American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Loco-Regional Gastric Adenocarcinoma: Systematic Review and Guidelines

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KEY

5-FU = 5-fluorouracil
aCRT = adjuvant concurrent chemoradiation therapy
aCT = adjuvant chemotherapy
AJCC = American Joint Committee on Cancer
AP/PA = anteroposterior/posteroanterior
ARS = American Radium Society™
AUC = Appropriate Use Criteria
aRT = adjuvant radiation therapy
ARTIST = Adjuvant Chemoradiotherapy in Stomach Tumors
CALGB = Cancer And Leukemia Group B
cCR = clinical complete response
CF = cisplatin, fluorouracil
CRITICS = ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach
CROSS = ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study
CRT = concurrent chemoradiation therapy
CT = Computed Tomography
CTV = Clinical Target Volume
dCRT = definitive concurrent chemoradiation therapy
DFS = disease-free survival
DMFS = distant metastases free survival
DOF = docetaxel, oxaliplatin, 5-fluouracil
ECF = epirubicin, cisplatin, fluorouracil
ECOG = Eastern Cooperative Oncology Group
ECX = Epirubicin, cisplatin and capecitabine
EGFR = epidermal growth factor receptor
EMR = Endoscopic mucosal resection
EOF = epirubicin, oxaliplatin fluorouracil
EOX = epirubicin, oxaliplatin, capecitabine
EUS = Endoscopic ultrasound
FFCD = Federation Francophone de Cancerologie Digestive
FLOT = 5-fluorouracil, leucovorin, oxaliplatin, docetaxel
FNA = fine needle aspiration
FOLFOX = Folinic acid, 5-Fluorouracil, and Oxaliplatin
FU = 5-fluorouracil
Fx = fractions
GEJ = gastroesophageal junction
GTV = Gross Tumor Volume
HRQoL = Health Related Quality-of-Life
ICRU = International Commission on Radiation Units
iCT = induction chemotherapy given before CRT
IGRT = image guided radiation therapy
IMRT = Intensity Modulated Radiation Therapy
LV = leucovorin
LVI = lymphovascular invasion
MAGIC = Medical Research Council Adjuvant Gastric Infusion Chemotherapy
MRC OE02 = Medical Research Council Oesophageal 02
MRC OE05 = Medical Research Council Oesophageal 05
MSI-H = microsatellite instability high
MSI-L = microsatellite instability low
NCCN = National Comprehensive Cancer Network
nCRT = neoadjuvant concurrent chemoradiation therapy
nCT = neoadjuvant chemotherapy
NEORES: NEOadjuvant Chemotherapy Versus Radiochemotherapy for cancer of the ESophagus or Cardia
NEOSCOPE: NEOadjuvant Study of Chemoradiotherapy in OesoPhagEal Cancer
nRT = neoadjuvant RT
OAR = organ-at-risk
OR = odds ratio
OS = overall survival
pCR = pathological complete response
PET/CT = Positron Emission Tomography/Computed Tomography
PFS = progression free survival
PICOS = Population, Intervention, Comparator, Outcome, Study design
poCT = perioperative chemotherapy
POET: PreOperative therapy in Esophagogastric adenocarcinoma Trial
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTV = Planning Target Volume
QoL = Quality of Life
RCT = randomized controlled trial
RR = risk ratio
RT = radiation therapy
RTOG = Radiation Therapy Oncology Group
SCC = squamous cell carcinoma
SOX = S-1 and oxaliplatin
TOPGEAR = Trial Of Preoperative therapy for Gastric and Esophagogastric junction Adenocarcinoma
TRG = tumor regression grade
UICC = Union for International Cancer Control
XELOX = capecitabine and oxaliplatin
INTRODUCTION

While the incidence of gastric cancer is declining, it continues to be associated with high mortality rates. Gastric cancer is the third leading cause of cancer deaths worldwide and the 6th most commonly diagnosed malignancy with slightly over one million new cases diagnosed in 2020\textsuperscript{1}. The highest incidence rates are in Asia and Latin America. In the United States, it is the 15th most common cause of cancer and cancer-related death, with an estimated 26,560 new cases diagnosed in 2020\textsuperscript{2}.

Screening for gastric cancer is only performed in countries with high incidence rates, such as Japan. Elsewhere, it is typically diagnosed when patients present with symptoms such as weight loss, early satiety, fatigue, anemia, and abdominal pain. Treatment and prognosis are determined by tumor stage; thus, an accurate staging evaluation is critical to managing patients with gastric cancer. Endoscopy with biopsy and endoscopic ultrasound (EUS) and contrast-enhanced computed tomography (CT) scans of the chest, abdomen, and pelvis are required to complete the staging evaluation. A PET/CT scan and laparoscopic staging to identify occult omental disease should be considered.\textsuperscript{3} Gastroesophageal junction (GEJ) tumors are often grouped with gastric cancers in studies, and are classified by Siewert staging, based on the location of their epicenter relative to the Z-line (Siewert I – 1-5 cm above the gastric cardia, Siewert II – 1 cm above to 2 cm below the gastric cardia, Siewert III – 2-5 cm below the start of the gastric cardia). Siewert I/II tumors are often treated as esophageal cancers whereas Siewert III are most often treated as gastric cancer.

Patients with disease no deeper than the submucosa can proceed directly to surgery, while the majority of other patients are recommended to undergo neoadjuvant therapy before surgical resection.\textsuperscript{3} The most recent version of the American Joint Committee on Cancer (AJCC) Staging
Manual (8th edition, 2017) includes pathologic stage groups following neoadjuvant therapy to reflect the increasing use of preoperative treatment for gastric cancer. Final pathologic stage is determined by findings at the time of surgery, which should include thorough dissection of the perigastric regional lymphatics (D1 dissection) as well as nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery (D2 dissection).

This manuscript provides evidence-based guidelines for the treatment of localized gastric cancer. Neoadjuvant, perioperative, and adjuvant approaches are reviewed in the case of operable gastric cancer and definitive concurrent chemoradiation therapy (dCRT) is presented as an option for inoperable patients.

**METHODOLOGY**

The evidence regarding treatment outcomes was assessed using the Population, Intervention, Comparator, Outcome, and Study design (PICO) framework. Through the use of randomized controlled trials (RCTs) and meta-analyses we sought to compare oncologic outcomes of neoadjuvant, and/or adjuvant treatment, surgery alone, or definitive chemoradiation (dCRT). Trial size required for inclusion was ≥50 patients for phase IIR and III RCTs, and ≥100 patients for meta-analyses, of which at least 20 cases were required to be adenocarcinoma. In situations with very limited prospective data, less than 50-patient Phase I and II trials were allowed. With librarian assistance, we developed literature search strategies using subject headings and combinations of keyword search terms (Table 1) to address our PICO question.

An extensive analysis of current medical literature covering 1/1/2010-5/1/2020 from peer-reviewed journals indexed in the Ovid Medline database and using the Preferred Reporting
Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines yielded a comprehensive set of relevant articles. The literature was reviewed for quality of study design, cohort size, selection bias, and methods of assessments. Two authors (R.K. and L.T.) independently screened the studies and full text articles to determine the final studies included in this review as detailed in the reference selection flow diagram (Figure 1). Any discrepancies between the reviewers were resolved by consensus. We reviewed the bibliographies of full articles for a comprehensive survey, and nine additional studies were included meeting all inclusion criteria except publication date (all published before 2010). Forward citation searching via the Cited Reference search option on the Web of Science database was then performed on the selected documents to determine if any eligible articles published no later than 5/6/2020 had been missed by the searches, and no additional references were added. A total of 51 articles were identified using the search strategy. Study type and quality for these references were assessed via American Radium SocietyTM (ARS) Appropriate Use Criteria (AUC) methodology (Appendix A), and the checklist confirming completion of essential elements for a PRISMA 2020 systematic review may be found in Appendix B.

A well-established consensus methodology (modified Delphi) was used by the expert panel with expertise in the management of gastric cancer to rate the appropriateness of the treatment procedures. Disagreement was defined as >1/3 votes occurring outside the rating category, which included (1) Usually not appropriate (U, score 1-3); (2) May be appropriate (M, score 4-6); (3) Usually appropriate (A, score 7-9). Studies within the introduction and future directions sections are referenced only to provide context, but are not included as supporting evidence for oncologic interventions.
SUMMARY OF LITERATURE REVIEW

Autopsy series have demonstrated a significant risk of both locoregional relapse (80-93% of patients) and distant relapse (49%) after surgery alone. Consequently, improvements in outcome have involved the addition of chemotherapy and/or radiation, either in the neoadjuvant, adjuvant, or perioperative setting. For patients in whom surgical resection is not possible, whether due to oncologic or patient factors, dCRT may be a treatment option, though cures are unlikely.

TOPIC 1. NEOADJUVANT TREATMENT

Neoadjuvant therapy has been investigated in randomized controlled trials (RCTs) for gastric and GEJ cancers, with the goal of tumor downstaging, improving surgical resectability, and treating micrometastatic disease. Neoadjuvant therapy trials have included chemotherapy alone, chemoradiation, and, rarely, radiation alone. Herein, we describe the outcomes of RCTs incorporating neoadjuvant therapy.

Subtopic 1. Neoadjuvant chemotherapy (nCT) vs Surgery alone

EORTC 40954 investigated the role of neoadjuvant chemotherapy (nCT) versus surgery alone in GEJ and gastric cancer patients. One hundred forty-four patients with stage III and IV (non-metastatic) gastric cancer were randomized to receive cisplatin, leucovorin (LV), and 5-fluorouracil (5-FU) for three cycles prior to surgery versus surgery alone. The trial closed early due to poor accrual, so subsequent assessments of outcomes were limited. The overall response rate to nCT was 30.4%. There was a lower tumor- and nodal- stage, and higher R0 resection rate,
seen with nCT. After a median follow up of 4.4 years, there was no difference in median overall survival (OS).

A 2018 meta-analysis compared nCT to surgery alone.\textsuperscript{12} Fifteen RCTs from 1987 through 2014 were included, 3 of which have been discussed in this paper.\textsuperscript{10,13,14} Despite heterogeneity in the specific treatment agents, the use of nCT led to risk ratio (RR) reductions in 1-year (RR=0.81), 2-year (RR=0.83), 3-year (RR=0.74), and 5-year (RR=0.82) mortality. No differences in morbidity were seen in either arm. Of note, five of the trials, including the largest, included adjuvant chemotherapy (aCT) as well as neoadjuvant chemotherapy.

Given the importance of neaCT was demonstrated in numerous studies relative to surgery alone, Japanese investigators sought to identify the most optimal preoperative regimen. The COMPASS trial was a 2x2 phase II RCT design in patients with resectable stage III-IV gastric cancer. Either 2 or 4 cycles of S-1 (combination tegafur/gimeracil/oteracil) + cisplatin or cisplatin + paclitaxel were found to be equivalent.\textsuperscript{11} The 3-year OS was 60.9% and R0 rate was 78%, leading the authors to conclude that 2 cycles of neoadjuvant S-1 and cisplatin should be utilized as a comparator arm for future Phase III trials.

Combination nCT regimens including epirubicin, cisplatin, and 5-FU (ECF), S-1 (alone or with cisplatin), and docetaxel, oxaliplatin, and 5-FU (DOF) are preferable to surgery alone for patients with operable, non-metastatic stage III-IV gastric cancer.

\textit{Subtopic 2. Perioperative chemotherapy vs Surgery alone}

The phase III Medical Research Council Adjuvant Gastric Infusion Chemotherapy (MAGIC) trial randomized 503 patients with Stage II or higher non-metastatic, resectable, adenocarcinoma of the stomach (74%), GEJ (14%), and distal esophagus (12%) to perioperative
chemotherapy (poCT) (3 cycles pre-operatively, and 3 cycles post-operatively) with ECF or surgery alone. D0 resections were completed in 15% of patients, D1 in 19%, D2 in 40%, and unknown/unspecified in the remainder. Perioperative ECF significantly improved 5-year OS (36% vs. 23%). The trial did not require staging by EUS, thereby potentially under-staging patients. Further, combination chemotherapy was difficult to tolerate for many patients, with only 41% of patients completing all assigned cycles of chemotherapy. Preoperative chemotherapy resulted in a larger number of patients with lower tumor and nodal stages at surgery, but with no pathologic complete responses (pCR). A smaller RCT of 224 patients from France similarly identified that poCT with cisplatin/5-FU improved 5-year OS vs. surgery alone.

Following the MAGIC trial, MRC investigators initiated an RCT comparing the MAGIC regimen (epirubicin, cisplatin, and capecitabine [ECX]) to the same regimen with the addition of bevacizumab (ECX-B). Most patients had either Siewert type III (20%) or gastric (36%) adenocarcinoma, though distal esophageal and Siewert I/II were eligible. D2 dissection was recommended but not required, and 83% of patients had ≥15 lymph nodes removed. Three-year OS was similar in both groups (50.3% versus 48.1%). There was no difference in pCR between groups. The intention-to-treat R0 resection rate was 60%, but this increased to 75% when including only those who proceeded to surgery after nCT. OS significantly correlated with R0 resection and higher tumor regression grade (TRG). These results confirmed that poCT with ECX is an appropriate treatment for resectable gastric cancer.

The German FLuorouracil, Oxaliplatin, doceTaxel x4 (FLOT4-AIO) trial established perioperative FLOT as the preferred regimen for resectable gastric cancer. This trial randomized 716 patients to either 6 cycles of ECF/ECX (3 given preoperatively and 3
postoperatively), or 8 cycles (4 preoperative and 4 postoperative) of FLOT (5-FU, LV, oxaliplatin, and docetaxel), with surgical resection including an extended lymphadenectomy (≥D2 in approximately 55% of patients). Gastric cancer patients (44%), Siewert II/III (32%), and Siewert I (24%) were included. FLOT and ECF/ECX resulted in similar preoperative completion rates (90% vs. 91%, respectively). In the postoperative setting, these rates dropped to 46% (FLOT) vs. 37% (ECF/ECX), reflecting the potential toxicity of each regimen with high rates of grade ≥3 toxicities in about half of the patients. Median and 5-year OS was significantly improved with FLOT at 50 vs. 35 months and 45% vs. 36%, respectively. Pathological downstaging was also improved with FLOT, with higher rates of ypT1 tumors, lower rates of positive nodes, and a better R0 resection rate.

With the publication of the FLOT4-AIO data, 4 cycles of FLOT before and after surgery has replaced ECF/X as the preferred perioperative regimen but it carries a high risk of toxicity (Tables 2-3: Variants 1-2).

Subtopic 3: Neoadjuvant radiation (nRT) vs Surgery alone

There is limited evidence to support the use of neoadjuvant radiation (nRT) versus surgery alone for patients with resectable gastric cancer. An RCT of 370 patients with gastric cardia adenocarcinoma treated with nRT to 40 Gray (Gy) using a two-dimensional approach compared to surgery alone was reported in 1998. Radiation resulted in improved 5-year OS rates (30 vs 20%, \( p \leq 0.01 \)), resection rates, and pathological downstaging. Importantly, radiation significantly reduced the local failure rate from 52% to 39% versus surgery alone; however, surgical technique, including nodal dissection, was not discussed in the manuscript. A meta-analysis of 9 trials examining the benefit of radiation therapy (RT) (preoperative, postoperative,
or intraoperative) vs surgery alone or surgery and chemotherapy demonstrated a benefit in 5-year OS with neoadjuvant radiation.\textsuperscript{18}

Neoadjuvant radiation alone is supported by limited data but may be considered in patients who are unable or unwilling to receive chemotherapy.

\textit{Subtopic 4. Neoadjuvant chemoradiation (nCRT) vs. Surgery alone}

RTOG 9904 is a Phase II trial assessing two cycles of induction chemotherapy (5-FU, LV, and cisplatin), followed by concurrent radiation with 5-FU and paclitaxel, and then surgery.\textsuperscript{19} Radiation was delivered to a dose of 45 Gy using a three-dimensional conformal RT (3DCRT) approach, and a D2 lymphadenectomy was recommended. With a median follow-up of only 22 months, the trial demonstrated a pCR rate of 26\%, R0 rate of 77\%, and a median OS of 23 months. An attempted Eastern Cooperative Oncology Group (ECOG) trial of neoadjuvant paclitaxel/cisplatin, followed by radiation with 5-FU/LV, was aborted due to significant toxicity, with only 3 patients completing all assigned treatment.

More recently, the updated results of the CROSS trial confirmed a long-term benefit of nCRT compared to surgery alone in esophageal cancer.\textsuperscript{21} In the trial, 368 patients (primarily Siewert I/II adenocarcinoma) were randomized to nCRT using carboplatin/paclitaxel/41.4 Gy vs surgery alone. While the greatest benefit to nCRT was noted for squamous cell carcinoma patients, the improvement was significant for the cohort overall as well as for patients with adenocarcinoma. In the adenocarcinoma subset, the median OS was 43.2 months with nCRT and 27.1 months for surgery alone (HR 0.73, p=0.038).

Two recently published small phase II trials investigated the role of induction chemotherapy followed by chemoradiation and surgery. In a trial by Liu and colleagues, 40
patients with resectable gastric cancer received neoadjuvant S-1 and oxaliplatin (SOX), followed by 45 Gy with concurrent S-1, surgery, and adjuvant SOX chemotherapy. The response rate was 42%, with a disease control rate of 86%. Fourteen percent of patients achieved a pCR. With a median follow up of 27 months, the 2-year OS rate was 56%, the median OS was 30.3 months, and the median DFS was 16.7 months. Kim and colleagues similarly reported their results of 42 patients treated with induction S-1, docetaxel, and cisplatin, followed by 45 Gy with weekly docetaxel, then surgery. The pCR and R0 rates were 39.4% and 85%, respectively, with a 3-year OS of 77.9% for Stage 0-I, 66.8% for Stage II-III, and 33.3% for unresectable patients.

Based on the Phase II data, nCRT results in improved pCR rates, R0 resection, and OS compared to surgery alone. Radiation doses of 40-45 Gy, along with concurrent 5-FU/cisplatin, 5-FU/paclitaxel, carboplatin/paclitaxel, and S-1 chemotherapy, are supported by the literature.

Subtopic 5: Neoadjuvant chemoradiation (nCRT) vs. Neoadjuvant chemotherapy (nCT)

Compared to chemotherapy alone, neoadjuvant chemoradiation (nCRT) with or without induction chemotherapy has been shown to be beneficial in patients with GEJ tumors. As noted previously, the data for nCRT has derived largely from esophageal adenocarcinoma. A meta-analysis of 22 studies in patients with GEJ adenocarcinoma (including Siewert 3) compared nCT to nCRT. In the analysis, 14,709 patients were treated with nCRT versus 3,551 with nCT alone. This meta-analysis demonstrated that, despite improved pCR (odds ratio [OR] 2.8, p<0.001) and locoregional failure (LRF) rates (OR 0.6, p=0.01), there was no improvement in OS when comparing nCT to nCRT.

The updated Scandinavian phase II RCT NeoRes-1 compared nCRT versus nCT in esophageal cancer patients, including GEJ tumors (Siewert I and II). Treatment arms were 3
cycles of cisplatin and 5-FU with or without 40 Gy. Of the 181 patients randomized, 131 patients (72%) had adenocarcinoma, though only 18% were GEJ tumors. Despite significant improvements in the primary outcome of pCR (28% with nCRT versus 9% with nCT), and R0 resection rate (87% vs 74%), there was no improvement in OS. In the adenocarcinoma subgroup, no benefit was identified with the use of nCRT versus nCT. It should be noted that a more extensive lymph node dissection occurred in 83% of patients in NeoRes-1 compared to 48% in CROSS, which may have impacted the results. Further, this trial was not powered for an OS benefit, as the primary outcome was histologic response.

An Australian phase II RCT investigated the addition of nCRT following induction chemotherapy (cisplatin/5-FU) for esophageal/GEJ adenocarcinoma patients with a poor response to initial chemotherapy by PET.26 Those without ≥35% reduction in their tumor volume on a PET obtained 15 days after treatment were randomized to docetaxel/cisplatin/5-FU chemotherapy with or without 45 Gy. The addition of radiation significantly improved the primary outcome, histologic response, as well as OS compared to patients receiving chemotherapy alone.

Based on the results of two trials have demonstrating that nCRT is superior to nCT in terms of pathologic response (with one also showing an OS benefit), nCRT may be considered following induction chemotherapy in patients with GEJ tumors.

TOPIC 2. ADJUVANT THERAPY

Both adjuvant chemoradiation (aCRT) and chemotherapy (aCT) alone have demonstrated an OS benefit in patients following curative resection in gastric cancer. Contemporary research has also compared these two modalities in the adjuvant setting.
Subtopic 1. Adjuvant Chemoradiation (aCRT) vs. Surgery alone

There are several trials investigating the role of adjuvant chemoradiation (aCRT) in the management of resectable gastric cancer. In 1982, Moertel randomized patients to aCRT with 37.5 Gy in 24 fractions and concurrent 5-FU versus surgery alone. Patients in the aCRT arm had significantly lower rates of locoregional recurrence and longer 5-year OS (23% vs 4%).

Intergroup/SWOG 0116 was a landmark trial randomizing 559 patients with stage IB-IV gastric adenocarcinoma to either surgery alone, or aCRT with 5-FU, LV, and 45 Gy. Patients were T3 and/or N+, and an R0 resection was required. The D2 dissection rate was low (10% - D2, 36% - D1, 54% <D1 resection). The 10-year update demonstrated a long-term local recurrence, relapse free survival (RFS), and OS benefit with the use of aCRT. Due to the low D2 rate, now required for resectable gastric cancer, the benefit of aCRT may be limited to patients receiving ≤D1 dissection, but survival rates are comparable to perioperative chemotherapy-based regimens. Also, this study incorporated radiation therapy quality assurance, and 35% of the treatment plans were found to contain major or minor deviations from the protocol, most of which were corrected before the start of radiotherapy. This radiation quality assurance is unique to this study and suggests that appropriate radiation field design for gastric cancer is a critical aspect in achieving the intended benefit of radiation therapy (Table 4: Variant 3).

Subtopic 2. Adjuvant Chemotherapy (aCT) vs. Surgery alone

Multiple contemporary trials have demonstrated a benefit to the use of aCT over surgery alone, frequently using S-1/platinum-based regimens in East Asia and 5-FU/platinum regimens in Europe and North America.
Sasako and colleagues reported results of their large, phase III RCT of 1,059 patients comparing one year of adjuvant S-1 chemotherapy vs observation in stage II/III gastric cancer patients resected with an R0/D2 gastrectomy.\textsuperscript{29} The 5-year updated results demonstrated improved DFS (65\% vs 53\%) and OS (72\% vs 61\%) with the addition of S-1.\textsuperscript{29} A small RCT indicated that alternating day S-1 may be better tolerated and more efficacious than daily S-1.\textsuperscript{30}

The capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC) phase III RCT helped establish adjuvant capecitabine and oxaliplatin (XELOX) as an appropriate standard of care following D2 resection in stage II-III gastric cancer.\textsuperscript{31} This trial randomized 1,035 patients to D2 surgery +/- XELOX. Two-thirds of the aCT group received all 8 cycles of chemotherapy. Statistically significant benefits in DFS and OS persisted at 5-years (68\% vs 53\% and 78\% vs 69\%, respectively).

A 2018 meta-analysis of 11 RCTs with 5,620 patients found adjuvant S-1- and XELOX-based regimens improved OS over surgery alone.\textsuperscript{32} This meta-analysis was heavily influenced by the Sasako, CLASSIC, and Tsuburaya data.\textsuperscript{29,31,33}

Two contemporaneous clinical trials attempted chemotherapy intensification in the adjuvant setting. An Italian study of $\geq$D1 resected gastric cancer added docetaxel/cisplatin after adjuvant FOLFIRI versus 5-FU/LV alone\textsuperscript{34} but neither DFS nor OS were improved. A Japanese 2 x 2 phase III trial compared aCT with four arms: tegafur/uracil alone, S-1 alone, paclitaxel followed by tegafur or uracil, or paclitaxel followed by S-1.\textsuperscript{33} Sequential therapy with paclitaxel did not improve OS, nor was tegafur/uracil superior to S-1 monotherapy, thereby confirming the role of adjuvant S-1 chemotherapy in this population. Less aggressive aCT with 5-FU, doxifluridine, or uracil/tegafur have been found beneficial only in Stage II disease, though based on a subgroup analysis of a small trial.\textsuperscript{35}
Recently reported results of adjuvant docetaxel and S-1 chemotherapy vs S-1 alone following D2 resection in 915 stage III gastric cancer patients suggest the superiority of the addition of docetaxel in this population. The primary outcome relapse-free survival (RFS) was improved with docetaxel, and although OS was not there were few deaths in either arm. In stage II gastric cancer, the Japanese standard of care is one year of adjuvant S-1 (8 cycles), as 6 months (4 cycles) is considered inferior.

In the adjuvant setting, XELOX (following D2 lymphadenectomy) or S-1 is appropriate. S-1 + docetaxel is appropriate in patients with Stage III gastric cancer.

Subtopic 3. Adjuvant Chemoradiation (aCRT) vs. Adjuvant Chemotherapy (aCT)

One of the earliest trials to assess the role of adjuvant radiation versus aCT was a randomized British trial published in 1994 of 436 patients which compared adjuvant radiation to adjuvant mitomycin, doxorubicin, and 5-FU chemotherapy versus surgery alone. While locoregional recurrence was improved with radiation, neither radiation nor chemotherapy was associated with an improved OS compared to surgery alone.

A series of phase III trials published in 2012 reported on outcomes of aCRT versus aCT alone. Kim and colleagues assessed the role of aCRT in patients following an R0 surgery and D2 lymph node dissection. Ninety patients were randomized to either 5-FU/LV and 45 Gy or 5-FU/LV alone. Locoregional control was improved with RT for all patients, but DFS was only improved in stage III patients. Similarly, a phase III trial by Zhu and colleagues randomized 404 patients to 5-FU/LV +/- aCRT (notably, with intensity-modulated radiation therapy [IMRT]). The addition of radiation was associated with improved RFS (36 vs 50 months), but this did not translate into a significant improvement in OS. Lastly, Yu and colleagues randomized 68 patients
with T3/T4 and/or N+ gastric adenocarcinoma to aCT with 5-FU/LV +/- 45 Gy radiation after a D1 or D2 dissection. This trial did report significant improvements in 1, 2, and 3-year OS (85.9% vs 68.0%, 73.4% vs 50.0%, and 67.7% vs 44.1%, respectively).

The phase III Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial randomized 458 patients to aCT with capecitabine and cisplatin (XP) +/- 45 Gy. Stage IB to IVA (M0) patients were enrolled and required to undergo D2 lymphadenectomy and an R0 resection. Chemoradiation significantly improved locoregional relapse (7% vs 13%), but no differences in the entire cohort were noted for DFS and OS. A subgroup analysis suggested an improvement in 3-year DFS in N+ patients and in patients with intestinal-type gastric cancer. However, no radiation quality assurance was conducted and the remnant stomach was not routinely included in the radiation field. A Phase II trial of adjuvant radiation and S-1 demonstrated a 3-year DFS of 76%.

Two meta-analyses suggested that aCRT may improve OS compared to aCT alone. Liang included 6 studies with 2,135 patients treated with aCRT or aCT following a D2 gastrectomy, demonstrating an improvement in 5-year OS and DFS with aCRT. Dai included 6 RCTs involving 1,171 patients. CRT improved 5-year DFS, locoregional recurrence (LRR), at the expense of increased neutropenia. However, aCRT did not improve 5-year OS, 3-year DFS, or distant metastases-free survival (DMFS). It is notable that the bulk of patients included in this meta-analysis were from 2 studies - ARTIST (39%) and Zhu (30%) and likely had a disproportionate effect on the results.

Given the success of ECF poCT, Cancer and Leukemia Group B (CALGB) investigators sought to improve on INT-0116 by utilizing ECF in place of 5-FU/LV. CALGB 80101 randomized 546 patients with Stage IB-IVA (M0) resected gastric adenocarcinoma (R0 required,
D2 not required), but this study was not intended to assess the role of radiation therapy. ECF before and after 45 Gy was not superior to 5-FU and LV before and after the same radiation. Both 5-year DFS (39% 5-FU/LV vs 37% ECF) and OS (44% in both arms) were similar in both groups, but fewer patients in the 5-F/LV arm discontinued therapy due to adverse events or treatment withdrawal. Only 55% of patients on the trial had ≥15 lymph nodes removed, and 11% had <7 examined. However, the number of lymph nodes examined did not correlate with OS with either treatment regimen.

The superiority of either chemotherapy or chemoradiation in the adjuvant setting has not yet been elucidated. When chemoradiation is used in the adjuvant setting, 5-FU/LV/45 Gy or 45 Gy/capecitabine is the appropriate regimen.

TOPIC 3: PERI-OPERATIVE CHEMOTHERAPY WITH OR WITHOUT ADJUVANT CHEMORADIATION

The presence of strong clinical trial data supporting a perioperative, as well as neoadjuvant and adjuvant approaches, has led to divergent treatment practices throughout the world.

In the phase III Dutch ChemoRadiotherapy after Induction chemotherAPY In Cancer of the Stomach (CRITICS) RCT, 788 patients with Stage IB-IVA resectable gastric or GEJ adenocarcinoma (Siewert II/III) were assigned to poCT or nCT with aCRT. Preoperative chemotherapy involved with 3 cycles of ECX/EOX in both arms, with patients then randomized to aCRT to 45 Gy with capecitabine/cisplatin vs. aCT with ECX/EOX for 3 cycles. A ≥D1 lymphadenectomy was required. Unlike the Intergroup 0116 trial, preoperative chemotherapy was given in the aCRT arm, and radiation quality assurance was not performed. Only 59% of
patients in the chemotherapy group initiated aCT and of those only 46% completed all 3 cycles. After a median follow-up of 61.4 months, the median and 5-year OS was similar between the chemotherapy alone and aCRT groups: 43 versus 37 months and 42% vs 40%, respectively). The authors concluded that there is limited benefit to aCRT versus aCT alone following nCT.

TOPIC 4. DEFINITIVE CHEMORADIATION (dCRT)

While surgery remains the therapeutic mainstay in gastric and GEJ adenocarcinoma, definitive radiation (dRT) has been utilized in patients who are unable or unwilling to undergo surgery. Prospective data has demonstrated the superiority of dCRT as opposed to either modality alone in non-surgical patients. Moertel and colleagues reported on their experience of 35-37.5 Gy in 24 fractions with or without chemotherapy, and found a significant improvement in 5-year OS with combination therapy (12% vs 0%). The Gastrointestinal Tumor Study Group (GITSG) compared 5-FU/lomustine +/- split-course radiation to 50 Gy, both arms followed by consolidative chemotherapy. Chemoradiation resulted in a significant benefit in 4-year OS (18% vs 7%).

Several small, non-randomized prospective trials have investigated dCRT in the unresectable setting. A phase I study by Xing and colleagues dose escalated docetaxel to 15 mg/m2 with cisplatin and radiation to 50.4 Gy/28 fractions, with an overall response rate of 66.7% (28.6% complete/38.1% partial response). A Phase II Polish trial reported on their results of cCRT with 45 Gy/25 fractions along with bolus 5-FU, though 6 of the 13 patients in this analysis did not receive all planned chemotherapy. With a median follow-up of 30 months, 1-year, 3-year, and median OS were 59%, 48%, and 17.1 months, respectively. Intriguingly, this study reported a complete clinical response in 5 of 12 patients that completed radiation (41.7%)
(Table 5: Variant 4). Most recently, a Phase II trial combined docetaxel/cisplatin/5-FU before and after RT to 50.4 Gy/28 fx + docetaxel in 36 patients who were medically inoperable, locally advanced, or declined surgery. The trial allowed a PS of up to 2, and no severe bleeding (Hb≥10). Local control was 81% for the entire cohort. The median and 2-year OS for the entire group was 25.8 months and 52%, respectively, with the best outcomes in the medically inoperable (37.0 months and 52%) or declined surgery groups (38.9 months and 67%), compared to those who were unresectable (17.7 months and 20%).

TOPIC 5. MOLECULAR AND TARGETED THERAPY IN LOCALIZED GASTRIC CANCER

Bevacizumab has been investigated in both the neoadjuvant and perioperative setting. However, a small RCT of 80 patients did not show an OS benefit to the use of DOF with bevacizumab compared to DOF alone. Despite improvements in the D2 resection rate, overall clinical response, R0 resection rate, and 3-year DFS, there was no difference in median OS between the two groups. Thus, there is no role for bevacizumab in either the neoadjuvant or the perioperative setting, given the results of trials failing to show a benefit when added to standard chemotherapy.

TOPIC 6. RADIATION THERAPY

Subtopic 1. Simulation

For gastric cancer patients who are candidates for RT, CT simulation is performed using appropriate immobilization (e.g., large moldable pillow) in the supine position with arms raised.
The patient should be instructed to be nil per os (NPO) at least 3 hours prior to simulation and a 4-dimensional CT scan should be incorporated to assess and account for respiratory motion.

*Subtopic 2. Radiation Volumes*

In the adjuvant setting, RT is targeted at the tumor bed, duodenal stump, regional nodes, anastomotic site, remnant stomach, and 2 cm beyond the proximal and distal margins of resection. The tumor bed is defined using pre-operative CT imaging, surgical clips, endoscopy, and operative reports. The standard nodal basins included in the clinical treatment volume (CTV) are the perigastric, celiac, local para-aortic, hepatoduodenal/hepatic-portal, pancreaticoduodenal, and, in some cases, splenic regions. Additional nodal stations may be covered based on the location of the primary tumor, per the Japanese Research Committee for Gastric Cancer. Paraesophageal nodes are included in the CTV for tumors of the GEJ. Elective nodal volumes should be covered even in the setting of a D2 dissection. An additional mucosal margin may be added proximally to include the distal esophagus, where appropriate. The planning target volume (PTV) is typically a 0.5-1 cm beyond the CTV but can be as large as 2 cm if needed to account for target motion if a 4D scan is not performed. Abdominal compression, among other techniques, may be utilized to minimize PTV margins.

*Subtopic 3. Dose*

In the adjuvant setting, the standard dose is 45 Gy delivered in 25 daily fx of 1.8 Gy. A boost of 9-10 Gy/5 fx can be added in the setting of close or positive margins if normal dose constraints can be met, particularly for the small bowel (Table 6: Variant 5). For patients receiving definitive RT, doses in the range of 45-50.4 Gy have been utilized.
Subtopic 4. Radiation Technique

Early trials of adjuvant radiation for gastric cancer used a 2D anteroposterior/posteroanterior (AP/PA) field arrangement, which resulted in high rates of grade 3 toxicity, with 54% and 33% of patients experiencing hematologic and gastrointestinal toxicity, respectively. Ringash et al compared 3DCRT to IMRT and found that IMRT resulted in superior target coverage as well as reduced dose to organs at risk. Minn et al noted fewer treatment breaks were needed when IMRT was used instead of 3DCRT techniques. While 3DCRT plans resulted in increased serum creatinine following therapy, a similar increase was not seen in patients treated with IMRT; however, kidney mean dose was higher in the IMRT versus the 3DCRT group (13.9 vs 11.1 Gy; P=.05) and there was no difference in the median V20. In a trial of nRT, IMRT planning resulted in excellent target coverage and organ sparing, but did not reduce acute toxicity, hospitalization rates, or tube feeding relative to patients treated with 3DCRT. A meta-analysis including 9 trials with 516 patients found a statistically significant improvement in local control, but no difference in OS or grade 2-4 toxicity with IMRT versus 3DCRT. Thus, the optimal radiation technique (3DCRT versus IMRT) remains unclear, but it is reasonable to favor IMRT when noting challenges with meeting dose constraints, particularly for the kidneys, with 3DCRT and to minimize treatment breaks.

TOPIC 7. LIMITATIONS

Although the literature search limited its results to papers, published between 2010 and 2020, 7 meta-analyses were included, many of which included papers published before this period. This increased the heterogeneity in staging practices and tumor location categorization, and stage migration occurred over time with PET/CT becoming part of the standard workup. Although a
strength of this manuscript is the inclusion of almost entirely phase 3 or randomized phase 2 experimental trials, many meta-analyses also included observational studies, thereby decreasing the overall study quality of those manuscripts. Further, due to the paucity of data regarding radiation techniques, 2 observational studies were included to address this topic.

TOPIC 8. FUTURE DIRECTIONS

Gastric cancer therapy is moving towards a personalized approach, with the goal of identifying prognostic and predictive biomarkers to guide neoadjuvant/adjuvant therapy. Individual patient biomarker analysis has been completed in multiple trials. Pietrantonio and colleagues assessed microsatellite instability (MSI) status in patients from the CLASSIC, MAGIC, ARTIST, and ITACA-S trials. As with data from other malignancies, the presence of MSI high (MSI-H) was associated with longer 5-year DFS and OS. Intriguingly, only MSI-low (MSI-L) patients benefitted from aCT following surgery. Further biomarker analysis from the CLASSIC trial supports the finding that MSI-H and programmed death ligand 1 (PD-L1) positivity are prognostic for favorable outcomes. Microsatellite stability (MSS) with PD-L1 negativity (by IHC) predicted for a positive therapeutic response to aCT. MSI-H patients, with or without PD-L1 expression, did not benefit from aCT. Future trials will likely randomize MSI-H patients to observation vs aCT, and may seek to escalate chemotherapy in MSI-L patients.

Several forthcoming clinical trials will help to further elucidate the role of neoadjuvant, adjuvant, and perioperative therapy in gastric cancer. The phase II Dutch CRITICS-II trial (NCT02931890) is enrolling patients onto one of three treatment arms: preoperative chemotherapy (docetaxel/oxaliplatin/capecitabine [DOC]) followed by D2 resection, induction DOC followed by nCRT followed by D2 resection, and nCRT followed by D2 resection.
no benefit to aRT was seen in the CRITICS trial, the ongoing trial aims to assess whether moving treatment to the neoadjuvant setting will improve treatment completion rates and optimize the benefit of each treatment arm. Additionally, Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR, NCT01924819), a Phase III trial comparing nCT with ECF, EOX, or FLOT, will be compared to the same chemotherapy with the addition of chemoradiation. D1+ surgery and aCT will be utilized in both arms, and the primary outcome will be 5-year OS. In the setting of esophageal adenocarcinoma, ESOPEC (NCT02509286) is an RCT comparing CROSS-protocol nCRT vs perioperative FLOT.

In the adjuvant setting, the ARTIST-II study has yet to publish its final report which will help inform the role of aCRT versus aCT in N+ gastric cancer. This study randomized 538 Stage II/III, D2 resected, N+ gastric cancer patients 1:1:1 to S-1, S-1 + oxaliplatin (SOX), or SOX + 45 Gy (SOXRT). The initial results presented in abstract form only indicate SOX and SOXRT are equivalent in the adjuvant setting, but either combination regimen is superior to S-1 alone.64

The forthcoming Perioperative ramucirumab in combination with FLOT versus FLOT alone for resectable esophagogastric adenocarcinoma (RAMSES/FLOT7) Phase III RCT involving perioperative FLOT +/- ramucirumab, a VEGFR2 inhibitor currently approved for metastatic gastric and GEJ cancers.

Trials investigating the addition of trastuzumab to a cytotoxic chemotherapy backbone are underway (TOXAG, INNOVATION, NCT01130337). While its role has not yet been established, preliminary data shows improvements in pathological downstaging and R0 resection rates with the addition of perioperative trastuzumab but survival outcomes have not been reported.65 RTOG 1010 has been presented in abstract form, with its preliminary results showing no improvement in DFS for HER2 overexpressing patients in esophageal adenocarcinoma.66
SUMMARY OF RECOMMENDATIONS/CONCLUSIONS

- For a patient with a medically operable gastric adenocarcinoma following neoadjuvant FLOT chemotherapy and a total gastrectomy with D2 lymph node dissection, but without significant treatment effect from preoperative chemotherapy, the panel strongly recommends that adjuvant chemotherapy alone is usually appropriate.

- In a medically operable patient with a Siewert III adenocarcinoma and a planned D2 gastrectomy, the panel strongly recommends that perioperative chemotherapy is usually appropriate.

- For a medically operable patient with a gastric adenocarcinoma treated with upfront surgical resection with a D1 lymph node dissection, the panel:
  1. Recommends that adjuvant chemoradiation (before or after chemotherapy) is usually appropriate.
  2. Recommends that adjuvant chemotherapy alone may be appropriate.

- For a medically inoperable patient with gastric adenocarcinoma and a good performance status (ECOG 0-2) without significant blood loss, the panel recommends that either definitive chemoradiation between cycles of chemotherapy, or definitive chemoradiation alone, is usually appropriate.

- For a medically operable nonmetastatic patient with gastric adenocarcinoma and a positive proximal margin and good performance status, the panel strongly recommends that adjuvant chemoradiation, before or after postoperative chemotherapy, is usually appropriate.

- Regarding the total planned radiation dose involving standard fractionation of 1.8 – 2.0 Gy per fraction for gastric cancer, the panel:
1. Recommends strongly that doses of 41.4-45 Gy are usually appropriate in the neoadjuvant setting.*

2. Recommends strongly that doses of 45-50.4 Gy are usually appropriate in the adjuvant and definitive setting.*

3. Recommends that a dose of 54.0 Gy is usually appropriate if the location of a positive margin may be identified in the adjuvant setting.*

*: Careful radiation field design is warranted to achieve the intended benefit of radiation therapy.

REFERENCES


2. About stomach cancer, American Cancer Society


Table 1: Search Strategy (1/1/2010- 5/6/20)

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**Table 2: Variant 1** - Stage III, uT3 N1 M0 gastric body adenocarcinoma, receives 4 cycles of preoperative FLOT chemotherapy, followed by a total gastrectomy with D2 lymph node dissection. Pathology reveals a ypT3N2 gastric adenocarcinoma, resected with negative margins and no significant treatment effect. Good performance status.

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Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories:  
- **A**: Usually appropriate;  
- **M**: May be appropriate;  
- **U**: Usually not appropriate

Final Tabulations:  
A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, … etc.)

Disagree:  
The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References:  
Lists the references associated with the recommendation.

SQ:  
- Study Quality (1, 2, 3, or 4) of the references listed;  
- N/A Not Applicable

SOE:  
- **S**: Strong;  
- **M**: Moderate;  
- **L**: Limited;  
- **EC**: Expert consensus;  
- **EO**: Expert opinion

SOR:  
- ↑ Strong Recommendation;  
- ↓ Weak Recommendation;  
- - Additional considerations do not strengthen or weaken the panel’s recommendation

‌While a cycle of chemotherapy was given prior to CRT in the INT-0116 trial, this was primarily done to allow time for RT quality assurance checks. The group therefore felt that chemotherapy prior to CRT could be considered.

Table 3: Variant 2 - Stage IIIB, uT3 N0 M0 adenocarcinoma, with the central aspect of the lesion located within the gastric cardia at 43 cm past the incisors (LES noted at 40 cm/Siewert III). Medically operable and good performance status.
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<td>3</td>
</tr>
<tr>
<td>45-46 Gy / 25-23 fx</td>
<td>A</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>50-50.4 Gy / 25-28 fx</td>
<td>M</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<tr>
<td>If RT: Volumes to be included in Clinical Target Volume</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>U</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>U</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>N/A</td>
</tr>
<tr>
<td>Para-esophageal</td>
<td>A</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Peri-gastric</td>
<td>A</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td>8</td>
<td>17, 19, 21-23, 28, 42-43, 47, 46-47, 49, 51</td>
</tr>
<tr>
<td>Celiac</td>
<td>A</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>SMA</td>
<td>M*</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>5*</td>
</tr>
<tr>
<td>Gastro-duodenal</td>
<td>A</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>3</td>
<td>7</td>
<td>19, 28, 49, 51</td>
</tr>
<tr>
<td>Porta hepatitis</td>
<td>M*</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>5*</td>
<td>X</td>
</tr>
<tr>
<td>Splenic</td>
<td>M*</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>5*</td>
<td>X</td>
</tr>
<tr>
<td>Tumor/Tumor bed</td>
<td>A</td>
<td>3</td>
<td>8</td>
<td>9</td>
<td>41-43, 46-47</td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td>Anastomosis</td>
<td>A</td>
<td>5</td>
<td>6</td>
<td>9</td>
<td>39-43, 46-47</td>
<td>1</td>
<td>S</td>
</tr>
</tbody>
</table>

1. **Rating**: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate
2. **Per the UCLA/RAND Appropriateness Method**: * Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.
3. **Strength of Evidence**: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion
Table 4: Variant 3 - Stage I, uT2 N0 M0 gastric antrum adenocarcinoma, undergoes total gastrectomy with D1 lymph node dissection (no neoadjuvant therapy delivered). Pathology confirms a pT2N1 adenocarcinoma, resected to negative margins. Good performance status.
### Rating Categories:
- **U** - Usually not appropriate
- **M** - May be appropriate
- **A** - Usually appropriate

### Final Tabulations:
- A histogram of the number of panel members who rated the recommendation as noted in the column heading (i.e., 1, 2, 3, ... etc.)

### Disagree:
The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

### References:
Lists the references associated with the recommendation.

### SQ:
Study Quality (1, 2, 3, or 4) of the references listed; **N/A** Not Applicable

### SOE:
- **S** - Strong
- **M** - Moderate
- **L** - Limited
- **EC** - Expert consensus
- **EO** - Expert opinion

### SOR:
- **↑** - Strong Recommendation
- **↓** - Weak Recommendation
- **-** - Not strong, not weak

---

### While a cycle of chemotherapy was given prior to CRT in the INT-0116 trial, this was primarily done to allow time for RT quality assurance checks. The group therefore felt that chemotherapy prior to CRT could be considered.
**Table 5: Variant 4** - Stage III, uT3 N1 M0 gastric body adenocarcinoma with hemoglobin of 10 and negative laparoscopic staging. Patient is medically inoperable, ECOG PS 0-2. 10% weight loss in the preceding 6 months.

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Ref</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>U</td>
<td>5 2 3 1 2</td>
<td>2</td>
<td>N/A</td>
<td>N/A</td>
<td>EO</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>CT alone</td>
<td>M</td>
<td>1 6 3 1 1 4</td>
<td>4</td>
<td>49</td>
<td>1</td>
<td>EO</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>A</td>
<td>1 2 5 2 3 7</td>
<td>7</td>
<td>49-52</td>
<td>1</td>
<td>M</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>CT → CRT → CT</td>
<td>A</td>
<td>1 3 6 2 8</td>
<td>N/A</td>
<td>N/A</td>
<td>EO</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT alone</td>
<td>M</td>
<td>1 1 7 3 1 4</td>
<td>4</td>
<td>48</td>
<td>1</td>
<td>L</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Best Supportive Care</td>
<td>U</td>
<td>1 1 8 1 1 3</td>
<td>3</td>
<td>N/A</td>
<td>N/A</td>
<td>EO</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

**If RT: Dose to Tumor**

- **20-37.5 Gy / 5-15 fx**
  - M* 1 2 5 1 2 5* X 49-52 1 L ↑
- **40-41.4 Gy / 20-23 fx**
  - M* 2 5 2 2 1 5* X N/A N/A EO ↓
- **45-46 Gy / 23-25 fx**
  - M* 1 3 6 2 5* X 51 2 L -
- **50-50.4 Gy / 25-28 fx**
  - A 1 4 4 3 8 49-50, 52 1 M ↑
- **54 Gy / 30 fx**
  - M* 1 3 6 1 5* X N/A N/A EO ↓
- **59.4-60 Gy / 30-33 fx**
  - U 1 8 1 1 1 3 N/A N/A EO ↑

**If RT: Dose to Elective nodes**

- **40-41.4 Gy / 20-23 fx**
  - M* 3 3 2 2 2 5* X N/A N/A EO ↓
- **45-46 Gy / 23-25 fx**
  - A 1 1 5 4 1 7 51 2 EO ↑
- **50-50.4 Gy / 25-28 fx**
  - M* 1 1 2 1 5 2 5* X 49-50, 52 1 M ↑

**If RT: Volumes to be included in Clinical Target Volume**

- **Mediastinal**
  - U 5 3 4 1 2 N/A N/A EO ↑
- **Para-esophageal**
  - U 1 2 7 1 1 3 51 2 L ↑
- **Peri-gastric**
  - A 2 4 7 9 51 2 L ↑
- **Celiac**
  - A 3 4 6 8 51 2 L ↑
- **SMA**
  - M* 1 4 5 2 5* X N/A N/A EO ↓
Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

**Rating Categories:**
- U - Usually not appropriate
- M - May be appropriate
- A - Usually appropriate

**Final Tabulations:**
A histogram of the number of panel members who rated the recommendation as noted in the column heading (i.e., 1, 2, 3, ... etc.)

**Disagree:**
The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

**References:**
Lists the references associated with the recommendation.

**SQ:**
- Study Quality (1, 2, 3, or 4) of the references listed; N/A Not Applicable

**SOE:**
- S - Strong
- M - Moderate
- L - Limited
- EC - Expert consensus
- EO - Expert opinion

**SOR:**
- ↑ - Strong Recommendation
- ↓ - Weak Recommendation
- - Additional considerations do not strengthen or weaken the panel’s recommendation

1. **Rating:** A - Usually appropriate; M - May be appropriate; U - Usually not appropriate
2. **Per the UCLA/RAND Appropriateness Method:** M* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.
3. **Strength of Evidence:** S - Strong; M - Moderate; L - Limited; EC - Expert consensus; EO - Expert opinion
4. **Strength of Recommendation:** ↑ - Strong Recommendation; ↓ - Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation
5. **Careful radiation field design is warranted to achieve the intended benefit of radiation therapy.**

**Table 6: Variant 5** - Stage III, uT3 N1 M0 gastric cardia adenocarcinoma, undergoes a total gastrectomy with a D2 lymph node dissection (no neoadjuvant therapy delivered). Surgical pathology demonstrates pT3N1 disease, with a positive proximal margin. Good performance status.

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Ref</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
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<td>8 2 3</td>
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<td>1</td>
<td>28-29, 31, 32, 35, 38</td>
<td>1</td>
<td>S</td>
<td>↑</td>
</tr>
<tr>
<td>CT alone</td>
<td>M*</td>
<td>3 1 4 3 1</td>
<td>5* X</td>
<td>1</td>
<td>28-32, 34-36-38, 40-42-45</td>
<td>1</td>
<td>S</td>
<td>↑</td>
</tr>
<tr>
<td>CT → CRT Or CRT → CT</td>
<td>A</td>
<td>9 2 8</td>
<td></td>
<td>28, 42-43, 46</td>
<td>1</td>
<td>S</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>RT alone</td>
<td>U</td>
<td>1 4 5 3</td>
<td>3</td>
<td>38</td>
<td>1</td>
<td>M</td>
<td>↑</td>
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<tr>
<td>IF RT: Dose to Tumor Bed/Nodal basin</td>
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<tr>
<td>36-41.4 Gy / 20-23 fx</td>
<td>U</td>
<td>2 8 2</td>
<td>3</td>
<td>N/A</td>
<td>N/A</td>
<td>EO</td>
<td>↑</td>
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<td>Rating Categories:</td>
<td>A - Usually appropriate; M - May be appropriate; U - Usually not appropriate</td>
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<td>A histogram of the number of panel members who rated the recommendation as noted in the column heading (i.e., 1, 2, 3, ... etc.)</td>
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<tr>
<td>Disagree:</td>
<td>The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.</td>
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<tr>
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<td>S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion</td>
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<tr>
<td>SOR:</td>
<td>↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak</td>
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</table>

### If RT: Total dose with boost to positive margin

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<tr>
<th>Dose</th>
<th>Rating</th>
<th>Tabulations</th>
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<tbody>
<tr>
<td>45-46 Gy / 25-26 fx</td>
<td>A</td>
<td>1 3 6 2 8</td>
</tr>
<tr>
<td>50-50.4 Gy / 25-28 fx</td>
<td>A</td>
<td>2 1 4 4 1 7</td>
</tr>
<tr>
<td>54 Gy / 30 fx</td>
<td>M*</td>
<td>2 4 1 4 1 5* X</td>
</tr>
<tr>
<td>59.4-60 Gy / 30-33 fx</td>
<td>M*</td>
<td>2 5 1 2 1 1 5* X</td>
</tr>
</tbody>
</table>

### If RT: Volumes to be included in Clinical Target Volume

<table>
<thead>
<tr>
<th>Volume</th>
<th>Rating</th>
<th>Tabulations</th>
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</thead>
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<tr>
<td>Mediastinal</td>
<td>U 6 2 4 1 2</td>
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</tr>
<tr>
<td>Para-esophageal</td>
<td>M* 3 1 1 5 1 5* X</td>
<td>27, 39, 46-47</td>
</tr>
<tr>
<td>Perigastric</td>
<td>A 1 5 7 9</td>
<td>27, 39, 46-47</td>
</tr>
<tr>
<td>Celiac</td>
<td>A 1 8 4 8</td>
<td>27-28</td>
</tr>
<tr>
<td>SMA</td>
<td>A 1 7 3 1 7</td>
<td>N/A</td>
</tr>
<tr>
<td>Porta hepatis</td>
<td>A 1 3 6 3 8</td>
<td>27-28</td>
</tr>
<tr>
<td>Gastroduodenal</td>
<td>A 1 4 5 3 8</td>
<td>27-28</td>
</tr>
<tr>
<td>Splenic</td>
<td>A 1 3 7 2 8</td>
<td>27-28</td>
</tr>
<tr>
<td>Tumor bed</td>
<td>A 1 4 8 9</td>
<td>27-28, 41-42, 46-47</td>
</tr>
<tr>
<td>Anastomosis</td>
<td>A 1 6 6 8</td>
<td>27-28, 39, 42, 46-47</td>
</tr>
</tbody>
</table>

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

1. Rating: A - Usually appropriate; M - May be appropriate; U - Usually not appropriate
2. Per the UCLA/RAND Appropriateness Method - M* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.
3. Strength of Evidence: S - Strong; M - Moderate; L - Limited; EC - Expert consensus; EO - Expert opinion
4. Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation
5. Careful radiation field design is warranted to achieve the intended benefit of radiation therapy.
Figure 1: PRISMA 2020 Study selection flow diagram for gastric adenocarcinoma systematic review

Identification of studies via databases and registers

Records identified from: Medline (n = 1355)

Records removed before screening:
Duplicate records removed (n = 118)

Records screened (n = 1237)

Records excluded (n = 1147)

Full-text reports sought for retrieval (n = 90)

Full-text reports assessed for eligibility (n = 90)

Studies included in review (n = 51)
Full-text reports of included studies (n = 51)

Identification of studies via forward/backward citation searching

Records identified from:
Forward citation searching (n = 0)
Backward citation Searching (n = 9)

Records excluded:
(n = 0)

Full-text reports sought for retrieval (n = 9)

Reports excluded:
(n = 0)

Full-text reports assessed for eligibility (n = 9)

Reports excluded:
(n = 0)

Insufficient number of patients (n = 14)
Poor quality (n = 14)
Not randomized (n = 20)