Review Article

Perioperative therapy landscape for locally advanced, resectable esophageal cancer: an updated literature review

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Background and Objective: The poor oncologic outcomes associated with esophageal cancer (EC) are primarily due to its presentation at an advanced stage and patient comorbidities. While multimodal therapy improves overall outcomes, there is a lack of uniform practice in terms of perioperative management, partly because this is a rapidly evolving field in a heterogeneous patient population. With numerous recent studies incorporating precision medicine with radiographic, pathologic, and genomic biomarkers and with emerging trials using targeted therapies, it is necessary for providers who care for these patients to be familiar with the current and evolving treatment standards to optimize patient outcomes. The objective of this paper is to perform an updated review of the main historical and recently emerging studies that impact the perioperative management of patients with locally advanced, upfront-resectable EC.

Methods: We mined and reviewed PubMed and American Society of Clinical Oncology databases for pivotal works shaping the current perioperative treatment landscape in locally advanced EC.

Key Content and Findings: EC are a vastly heterogeneous disease, and treatment options vary based on tumor anatomic location, histology, and patient comorbidities. Perioperative chemotherapy (CTX), chemoradiation (CRT), and, recently, immunotherapy have improved survival in patients with locally advanced disease. However, optimizing sequencing, de-escalating therapy, and incorporating novel targeted therapies in the perioperative setting are promising strategies that are under ongoing investigation to improve patient outcomes further.

Conclusions: There is an ongoing need to identify predictive biomarkers and novel treatment strategies to personalize perioperative approaches and optimize outcomes of patients with EC.

Keywords: Esophageal cancer; perioperative chemotherapy; chemoradiation; immunotherapy

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Introduction

Esophageal cancer (EC) is the seventh most diagnosed cancer and the sixth most common cause of cancer-related death worldwide (1). In the United States (US), it accounts for 1.0% of all new cancer cases and 2.7% of all cancer-related deaths (2). Unfortunately, only about 51% of ECs are diagnosed early enough to be eligible for curative-intent surgery. Despite modern therapies, localized disease is associated with a 5-year overall survival (OS) rate of 47% and locally advanced disease, 26%. This less-than-ideal OS suggests a high rate of relapse (2).

Surgical and perioperative approaches vary based on initial TNM staging, tumor location, histology [adenocarcinoma (AC) *vs.* squamous cell carcinoma (SCC)], and surgical candidacy (3). For select early-stage, superficial tumors without lymph node (LN) metastases, an endoscopic resection, with or without ablation, is an acceptable option with curative intent (3). However, as the depth of invasion increases, specifically in the submucosa and beyond, and especially if there is LN involvement, the disease becomes locally advanced, whereby an esophagectomy with regional LN dissection and perioperative therapy become critical to optimize outcomes.

Landmark studies have confirmed survival advantages by adding perioperative therapies, such as chemotherapy (CTX) and chemoradiation (CRT), to surgery (4,5). Recent shifts in treatment paradigms are being implemented where non-surgical approaches are increasingly adopted given pathologic response successes with CRT alone with preservation of esophagectomy for recurrence (6,7). In addition, targeted therapies against human epidermal growth factor receptor 2 (HER2) amplifications, microsatellite instability-high (MSI-H) status, programmed death-ligand 1 (PD-L1) expression, and neurotrophic tyrosine receptor kinase gene fusions, as well as tumor mutational burden, are used to improve outcomes in advanced disease, and emerging studies demonstrate some efficacy in the perioperative setting (8-10).

Notably, historical trials leading to the perioperative standard of care (SOC) protocols used today have varied in design and patient populations. They have combined cases of EC, gastroesophageal junction cancers (GEJ), and gastric cancers (GC), and their histologies have varied. We now understand that these tumors are heterogeneous and that treatment response may vary depending on anatomic location, histology, and genomic profiles (11). While significant progress has been made (*Figure 1*), inconsistency remains in the management of EC by oncologists and surgeons alike. As the field evolves, providers must be cognizant of the rationale for perioperative therapies, up-to-date with the available options, and aware of how molecular profiling integrates into decision-making to ensure an optimal upfront treatment strategy. Herein, we perform an updated review of the main historical and recently emerging studies that may impact the perioperative management of patients with locally advanced, upfront-resectable EC (cT2-T4aN0-3M0). We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-27/rc).

Methods

The authors performed a literature review of pivotal studies in the perioperative management of locally advanced EC (*Table 1*).

Neoadjuvant treatment

Neoadjuvant chemotherapy

Many clinical trials have demonstrated survival benefits when neoadjuvant CTX (nCTX) is added to surgery in locally advanced esophageal AC and SCC (*Table 2*). The landmark phase 3 OEO2 study included patients with resectable esophageal AC (66%) and SCC (31%), and surgical outcome and 2-year OS were better with 2 cycles of neoadjuvant cisplatin and 5-fluorouracil (5-FU) (regimen referred to as CF) than with surgery alone: complete resection rates were 60% with CF plus surgery *vs.* 54% with surgery alone (P<0.0001), and 2-year OS was 43% *vs.* 34% [difference 9%; 95% confidence interval (CI): 3–14%] (15). Five-year OS was 23% *vs.* 17.1% [hazard ratio (HR) 0.84; 95% CI: 0.72–0.98; P=0.03], and the benefit was unrelated to tumor histology (16). Notably, RTOG 8911, another large randomized controlled trial (RCT), had reported conflicting results almost a decade earlier: neoadjuvant CF added to surgery did not improve OS (12). Locoregional failures and rates of complete microscopic, margin negative (R0) resections were also not statistically significantly different. However, in subgroup analyses, patients with an R0 resection experienced good long-term survival, irrespective of whether they received nCTX, whereas patients with a microscopic positive margin resection (R1) had poor survival (13). Another study evaluating 2 to

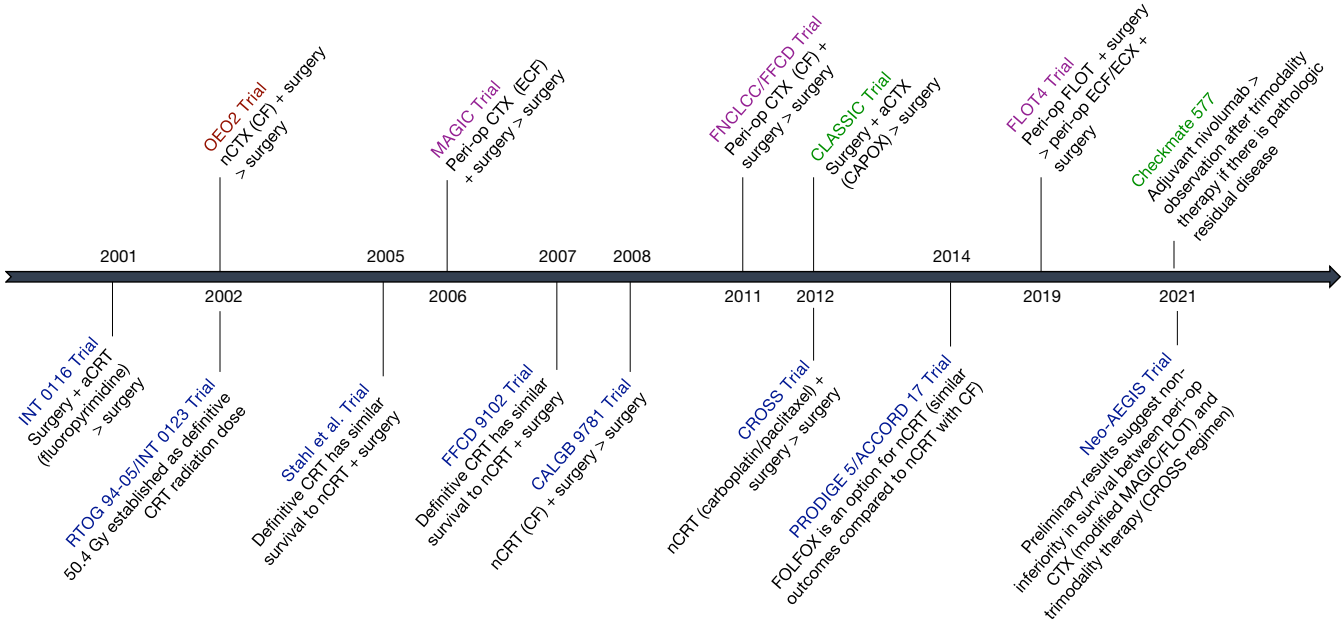

Figure 1 Timeline of landmark prospective perioperative trials in esophageal and gastric cancers. >: superior to; nCTX trials: peri-op CTX trials, adjuvant systemic therapy trials, radiation-based trials. aCRT, adjuvant chemoradiation; aCTX, adjuvant chemotherapy; CAPOX, capecitabine + oxaliplatin; CF, cisplatin + 5-fluorouracil; CRT, chemoradiation; CTX, chemotherapy; ECF, epirubicin + cisplatin + 5-fluorouracil; ECX, epirubicin + cisplatin + capecitabine; FLOT, 5-fluorouracil + leucovorin + oxaliplatin + docetaxel; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; nCRT, neoadjuvant chemoradiation; nCTX, neoadjuvant chemotherapy; peri-op, perioperative.

Table 1 Search strategy table

Items	Specification
Last search date	January 10, 2023
Databases and other sources searched	PubMed, American Society of Clinical Oncology
Search terms used	Esophageal cancer, neoadjuvant, perioperative, chemotherapy, radiation, chemoradiation, surgery, definitive therapy, immunotherapy, targeted therapy, ctDNA, HER2
Timeframe	1990–present
Inclusion/exclusion criteria	Prospective phase 1, 2, 3, observational, retrospective, and meta-analyses studies were included. Studies reported in a non-English language were excluded
Selection process	All authors participated in the literature selection and agreed to prioritize the review of global, practice-changing, and prospective studies and earlier-phase studies evaluating novel approaches

ctDNA, circulating tumor DNA; HER2, human epidermal growth factor receptor 2.

3 cycles of neoadjuvant CF in 96 patients with EC SCC demonstrated no OS benefit (P=0.55), but subgroups with R0 resections and clinical responses to nCTX tended to benefit more (14). While these were negative nCTX studies, their subgroup analyses highlighted the prognostic value of clinical responses to nCTX and R0 resection status. Incomplete resections may offset potential CTX benefits.

Several prospective studies have evaluated nCTX in AC and SCC independently. The Japanese JCOG9204 trial in SCC patients, in which OS was higher with 2 cycles of

Table 2 Major prospective neoadjuvant chemotherapy trials

Trial [year/phase], reference	Tumor location; histology; sample size	Study sites	Treatment groups	R0 resection rate	ypCR	Survival	Summary of findings
RTOG8911 [1998, 2007/3], (12,13)	EC/GEJ; AC/SCC; N=443	United States	CF → surgery; Surgery	63%; 59% (P=0.5137)	NR; NR	mOS 14.9 mo; mOS 16.1 mo (P=0.49) Subgroup analysis in all pts (mOS): R0, 2.2 y; R1, 1.0 y; R2, 0.6 y; unresected, 0.24 y Subgroup analyses in all pts (mOS): CTX responder, 3.0 y; CTX non-responder, 1.1 y; surgery only, 1.3 y	No OS difference between arms R0 resection (P<0.0001) had improved OS over R1, R2, and unresected status (P<0.0001) nCTX responders (P<0.0001) had improved OS over non-responders
Anacona *et al.* [2001], (14)	EC; SCC; N=94	Italy	CF → surgery; surgery	79%; 74% (P reported as "not significant")	12.8%; NR	5-y OS: 22%; 5-y OS: 34% (P=0.55) Subgroup analyses (5-y OS): nCTX responders, 60%; nCTX non-responders, 12% (P=0.0002 compared to CTX responder); R0 resection without CTX, 26% (P=0.01 compared to CTX responder); ypCR, 100%; partial response, 44% (P=0.05 compared to ypCR); CTX non-responder, 19%; R0 resection without CTX, 26% (P=0.01 compared to ypCR)	No OS difference between arms nCTX responders and ypCR predicted improved OS
OEO2 [2002, 2009/3], (15,16)	EC/GEJ; AC/SCC; N=871	United Kingdom	CF → surgery; surgery	60%; 54% (P<0.0001)	NR; NR	5-y OS 23%; 5-y OS 17.1% (P=0.03)	Improved R0 rate and OS with neoadjuvant CF Supported neoadjuvant CF as a SOC
OEO5 [2017/3], (17)	EC/GEJ; AC; N=897	United Kingdom	Epirubicin-cisplatin-capecitabine → surgery; CF → surgery	66%; 59%	7%; 1%	3-y OS 42%; 3-y OS 39% (P=0.19)	No OS improvement with triplet nCTX over CF
Boonstra J *et al.* [2011], (18)	EC; SCC; N=169	The Netherlands	Cisplatin-etoposide → surgery; surgery	71%; 57% (P=0.03)	7%; NR	5-y OS 26%; 5-y OS 17% (P=0.03)	Improved R0 rate and OS with nCTX over surgery alone
JCOG 9907 [2012/3], (19)	EC; SCC; N=330	Japan	CF → surgery; surgery → CF	96%; 91% (P=0.04)	NR; NR	5-y OS 55%; 5-y OS 43% (P=0.04)	Supported neoadjuvant CF over adjuvant CF
JCOG 1109 [2022/3], (20)	EC; SCC; N=601	Japan	DCF → surgery; CF → surgery; nCRT (CF) → surgery	85.6%; 84.4%; 87.5%	19.8%; 2.1%; 38.5%	3-y OS 72.1%; 3-y OS 62.6%; 3-y OS 68.3%	OS improved with neoadjuvant DCF over CF (HR 0.68; 95% CI: 0.50–0.92) but not statistically improved when comparing nCRT to CF (HR 0.84; 95% CI: 0.63–1.12)

AC, adenocarcinoma; CF, cisplatin + 5-fluorouracil; CI, confidence interval; CTX, chemotherapy; DCF, docetaxel + cisplatin + 5-fluorouracil; EC, esophageal cancer; GEJ, gastroesophageal junction; HR, hazard ratio; mo, months; mOS, median overall survival; nCRT, neoadjuvant chemoradiation; nCTX, neoadjuvant chemotherapy; NR, not reported; OS, overall survival; pts, patients; R0, margin-free resection; R1, microscopic margin positive resection; R2, gross residual disease resection; SCC, squamous cell carcinoma; SOC, standard of care; y, years; ypCR, pathologic complete response.

neoadjuvant CF than with upfront surgery and 2 cycles of adjuvant CF, led to wide acceptance of the neoadjuvant CF approach in Eastern countries where SCC is more prevalent (19). In 2022, the JCOG1109 phase 3 study demonstrated improved OS when nCTX was intensified from 2 cycles of CF to 3 cycles of 5-FU, cisplatin, and docetaxel (DCF) (20). Although these studies support an nCTX approach in SCC, the general preference in Western countries is to use nCRT over nCTX for locally advanced SCC (3,5), which will be discussed later in this review.

In AC, the phase 3 EORTC 40954 study of 144 GEJ (53%)/GC (47%) failed to demonstrate patient survival benefit with 2 cycles of neoadjuvant CF over subtotal gastrectomy with D1 or D2 lymphadenectomy alone. However, the interpretation of this study for EC and GEJ tumors is limited by low statistical power and omission of EC patients undergoing esophagectomy (21). nCTX did, however, improve R0 resection rates (81.9% *vs.* 66.7%, P=0.036). The OEO5 trial, which accrued patients with resectable EC/GEJ AC, attempted to expand on the positive results of OEO2. However, the study failed to demonstrate OS benefit with 4 cycles of intensified CTX with epirubicin, cisplatin, and capecitabine (ECX) over 2 cycles of standard CF (17). In thoracic EC/GEJ AC, CF is still the recommended nCTX regimen (3).

In summary, nCTX is tolerable and may improve R0 resection rates and OS. Survival benefit is mainly seen in patients undergoing high-quality R0 resections. In the US, neoadjuvant CF in thoracic EC/GEJ AC is the recommended regimen. Nonetheless, as discussed later in this review, other approaches are often practiced, such as nCRT or perioperative CTX for AC and nCRT for SCC (3).

Neoadjuvant plus adjuvant chemotherapy

The MAGIC phase 3 study published in 2006 established perioperative CTX as another SOC approach in AC (4). The study randomized 503 patients with GC (372 patients; approx. 74%), lower EC (73; 14.5%), and GEJ AC (58; 11.5%) to surgery with or without perioperative epirubicin, cisplatin, and 5-FU (ECF). Perioperative ECF improved progression-free survival (PFS) (HR 0.66; 95% CI: 0.53–0.81; P<0.001) and OS (HR 0.75; 95% CI: 0.60–0.93; P=0.009). The 5-year OS was higher with perioperative CTX (36%) than without (23%). Similar survival benefits and improved curative resection rates were reported in the FNLCC/Francophone Federation of Digestive Cancer Research (FFCD) phase 3 trial, which compared perioperative CF to surgery alone (*Table 3*) (22).

However, in 2019, the landmark FLOT4 phase 2/3 trial led to the current SOC perioperative CTX regimen for AC: 4 cycles of neoadjuvant and adjuvant 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) (23). The FLOT regimen was compared with the MAGIC regimen in 716 patients with non-metastatic, resectable GC (44%) and GEJ cancer [Siewert I (23%) and II or III (33%)], the clinical stages of which were cT2 or higher with or without positive nodes (23). The FLOT regimen resulted in improved PFS (30 *vs.* 18 months; HR 0.75; 95% CI: 0.62–0.91; P=0.004), OS (50 *vs.* 35 months; HR 0.77; 95% CI: 0.63–0.94; P=0.012), and R0 resection rates (85% *vs.* 78%; P=0.0162). The FLOT group also had more downstaging with improved ypT1 (49% *vs.* 41%; P=0.025) and ypN0 rates (49% *vs.* 41%; P=0.025). Consequently, FLOT became a current SOC perioperative approach for clinically staged T2+/any N GEJ/GC AC (25).

Although limited in number, studies in SCC have demonstrated superior OS and recurrence-free survival in patients with EC when perioperative CTX is used over nCTX alone (3,24).

Neoadjuvant chemoradiation

Many trials also elucidated the benefits of neoadjuvant CRT (nCRT) (*Table 4*). The landmark CROSS trial, published in 2012, established the contemporary SOC nCRT approach and set the current benchmarks for 5-year survival and pathologic complete response (ypCR) rates (5). Three hundred and sixty-eight patients with EC (73%)/GEJ (24%)/unknown (3%) (75% AC, 23% SCC, 2% other) were randomized to 5 cycles of weekly paclitaxel plus carboplatin with concurrent 41.4 Gy radiation (23 fractions of 1.8 Gy) followed by surgery 4–6 weeks after completion *vs.* surgery alone. nCRT resulted in higher R0 resection (92% *vs.* 69%; P<0.001) and no notable differences in postoperative complications. The median OS was 49.4 *vs.* 24.0 months, and 5-year OS rates were 47% *vs.* 34% (HR 0.657; 95% CI: 0.495–0.871; P=0.003), favoring nCRT. At a median follow-up time of 84.1 months, further analysis demonstrated that the median OS benefit persisted, which was greater with nCRT than with surgery alone (48.6 *vs.* 24.0 months; HR 0.48, 95% CI: 0.53–0.88; P=0.003) (31). OS benefits were also sustained in AC (10-year OS 36% with nCRT *vs.* 26% with surgery alone) and notably to a greater extent in SCC (10-year OS 46% with nCRT *vs.* 23% with surgery alone) subgroups.

Table 3 Major prospective perioperative chemotherapy trials

Trial [year/phase], reference	Tumor location; histology; sample size	Study sites	Treatment groups	R0 resection rate	Pathologic responses	Survival	Summary of findings
FFCD/ FNCLCC [2011/3], (22)	EC/GEJ/GC; AC; N=224	France	nCTX (CF) → surgery → CTX (CF); surgery alone	84%; 73% (P=0.04)	ypCR NR Similar ypT staging between arms (P=0.17) with trends for decreased ypN+ metastases after nCTX (67% *vs.* 80%, P=0.054)	5-y OS 38%; 5-y OS 24% (P=0.02)	Perioperative CF provides better R0 resection and survival rates than surgery alone
MAGIC [2006/3], (4)	EC/GEJ/GC; AC; N=503	United Kingdom	nCTX (ECF) → surgery → CTX (ECF); surgery alone	Curative surgery rate 69.3%; curative surgery rate 66.4%; R0 rates NR	0%; there was a greater proportion of less-advanced pT1/2 status (51.7% *vs.* 36.8%, P=0.002) and pN0/1 (84.4% *vs.* 70.5%, P=0.01) with ECF	5-y OS 36%; 5-y OS 23% (P=0.009)	Perioperative ECF downstages tumors and provides better patient survival than surgery alone
FLOT4 [2019/3], (23)	GEJ/GC; AC; N=716	Germany	nCTX (FLOT) → surgery → CTX (FLOT); nCTX (ECF) → surgery → CTX (ECF)	85%; 78% (P=0.0162)	More ypT and N downstaging with FLOT	mOS 50 mo; mOS 35 mo (P=0.012)	FLOT rather than ECF was established as the new SOC perioperative regimen
Zhao *et al.* [2015/3], (24)	EC; SCC; N=346	China's Mainland	nCTX (PCF) → surgery → CTX (PCF); nCTX (PCF) → surgery	82.5% of all patients collectively undergoing surgery	24.1% of all patients collectively who underwent surgery after nCTX	5-y OS 38%; 5-y OS 22% (P<0.001)	In resectable EC SCC cases, perioperative CTX leads to better OS than nCTX only

AC, adenocarcinoma; CF, cisplatin + 5-fluorouracil; CTX, chemotherapy; EC, esophageal cancer; ECF, epirubicin + cisplatin + 5-fluorouracil; FLOT, 5-fluorouracil + leucovorin + oxaliplatin + docetaxel; GC, gastric cancer; GEJ, gastroesophageal junction; mo, months; mOS, median overall survival; nCTX, neoadjuvant chemotherapy; NR, not reported; OS, overall survival; PCF, paclitaxel + cisplatin + 5-fluorouracil; R0, margin-free resection; SCC, squamous cell carcinoma; SOC, standard of care; y, years; yp, pathologic staging (post-neoadjuvant); ypCR, pathologic complete response.

The CROSS arm demonstrated 29% ypCR rates. ypCR rates were significantly higher in SCC (49%) than in AC (23%), P=0.008 (5). Subsequent analysis of data from 422 patients from the CROSS and preceding phase 2 trials revealed that locoregional recurrence was lower for the nCRT arm (14%) than for the surgery-alone arm (34%), P<0.001, and the occurrence of peritoneal carcinomatosis (4% *vs.* 14%; P<0.001) and reduced distant metastases (29% *vs.* 35%; P=0.025) followed the same trend. The overall recurrence rates were also lower (35%) for nCRT than for surgery alone (58%) (32). Notably, patients who achieved a ypCR had lower recurrence rates (17%) than those with residual pathologic disease (42%). This study, among others, supported ypCR as a prognostic biomarker for survival and relapse (33-35).

nCRT with concurrent FOLFOX (5-FU, leucovorin, oxaliplatin) has also achieved a 28% ypCR rate and a 3-year OS rate of 45% in patients with stage 2/3 EC AC (28). FOLFOX and the CROSS regimens are being compared in the ongoing phase 2 PROTECT-1402 study (NCT02359968). The ypCR rates from nCRT trials are generally higher than those historically reported (2–20%) with nCTX alone, especially in SCC (19,36,37). Therefore, in addition to the option of perioperative CTX, the CROSS regimen or nCRT with FOLFOX is recommended for locally advanced EC/GEJ AC and

Table 4 Major prospective neoadjuvant and definitive chemoradiation trials

Trial [year/phase], reference	Tumor location; histology; sample size	Study sites	Treatment groups	R0 resection rate	ypCR	Survival	Summary of findings
NEOCRTEC5010 [2018/3], (26)	EC; SCC; N=451	China's Mainland	nCRT (cisplatin-vinorelbine) → surgery; surgery	98.4%; 91.2% (P=0.002)	43.20%	mOS 100.1 mo; mOS 66.5 mo (P=0.025)	nCRT improves OS over surgery alone
CALGB 9781 [2008/3], (27)	EC/GEJ; AC/SCC; N=56	United States	nCRT (CF) → surgery; surgery	NR	ypCR in 40% of evaluable pts	5-y OS 39%; 5-y OS 16% (P=0.002)	nCRT provided better PFS and OS than surgery alone
CROSS [2012/3], (5)	EC/GEJ; AC/SCC; N=363	The Netherlands	nCRT (carboplatin-paclitaxel) → surgery; surgery	92%; 69% (P<0.001)	29% [28% in AC and 49% in SCC (P=0.008)]	mOS 49.4 mo; mOS 24.0 mo (P=0.003) SCC had greater OS benefit (HR 0.453) than AC (HR 0.732)	nCRT with carboplatin-paclitaxel is an nCRT SOC regimen
Leichman *et al.* [2011/2], (28)	EC/GEJ; AC; N=93	United States	nCRT (5-FU-oxaliplatin)	67.7%	28%	3-y OS 45.1%	nCRT with 5-FU and oxaliplatin is an active regimen
PRODIGE5/ ACCORD 17 [2014/2, 3], (29)	EC; AC/SCC; N=134	France	Definitive nCRT (FOLFOX); definitive nCRT (CF)	Not applicable	Clinical CR 44%; clinical CR 43% ypCR not applicable	mOS 20.2 mo; mOS 17.5 mo (P=0.70)	Similar grade 3/4 toxicities FOLFOX can be considered as an alternative CTX backbone in nCRT to CF
Stahl *et al.* [2005/3], (30)	EC; SCC; N=172	Germany	nCTX (CF-etoposide) → nCRT (cisplatin-etoposide) → surgery; definitive nCTX → nCRT	Not applicable	ypCR rate in all patients who underwent surgery was 35%	2-y OS 39.9%; 2-y local PFS 64.3%; 2-y OS 35.4% (P=0.007); 2-y local PFS 40.7% (P=0.003)	Less treatment-related mortality 12.8% *vs.* 3.5% (P=0.03), favoring the non-surgery arm Upfront surgery after CRT improves local control but does not improve survival
FFCD 9102 [2007/3], (7)	EC; AC/SCC; N=259	France	All received CRT (CF). If respond, then randomize to surgery; definitive CRT (CF)	–	–	2-y OS 34%; 2-y local control 66.4%; 2-y OS 40% (P=0.44); 2-y local control 57% (no P value)	In pts who respond to nCRT, no survival benefit difference was seen between surgery and continuation of definitive CRT

5-FU, 5-fluorouracil; AC, adenocarcinoma; CF, cisplatin + 5-fluorouracil; CRT, chemoradiation; CTX, chemotherapy; EC, esophageal cancer; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; GEJ, gastroesophageal junction; HR, hazard ratio; mo, months; mOS, median overall survival; nCRT; nCTX; NR, not reported; OS, overall survival; PFS, progression-free survival; R0, margin-free resection; SCC, squamous cell carcinoma; SOC, standard of care; y, years; ypCR, pathologic complete response.

particularly for SCC (3).

Chemoradiation versus chemotherapy

Only a few studies have directly compared nCTX with nCRT; however, these studies have yielded controversial results (36-41). Phase 2 studies such as that by Burmeister *et al.* (albeit underpowered and closed prematurely) and the NeoRes study have demonstrated higher ypCR rates with nCRT (28–31%) than with nCTX (8–9%). Improved R0 resection rates but no significantly improved survival rates have been observed, except in subgroups with ypCR (36,37). Meta-analysis of 5,496 patients from 31 RCTs reported better OS with nCRT than with nCTX, surgery alone, or neoadjuvant radiation, albeit at the expense of an increased risk of postoperative mortality (40). In addition, a systematic review of 5 RCTs, collectively accruing 709 patients, reported that nCRT in AC/SCC produced better R0 and ypCR rates than nCTX; however, nCRT improved 3-year OS in SCC only (41).

In SCC, an interim analysis from a recent Chinese RCT demonstrated improved pathological response rates with nCRT over nCTX (using a CF backbone) with no survival benefit (42). However, 3-year OS results (the primary endpoint) are pending. Similar patterns of improved pathologic responses but no survival benefit were noted in the JCOG 1109 phase 3 trial of nCTX *vs.* nCRT using CF in SCC (20). In AC, the phase 3 German POET study compared nCTX to nCRT using CF backbones in GEJ tumors, but the nCRT arm also received induction CF before nCRT. The nCRT arm had improved pathological outcomes (ypCR 15.6% *vs.* 2%; P=0.03) but no statistically significant OS benefit (46.7% *vs.* 26.1%; P=0.07), although this study was underpowered (38).

In the US, for AC, both perioperative FLOT and CROSS are SOC options for EC/GEJ AC. Although each approach achieved similar 5-year OS rates (45% and 47%, respectively), their respective trials varied in design, especially as FLOT4 included only gastric AC (44%) and GEJ AC (56%) and CROSS included both SCC and AC [mostly esophageal (73%) and GEJ (24%); no gastric]. The European NeoAegis phase 3 study was the first RCT to compare CROSS with perioperative CTX (either the MAGIC regimen or FLOT after its approval in 2019) in 377 patients with locally advanced EC/GEJ AC (43). Although CROSS resulted in improved R0 resection rates and pathologic outcomes, the estimated 3-year OS was not statistically significantly different after a median follow-up of 34.2 months. However, any strict interpretation of this study is limited because of the fact that 85% of patients in the perioperative CTX arm were treated with the sub-standard MAGIC regimen, the adjuvant SOC after CROSS has since changed, and the fact that patterns of recurrence and quality of life data are pending.

Whether nCRT or perioperative CTX should be used in lower EC/GEJ AC is still under debate. Ongoing phase 3 studies, such as the ESOPEC trial—which uses current protocols—will hopefully answer this question (NCT02509286). Providers often consider nCRT in EC, bulky tumors, and GEJ (Siewert I/II), whereas FLOT is considered in GEC (Siewert III) and GC, although these approaches may vary by institution. In SCC, nCRT remains the preferred approach in the US. This standard is based on CROSS and other trials demonstrating improved downstaging and ypCR rates with nCRT. In fact, with high ypCR rates, many SCC patients may be cured with CRT alone, and this non-surgical approach is increasingly adopted (3).

Sequential chemotherapy and chemoradiation

Although nCRT yields better survival rates and local control than surgery alone, it has failed to significantly improve distant metastatic recurrence rates, which are commonly around 27–28% (44). The idea of sequentially delivering nCTX and nCRT is theoretically attractive as it may increase systemic therapy compliance, induce earlier clinical responses in symptomatic patients, and address micro-metastatic disease earlier. Only a few studies have tested nCRT with and without induction CTX but have failed to provide robust data to support a ypCR or OS advantage with induction CTX (45,46).

Ajani *et al.* randomized 162 EC/GEJ AC/SCC patients in a phase 2 trial to nCRT (50.4 Gy with FOLFOX) with and without 8 weeks of induction FOLFOX and found no improvement in the primary endpoint of ypCR rates and no OS benefit (45). An Alliance phase 2 trial randomized 55 EC/GEJ AC patients to nCRT (50.4 Gy with FOLFOX) with and without induction docetaxel, oxaliplatin, and capecitabine. The study demonstrated futility and was terminated when its primary endpoint of ypCR was not met (28.6% *vs.* 40.7%, P=0.34). However, long-term follow-up demonstrated a more prolonged median OS with induction CTX, especially in well-to-moderately differentiated tumors (46). Although no RCT has demonstrated an adequately powered survival benefit with an induction

CTX approach, emerging clinical response data following induction therapy to optimize neoadjuvant regimens are promising.

Positron emission tomography (PET)-guided neoadjuvant therapy

Studies suggest that patients who lack early radiographic or PET-metabolic tumor responses after a course of nCTX have poor prognoses compared to their counterparts and may not be benefiting from a given therapy (13,47,48). Metabolic non-responders have worse survival, higher recurrence rates, and lower ypCR rates. The concept of switching nCTX according to early PET-response evaluation was evaluated in the recent CALGB 80803 trial (49). EC/GEJ AC patients with PET-avid locally advanced disease were randomized to induction FOLFOX versus induction carboplatin and paclitaxel. After a course of induction CTX, if patients in either arm had a response by PET [≥35% decrease in standardized uptake value (SUV)], they were to continue with the same CTX backbone with concurrent radiation added prior to surgery. If patients were non-responders, they were switched over to the other CTX regimen with radiation.

After a median follow-up time of 5.2 years, there was no statistically significant difference in OS between responders and non-responders (HR 1.34; 95% CI: 0.94–1.92), suggesting that a switch in therapy in non-responders improved their survival. ypCR rates in non-responders also improved. While FOLFOX responders who continued FOLFOX with CRT had the best 5-year OS of 53%, the study was not powered to compare the induction CTX regimens head-to-head. Overall, this trial supported utilizing a PET-adapted approach in optimizing an individual's neoadjuvant regimen. This approach could also potentially be applied when testing novel therapies in this setting.

Role of targeted therapies

With several Food and Drug Administration (FDA) approvals for targeted therapy in the advanced setting, there is growing interest in studying these therapies in the perioperative setting. Although targeted therapies like anti-epidermal growth factor receptor antibodies and anti-vascular endothelial growth factor antibodies have failed to improve outcomes, testing of alternative systemic agents continues (50,51).

Amplifications of HER2, a receptor tyrosine kinase in the epidermal growth factor family, drive oncogenesis in about 10–40% of EC (8,52). Trastuzumab, an anti-HER2 monoclonal antibody, improved OS when added to front-line CTX in advanced/metastatic disease and is now SOC in patients with HER2-amplified GEJ/GC (53). Unfortunately, a phase 3 trial failed to demonstrate that adding trastuzumab to trimodal therapy in HER2-amplified disease improved ypCR rates (27% with trastuzumab *vs.* 29% without trastuzumab) and DFS (HR 0.99; 95% CI: 0.71–1.39; P=0.97) (54). However, the single-arm, phase 2 TRAP study demonstrated promising results with nCRT, trastuzumab, and pertuzumab (another anti-HER2 monoclonal antibody), with a 100% R0 resection rate, 34% ypCR, and 71% 3-year OS rates (8).

The PETRARCA randomized phase 2 study compared FLOT to FLOT with perioperative trastuzumab and pertuzumab in HER2-amplified GEJ/GC AC. The trial demonstrated similar post-surgical R0 resection rates and mortality but improved ypCR (35% *vs.* 12%; P=0.02; primary endpoint) and tumor downstaging in favor of the HER2-targeting arm (9). In a highly HER2 amplified subgroup [HER2 3+ immunohistochemistry (IHC)], ypCR rates were strikingly higher in the experimental arm (41%) than in the FLOT arm (12%) (P=0.066) (55). Unfortunately, the study closed prematurely and did not proceed to the phase 3 portion after negative results from the JACOB trial, which used trastuzumab, pertuzumab, and CTX to treat patients with advanced disease (56). Nonetheless, the median DFS in the PETRARCA study was greater (not reached) in the experimental arm than in the control arm (26 months; P=0.14). The median OS was not reached in both arms at a median 22-month follow-up. The results of the ongoing phase 2 EORTC 1203 trial are pending. When released, it is hoped that they will help ascertain the benefits of adding either trastuzumab alone or trastuzumab plus pertuzumab to perioperative CTX compared to CTX alone (57). Until there is robust RCT survival data supporting the incorporation of HER2-targeting agents into treatment regimens for HER2-amplified tumors, nCRT and nCTX will likely remain the perioperative SOC.

More recently, immunotherapy with immune checkpoint inhibitor (ICI) monoclonal antibodies has been studied in the neoadjuvant setting, given its successes and FDA approvals in advanced-stage disease (58,59). ICIs target and inhibit tumor and immune cell-surface markers; for example, programmed death-1 (PD-1), PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which are often implicated in tumor immune evasion.

A phase 2 trial demonstrated 30% ypCR rates when atezolizumab (anti-PD-L1) was added to CROSS. However, when outcomes were compared to a propensity score-matched nCRT cohort, there was no significant difference in response or survival (60). Exploratory tumor-biopsy and PD-L1 expression biomarker analyses failed to identify response or survival differences, although there were trends toward improved outcomes with higher PD-L1 expression. Higher baseline tumor type II interferon gene signatures were linked with tumor response. In contrast, on-treatment biopsies enriched with cytotoxic lymphocytes and genes associated with T-cell exhaustion were linked to non-response.

A US phase 2 trial treated locally advanced EC/GEJ AC patients with nCRT combined with pembrolizumab (PD-1 inhibitor) and adjuvant pembrolizumab (61). The primary endpoint of major pathologic response (MPR) (defined as ypCR or near-ypCR) in 31 evaluable patients was striking at 50% and was much higher than historical controls (around 30%). MPR rates were higher in EC than GEJ (73.3% *vs.* 33.3%; P=–0.02) and predicted improved DFS (1-year DFS 100% *vs.* 31.8% in non-MPR patients; P=0.002). Correlative tissue analysis suggested that tumor microenvironment immune signatures varied by tumor location (EC *vs.* GEJ) and correlated with response. For example, responders were enriched with $CD8^+$ T cells and monocytes, whereas poor responders were enriched with dendritic cells and activated B-cells.

Single-arm trials have demonstrated promising ypCR rates (33.3%) for non-radiation regimens when combining nCTX with PD-1 inhibitors in EC (62). The DANTE phase 2 study randomized patients with GEJ/GC AC to perioperative FLOT with and without atezolizumab. Interim results recently published showed similar rates of R0 resection but higher rates of pathologic tumor regression, especially in patients with tumors with higher PD-L1 expression (63). A recent meta-analysis of phase 2 non-randomized trials using neoadjuvant ICI either alone or in combination with other therapies in over 800 resectable EC patients reported pooled ypCR rates of 31.4% [with higher rates in SCC (32.4%) compared to AC (25.2%)] and high rates of R0 resections (98.6%) (57). Collectively, these data demonstrate promising early results and potential predictive biomarkers which require further study. More extensive confirmatory studies with longer follow-ups demonstrating survival advantages may be needed before ICIs are incorporated as SOC in neoadjuvant regimens, and there are many ongoing trials (*Table 5*).

MSI-H/deficient mismatch repair status (dMMR) is a well-established predictive biomarker associated with improved ICI efficacy across many tumor types, partly attributed to resultant hypermutated tumors, higher neoantigen loads, and enhanced tumor immunogenicity (64). However, this biomarker is not always checked in early-stage EC, and CRT/CTX remains the SOC regardless of microsatellite status. In 2022, a phase 2 study evaluating combined nivolumab and ipilimumab (anti-CTLA4) without nCTX/CRT and postoperative nivolumab in MSI-H/dMMR GEJ/GC patients revealed 100% R0 resection rates and a remarkable 59% ypCR rate, with 94% of patients remaining event-free at a 12-month median follow-up (10). More recently, in 2023, the phase 2 INFINITY trial using neoadjuvant durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA4) resulted in 60% ypCR and 80% major-complete pathologic response rates (65). Although longer follow-up is needed, ICIs alone will probably become a treatment of choice in the MSI-H/dMMR tumor subset (66).

Several ongoing trials are assessing the role of immunotherapy in the perioperative setting, with a potential shift in the treatment paradigm in the coming years (*Table 5*). Currently, molecular profiling to guide targeted therapy is primarily reserved for patients with advanced disease. However, with expanding commercialized tissue/plasma next-generation sequencing assays and targeted perioperative clinical trials, its role may become increasingly relevant in earlier disease stages.

Definitive chemoradiation

The idea of forgoing surgery after CRT has been evaluated over decades, particularly in SCC. Esophageal SCC tends to be more radiosensitive and develops higher in the esophagus, where surgery may be morbid and challenging (*Table 4*). Two major RCTs have compared definitive CRT with nCRT and surgery. Stahl *et al.* randomized 172 upper and mid-third T3-4N0-1 SCC patients to induction CTX followed by CRT (40 Gy) and surgery or definitive induction CTX followed by CRT (65 Gy). The investigators found that pursuing surgery improved local control but resulted in higher post-treatment mortality without OS improvement (30). Similar findings were reported by the FFCD 9102 study, which mainly included SCC patients (89%) (7). A multicenter, retrospective study of 616 patients also reported no DFS or OS difference between trimodal therapy and definitive CRT with salvage surgery in the event of persistent or recurrent resectable

Table 5 Select ongoing trials utilizing immune checkpoint inhibitors in perioperative management

Trial [phase]	Target population	Intervention	Primary endpoint	Study start	Estimated completion	Study sites
Chemotherapy-based neoadjuvant treatment						
KEYNOTE-585 [3], NCT03221426	Resectable/untreated GEJ/GC AC	Peri-op CTX (CF/cisplatin-capecitabine/FLOT) + pembrolizumab	ypCR, EFS, OS	2017	2024	Global
MATTERHORN [3], NCT04592913	Resectable/untreated GEJ/GC AC	Peri-op FLOT + durvalumab	EFS	2020	2025	Global
HCHTOG1909 [3], NCT04280822	Resectable/untreated EC SCC	nCTX (cisplatin-paclitaxel) + toripalimab (anti-PD-1) and adjuvant toripalimab	EFS	2020	2028	China's Mainland
INFINITY [2], NCT04817826	Resectable MSI-H/dMMR, EBV negative GEJ/GC	Neoadjuvant tremelimumab-durvalumab → surgery	ypCR and negative ctDNA status	2021	2025	Italy
IMAGINE [2], NCT04062656	Resectable/untreated GEJ/GC AC	Peri-op nivolumab *vs.* peri-op nivolumab +/– relatlimab (anti-LAG3) + CTX stratified by early response evaluation	ypCR	2019	2025	Germany
ICONIC [2], NCT03399071	Resectable/untreated EC/GEJ/GC AC	Peri-op FLOT + avelumab	ypCR	2017	2025	United Kingdom
PANDA [2], NCT03448835	Resectable/untreated GEJ/GC AC	Neoadjuvant atezolizumab-capecitabine-oxaliplatin-docetaxel	Adverse events	2018	2022	The Netherlands
DANTE [2], NCT03421288	Resectable/untreated GEJ/GC AC	Peri-op FLOT + atezolizumab	DFS/PFS	2018	2025	Germany, Switzerland
Immunotherapy-only approach in MSI-H/dMMR subgroup						
NEONIPIGA [2], NCT04006262	Resectable/untreated T2-T4NxM0 MSI-H/dMMR GEJ/GC AC	Neoadjuvant nivolumab-ipilimumab → surgery → adjuvant nivolumab	ypCR	2019	2024	France
IMHOTEP [2], NCT04795661	Resectable MSI-H/dMMR EC/GEJ/GC or EBV-positive GC	Neoadjuvant pembrolizumab → surgery	ypCR	2021	2026	France
Chemoradiation-based neoadjuvant treatment						
KEYNOTE-975 [3], NCT04210115	Untreated EC/GEJ AC and SCC suitable for definitive CRT	Definitive CRT (CF/FOLFOX) + pembrolizumab	OS and EFS	2020	2026	Global
ECOG-ACRIN 2174 [2/3], NCT03604991	Resectable/untreated EC/GEJ AC	Neoadjuvant CRT (carboplatin-paclitaxel +/– nivolumab) → adjuvant nivolumab +/– ipilimumab	neoadjuvant: ypCR; adjuvant: DFS	2019	2023	United States
RATIONALE 311 [3], NCT03957590	Unresectable EC SCC suitable for definitive CRT (or unwilling to undergo surgery)	Definitive CRT +/– tislelizumab	PFS	2019	2023	China's Mainland

Table 5 (*continued*)

Table 5 (*continued*)

Trial [phase]	Target population	Intervention	Primary endpoint	Study start	Estimated completion	Study sites
KUNLUN [3], NCT04550260	Unresectable EC SCC (or unwilling to undergo surgery)	Neoadjuvant CRT +/– durvalumab	PFS	2020	2026	Global
KEYSTONE-002 [3], NCT04807673	Resectable EC SCC	Neoadjuvant pembrolizumab-paclitaxel-cisplatin → surgery → pembrolizumab *vs.* nCRT → surgery	EFS	2021	2028	China's Mainland
NCT04426955 [3]	EC SCC planning definitive CRT	Definitive CRT (cisplatin-paclitaxel) +/– camrelizumab (anti-PD-1)	PFS	2020	2023	China's Mainland
SKYSCRAPER-07 [3], NCT04543617	Unresectable EC SCC (or unwilling to undergo surgery) without progression after definitive CRT	Tiragolumab (anti-TIGIT)-atezolizumab *vs.* placebo-atezolizumab *vs.* double placebo	PFS and OS	2020	2025	Global
Adjuvant treatment						
NCT03443856, VESTIGE [2]	EC/GEJ/GC AC after nCRT and surgery with D2 LND and R0/ypN1-3 or R1	Adjuvant nivolumab + ipilimumab	DFS	2019	2026	Europe
BrUOG413 [2], NCT05480384	Resected HER2-positive EC/GEJ AC after nCRT and surgery with R0 resection but not ypCR	Adjuvant trastuzumab deruxtecan + nivolumab	Safety	Estimated March 2023 (not yet recruiting)	2027	United States

AC, adenocarcinoma; CF, cisplatin + 5-fluorouracil; CRT, chemoradiation; ctDNA, circulating tumor DNA; CTX, chemotherapy; DFS, disease-free survival; dMMR, deficient mismatch repair; EBV, Epstein-Barr virus; EC, esophageal cancer; EFS, event-free survival; FLOT, 5-fluorouracil + leucovorin + oxaliplatin + docetaxel; GC, gastric cancer; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; LAG3, lymphocyte activation gene 3; LND, lymph node dissection; MSI-H, microsatellite instability-high; nCRT, neoadjuvant chemoradiation; nCTX, neoadjuvant chemotherapy; OS, overall survival; PD-1, programmed cell death protein-1; peri-op, perioperative; PFS, progression-free survival; R0, margin-free resection; R1, microscopic margin positive resection; SCC, squamous cell carcinoma; TIGIT, T cell immunoreceptor with Ig and ITIM domains; yp, pathologic staging (post-neoadjuvant); ypCR, pathologic complete response.

disease (67). However, salvage surgery was associated with more anastomotic leaks and surgical site infections. Other prospective studies like RTOG 0246 have demonstrated promising survival rates when using a selective surgical approach in patients with AC/SCC, showing clinical complete responses (cCR) by biopsy and imaging after nCRT (68). Only 20% of patients with cCR required a salvage procedure, and of patients who did not achieve cCR patients, 80% were able to have their tumor resected with minimal morbidity. However, to successfully employ a selective surgical approach, accurate prediction of residual disease is critical.

Our current radiology and biopsy techniques and attempted prediction models using clinical and molecular data are insufficient for predicting residual disease independently (44,69,70). However, the Pre-SANO trial determined that combining modern diagnostics (endoscopy, ultrasound, improved biopsy techniques, and PET scans) was adequate in detecting residual disease (71). These diagnostics are now being used in ongoing, randomized, phase 3 trials (SANO and ESOSTRATE) to evaluate active surveillance *vs.* surgery in patients with cCR prospectively.

Today, definitive CRT, with surgery reserved as a salvage measure, is an acceptable approach for select patients with cCR after nCRT, particularly for SCC patients. Although this approach can be discussed with AC patients who achieve cCR, the lower ypCR rates and fewer data in AC mean that SOC trimodal therapy is often preferred and still considered SOC. A definitive CRT approach is desirable

Table 6 Major prospective adjuvant trials

Trial [year/phase], reference	Tumor location; histology; sample size	Study sites	Treatment groups	DFS/RFS/EFS	OS	Summary of findings
INT 0016 [2001/3], (89)	GEJ/GC; AC; N=275; [note: no neoadjuvant treatment, R0 resections only included, D2 dissection not required (only 10% had D2 resection)]	United States	Surgery alone; surgery → adjuvant CRT (bolus 5-FU, leucovorin, 4.5 Gy)	3-y RFS 31%; 3-y RFS 48% (P<0.001)	3-y OS 41%; 3-y OS 50% (P=0.005)	Only 64% of pts completed adjuvant therapy Adjuvant CRT provides lower relapse rates and better survival than surgery alone in a population with primarily D0/D1 dissections
Lv *et al.* [2010], (90)	EC; SCC; N=238 (note: no neoadjuvant treatment; R0 resections only included)	China's Mainland	nCRT (cisplatin, paclitaxel, 50 Gy) → surgery; surgery → adjuvant CRT; surgery alone	5-y PFS 37.5%; 5-y PFS 37.2%; 5-y PFS 25.9% (P=0.706)	5-y OS 43.5%; 5-y OS 42.3%; 5-y OS 33.8% (P=0.498)	OS (P=0.0389) and PFS (P=0.0203) were better with either nCRT or adjuvant CRT than with surgery alone Adjuvant CRT provides better PFS and OS than surgery alone
Ni *et al.* [2021/3], (91)	EC; SCC; N=172 (note: no neoadjuvant treatment; R0 resections only included)	China's Mainland	Surgery alone; surgery → adjuvant RT (54 Gy); surgery → adjuvant CRT (platinum, paclitaxel, 50.4 Gy RT)	3-y DFS 36.7%; 3-y DFS 50.0%; 3-y DFS 57.3% (P=0.048)	3-y OS 48.0%; 3-y OS 60.8%; 3-y OS 66.5% (P=0.048)	Adjuvant CRT or RT, especially CRT, improves DFS and OS
JCOG 9204 [2003], (92)	EC; SCC; N=242 (note: no neoadjuvant treatment, R0 resections only)	Japan	Surgery alone; surgery → adjuvant CTX (CF)	5-y DFS 45%; 5-y DFS 55% (P=0.037) [note: in subgroup analyses, those with ypN0 did not benefit (P=0.433) while those with ypN1 did benefit (P=0.041)]	5-y OS 52%; 5-y OS 61% (P=0.13)	75% completed adjuvant CTX Adjuvant CTX (CF) is better able to prevent relapse than surgery alone
CLASSIC [2014/3], (93)	GEJ/GC; AC; N=1035; (note: no nCRT/CTX after D2 gastrectomy; the majority were GC)	South Korea, China's Mainland, Taiwan region	Surgery alone; adjuvant CTX (CAPOX)	5-y DFS 53%; 5-y DFS 68% (P<0.0001)	5-y OS 69%; 5-y OS 78%	Adjuvant CTX (CAPOX) improves DFS and OS after upfront D2 gastrectomy
CRITICS [2018/3], (94)	GEJ/GC; AC; N=788; [note: needed at least D1 dissection (5–8% had D2 dissections); the majority were GC]	The Netherlands	nCTX (EC[O]X) → surgery → adjuvant CTX (EC[O]X); nCTX (EC[O]X) → surgery → adjuvant CRT (capecitabine + cisplatin)	5-y EFS 39%; 5-y EFS 38% (P=0.92)	5-y OS 42%; 5-y OS 40% (P=0.90)	After nCTX, adjuvant CRT did not improve survival over adjuvant CTX
CheckMate 577 [2021/3], (66)	EC/GEJ; AC/SCC (note: enrolled after nCRT and surgery with ypT/N+ disease)	Global	Adjuvant nivolumab; placebo	mDFS 22.4 mo; mDFS 11.0 mo (P<0.001)	Pending	mDFS 22.4 *vs.* 11.0 months (HR 0.69; 96.4% CI: 0.56–0.86; P<0.001), favoring adjuvant nivolumab Adjuvant nivolumab should be considered in patients with yp residual disease after trimodal therapy

5-FU, 5-fluorouracil; AC, adenocarcinoma; CAPOX, capecitabine + oxaliplatin; CF, cisplatin + 5-fluorouracil; CI, confidence interval; CRT, chemoradiation; CTX, chemotherapy; DFS, disease-free survival; EC, esophageal cancer; EC(O)X, epirubicin + cisplatin (or oxaliplatin) + capecitabine; EFS, event-free survival; GC, gastric cancer; GEJ, gastroesophageal junction; HR, hazard ratio; mDFS, median disease-free survival; nCRT, neoadjuvant chemoradiation; nCTX, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival; R0, margin-free resection; RFS, recurrence-free survival; RT, radiation therapy; SCC, squamous cell carcinoma; y, years; yp, pathologic staging (post-neoadjuvant).

for poor surgical candidates with comorbidities or patients who decline surgery. Of note, the recommended radiation dose of 50.4 Gy for definitive CRT is higher than that of a standard nCRT regimen (5,72).

Surgical approach

While open esophagectomy has historically been the SOC surgical approach, minimally invasive esophagectomy (MIE) has been increasingly pursued. Compared to an open approach, MIE has demonstrated excellent oncologic outcomes and decreased blood loss, lengths of hospital stays, and perioperative mortality (73-78). Much of these data come from single-institution studies. A multicenter RCT (TIME) comparing the approaches identified lower rates of pulmonary complications (9% *vs.* 29%, P=0.005) and shorter hospital stays (median 11 *vs.* 14 days, P=0.044) in the MIE group with a similar rate of anastomotic leaks (12% *vs.* 7%, P=0.39) (79). A subsequent study focusing on long-term outcomes found no significant differences in 3-year OS (41% *vs.* 43%) and DFS (37% *vs.* 43%) between the open and MIE groups, respectively (80). Large database studies comparing the techniques have also reported shorter hospital stays and similar rates of anastomotic leaks, 30-day mortality, and oncologic survival with MIE (77,81). Recently, the ROBOT trial evaluating robotic-assisted MIE and open esophagectomy reported lower rates of postoperative blood loss, cardiopulmonary complications, and pain scores with the robotic approach (82). Although MIE is technically demanding, multiple studies have demonstrated its safety and feasibility, comparable oncologic outcomes, and association with improved postoperative morbidity.

Adjuvant therapy

Following neoadjuvant chemoradiation

While nCRT emerged as a SOC approach in the US and Western Europe, the benefits of adjuvant CTX (aCTX) in this setting were not well defined. There is an understanding that patients with pathologic residual disease or involved LNs after neoadjuvant therapy are at high risk for poor outcomes. Nevertheless, contemporary studies, such as CROSS, which guide our SOC management today, evaluated all therapies pre-operatively without mandating adjuvant treatment or randomizing patients into adjuvant treatment arms (33-35,83).

Large retrospective studies like a propensity-matched National Cancer Database (NCDB) cohort study that included EC/GEJ AC treated with nCRT before curative-intent surgery suggested better OS with aCTX than mere observation (84). Another similar retrospective, propensity-score-matched NCDB study of EC AC treated with nCRT and R0 resection but only including patients with ypN+ status demonstrated greater OS benefit with aCTX than observation (85). A third NCDB retrospective study, this time including AC (85%) and SCC (15%) regardless of ypT or N status, reported improved OS, especially in ypN+ cases, with aCTX (86). While these studies suggested survival benefits, especially in patients with pathologic residual disease, robust prospective data are lacking, and the optimal CTX regimen is unclear. In addition, it is challenging to administer cytotoxic CTX after a major esophagectomy: less than 50% of patients can tolerate and complete intended adjuvant regimens (4,87). Therefore, many providers previously recommended practicing patient observation regardless of pathologic status after nCRT.

However, in 2021, the Checkmate 577 study changed the treatment paradigm in this space and reduced the clinical relevance of aCTX. The ICI nivolumab (anti-PD-1) was studied in the adjuvant setting after trimodal therapy for EC in the randomized, double-blind, phase 3 trial (66). Patients with at least ypT1 or ypN1 resected AC/SCC were randomly assigned to nivolumab or placebo irrespective of PD-L1 status for up to 1 year. The median DFS doubled in the treatment arm (24.4 *vs.* 11 months; P<0.001) without compromising patient quality of life. All subgroups benefited irrespective of the pathological tumor status, LN involvement, stage at initial diagnosis, location of the tumor, or PD-L1 expression. The FDA approved nivolumab on May 20, 2021, and the current National Comprehensive Cancer Network (NCCN) guidelines recommend up to 1 year of adjuvant nivolumab for SCC and AC patients who received nCRT followed by an R0 resection with pathological residual disease. However, observation until progression is an alternative option (3,88). The role of ICI in definitive CRT is unknown but is currently being evaluated. After trimodal therapy, surveillance is recommended for AC/SCC patients with R0 resections and ypT0N0 status. With an R1 resection, re-resection (for AC) or observation until progression are options, while palliative management is considered for R2 resections per NCCN guidelines (3).

Following neoadjuvant chemotherapy

For those pursuing perioperative CTX, the landmark

studies (such as the MAGIC and FLOT trials) were designed to continue the same CTX regimen post-operatively regardless of whether there were pathologic responses or nodal involvement at the time of surgery. Currently, there are no available trial data to guide switching adjuvant therapies on the basis of pathological or clinical responses, although studies in this space are likely warranted (*Table 6*).

The CRITICS phase 3 trial aimed to determine if GEJ/GC AC patients receiving nCTX (using a MAGIC CTX backbone) and surgery benefited from adjuvant CRT (aCRT) rather than aCTX (94). The results showed no significant local control, distant metastases, or survival benefit with aCRT over aCTX. However, patients in this study may have been under-staged (only 10% had diagnostic laparoscopy, which is more commonly used today to diagnose metastatic disease upfront), and most patients underwent an inferior LN dissection by today's standards (less than 10% had D2 lymphadenectomies). Additionally, the MAGIC regimen is currently substandard. While this study does not support a standard nCTX and aCRT approach in patients with R0 resections, if pathology reveals an R1 resection after the nCTX component of perioperative therapy, aCRT should be considered today for local control. aCRT, palliative systemic therapies, or best supportive care are options for patients with an R2 resection, depending on the individual's functional status (3).

Following upfront surgery

Although most patients clinically staged with locally advanced disease should undergo some form of neoadjuvant treatment for various reasons, some patients may undergo an upfront resection or be upstaged at the time of pathologic review. In these cases, adjuvant therapy in the form of CTX or CRT is often recommended, especially for AC EC/GEJ.

In the phase 3 Intergroup 0116 study, 556 patients with resected T3+ and/or N+ GEJ/GC AC who underwent upfront R0 resections were randomly assigned to observation *vs.* aCRT (89). There was a relapse-free survival benefit (30 *vs.* 19 months; P<0.001) and OS benefit (36 *vs.* 27 months; P=0.005) in favor of aCRT arm (P=0.005). Although only 10% of patients underwent what is today an optimal lymphadenectomy, this study established aCRT as a potential SOC approach, especially in node-positive disease, and the results are extrapolated to manage higher EC ACs as well. Of note, a recent meta-analysis including 13 studies and 2,165 AC and SCC also demonstrated notable improvement in 5-year OS when comparing patients who received aCRT to those who had no aCRT. (95). There was also a reduction in local-regional recurrence rates (OR 0.58; 95% CI: 0.46–0.72; P<0.00001) but no significant difference in distant metastasis (OR 0.94; 95% CI: 0.68–1.30; P=0.70).

aCTX without radiation may also improve survival, but randomized studies in EC are scant. For AC, the single-arm, phase 2 ECOG 8296 study reported an encouraging 2-year OS rate (60%), which was improved from historical controls (P=0.0008) when 4 cycles of adjuvant cisplatin and paclitaxel were used in 59 distal EC/GEJ AC patients with R0 resections (96). The NCCN guideline recommendations of aCTX for EC/GEJ AC using FOLFOX or capecitabine plus oxaliplatin are mostly extrapolated from the CLASSIC trial. This trial primarily enrolled GC patients who had undergone tumor resection, including a D2 lymphadenectomy, and in whom 6 months of aCTX provided better 5-year DFS (68% *vs.* 53%; HR 0.58; 95% CI: 0.51–0.85; P=0.037) and 5-year OS (78% *vs.* 69%; HR 0.66; 95% CI: 0.51–0.85; P=0.0015) than no adjuvant therapy (93).

While there are demonstrable benefits with aCRT/aCTX over observation for patients with lower EC/GEJ/GC treated upfront with surgery, this is understudied for higher ECs, specifically SCC. In SCC, the JCOG 9904 study, including 242 patients, is the only major RCT evaluating aCTX versus no aCTX in EC SCC and reported a 5-year DFS (55% *vs.* 45%; P=0.037) but not OS benefit (P=0.13) with aCTX (92). There are also scant data comparing aCRT to CTX to guide the decision of choosing one over the other. Currently available data have led the NCCN to recommend surveillance following surgery in SCC with an R0 resection, regardless of pathological staging; aCRT with an R1 resection; and aCRT or palliative systemic treatment, if appropriate, with an R2 resection (3). For locally advanced AC diagnosed after upfront surgery, including some T2N0 disease with high-risk features (>2 cm, poorly-differentiated, lymphovascular invasion, perineural invasion) or in patients <50 years of age, some form of postoperative therapy is often indicated, including aCRT or CTX, although surveillance remains an alternative (3).

Potential role of circulating tumor DNA (ctDNA)

To date, physicians primarily use risk factors, as noted on a pathology report to guide whether to give adjuvant therapy. In addition, radiography and endoscopic evaluation, which

lack accuracy in detecting residual disease or complete eradication of disease, are used to guide surgical or organ-sparing decisions. Improved modern tools are needed to risk-stratify patients for treatment escalation or de-escalation.

ctDNA, or circulating cell-free DNA derived from tumor cells, is a promising tool with prognostic and predictive potential. With advancements in genomic profiling, commercialized tests have emerged that can detect microscopic levels of cancer cells through ctDNA detection in the peripheral blood (97-99). In general, assays may be tumor-informed tests, in which specific mutations known to exist in a patient's tumor are assessed in the blood using highly specific and sensitive personalized assays or plasma-only. Single genes, hot-spot mutations, or a broad collection of cancer-associated genes can also be assessed in the blood without requiring knowledge of pre-existing tumor mutations. Positive tests, signifying the presence of ctDNA, have demonstrated strong prognostic value as they identify residual disease with a lead time of months prior to radiographic relapse and predict worse DFS and OS (100). Amongst gastrointestinal cancers, most data published to date about the utility of ctDNA is in colorectal cancer, although studies evaluating ctDNA in EC/GEJ/GC are emerging. In a prospective study including 97 EC patients, cancer-specific survival (HR 5.55; 95% CI: 2.42–12.71; P=0.0003) and DFS (HR 2.35; 95% CI: 1.18–4.72; P=0.01) were worse in postoperative ctDNA-positive patients than in ctDNA-negative patients (101). ctDNA detection was also associated with worse PFS in a larger study, including 254 patients with EC/GEJ/GC (102). In another prospective study of 45 EC patients, ctDNA positivity after CRT equated to an 18.7 times higher risk of progression and 32.1 times higher risk of distant metastases, with ctDNA detection preceding radiographic release by an average of 2.8 months (103). Interestingly, ctDNA combined with metabolic imaging after CRT had higher accuracy in detecting tumor progression than ctDNA or metabolic imaging used independently (P<0.001). These studies demonstrate ctDNA as a potential tool in identifying a high-risk group of patients destined for relapse who may benefit from completion surgery or augmented adjuvant therapy.

While these studies highlight the prognostic value of a positive ctDNA test, they are primarily observational and include small numbers of patients. Providers must know the sensitivity limitations related to tumor stage, histology, and anatomic location. These tumor characteristics may affect the degree of "ctDNA tumor shedding". So, too, providers must be aware of false positives due to clonal non-malignant processes in hematological cells in aging populations, called clonal hematopoiesis of indeterminate potential (104-106). Well-populated, prospective, randomized studies are needed to validate ctDNA as a predictive tool before physicians can use it to guide surgery and perioperative escalation or de-escalation strategies.

Conclusions

In summary, nCRT or definitive CRT with salvage surgery are the preferred approaches for SCC based on higher radiosensitivity, impressive ypCR rates, and survival benefits based on CROSS and definitive CRT trials. In AC, completion surgery is recommended due to lower ypCR rates with nCTX/nCRT, and nCRT is recommended for proximal tumors, while nCRT or perioperative CTX are both acceptable options for lower EC/GEJ tumors based on the CROSS, FLOT4, and NeoAegis trials. Novel strategies to build upon the successes of perioperative CTX and CRT are imperative for EC patients. Precision medicine using tissue/blood-based genomic biomarkers is becoming increasingly relevant and has the potential to revolutionize perioperative treatments for EC. With continued research and improved funding for such a fatal disease, we hope to better understand the molecular mechanisms of this aggressive malignancy and personalize therapies to improve oncologic outcomes.

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