



Published in final edited form as:

Pract Radiat Oncol. 2026 ; 16(2): 119–141. doi:10.1016/j.prro.2025.10.010.

Radiation Therapy for Gastric Cancer: An ASTRO Clinical Practice Guideline

Christopher J. Anker, MD^{a,*}, Junaid Arshad, MD, MS^b, Francesco Cellini, MD^c, Ahmed Dehal, MD, MPH^d, Jennifer Dolan, PhD^e, Sarah R. Gillett, MD, PhD^f, Michael G. Haddock, MD^g, Karin Haustermans, MD, PhD^h, Theodore S. Hong, MDⁱ, Krisha J. Howell, MD^j, Salma K. Jabbour, MD^k, Mio Kitano, MD, MPH^l, Chi Lin, MD, PhD, MS^m, Shane Lloyd, MDⁿ, John Peterson, MD^o, Falk Roeder, MD^p, Grace L. Smith, MD, PhD, MPH^q, Jeffrey Stewart, BA, MBA^r, Leila T. Tchelebi, MD^s, Lisa Bradfield, BA^t, Christopher G. Willett, MD^u

^aDivision of Radiation Oncology, University of Vermont Cancer Center, Burlington, Vermont

^bDepartment of Medical Oncology, University of Arizona Cancer Center, Tucson, Arizona

^cDepartment of Radiation Oncology, Fondazione Policlinico A. Gemelli Università Cattolica del Sacro Cuore, Rome, Italy

*Corresponding author: Christopher J. Anker, MD.; Chris.Anker@uvmhealth.org.

Disclaimer and Adherence: ASTRO guidelines present scientific, health, and safety information and may reflect scientific or medical opinion. They are available to ASTRO members and the public for educational and informational purposes only and do not constitute medical or treatment advice. Commercial use of any content in this guideline without the prior written consent of ASTRO is prohibited.

Adherence to this guideline does not ensure successful treatment in every situation. This guideline should not be deemed inclusive of all proper methods of care or of all factors influencing the treatment decision, nor is it intended to be exclusive of other methods reasonably directed to obtaining the same results. The information provided is not intended to replace the independent judgment of the treating physician in the context of individual patient circumstances and should be reviewed with the patient as part of shared decision-making. ASTRO assumes no liability for the information contained in its guidelines. This guideline is based on information available at the time the task force conducted its research and discussions on this topic. There may be new developments that are not reflected in this guideline and that may, over time, be a basis for updating the guideline.

Disclosures

All task force members' disclosure statements were reviewed before being invited and were shared with other task force members throughout the guideline's development. Those disclosures are published within this guideline. Where potential conflicts were detected, remedial measures to address them were taken.

Christopher Anker (vice chair): Ohio State University (consultant), Northern New England Clinical Oncology Society (honoraria); **Junaid Arshad (American Society of Clinical Oncology representative):** Bristol Myers Squibb (consultant-ended 7/2024), Deciphera (consultant-ended 1/2024), Exelixis (consultant-ended 2/2024), OncLive (meeting faculty-ended 6/2024); **Francesco Cellini (European Society for Radiotherapy and Oncology [ESTRO] representative):** *Cancers* (editorial/topic advisory panel), International Organisation for Radiotherapy for Benign Conditions (advisory board); **Karin Haustermans (ESTRO representative):** ESTRO (meeting faculty, travel expenses), European Society for Medical Oncology (meeting faculty, travel expenses); **Theodore Hong:** AstraZeneca, Bristol Myers Squibb, IntraOp, Ipsen, and Taiho (all research-PI), Lustgarten Foundation (advisory board), NextCure (consultant), PanTher (advisory board); **Krisha Howell:** Cognito Therapeutics (stock-family member), Health Alliance Plan (advisory board-family member), Boston Scientific, NRG Oncology, Palette Life Sciences, Radiation Therapy Oncology Group Trial, and RayzeBio (all research-site PI); **Salma Jabbour:** Beigene (research-site PI), IMX Medical (consultant), *International Journal of Radiation Oncology, Biology, and Physics* (deputy editor), Merck (research-site PI), Radialogica (consultant); **Mio Kitano (Society of Surgical Oncology [SSO] representative):** Advanced Surgical Retractor Systems (stock), UT Health San Antonio (research-site PI); **Chi Lin:** Biometix (research-site PI), Buffett Cancer Center (program leader), National Institutes of Health (research), SANTRO (executive cmt president); **Shane Lloyd:** Cancer Study Group (consultant), Naveris (travel expenses-ended 3/2024); **Falk Roeder (ESTRO representative):** Austrian Breast & Colorectal Group (executive cmt member), Baidisheng Publishing Group (editorial board), ESTRO (gastrointestinal subgroup cmt, chair), *Gastroenterology Insights* (editorial board), Springer Nature (editorial board); **Grace Smith:** National Institutes of Health (research), Oncora Medical (royalty/equity-family member); **Jeffrey Stewart (patient representative):** Syneos Health (stock-ended 3/2025); **Leila Tchelebi:** American College of Radiation Oncology (chart reviewer); **Christopher Willett (chair):** Ion Beam Applications (honoraria, meeting faculty), *UpToDate* (consultant, editor). **Lisa Bradfield, Ahmed Dehal (SSO representative), Jennifer Dolan, Sarah Gillett, Michael Haddock, and John Peterson** reported no disclosures.

^dDepartment of Surgical Oncology, Southern California Permanente Medical Group, Los Angeles, California

^eDepartment of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, California

^fDivision of Hematology/Oncology, University of Vermont Cancer Center, Burlington Vermont

^gDepartment of Radiation Oncology, Mayo Clinic, Rochester, Minnesota

^hDepartment of Radiation Oncology, Particle Therapy Interuniversity Center, Leuven, Belgium

ⁱDepartment of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts

^jDepartment of Radiation Oncology, Michigan Healthcare Professionals, Troy, Michigan

^kDepartment of Radiation Oncology, Rutgers Cancer Institute, New Brunswick, New Jersey

^lDivision of Surgical Oncology & Endocrine Surgery, University of Texas Health, San Antonio, Texas

^mDepartment of Radiation Oncology, University of Nebraska Medical Center, Omaha, Nebraska

ⁿDepartment of Radiation Oncology, University of Utah, Salt Lake City, Utah

^oDepartment of Radiation Oncology, Moffitt Cancer Center, Tampa, Florida

^pDepartment of Radiation Oncology, Paracelsus Medical University Hospital, Salzburg, Austria

^qDepartment of GI Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas

^rPatient Representative, Morrisville, North Carolina

^sDepartment of Radiation Oncology, Northwell Health, Mount Kisco, New York

^tAmerican Society for Radiation Oncology, Arlington, Virginia

^uDepartment of Radiation Oncology, Duke University, Durham, North Carolina

Abstract

Purpose: This guideline provides evidence-based recommendations addressing the indications for radiation therapy (RT) for gastric cancer in a variety of clinical settings, ranging from patients with resectable locoregional disease to metastatic and symptomatic disease.

Methods: The American Society for Radiation Oncology convened a task force to address 3 key questions: (1) indications for and timing of RT for patients with resectable and nonmetastatic gastric cancer; (2) indications for and timing of RT in patients with unresectable locoregional disease, oligometastases, and/or requiring palliation; and (3) appropriate RT dose-fractionation regimens, target volumes, and techniques in these clinical settings. Recommendations are based on a systematic literature review and were created using a predefined consensus-based methodology with a system for grading evidence quality and recommendation strength.

Results: Multidisciplinary evaluation and decision-making are recommended for all patients. For patients with cT2–4 and/or N+ resectable gastric cancer, perioperative chemotherapy is recommended, preferably FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel). Recently,

perioperative durvalumab and FLOT has shown a significant improvement in event-free survival versus FLOT only for patients with resectable disease and is now being adopted as a standard of care. Preoperative chemoradiation is recommended for patients who are not candidates for perioperative chemotherapy and conditionally recommended if there is concern for a margin-positive (R1) or incomplete (R2) resection. Postoperative chemoradiation is conditionally recommended for patients who are not candidates for perioperative or postoperative chemotherapy or if a suboptimal resection was done (eg, <D2 or R1-R2) for those who proceeded directly to surgery. Definitive chemoradiation may provide durable control for nonmetastatic patients who are inoperable either at initial diagnosis or at the time of locoregional recurrence. For patients with oligometastatic gastric cancer, metastasis-directed therapy along with systemic therapy is conditionally recommended. Palliative RT is efficacious for patients with bleeding, pain, and obstruction. Target coverage goals and dose guidance for normal tissues are provided.

Conclusions: These evidence-based recommendations guide clinical practice on the use of RT for gastric cancer. Future studies will further refine the indications and role of RT in the management of these patients.

Preamble

As a leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision-making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy—

ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before the initiation of the writing effort. Disclosures for the chair and vice chair go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplementary Materials, Appendix E1). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members—

ASTRO strives to avoid bias and is committed to creating a task force that includes a diverse and multidisciplinary group of experts. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology—

ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.^{1,2} The

evidence identified from key questions (KQs) is assessed using the Population, Intervention, Comparator, Outcome, Timing, Setting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Appendix E2 in Supplementary Materials for a list of abbreviations used in the guideline.

Consensus Development—

Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from “strongly agree” to “strongly disagree.” A prespecified threshold of $\geq 75\%$ ($\geq 90\%$ for expert opinion recommendations) of raters who select “strongly agree” or “agree” indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submitting for approval.

Annual Evaluation and Updates—

Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, ASTRO's Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Introduction

According to GLOBOCAN 2022 estimates, gastric cancer is the fifth most common malignancy globally and fifth in mortality, with significant geographic variability.³ The highest rates are observed in Eastern Asia, Eastern Europe, and South America, with the lowest rates in Africa.³ Stomach cancer can be divided into 2 main types based on location: cardia (upper stomach) and noncardia (lower stomach), which have distinct epidemiologic profiles.³ Noncardia gastric cancer is primarily caused by chronic *Helicobacter pylori* (*H. pylori*) infection, with other risk factors including alcohol, smoking, and certain dietary patterns; cardia cancers are primarily associated with obesity and reflux disease. Although overall stomach cancer rates have declined over the past 50 years, mainly because of better food preservation and a decreased prevalence of *H. pylori*, recent increases among younger individuals may be linked to autoimmune gastritis and changes in the gastric microbiome.³ The risk of gastric cancer increases with age, with the majority of patients diagnosed over 65 years of age.⁴ Sex disparities are also significant, with males at highest risk, likely because of both hormonal and environmental factors.⁵ In the United States, gastric cancer is often diagnosed at advanced stages, with approximately one-third of patients presenting with resectable disease, one-third with unresectable but localized disease, and one-third with metastatic disease.⁶ In contrast, for countries with an increased incidence of gastric cancer (eg, Japan and South Korea), the adoption of extensive screening programs has led to rates of over 50% of patients with local-only disease.^{7,8} The treatment of gastric cancer is complex and multidisciplinary, employing surgery, systemic therapy, and radiation therapy (RT). Although other investigators and clinical societies have published guidelines for

gastric cancer,^{9–11} there is a need for expert-based guidance on interpreting contemporary literature. In these guidelines, ASTRO seeks to clarify the role of RT in the management of all stages of gastric cancer, providing evidence-based recommendations to guide clinical practice in a multifaceted and evolving treatment paradigm.

RT is used in several clinical scenarios across the disease spectrum. First, patients should undergo full staging work up including history and physical examination, imaging, endoscopy, consideration of diagnostic laparoscopy, and medical evaluation, followed by discussion in a multidisciplinary care team regarding therapeutic options. Appropriate biomarkers and pathological evaluation should be performed. Factors including comorbidities, performance status, and age may be considered when offering different RT approaches because of tolerance and toxicity concerns. The FLOT4 trial has established the curative role of perioperative chemotherapy (3–4 cycles of chemotherapy preoperatively and postoperatively) in the treatment of patients with gastric cancer.¹² Recently, the addition of durvalumab for patients receiving perioperative 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) has shown superior event-free survival rates versus FLOT-only patients.¹³ Although studies have not shown an overall survival (OS) benefit to preoperative or postoperative chemoradiation over perioperative chemotherapy with surgery,^{14,15} RT may play a therapeutic role depending on the stage, as well as the adequacy and timing of surgery. Further, efforts to define the role of RT for patients with nonmetastatic gastric cancer that is locally unresectable, marginally resectable, or locoregionally recurrent are discussed. Given prospective and randomized data showing a potential benefit to metastasis-directed therapy (MDT) via metastasectomy, including for non-regional para-aortic lymph nodes (eg, nodal stations 16a1 or 16a2),^{16,17} these guidelines assess the data for RT as an MDT.^{18–21} Further, the role of palliative RT in relieving bleeding, obstruction, and pain from gastric cancer is examined.

Lastly, this guideline serves to investigate how disparities and social determinants of health may contribute to differences in outcomes in the management of gastric cancer. It should be acknowledged that not every clinical presentation of gastric cancer can be addressed, and clinical trials are essential in improving outcomes.

Methods

Task force composition

The task force consisted of a multidisciplinary team of radiation, medical, and surgical oncologists; a radiation oncology resident; a medical physicist; and a patient representative. This guideline was developed in collaboration with the American Society of Clinical Oncology, European Society for Radiotherapy and Oncology, and Society of Surgical Oncology, who provided representatives and peer reviewers.

Document review and approval

The guideline was reviewed by 15 official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from March to April 2025. The final guideline was approved by the ASTRO

Board of Directors and endorsed by the American Radium Society, European Society for Radiotherapy and Oncology, Royal Australian and New Zealand College of Radiologists, and the Society of Surgical Oncology.

Evidence review

KQs were developed by the ASTRO guideline subcommittee in conjunction with the guideline chairs and then reviewed by the full task force. Using the PICOTS framework (Table 2), a systematic search of human participant studies retrieved from the Ovid MEDLINE database was conducted for English-language publications between January 1, 2001, and July 31, 2024. Because of the publication of potentially practice-changing studies during guideline development, the search was updated through October 14, 2024, and again through June 9, 2025, resulting in 4 additional studies incorporated into the evidence tables.^{13,15,22,23} For publications from 2001 to 2013, only randomized controlled trials (RCTs) were included. From 2014 onward, allowable publication types comprised prospective studies including RCTs or subgroup analyses of RCTs (RCT/RCT subgroup analysis required if study involved systemic therapy without RT), meta-analyses (published from 2019 onward requiring analyses of RCTs and prospective studies only for KQ1, and any study type for KQs 2 and 3), and retrospective studies (KQ2 and 3 only). The population of interest was adults (age ≥ 18 years) with a diagnosis of gastric cancer or Siewert III gastroesophageal junction (GEJ) cancer (ie, tumor center located 2–5 cm below the GEJ). The following requirements for study size were applied: (1) ≥ 200 patients for meta-analyses; (2) ≥ 100 patients for RCTs, except only ≥ 50 patients for the less common studies focused on preoperative chemoradiation; (3) ≥ 100 patients for KQ1 prospective studies; and (4) no threshold for prospective or retrospective studies for KQs 2 and 3. Universal exclusion criteria included: preclinical and nonhuman studies; publication types including abstract only, review articles, comments, or editorials; study types such as health economics/cost analysis studies, or large registry/database studies (except for studies related to health disparities); and studies that included only Siewert I and II GEJ cancer or pediatric patients. For specific subquestions where limited data were available, expert opinion was relied on to support recommendations. Full-text articles were assessed by the task force to determine the final included study list resulting in a total of 87 studies influencing Section 3: “KQs and Recommendations” (see the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] flow diagram showing the number of articles screened, excluded, and included in the evidence review and Appendix E3 in Supplementary Materials for the literature search strategy, which includes the evidence search parameters and inclusion/exclusion criteria).

The data used by the task force to formulate recommendations are summarized in evidence tables available in Supplementary Materials, Appendix E4. References selected and published in this document are representative and not all-inclusive. Additional ancillary articles not in the evidence tables are included in the text; these were not used to support the evidence-based recommendations but may have informed expert opinion.

Scope of the guideline

This guideline examines the potential role of RT for patients with gastric cancer. As is typically done, Siewert Type III GEJ cancers are classified as gastric cancers throughout this guideline. The scope was broad, including nonmetastatic resectable, borderline resectable, and unresectable disease, locoregionally recurrent disease, and metastatic disease including oligometastases. Prospective studies and secondary analyses of prospective studies were evaluated for health disparities leading to differences in outcomes.

The key outcomes included OS, local control, progression-free survival (PFS), acute and late toxicity, and quality of life (QoL) metrics. This guideline addresses only topics specified in the KQs (Table 2). There are several important questions in the management of gastric cancer that are outside the scope of this guideline, including indications and treatment details for brachytherapy and intraoperative RT, RT technique and treatment details for oligometastatic disease, and detailed discussions of endoscopic/surgical approaches and systemic therapy regimens outside of resectable disease.

KQs and Recommendations

KQ1: Indications for preoperative, perioperative, and postoperative therapies

(Table 3): See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ1 and Fig. 1.

For patients with resectable and nonmetastatic gastric cancer, what are the indications for preoperative, perioperative, and postoperative therapies, including systemic therapy and RT?

The KQ1 recommendations apply to patients with resectable gastric cancer, meaning technically and medically appropriate candidates for surgery determined by imaging and multidisciplinary evaluation. However, in the setting of borderline resectable tumors, the addition of chemoradiation to perioperative chemotherapy is an option to help achieve an R0 resection. When chemoradiation is discussed or recommended, the intended concurrent chemotherapy is 5-fluorouracil (5-FU) or capecitabine.^{15,43}

Perioperative chemotherapy: Perioperative chemotherapy and surgery are recommended for patients with resectable cT2–4, and/or N+, M0 gastric cancer. Early studies demonstrated that perioperative chemotherapy with ECF (epirubicin, cisplatin, and 5-FU) and surgery resulted in superior OS over surgery alone.²⁴ Subsequently, the FLOT4 trial, which compared 4 cycles of perioperative FLOT versus 3 cycles of ECF or epirubicin, cisplatin, and capecitabine (ECX), showed a significantly improved OS with FLOT (median OS, 50 months vs 35 months).¹² Although FLOT was found to have more hematologic, neuropathic, and lower gastrointestinal adverse events than ECF or ECX, the number of patients with severe adverse events related to treatment or hospitalizations related to toxicity was similar (~25%) in both groups.¹² Therefore, perioperative FLOT and surgery are preferred over ECF or ECX for patients with good performance status, while ECF or ECX may be preferred in those with poor functional status, uncontrolled medical conditions, severe neuropathy, or insufficient organ function.¹²

Studies looking at perioperative chemotherapy versus postoperative chemotherapy have shown superior outcomes for perioperative therapy.^{23,42} There are limited data for preoperative chemotherapy alone, and this is not recommended in patients who can tolerate perioperative chemotherapy.⁴⁶ In Asian countries, a fixed dose combination of tegafur, gimeracil, and oteracil (a 3-drug regimen known as S-1) is often used instead of other fluoropyrimidines. In these countries, perioperative S-1 and oxaliplatin (SOX) chemotherapy has been examined with comparable efficacy/toxicity found compared with multiagent regimens that use 5-FU or capecitabine (eg, FOLFOX), with a common side effect being thrombocytopenia.⁴⁷

Preoperative chemoradiation: Preoperative chemoradiation is a feasible preoperative treatment option in the setting of concerns of patient tolerance to multiagent or triplet chemotherapy.^{25–27} Significant toxicity rates have been reported in patients receiving perioperative chemotherapy. In the FLOT4 trial, the number of patients with serious adverse events (including those occurring during hospital stay for surgery) was similar in the 2 groups (27% in the ECF or ECX group vs 27% in the FLOT group), as was the number of toxic deaths (<1% in both groups). Hospitalization from toxicity occurred in 26% of patients in the ECF or ECX group and 25% patients in the FLOT group.¹² TOPGEAR (Trial Of Preoperative therapy for Gastric and Esophagogastric junction Adenocarcinoma), was a phase 3 trial that compared preoperative chemoradiation combined with perioperative chemotherapy versus perioperative chemotherapy alone using ECF or ECX for 3 cycles or FLOT for 4 cycles.¹⁵ This study reported that the addition of preoperative chemoradiation to perioperative chemotherapy did not improve OS or PFS compared with perioperative chemotherapy alone. For patients who are not considered suitable candidates for perioperative chemotherapy with FLOT, ECF, or ECX, preoperative chemoradiation with concurrent 5-FU or capecitabine is recommended.^{15,25,26} Because TOPGEAR reported a trend of poorer OS in a subset analysis of patients with tumors in the lower third of the stomach in the experimental arm, the strong recommendation for preoperative chemoradiation among patients who are not candidates for perioperative chemotherapy and conditional recommendation in borderline resectable patients is limited to patients with GEJ or upper/middle third gastric tumors.^{15,25} For patients with tumors in the lower third of the stomach in these conditions, the consideration of preoperative chemoradiation should be weighed against other available treatment options, including clinical trial therapies.

Preoperative chemoradiation is conditionally recommended for patients with borderline resectable tumors.^{15,25–27} The term “borderline resectable” characterizes a subgroup of tumors that are technically resectable but at high risk of margin-positive resection (R1, R2) and/or early recurrence after surgery. One randomized phase 2 trial compared preoperative chemoradiation versus preoperative chemotherapy and reported higher tumor response rates in patients receiving preoperative chemoradiation.²⁶ Importantly, in TOPGEAR, preoperative chemoradiation resulted in a statistically significantly higher percentage of patients achieving a pathologic complete response (pCR) (17% vs 8%) and enhanced tumor downstaging (32% vs 25%).¹⁵ Downstaging by preoperative chemoradiation may aid in converting borderline resectable tumors at risk for R1–2 resection to an R0 resection.

The suggested treatment sequence is multiagent chemotherapy, chemoradiation, and then surgery.

Immunotherapy: The role of perioperative immunotherapy for patients with microsatellite stable/mismatch repair-proficient gastric cancer continues to evolve. The KEYNOTE-585 trial randomized patients with resectable gastric or GEJ cancer to perioperative chemotherapy (2:1 ratio of doublet cisplatin-based chemotherapy to FLOT) with or without pembrolizumab.²⁹ Although study results showed an improvement in pCR in patients receiving pembrolizumab (12.9% vs 2.0%), this did not translate to an improvement in event-free survival or OS.²⁹ An unplanned subgroup analysis from KEYNOTE-585 revealed a benefit of pembrolizumab in patients with high microsatellite instability (MSI-H), but patient numbers were low in this unplanned analysis.²⁹ Similar to KEYNOTE-585, the MATTERHORN trial was a randomized, double-blind, phase 3 trial evaluating perioperative chemoimmunotherapy in patients with stage II-IVA, resectable gastric/GEJ cancer.¹³ Microsatellite stability was confirmed in about two-thirds of patients. The regimen employed perioperative FLOT and either durvalumab or placebo, with the perioperative FLOT plus durvalumab arm resulting in significantly improved pCR and event-free survival rates and a trend toward improved OS. Event-free survival events were defined as time from randomization to disease progression that precluded surgery or required nonprotocol therapy during neoadjuvant treatment, progression, or recurrence during adjuvant treatment, or discovered during surgery, progression, or recurrence after surgery, or death from any cause. A key strength of the MATTERHORN trial was its worldwide reach, which reflected the global population with gastric or GEJ adenocarcinoma eligible for perioperative FLOT, including patients across Europe, the Americas, and East Asia. No new safety signals were observed. The investigators concluded that the findings of the MATTERHORN trial support the use of perioperative durvalumab combined with FLOT as a potential first-line treatment for resectable gastric or GEJ adenocarcinoma.¹³ In the postoperative setting, the ATTRACTION-5 study randomized patients with resected stage III gastric or GEJ cancer (principally PD-L1 negative) to postoperative nivolumab plus chemotherapy versus placebo plus chemotherapy. No difference in relapse-free survival with the addition of nivolumab to postoperative chemotherapy was reported.²⁸ Given the positive results of MATTERHORN in patients with microsatellite stable/mismatch repair-proficient, cT3–4 and/or N+ resectable gastric cancer, perioperative immunotherapy with chemotherapy is conditionally recommended in this setting.^{12,13,28,29}

There are limited data assessing the value of perioperative immunotherapy for patients with gastric cancers with MSI-H status, which is a result of deficient DNA mismatch repair. A systematic review and meta-analysis of 21 prospective phase 1/2 studies comprising 687 patients revealed promising pCR and toxicity results for MSI-H and PD-L1 high patients.³⁰ MATTERHORN included 5% MSI-H and 90% PD-L1 $\geq 1\%$ patients, with all subgroups benefiting from the addition of immunotherapy to chemotherapy.¹³ However, long-term OS data and phase III validation with greater patient numbers are still needed, leading to a conditional rather than a strong recommendation for immunotherapy with or without chemotherapy for patients with locoregionally advanced MSI-H disease. Because of promising data that did not meet criteria for inclusion in this guideline, the field overall is

moving toward front-line treatment with immunotherapy for patients with MSI-H/mismatch repair-deficient tumors.^{48,49}

Postoperative chemotherapy: For patients with gastric cancer not receiving perioperative chemotherapy or preoperative therapy, the use of postoperative multiagent chemotherapy is supported by multiple RCTs.^{23,31–33,35–42} The CLASSIC (Capecitabine and oxaLiplitin Adjuvant Study in Stomach Cancer) study demonstrated that postoperative chemotherapy with capecitabine and oxaliplatin significantly improved OS over observation alone in patients with pT1N2–3, pT2N+, or pT3–4 any N stage gastric cancer following an R0, D2 gastrectomy.³² A D2 resection incorporates removal of perigastric (D1) nodes along with the left gastric artery, common hepatic artery, celiac axis, and splenic artery and hilum nodes. The ACTS-GC (Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer) trial showed that S-1 monotherapy improved OS and relapse-free survival over observation alone in patients with stage II to III gastric cancer (per Japanese classification of gastric carcinoma-2nd Edition),⁵⁰ who received an R0, D2 gastrectomy.³⁶ Therefore, for patients with pT1N2–3, pT2N+, and/or pT3–4 any N stage disease following R0 resection and D2 lymphadenectomy, postoperative chemotherapy alone is recommended.^{23,31–42}

The results of the ARTIST 2 trial showed that patients had improved disease-free survival (DFS) when oxaliplatin was added to S-1 alone.³⁵ Regarding the use of S-1, it is included as a component of the recommended regimens because this guideline is intended for an international audience, and S-1 is widely used with demonstrated efficacy in Eastern countries despite not being FDA-approved in the United States.^{35,38,39,42} In CALGB 80101, postoperative 5-FU plus leucovorin before and after combined 5-FU and RT (5-FU plus leucovorin arm) provided equivalent OS and DFS versus postoperative ECF before and after combined 5-FU and RT (ECF arm).⁴⁵ Therefore, preferred adjuvant chemotherapy regimens include fluoropyrimidine-based therapies (eg, 5-FU, capecitabine, or S1) with a platinum agent (eg, oxaliplatin).^{32,42,51}

Postoperative chemoradiation: While D2 and R0 resection is a standard goal for patients with gastric cancer, this may not be achieved for patients brought to surgery emergently, or for patients with gastric cancers found on pathologic review to be more advanced than expected before surgery. In the setting of suboptimal surgery, a key clinical trial examining the efficacy of postoperative chemoradiation was Intergroup 0116, which randomized 559 patients with margin-negative resected stage IB–IV (M0) adenocarcinoma of the stomach or GEJ to observation or adjuvant treatment with 5-FU plus leucovorin, 4500 cGy of RT in 25 fractions concurrent with 5-FU and leucovorin, followed by 2 additional cycles of 5-FU plus leucovorin.⁴³ While adjuvant chemoradiation was associated with improved OS and relapse-free survival versus observation, the majority of patients had <D2 dissection, leading to the question as to whether an adequate lymphadenectomy (eg, D2 resection) could mitigate the benefit from RT.⁴³

To investigate the role of adjuvant chemoradiation following a D2, R0 gastrectomy, the ARTIST (Adjuvant chemoRadioTherapy In Stomach Tumors) trial compared 2 treatment regimens: 6 cycles of postoperative capecitabine plus cisplatin versus 2 cycles of cisplatin followed by concurrent capecitabine with RT and 2 additional cycles of cisplatin.⁵¹ The trial

reported no difference in recurrence rates between the 2 therapies in the overall population. However, due to a superior DFS with the addition of RT for an unplanned subset of patients with lymph node metastases, the ARTIST 2 trial was designed.³⁵ The trial randomized patients with D2-resected, stage II and III, node-positive gastric cancer to 1 of 3 adjuvant regimens: oral S-1 for 1 year, SOX for 6 months, or SOX plus chemoradiation 4500 cGy. In patients with curatively D2-resected, stage II to III, node-positive gastric cancer, adjuvant SOX or SOX plus chemoradiation was more effective in prolonging DFS than S-1 monotherapy.³⁵ The addition of RT to SOX did not significantly reduce the rate of recurrence after D2 gastrectomy. Limitations of this trial included that the study was not designed for a direct statistical comparison between chemotherapy and chemoradiation, and recruitment of fewer patients than planned (546 patients rather than 900), which reduced the statistical power. One study compared postoperative intensity modulated radiation therapy (IMRT) to 4500 cGy in 25 fractions plus chemotherapy with chemotherapy alone in an R0, D2 population; the IMRT plus chemotherapy arm was associated with improved recurrence-free survival but not OS. Side effects were similar, and the authors noted that IMRT plus chemotherapy was feasible and well tolerated.⁴⁴ Ultimately, it may be concluded that there is no expected benefit to adjuvant chemoradiation in the setting of a D2 and R0 resection without preoperative chemotherapy.

Next, the CRITICS (ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach) RCT investigated postoperative chemoradiation versus chemotherapy for patients who received preoperative chemotherapy.¹⁴ The authors found similar OS and PFS between the arms. While most patients received <D2 dissection, 84% received at least a D1+ dissection as planned. This D1+ dissection, defined as removal of the N1 and N2 lymph nodes (stations 1–9 and 11) and a minimum of 15 lymph nodes, was likely to be a much more extensive surgery than that performed on the Intergroup 0116 trial.⁴³ Based on Intergroup 0116, for patients with pT1N2–3, pT2N+, and/or pT3–4 any N stage resected gastric cancer who have <D2 lymphadenectomy, postoperative chemoradiation with or without postoperative chemotherapy is conditionally recommended.^{14,43} While there were key limitations of the CRITICS trial, which included poor patient compliance and high drop-out rates with potential underestimation of treatment effect, a patient who receives a D1+ dissection and perioperative chemotherapy is not likely to benefit from adjuvant RT.¹⁴

While no data were found meeting the search criteria supporting postoperative chemoradiation for R1–2 resection, consensus expert opinion of the task force resulted in a conditional recommendation for postoperative chemoradiation for R1–2 disease, with or without postoperative chemotherapy, and whether or not preoperative systemic therapy was given. There are insufficient data to comment on whether RT dose escalation is necessary for patients with R1–2 resections. However, when patients can receive multiagent chemotherapy in the setting of an R0 and D2 dissection, there is no benefit to adding RT, and postoperative chemotherapy alone is recommended.^{14,35} However, for patients who are not candidates for perioperative or postoperative multiagent chemotherapy, postoperative chemoradiation (with concurrent 5-FU or capecitabine) is conditionally recommended.^{43–45}

KQ2: Indications for definitive and palliative RT (Table 4)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ2 and Fig. 1.

For patients with unresectable and/or metastatic gastric cancer, what are the indications for definitive and palliative RT, with or without systemic therapy?

Nonoperable and nonmetastatic locoregional disease: RT can be employed for patients with localized gastric cancer not undergoing surgery, in the setting of medical comorbidities, patient preference, or tumor unresectability.^{52,53} Patients should undergo a full staging work up including endoscopy, imaging, consideration of diagnostic laparoscopy, and medical evaluation, followed by discussion in a multidisciplinary tumor board regarding therapeutic options. Factors, including comorbidities, performance status, and age, may be considered when offering definitive RT approaches because of tolerance and toxicity concerns.

There are limited data reporting the outcome of patients unsuitable for surgery treated with chemoradiation alone. In 2 small prospective studies of patients receiving predominantly chemoradiation and chemotherapy, overall response rates exceeding 80% were reported with median OS of 1.5 to 2 years.^{52,53} Long-term OS was achieved in approximately one-third to almost one-half of patients, with recurrences being rare after 2 to 3 years. Although a clinical complete response was achieved in only one-third of patients in one of these 2 studies, this group had a relatively high 2-year OS of 84% with about two-thirds of these patients alive long term.⁵² Based on these data, definitive RT with concurrent chemotherapy is a therapeutic option for patients in this clinical setting.^{52,53} Of note, patients who declined surgery had longer OS than other cohorts. Although the data are insufficient to recommend specific induction or concurrent chemotherapy regimens, 5-FU or capecitabine with RT may be advised.⁵³ Although the number of patients in these studies is small,^{52,53} the OS rates are encouraging, leading to a strong recommendation for definitive chemoradiation with or without induction/consolidation chemotherapy for patients with nonmetastatic gastric cancer who either are not candidates for surgery or decline surgery.

Locoregional recurrent disease: Patients with locoregional recurrent gastric cancer should undergo staging and multidisciplinary evaluation similar to patients with gastric cancer at initial diagnosis. This includes an evaluation regarding the technical and medical appropriateness of RT, surgery, and available systemic regimens, as well as the sequencing of these approaches. Patients who are not candidates for surgery with only locoregional and/or regional lymph node recurrence may be candidates for definitive chemoradiation.^{54–56}

In a study of 34 patients with a predominantly regional lymph node pattern of recurrence (most often station 7–16b) after resection with D2 lymphadenectomy, the objective response rate was 88.3% for patients receiving chemoradiation.⁵⁶ Median OS and PFS were 18 months and 13 months, whereas 1-year OS and PFS were 91.2% and 70.6%, respectively. Another study reported the outcomes of 81 patients with locoregionally recurrent gastric cancer who were treated with involved field RT with oral capecitabine and weekly docetaxel

or chemotherapy alone.⁵⁴ There was an improved response rate of 79.5% (chemoradiation) versus 54.8% (chemotherapy alone) and improved OS (14.2 months with chemoradiation vs 6.4 months with chemotherapy alone). Patients receiving chemoradiation had higher rates of palliation of bleeding (87.5% vs 63.2%), pain (75% vs 50%), and dysphagia/obstruction (71.4% vs 28.6%) compared with chemotherapy alone.⁵⁴ An additional study of 79 patients with locoregionally recurrent gastric cancer treated with RT and concurrent CAPOX (capecitabine and oxaliplatin) followed by CAPOX or CAPOX alone, objective response rate, OS, and symptom control were improved with chemoradiation, with no differences in treatment tolerance.⁵⁵ For patients with inoperable localized de novo gastric cancer or locoregional recurrent gastric cancer, definitive chemoradiation is conditionally recommended if no prior RT was given.^{52–56}

Palliation: RT is an effective palliative tool for treatment of patients with bleeding, pain, or obstruction from gastric cancer.^{57–66} For patients with locally advanced or metastatic gastric cancer experiencing cancer-associated bleeding, palliative RT is recommended for bleeding control. Multiple studies underscore its effectiveness in achieving hemostasis.^{57–59,63–66} A meta-analysis demonstrated a bleeding response rate of 76%,⁵⁷ with individual studies reporting bleeding control rates up to 80% to 90%.^{58,59,63–66} Relief is typically achieved within a few days to 2 weeks after starting RT, with maximum benefit by 1 to 2 months, and lasting 2 to 6 months, which is comparable to the median OS reported for most series. Overall, palliative RT offers a consistent and effective approach for managing bleeding, improving hemoglobin levels, and reducing transfusion dependency, thereby enhancing the QoL for patients with a life expectancy of ≥ 3 months.⁵⁷ Reirradiation may also be considered for rebleeding after an initial palliative course of RT.^{59,62} Although patients may have resolution of their bleeding following a second course of lower dose RT, selection of this treatment must be balanced with the fact that patients receiving reirradiation usually live only several months after the second RT course, leading to a conditional recommendation.^{59,62}

Other gastric cancer symptoms can be relieved by RT, including pain^{58,64,66} and obstruction/dysphagia.^{64,66} Time to and duration of symptom palliation are similar to those noted previously for bleeding. Overall, palliative RT is effective for control of pain^{58,64,66} and obstruction^{64,66} with reported response rates ranging from 50% to 100% for each and a low rate of toxicity (grade 3 $\leq 3\%$).⁶⁴ However, studies supporting palliation are largely retrospective with small numbers of patients treated for obstruction.^{64,66} Given the varying quality of evidence, palliative RT has a strong recommendation to address bleeding and pain,^{57–66} and a conditional recommendation for obstruction.^{64,66} Other mechanical interventions, such as stenting or palliative surgical or endoscopic gastrojejunostomy bypass, may be possible for obstruction, but an advantage to receiving RT is that it is a therapeutic palliative intervention. Of note, patient-reported outcomes following palliative RT have shown improvements in symptoms such as fatigue and physical, emotional, and social functioning, expanding the potential benefits.⁵⁸

Metastatic disease: In the setting of synchronous or metachronous oligometastases, staging with positron emission tomography/computed tomography (CT), consideration

of diagnostic laparoscopy, and multidisciplinary tumor board discussion is advised. For patients with de novo oligometastatic gastric cancer (ie, defined as oligometastatic at initial diagnosis), treatment paradigms of MDT with RT or surgery alone or combined with induction or consolidation, or postoperative systemic therapy are conditionally recommended to attempt disease control.^{18–21,65,67} Treatment approaches evaluating the role of MDT in oligometastatic gastric cancer have included both patients with esophageal and gastric cancer, often with smaller numbers of patients with gastric cancer versus esophageal cancer.^{18–21,67}

Different definitions of oligometastatic gastric cancer have been reported in the literature, including ≤ 2 to ≤ 5 distant metastases, often with only 1 organ or 1 extra-regional lymph node station involved,^{18,19} but these thresholds were most often defined with CT staging.¹⁹ Several series, including a meta-analysis, reported improved OS with MDT consisting of stereotactic body RT or surgery integrated with systemic therapy compared with systemic therapy alone.^{18–20,67} However, a population-based cohort study noted a serious risk of biases in the included publications and a publication bias toward positive findings. Additional data have shown improved OS with a controlled primary tumor versus an uncontrolled primary tumor.²¹

For patients with metastatic gastric cancer and stable or regressing metastases, RT to the primary tumor is conditionally recommended.⁶⁸ One study reported that after 3 months of chemotherapy, patients had a higher local control rate and longer time to local progression with the addition of palliative RT to the primary tumor.⁶⁸ This approach may be applied to patients responding well to systemic therapy and may help to delay or avoid local tumor symptoms. Of note, this recommendation should be a part of a multidisciplinary discussion, especially important in the setting of no targetable mutations, as the evidence supporting it is based on studies before the advent of immunotherapy or targeted therapy options.

KQ3: Optimal dose-fractionation regimens, target volumes, and treatment planning/delivery techniques (Table 5)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ3.

For patients with gastric cancer receiving RT, what are the optimal dose-fractionation regimens, target volumes, and treatment planning and delivery techniques?

Curative intent RT dosing for the nonmetastatic preoperative/postoperative

setting: No clinical trials have examined the efficacy of treatment by varying the RT dose. In the preoperative and postoperative settings, doses of 4500 cGy in 25 fractions combined with 5-fluoropyrimidine–based chemotherapy have been used in clinical trials and practice.^{14,15,25,26,33,35,40,43–45,51} Results of Intergroup 0116 established the efficacy of postoperative chemoradiation for patients with T3–4 and/or node-positive gastric cancer.⁴³ Patients were treated to a total dose of 4500 cGy in 25 fractions concurrently with 5-FU. This trial established the foundation of postoperative chemoradiation, which was further examined in the CRITICS,¹⁴ CALGB 80101 (Cancer and Leukemia Group B),⁴⁵ and ARTIST trials.^{33,35,51} In the preoperative setting, an interim analysis of TOPGEAR

demonstrated the tolerance to and safety of 4500 cGy in 25 fractions with concurrent infusional 5-FU.²⁵ Although no OS benefit was seen in patients randomized to preoperative chemoradiation and perioperative chemotherapy versus perioperative chemotherapy alone in the final analysis,¹⁵ this dose and fractionation have been used in subsequent clinical trials and practice.^{27,71,72} An in-depth analysis of the ARTIST trial revealed a significant decrease in regional recurrence and improved locoregional recurrence-free survival for patients treated with 4500 cGy in the postoperative setting, supporting this dose-fractionation regimen as effective.⁷⁰ However, the predominant pattern of failure was peritoneal in ARTIST, and the subsequent ARTIST 2 trial did not confirm a benefit to postoperative chemoradiation in the R0 and D2 setting, even with positive nodes.^{35,51} Recognizing the lack of variability in dosing in clinical trials and in settings where preoperative or postoperative chemoradiation is indicated, 4500 cGy in 25 fractions is the recommended dose.^{14,15,33,45,51}

Curative intent RT volumes/planning for the nonmetastatic preoperative/postoperative setting: The definition of target volumes has varied in clinical trials based on RT sequence (preoperative vs postoperative), and anatomical differences in the gastric cancer location (Table 6). In the postoperative Intergroup 0116 trial, treatment volumes included the tumor bed, regional nodes, anastomoses, and 2 cm beyond the proximal and distal margins of resection.⁴³ The tumor bed was based on tumor location on endoscopy, preoperative CT, barium swallow, and surgical clips, when applicable. Regional nodes included perigastric, celiac, local para-aortic, splenic, hepatoduodenal or hepatic-portal, and pancreaticoduodenal lymph nodes. Most of the patients treated in Intergroup 0116 received <D2 dissection; however, patterns-of-failure analyses in nonirradiated patients have consistently shown high failure rates in the regional para-aortic, celiac, and hepatoduodenal nodes even after a D2 dissection, indicating that these nodal basins should be routinely treated independent of the extent of dissection.^{70,73,74} Importantly, Intergroup 0116 mandated pretreatment review and approval of RT field design and treatment planning to ensure protocol compliance before treatment could begin.⁴³

In subsequent postoperative trials, target volumes have been based on the Intergroup 0116 protocol.⁴³ In the CALGB 80101 trial, for node-negative patients with ≥ 10 nodes dissected and clear surgical margins (defined as ≥ 5 cm), the RT target included residual stomach, but nodal basin treatment was not mandated.⁴⁵ In ARTIST, the treatment volume included the anastomosis, regional nodes, and 2 cm beyond the proximal and distal margins of resection, and the duodenal stump if surgical resection margins were ≤ 3 cm.^{51,75} The tumor bed was included only for T4 tumors, and the remnant stomach was not routinely treated. Although there were no differences in the local recurrence rates between arms, regional recurrence rates were significantly lower in the chemoradiation arm, especially in pN+ patients, supporting adequate nodal coverage.⁷⁰ Only 2% of failures occurred in the gastric remnant regardless of RT, indicating that it may not need to be routinely treated. Therefore, inclusion of the gastric remnant is conditionally recommended for positive margins only.^{51,70} The follow-up ARTIST 2 trial investigated the use of postoperative chemoradiation in only patients with node-positive gastric cancer after D2 dissection.³⁵ Target volumes included regional lymph nodes, the tumor bed in T4 cancers, and if

surgical resection margins were ≤ 3 cm, the anastomosis and duodenal stump were also included.^{35,51,75} In the CRITICS trial, the gastrojejunal anastomosis and duodenal stump were included in the clinical target volume (CTV).¹⁴ After a total gastrectomy for proximal and GEJ tumors, the esophagojejunal anastomosis was part of the CTV. In summary, for patients with nonmetastatic gastric cancer receiving postoperative chemoradiation, inclusion of the tumor bed, anastomoses, and regional nodes is recommended.^{14,33,45,51}

The CTV differs between preoperative and postoperative strategies based on anatomy. In TOPGEAR, employing preoperative chemoradiation in the experimental arm, the CTV included the gross tumor volume (GTV) and involved lymph nodes, including perigastric tumor extension and any sites of adherence and/or invasion for T4 lesions.¹⁵ The GTV was delineated by clinical and endoscopic findings, endoscopic ultrasound, CT, and positron emission tomography when available. The CTV included the entire stomach, with proximal and distal margins based on tumor location, as well as regional lymph nodes, regardless of primary tumor location.¹⁵ At least 1 cm of proximal esophagus was included, increased to 4 cm for tumors involving the cardia, GEJ, or distal esophagus. Similarly, a 1 cm margin of duodenum beyond the pylorus was included, increased to 4 cm for tumors involving the pylorus or proximal duodenum. Therefore, for patients with nonmetastatic gastric cancer receiving preoperative chemoradiation, coverage of the entire stomach, perigastric extension, and regional lymph nodes is recommended (Table 6).^{15,26,27,69} Regional lymph nodes included in the CTV were the perigastric, celiac, splenic hilar, hepatoduodenal, portahepatic, suprapancreatic, and pancreaticoduodenal, as well as para-aortic nodes along the length of the aforementioned CTV regions. Similar to Intergroup 0116, RT design and planning were reviewed prospectively, and up to one-third of treatment plans required resubmission before starting treatment. This highlights the importance of careful target volume delineation.⁷⁶ The planning target volume (PTV) is at the discretion of the treating physician, depending on the expected variability in setup and internal target motion, and motion due to respiration and gastric filling should be accounted for. The PTV margin may be reduced from 1 cm to as low as 0.5 cm in cases when 4-dimensional CT and daily image guided RT are used, and thus, daily image guided RT is encouraged.^{14,25}

Currently, limited data are available to guide the optimal RT treatment techniques for use in either postoperative or preoperative settings. Early trials of RT for gastric cancer, including the Intergroup 0116 trial and ARTIST, used parallel opposed AP/PA fields.^{43,51} The follow-up ARTIST 2 study used 3-D conformal RT (3-D CRT) planning.³⁵ More modern RT trials, including TOPGEAR and CRITICS, permitted 3-D CRT or IMRT planning.^{14,25} Treatment technique should permit adequate target coverage while achieving the recommended organ-at-risk dose constraints,⁷⁷ and either IMRT or 3-D CRT techniques are recommended.^{14,15,33,45,51} See Table 7 and Table 8 for RT target dosimetric goals and organ-at-risk constraints.

Curative intent RT planning for the nonmetastatic, unresectable setting: For patients with locoregional-only disease not undergoing surgery, treatment with curative intent chemoradiation has been shown to be safe and effective.^{52,53} In a phase 2 trial, patients with inoperable gastric cancer (because of patient preference or comorbidities) were treated to a total dose of 4500 cGy in 25 fractions with concurrent bolus 5-FU.⁵³

The treatment volume included the stomach and regional nodes (ie, perigastric, celiac, gastroduodenal, porta hepatic, splenic, suprapancreatic, retropancreaticoduodenal, and lower esophageal; Table 6). Margins of 5 cm were expanded into the esophagus or duodenum based on tumor location. Treatment could be delivered using 3-D CRT or IMRT. In another study, patients with only locoregional gastric cancer who were inoperable or medically unresectable were treated to a total dose of 4500 cGy in 25 fractions with a 540 cGy in 3 fraction boost to the gross primary disease and involved nodes.⁵² The CTV included the gross disease with a 2 to 3 cm margin along the stomach and regional nodes (ie, perigastric, celiac, porta hepatic, gastroduodenal, splenic, suprapancreatic, retropancreaticoduodenal, and para-aortic; Table 6). A 0.5 cm margin was added to the CTV to create the PTV. Because of the small size of the studies and low quality of evidence, a dose of 4500 to 5040 cGy in 25 to 28 fractions is conditionally recommended for patients with nonmetastatic gastric cancer who are medically inoperable, have unresectable disease, or decline surgery.^{52,53}

Curative intent RT planning for the nonmetastatic, locoregionally recurrent, unresectable setting: For recurrences involving the anastomosis, perigastric soft tissue, or gastric remnant, doses of 4500 to 5040 cGy in 25 to 28 fractions are recommended.^{54,55} For isolated regional lymph node-only recurrences, one series employed doses ranging from 3000 to 6600 cGy in 180 to 300 cGy daily fractions.⁵⁶ In multivariable analysis, RT doses ≥ 5400 cGy versus < 5400 cGy had significantly higher PFS and OS rates. For nodal-only recurrences, doses exceeding 5040 cGy may be appropriate if normal tissue tolerances and constraints are achieved.

Simulation for RT planning: Patients with gastric cancer treated with curative intent are usually simulated in the supine position with arms placed above their head in an immobilization device. Pretreatment imaging, endoscopic findings, and surgical reports, where applicable, are used for target volume delineation. The use of oral contrast is useful to delineate the small bowel, and IV contrast is encouraged. While the majority of clinical trials have not given guidance on whether to fast before simulation, TOPGEAR recommended that patients undergo simulation and treatment early in the morning following a light breakfast.¹⁵ Therefore, to minimize the size of the gastric target in the neoadjuvant or definitive setting, fasting for ≥ 2 hours or limiting oral intake to a light meal before simulation and treatment may be advised. Four-dimensional CT may be used to account for intrafraction motion, and respiratory management techniques are appropriate.⁵²

Palliative RT dose, fractionation, and targets: Prospective data to guide the application of RT in the palliative setting remain scarce. Retrospective analyses have consistently demonstrated efficacy in palliating symptoms such as bleeding, pain, or obstruction;^{60,62–65} however, the optimal palliative dose has not been established. A multicenter prospective observational study, JROSG 17–3 (Japanese Radiation Oncology Study Group), investigated the effectiveness of palliative RT and whether total dose correlated with OS, response, or rebleeding.⁶¹ RT was found to be effective, with 90% response rates at 8 weeks posttreatment. Biologically effective dose (BED) was not associated with OS, treatment response, or rebleeding. A retrospective analysis of patients

treated with palliative RT for bleeding, pain, and/or obstruction showed no difference in response or OS rates, which used low (≤ 3900 cGy₁₀, ie, ≤ 3000 cGy in 10 fractions) and high (> 3900 cGy₁₀) BED regimens ($\alpha/\beta = 10$).⁶⁴ In a subsequent follow-up phase 2 study evaluating the response rates to palliative RT, a total dose of 3600 cGy in 12 fractions was given.⁶⁶ Response rates were excellent, with 80% of patients with bleeding responding to treatment. A systematic review and meta-analysis of observational studies evaluating palliation of bleeding in patients with gastric cancer did show a dose-response relationship.⁵⁷ These investigators concluded that a BED of < 3000 cGy₁₀ (eg, namely 800 cGy in 1 fraction) was not advised.⁵⁷ In contrast, the JROSG secondary analysis showed no therapeutic gain with higher BED.⁵⁸ In fact, patients treated with a lower BED (≤ 1440 cGy₁₀) had significant improvement in fatigue and distress (predominantly 800 cGy in 1 fraction) in patient-reported outcomes. The authors hypothesized that this was because a shorter course caused less psychological burden on the patient/caregiver.⁵⁸ These data underscore the importance of balancing the pros/cons of different regimens based on the clinical setting and individual patient preferences. Given the inconsistencies regarding cancer control benefit to doses > 3900 cGy₁₀ (ie, > 3000 cGy in 10 fractions), and recognizing the QoL benefits with shorter regimens, palliative RT regimens involving 1 to 10 fractions with a BED range of 1440 to 3900 cGy₁₀ is recommended (eg, 800 cGy in 1 fraction, 2000 cGy in 5 fractions, or 3000 cGy in 10 fractions).^{57–64,66} The data evaluating the use of reirradiation are limited and are only reported in the setting of prior palliative doses of RT up to 3000 cGy in 10 fractions. Small patient subsets involving reirradiation doses of 1500 cGy in 5 fractions (following 2000 cGy in 5 fractions) and 2000 cGy in 10 fractions (following 3000 cGy in 10 fractions) reported responses in all patients with no grade ≥ 3 toxicity observed.^{59,62} Of note, the duration between treatments was infrequently described in these studies. Based on these limited data, reirradiation regimens of 1 to 10 fractions with a BED range of 1440 to 2800 cGy₁₀ are conditionally recommended (eg, 800 cGy in 1 fraction, 1500 cGy in 5 fractions, or 2000 cGy in 10 fractions).^{59,62}

The optimal treatment technique for palliative RT in gastric cancer is unknown; however, a meta-analysis found that studies using 3-D CRT planning had improved bleeding response compared with those using 2-dimensional planning, likely due to superior target volume visualization with 3-D techniques.⁵⁷ All patients accrued to a prospective phase 2 study were treated with 3-D CRT techniques.⁶⁶ Similarly, there are limited data guiding the definition of target volumes. When visible, the GTV plus a PTV margin may be used.⁶⁶ A prospective pilot study investigating RT for palliation of gastric bleeding included the whole stomach at initial treatment and only the tumor with a margin with GTV delineation supported by endoscopically placed clips in the retreatment setting.⁵⁹ In a phase 2 study, the entire stomach was typically included, but when visible, targeting the GTV was allowed with a 0.5 cm margin for CTV and 1 cm for PTV.⁶⁶ To decrease the PTV size to ≤ 0.5 cm, 4-dimensional simulation may also be performed in the palliative setting.^{62,63,65}

There were no data meeting inclusion criteria for proton therapy, so a recommendation addressing this modality could not be made.

Guidance on target volume coverage and normal tissue constraints is outlined in Table 7 and Table 8.

Health Disparities

Analyses of outcome disparities have reported that male sex portends a worse prognosis but better treatment tolerance,⁸³ including for MSI-H patients.^{84,85} In a subset analysis of the CRITICS trial, female patients were more likely to be younger than males and have higher rates of adverse pathologic features such as diffuse type tumors and positive distal margins.⁸⁶ In both this analysis and a pooled analysis of individual patient data from multiple prospective studies, toxicity rates were higher for female patients despite the same radiation dose and resection rates.^{83,86} Proposed explanations for this are that maximum tolerated doses of drugs are often determined in male-predominant phase 1 and 2 studies, and female patients might be being treated with doses above those necessary for efficacy, potentially at the cost of increased toxicity.

In some studies, older age has been associated with higher rates of toxicity and treatment noncompliance,^{87–89} and inferior oncologic outcomes.^{88,89} However, other data suggest similar outcomes regardless of age.⁸³ With respect to institutional experience, a subset analysis of the CRITICS trial found that OS and PFS were significantly higher in patients undergoing surgery at high versus low volume hospitals. Regarding the effect of race, a secondary analysis of RCT data showed improved outcomes for Asian Americans compared with White or Black American patients.⁹⁰ Although diagnosis at an earlier stage has been used to explain why Asians have a better prognosis in general, this cannot be used to explain the differences in this study, where stages are matched across the races assessed. Although explanations such as environmental/social and biological subtype (eg, association with *H. pylori*) differences were proposed, the task force notes that further study is required to explain the variance in outcomes. These differences indicate opportunities to improve both oncologic and QoL metrics for patients at risk for worse outcomes.

Conclusions and Future Directions

Gastric cancer is a significant global health challenge because of its high incidence and mortality rates, particularly in Eastern Asia, Eastern Europe, and South America. Although some high-income countries have witnessed declines in both incidence and mortality rates, the overall global burden of gastric cancer remains substantial. These disparities likely arise from variations in dietary habits, socioeconomic status, and the prevalence of *H. pylori* infection, a well-established risk factor for gastric cancer.⁴

Achieving optimal outcomes is challenging due to late-stage diagnosis and disease heterogeneity. Current treatment modalities include surgery, systemic therapy (chemotherapy, targeted therapy, and immunotherapy), and RT. The FLOT perioperative regimen is standard for patients with resectable gastric cancer who are deemed well enough to tolerate it. The MATTERHORN trial has shown that for patients with resectable disease, regardless of PD-L1 or microsatellite stability status, immunotherapy added to perioperative chemotherapy has improved pCR and event-free survival rates.¹³ Although further study is needed to determine if patient-focused outcomes such as OS and/or QoL are also improved, a trend toward improved OS in MATTERHORN suggests the possibility of statistical significance with longer follow-up.^{13,29,49}

RT is used in several clinical scenarios across the disease spectrum. Although phase 3 studies have not shown a benefit to preoperative or postoperative chemoradiation with perioperative chemotherapy and surgery, RT may be a therapeutic option depending on the stage, patient performance status, and adequacy and timing of surgery. For patients with nonmetastatic gastric cancer who decline or are not candidates for surgery, RT may have the potential to contribute to meaningful disease control. RT has long been recognized as an effective tool in the palliation of bleeding, pain, and obstruction. Like surgery, RT may also play an important role in the treatment of oligometastases. With innovations in RT (eg, stereotactic body RT, respiratory management, image guidance, adaptive planning, increases in safely deliverable dose), the indications for its use have extended, and robust studies with novel systemic therapies, including immunotherapy, as well as surgery, may identify new therapeutic strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to Christopher J. Anker, MD, from the University of Vermont, for collaborating on the creation of the search strategy and methodological support. The task force thanks John Peterson, MD (lead resident), Cecil Benitez, MD, PhD, MS, Raj Upadhyay, MBBS, MD, and Parisa Shamsesfandabadi, MD, for literature review assistance. The task force also thanks the peer reviewers for their comments and time spent reviewing the guideline. See Appendix E1 for their names and disclosures.

Source of support:

This work was funded by the American Society for Radiation Oncology.

References

1. Institute of Medicine (US). Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. In: Graham R, Mancher M, Miller Wolman D, Steinberg E, eds. Clinical Practice Guidelines We Can Trust. National Academies Press; 2011.
2. Institute of Medicine (US). Committee on Standards for Systematic Reviews of Comparative Effectiveness. In: Eden J, Levit L, Berg A, Morton S, eds. Finding What Works In Health Care: Standards for Systematic Reviews. National Academies Press; 2011.
3. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74:229–263. [PubMed: 38572751]
4. Mamun TI, Younus S, Rahman MH. Gastric cancer-Epidemiology, modifiable and non-modifiable risk factors, challenges and opportunities: An updated review. *Cancer Treat Res Commun.* 2024;41:100845. [PubMed: 39357127]
5. Seo JHKB, Cho JY. Gender differences in gastric cancer: Molecular and epidemiological perspectives. *Cancers.* 2020;12:1586. [PubMed: 32549375]
6. National Cancer Institute. Surveillance, Epidemiology, and EndResults Program. Cancer stat facts: stomach cancer. 2025. Accessed June 1, 2025. <https://seer.cancer.gov/statfacts/html/stomach.html>
7. Park SH, Kang MJ, Yun EH, Jung KW. Epidemiology of gastric cancer in Korea: Trends in incidence and survival based on Korea Central Cancer Registry data (1999–2019). *J Gastric Cancer.* 2022;22:160–168. [PubMed: 35938363]
8. Noguchi Y, Yoshikawa T, Tsuburaya A, Motohashi H, Karpeh MS, Brennan MF. Is gastric carcinoma different between Japan and the United States? *Cancer.* 2000;89:2237–2246. [PubMed: 11147594]

9. Shitara K, Fleitas T, Kawakami H, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with gastric cancer. *ESMO Open*. 2024;9:102226. [PubMed: 38458658]
10. Wang FH, Zhang XT, Tang L, et al. The Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer, 2023. *Cancer Commun (Lond)*. 2024;44:127–172. [PubMed: 38160327]
11. Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022;33:1005–1020. [PubMed: 35914639]
12. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): A randomised, phase 2/3 trial. *Lancet*. 2019;393:1948–1957. [PubMed: 30982686]
13. Janjigian YY, Al-Batran SE, Wainberg ZA, et al. Perioperative durvalumab in gastric and gastroesophageal junction cancer. *N Engl J Med*. 2025;393:217–230. [PubMed: 40454643]
14. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): An international, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19:616–628. [PubMed: 29650363]
15. Leong T, Smithers BM, Michael M, et al. Preoperative chemoradiotherapy for resectable gastric cancer. *N Engl J Med*. 2024;391:1810–1821. [PubMed: 39282905]
16. Fujitani K, Yang H-K, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): A phase 3, randomised controlled trial. *Lancet Oncol*. 2016;17:309–318. [PubMed: 26822397]
17. Al-Batran SE, Lorenzen S LS, Riera J, et al. Effect of chemotherapy/targeted therapy alone vs. chemotherapy/targeted therapy followed by radical surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction: The IKF-575/RENAISSANCE phase III trial. *J Clin Oncol*. 2024;42(17_suppl). LBA4001–LBA4001.
18. Kroese TE, Christ SM, van Rossum PSN, et al. Incidence and survival of patients with oligometastatic esophagogastric cancer: A multicenter cohort study. *Radiother Oncol*. 2022;173:269–276. [PubMed: 35753555]
19. Kroese TE, van Laarhoven HWM, Nilsson M, et al. Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment: A systematic review and meta-analysis. *Eur J Cancer*. 2022;166:254–269. [PubMed: 35339868]
20. Franceschini D, Teriaca MA, Di Cristina L, et al. Stereotactic radiation therapy for oligometastatic esophagogastric adenocarcinoma: Outcome and prognostic factors. *Br J Radiol*. 2023;96:20220771. [PubMed: 36809197]
21. Kroese TE, Jorritsma NKN, van Laarhoven HWM, et al. Stereotactic radiotherapy or metastasectomy for oligometastatic esophagogastric cancer: A nationwide population-based cohort study. *Clin Transl Radiat Oncol*. 2022;37:109–115. [PubMed: 36186924]
22. Noronha V, Patil VM, Menon N, et al. Phase III randomized trial comparing palliative systemic therapy to best supportive care in advanced esophageal/GEJ cancer. *Int J Cancer*. 2024;155:2232–2245. [PubMed: 39093841]
23. Zhang X, Liang H, Li Z, et al. Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): An open-label, superiority and non-inferiority, phase 3 randomised controlled trial. *Lancet Oncol*. 2021;22:1081–1092. [PubMed: 34252374]
24. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11–20. [PubMed: 16822992]
25. Leong T, Smithers BM, Haustermans K, et al. TOPGEAR: A randomized, phase III trial of perioperative ECF chemotherapy with or without preoperative chemoradiation for resectable gastric cancer: Interim results from an international, intergroup trial of the AGITG, TROG, EORTC and CCTG. *Ann Surg Oncol*. 2017;24:2252–2258. [PubMed: 28337660]

26. Wang X, Zhao DB, Yang L, et al. Preoperative concurrent chemoradiotherapy versus neoadjuvant chemotherapy for locally advanced gastric cancer: Phase II randomized study. *Front Oncol.* 2022;12:870741. [PubMed: 35574368]
27. Wang F, Qu A, Sun Y, et al. Neoadjuvant chemoradiotherapy plus postoperative adjuvant XELOX chemotherapy versus postoperative adjuvant chemotherapy with XELOX regimen for local advanced gastric cancer-A randomized, controlled study. *Br J Radiol.* 2021;94:20201088. [PubMed: 34260297]
28. Kang YK, Terashima M, Kim YW, et al. Adjuvant nivolumab plus chemotherapy versus placebo plus chemotherapy for stage III gastric or gastro-oesophageal junction cancer after gastrectomy with D2 or more extensive lymph-node dissection (ATTRACTION-5): A randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol.* 2024;9:705–717. [PubMed: 38906161]
29. Shitara K, Rha SY, Wyrwicz LS, et al. Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): An interim analysis of the multicentre, double-blind, randomised phase 3 study. *Lancet Oncol.* 2024;25:212–224. [PubMed: 38134948]
30. Li S, Xu Q, Dai X, et al. Neoadjuvant therapy with immune checkpoint inhibitors in gastric cancer: A systematic review and meta-analysis. *Ann Surg Oncol.* 2023;30:3594–3602. [PubMed: 36795255]
31. Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol.* 2014;15:1389–1396. [PubMed: 25439693]
32. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): A phase 3 open-label, randomised controlled trial. *Lancet.* 2012;379:315–321. [PubMed: 22226517]
33. Park SH, Sohn TS, Lee J, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: Final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. *J Clin Oncol.* 2015;33:3130–3136. [PubMed: 25559811]
34. Nie RC, Chen GM, Yuan SQ, et al. Adjuvant chemotherapy for gastric cancer patients with mismatch repair deficiency or microsatellite instability: Systematic review and meta-analysis. *Ann Surg Oncol.* 2022;29:2324–2331. [PubMed: 34796431]
35. Park SH, Lim DH, Sohn TS, et al. A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: The ARTIST 2 trial. *Ann Oncol.* 2021;32:368–374. [PubMed: 33278599]
36. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol.* 2011;29:4387–4393. [PubMed: 22010012]
37. Koda Y, Yoshida K, Kochi M, et al. Addition of docetaxel to S-1 results in significantly superior 5-year survival outcomes in stage III gastric cancer: A final report of the JACCRO GC-07 study. *Gastric Cancer.* 2023;26:1063–1068. [PubMed: 37548812]
38. Iwasaki Y, Terashima M, Mizusawa J, et al. Gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer (JCOG0501): An open-label, phase 3, randomized controlled trial. *Gastric Cancer.* 2021;24:492–502. [PubMed: 33200303]
39. Yoshikawa T, Terashima M, Mizusawa J, et al. Four courses versus eight courses of adjuvant S-1 for patients with stage II gastric cancer (JCOG1104 [OPAS-1]): An open-label, phase 3, non-inferiority, randomised trial. *Lancet Gastroenterol Hepatol.* 2019;4:208–216. [PubMed: 30679107]
40. Bamias A, Karina M, Papakostas P, et al. A randomized phase III study of adjuvant platinum/docetaxel chemotherapy with or without radiation therapy in patients with gastric cancer. *Cancer Chemother Pharmacol.* 2010;65:1009–1021. [PubMed: 20130877]
41. Kulig J, Kolodziejczyk P, Sierzega M, et al. Adjuvant chemotherapy with etoposide, adriamycin and cisplatin compared with surgery alone in the treatment of gastric cancer: A phase III randomized, multicenter, clinical trial. *Oncology.* 2010;78:54–61. [PubMed: 20215786]

42. Zhang X, Liang H, Li Z, et al. Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): Final report of a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2025;26:312–319. [PubMed: 39952264]
43. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: A phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol.* 2012;30:2327–2333. [PubMed: 22585691]
44. Zhu WG, Xua DF, Pu J, et al. A randomized, controlled, multicenter study comparing intensity-modulated radiotherapy plus concurrent chemotherapy with chemotherapy alone in gastric cancer patients with D2 resection. *Radiother Oncol.* 2012;104:361–366. [PubMed: 22985776]
45. Fuchs CS, Niedzwiecki D, Mamon HJ, et al. Adjuvant chemoradiotherapy with epirubicin, cisplatin, and fluorouracil compared with adjuvant chemoradiotherapy with fluorouracil and leucovorin after curative resection of gastric cancer: Results from CALGB 80101 (Alliance). *J Clin Oncol.* 2017;35:3671–3677. [PubMed: 28976791]
46. Tian Y, Yang P, Guo H, et al. Neoadjuvant docetaxel, oxaliplatin plus capecitabine versus oxaliplatin plus capecitabine for patients with locally advanced gastric adenocarcinoma: Long-term results of a phase III randomized controlled trial. *Int J Surg.* 2023;109:4000–4008. [PubMed: 37678277]
47. Yu J, Gao Y, Chen L, et al. Effect of S-1 plus oxaliplatin compared with fluorouracil, leucovorin plus oxaliplatin as perioperative chemotherapy for locally advanced, resectable gastric cancer: A randomized clinical trial. *JAMA Netw Open.* 2022;5:e220426. [PubMed: 35226081]
48. Cercek A, Foote MB, Rousseau B, et al. Nonoperative management of mismatch repair-deficient tumors. *N Engl J Med.* 2025;392:2297–2308. [PubMed: 40293177]
49. Andre T, Tougeron D, Piessen G, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: The GERCOR NEONIPGA phase II study. *J Clin Oncol.* 2023;41:255–265. [PubMed: 35969830]
50. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma - 2nd English Edition. *Gastric Cancer.* 1998;1:10–24. [PubMed: 11957040]
51. Lee J, Lim DH, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: The ARTIST trial. *J Clin Oncol.* 2012;30:268–273. [PubMed: 22184384]
52. Liu Y, Zhao G, Xu Y, et al. Multicenter phase 2 study of peri-irradiation chemotherapy plus intensity modulated radiation therapy with concurrent weekly docetaxel for inoperable or medically unresectable nonmetastatic gastric cancer. *Int J Radiat Oncol Biol Phys.* 2017;98:1096–1105. [PubMed: 28721893]
53. Wydmanski J, Grabinska K, Polanowski P, et al. Radiotherapy and chemoradiotherapy as a novel option for the treatment of locally advanced inoperable gastric adenocarcinoma: A phase II study. *Mol Clin Oncol.* 2014;2:1150–1154. [PubMed: 25279214]
54. Xie J, Liang N, Qiao L, et al. Docetaxel, capecitabine and concurrent radiotherapy for gastric cancer patients with postoperative locoregional recurrence. *Tumori.* 2015;101:433–439. [PubMed: 25983095]
55. Yuan ST, Wang FL, Liu N, et al. Concurrent involved-field radiotherapy and XELOX versus XELOX chemotherapy alone in gastric cancer patients with postoperative locoregional recurrence. *Am J Clin Oncol.* 2015;38:130–134. [PubMed: 23608834]
56. Cai L, Ouyang G, Wang X, Li Z, Shen Y. Radiotherapy combined with chemotherapy for regional lymph node recurrence in gastric cancer. *Cancer Manag Res.* 2020;12:13339–13346. [PubMed: 33380839]
57. Viani GA, Arruda CV, Hamamura AC, et al. Palliative radiotherapy for gastric cancer: Is there a dose relationship between bleeding response and radiotherapy? *Clinics (Sao Paulo).* 2020;75:e1644. [PubMed: 32901671]
58. Kawamoto T, Saito T, Kosugi T, et al. Temporal profiles of symptom scores after palliative radiotherapy for bleeding gastric cancer with adjustment for the palliative prognostic index: An

- exploratory analysis of a multicentre prospective observational study (JROSG 17–3). *Clin Oncol (R Coll Radiol)*. 2022;34:e505–e514. [PubMed: 35654667]
59. Tanaka O, Sugiyama A, Omatsu T, Tawada M, Makita C, Matsuo M. Hemostatic radiotherapy for inoperable gastric cancer: A pilot study. *Br J Radiol*. 2020;93:20190958. [PubMed: 32356453]
 60. Andleeb A, Fatima K, Nasreen S, et al. Bleeding control in advanced gastric cancer; role of radiotherapy. *Indian J Palliat Care*. 2023;29:279–284. [PubMed: 37700893]
 61. Saito T, Kosugi T, Nakamura N, et al. Treatment response after palliative radiotherapy for bleeding gastric cancer: A multicenter prospective observational study (JROSG 17–3). *Gastric Cancer*. 2022;25:411–421. [PubMed: 34580795]
 62. Lee J, Byun HK, Koom WS, Lee YC, Seong J. Efficacy of radiotherapy for gastric bleeding associated with advanced gastric cancer. *Radiat Oncol*. 2021;16:161. [PubMed: 34425855]
 63. Yu J, Jung J, Park SR, et al. Role of palliative radiotherapy in bleeding control in patients with unresectable advanced gastric cancer. *BMC Cancer*. 2021;21:413. [PubMed: 33858353]
 64. Tey J, Choo BA, Leong CN, et al. Clinical outcome of palliative radiotherapy for locally advanced symptomatic gastric cancer in the modern era. *Medicine (Baltimore)*. 2014;93:e118. [PubMed: 25396330]
 65. Takeda K, Sakayauchi T, Kubozono M, et al. Palliative radiotherapy for gastric cancer bleeding: A multi-institutional retrospective study. *BMC Palliat Care*. 2022;21:52. [PubMed: 35413824]
 66. Tey J, Zheng H, Soon YY, et al. Palliative radiotherapy in symptomatic locally advanced gastric cancer: A phase II trial. *Cancer Med*. 2019;8:1447–1458. [PubMed: 30790469]
 67. Xu C, Xie J, Liang N, et al. Concurrent involved-field radiotherapy and XELOX in gastric cancer patients with postoperative oligometastatic recurrence. *J Cancer Res Ther*. 2014;10(Suppl):267–271. [PubMed: 25693933]
 68. Hingorani M, Dixit S, Johnson M, et al. Palliative radiotherapy in the presence of well-controlled metastatic disease after initial chemotherapy may prolong survival in patients with metastatic esophageal and gastric cancer. *Cancer Res Treat*. 2015;47:706–717. [PubMed: 25687854]
 69. Wang JJ, Shao H, Zhang L, et al. Preoperative chemoradiation-induced hematological toxicity and related vertebral dosimetry evaluations in patients with locally advanced gastric cancer: Data from a phase III clinical trial. *Radiat Oncol*. 2023;18:100. [PubMed: 37365597]
 70. Yu JI, Lim DH, Ahn YC, et al. Effects of adjuvant radiotherapy on completely resected gastric cancer: A radiation oncologist's view of the ARTIST randomized phase III trial. *Radiation Oncol*. 2015;117:171–177. [PubMed: 26299196]
 71. Barbour AP, Walpole ET, Mai GT, et al. Preoperative cisplatin, fluorouracil, and docetaxel with or without radiotherapy after poor early response to cisplatin and fluorouracil for resectable oesophageal adenocarcinoma (AGITG DOCTOR): Results from a multicentre, randomised controlled phase II trial. *Ann Oncol*. 2020;31:236–245. [PubMed: 31959340]
 72. Reed VK, Krishnan S, Mansfield PF, et al. Incidence, natural history, and patterns of locoregional recurrence in gastric cancer patients treated with preoperative chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2008;71:741–747. [PubMed: 18164837]
 73. Xu J, Shen L, Shui Y, et al. Patterns of recurrence after curative D2 resection for gastric cancer: Implications for postoperative radiotherapy. *Cancer Med*. 2020;9:4724–4735. [PubMed: 32420703]
 74. Yang W, Zhou M, Hu R, et al. Patterns of regional nodal relapse after D2 lymphadenectomy in gastric cancer: Rethinking the target volume. *Onco Targets Ther*. 2018;11:8015–8024. [PubMed: 30519043]
 75. Yu JI, Lim DH, Lee J, et al. Necessity of adjuvant concurrent chemoradiotherapy in D2-resected LN-positive gastric cancer. *Radiation Oncol*. 2018;129:306–312. [PubMed: 30037498]
 76. Lukovic J, Moore AJ, Lee MT, et al. The feasibility of quality assurance in the TOPGEAR international phase 3 clinical trial of neoadjuvant chemoradiation therapy for gastric cancer (an intergroup trial of the AGITG/TROG/NHMRC CTC/EORTC/CCTG). *Int J Radiat Oncol Biol Phys*. 2023;117:1096–1106. [PubMed: 37393022]
 77. Wang X, Shen Y, Zhu H, et al. A phase II trial of concurrent 3D-CRT/IMRT and oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX) in gastric cancer patients with R0 gastrectomy and D2 lymph node dissection. *Gastric Cancer*. 2016;19:245–254. [PubMed: 25609451]

78. Pan CC, Kavanagh BD, Dawson LA, et al. Radiation-associated liver injury. *Int J Radiat Oncol Biol Phys.* 2010;76(3 suppl):S94–S100. [PubMed: 20171524]
79. Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys.* 2010;76(3 suppl):S70–S76. [PubMed: 20171521]
80. Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. *Int J Radiat Oncol Biol Phys.* 2010;76(3 suppl):S77–S85. [PubMed: 20171522]
81. Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. *Int J Radiat Oncol Biol Phys.* 2010;76(3 suppl):S42–S49. [PubMed: 20171517]
82. Dawson LA, Kavanagh BD, Paulino AC, et al. Radiation-associated kidney injury. *Int J Radiat Oncol Biol Phys.* 2010;76(3 suppl):S108–S115. [PubMed: 20171504]
83. Athauda A, Nankivell M, Langley RE, et al. Impact of sex and age on chemotherapy efficacy, toxicity and survival in localised oesophagogastric cancer: A pooled analysis of 3265 individual patient data from four large randomised trials (OE02, OE05, MAGIC and ST03). *Eur J Cancer.* 2020;137:45–56. [PubMed: 32745964]
84. Quaas A, Biesma HD, Wagner AD, et al. Microsatellite instability and sex differences in resectable gastric cancer - A pooled analysis of three European cohorts. *Eur J Cancer.* 2022;173:95–104. [PubMed: 35863110]
85. Raimondi A, Kim YW, Kang WK, et al. Prognostic and predictive impact of sex in locally advanced microsatellite instability high gastric or gastroesophageal junction cancer: An individual patient data pooled analysis of randomized clinical trials. *Eur J Cancer.* 2024;203:114043. [PubMed: 38598921]
86. Caspers IA, Slagter AE, Lind P, et al. The impact of sex on treatment and outcome in relation to histological subtype in patients with resectable gastric cancer: Results from the randomized CRITICS trial. *J Surg Oncol.* 2024;129:734–744. [PubMed: 38073160]
87. Slagter AE, Tudela B, van Amelsfoort RM, et al. Older versus younger adults with gastric cancer receiving perioperative treatment: Results from the CRITICS trial. *Eur J Cancer.* 2020;130:146–154. [PubMed: 32208351]
88. Tsuburaya A, Guan J, Yoshida K, et al. Clinical biomarkers in adjuvant chemotherapy for gastric cancer after D2 dissection by a pooled analysis of individual patient data from large randomized controlled trials. *Gastric Cancer.* 2021;24:1184–1193. [PubMed: 34365541]
89. Chang SH, Kim SN, Choi HJ, et al. Adjuvant chemotherapy for advanced gastric cancer in elderly and non-elderly patients: Meta-analysis of randomized controlled trials. *Cancer Res Treat.* 2017;49:263–273. [PubMed: 27384158]
90. Abdel-Rahman O Asian Americans have better outcomes of nonmetastatic gastric cancer compared to other United States racial groups: A secondary analysis from a randomized study. *World J Gastrointest Oncol.* 2019;11:1151–1160. [PubMed: 31908720]
91. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Rev Esp Cardiol (Engl Ed).* 2021;74:790–799. [PubMed: 34446261]
92. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. *BMJ.* 2021;372:n160. [PubMed: 33781993]

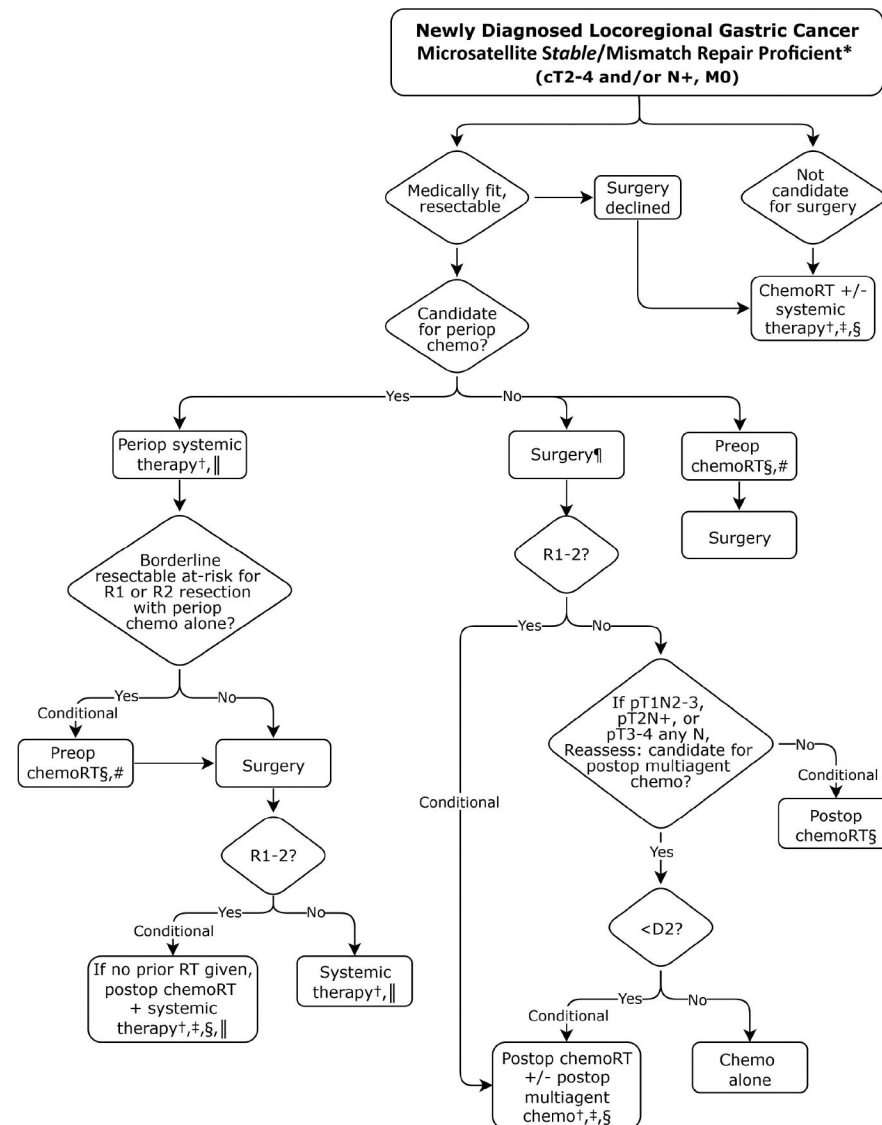


Figure 1.
Newly diagnosed locoregional gastric cancer.

Abbreviations: chemo = chemotherapy; chemoRT = chemoradiation; ECF = epirubicin, cisplatin, and 5-fluorouracil; ECX = epirubicin, cisplatin, and capecitabine; GEJ = gastroesophageal junction; periop = perioperative; postop = postoperative; preop = preoperative; RT = radiation therapy.

*For patients with microsatellite unstable/mismatch repair-deficient, cT2–4 and/or N+ resectable gastric cancer, perioperative immunotherapy with or without chemotherapy is conditionally recommended.

†FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) is recommended over ECF or ECX (epirubicin, cisplatin, and 5-fluorouracil or capecitabine).

‡Induction and/or consolidation systemic therapy may be given with chemoRT, as tolerated.

§ChemoRT should involve concurrent 5-FU or capecitabine.

¶¶Perioperative immunotherapy with chemotherapy is conditionally recommended for cT3–4 and/or N+.

¶¶Surgery first is generally expected to occur only under emergent indications.

#Limit preop chemoRT to patients with Siewert III GEJ or upper/middle third gastric cancer. Recommendations are “strong” unless otherwise indicated as “conditional.” This algorithm focuses on RT-based recommendations, so there may be other treatment options.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

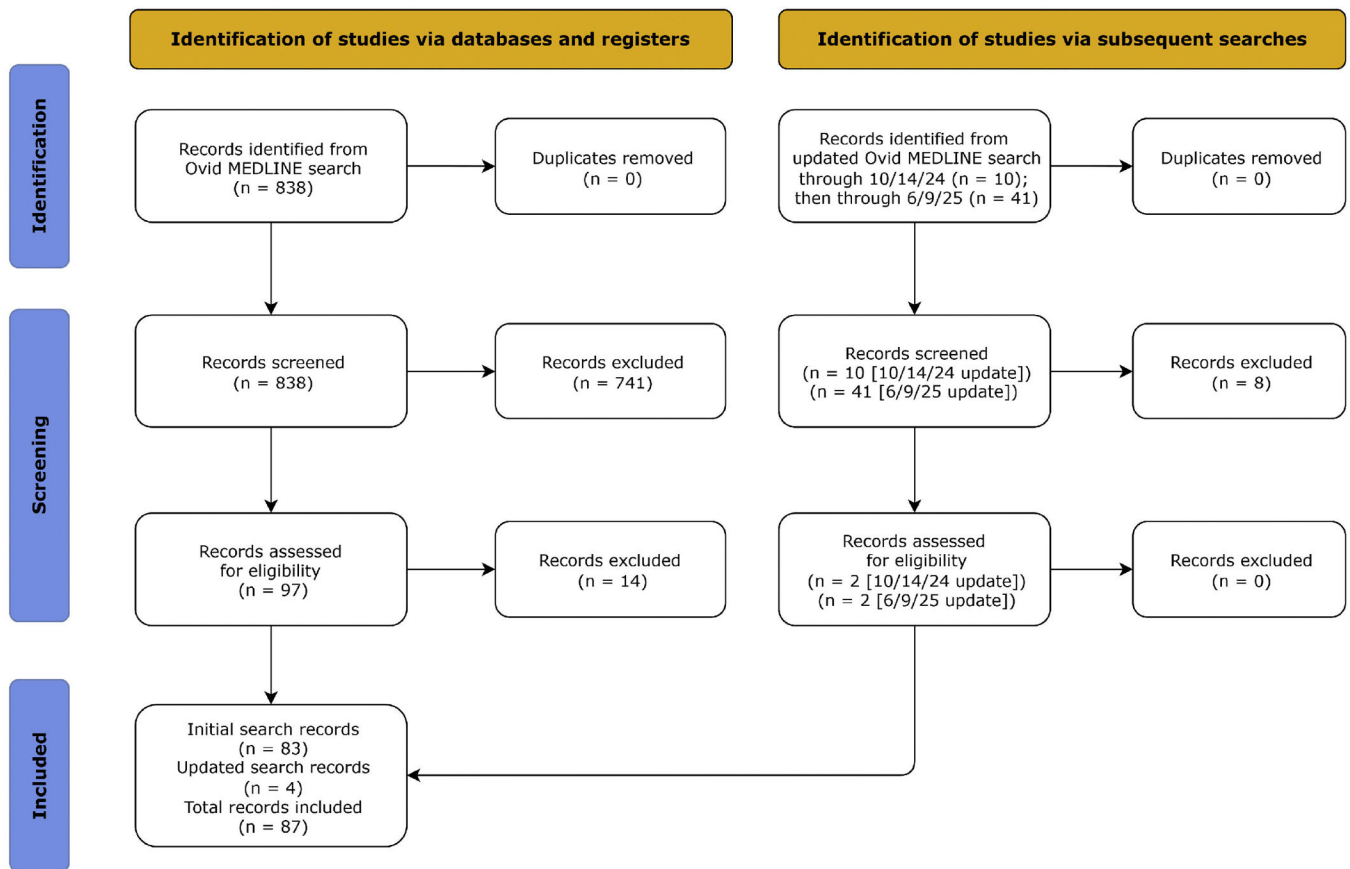


Figure 2.

Table 1

ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE and panel consensus, which, among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.			
Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/Should"
Conditional	• Benefits are finely balanced with risks and burden, or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"
Overall QoE Grade	Type/Quality of Study	Evidence Interpretation	
High	• 2 or more well-conducted and highly generalizable RCTs or well-conducted meta-analyses of such randomized trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.	
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis including such a trial OR • 2 or more RCTs with some weaknesses of procedure or generalizability OR • 2 or more well-conducted and highly generalizable observational or single-arm prospective interventional studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.	
Low	• 1 RCT with some weaknesses of procedure or generalizability OR • 1 or more RCTs with serious deficiencies of procedure or generalizability OR • 1 well-conducted observational or single-arm prospective interventional study OR • 2 or more observational or single-arm prospective interventional studies with some weaknesses of procedure or generalizability. • Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.	
Expert Opinion*		Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect.	

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCT(s) = randomized controlled trial(s).

* A lower QoE, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. Although each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.

Table 2

KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1	For patients with resectable and nonmetastatic gastric cancer, what are the indications for preoperative, perioperative, and postoperative therapies, including systemic therapy and RT?			
	Adults with nonmetastatic resectable gastric/Siewert III GEJ cancer	+/- Systemic therapy +/- RT +/- Chemoradiation	Surgery alone	- Overall survival - Progression-free survival - Locoregional control - Metastasis-free survival - Patterns-of-failure - Patient- and provider-reported QoL, adverse events, and toxicities - Disparities in oncologic and QoL outcomes - Symptom relief
2	For patients with unresectable and/or metastatic gastric cancer, what are the indications for definitive and palliative RT, with or without systemic therapy?			
	Adults with localized, unresectable, and/or metastatic gastric/Siewert III GEJ cancer	- RT - Chemoradiation	Systemic therapy alone	Same as KQ1
3	For patients with gastric cancer receiving RT, what are the optimal dose-fractionation regimens, target volumes, and treatment planning and delivery techniques?			
	Adults with gastric/Siewert III GEJ cancer undergoing RT, including nonmetastatic, oligometastatic, and palliative	3-D CRT - IMRT (including VMAT) - Proton beam therapy - Alternative thresholds for OARs	Differential organ sparing across techniques (IMRT, proton therapy, 3-D CRT)	Same as KQ1

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; GEJ = gastroesophageal junction; IMRT = intensity modulated radiation therapy; KQ(s) =key question(s); OARs = organs at risk; PICO = Population, Intervention, Comparator; Outcome; QoL = quality of life; RT = radiation therapy; VMAT = volumetric modulated arc therapy.

Table 3
Indications for preoperative, perioperative, and postoperative therapies, including systemic therapy and RT

	KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
Perioperative chemotherapy			
1.	For patients with cT2-4 and/or N+ resectable gastric cancer, perioperative chemotherapy is recommended.	Strong	High ^{12,15,24,25}
2.	For patients with cT2-4 and/or N+ resectable gastric cancer receiving perioperative chemotherapy, FLOT is recommended over ECF or ECX.	Strong	High ^{12,15}
Preoperative chemoradiation			
3.	For patients with cT2-4 and/or N+ resectable gastric cancer who are not candidates for perioperative chemotherapy with FLOT, ECF, or ECX, preoperative chemoradiation with concurrent 5-FU or capecitabine is recommended. <u>Implementation remark:</u> Limit preoperative chemoradiation to patients with Siewert III GEJ or upper/middle third gastric cancer.	Strong	Moderate ^{15,25,26}
4.	For patients with borderline resectable gastric cancer at risk of R1 or R2 resection with perioperative chemotherapy alone, adding preoperative chemoradiation with concurrent 5-FU or capecitabine is conditionally recommended. <u>Implementation remarks:</u> • Limit preoperative chemoradiation to patients with Siewert III GEJ or upper/middle third gastric cancer. • Suggested treatment sequence: (1) chemotherapy, (2) chemoradiation, then (3) surgery.	Conditional	Low ^{15,25-27}
Immunotherapy			
5.	For patients with microsatellite <i>stable</i> /mismatch repair-proficient, cT3-4 and/or N+ resectable gastric cancer, perioperative immunotherapy with chemotherapy is conditionally recommended. <u>Implementation remark:</u> FLOT is preferred over ECF or ECX.	Conditional	Moderate ^{12,13,28,29}
6.	For patients with microsatellite <i>unstable</i> /mismatch repair-deficient, cT2-4 and/or N+ resectable gastric cancer, perioperative immunotherapy with or without chemotherapy is conditionally recommended. <u>Implementation remark:</u> FLOT is preferred over ECF or ECX.	Conditional	Low ^{13,30}
Postoperative chemotherapy			
7.	For patients with pT1N2-3, pT2N+, and/or pT3-4 any N stage disease following R0 resection and D2 * lymphadenectomy, postoperative chemotherapy alone is recommended. <u>Implementation remark:</u> Preferred regimens include fluoropyrimidine-based therapies (eg, 5-FU, capecitabine, or S1) with a platinum agent (eg, oxaliplatin).	Strong	Moderate ^{23,31-42}
Postoperative chemoradiation			
8.	For patients with pT1N2-3, pT2N+, and/or pT3-4 any N stage resected gastric cancer who are not candidates for perioperative or postoperative multiagent chemotherapy, postoperative chemoradiation (with concurrent 5-FU or capecitabine) is conditionally recommended.	Conditional	Moderate ⁴³⁻⁴⁵
9.	For patients with pT1N2-3, pT2N+, and/or pT3-4 any N stage resected gastric cancer who have <D2 * lymphadenectomy, postoperative chemoradiation (with concurrent 5-FU or capecitabine) with or without postoperative chemotherapy is conditionally recommended.	Conditional	Low ⁴³
10.	For patients with cT2-4 and/or N+ resected gastric cancer with R1-2 resection, postoperative chemoradiation (with concurrent 5-FU or capecitabine) with or without postoperative chemotherapy is conditionally recommended, whether or not preoperative systemic therapy was given.	Conditional	Expert Opinion

Abbreviations: 5-FU = 5-fluorouracil; ECF = epirubicin, cisplatin, and 5-fluorouracil; ECX = epirubicin, cisplatin, and capecitabine; FLOT = 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ = gastroesophageal junction; KQ = key question; RT = radiation therapy; S1 = tegafur, gimeracil, and oteracil.

* D2 indicates removal of perigastric (D1) nodes along with the left gastric artery, common hepatic artery, celiac axis, and splenic artery and hilum nodes.

Table 4
Indications for definitive and palliative RT with or without systemic therapy

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
Nonmetastatic, initial diagnosis, curative intent		
1. For patients with nonmetastatic gastric cancer who are not candidates for surgery or decline surgery, chemoradiation with or without induction and/or consolidation systemic therapy is recommended.	Strong	Low ^{52,53}
Nonmetastatic, recurrent, curative intent		
2. For RT-naïve patients with nonmetastatic and locoregional recurrent gastric cancer after gastrectomy, definitive chemoradiation with or without induction and/or consolidation systemic therapy is conditionally recommended if the tumor is medically inoperable or unresectable.	Conditional	Low ^{54–56}
Symptomatic, noncurative intent		
3. For patients with gastric cancer-associated bleeding and/or pain from the primary tumor, palliative RT is recommended.	Strong	Moderate (bleeding) ^{57–65}
4. For patients with gastric cancer-associated obstruction from the primary tumor, palliative RT is conditionally recommended.	Conditional	Low (pain) ^{58,64,66}
5. For patients with gastric cancer who received prior RT, reirradiation is conditionally recommended for palliation of gastric bleeding.	Conditional	Low ^{64,66} Low ^{59,62}
Metastatic disease		
6. For patients with de novo oligometastatic gastric cancer, metastasis-directed therapy to all metastatic lesions with systemic therapy is conditionally recommended. <u>Implementation remark:</u> Oligometastatic disease diagnosis may require PET-CT and/or laparoscopy to rule out peritoneal carcinomatosis.	Conditional	Low ^{18–21,67}
7. For patients with metastatic gastric cancer and controlled systemic burden, RT to the primary tumor is conditionally recommended.	Conditional	Low ⁶⁸

Abbreviations: KQ = key question; PET-CT = positron emission tomography-computed tomography; RT = radiation therapy.

Table 5
Optimal dose-fractionation, target volumes, and planning/delivery techniques

KQ3 Recommendations		Strength of Recommendation	Quality of Evidence (Refs)
Nonmetastatic, resectable/resected, initial diagnosis, curative intent			
1.	For patients with nonmetastatic gastric cancer receiving preoperative or postoperative chemoradiation (with concurrent 5-FU or capecitabine), 4500 cGy in 25 fractions is recommended.	Strong	High ^{14,15,33,45,51}
2.	For patients with nonmetastatic gastric cancer receiving preoperative chemoradiation, coverage of the entire stomach and perigastric extension and regional lymph nodes is recommended.	Strong	High ^{15,26,27,69}
3.	For patients with nonmetastatic gastric cancer receiving postoperative chemoradiation, inclusion of the tumor bed, anastomoses, and regional nodes is recommended.	Strong	High ^{14,33,45,51}
4.	For patients with nonmetastatic gastric cancer receiving postoperative chemoradiation, inclusion of the gastric remnant is conditionally recommended for positive margins only.	Conditional	Low ^{51,70}
5.	For patients with nonmetastatic gastric cancer receiving preoperative or postoperative chemoradiation, IMRT (including VMAT) or 3-D CRT is recommended.	Strong	High ^{14,15,33,45,51}
Implementation remark: If using IMRT (including VMAT), 4-D CT planning and/or respiratory motion management techniques with daily image guidance are appropriate.			
Nonmetastatic, initial diagnosis, definitive RT with curative intent			
6.	For patients with nonmetastatic gastric cancer who are medically inoperable, have unresectable disease, or decline surgery, definitive chemoradiation using a dose of 4500–5040 cGy in 25–28 fractions is conditionally recommended.	Conditional	Low ^{52,53}
Nonmetastatic, locoregionally recurrent, definitive RT with curative intent			
7.	For patients with RT-naïve, nonmetastatic, locoregionally recurrent gastric cancer after gastrectomy, chemoradiation with an RT dose of 4500–5040 cGy in 25–28 fractions is conditionally recommended if the tumor is medically inoperable or unresectable.	Conditional	Low ^{54–56}
Symptomatic, palliative intent			
8.	For patients with gastric cancer receiving palliative RT for symptoms related to the primary tumor, regimens of 1–10 fractions with a BED range of 1440–3900 cGy ₁₀ (eg, 800 cGy in 1 fraction, 2000 cGy in 5 fractions, or 3000 cGy in 10 fractions) are recommended.	Strong	Moderate ^{57–64,66}
9.	For patients with gastric cancer receiving palliative RT, limiting the treatment volume to the GTV with a margin for PTV is conditionally recommended.	Conditional	Moderate ^{59,66}
Implementation remarks:			
• If the extent of the GTV is not discernible, include the whole stomach as the CTV with a margin for PTV. • 3-D CRT or IMRT (including VMAT) planning is preferred over 2-D planning.			
10.	For patients with gastric cancer, reirradiation regimens of 1–10 fractions with a BED range of 1440–2800 cGy ₁₀ (eg, 800 cGy in 1 fraction, 1500 cGy in 5 fractions, or 2000 cGy in 10 fractions) are conditionally recommended for palliation of gastric bleeding.	Conditional	Low ^{59,62}

Abbreviations: 2-D = 2-dimensional; 3-D CRT = 3-dimensional conformal radiation therapy; 4-D = 4-dimensional; 5-FU = 5-fluorouracil; BED = biologically effective dose; cGy₁₀ = BED with alpha/beta ratio of 10; CTV = clinical target volume; GTV = gross tumor volume; IMRT = intensity modulated radiation therapy; KQ = key question; PTV = planning target volume; RT = radiation therapy; VMAT = volumetric modulated arc therapy.

Table 6

Target volumes including elective lymph node stations

Target	GTV	CTV	Lymph Nodes to Include in CTV
Preoperative	Primary tumor, involved lymph nodes, and regions of perigastric tumor extension	GTV + entire stomach, ≥1 cm of proximal esophagus (more for GEJ/cardia tumors)	Common hepatic, splenic, left gastric, celiac, hepatogastric, splenic hilum, superior retropancreatic, hepatoduodenal, infrapyloric, pancreaticoduodenal, peripancreatic, SMA, regional para-aortic
Postoperative	N/A	• Tumor bed, gastric remnant, anastomoses, and regional nodes • Duodenal stump and 2 cm beyond the proximal and distal margins of resection⁷⁰	• Perigastric, celiac, splenic, pancreaticoduodenal, suprapancreatic, porta hepatic, and regional para-aortic • For proximal 1/3 lesions, also include: para-esophageal, hepatogastric • For middle and distal 1/3, also include suprapyloric and infrapyloric

Abbreviations: CTV = clinical target volume; GEJ = gastroesophageal junction; GTV = gross tumor volume; N/A = not applicable; SMA = superior mesenteric artery.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 7

Guidance on target volume coverage

Structure	Metric
PTV ¹⁵ (preoperative)	95% of PTV receives at least 95% Rx (42.8 Gy)
	Minimum dose to PTV 90% Rx (>40.5 Gy)
	Maximum dose (in a volume of $\geq 2\text{ cm}^3$) $\leq 107\%$ Rx
PTV ^{14,45} (postoperative)	Minimum dose 95% Rx
	Maximum dose 107% Rx

Abbreviations: PTV = planning target volume; Rx = prescription dose.
This table is a combination of evidence-based constraints and expert opinion.

Table 8

Dose constraint guidance on organs at risk

Structure	QUANTEC	Protocol	4500–5040 cGy in 25–28 Fractions (Protocol Goals)
Liver	Mean ≤32 Gy ⁷⁸	TOPGEAR ¹⁵	Dose to 1/3 of liver ≤50 Gy Dose to 2/3 of liver ≤35 Gy Mean <30 Gy
		CRITICS ¹⁴	≤30% of liver volume receives >30 Gy
		CALGB 80101 ⁴⁵	V20 Gy ≤30%
Lung	V20 Gy <30%–35% (20% pneumonitis risk) Mean ≤20–23 Gy ⁷⁹	TOPGEAR ¹⁵	Mean <18 Gy V40 Gy <30%
		TOPGEAR and CRITICS ^{14,15}	≤50% of heart volume receives 25 Gy (ideal)
Heart *	V30 Gy ≤46% ⁸⁰ V25 Gy <10%	CALGB 80101 ⁴⁵	≤75% of heart volume receives 25 Gy (acceptable)
Spinal cord	D0.03 cc ≤50 Gy ^{†,81}	TOPGEAR, CRITICS, CALGB 80101 ^{14,15,45}	D0.03 cc ≤45 Gy [‡]
Kidney	Mean <18 Gy ⁸² V12 Gy <55% V20 Gy <32%	TOPGEAR ¹⁵	Dose to 1/3 of either kidney ≤35 Gy Dose to 2/3 of kidney ≤20 Gy Mean to either kidney ≤23 Gy
		CRITICS ¹⁴	At least 2/3 of one normally functioning kidney <40% Rx
		CALGB 80101 ⁴⁵	≤50% of combined kidneys receive ≤20 Gy

Abbreviations: Rx = prescription dose.

* Cardiac dose should be constrained as low as reasonably achievable.

[†] Although the term “Dmax” is found in the protocols, D0.03 cc is used instead to reflect contemporary ways of noting maximum dose.
This table is a combination of evidence-based constraints and expert opinion.