Preoperative and Postoperative Approaches to Gastroesophageal Cancer: What is All the Fuss About

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ABSTRACT

Gastroesophageal cancers carry poor prognoses, and are a leading cause of cancer-related morbidity and mortality worldwide. Even in those with resectable disease, more than half of patients treated with surgery alone experience disease recurrence. Multimodality approaches using preoperative and postoperative chemotherapy and/or radiotherapy have been established, resulting in incremental improvements in outcomes. Globally, there is no standardized approach, and treatment varies with geographic location. The question remains of how to select the optimal perioperative treatment that will maximize benefit for patients while avoiding toxicities from unnecessary therapies. This article reviews currently available evidence supporting preoperative and postoperative therapy in gastroesophageal cancers, with an emphasis on recent practice-changing trials and ongoing areas of investigation, including the role of immune checkpoint inhibition and biomarker-guided treatment.

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Gastroesophageal cancers are a heterogeneous group of cancers that develop insidiously and carry poor prognoses.^{1,2} Worldwide, gastric adenocarcinoma and esophageal cancer represent the fourth and sixth most common causes of cancer-related death, respectively.³ Surgery is the primary curative treatment modality, except for esophageal squamous cell carcinomas (SCCs), for which definitive chemoradiotherapy (CRT) can be considered.^{4,5} Despite advances in surgical techniques, prognosis with surgery alone remains poor, with 5-year overall survival (OS) rates ranging from 30% to 40%.^{6,7} Multimodality approaches incorporating preoperative and postoperative chemotherapy and/or radiotherapy have been established; however, there is no standardized approach and notable geographic variation in treatment exists. Up-front surgery with adjuvant chemotherapy is favored in Asian countries, whereas neoadjuvant or perioperative treatment is preferred in Europe and North America.^{8–11} The perioperative approach to gastroesophageal cancers is further complicated by the fact that esophageal cancers comprise 2 different histologies, each with different molecular characteristics. The genomic profile of esophageal SCC has been shown to share more similarities to other aerodigestive SCCs, whereas that of esophageal adenocarcinomas resembles the chromosomally unstable variant of gastric adenocarcinoma.^{12,13} Although in clinical trials gastroesophageal junction (GEJ) cancers have traditionally been grouped with either esophageal or gastric cancer depending on the tumor's anatomic Siewert classification, molecular profiling studies suggest that basing treatment on histology may be more appropriate.

The high morbidity of surgery often limits the ability to deliver treatment postoperatively, highlighting the need for novel strategies to either develop more active preoperative treatment or more tolerable postoperative therapies. This article reviews currently available evidence

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See page 100 for related commentary.

supporting preoperative and postoperative approaches in gastroesophageal cancer, with an emphasis on recent practice-changing trials and ongoing areas of investigation, including the role of immune checkpoint inhibition and biomarker-driven approaches to treatment.

Approaches to Resectable Gastric Cancer

Postoperative Chemotherapy

Given the high risk of recurrence following surgical resection, several randomized phase III trials investigating

Table 1. Phase III Trials Supporting Postoperative Therapy in Resectable Gastric and GEJ Cancer

Trial	Year	Phase	Patients	Investigational Arm	Control	Survival Outcomes	HR
Postoperative chemotherapy							
ACTS-GC ^{8,14}	2007	III	Japan: resected gastric adenocarcinoma Stage II–IIIB R0 resection and D2 lymphadenectomy required (N=1,059)	Adjuvant S-1 daily, 4 wk on and 2 wk off, for 12 mo	Surgery only	5-y OS: 71.7% vs 61.1% (control) 5-y RFS: 65.4% vs 53.1% (control)	HR for OS, 0.669 (95% CI, 0.540–0.828) HR for RFS, 0.653 (95% CI, 0.537–0.793)
CLASSIC ^{9,15}	2012	III	South Korea, China, Taiwan: resected gastric adenocarcinoma Stage II–IIIB R0 resection and D2 lymphadenectomy required (N=1,035)	Adjuvant capecitabine and oxaliplatin every 3 wk for 8 cycles	Surgery only	5-y OS: 78% vs 69% (control) 5-y DFS: 68% vs 53% (control)	HR for OS, 0.66 (95% CI, 0.51–0.85; P=.0015) HR for DFS, 0.58 (95% CI, 0.47–0.72; P<.0001)
Postoperative CRT							
INT-0116 ^{18,19}	2001	III	United States: resected gastric or GEJ adenocarcinoma Stage IB–IVA R0 resection required D0–2 lymphadenectomies included (N=556)	Adjuvant CRT Adjuvant 5-FU + leucovorin (days 1–5) for 1 cycle; RT (45 Gy) with concurrent 5-FU + leucovorin (first 4 and last 3 days of RT); 2 cycles of 5-FU + leucovorin (days 1–5)	Surgery only	3-y OS: 50% vs 41% (control) 3-y RFS: 48% vs 31% (control)	HR for OS, 1.32 (95% CI, 1.10–1.60; P=.0046) HR for RFS, 1.51 (95% CI, 1.25–1.83; P<.001)
ARTIST ^{21,22}	2012	III	South Korea: resected gastric adenocarcinoma Stage IB–IVA R0 resection and D2 lymphadenectomy required (N=458)	Adjuvant CRT: XP every 3 wk for 2 cycles; RT (45 Gy) with concurrent capecitabine (daily); 2 cycles of XP	Adjuvant chemotherapy: XP every 3 wk, for 6 cycles	5-y OS: 75% (CRT) vs 73% (XP) 3-y DFS: 78.2% (CRT) vs 74.2% (XP) 3-y DFS in node-positive: 77.5% (CRT) vs 72.3% (XP)	HR for OS, 1.130 (95% CI, 0.775–1.647; P=.5272) HR for DFS, 0.74 (95% CI, 0.52–1.05; P=.0922)
CALGB 80101 ²⁰	2017	III	United States: resected gastric or Siewert III GEJ adenocarcinoma Stage IB–IVA R0 resection required D1–2 lymphadenectomies included (N=546)	Adjuvant ECF; RT (45 Gy) with concurrent 5-FU (daily); 2 additional cycles of ECF	Adjuvant 5-FU (days 1–5) for 1 cycle; RT (45 Gy) with concurrent 5-FU (daily); 2 additional cycles of 5-FU (days 1–5)	5-y OS: 44% (ECF) vs 44% (5-FU) 5-y DFS: 37% (ECF) vs 39% (5-FU)	HR for OS, 0.98 (95% CI, 0.78–1.24; P=.69) HR for DFS, 0.96 (95% CI, 0.77–1.20; P=.94)
ARTIST 2 ²³	2020	III	South Korea: resected gastric adenocarcinoma Stage II–IVA, lymph node positive R0 resection and D2 lymphadenectomy required (N=546)	SOXRT: adjuvant SOX for 2 cycles; RT (45 Gy) with concurrent S-1 (daily); 4 additional cycles of SOX	SOX: adjuvant S-1 (days 1–14) and oxaliplatin (day 1) every 3 wk for 8 cycles S-1: adjuvant S-1 daily, 4 wk on and 2 wk off for 8 cycles	3-y DFS: 72.8% (SOXRT) vs 74.3% (SOX) vs 64.8% (S-1)	HR for DFS: SOXRT vs SOX, 0.971 (95% CI, 0.663–1.421; P=.879) HR for DFS: SOXRT vs S-1, 0.724 (95% CI, 0.507–1.032; P=.074) HR for DFS: SOX vs S-1, 0.693 (95% CI, 0.409–0.987; P=.042)

Abbreviations: CRT, chemoradiotherapy; DFS, disease-free survival; ECF, epirubicin/cisplatin/5-FU; GEJ, gastroesophageal junction; HR, hazard ratio; OS, overall survival; RFS, relapse-free survival; RT, radiotherapy; S-1, oral chemotherapy comprised of tegafur, gimeracil, and oteracil; SOX, S-1/oxaliplatin; SOXRT, S-1/oxaliplatin and radiotherapy; XP, capecitabine/cisplatin.

adjuvant chemotherapy have been conducted (Table 1). The Japanese ACTS-GC trial assigned 1,059 patients following gastrectomy and D2 lymphadenectomy to receive adjuvant S-1 for 12 months or surgery alone.⁸ There was a significant survival advantage with S-1, with superior relapse-free survival (RFS) (65.4% vs 53.1%; hazard ratio [HR], 0.653) and OS (71.7% vs 61.1%; HR, 0.669) with S-1 at 5 years.¹⁴ The CLASSIC study, conducted in South Korea, China, and Taiwan, investigated adjuvant chemotherapy (8 cycles of capecitabine and oxaliplatin) following D2 gastrectomy compared with surgery alone.⁹ The chemotherapy group had improved disease-free survival (DFS) (68% vs 53%; HR, 0.58) and OS (78% vs 69%; HR, 0.66) at 5 years, although with high rates of toxicity (56% with ≥ 1 grade 3 or 4 adverse events).¹⁵ Based on these trials, surgery with adjuvant chemotherapy is the preferred approach for resectable gastric cancer in Asian countries.

Postoperative CRT

Treatment strategies involving postoperative CRT have also been explored, based on the observation that locoregional recurrence occurred in up to 40% to 65% of patients after curative-intent gastric resection in North America (Table 1).^{16,17} The INT-0116 study randomized 556 patients with gastric or GEJ adenocarcinoma to postoperative CRT (1 cycle of fluorouracil/leucovorin, then 45 Gy of radiation + fluorouracil/leucovorin, followed by 2 cycles of fluorouracil/leucovorin) or observation following surgical resection.¹⁸ Rates of grade 3 and 4 toxicity with CRT were high (41% and 32%, respectively) and only 64% of patients completed the planned treatment. Although the study reported significant improvement in RFS and OS with CRT, primarily driven by decreased local recurrences, a major limitation of INT-0116 was that only 10% of patients underwent D2 lymphadenectomy, whereas 36% had a D1 and 54% had a D0 dissection, calling into question whether the benefits of CRT would still be seen if all patients had received optimal surgery.¹⁹ The follow-up CALGB 80101 study showed that changing the postoperative CRT regimen to epirubicin/cisplatin/infusional fluorouracil (ECF) did not improve OS, although ECF was better tolerated.²⁰

The ARTIST trial sought to elucidate the role of CRT in 458 patients who underwent curative resection with D2 lymph node dissection.²¹ Following surgery, patients were randomized to receive chemotherapy alone (6 cycles of capecitabine + cisplatin [XP]) or chemotherapy + CRT (2 cycles of XP, 45 Gy of radiation with concurrent capecitabine, 2 further cycles of XP). Overall, no DFS benefit was seen with the addition of CRT (3-year DFS, 78.2% CRT vs 74.2% chemotherapy; $P=.0862$). A subgroup analysis suggested DFS improvement in those with pathologic lymph node positivity, prompting the subsequent ARTIST 2 study.²² In ARTIST 2, 546 patients with D2-resected node-positive gastric cancer were randomized to 1 of 3 arms: S-1

for 1 year, S-1 + oxaliplatin (SOX) for 6 months, or SOX + CRT (SOXRT).²³ The trial was terminated prematurely, and did not show a DFS difference between SOX and SOXRT (3-year DFS, 74.3% vs 72.8%, respectively; HR, 0.971).

Taken together, these studies do not support the routine use of postoperative CRT in patients who have undergone D2 lymphadenectomy.

Perioperative Chemotherapy

Another strategy is the use of perioperative chemotherapy (Table 2). The UK Medical Research Council (MRC) MAGIC trial was a landmark trial that randomized 503 patients with adenocarcinoma of the stomach (74%), GEJ (11.5%), or lower esophagus (14.5%) to receive 3 cycles of preoperative and postoperative ECF or surgery alone.²⁴ The perioperative chemotherapy arm had significantly improved progression-free survival (PFS) (HR, 0.66; $P<.001$) and OS (HR, 0.75; $P=.009$), with a 13% improvement in 5-year OS. This benefit was seen despite only 42% of patients in the perioperative arm completing all 6 cycles of chemotherapy. The French FNCLCC ACCORD-07/FFCD 9703 trial of perioperative cisplatin and fluorouracil similarly found significant improvement in DFS (HR, 0.65; $P=.003$) and OS (HR, 0.69; $P=.02$) compared with surgery alone.²⁵ Again, only 23% completed all postoperative therapy.

The FLOT4-AIO study was a practice-changing trial comparing the perioperative ECF regimen used in the MAGIC trial with 4 cycles of preoperative and postoperative FLOT (fluorouracil/leucovorin/oxaliplatin/docetaxel).¹¹ In total, 716 patients with gastric (44%) or GEJ adenocarcinoma (23% Siewert 1; 32% Siewert 2 or 3) were included. FLOT significantly improved PFS (HR, 0.75; $P=.004$) and OS (HR, 0.77; $P=.012$). Consistent with previous trials, only 60% of patients in the FLOT group started postoperative chemotherapy, and only 46% completed all 8 cycles of FLOT.

Taken together, these studies show significant survival benefit with the use of perioperative chemotherapy, with FLOT being the preferred regimen. Notably, completing planned chemotherapy following surgery was a challenge in each study. To address this issue, the EORTC 40954 trial investigated a neoadjuvant chemotherapy approach using cisplatin, fluorouracil and leucovorin; however, the study was closed early due to poor accrual and failed to demonstrate a survival benefit.²⁶ Given the challenges of treating these patients postoperatively, and lack of success using preoperative chemotherapy only, strategies are needed to either improve neoadjuvant therapies or develop more tolerable postoperative regimens.

How to Improve Perioperative Treatment

Even in patients who receive perioperative FLOT, the estimated 5-year OS rate is only 45%, highlighting the need for further improvements to treatment efficacies. The CRITICS study examined the addition of postoperative

Table 2. Phase III Trials Supporting Perioperative Therapy in Gastroesophageal Cancer

Trial	Year	Phase	Patients	Investigational Arm	Control	Survival Outcomes	HR
Pre- and perioperative chemotherapy							
MAGIC ²⁴	2006	III	United Kingdom: esophageal, GEJ and gastric adenocarcinoma Stage II–III (N=503)	Neoadjuvant ECF every 3 wk for 3 cycles; surgery; adjuvant ECF for 3 cycles	Surgery only	5-y OS: 36.3% vs 23% (control)	HR for OS, 0.75 (95% CI, 0.60–0.93; <i>P</i> =.009) HR for PFS, 0.66 (95% CI, 0.53–0.81; <i>P</i> <.001)
EORTC 40954 ²⁶	2010	III	Europe: gastric and Siewert I–III GEJ adenocarcinoma Stage III–IVA D1–2 lymphadenectomies included (N=144)	Neoadjuvant 5-FU (days 1, 8, 15, 22, 29, 36) and cisplatin (days 1, 15, 29)	Surgery alone	2-y OS: 72.7% vs 69.9% (control)	HR for OS, 0.84 (95% CI, 0.52–1.35; <i>P</i> =.466) HR for PFS, 0.76 (95% CI, 0.49–1.16; <i>P</i> =.20)
FNCLCC ACCORD-07/FFCD 9703 ²⁵	2011	III	France: esophageal, GEJ and gastric adenocarcinoma Stage II–III (N=224)	Neoadjuvant 5-FU (days 1–5) and cisplatin (day 1) every 3 wk, for 2–3 cycles; surgery; adjuvant 5-FU (days 1–5) and cisplatin (day 1) every 3 wk, for 3–4 cycles (up to 6 total cycles)	Surgery only	5-y OS: 38% vs 24% (control) 5-y DFS: 34% vs 19% (control)	HR for OS, 0.69 (95% CI, 0.50–0.95; <i>P</i> =.02) HR for DFS, 0.65 (95% CI, 0.48–0.89; <i>P</i> =.003)
FLOT4-AIO ¹¹	2019	III	Germany: gastric or Siewert GEJ adenocarcinoma Stage IB–III (N=716)	Neoadjuvant FLOT every 2 wk for 4 cycles; surgery; adjuvant FLOT for 4 cycles	Neoadjuvant ECX or ECF for 3 cycles; surgery; adjuvant ECX or ECF for 3 cycles	5-y OS: 45% (FLOT) vs 36% (ECX/ECF)	HR for OS, 0.77 (95% CI, 0.63–0.94; <i>P</i> =.012) HR for DFS, 0.75 (95% CI, 0.62–0.91; <i>P</i> =.0036)
Perioperative chemotherapy with pre- or postoperative CRT							
CRITICS ²⁷	2018	III	Europe: gastric and Siewert III GEJ adenocarcinoma Stage IB–IVA (N=788)	CRT: Neoadjuvant ECX for 3 cycles; surgery; adjuvant radiation (45 Gy) with concurrent cisplatin (weekly × 5) and capecitabine (daily)	Chemotherapy: ECX for 3 cycles; surgery; adjuvant ECX for 3 cycles	5-y OS: 40% (CRT) vs 42% (chemotherapy) 5-y EFS: 38% (CRT) vs 39% (chemotherapy)	HR for OS, 1.01 (95% CI, 0.84–1.22; <i>P</i> =.90) HR for EFS, 0.99 (95% CI, 0.82–1.19; <i>P</i> =.92)

Abbreviations: CRT, chemoradiotherapy; DFS, disease-free survival; ECF, epirubicin/cisplatin/5-FU; ECX, epirubicin/cisplatin/capecitabine; EFS, event-free survival; FLOT, fluorouracil/leucovorin/oxaliplatin/docetaxel; GEJ, gastroesophageal junction; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; RT, radiotherapy.

CRT to perioperative chemotherapy.²⁷ A total of 788 patients (83% gastric, 17% Siewert 2 or 3 GEJ adenocarcinoma) underwent 3 cycles of preoperative chemotherapy (epirubicin, cisplatin, or oxaliplatin, and capecitabine; Table 2) followed by surgery and went on to receive either 3 cycles of the same chemotherapy or 45 Gy of radiotherapy with concurrent cisplatin and capecitabine. There was no difference in OS between the 2 cohorts (43 vs 37 months, respectively; HR, 1.01; *P*=.90).

The ongoing TOPGEAR trial is examining the addition of neoadjuvant CRT to perioperative chemotherapy and will provide insight about whether adding another treatment modality in the neoadjuvant setting when patients are better able to tolerate therapy will improve outcomes (Table 3).²⁸ CRITICS II is another ongoing trial

studying 3 preoperative approaches: chemotherapy alone versus chemotherapy followed by CRT versus CRT alone (Table 3).²⁹

Approaches to Esophageal Cancer

Management of Esophageal SCC

Definitive CRT can be considered for curative-intent treatment of esophageal SCC, leaving surgery for salvage. The few randomized trials comparing definitive CRT with trimodality (CRT followed by surgery) treatment have not shown a significant OS difference, although a trimodality approach may improve locoregional control (Table 4).^{4,5,30}

Table 3. Ongoing Trials Investigating Novel Approaches to Resectable Gastroesophageal Cancer

Trial	Treatment Approach	Phase	Patients	Investigational Arm	Control	Outcomes
Perioperative chemotherapy and RT						
TOPGEAR ²⁸	Perioperative	II/III	Australia, Canada: gastric and Siewert II–III GEJ adenocarcinoma Stage IB–IIIC	Neoadjuvant MAGIC for 2 cycles OR FLOT for 3 cycles; RT (45 Gy) with concurrent capecitabine or FU (daily); surgery; adjuvant MAGIC for 3 cycles OR FLOT for 4 cycles	Neoadjuvant MAGIC for 3 cycles OR FLOT for 4 cycles; surgery; adjuvant MAGIC for 3 cycles OR FLOT for 4 cycles	Primary outcome (phase III): OS Secondary outcome (phase III): DFS
CRITICS II ²⁹	Preoperative	II	Netherlands: gastric cancer Stage IB–IIIC	Arm 1: neoadjuvant DOC for 2 cycles, followed by CROSS-protocol CRT Arm 2: neoadjuvant CROSS-protocol CRT	Arm 3: neoadjuvant DOC for 4 cycles	Primary: EFS Secondary: OS
ESOPEC ³⁶	Perioperative	III	Germany: esophageal and Siewert I–III GEJ adenocarcinoma stage IB–IVA	Perioperative FLOT	Neoadjuvant CROSS-protocol CRT	Primary outcome: OS Secondary outcome: PFS
POWERRANGER	Perioperative	II/III	Canada: esophageal and Siewert I–III GEJ adenocarcinoma Stage IB–IVA	Perioperative MAGIC or FLOT	Neoadjuvant CROSS-protocol CRT	Primary outcomes: treatment compliance, response rates Secondary outcomes: 3-y DFS, 3-y OS
Immunotherapy trials						
KEYNOTE-585 ³⁷	Perioperative	III	Global: gastric or GEJ adenocarcinoma Stage II–III	Perioperative chemotherapy (FLOT, cisplatin and capecitabine or cisplatin and FU); surgery; adjuvant pembrolizumab started with adjuvant chemotherapy and continued for 11 cycles total	Perioperative chemotherapy Adjuvant placebo started with adjuvant chemotherapy and continued for 11 cycles total	Primary outcomes: EFS, OS
MATTERHORN ³⁸	Perioperative	III	Global: gastric or GEJ adenocarcinoma Stage II–III	Neoadjuvant FLOT for 4 cycles with durvalumab every 4 wk for 2 cycles; surgery; adjuvant FLOT for 4 cycles with durvalumab for 2 cycles, followed by maintenance durvalumab for 10 cycles	Neoadjuvant FLOT for 4 cycles with placebo; surgery; adjuvant FLOT for 4 cycles with placebo, followed by maintenance placebo for 10 cycles	Primary outcome: EFS Secondary outcome: OS
DANTE ³⁹	Perioperative	II	Germany, Switzerland: gastric or Siewert I–III GEJ adenocarcinoma Stage II–III	Neoadjuvant FLOT with atezolizumab for 4 cycles; surgery; adjuvant FLOT with atezolizumab for 4 cycles; maintenance atezolizumab for 8 additional cycles	Neoadjuvant FLOT for 4 cycles; surgery; adjuvant FLOT for 4 cycles	Primary outcomes: DFS/PFS Secondary outcomes: OS
ATTRACTION-05 ⁴⁰	Perioperative	III	China, Japan, Korea, Taiwan: gastric and GEJ adenocarcinoma Pathologic stage III	Adjuvant chemotherapy (S-1 for 1 y or CAPOX for 6 mo) with nivolumab (1 y)	Adjuvant chemotherapy (S-1 for 1 y or CAPOX for 6 mo) with placebo (1 y)	Primary outcome: RFS Secondary outcome: OS

(continued on next page)

Table 3. Ongoing Trials Investigating Novel Approaches to Resectable Gastroesophageal Cancer (cont.)

Trial	Treatment Approach	Phase	Patients	Investigational Arm	Control	Outcomes
Immunotherapy trials (cont.)						
EA2174 ⁴¹	Perioperative	II/III	United States: esophageal or Siewert I–II GEJ adenocarcinoma Stage II–III	Arm A: neoadjuvant RT (50.4 Gy) with concurrent carboplatin AUC 2 and paclitaxel (weekly for 5 wk), and nivolumab (days 1, 15); surgery; adjuvant nivolumab for 12 cycles Arm B: neoadjuvant RT (50.4 Gy) with concurrent carboplatin AUC 2 and paclitaxel (weekly for 5 wk), and nivolumab (days 1, 15); surgery; adjuvant nivolumab for 12 cycles with ipilimumab on cycles 1, 4, 7, 10	Neoadjuvant CRT only	Primary outcomes: pCR rate, DFS Secondary outcome: OS

Abbreviations: AUC, area under the curve; CAPEOX, capecitabine/oxaliplatin; CRT, chemoradiotherapy; DFS, disease-free survival; DOC, docetaxel/oxaliplatin/capecitabine; EFS, event-free survival; FLOT, fluorouracil/leucovorin/oxaliplatin/docetaxel; FU, fluorouracil; GEJ, gastroesophageal junction; OS, overall survival; pCR, partial complete response; PFS, progression-free survival; RFS, relapse-free survival; RT, radiotherapy.

Aside from definitive CRT trials, esophageal SCC has generally been grouped with esophageal adenocarcinoma in clinical trials. Based on the differing molecular characteristics suggesting that these are distinct diseases, future trials should separate the 2 histologies.

Neoadjuvant CRT

The pivotal CROSS trial established the benefit of neoadjuvant CRT in esophageal and GEJ cancer, randomizing 366 patients (75% adenocarcinoma, 23% SCC) to receive preoperative CRT (41.4 Gy) with weekly carboplatin and paclitaxel followed by resection, or surgery alone¹⁰ (Table 4). Neoadjuvant CRT was well tolerated, with 91% completing the full treatment regimen and no significant increase in postoperative morbidity compared with surgery alone. The CRT arm had significantly improved OS over surgery alone (HR, 0.657; $P=.003$), with absolute 5- and 10-year OS benefit of 14% (47% vs 33%) and 13% (38% vs 25%), respectively.^{31,32} A greater magnitude of benefit was seen in the SCC subgroup, although those with adenocarcinoma derived benefit as well. As a result, the CROSS protocol became the standard of care for resectable esophageal cancer in North America.

Adjuvant Immunotherapy

Although the use of multimodality treatment has achieved incremental progress in improving outcomes in gastroesophageal cancers, up to half of patients will experience cancer recurrence, highlighting the persisting unmet need for better therapies. CheckMate 577 was a global trial investigating a 1-year course of adjuvant nivolumab compared with surveillance in patients with

resected esophageal (60%) or GEJ (40%) cancer who had residual pathologic disease after neoadjuvant CRT and surgery.³³ Of the 794 patients, 71% had adenocarcinoma and 29% SCC. A significant DFS improvement was seen with nivolumab, with a median DFS of 22.4 versus 11.0 months (HR, 0.69; $P<.001$). Nivolumab was well tolerated, with no reduction in health-related quality of life.³⁴ Although OS data are pending, we anticipate adjuvant nivolumab will yield a significant OS benefit, given the doubling in DFS. This trial establishes adjuvant nivolumab as a new standard of care in this patient population.

Remaining Questions and Future Approaches

Neoadjuvant CRT Versus Perioperative Chemotherapy in GEJ Adenocarcinoma

Although both perioperative chemotherapy and preoperative CRT have been established as standard of care in resectable gastroesophageal cancer, a subset of patients will fit the criteria for both approaches. The optimal strategy for these patients remains a crucial question that several trials have been designed to address.

The Neo-AEGIS study presented at the 2021 ASCO Annual Meeting randomized 377 patients with esophageal or GEJ adenocarcinoma to receive perioperative chemotherapy (85% MAGIC, 15% FLOT) or preoperative CRT with CROSS.³⁵ Initially designed as a superiority trial, this was modified to a noninferiority analysis with a margin of 5%. Survival was similar between the 2 arms, meeting noninferiority criteria, with 3-year OS of 56% with CROSS and 57% with perioperative chemotherapy (HR, 1.02; 95% CI, 0.74–1.42). Outcomes including rates of pathologic complete response, R0 resection, and nodal

Table 4. Phase III Trials Supporting Definitive or Preoperative CRT for Resectable Esophageal and GEJ Cancer

Trial	Year	Phase	Patients	Investigational Arm	Control	Survival Outcomes	HR
Definitive CRT							
Stahl et al ^{4,30}	2005	III	Germany: upper or mid third esophageal SCC Stage II–III (N=172)	CRT and surgery: neoadjuvant 5-FU, etoposide, cisplatin for 3 cycles; RT (40 Gy) with concurrent cisplatin and etoposide (days 2–8); surgery	Definitive CRT: neoadjuvant 5-FU, etoposide, cisplatin for 3 cycles; RT (40 Gy) with concurrent cisplatin and etoposide (days 2–8); RT to complete 65 Gy	2-y OS: 39.9% (surgery) vs 35.4% (definitive CRT) 2-y PFS: 64.3% (surgery) vs 40.7% (definitive CRT)	OS log-rank test for equivalence $P<.05$ HR for PFS, 2.1 (definitive CRT vs surgery) (95% CI, 1.3–3.5; $P=.003$)
FFCD 9102 ⁵	2007	III	France: thoracic esophageal SCC (88.8%) or adenocarcinoma (11.2%) Stage II–III (N=259)	CRT and surgery: neoadjuvant RT (46 Gy) with 2 cycles concurrent cisplatin (day 1–5, 22–26) and 5-FU (day 1–5, 22–26); surgery	Definitive CRT: RT (46 Gy) with 2 cycles concurrent cisplatin (day 1–5, 22–26) and 5-FU (day 1–5, 22–26); 20 Gy (to complete total 66 Gy) with 3 cycles cisplatin and 5-FU	2-y OS: 33.6% (surgery) vs 39.8% (definitive CRT) 2-y local control: 66.4% (surgery) vs 57% (definitive CRT)	HR for OS (definitive CRT vs surgery), 0.90; $P=.44$
Preoperative CRT							
CROSS ^{10,31,32}	2012	III	Netherlands: esophageal or Siewert I–II GEJ adenocarcinoma, SCC, or LCUD Stage IB–IIIB (N=368)	Neoadjuvant CRT: RT (41.1 Gy) with concurrent carboplatin AUC 2 and paclitaxel (both given once per week for 5 wk)	Surgery alone	5-y OS: 47% vs 33% (control) 5-y PFS: 44% vs 27% (control) 10-y OS: 38% vs 25% (control)	HR for OS, 0.657 (95% CI, 0.495–0.871; $P=.003$) HR for PFS, 0.498 (95% CI, 0.357–0.693; $P<.001$)
Neo-AEGIS ³⁵	2021	III	Europe: esophageal or Siewert I–II GEJ adenocarcinoma Stage IB–IIIB (N=377)	Neoadjuvant CROSS-protocol CRT	Perioperative ECX/ECF (MAGIC) or FLOT	3-y OS: 56% (CROSS) vs 57% (MAGIC/FLOT)	HR for OS, 1.02 (95% CI, 0.74–1.42)
Adjuvant immunotherapy following preoperative CRT and surgery							
CheckMate 577 ³³	2021	III	Global: esophageal and Siewert I–II GEJ adenocarcinoma or SCC Stage II–III Residual pathologic disease on resected specimen (N=794)	Neoadjuvant CROSS-protocol CRT; surgery; adjuvant nivolumab every 2 wk for 8 cycles, then every 4 wk for 8 cycles (total 12 mo)	Neoadjuvant CROSS; surgery	Median DFS, 22.4 vs 11 mo (control)	HR for DFS, 0.69 (96.4% CI, 0.56–0.86; $P<.001$)

Abbreviations: 5-FU, 5-fluorouracil; AUC, area under the curve; CRT, chemoradiotherapy; DFS, disease-free survival; ECF, epirubicin/cisplatin/5-FU; ECX, epirubicin/cisplatin/capecitabine; FLOT, fluorouracil/leucovorin/oxaliplatin/docetaxel; GEJ, gastroesophageal junction; HR, hazard ratio; LCUD, large cell undifferentiated carcinoma; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma; RT, radiotherapy.

downstaging favored the CROSS arm. Overall, this study showed that either approach is likely reasonable, leaving clinicians to consider factors such as patient fitness, regimen tolerability, and differing patterns of recurrence with each approach to guide decision-making. Because this trial opened before the FLOT4-AIO results were available, most patients in the perioperative chemotherapy arm received ECF/ECX. Whether similar results would be achieved using FLOT is under investigation in the ongoing ESOPEC and POWERRANGER trials (Table 3). However, the target HR of 0.645 in ESOPEC will

be difficult to meet, and it is uncertain whether this study will be able to adequately address this question.³⁶

With the results of CheckMate 577, which included only patients who underwent neoadjuvant CRT, an additional question raised is the role of immune checkpoint inhibition in those receiving chemotherapy without radiation. The KEYNOTE-585 study is investigating the combination of pembrolizumab with perioperative chemotherapy.³⁷ MATTERHORN is studying the addition of durvalumab to perioperative FLOT.³⁸ The phase II DANTE trial is studying atezolizumab

with perioperative FLOT.³⁹ These trials will help answer whether patients undergoing perioperative chemotherapy derive a similar benefit to that seen in CheckMate 577, or whether the abscopal effect induced by radiotherapy is a crucial component driving this benefit (Table 3).

Other trials of immunotherapy in resectable gastroesophageal cancer include ATTRACTION-05, a trial being conducted in Japan, Korea, and China investigating nivolumab in combination with adjuvant S-1 or CAPOX chemotherapy, as well as the phase II/III EA2174 study of preoperative CRT with nivolumab followed by postoperative nivolumab ± ipilimumab (Table 3).^{40,41}

Biomarker-Driven Preoperative and Postoperative Approaches

In the era of personalized cancer medicine, predictive biomarkers are urgently needed to help determine the optimal treatment to maximize benefit for individual patients and to spare patients from toxicities of unnecessary therapies. In advanced gastroesophageal cancer, a higher combined positive score (CPS), a measure of PD-L1 expression on tumor cells and tumor-associated immune cells, has been shown to predict benefit from

immune checkpoint inhibitors.⁴² A post hoc analysis of PD-L1 CPS expression in CheckMate 577 has yielded similar findings, wherein adjuvant nivolumab was associated with significant DFS improvement in the CPS ≥5 subgroup (HR, 0.62; 95% CI, 0.45–0.83) but not necessarily in CPS <5 (HR, 0.89; 95% CI, 0.65–1.22).³³ Future studies should prospectively incorporate biomarker analysis into trial design, and further development of new predictive biomarkers is needed.

Microsatellite Instability

Patients with mismatch repair deficiency (dMMR) or high levels of microsatellite instability (MSI-H) represent another subgroup of patients who warrant special consideration in the perioperative setting. An individual patient data meta-analysis of the MAGIC, CLASSIC, ARTIST, and ITACA-S trials has suggested lack of benefit from perioperative or adjuvant chemotherapy in patients with MSI-H/dMMR gastric cancer.⁴³ In the advanced/metastatic setting, treatment with immune checkpoint inhibitors achieve response rates of >55% in patients with MSI-H/dMMR gastric cancer; however, there is a paucity of prospective data in patients treated with curative intent.^{44,45} Wherever possible, patients with resectable MSI-H/

Table 5. Phase II/III Trials Investigating HER2 Inhibition in Resectable Gastroesophageal Cancer

Trial	Year	Phase	Patients	Investigational Arm	Control	Survival Outcomes	HR
PETRARCA ⁵¹	2020	II	Germany: esophageal, GEJ, and gastric adenocarcinoma Stage IB–IVA (N=81)	Neoadjuvant FLOT for 4 cycles with trastuzumab and pertuzumab every 3 wk; surgery; adjuvant FLOT for 4 cycles with trastuzumab and pertuzumab every 3 wk; maintenance trastuzumab and pertuzumab for 9 more cycles	Perioperative FLOT	2-y OS: 84% vs 77% (control) 2-y DFS: 70% vs 54% (control)	HR for DFS, 0.58 (95% CI, 0.278–1.139; P=.14)
RTOG 1010 ⁵²	2020	III	United States: esophageal or Siewert I–II GEJ adenocarcinoma, HER2-amplified Stage II–III (N=203)	Neoadjuvant RT (50.4 Gy) with concurrent carboplatin AUC 2, paclitaxel and trastuzumab (weekly for 6 wk); surgery; adjuvant trastuzumab every 3 wk for 13 cycles	Neoadjuvant RT (50.4 Gy) with concurrent carboplatin AUC 2 and paclitaxel (weekly for 6 wk)	4-y DFS: 33.1% vs 30.1% (control) Median OS: 38.5 vs 38.9 mo (control)	HR for DFS, 0.97 (95% CI, 0.69–1.36; P=.85) HR for OS, 1.01 (95% CI, 0.69–1.47; P=.95)
Ongoing Trial	Phase	Patients	Investigational Arms			Outcomes	
INNOVATION ⁵³	II	Europe and Asia: gastric and GEJ adenocarcinoma, HER2-overexpressed (IHC or FISH) Stage IB–III	Arm 1: neoadjuvant chemotherapy (any of FLOT, cisplatin and capecitabine, cisplatin and fluorouracil, CAPOX, or FOLFOX) with trastuzumab. Adjuvant chemotherapy with trastuzumab, followed by maintenance trastuzumab for a total of 17 cycles	Arm 2: neoadjuvant chemotherapy with trastuzumab and pertuzumab. Adjuvant chemotherapy with trastuzumab and pertuzumab, followed by maintenance trastuzumab and pertuzumab for a total of 17 cycles	Arm 3: neoadjuvant and adjuvant chemotherapy only	Primary outcome: pathologic response rate Secondary outcomes: PFS, OS	

Abbreviations: AUC, area under the curve; CAPOX, capecitabine/oxaliplatin; DFS, disease-free survival; FISH, fluorescence in situ hybridization; FLOT, fluorouracil/leucovorin/oxaliplatin/docetaxel; FOLFOX, 5-FU/leucovorin/oxaliplatin; GEJ, gastroesophageal junction; HR, hazard ratio; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

dMMR gastric cancer should be referred for clinical trials of chemotherapy omission or immune checkpoint inhibition strategies. Outside of a trial setting, patients should be individually counseled about the risks and potential benefits to come to an informed decision about cytotoxic chemotherapy.

HER2 Inhibition

In advanced or metastatic HER2-overexpressed or HER2-amplified gastroesophageal adenocarcinoma, the addition of HER2-targeted therapy to chemotherapy is an established standard of care.⁴⁶ HER2-directed therapies are under investigation in the curative-intent setting, with several single-arm phase II studies demonstrating the feasibility of incorporating HER2 blockade in the perioperative setting.^{47–50} Unfortunately, no randomized studies have demonstrated a survival benefit (Table 5). The phase II PETRARCA study found that adding trastuzumab and pertuzumab to perioperative FLOT increased the pathologic complete response rate; however, with increased toxicity and no significant DFS advantage, the trial closed before proceeding to phase III.⁵¹ Similarly, the phase III RTOG 1010 trial combining trastuzumab with preoperative CRT failed to show survival benefit.⁵² The ongoing phase II INNOVATION trial is studying the addition of trastuzumab ± pertuzumab to perioperative chemotherapy.⁵³ Given the results from previous studies, we anticipate this too will fail to improve survival. In the current treatment landscape of resectable gastroesophageal cancer, there is no role for HER2-targeted therapy in routine practice. Patients with HER2-positive cancers should be considered for clinical trials if available, or should otherwise receive the same treatment as HER2-negative patients.

Conclusions

The management of resectable gastroesophageal cancers has seen incremental changes over the past 2 decades, with clear evidence that multimodal approaches improve survival and that postoperative chemotherapy is difficult to complete, highlighting the need to develop either more active preoperative treatment or more tolerable postoperative therapies. The question of neoadjuvant versus perioperative therapy remains, and ongoing trials comparing the 2 strategies will provide further insight. Adjuvant immunotherapy following trimodality treatment has emerged as a practice-changing therapy, and OS results are eagerly awaited, as are results from perioperative immunotherapy trials. Prospective incorporation of biomarker analysis in the design of future clinical trials is encouraged to aid in the development of predictive biomarkers to guide decision-making and optimize treatment selection in the curative-intent setting.

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