9-1-2022

American Radium Society (ARS) Appropriate Use Criteria (AUC) for Locoregional Gastric Adenocarcinoma: Systematic Review and Guidelines

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Recommended Citation

Kumar R, Tchelebi L, Anker CJ, Sharma N, Bianchi NA, Dragovic J, Goodman KA, Herman JM, Jiang Y, Jones WE, 3rd, Kennedy TJ, Lee P, Kundranda M, Russo S, Small W, Suh WW, Yee N, and Jabbour SK. American Radium Society (ARS) Appropriate Use Criteria (AUC) for Locoregional Gastric Adenocarcinoma: Systematic Review and Guidelines. Am J Clin Oncol 2022; 45(9):391-402.

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American Radium Society (ARS) Appropriate Use Criteria (AUC) for Locoregional Gastric Adenocarcinoma

Systematic Review and Guidelines

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Objective: The objective of this study was to systematically evaluate the data regarding the use of neoadjuvant, perioperative, surgical, and adjuvant treatment options in localized gastric cancer patients and to develop Appropriate Use Criteria recommended by a panel of experts convened by the American Radium Society.

Methods: Preferred reporting items for systematic reviews and meta-analyses methodology was used to develop an extensive analysis of peer-reviewed phase 2/2R/3 trials, as well as meta-analyses found within the Ovid Medline database between 2010 and 2020. The expert panel then rated the appropriateness of various treatments in 5 representative clinical scenarios through a well-established consensus methodology (modified Delphi).

Results: For patients with medically operable locally advanced gastric cancer, the strongest recommendation was for perioperative chemotherapy based on high-quality data. Acceptable alternatives included surgery followed by either chemotherapy or concurrent chemoradiotherapy (CRT). For patients with upfront resection of stages I to III gastric cancer (no neoadjuvant therapy), the group strongly recommended adjuvant therapy with either chemotherapy alone or CRT, based on high-quality data. For patients with locally advanced disease who received preoperative chemotherapy without tumor regression, the group strongly recommended postoperative chemotherapy or postoperative CRT. Finally, for medically inoperable gastric cancer patients, there was moderate consensus recommending definitive concurrent CRT.

Conclusions: The addition of chemotherapy and/or radiation, either in the neoadjuvant, adjuvant, or perioperative setting, results in improved survival rates for patients compared with surgery alone. For inoperable patients, definitive CRT is a reasonable treatment option, though largely palliative.

Key Words: gastric cancer, gastroesophageal cancer, neoadjuvant therapy, neoadjuvant chemoradiation, perioperative chemotherapy, meta-analysis

(*Am J Clin Oncol* 2022;45:391–402)

Gastric cancer is the third leading cause of cancer death worldwide and the sixth most commonly diagnosed malignancy, with approximately 1 million new cases diagnosed in 2020.[1] The highest incidence rates are in Asia and Latin America.

The most recent version of the *American Joint Committee on Cancer (AJCC) Staging Manual* (8th edition, 2017) includes pathologic stage groups after neoadjuvant therapy to reflect the increasing use of preoperative treatment for gastric cancer.[2] 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).[3]

This manuscript provides evidence-based guidelines for the treatment of localized gastric cancer, including gastroesophageal junction (GEJ) tumors, included in gastric trials.

METHODOLOGY

The methodology is described in detail in Appendix A (Supplemental Digital Content 1, http://links.lww.com/AJCO/A422). In brief, the evidence regarding treatment outcomes was assessed using the Population, Intervention, Comparator, Outcome, and Study design (PICO) framework.

Analysis of medical literature covering January 1, 2010 through June 5, 2020, from peer-reviewed journals indexed in the Ovid Medline database and using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines yielded a comprehensive set of relevant articles (Table 1).[4,5] Two

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The authors declare no conflicts of interest.

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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.amjclinicaloncology.com.

ISSN: 0277-3732/22/4509-0391
DOI: 10.1097/COC.0000000000000930

TABLE 1. Search Strategy (January 1, 2010 to June 5, 20)

1	(gastric* or stomach* or gastroesophag* or gastro-esophag* or gastro-oesophag* or esophagogastr* or oesophagogastr*).ti,ab,kf. (356446)
2	(cancer* or carcinoma* or neoplas* or adenocarcinoma* or signet* or malignan* or tumor* or tumour*).ti,ab,kf. (3375409)
3	1 and 2 (136590)
4	exp *Stomach Neoplasms/ (82183)
5	exp *Neoplasms/ (2928854)
6	exp *Stomach/ (78156)
7	5 and 6 (12005)
8	3 or 4 or 7 (148945)
9	(gastrectom* or esophagogastrecto* or oesophagogastrecto* or resect* or unresect* or surg* or opera* or inopera* or adjuvant* or neoadjuvant*).ti,ab,kf. (2966119)
10	exp Gastrectomy/ (35441)
11	su.fs. (1983519)
12	9 or 10 or 11 (3813827)
13	(anticancer* or antineoplas* or antitumo* or radiotherap* or radiat* or irradiat* or chemoradi* or chemotherap* or adjuvant* or neoadjuvant*).ti,ab,kf. (1261456)
14	exp Radiotherapy/ (185330)
15	exp antineoplastic agents/ or exp antineoplastic protocols/ (1139277)
16	exp combined modality therapy/ (263121)
17	rt.fs. (191097)
18	th.fs. (1862421)
19	or/13-18 (3786782)
20	(“phase II*“ or “phase 2*“ or “phase III*“ or “phase 3*“ or “meta-analys*“ or “metaanalys*“ or “randomi*“ or “phase IV*“ or “phase 4*“).ti,ab,kf. (847958)
21	clinical trial, phase II/ or clinical trial, phase III/ or clinical trial, phase IV/ (50765)
22	exp Meta-Analysis/ (117540)
23	exp controlled clinical trial/ (599988)
24	or/20-23 (1147640)
25	8 and 12 and 19 and 24 (2597)
26	limit 25 to yr = “2010 - 2020” (1284)
27	limit 26 to English language (1192)

authors (R.K. and L.T.) independently screened the full-text articles to determine the final studies included in this review as detailed in the reference selection flow diagram (Fig. 1). Study type and quality for these references were assessed via American Radium Society Appropriate Use Criteria methodology (Appendix B, Supplemental Digital Content 2, http://links.lww.com/AJCO/A423),[6] and the checklist confirming the completion of essential elements for a PRISMA 2020 systematic review may be found in Appendix C (Supplemental Digital Content 3, http://links.lww.com/AJCO/A424).

A well-established consensus methodology (modified Delphi) was used by the expert panel to rate the appropriateness of the treatment procedures.[7] Disagreement was defined as less than one-third votes occurring outside the rating category, which included (1) usually not appropriate (U, score: 1 to 3); (2) may be appropriate (M, score: 4 to 6); (3) usually appropriate (A, score: 7 to 9).

SUMMARY OF LITERATURE REVIEW

Topic 1. Neoadjuvant Treatment

Subtopic 1. Neoadjuvant Chemotherapy Versus Surgery Alone

EORTC 40954 investigated the role of neoadjuvant chemotherapy (nCT) versus surgery alone in GEJ and gastric cancer patients. Patients (n = 144) with stages III and IV (nonmetastatic) gastric cancer were randomized to receive cisplatin, leucovorin (LV), and 5-fluorouracil (5-FU) for 3 cycles before surgery versus surgery alone.[8] 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-stage and nodal-stage, and higher R0 resection rate, 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 with surgery alone.[9] Despite the 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. There was no difference in morbidity. Of note, 5 of the trials, including the largest, included adjuvant chemotherapy (aCT) in addition to nCT.

Japanese investigators sought to identify the optimal preoperative regimen. The COMPASS trial was a 2×2 phase II randomized controlled trial (RCT) design in patients with resectable stages III and IV gastric cancer. Either 2 or 4 cycles of S-1 (combination tegafur/gimeracil/oteracil) + cisplatin or cisplatin + paclitaxel were found to be equivalent.[10] 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.

Subtopic 2. Perioperative Chemotherapy Versus Surgery Alone

The phase III Medical Research Council Adjuvant Gastric Infusion Chemotherapy (MAGIC) trial randomized 503 patients with stage II or higher nonmetastatic, resectable adenocarcinoma of the stomach (74%), GEJ (14%), and distal esophagus (12%) to perioperative chemotherapy (poCT) (3 cycles preoperatively and 3 postoperatively), with epirubicin cisplatin and 5-FU (ECF) or surgery alone.[11] 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 understaging patients. Furthermore, combination chemotherapy was difficult to tolerate for many patients, with only 41% of patients completing all assigned cycles of chemotherapy. A smaller RCT of 224 patients from France similarly identified that poCT with cisplatin/5-FU improved 5-year OS versus surgery alone.[12]

After the MAGIC trial, Medical Research Council investigators initiated a RCT comparing the MAGIC regimen (epirubicin, cisplatin, and capecitabine [ECX]) to the same regimen with the addition of bevacizumab (ECX-B).[13] 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% vs. 48.1%). There was no difference in pathologic complete response (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.

The German FLuorouracil, Oxaliplatin, doceTaxel x4 (FLOT4-AIO) trial established perioperative FLOT as the preferred regimen for resectable gastric cancer.[14] Seven hundred sixteen patients were randomized to 6 cycles of ECF/ECX (3 given preoperatively and 3 given postoperatively), or 8 cycles (4 preoperative and 4 postoperative) of FLOT (5-FU, LV, oxaliplatin, and docetaxel). Surgical resection included an extended lymphadenectomy (≥D2 in ~55% of patients).

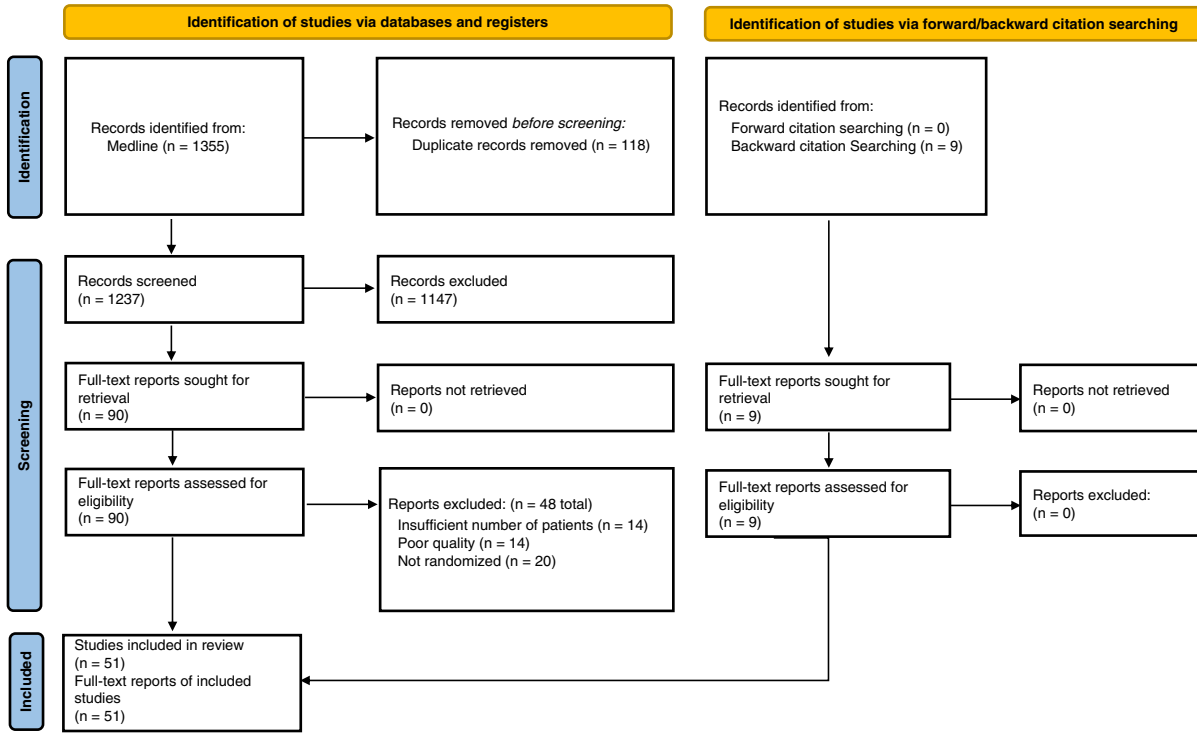

FIGURE 1. Selection flow chart for the systematic review. full color online

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) versus 37% (ECF/ECX), reflecting significant grade ≥ 3 toxicity with each regimen. Median and 5-year OS was significantly improved with FLOT at 50 versus 35 months and 45% versus 36%, respectively.

Subtopic 3: Neoadjuvant Radiation Versus Surgery Alone

A RCT of 370 patients with gastric cardia adenocarcinoma treated with neoadjuvant radiation (nRT) to 40 Gray (Gy) using a 2-dimensional approach compared with surgery alone was reported in 1998.[15] Radiation resulted in improved 5-year OS rates (30 vs. 20%, $P \leq 0.01$), resection rates, and pathologic downstaging. Importantly, radiation therapy (RT) 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 RT (preoperative, postoperative, or intraoperative) versus surgery alone or surgery and chemotherapy demonstrated a benefit in 5-year OS with nRT.[16]

Subtopic 4. Neoadjuvant Chemoradiation Versus Surgery Alone

RTOG 9904 is a phase II trial assessing 2 cycles of induction chemotherapy (5-FU, LV, and cisplatin), followed by concurrent radiation with 5-FU and paclitaxel, and then surgery.[17] Radiation was delivered to a dose of 45 Gy using a 3-dimensional conformal RT (3DCRT) approach, and a D2 lymphadenectomy was recommended. With a median follow-up of 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 trial of neoadjuvant paclitaxel/cisplatin, followed by radiation with 5-FU/LV, was aborted because of significant toxicity, with only 3 patients completing all assigned treatment.

The updated results of the CROSS trial confirmed a long-term benefit of neoadjuvant chemoradiation (nCRT) compared with surgery alone in esophageal and GEJ cancer.[18] Primarily Siewert I/II adenocarcinoma patients (n = 368) were randomized to nCRT using carboplatin/paclitaxel/41.4 Gy versus surgery alone. Although the greatest benefit to nCRT was noted for squamous cell carcinoma patients, the improvement was significant for the cohort overall and for patients with adenocarcinoma. In the adenocarcinoma subset, the median OS was 43.2 months with nCRT and 27.1 months for surgery alone (hazard ratio 0.73, $P = 0.038$).

Two small phase II trials investigated the role of induction chemotherapy followed by CRT and surgery. In a trial by Liu et al,[19] 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%, and pCR in 14%. 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 disease free survival (DFS) was 16.7 months. Kim et al[20] 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 and I, 66.8% for Stage II to III, and 33.3% for unresectable patients.

Subtopic 5: nCRT Versus nCT

A meta-analysis of 22 studies in patients with GEJ adenocarcinoma (including Siewert III) compared nCT with nCRT.[21] In the analysis, 14,709 patients were treated with

nCRT versus 3551 with nCT alone. This meta-analysis demonstrated that, despite the improved pCR (odds ratio: 2.8, $P < 0.001$) and locoregional failure rates (odds ratio: 0.6, $P = 0.01$), there was no improvement in OS when comparing nCT with nCRT.

The updated Scandinavian phase II RCT NeoRes-1 compared nCRT versus nCT in esophageal cancer patients, including GEJ tumors (Siewert I and II).[22] 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 the significant improvements in the primary outcome of pCR (28% with nCRT vs. 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. Of note, a more extensive lymph node dissection occurred in 83% of patients in NeoRes-1 compared with 48% in CROSS, which may have impacted the results. Furthermore, 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 after induction chemotherapy (cisplatin/5-FU) for esophageal/GEJ adenocarcinoma patients with a poor response to initial chemotherapy by positron emission tomography (PET).[23] Those without $\geq 35\%$ 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, and OS compared with patients receiving chemotherapy alone.

Topic 2. Adjuvant Therapy

Subtopic 1. Adjuvant Chemoradiation Versus Surgery Alone

In 1982, Moertel et al[24] randomized patients to adjuvant chemoradiation (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 (LRR) and longer 5-year OS (23% vs. 4%).

Intergroup/Southwest Oncology Group 0116 was a landmark trial randomizing 559 patients with stage IB to IV gastric adenocarcinoma to either surgery alone, or aCRT with 5-FU, LV, and 45 Gy.[25] 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.[25] Because of the low D2 rate, now required for resectable gastric cancer, the benefit of aCRT may be limited to patients receiving $\leq$D1 dissection, but survival rates are comparable to poCT-based regimens. Also, this study incorporated RT 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 RT (Tables 2–4: Variant 3).

Subtopic 2. aCT Versus Surgery Alone

Sasako et al[26] reported the results of their large, phase III RCT of 1059 patients comparing 1 year of adjuvant S-1 chemotherapy versus observation in stage II/III gastric cancer patients resected with an R0/D2 gastrectomy. The 5-year updated results demonstrated improved DFS (65% vs. 53%) and OS (72% vs. 61%), with the addition of S-1.[26] A small RCT indicated that alternating day S-1 may be better tolerated and more efficacious than daily S-1.[27]

The capecitabine and oxaliplatin adjuvant study in stomach cancer phase III RCT helped establish adjuvant capecitabine and oxaliplatin (XELOX) as an appropriate standard of care following D2 resection in stage II and III gastric cancer.[28] This trial randomized 1035 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 5620 patients found adjuvant S-1-based and XELOX-based regimens improved OS over surgery alone.[29]

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[30] but neither DFS nor OS was improved. A Japanese 2×2 phase III trial compared aCT with 4 arms: tegafur/uracil alone, S-1 alone, paclitaxel followed by tegafur or uracil, or paclitaxel followed by S-1.[31] 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.[32]

Recently reported results of adjuvant docetaxel and S-1 chemotherapy versus S-1 alone after D2 resection in 915 stage III gastric cancer patients suggest the superiority of the addition of docetaxel in this population.[33] The primary outcome 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 1 year of adjuvant S-1 (8 cycles), as 6 months (4 cycles) is considered inferior.[34]

Subtopic 3. aCRT Versus 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.[35] Although LRR was improved with radiation, neither radiation nor chemotherapy was associated with an improved OS compared with surgery alone.

A series of phase III trials published in 2012 reported outcomes of aCRT versus aCT alone. Kim et al[36] assessed the role of aCRT in patients after 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 et al[37] randomized 404 patients to 5-FU/LV +/− aCRT (notably, with intensity-modulated radiation therapy [IMRT]). Radiation improved RFS (36 vs. 50 mo), but not OS. Lastly, Yu et al[38] 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 reported significant improvements in 1-year, 2-year, 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.[39] 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

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

		Final Tabulations													
Treatment	**Rating Category**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Group Median Rating**	**Disagree**	**References**	**SQ**	**SOE**	**SOR**
Treatment options																
Observation	U	7	1	4	—	1	—	—	—	—	1	—	10–12	1	S	↑
CT alone	A	—	—	—	—	1	1	3	6	2	8	—	13–16,45,47	1	S	↑
CT→ CRT Or CRT→ CT*	M*	—	—	—	—	2	3	4	2	—	5*	X	45,47	1	S	↑
RT alone	U	2	3	8	—	—	—	—	—	—	3	—	NA	NA	EO	↑
If RT: dose to tumor bed																
40–41.4 Gy / 20–23 fx	U	1	1	7	3	—	—	—	—	—	3	—	NA	NA	EO	↑
45–46 Gy / 25–23 fx	A	—	—	—	—	1		4	4	3	8	—	45,47	1	M	↑
50–50.4 Gy / 25–28 fx	M	—	—	1	2	3	4	2	—	—	5.5	—	NA	NA	EO	↑
54 Gy / 30 fx	U	—	2	8	1	1	—	—	—	—	3	—	NA	NA	EO	↑
59.4–60 Gy / 33–30 fx	U	2	1	7	2	—	—	—	—	—	3	—	NA	NA	EO	↑
If RT: dose to elective nodes																
36 Gy / 18–20 fx	U	5	2	5	—	1	—	—	—	x	2	—	NA	NA	EO	↑
40–41.4 Gy /20–23 fx	M*	—	1	5	1	2	1	—	—	—	5*	X	NA	NA	EO	↓
45-46 Gy / 23–25 fx	A	—	—	—	—	—	—	5	4	3	8	—	45,47	1	M	↑
50-50.4 Gy / 25-28 fx	M*	—	1	5	2	2	2	—	—	—	5*	X	NA	NA	EO	↓
If RT: volumes to be included in clinical target volume[5]																
Mediastinal	U	5	2	5	—	1	—	—	—	—	2		NA	NA	EO	↑
Paraesophageal	M*	2	1	6	4	—	—	—	—	—	5*	X	47	1	L	↑
Perigastric	A	—	—	—	—	—	—	4	3	6	8	—	47	1	L	↑
Celiac	A	—	—	—	—	—	—	5	2	6	8	—	47	1	L	↑
SMA	A	—	—	—	—	1	2	6	1	3	7	—	NA	NA	EO	↑
Gastroduodenal	A	—	—	—	—	—	1	7	1	4	7	—	47	1	L	↑
Porta hepatis	A	—	—	—	—	—	1	5	3	4	8	—	47	1	L	↑
Splenic	A	1	—	—	—	—	1	5	3	3	7	—	47	1	L	↑
Tumor bed	A	—	—	—	—	—	—	—	5	6	9	—	47	1	—	↑
Anastomosis	A	—	—	—	—	—	—	—	5	6	9	—	47	1	—	↑

Pathology reveals a ypT3N2 gastric adenocarcinoma, resected with negative margins and no significant treatment effect. Good performance status.

1. Rating: A—usually appropriate; M—may be appropriate; U—usually not appropriate.

2. Per the UCLA/RAND appropriateness method: M*—disagreement, that is, 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.

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 (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; NA—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 before CRT in the INT-0116 trial, this was primarily done to allow time for RT quality assurance checks. The group therefore felt that chemotherapy before CRT could be considered.

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%.[40]

Two meta-analyses suggested that aCRT may improve OS compared with aCT alone.[41,42] Liang included 6 studies with 2135 patients treated with aCRT or aCT after a D2 gastrectomy, demonstrating an improvement in 5-year OS and DFS with aCRT. Dai[42] included 6 RCTs involving 1171 patients. CRT improved 5-year DFS, LRR, at the expense of increased neutropenia. However, aCRT did not improve 5-year OS, 3-year DFS, or distant metastases-free survival. 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.

Cancer and Leukemia Group B investigators sought to improve on INT-0116 by utilizing ECF in place of 5-FU/LV.[43] Cancer and Leukemia Group B 80101 randomized 546 patients with stage IB to IVA (M0)–resected gastric adenocarcinoma (R0 required, D2 not required), but this study was not intended to assess the role of radiation. 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

TABLE 3. Variant 2—Stage IIB, 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)

		Final Tabulations													
Treatment	**Rating Category**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Group Median Rating**	**Disagree**	**References**	**SQ**	**SOE**	**SOR**
Treatment options																
S only	U	6	2	5	—	—	—	—	—	—	2	—	10–14,17,18,21,27–29,31,32,35,38,	1	S	↑
S→CRT +/– CT	M*	—	—	2	1	2	4	2	—	—	5*	X	27,28,39–42,44–46	1	S	↑
S→CT	M	—	—	2	—	8	1	—	—	—	5	—	29–42,45,47	1	S	↑
S→RT	U	1	3	7	—	2	—	—	—	—	3	—	27,38	1	M	↑
CT→S→CT (poCT)	A	—	—	—	—	—	1	4	2	6	8	—	13–16,47	1	S	↑
CRT→S	M*	—	—	—	—	2	2	6	—	1	5*	X	19–22,24–26	1	S	↑
CT→S	M	—	—	—	1	4	3	2	1	—	6	—	8–12,24–26	1	S	↑
If RT: dose to tumor																
30–30.6 Gy / 15–17 fx	U	2	2	5	2	1	—	—	—	—	3	—	NA	NA	EC	↑
40–41.4 Gy / 20–23 fx	M*	—	—	2	1	3	—	1	—	1	5*	X	17,21,48	1	S	↑
45–46 Gy / 23–25 fx	A	1	—	—	—	—	2	5	2	2	7	—	19,22,24,26,28,39–47,51	1	S	↑
50–50.4 Gy / 25–28 fx	M*	—	—	1	2	2	1	5	—	—	5*	X	49,50,52	1	M	↑
54 Gy / 30 fx	U	—	2	9	—	—	—	—	—	—	3	—	NA	NA	EC	↑
59.4–60 Gy / 30–33 fx	U	2	3	6	1	—	—	—	—	—	3	—	NA	NA	EC	↑
If RT: dose to elective nodes																
30–30.6 Gy / 15–17 fx	U	2	1	8	—	1	—	—	—	—	3	—	NA	NA	EC	↑
36 Gy / 18–20 fx	U	2	—	7	—	2	1	—	—	—	3	—	NA	NA	EC	↑
40–41.4 Gy /20–23 fx	M*	1	—	—	1	3	1	3	3	1	5*	X	17,21,48	1	S	↑
45–46 Gy / 25–23 fx	A	1	—	1	—	—	1	4	4	1	7	—	19,22,24,26,28,39–47,51	1	S	↑
50–50.4 Gy / 25–28 fx	M	2	—	3	1	1	2	2	1	—	4.5	—	49,50,52	1	M	↑
If RT: volumes to be included in clinical target volume[5]																
Supraclavicular	U	6	3	3	—	1	—	—	—	—	2	—	NA	NA	EO	↑
Mediastinal	U	1	3	7	—	—	—	—	1	—	3	—	NA	NA	EO	↑
Paraesophageal	A	—	—	—	1	1	—	5	3	2	7	—	17,19,21–23,26,28,46,47,51	1	S	↑
Perigastric	A	—	—	—	—	—	—	2	7	4	8	—	17,19,21–23,28,42,43,46,47,49,51	1	S	↑
Celiac	A	1	—	1	—	—	—	3	6	2	8		17,19,28,49,51	1	S	↑
SMA	M*	—	1	—	2	1	—	7	1	—	5*	X	NA	NA	EO	↓
Gastroduodenal	A	—	—	1	1	—	—	7	3	—	7	—	19,28,49,51	1	S	↑
Porta hepatis	M*	—	—	—	—	1	4	4	3	—	5*	X	17,19,28,49,51	1	S	↑
Splenic	M*	—	—	—	—	2	4	4	2	—	5*	X	17,19,28,49,51	1	S	↑
Tumor/Tumor bed	A	—	—	—	—	—	—	—	3	8	9	—	41–43,46,47	1	S	↑
Anastomosis	A	—	—	—	—	—	—	—	5	6	9	—	39–43,46,47	1	S	↑

Medically operable and good performance status.

1. Rating: A—usually appropriate; M—may be appropriate; U—usually not appropriate.

2. Per the UCLA/RAND Appropriateness Method: M*—disagreement, that is, 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.

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 (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; NA—not applicable.

SOE: S—strong; M—moderate; L—limited; EC—expert consensus; EO—expert opinion.

SOR: ↑ strong recommendation; ↓ weak recommendation; — not strong, not weak.

TABLE 4. Variant 3—Stage I, uT2 N0 M0 Gastric Antrum Adenocarcinoma, Undergoes Total Gastrectomy With D1 Lymph Node Dissection (No Neoadjuvant Therapy Delivered)

		Final Tabulations													
Treatment	Rating Category	1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	References	SQ	SOE	SOR
Treatment options																
Observation	U	3	5	4	—	1	—	—	—	—	2	—	27–29,32,35,38	1	S	↑
CT alone	M*		—	1	—	2	3	3	3	1	5*	X	32,34–38,41,45,46	1	S	↑
CT → CRT Or CRT → CT*	A	—	—	—	—	—	1	5	4	1	7	—	28,43	1	S	↑
RT alone	U	1	1	6	2	1	—	—	—	—	3	—	38	1	L	↑
If RT: dose to tumor bed																
40–41.4 Gy / 20–23 fx	M*	—	1	6	2	2	1	—	—	—	5*	X	NA	NA	EO	↓
45–46 Gy / 23–25 fx	A	—	—	—	—	—	—	7	3	2	7	—	28,41,46	1	S	↑
50–50.4 Gy / 25–28 fx	M*	—	1	2	1	3	4	1	—	—	5*	X	NA	NA	EO	↓
54 Gy / 30 fx	U	—	3	7	1	—	1	—	—	—	3	—	NA	NA	EO	↑
59.4–60 Gy / 33–30 fx	U	3	2	6		1					3		NA	NA	EO	↑
If RT: dose to elective nodes																
36 Gy / 18–20 fx	U	1	3	6	2	—	—	—	—	—	3	—	NA	NA	EO	↑
40–41.4 Gy /20–23 fx	M	—	—	2	5	2	2	—	1	—	4	—	NA	NA	EO	↑
45–46 Gy / 25–23 fx	A	—	—	—	—	—	1	5	4	2	7.5	—	28,41,46	1	S	↑
50–50.4 Gy / 25–28 fx	U	—	4	3	3	1	1	—	—	—	3	X	NA	NA	EO	↓
If RT: volumes to be included in clinical target volume[5]																
Mediastinal	U	5	2	5	—	1	—	—	—	—	2	—	NA	NA	EO	↑
Paraesophageal	U	3	3	5	—	1	1	—	—	—	3	—	28,46	1	S	↑
Perigastric	A	—	—	—	—	—	—	3	7	3	8	—	28,46	1	S	↑
Celiac	A	—	—	—	—	—	—	3	6	4	8	—	28	1	S	↑
SMA	A	—	1	—	1	—	1	5	1	2	7	—	NA	NA	EO	↑
Porta hepatis	A	—	—	—	—	—	2	4	6	1	8	—	28	1	S	↑
Gastroduodenal	A	—	—	—	—	—	1	6	3	3	7	—	28	1	S	↑
Splenic	M*	—	—	—	2	1	2	8	—	—	5*	X	28	1	S	↑
Tumor bed	A	—	—	—	—	—	—	3	5	5	8	—	28,41,46	1	S	↑
Anastomosis	A	—	—	—	—	—	—	1	4	6	9	—	28	1	—	↑

Pathology confirms a pT2N1 adenocarcinoma, resected to negative margins. Good performance status.

1 Rating: A—usually appropriate; M—may be appropriate; U—usually not appropriate.

2 Per the UCLA/RAND appropriateness method: M*—Disagreement, that is, 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.

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 (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; NA—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 before CRT in the INT-0116 trial, this was primarily done to allow time for RT quality assurance checks. The group therefore felt that chemotherapy before CRT could be considered.

examined. However, the number of lymph nodes examined did not correlate with OS with either treatment regimen.

Topic 3: Perioperative Chemotherapy With or Without aCRT

In the phase III Dutch ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach (CRITICS) RCT, 788 patients with Stage IB to IVA resectable gastric or GEJ adenocarcinoma (Siewert II/III) were assigned to poCT or nCT with aCRT.[44] Preoperative chemotherapy involved with 3 cycles of ECX/EOX in both arms, with patients then randomized to aCRT to 45 Gy with capecitabine/cisplatin versus aCT with ECX/EOX for 3 cycles. A ≥D1 lymphadenectomy was required. Unlike intergroup 0116, 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 were similar between the chemotherapy alone and aCRT groups (43 vs. 37 mo and

TABLE 5. Variant 4—Stage III, uT3 N1 M0 Gastric Body Adenocarcinoma With Hemoglobin of 10 and Negative Laparoscopic Staging

		Final Tabulations														
Treatment	Rating Category	1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	Ref	SQ	SOE	SOR
Treatment options																
Observation	U	5	2	3	1	2	—	—	—	—	2	—	NA	NA	EO	↑
CT alone	M	—	—	1	6	3	—	1	1	—	4	—	49	1	EO	↑
CRT	A	—	—	—	1	—	2	5	2	3	7	—	49–52	1	M	↑
CT → CRT → CT	A	—	—	1	—	—	—	3	6	2	8	—	NA	NA	EO	↑
RT alone	M	—	1	1	7	3	1	—	—	—	4	—	48	1	L	↑
Best supportive care	U	1	1	8	—	1	1	—	—	—	3	—	NA	NA	EO	↑
If RT: dose to tumor																
20–37.5 Gy / 5–15 fx	M*	1	2	5	1	2	—	1	—	—	5*	X	49	1	L	↑
40–41.4 Gy / 20–23 fx	M*	—	2	5	2	2	1	—	—	—	5*	X	NA	NA	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	NA	NA	EO	↓
59.4–60 Gy / 30–33 fx	U	—	1	8	—	1	1	1	—	—	3	—	NA	NA	EO	↑
If RT: dose to elective nodes																
40–41.4 Gy /20–23 fx	M*	—	—	3	3	2	2	2	—	—	5*	X	NA	NA	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[5]																
Mediastinal	U	5	3	4	—	1	—	—	—	—	2	—	NA	NA	EO	↑
Paraesophageal	U	1	2	7	1	—	1	—	—	—	3	—	51	2	L	↑
Perigastric	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	NA	NA	EO	↓
Porta hepatis	A	—	—	—	—	2	1	3	4	3	8	—	51	2	L	↑
Gastroduodenal	A	—	—	—	—	—	1	6	3	3	7	—	51	2	L	↑
Splenic	A	—	—	—	—	—	1	9	2	—	7	—	51	2	L	↑
Whole stomach	M*	—	—	1	—	—	3	4	3	1	5*	X	51	2	L	—
Tumor + margin	A	—	—	—	—	1	1	4	6	—	7.5		51	2	L	↑

Patient is medically inoperable, ECOG PS 0-2. 10% weight loss in the preceding 6 months.

1. Rating: A—usually appropriate; M—may be appropriate; U—usually not appropriate.

2. Per the UCLA/RAND appropriateness method: M*—disagreement, that is, 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.

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 (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; NA—not applicable.

SOE: S—strong; M—moderate; L—limited; EC—expert consensus; EO—expert opinion.

SOR: ↑ strong recommendation; ↓ weak recommendation; — not strong, not weak.

42% vs. 40%, respectively). The authors concluded that there is limited benefit to aCRT versus aCT alone after nCT, but this trial did not appear to have radiation quality assurance.

Topic 4. Definitive Chemoradiation

While surgery remains the therapeutic mainstay in gastric and GEJ adenocarcinoma, definitive radiation has been utilized in patients who are unable or unwilling to undergo surgery. Prospective data demonstrated the superiority of definitive chemoradiation (dCRT) as opposed to either modality alone in nonsurgical patients.[45,46] A phase I study by Xing et al[47] dose escalated docetaxel to 15 mg/m^2 with cisplatin and radiation to 50.4 Gy/28 fractions, with an overall response rate of 66.7% (28.6% complete response). A phase II Polish trial reported on their results of cCRT with 45 Gy/25 fractions along with bolus 5-FU and found that 1-year, 3-year, and median OS were 59%, 48%, and 17.1 months, respectively.[48] There was a complete clinical response in 5 of 12 patients who completed radiation (41.7%) (Table 5: Variant 4). A more recent 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.[49] Local control was 81% and the median and 2-year OS were 25.8 months and 52%, respectively, with the best outcomes in the medically inoperable (37.0 mo and 52%) or declined surgery groups (38.9 mo and 67%) compared with those who were unresectable (17.7 mo and 20%).

Topic 5. Molecular and Targeted Therapy in Localized Gastric Cancer

Bevacizumab has been investigated in both the neoadjuvant and perioperative setting but has failed to improve outcomes

in patients with gastric cancer when added to standard chemotherapy.[13,50]

Topic 6. RT

Subtopic 1. 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.[36,51,52] The tumor bed is defined using preoperative CT imaging, surgical clips, endoscopy, and operative reports.[51] 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.[36,51] Additional nodal stations may be covered based on the location of the primary tumor, as per the Japanese Research Committee for Gastric Cancer.[53] Para-esophageal nodes are included in the CTV for tumors of the GEJ.[51] Elective nodal volumes should be covered even in the setting of a D2 dissection.[44,52] An additional mucosal margin may be added proximally to include the distal esophagus, where appropriate.[54] The planning target volume is typically a 0.5 to

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)

		Final Tabulations													
Treatment	Rating Category	1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	Ref	SQ	SOE	SOR
Treatment options																
Observation	U	8	2	3	—	—	—	—	—	—	1	—	28,29,31,32,35,38	1	S	↑
CT alone	M*	—	—	3	1	4	3	1	—	—	5*	X	28–32,34,36–38,40–42,45	1	S	↑
CT → CRT Or CRT → CT	A	—	—	—	—	—	—	—	9	2	8	—	28,42,43,46	1	S	↑
RT alone	U	1	4	5	3	—	—	—	—	—	3	—	38	1	M	↑
If RT: dose to tumor bed/nodal basin																
36–41.4 Gy / 20–23 fx	U	—	2	8	2	—	—	—	—	—	3	—	NA	NA	EO	↑
45–46 Gy / 25–26 fx	A	—	—	—	—	1	—	3	6	2	8	—	28,39–44,46,47	1	S	↑
50–50.4 Gy / 25–28 fx	A	—	—	—	—	2	1	4	4	1	7	—	NA	NA	EO	↑
54 Gy / 30 fx	M*	—	2	4	—	1	4	1	—	—	5*	X	NA	NA	EO	↓
If RT: total dose with boost to positive margin																
45—46 Gy / 25–26 fx	A	—	—	—	—	—	—	3	5	4	8	—	28,39–44,46,47	1	S	↑
50–50.4 Gy / 25–28 fx	A	—	1	—	1	—	—	4	3	2	7	—	NA	NA	EO	↑
54 Gy/ 30 fx	A	—	—	—	1	—	1	4	6	—	7.5	—	NA	NA	EO	↑
59.4–60 Gy/ 30–33 fx	M*	—	2	5	—	1	2	1	—	1	5*	X	NA	NA	EO	↓
If RT: volumes to be included in clinical target volume[5]																
Mediastinal	U	6	2	4	1	—	—	—	—	—	2	—	NA	NA	EO	↑
Paraesophageal	M*			3	1		1	1	5	1	5*	X	27,39,46,47	1	S	↑
Perigastric	A	—	—	—	—	—	—	1	5	7	9	—	27,39,46,47	1	S	↑
Celiac	A	—	—	—	—	—	—	1	8	4	8	—	27,28	1	S	↑
SMA	A	—	—	—	—	—	1	7	3	1	7	—	NA	NA	EO	↑
Porta hepatis	A	—	—	—	1	—	—	3	6	3	8	—	27,28	1	S	↑
Gastroduodenal	A	—	—	—	—	—	1	4	5	3	8	—	27,28	1	S	↑
Splenic	A	—	—	1	—	—	—	3	7	2	8	—	27,28	1	S	↑
Tumor bed	A	—	—	—	—	—	—	1	4	8	9	—	27,28,41,42,46,47	1	S	↑
Anastomosis	A	—	—	—	—	—	—	1	6	6	8	—	27,28,39,42,46,47	1	S	↑

Surgical pathology demonstrates pT3N1 disease, with a positive proximal margin. Good performance status.

1. Rating: A—usually appropriate; M—may be appropriate; U—usually not appropriate.

2. Per the UCLA/RAND Appropriateness Method: M*—Disagreement, that is, 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.

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 (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, NA—not applicable.

SOE: S—strong; M—moderate; L—limited; EC—expert consensus; EO—expert opinion.

SOR: ↑ strong recommendation; ↓ weak recommendation; — not strong, not weak.

1 cm beyond the CTV but can be as large as 2 cm if needed to account for target motion if a 4-dimensional scan is not performed.[55]

Subtopic 2. Dose

The standard adjuvant dose is 45 Gy delivered in 25 daily fx of 1.8 Gy.[36,51,52] A boost of 9 to 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).[36] For patients receiving definitive RT, doses in the range of 45 to 50.4 Gy have been utilized.[47–49]

Subtopic 3. Radiation Technique

Early trials of adjuvant radiation for gastric cancer used a 2-dimensional anteroposterior/posteroanterior field arrangement, resulting in high rates of grade 3 toxicity, with 54% and 33% of patients experiencing hematologic and gastrointestinal toxicity, respectively.[25] Ringash et al[55] compared 3DCRT with IMRT and found that IMRT resulted in superior target coverage and reduced dose to organs at risk. Minn et al[56] noted fewer treatment breaks were needed when IMRT was used instead of 3DCRT. 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.[57] A meta-analysis including 9 trials with 516 patients found a statistically significant improvement in local control, but no difference in OS or grades 2 to 4 toxicity with IMRT versus 3DCRT.[58]

Topic 7. Limitations

Seven meta-analyses were included, many of which included papers published before 2010. This increased the heterogeneity in staging, tumor location categorization, and stage migration occurred over time with PET/CT becoming part of the standard workup. Although this study was mostly limited to phase 2 or 3 randomized trials, many meta-analyses included observational studies, thereby decreasing the overall study quality of those manuscripts. Furthermore, because of the paucity of data regarding radiation techniques, 2 observational studies were included to address this topic.

Topic 8. Future Directions

Biomarkers are under investigation given existing data showing that the presence of microsatellite instability is associated with patient outcomes and predicts response to adjuvant therapy.[59,60] Ongoing trials are further elucidating the role of preoperative therapies, including the phase II Dutch CRITICS-II trial (NCT02931890) and phase III TOPGEAR (NCT01924819), which are assessing the role of nCRT in addition to nCT, and the ESOPEC trial for esophageal adenocarcinoma comparing the CROSS regimen to perioperative FLOT. In the adjuvant setting, the preliminary results of ARTIST-II indicate that postoperative SOX and SOXRT are equivalent, but either is superior to S-1 alone.[61] Finally, in the perioperative setting, the RAMSES/FLOT7 (NCT02661971) is investigating the role of remucirumab in combination with perioperative FLOT and preliminary data from TOXAG/INNOVATION (NCT 01130337) showed that perioperative trastuzumab improves pathologic downstaging and R0 rates, but survival outcomes have not been reported.[62] RTOG 1010 has been presented in abstract form, with its preliminary results showing no improvement in DFS for HER2 overexpressing patients in esophageal adenocarcinoma.[63]

It should be noted that since the completion of the literature search and committee voting, ARTIST-II, TOXAG, and RTOG 1010 have been published in manuscript form. However, to preserve the integrity of the literature search and voting methodology, these studies were not included in these guidelines.

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