for more conformal doses to be delivered to the esophagus, which is located at the center of thorax and along the lung and heart. Radiation dose to the lungs can result in pneumonitis, and radiation dose to the heart can result in pericarditis, cardiac effusion, and myocardial infarction (35). Theoretically, protons are ideally suited for the treatment of esophageal cancers because of their characteristic Bragg peak, which allows for a rapid dose fall off at the distal edge of the target, sparing the heart and lung.

Several studies (36-40) have shown that PBT is dosimetrically superior to photon therapy, and several clinical reports have also shown reduced toxicities with PBT compared to photon therapy. A phase IIb trial by Lin *et al.* (41) prospectively randomized 107 patients with esophageal cancer to receive PBT (N=46) or intensity modulated radiation therapy (IMRT) (N=61) to a dose of 50.4 Gy in 28 fractions. The primary endpoint was total toxicity burden. 51 patients (30 IMRT, 21 PBT) underwent esophagectomy; 80% of PBT was passive scattering. The total toxicity burden was 2.3 times higher for IMRT than PBT, and the postoperative complication rate was 7.6 times higher for IMRT than PBT. The 3-year PFS rate (50.8% *vs.* 51.2%) and the 3-year OS rate (44.5% *vs.* 44.5%) were similar for both arms. Authors concluded that PBT reduced the risk and severity of adverse effects compared with IMRT while maintaining similar PFS and OS. Several retrospective studies (42-44) have also found lower rates of grade 4 lymphopenia with definitive chemoradiation treated with PBT compared to IMRT. A comparison of patient-reported health-related quality of life (HRQOL) in a prospective registry by Garant *et al.* (45) found that 189 patients with esophageal cancer treated with PBT reported less decline in HRQOL compared to patients treated with IMRT based on the functional assessment of cancer therapy-esophageal (FACT-E) scoring system. These studies and others support the use of PBT in the treatment of esophageal cancer to lessen toxicities and improve quality of life (46-48).

Combining immunotherapy with chemoradiation in esophageal cancer

The benefit of adjuvant nivolumab after partial response to neoadjuvant chemoradiation was established by the CheckMate 577 (22) study. An active area of investigation is whether immunotherapy may also improve outcomes in the neoadjuvant setting when combined with chemoradiation. The PERFECT (49) study was a single-arm phase II feasibility trial that included 40 patients with resectable esophageal cancer treated with neoadjuvant chemoradiation plus atezolizumab. 83% of patients treated with this regimen underwent surgery, lower than historical controls of 89% with neoadjuvant chemoradiation alone (26) and 94% with chemotherapy alone (15). Reasons for not undergoing surgery were progression (10%), patient choice (5%), and death (2.5%). The pCR rate was 25%, which appears similar to the pCR rate of 29% in the CROSS trial (26). However, the pCR rate was much higher at 37.5% in patients with PD-L1 scores ≥25 and high interferon-gamma signatures, highlighting the need for optimal patient selection based on immunologic factors.

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Table 3 Summary of studies examining the combination of EGFR inhibitors with chemoradiation

Trial	Phase	Patients	Treatment arms	OS	PFS	Toxicity
SCOPE1 (52)	III	Stage I-III esophageal cancer (N=258)	Definitive 50 Gy plus cisplatin/capecitabine with cetuximab *vs.* without cetuximab	Median 22 *vs.* 25 months	Median 16 *vs.* 22 months	Grade 3+ non-heme 79% *vs.* 63%
RTOG 0436 (53)	III	T1 N1 or T2-4 esophageal or GEJ cancer (N=344)	Definitive 50.4 Gy plus cisplatin/paclitaxel with cetuximab *vs.* without cetuximab	34% *vs.* 28% at 3 years	51% for both at 3 years	Grade 3+ 73% *vs.* 68%
LEOPARD-2 (54)	II	Unresectable esophageal cancer (N=68)	Definitive 50.4 Gy plus cisplatin/5-FU with cetuximab *vs.* without cetuximab	71% *vs.* 53% at 2 years	56% *vs.* 44% at 2 years	Grade 3+ 76% *vs.* 79%
Xie *et al.* (55)	III	Medically inoperable esophageal SCC (N=352)	Definitive 60 Gy plus cisplatin/paclitaxel with erlotinib *vs.* without erlotinib	40% *vs.* 27% at 5 years	37% *vs.* 24% at 5 years	Grade 3+ esophageal stenosis 11% *vs.* 10%
SAKK 75/08 (56)	III	T2 N1–3 or T3–4 esophageal and GEJ cancer (N=300)	Preop cisplatin/docetaxel x2 followed by 45 Gy plus cisplatin/docetaxel followed by surgery with cetuximab *vs.* without cetuximab	Median 5.1 *vs.* 3.0 years	Median 2.9 *vs.* 2.0 years	Postop mortality 6% for both

EGFR, epidermal growth factor receptor; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma; GEJ, gastroesophageal.

Serious adverse effects leading to hospitalization or death were observed in 13 (33%) of patients treated with this regimen; therefore, caution should be taken in treating patients with this regimen in the future. Several other trials examining the benefit of combination immunotherapy with chemoradiation in both the neoadjuvant and definitive setting are currently underway, with at least 30 trials listed on Clinicaltrials.gov. One of the largest ongoing trials is KEYNOTE-975 (50), which aims to examine the safety and efficacy of pembrolizumab combined with definitive chemoradiation in locally advanced esophageal cancer.

Combining targeted therapies with chemoradiation in esophageal cancer

Several targeted therapies have shown promise in pairing with radiation in preclinical and clinical studies, including epidermal growth factor receptor (EGFR) inhibitors, receptor tyrosine kinase (RTK) inhibitors, cell cycle checkpoint inhibitors (Wee1, Chk1/2), and vascular endothelial growth factor (VEGF) inhibitors, among others (51). Regarding EGFR inhibitors, the data supporting its use in combination with chemoradiation for esophageal cancer has been mixed. In the definitive setting, the SCOPE1 (52) and RTOG 0436 (53) trials both showed no benefit with adding cetuximab to chemoradiation, while the LEOPARD-2 (54) and Xie *et al.* (55) trials both showed a benefit. In the neoadjuvant setting, the SAKK 75/08 (56) showed a benefit with adding cetuximab to chemoradiation. It is unclear why outcomes differed so greatly between studies, but it is hypothesized that outcomes were less favorable in the SCOPE1 trial because a higher proportion of patients did not receive radiation (19%) or were unable to receive the full dose of radiation (22%) in the cetuximab arm. In the RTOG 0436 trial, it is hypothesized that outcomes were less favorable compared to other studies because a smaller proportion of patients had SCC histology (37%) compared to the SCOPE1 (71%), LEOPARD-2 (84%), and Xie *et al.* (100%) trials. Optimal patient selection is important in maximizing the benefit of cetuximab in esophageal cancer, and EGFR overexpression is the only biomarker that is associated with improved outcomes when combining EGFR inhibitors with chemoradiation thus far (55). A summary of these studies can be seen in *Table 3*. Further study is needed to better clarify which patients may benefit the most from this combination therapy (57,58).

HER2 inhibitors have also been tested in combination with chemoradiation in HER2+ esophageal cancer, although results show limited efficacy. HER2 was the first RTK pathway to be successfully targeted in GEJ and gastric cancer based on the ToGA trial (59), which found an OS

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benefit with the addition of trastuzumab to chemotherapy for locally advanced or metastatic HER2+ GEJ and gastric cancer. RTOG 1010 (60) was a phase III randomized trial that included 606 patients with HER2+ esophageal adenocarcinoma treated with trimodality therapy with concurrent and maintenance trastuzumab *vs.* placebo. With a median follow-up of 2.8 years, there was no difference in OS (median 38.5 *vs.* 38.9 months, P=0.85) or disease-free survival (DFS) (median 19.6 *vs.* 14.2 months, P=0.97) between the trastuzumab arm *vs.* placebo arm. The rate of grade 3+ toxicities were similar between the two arms (64% *vs.* 76%), with the most common being hematologic. The benefit of HER2 inhibitors in combination with chemoradiation appears to be limited for this patient population.

Currently, the only other targeted therapies being studied in combination with chemoradiation include the Wee1 inhibitor adavosertib (61), the VEGF inhibitor bevacizumab (62), and the Hsp90 inhibitor ganetespib (63). The results of these ongoing trials are eagerly awaited.

Limitations

While this narrative review aims to present a comprehensive, unbiased review of the current state of radiotherapy for esophageal cancer, there are a few limitations. First, the review prioritizes large prospective phase III trials in its discussion and therefore may overlook several smaller retrospective studies. Secondly, this review aims to summarize the rationale for current treatment strategies but does not spend significant time discussing radiation treatment planning or systemic therapy administration or dosing. Lastly, certain sections had limited data available for discussion, but we attempted to include as much information as possible to cover emerging areas of investigation.

Conclusions

Esophageal cancer is an aggressive tumor and is expected to increase in incidence over the next 10 years (1). The landmark CROSS (2) trial has defined the standard of care for resectable esophageal cancer over the past decade, although alternative treatment options including perioperative chemotherapy for esophageal and GEJ adenocarcinoma or definitive chemoradiation with selective esophagectomy for esophageal SCC may be considered (4,5). The notion of radiation dose escalation to improve outcomes for all patients with locally advanced esophageal cancer has been laid to rest by the recent ARTDECO (8) and CONCORDE (9) trials, although selective dose escalation for early PET non-responders is currently being studied in the SCOPE2 (34) trial. The use of proton beam therapy and the combination of immunotherapy or targeted therapies with chemoradiation is an active area of investigation that should continue to improve outcomes in this patient population.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.

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2. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
3. Esophageal and Esophagogastric Junction Cancers. NCCN Guidel. 2022. Available online: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1433
4. Shah MA, Kennedy EB, Catenacci DV, et al. Treatment of Locally Advanced Esophageal Carcinoma: ASCO Guideline. J Clin Oncol 2020;38:2677-94.
5. Vitzthum LK, Hui C, Pollom EL, et al. Trimodality Versus Bimodality Therapy in Patients With Locally Advanced Esophageal Carcinoma: Commentary on the American Society of Clinical Oncology Practice Guidelines. Pract Radiat Oncol 2021;11:429-33.
6. Anker CJ, Dragovic J, Herman JM, et al. Executive Summary of the American Radium Society Appropriate Use Criteria for Operable Esophageal and Gastroesophageal Junction Adenocarcinoma: Systematic Review and Guidelines. Int J Radiat Oncol Biol Phys 2021;109:186-200.
7. 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;20:1167-74.
8. Hulshof MCCM, 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;39:2816-24.
9. Crehange G, M'vondo C, Bertaut A, Pereira R, Rio E, Peiffert D, et al. Exclusive Chemoradiotherapy With or Without Radiation Dose Escalation in Esophageal Cancer: Multicenter Phase 2/3 Randomized Trial CONCORDE (PRODIGE-26). Int J Radiat Oncol 2021;111:S5.
10. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12:681-92.
11. Chan KKW, Saluja R, Delos Santos K, et al. Neoadjuvant treatments for locally advanced, resectable esophageal cancer: A network meta-analysis. Int J Cancer 2018;143:430-7.
12. Eyck BM, van Lanschot JJB, Hulshof MCCM, et al. Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial. J Clin Oncol 2021;39:1995-2004.
13. Yau KK, Siu WT, Wong DC, et al. Non-operative management of small cell carcinoma of esophagus. Dis Esophagus 2007;20:487-90.
14. Haque W, Verma V, Butler EB, et al. Radiation dose in neoadjuvant chemoradiation therapy for esophageal cancer: patterns of care and outcomes from the National Cancer Data Base. J Gastrointest Oncol 2018;9:80-9.
15. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019;393:1948-57.
16. Reynolds J V. NEOadjuvant Trial in Adenocarcinoma of the oEsophagus and oesophagoGastric Junction International Study (Neo-AEGIS). Clinicaltrials.gov [Internet]. NCT01726452. Available from: http://ukctg.nihr.ac.uk/trialdetails/NCT01726452
17. 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.
18. Hofheinz R. Neoadjuvant RCT Versus CT for Patients With Locally Advanced, Potentially Resectable Adenocarcinoma of the GEJ. Clinicaltrials.gov. :NCT04375605.
19. Buduhan G. Preoperative Chemotherapy vs. Chemoradiation in Esophageal / GEJ Adenocarcinoma (POWERRANGER). Clinicaltrials.gov [Internet]. NCT01404156. Available online: https://clinicaltrials.gov/ct2/show/NCT01404156
20. Reynolds JV, Preston SR, O'Neill B, et al. Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol). (NCT01726452). J Clin Oncol 2021;39:4004.
21. Ahmed N, Owen J, Abdalmassih M, et al. Outcome of Locally Advanced Esophageal Cancer Patients Treated With Perioperative Chemotherapy and Chemoradiotherapy Followed by Surgery. Am J Clin Oncol 2021;44:10-7.
22. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction

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Cancer. N Engl J Med 2021;384:1191-203.
23. Eads JR, Weitz M, Gibson MK, et al. A phase II/III study of perioperative nivolumab and ipilimumab in patients (pts) with locoregional esophageal (E) and gastroesophageal junction (GEJ) adenocarcinoma: A trial of the ECOG-ACRIN Cancer Research Group (EA2174). J Clin Oncol 2020;38:TPS4651.
24. Bang YJ, Van Cutsem E, Fuchs CS, et al. KEYNOTE-585: Phase III study of perioperative chemotherapy with or without pembrolizumab for gastric cancer. Future Oncol 2019;15:943-52.
25. Janjigian YY, Van Cutsem E, Muro K, et al. MATTERHORN: Efficacy and safety of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy in resectable gastric and gastroesophageal junction cancer—A randomized, double-blind, placebo-controlled, phase 3 study. J Clin Oncol 2021;39:abstr TPS4151.
26. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
27. Xi M, Xu C, Liao Z, et al. The impact of histology on recurrence patterns in esophageal cancer treated with definitive chemoradiotherapy. Radiother Oncol 2017;124:318-24.
28. 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;23:2310-7.
29. Bedenne L, Michel P, Bouché O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25:1160-8.
30. 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). Radiation Therapy Oncology Group. JAMA 1999;281:1623-7.
31. Swisher SG, Moughan J, Komaki RU, et al. Final Results of NRG Oncology RTOG 0246: An Organ-Preserving Selective Resection Strategy in Esophageal Cancer Patients Treated with Definitive Chemoradiation. J Thorac Oncol 2017;12:368-74.
32. Markar S, Gronnier C, Duhamel A, et al. Salvage Surgery After Chemoradiotherapy in the Management of Esophageal Cancer: Is It a Viable Therapeutic Option? J Clin Oncol 2015;33:3866-73.
33. Goodman KA, Ou FS, 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;39:2803-15.
34. Nixon L. Study of Chemoradiotherapy in Oesophageal Cancer Including PET Response and Dose Escalation (SCOPE2). Clinicaltrials.gov [Internet]. NCT02741856. Available online: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01595329/full
35. Karube M, Nakayama H. Proton therapy for patients with esophageal cancer: History, characteristics, clinical outcome and future direction of proton beam therapy. Glob Health Med 2021;3:149-56.
36. Hirano Y, Onozawa M, Hojo H, et al. Dosimetric comparison between proton beam therapy and photon radiation therapy for locally advanced esophageal squamous cell carcinoma. Radiat Oncol 2018;13:23.
37. Isacsson U, Lennernäs B, Grusell E, et al. Comparative treatment planning between proton and x-ray therapy in esophageal cancer. Int J Radiat Oncol Biol Phys 1998;41:441-50.
38. Ling TC, Slater JM, Nookala P, et al. Analysis of Intensity-Modulated Radiation Therapy (IMRT), Proton and 3D Conformal Radiotherapy (3D-CRT) for Reducing Perioperative Cardiopulmonary Complications in Esophageal Cancer Patients. Cancers (Basel) 2014;6:2356-68.
39. Shiraishi Y, Xu C, Yang J, et al. Dosimetric comparison to the heart and cardiac substructure in a large cohort of esophageal cancer patients treated with proton beam therapy or Intensity-modulated radiation therapy. Radiother Oncol 2017;125:48-54.
40. Singh AK, Winslow TB, Kermany MH, et al. A Pilot Study of Stereotactic Body Radiation Therapy Combined with Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma. Clin Cancer Res 2017;23:5055-65.
41. 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;38:1569-79.
42. Fang P, Shiraishi Y, Verma V, et al. Lymphocyte-Sparing Effect of Proton Therapy in Patients with Esophageal Cancer Treated with Definitive Chemoradiation. Int J Part Ther 2018;4:23-32.
43. Shiraishi Y, Fang P, Xu C, et al. Severe lymphopenia during neoadjuvant chemoradiation for esophageal cancer: A propensity matched analysis of the relative risk of proton versus photon-based radiation therapy. Radiother Oncol 2018;128:154-60.

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44. Routman DM, Garant A, Lester SC, et al. A Comparison of Grade 4 Lymphopenia With Proton Versus Photon Radiation Therapy for Esophageal Cancer. Adv Radiat Oncol 2019;4:63-9.
45. Garant A, Whitaker TJ, Spears GM, et al. A Comparison of Patient-Reported Health-Related Quality of Life During Proton Versus Photon Chemoradiation Therapy for Esophageal Cancer. Pract Radiat Oncol 2019;9:410-7.
46. Kato K, Igaki H, Ito Y, Mizusawa J, et al. Next study (JCOG1109): A three-arm randomized phase III study comparing preoperative CDDP+5-FU(CF) versus docetaxel+CF versus CF-radiation followed by esophagectomy with D2-3 lymphadenectomy for locally advanced esophageal squamous cell cancer. J Clin Oncol 2013;31:TPS4152.
47. Nishimura Y, Koike R, Ogawa K, et al. Clinical practice and outcome of radiotherapy for esophageal cancer between 1999 and 2003: the Japanese Radiation Oncology Study Group (JROSG) Survey. Int J Clin Oncol 2012;17:48-54.
48. Takada A, Nakamura T, Takayama K, et al. Preliminary treatment results of proton beam therapy with chemoradiotherapy for stage I-III esophageal cancer. Cancer Med 2016;5:506-15.
49. 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;27:3351-9.
50. Shah MA, Bennouna J, Doi T, et al. KEYNOTE-975 study design: a Phase III study of definitive chemoradiotherapy plus pembrolizumab in patients with esophageal carcinoma. Future Oncol 2021;17:1143-53.
51. Jabbour SK, Williams TM, Sayan M, et al. Potential Molecular Targets in the Setting of Chemoradiation for Esophageal Malignancies. J Natl Cancer Inst 2021;113:665-79.
52. Crosby T, Hurt CN, Falk S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol 2013;14:627-37.
53. Suntharalingam M, Winter K, Ilson D, et al. Effect of the addition of cetuximab to paclitaxel, cisplatin, and radiation therapy for patients with esophageal cancer the NRG oncology RTOG 0436 phase 3 randomized clinical trial. JAMA Oncol 2017;3:1520-8.
54. Rades D, Bartscht T, Hunold P, et al. Radiochemotherapy with or without cetuximab for unresectable esophageal cancer: final results of a randomized phase 2 trial (LEOPARD-2). Strahlenther Onkol 2020;196:795-804.
55. Xie C, Jing Z, Luo H, et al. Chemoradiotherapy with extended nodal irradiation and/or erlotinib in locally advanced oesophageal squamous cell cancer: long-term update of a randomised phase 3 trial. Br J Cancer 2020;123:1616-24.
56. Ruhstaller T, Thuss-Patience P, Hayoz S, et al. Neoadjuvant chemotherapy followed by chemoradiation and surgery with and without cetuximab in patients with resectable esophageal cancer: a randomized, open-label, phase III trial (SAKK 75/08). Ann Oncol 2018;29:1386-93.
57. Crosby T. Cisplatin, Capecitabine, and Radiation Therapy With or Without Cetuximab in Treating Patients With Esophageal Cancer. Clinicaltrials.gov.: NCT00509561.
58. Suntharalingam M. Paclitaxel, Cisplatin, and Radiation Therapy With or Without Cetuximab in Treating Patients With Locally Advanced Esophageal Cancer. Clinicaltrials.gov [Internet]. NCT00655876. Available online: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02045238/full
59. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.
60. Safran HP, Winter K, Ilson DH, et al. Trastuzumab with trimodality treatment for oesophageal adenocarcinoma with HER2 overexpression (NRG Oncology/RTOG 1010): a multicentre, randomised, phase 3 trial. Lancet Oncol 2022;23:259-69.
61. Miller E. Testing the Addition of an Anti-cancer Drug, Adavosertib, to Radiation Therapy for Patients With Incurable Esophageal and Gastroesophageal Junction Cancers. Clinicaltrials.gov. NCT04460937.
62. Cheng J. Neoadjuvant CCRT With/Without Bevacizumab for Locally Advanced ESCC. Clinicaltrials.gov [Internet]. NCT02812641. Available online: https://uhn.idm.oclc.org/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=cctr&AN=CN-01559334 http://nt2yt7px7u.search.serialssolutions.com/?sid=OVID:Cochrane+Central+Register+of+Controlled+Trials&genre=article&id=pmid:822445

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63. Lin S. Ganetespib in Combination With Paclitaxel, Carboplatin, and Radiation Therapy in Treating Patients With Stage II-III Esophageal Cancer. Clinicaltrials.gov [Internet]. NCT02389751. Available online: https://clinicaltrials.gov/ct2/show/NCT02389751?term=hsp90+inhibitor&cond=Cancer&draw=12&rank=48

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