Evolving Standards of Care for Neoadjuvant and Adjuvant Therapy in Esophageal, Gastroesophageal Junction, and Gastric Cancer

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Abstract: Multimodality therapy, which can include systemic therapy, radiation therapy, and surgery, is the preferred approach for most localized, clinical T2 to T4, and/or node-positive esophageal, gastroesophageal junction, and gastric cancers. The optimal content and sequence of perioperative treatment of patients with different sites of disease and tumor histologic types continue to evolve. This review highlights the current standard-of-care approaches and areas of ongoing clinical research, including biomarker-directed therapy, pertaining to the treatment of esophageal, gastroesophageal junction, and gastric cancers in patients who are candidates for therapy with curative intent.

Introduction

More than 45,000 new cases of esophageal and gastric cancer are diagnosed in the United States each year, and these result in more than 27,000 deaths annually. Gastric cancer and esophageal cancer are the third- and sixth-leading causes of cancer death worldwide, respectively.[1,2] For selected cases of early-stage esophageal, gastroesophageal junction (GEJ), or gastric cancer, surgery is the primary treatment. For some clinical T2 (cT2) and nearly all cT3/cT4 and/or node-positive esophageal, GEJ, and gastric cancers, a multimodality approach is now the standard of care. This review aims to clarify the current state of clinical practice and clinical research pertaining to the preoperative and postoperative treatment of patients with a diagnosis of cT2 or higher esophageal, GEJ, or gastric cancer.

Preoperative Treatment Approaches for Esophageal and GEJ Cancer

Neoadjuvant Chemoradiation in Esophageal and GEJ Cancer

The preferred perioperative treatment approach for patients with esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma, or Siewert I/II GEJ adenocarcinoma is trimodality therapy

with chemoradiation followed by surgery. This was initially demonstrated in CALGB 9781 from the Cancer and Leukemia Group B, a trial that randomly assigned 56 patients with ESCC, esophageal adenocarcinoma, or Siewert I/II GEJ adenocarcinoma to preoperative chemoradiation with 5-fluorouracil (5-FU) plus cisplatin followed by surgery or to surgery alone. The study demonstrated a significant overall survival (OS) benefit in favor of trimodality therapy (median OS, 4.48 vs 1.79 years; *P*=.002), although the trial was closed early owing to poor accrual.[3] More-definitive evidence for the trimodality approach was established in the CROSS trial, in which 366 patients with ESCC, esophageal adenocarcinoma, or GEJ adenocarcinoma (75% of whom had adenocarcinoma histology) were randomly assigned to chemoradiation therapy with carboplatin and paclitaxel chemotherapy plus 41.4 Gy of concurrent radiation therapy followed by surgery or to surgery alone.[4] OS was better with trimodality therapy than with surgery alone in the overall population (median OS, 49.4 vs 24.0 months; hazard ratio [HR], 0.66; 95% CI, 0.50-0.87; *P*=.03). In a subgroup analysis, the patients with ESCC (HR, 0.45; 95% CI, 0.24-0.84) derived a larger benefit than the patients with adenocarcinoma (HR, 0.66; 95% CI, 0.50-0.87) and had a higher rate of pathologic complete response (pCR; 49% vs 23%).[4] The magnitude of the survival benefit of trimodality therapy for ESCC was similar in long-term follow-up, whereas the benefit for adenocarcinoma appeared to be smaller and was not statistically significant (unadjusted HR, 0.77; 95% CI, 0.58-1.01).[5,6] Thus, the CROSS trial established trimodality therapy with chemoradiation followed by surgery as the standard of care for patients with resectable ESCC, esophageal adenocarcinoma, or GEJ adenocarcinoma, with the greatest benefit seen in patients with ESCC.

No study to date has defined the superiority of any one chemotherapy regimen given concurrently with neoadjuvant radiation. Several single-arm phase 2 studies in patients with esophageal or GEJ adenocarcinoma have evaluated the safety and efficacy of leucovorin, 5-FU, and oxaliplatin (FOLFOX) in conjunction with radiation therapy. These trials identified pCR rates of 28% to 38%, with pCR serving as an important surrogate endpoint in esophageal and GEJ cancers given its consistent association with OS in observational studies.[7-11] These phase 2 studies serve as the basis for the use of FOLFOX with radiation treatment as an alternative to carboplatin plus paclitaxel for patients with esophageal or GEJ adenocarcinoma. PROTECT-1402 is an ongoing trial that is directly comparing neoadjuvant chemoradiation (41.4 Gy of radiation) with FOLFOX vs carboplatin plus paclitaxel, with outcomes including the complete resection rate, postoperative morbidity rate, and disease-free survival. This latter study may help guide future decisions regarding the optimal chemotherapy regimen to be used in conjunction with radiation therapy.[12]

Ongoing research is also evaluating modifications to neoadjuvant chemoradiation therapy, including the EA2174 trial, which is evaluating the role of nivolumab (Opdivo, Bristol Myers Squibb) in combination with standard preoperative chemoradiation therapy for patients with esophageal or GEJ adenocarcinoma.[13]

Induction Chemotherapy Followed by Neoadjuvant Chemoradiation in Esophageal and GEJ Cancer

Much interest has been shown in evaluating the potential benefit of induction chemotherapy before neoadjuvant chemoradiation in patients with esophageal or GEJ adenocarcinoma (Table 1). Several potential advantages of this strategy include (1) that an earlier clinical response is possible, obviating the need for a feeding tube to maintain nutrition during chemoradiation and (2) that induction chemotherapy may allow the response to a specific chemotherapy regimen to be assessed before chemoradiation is initiated. Ajani and colleagues performed a randomized phase 2 trial that compared induction FOLFOX followed by chemoradiation vs chemoradiation alone (each arm with a plan for surgery) and found no significant difference in OS (median OS, 43.7 vs 45.6 months; *P*=.69) or rate of pCR (26% vs 13%; *P*=.094).[14] The North Central Cancer Treatment Group (NCCGT) N0849 phase 2 randomized trial compared neoadjuvant FOLFOX chemoradiation with or without induction docetaxel, capecitabine, and oxaliplatin in patients with esophageal or GEJ adenocarcinoma. The study was closed early because of futility for the primary endpoint of pCR (28.6% in the induction chemotherapy group vs 40.7% in the chemoradiation-alone group).[15] Despite the lower pCR rate, a trend toward improved OS was observed for induction chemotherapy (HR, 0.70; 95% CI, 0.35-1.40; *P*=.30), but the difference was not statistically significant.[15] The collective results of these trials suggest that additional study of the potential benefits of induction chemotherapy for improving OS is warranted.

The CALGB 80803 phase 2 trial evaluated a positron emission tomography (PET)–adapted approach, with induction chemotherapy followed by chemoradiation therapy.[16] This study randomly assigned 257 patients with surgically resectable esophageal or GEJ adenocarcinoma to induction chemotherapy with FOLFOX or carboplatin/paclitaxel followed by repeat PET/computed tomography (CT) after the completion of induction chemotherapy. Patients were categorized as PET responders if their tumor demonstrated a decrease of at least 35% in standard uptake value (SUV) from baseline. If patients were classified as PET responders, they continued chemoradiation therapy

Table 1. Trials Examining Induction Chemotherapy Followed by Neoadjuvant Chemoradiation in Patients With Esophageal, GEJ, or Gastric Adenocarcinoma

Trial	Phase, Design, N	Site	Histology	Intervention	Control	Median OS, Int, Con, mo	HR for OS[c]	pCR Rate, Int, Con
RTOG 9904[63]	2, single arm, 49	Gastric	100% AC	Induction with 5-FU/cisplatin; chemoradiation with 5-FU/paclitaxel	NA	23.2, NA	NA	26%, NA
Rivera et al, 2009[64]	2, single arm, 23	Gastric, GEJ	100% AC	Induction and chemoradiation with irinotecan/cisplatin	NA	14.5, NA	NA	9%, NA
SAKK 75/02[65]	2, single arm, 66	Esophageal, GEJ[a]	55% AC, 45% ESCC	Induction and chemoradiation with docetaxel/cisplatin	NA	36.5, NA	NA	24%, NA
Ajani et al, 2013[14]	2, randomized, 126	Esophageal, GEJ[b]	96.8% AC, 3.2% ESCC	Induction and chemoradiation with FOLFOX	Chemoradiation with FOLFOX	43.7, 45.6	NA	26%, 13%
Ilson et al, 2012[66]	2, single arm, 55	Esophageal, GEJ	75% AC, 25% ESCC	Induction and chemoradiation with irinotecan/cisplatin	NA	31.7, NA	NA	16%, NA
CALGB 80803[16]	2, randomized, 257	Esophageal, GEJ	100% AC	Induction with FOLFOX or carboplatin/paclitaxel; switch chemotherapy for chemoradiation if PET nonresponse	NA	41.2, NA	NA	24%, NA
NCCTG N0849[15]	2, randomized, 55	Esophageal, GEJ	100% AC	Induction with docetaxel, oxaliplatin, capecitabine; chemoradiation with FOLFOX	Chemoradiation with FOLFOX	56.4, 19.2	0.70 (0.35-1.40)	28.6%, 40.7%

[a]Siewert I GEJ adenocarcinoma.
[b]Siewert I and II GEJ adenocarcinoma.
[c]HR for OS with 95% CI.

5-FU, 5-fluorouracil; AC, adenocarcinoma; Con, control group; ESCC, esophageal squamous cell carcinoma; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; GEJ, gastroesophageal junction; HR, hazard ratio; Int, intervention group; NA, not applicable or not reported; OS, overall survival; pCR, pathologic complete response; PET, positron emission tomography.

(radiation at 50.4 Gy in 28 fractions) and the same chemotherapy regimen they had received during induction therapy. If they were classified as PET nonresponders, they proceeded to chemoradiation therapy, but with the chemotherapy regimen that they did not receive during induction. The primary endpoint of a pCR rate greater than 5% among PET nonresponders was met for FOLFOX induction nonresponders (pCR, 18%; 95% CI, 7.5-33.5) and carboplatin/paclitaxel nonresponders (pCR, 20%; 95% CI, 10-33.7). The pCR rate for the PET responders in the induction FOLFOX group was significantly higher than the pCR rate for the PET responders in the induction carboplatin plus paclitaxel group (pCR, 40.3% vs 14.1%; *P*=.001). Additionally, pathologic node-negative rates were higher for patients receiving induction FOLFOX (84.1% for PET responders, 71.4% for PET nonresponders) than for those receiving induction carboplatin plus paclitaxel (66.7% for PET responders, 59.0% for PET nonresponders). Median OS for the overall study population was 41.2 months (95% CI, 30.9 to not reached), with a 5-year OS rate of 44.9% (95% CI, 38.8-52.0). This study did not compare OS in the 2 induction chemotherapy arms. It must be stated that no randomized trial has demonstrated the superiority of induction chemotherapy followed by

Table 2. Trials Examining the Efficacy of Perioperative Chemotherapy in Patients With Esophageal, GEJ, or Gastric Adenocarcinoma

Trial	Phase, Design, N	Site	Histology	Intervention	Control	Median OS, Int, Con, mo	HR (95% CI) for OS	5-y OS Rate (95% CI), Int, Con
MAGIC[18]	3, randomized, 503	Gastric, GEJ, lower esophageal	100% AC	Perioperative ECF	Surgery	NA, NA	0.75 (0.60-0.93)	36.3% (29.5-43.0), 23.0% (16.6-29.4)
FLNCLCC ACCORD 07[17]	3, randomized, 224	Gastric, GEJ, lower esophageal	100% AC	Perioperative 5-FU/cisplatin	Surgery	NA, NA	0.69 (0.50-0.95)	38% (29-47), 24% (17-33)
FLOT4[19]	3, randomized, 716	Gastric, GEJ	100% AC	Perioperative FLOT	Perioperative ECF/ECX	50, 35	0.77 (0.63-0.94)	45% (38-51), 36% (30-42)

5-FU, 5-fluorouracil; AC, adenocarcinoma; Con, control group; ECF, epirubicin, cisplatin, and 5-FU; ECX, epirubicin, cisplatin, and capecitabine; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; GEJ, gastroesophageal junction; HR, hazard ratio; Int, intervention group; mo, months; NA, not applicable or not reported; OS, overall survival; y, year.

chemoradiation therapy over neoadjuvant chemoradiation therapy alone, and the CALGB 80803 trial does not address this question. The induction chemotherapy approach may be considered for selected patients following multidisciplinary discussion and is an important avenue for continued research.

Perioperative Chemotherapy in Esophageal and GEJ Cancer

Several large phase 3 trials have established the benefit of perioperative chemotherapy in comparison with surgery alone in patients with esophageal, GEJ, or gastric adenocarcinoma (Table 2).[17-19] Although the perioperative chemotherapy paradigm is most consistently applied in the setting of localized gastric adenocarcinoma, each of the referenced trials included patients with GEJ adenocarcinoma and/or lower esophageal adenocarcinoma. The MAGIC trial was the first to demonstrate a significant OS benefit of perioperative epirubicin, cisplatin, and 5-FU (ECF) chemotherapy in comparison with surgery alone in patients who had lower esophageal (14.5%), GEJ (11.5%), or gastric adenocarcinoma (74%).[18] A test for heterogeneity did not detect significant differences between effects by disease site, which suggested efficacy across disease sites. Similarly, the Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) ACCORD 07 trial randomly assigned patients with adenocarcinoma of the lower esophagus (11%), GEJ (64%), or stomach (25%) to perioperative chemotherapy with 5-FU/cisplatin or to surgery alone and demonstrated better OS in the perioperative chemotherapy group (HR, 0.69; 95% CI, 0.50-0.95; *P*=.02).[17] In the subgroup analysis, a significant benefit of perioperative chemotherapy was observed in patients with GEJ adenocarcinoma (HR, 0.57; 95% CI, 0.39-0.83), and no significant benefit was observed in those with esophageal or gastric adenocarcinoma, who represented smaller subgroups in this study. Most recently, the FLOT4 trial demonstrated a statistically significant survival benefit of perioperative chemotherapy with 5-FU/leucovorin, oxaliplatin, and docetaxel (FLOT) in comparison with perioperative chemotherapy with ECF (or ECX, which replaces 5-FU with capecitabine) in patients with GEJ (56%) or gastric (44%) adenocarcinoma, and these results were consistent across disease site subgroups.[19] This latter study has led to the establishment of perioperative FLOT chemotherapy as the standard of care for fit patients with operable gastric adenocarcinoma, and as an option for patients with GEJ adenocarcinoma.

Choosing Between Neoadjuvant Chemoradiation and Perioperative Chemotherapy in Esophageal and GEJ Cancer

Although the evidence suggests a significant survival benefit of perioperative FLOT in comparison with either perioperative ECF/ECX or surgery alone in patients with GEJ adenocarcinoma, perioperative FLOT has not been directly compared with neoadjuvant chemoradiation in this patient population.[4] The Neo-AEGIS trial was designed to compare ECF/ECX perioperative chemotherapy vs neoadjuvant chemoradiation therapy with carboplatin plus paclitaxel (the CROSS regimen).[20] However, during accrual for the study, the FLOT4 trial demonstrated the superiority of FLOT to ECF/ECX,[19] which led to a protocol amendment allowing FLOT as a perioperative chemotherapy regimen. At completion

of the study, only 15% of the patients in the perioperative chemotherapy arm had received FLOT, making a comparison of the role of perioperative FLOT vs that of chemoradiation not statistically achievable. The ESOPEC trial, which completed accrual in April 2020, aims to answer this outstanding question: Is perioperative chemotherapy with FLOT or neoadjuvant chemoradiation with the CROSS regimen superior for prolonging OS in patients with surgically resectable esophageal or GEJ adenocarcinoma?[21] Importantly, the study is powered to detect a relatively large difference in OS between the treatment arms (HR, 0.645) but may be underpowered to detect smaller, potentially clinically significant survival benefits in one treatment arm or the other.[21]

Our general practice is to treat patients with esophageal or Siewert I or II GEJ adenocarcinoma with neoadjuvant chemoradiation therapy and use a perioperative chemotherapy paradigm for patients with Siewert III GEJ adenocarcinoma. However, the decision requires a consideration of individual patient and disease characteristics, including the distribution of lymph node involvement, and should ideally be made following multidisciplinary discussion.

Postoperative Treatment Approaches in Patients With Esophageal or GEJ Cancers

Adjuvant Chemotherapy for Patients With Esophageal or GEJ Cancers Who Received Neoadjuvant Chemoradiation and Surgery

Among patients with esophageal or GEJ cancers who receive neoadjuvant chemoradiation therapy and surgery, no prospective, randomized data have demonstrated a benefit of adjuvant chemotherapy. Several analyses of the National Cancer Database have attempted to identify whether patients in a real-world setting benefit from adjuvant chemotherapy. Mokdad and colleagues, in a propensity score–matched analysis, found that among patients with esophageal or GEJ adenocarcinoma who received prior neoadjuvant chemoradiation and surgery, median OS was 40 months in those who received adjuvant chemotherapy vs 30 months in those who did not receive adjuvant chemotherapy.[22] Burt and colleagues attempted to identify subgroups of patients who might benefit most from adjuvant chemotherapy, and among patients with residual nodal disease at the time of surgery, they found a 30% reduced risk for death in those who received adjuvant chemotherapy in comparison with those who did not receive adjuvant chemotherapy.[23] However, the clinical relevance of these data has been reduced owing to the recent reporting on the efficacy of adjuvant immunotherapy in this setting, which has become the new standard of care.

Adjuvant Immunotherapy for Patients With Esophageal or GEJ Cancers Who Received Neoadjuvant Chemoradiation and Had Residual Disease at the Time of Surgery

The CheckMate 577 study, which was recently reported, changed the paradigm for adjuvant therapy in patients with esophageal or GEJ cancer. This study evaluated patients with esophageal or GEJ cancer (71% adenocarcinoma) who underwent neoadjuvant chemoradiation and were found to have pathologic residual disease upon resection (non-pCR). Within 4 to 16 weeks after surgery, patients were randomly assigned to nivolumab for 1 year or to placebo. Adjuvant therapy with nivolumab was associated with improved disease-free survival (HR, 0.69; 95% CI, 0.56-0.86; $P<.001$), and the benefit was observed across subgroups including histologic subtype and programmed death ligand 1 (PD-L1) expression (both tumor positive score and combined positive score).[24] OS data have not yet been reported; we await these results. The disease-free survival benefit supports the use of adjuvant nivolumab as the standard of care in patients with esophageal or GEJ cancers who have undergone neoadjuvant chemoradiation and have pathologic residual disease upon surgical resection. Ongoing trials are examining combination immunotherapy in the adjuvant setting, including EA2174, which is evaluating the addition of ipilimumab (Yervoy, Bristol Myers Squibb) to nivolumab in this clinical setting.[13]

Surgery-Sparing Treatment Options in Esophageal and GEJ Cancers

Role of Esophagectomy in Patients With Noncervical ESCC Undergoing Chemoradiation

Given that chemoradiation provides greater benefit to patients with ESCC than to those with adenocarcinoma, several studies have examined the question of whether the addition of surgery improves outcomes in comparison with chemoradiation alone. One such study examined 444 patients who had ESCC (88.8%) or esophageal adenocarcinoma and a clinical response to chemoradiation therapy with 5-FU plus cisplatin; the patients were subsequently randomly assigned to surgery or continuation of chemoradiation therapy.[25] A second study evaluated 172 patients with ESCC of the middle or upper esophagus and randomly assigned them to induction chemotherapy followed by chemoradiotherapy followed by surgery, or to the same course without surgery.[26] Although these trials differed in inclusion criteria and interventions, a meta-analysis incorporating the 2 studies found no difference in OS between the patients who were randomly assigned to surgery and those assigned to no surgery (HR, 0.99; 95% CI, 0.79-1.24; $P=.92$), although it did

demonstrate a probable improvement in freedom from locoregional relapse in the patients who were randomly assigned to receive surgery (HR, 0.55; 95% CI, 0.39-0.76; *P*=.0004).[27] Despite some degree of equipoise surrounding this question, the ongoing standard of care for patients with noncervical, high-risk cT2 or higher ESCC is to recommend trimodality therapy with neoadjuvant chemoradiation and surgery; however, definitive chemoradiation therapy remains an acceptable option.[28] In contrast, for patients with cervical cT2 or higher disease, definitive chemoradiation therapy is the preferred approach.[28]

Among patients who do not undergo initial surgery and then experience local recurrence, those who remain surgical candidates may undergo salvage esophagectomy. A recent systematic review and meta-analysis documented outcomes in patients (76.7% with ESCC) who underwent salvage esophagectomy for persistent or recurrent local disease following neoadjuvant or definitive-intent chemoradiation therapy.[29] Salvage surgery is associated with high rates of complications, including anastomotic leak (17.2%), pulmonary complications (29.3%), and 90-day mortality (8.0%). However, 80.7% of patients in the included studies underwent R0 resection and the 5-year OS rate was 19.4%, indicating that salvage surgery is feasible and can be curative for a subset of patients.

Definitive Chemoradiation Therapy for Patients With Esophageal or GEJ Adenocarcinoma or ESCC Who Are Not Surgical Candidates

For patients with esophageal or GEJ cancer who are not surgical candidates or who elect not to pursue surgery, definitive-intent chemoradiation therapy is the preferred approach to provide symptomatic benefit, improve survival, and cure a subset of patients. The RTOG 85-01 study compared radiation therapy plus 5-FU and cisplatin vs radiation therapy alone and found that chemoradiation was associated with superior OS (median OS, 14 vs 9 months; 5-year OS, 27% vs 0%; *P*<.001).[30,31] In addition to 5-FU plus cisplatin, FOLFOX and carboplatin plus paclitaxel are standard chemotherapy options to be used with definitive-intent chemoradiation. The PRODIGE5/ACCORD17 trial compared definitive-intent chemoradiation with FOLFOX vs 5-FU plus cisplatin and found no difference in progression-free survival, rates of grade 3/4 adverse events, or measures of health-related quality of life. The investigators did, however, note potential advantages in convenience of administration with FOLFOX, and they established this regimen as an option to be used with definitive-intent chemoradiation therapy.[32,33] Although no large, prospective trials have evaluated carboplatin plus paclitaxel in the setting of definitive-intent chemoradiation, its use in neoadjuvant chemoradiation therapy as part of the CROSS trial and retrospective data documenting its safety and efficacy in this setting have made it a preferred option as part of definitive-intent chemoradiation.[4,34] The INT 0123 trial examined higher doses of radiation therapy as part of definitive-intent chemoradiation therapy (standard dose of 50.4 Gy vs high dose of 64.8 Gy) in patients with ESCC (85%) or esophageal or GEJ adenocarcinoma and found no difference in OS (median OS, 18 months with the standard dose vs 13 months with the high dose) or rates of locoregional persistence or failure (56% with the high dose vs 52% with the standard dose).[35]

Promising avenues of ongoing research to improve outcomes with definitive-intent chemoradiation therapy include the addition of immunotherapy to this paradigm. The KEYNOTE-975 trial is examining concurrent and adjuvant pembrolizumab (Keytruda, Merck) in patients with ESCC or esophageal or Siewert I GEJ adenocarcinoma undergoing definitive-intent chemoradiation therapy, and the SKYSCRAPER-07 trial is examining atezolizumab (Tecentriq, Genentech) with or without tiragolumab for patients with unresectable ESCC after definitive-intent chemoradiation therapy.[36,37]

Approach to Localized Gastric Adenocarcinoma

Perioperative Chemotherapy in Gastric Adenocarcinoma

Perioperative chemotherapy is the standard-of-care approach in patients with locoregional gastric cancer (≥cT2) on the basis of randomized trials that demonstrated a significant survival benefit (Table 2). As previously discussed, the MAGIC trial randomly assigned 503 patients (74% with gastric adenocarcinoma) to perioperative chemotherapy with ECF or surgery alone and found a significant OS benefit with perioperative chemotherapy (HR, 0.75; 95% CI, 0.60-0.93; *P*=.009).[18] The FLOT4 trial subsequently randomly assigned 716 patients (44% with gastric adenocarcinoma) to perioperative chemotherapy with FLOT or to perioperative chemotherapy with ECF/ECX and found a significant OS benefit with FLOT (HR, 0.77; 95% CI, 0.63-0.94; *P*=.012); the effect was consistent across gastric and GEJ adenocarcinoma subgroups.[19] Although more effective than ECF/ECX, FLOT is associated with significant toxicity, and 25% of the patients who received FLOT were hospitalized for toxicity. Therefore, FLOT is the recommended perioperative chemotherapy option for patients with localized disease; however, patients must be medically fit. Alternative options for perioperative chemotherapy include FOLFOX and 5-FU plus cisplatin. The combination of 5-FU plus cisplatin was evaluated in the FNCLCC

ACCORD-07 trial (25% with gastric adenocarcinoma) and demonstrated a significant survival benefit compared with surgery alone.[17]

The unreported TOPGEAR trial is comparing perioperative chemotherapy with ECF or FLOT vs induction chemotherapy with ECF or FLOT followed by neoadjuvant chemoradiation, surgery, and postoperative chemotherapy to clarify if there is a role for the addition of neoadjuvant chemoradiation in the perioperative chemotherapy paradigm.[38] Several ongoing large phase 3 trials are examining the addition of perioperative immunotherapy to perioperative chemotherapy, including KEYNOTE-585 and MATTERHORN, which are examining the addition of pembrolizumab and durvalumab (Imfinzi, AstraZeneca), respectively, to perioperative chemotherapy.[39,40]

Postoperative Therapy in Gastric Adenocarcinoma

For patients with gastric adenocarcinoma who do not receive preoperative therapy, options include postoperative chemotherapy and/or postoperative chemoradiation therapy. The benefit of postoperative chemotherapy in the era of D2 lymph node dissection with gastrectomy was established by the CLASSIC trial, which randomly assigned 1035 patients with gastric adenocarcinoma to D2 gastrectomy followed by adjuvant chemotherapy with capecitabine plus oxaliplatin (CAPOX) or to D2 gastrectomy alone. Adjuvant CAPOX was associated with superior disease-free survival (HR, 0.56; 95% CI, 0.44-0.72; *P*<.0001) and OS (HR, 0.66; 95% CI, 0.51-0.85; *P*=.0015) in comparison with D2 gastrectomy alone.[41,42]

The INT-0116 trial found an OS and relapse-free survival benefit of postoperative chemotherapy plus chemoradiation therapy via the Macdonald regimen (a sandwich regimen of adjuvant 5-FU/leucovorin before and after 5-FU/leucovorin–based chemoradiation therapy), but the trial was conducted in the era before widespread D2 lymph node dissection with gastrectomy, and only 10% of the patients underwent formal D2 lymph node dissection.[43,44] The ARTIST and ARTIST II trials failed to establish the benefit of adding chemoradiation to adjuvant chemotherapy in patients who previously underwent D2 lymph node dissection.[45-47] A retrospective study of patients enrolled in phase 1/2 trials of postoperative chemoradiation and patients in the Dutch Cancer Group Trial who received surgery alone with D1 or D2 lymph node dissection found that among the patients who received D1 lymph node dissection, the risk for local recurrence was lower in those who underwent postoperative chemoradiation therapy than in those who underwent surgery alone (2% vs 8%; *P*=.001). In the D2 lymph node dissection group, no difference was observed between the local recurrence rates of patients who underwent postoperative chemoradiation and the rates of those who had surgery alone.[48] Thus, postoperative chemoradiation in addition to postoperative chemotherapy is recommended only for patients who underwent less than a D2 lymph node dissection.

Biomarker-Driven Alterations to Perioperative Therapy in Esophageal, GEJ, and Gastric Cancers

Microsatellite Instability in Gastric Adenocarcinoma

High-level microsatellite instability (MSI-H) or mismatch repair deficiency (MMRd) occurs in 9% to 22% of gastric adenocarcinomas and is concentrated in earlier-stage disease.[49,50] MSI-H/MMRd is associated with response to immune checkpoint blockade, and the overall response rate of patients who have advanced MSI-H/MMRd gastric adenocarcinoma treated with pembrolizumab is 45.8%, with durable responses (median duration of response not reached).[51] However, data are currently too limited to guide decision making regarding the role of immunotherapy in the perioperative setting for patients with MSI-H/MMRd localized disease, and to determine the degree to which the current paradigm of perioperative chemotherapy benefits these patients. A retrospective review of the MAGIC trial identified 20 patients with MSI-H gastric adenocarcinoma, although only 303 of a total of 503 patients were evaluable for MSI. The study found that in patients with MSI-H tumors, median OS was longer in those who received surgery alone (median OS, not reached; 95% CI, 4.4 months to not reached) than in those who received perioperative chemotherapy plus surgery (median OS, 9.6 months; 95% CI, 0.1-21.9 months).[52] A patient-level meta-analysis of the MAGIC, CLASSIC, ARTIST, and ITACA-S trials aimed to determine the predictive value of MSI-H (121 patients) as a biomarker for the benefit of chemotherapy in patients with esophageal, GEJ, or gastric adenocarcinoma. The test of interaction for differential outcomes according to MSI status in patients with chemotherapy-treated and non–chemotherapy-treated disease was not significant, although this test was likely underpowered given the small sample size. When the sample was limited to patients with MSI-H disease, no benefit to chemotherapy vs surgery alone was observed (HR, 1.50, 95% CI, 0.55-4.12).[53] These results are considered exploratory, but they raise questions about the optimal treatment approach for patients with MSI-H/MMRd esophageal, GEJ, or gastric cancers in the perioperative setting. The ongoing IMHOTEP trial is investigating neoadjuvant pembrolizumab in patients with MSI-H/MMRd localized cancers, including gastric cancer, and the INFINITY trial is investigating neoadjuvant durvalumab plus tremelimumab in MSI-H/

MMRd localized gastric cancers.[54,55] Although not limited to patients with MSI-H/MMRd disease, the MATTERHORN and KEYNOTE-585 trials examining the addition of perioperative durvalumab and pembrolizumab, respectively, to perioperative chemotherapy are testing a paradigm that may be especially beneficial to patients with MSI-H/MMRd disease.[39,40]

HER2-Overexpressing Esophageal, GEJ, and Gastric Adenocarcinomas

Human epidermal growth factor receptor 2 (HER2) overexpression, defined as 3+ staining by immunohistochemistry (IHC) or 2+ by IHC with amplification by fluorescence in situ hybridization (FISH), occurs in up to 22% of gastric adenocarcinomas, up to 32% of GEJ adenocarcinomas, and up to 17% of esophageal adenocarcinomas.[56,57] A series of trials has evaluated the addition of HER2-directed therapy to neoadjuvant or perioperative treatment in this patient population. The RTOG 1010 study randomly assigned 571 patients with HER2-overexpressing esophageal, GEJ, or proximal gastric adenocarcinoma to neoadjuvant chemoradiation with or without trastuzumab, followed by surgery. The investigators found no benefit in disease-free survival (HR, 0.97; 95% CI, 0.69-1.36) or OS (HR, 1.01; 95% CI, 0.69-1.47) with the addition of trastuzumab.[58] A single-arm phase 2 trial examined the feasibility and safety of adding trastuzumab and pertuzumab (Perjeta, Genentech) to neoadjuvant chemoradiation in patients with HER2-overexpressing esophageal adenocarcinoma. It found promising activity, with a pCR rate of 34%, and the addition of HER2-targeted therapy was associated with better OS than the OS in a propensity score–matched historical control group that had undergone neoadjuvant chemoradiation therapy alone.[59] However, to our knowledge, no ongoing phase 3 trials are addressing the value of HER2-targeted therapies as part of neoadjuvant chemoradiation in esophageal adenocarcinoma. The PETRARCA phase 2 study randomly assigned patients with HER2-overexpressing gastric adenocarcinoma to perioperative FLOT with or without trastuzumab plus pertuzumab. The study was closed early after 81 patients had been randomly assigned owing to a failure to establish a benefit of this regimen in the metastatic setting in the JACOB trial.[60] However, the addition of trastuzumab and pertuzumab in the perioperative setting was associated with a higher pCR rate (35% vs 12%; *P*=.02) and a higher pathologic node negativity rate (68% vs 39%).[61] The ongoing phase 3 INNOVATION trial is randomly assigning patients with HER2-overexpressing resectable gastric adenocarcinoma to perioperative chemotherapy vs perioperative chemotherapy plus trastuzumab vs perioperative chemotherapy plus trastuzumab and pertuzumab.[62]

Conclusion

For most patients with nonmetastatic esophageal and GEJ cancers, neoadjuvant chemoradiation therapy before surgery remains the standard of care. Ongoing trials will assess the optimal chemotherapy regimen, with recent data demonstrating the benefit of adjuvant nivolumab in patients who have residual disease at the time of surgery. Ongoing research will also clarify the role of perioperative chemotherapy vs that of neoadjuvant chemoradiation for patients with esophageal cancer or GEJ cancer, as well as the potential role of induction chemotherapy. For patients who have gastric adenocarcinoma, perioperative chemotherapy with FLOT is now the standard of care, although toxicities are limiting and FLOT is for the most part feasible only in fit patients. Research into the addition of immunotherapy and HER2-directed therapy in the perioperative setting for esophageal, GEJ, and gastric cancer is ongoing.

Disclosures

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