Treatment of Locally Advanced Esophageal Carcinoma: ASCO Guideline

Manish A. Shah, MD[1]; Erin B. Kennedy, MHSc[2]; Daniel V. Catenacci, MD[3]; Dana C. Deighton[4]; Karyn A. Goodman, MD[5]; Narinder K. Malhotra, MD[6]; Christopher Willett, MD[7]; Brendon Stiles, MD[1]; Prateek Sharma, MD[8]; Laura Tang, MD, PhD[9]; Bas P. L. Wijnhoven, MD, PhD[10]; and Wayne L. Hofstetter, MD[11]

abstract

PURPOSE To develop an evidence-based clinical practice guideline to assist in clinical decision making for patients with locally advanced esophageal cancer.

METHODS ASCO convened an Expert Panel to conduct a systematic review of the more recently published literature (1999-2019) on therapy options for patients with locally advanced esophageal cancer and provide recommended care options for this patient population.

RESULTS Seventeen randomized controlled trials met the inclusion criteria. Where possible, data were extracted separately for squamous cell carcinoma and adenocarcinoma.

RECOMMENDATIONS Multimodality therapy for patients with locally advanced esophageal carcinoma is recommended. For the subgroup of patients with adenocarcinoma, preoperative chemoradiotherapy or perioperative chemotherapy should be offered. For the subgroup of patients with squamous cell carcinoma, preoperative chemoradiotherapy or chemoradiotherapy without surgery should be offered. Additional subgroup considerations are provided to assist with implementation of these recommendations. Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

J Clin Oncol 38:2677-2694. © 2020 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 1, 2020 and published at ascopubs.org/journal/jco on June 22, 2020: DOI https://doi.org/10.1200/JCO.20.00866

Clinical Practice Guideline Committee Approved: February 19, 2020.

Reprint Requests: 2318 Mill Road, Suite 800, Alexandria, VA 22314; guidelines@asco.org.

INTRODUCTION

Esophageal cancer is the sixth most common cancer worldwide, with an estimated 450,000 deaths per year.[1] There are 2 distinct histologic types of esophageal carcinoma: squamous cell carcinoma and adenocarcinoma. Esophageal squamous cell carcinoma is more common in East Asian and Middle Eastern countries, such as China, Iran, and Turkmenistan, whereas adenocarcinoma is more prevalent in Western countries.[2] The prevalence of adenocarcinoma has increased over the past several decades, while rates of squamous cell carcinoma have remained stable.[3]

Patients with locally advanced esophageal cancer have tumors that invade local structures or involve regional lymph nodes but no distant metastases (ie, American Joint Committee on Cancer [AJCC] stage ≥ T2 or N+, M0).[4] Surgery has been the main curative treatment of resectable locally advanced esophageal cancer, but the overall prognosis is poor with esophagectomy alone, particularly in squamous cell carcinoma. For this reason, many studies have explored adjuvant and neoadjuvant therapy options[5]; these include radiation therapy (RT) intended to downsize the tumor, increase local control,[6] and improve rates of complete tumor resection as well as chemotherapy (CT) prior to resection or postoperatively (or both) to eradicate undetected metastatic disease.[7,8] The benefits and potential adverse events associated with the addition of CT and chemoradiotherapy (CRT) to surgery have been demonstrated in previous reviews and meta-analyses.[5,9-13] Within this guideline, the Expert Panel (Appendix Table A1, online only) provides a review of recent evidence for these therapy options in locally advanced esophageal cancer and addresses ongoing areas of controversy, including where the addition of radiation to surgery and CT (ie, trimodality therapy) is appropriate as well as the addition of surgery to CRT in squamous cell carcinoma.

The overall purpose of this guideline is to provide evidence- and consensus-based recommendations for treatment options for patients with locally advanced esophageal and Siewert I/II gastroesophageal junction adenocarcinoma who are candidates for resection. Results and recommendations are provided for specific histologic subtypes because of the differing risk

THE BOTTOM LINE

Treatment of Locally Advanced Esophageal Carcinoma: ASCO Guideline

Guideline Question

What treatment options are recommended for patients with locally advanced esophageal adenocarcinoma or squamous cell carcinoma?

Target Population

Patients diagnosed with locally advanced esophageal adenocarcinoma or squamous cell carcinoma.

Target Audience

Medical oncologists, radiation oncologists, surgeons, gastroenterologists.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Recommendation 1. Multimodality therapy should be offered to patients with locally advanced esophageal carcinoma (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Note: Although outside the scope of recommendations for locally advanced esophageal cancer, the Expert Panel recommends that for patients with clinical earlier-stage esophageal cancer (T2, N0), surgery alone may be considered after discussion with a multidisciplinary team.[6,13] Within this group, surgery alone may be more appropriate for patients with low-risk cT2N0 lesions (ie, well-differentiated, < 2 cm)[14] and where there is a sufficient degree of confidence in the results of pretreatment staging.

Recommendation 2. Preoperative chemoradiotherapy (CRT) or perioperative chemotherapy (CT) should be offered to patients with locally advanced esophageal adenocarcinoma (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Subgroup considerations:

- For the subgroup of patients for whom surgery is not feasible, CRT without surgery is recommended.
- Preoperative CT should be considered for patients who are not candidates for radiation or postoperative CT.[15,16]
- Postoperative complications may be more severe with CRT as compared with CT.[17] Consider the potential for patient tolerance of the addition of radiation therapy (RT) based on tumor location and other factors.[18]
- The addition of RT is expected to be more beneficial in the setting of less optimal or less extensive surgery. Adequate quality and extent of surgery includes clear surgical margins and adequate nodal dissection within appropriate nodal fields (eg, abdominal and thoracic), with a goal of obtaining at least 16-18,[19] and preferably > 20, lymph nodes.[20] Lymphadenectomy fields and extent of surgery will be affected by tumor location. Detailed recommendations for surgical approach are beyond the scope of this guideline.

Note: While outside the scope of the systematic review, the Expert Panel recognizes docetaxel, oxaliplatin, leucovorin, and fluorouracil (FLOT) as the standard of care for perioperative CT in esophageal adenocarcinoma. The FLOT regimen includes 4 preoperative and 4 postoperative 2-week cycles of 50 mg/m^2 docetaxel, 85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin, and 2,600 mg/m^2 fluorouracil as 24-hour infusion on day 1.[22] Where the FLOT regimen is not available or feasible, the Expert Panel suggests cisplatin and fluorouracil (2 3-weekly cycles of cisplatin [80 mg/m^2 intravenously on day 1] and fluorouracil [1 g/m^2 per day intravenously on days 1–4])[23] or a similar platinum-based regimen.

Recommendation 3. Preoperative CRT or CRT without surgery (definitive CRT) should be offered to patients with locally advanced esophageal squamous cell carcinoma (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Subgroup considerations:

- Historical studies suggested that in patients who respond completely to CRT, the addition of surgery may offer minimal benefit.[24,25] In patients with squamous cell carcinoma who appear to have a complete response to CRT, the option of surveillance and salvage surgery upon progression may be considered where salvage esophagectomy is practiced.[26] At this time, a randomized controlled trial is exploring the question of surveillance and salvage surgery after CRT compared with planned surgery after CRT[27] using the clinical assessment criteria established in the pre-SANO trial[28]; a similar study is under way in France.[29]
- In patients for whom radiation is not an option, preoperative CT (without radiation) may be considered.[16]

(continued on following page)

THE BOTTOM LINE (CONTINUED)

- Definitive CRT is recommended for patients with tumors located in the cervical esophagus; surgery should be considered in the event of persistent or recurrent disease.
- While CRT and surgery are preferred, definitive CRT is an option for patients who cannot tolerate or choose not to undergo surgery.

Practice Statement. For patients with esophageal squamous cell carcinoma, the decision to undertake surgery should be considered in the context of shared decision making, considering age, comorbidities, patient preference, caregiver support, and other factors (Type: consensus based; Strength of recommendation: high).

Additional Resources. More information, including a Data Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

factors, pathogenesis, prognosis after surgical resection, and pattern of lymph node metastases associated with adenocarcinoma and squamous cell carcinoma.[3]

GUIDELINE QUESTIONS

This clinical practice guideline addresses the following clinical questions for patients with locally advanced esophageal cancer (≥ T2 or N+, M0)[4]:

1. Is neoadjuvant or adjuvant therapy in addition to surgery recommended compared with surgery alone?
2. What is the preferred modality of neoadjuvant or adjuvant therapy for patients with locally advanced esophageal adenocarcinoma?
3. What is the preferred modality of neoadjuvant or adjuvant therapy for patients with locally advanced esophageal squamous cell carcinoma?

METHODS

Guideline Development Process

This systematic review–based guideline was developed by a multidisciplinary Expert Panel that included a patient representative and an ASCO guidelines staff with health research methodology expertise. The Expert Panel had one in-person meeting, conducted other meetings via teleconference and/or webinar, and corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for open comment prior to submission to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee prior to publication. All funding for the administration of the project was provided by ASCO.

Initial searches for existing guidelines based on systematic reviews were conducted. Where possible, the evidence base contained in existing systematic reviews was used, provided that no serious methodological issues were identified through an Assessment of Multiple Systematic Reviews II (AMSTAR II) assessment.[30] Fully published or recent meeting presentations of English-language phase II or III randomized controlled trials (RCTs) and systematic reviews with or without meta-analysis were eligible for inclusion based on the following criteria:

- Population: Patients with locally advanced esophageal cancer and Siewert I/II gastroesophageal junction adenocarcinoma.
- Interventions: Neoadjuvant or adjuvant therapy options, including preoperative CT, preoperative or postoperative CRT, perioperative CT, or definitive CRT (ie, CRT without surgery).
- Comparisons: Surgery alone or a comparison between interventions listed above.
- Outcomes of interest: Overall survival, progression-free survival or disease-free survival or relapse-free survival, complications, post-treatment mortality, and rate of complete tumor resection with negative surgical margins (ie, R0 resection).[31]

Articles were selected for inclusion if the patient population was accrued, at least in part, after 1999, regardless of publication date. In the case of the comparison of preoperative CT versus surgery alone, the Expert Panel was aware that the evidence base would be older; therefore, the inclusion criteria for this comparison were modified to include studies with initial full-text publication after 1999, regardless of patient accrual date.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; (3) published in a non-English language; or (4) studies that compared one CT regimen to another.

Data extraction was conducted by the guideline methodologist, and a data audit was conducted by an ASCO staff member. The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[32] Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

Assessment of Data Quality

Certainty of the evidence (ie, evidence quality) for each outcome was assessed using the Cochrane Risk of Bias tool[33] and elements of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality assessment and recommendations development process.[34] To facilitate the quality assessment ratings, MAGICApp guideline development software was used[32a]; within this framework, outcomes from RCTs are rated high quality and can subsequently be downgraded as factors that affect quality (ie, certainty) are identified.[34] GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel.

Data Analysis

Hazard ratios (HRs) were extracted where available for time-to-event data; for dichotomous outcomes, relative risk (RR) was extracted where available or calculated using reported events and population totals in the treatment and control groups. Statistics were based on numbers from intention-to-treat analyses. Where more than one study was available, data were pooled in meta-analyses using a random-effects model and the generic inverse variance function in RevMan 5.3. Where HRs were combined in a meta-analysis, log of the HR and its SE were calculated and entered in RevMan 5.3. RRs were calculated using the OpenEpi software program (www.openepi.com). Heterogeneity was assessed and considered to be low where the I^2 statistic was $\leq 40\%$.[33] Analyses were conducted separately for adenocarcinoma and squamous cell carcinoma histologic subtypes wherever data for at least 50 patients were available.

Guideline Updating

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the "Signals" approach to guideline updating. This is the most recent information as of the publication date.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Several existing systematic reviews address the comparisons of interest for this guideline.[5,9-13] The most recent of those reviews (National Institute for Health and Care

Excellence [NICE] NG83 Oesophago-Gastric Cancer: Assessment and Management in Adults)[11] scored well on the AMSTAR II tool[30] (Data Supplement, online only). NICE incorporated studies from other existing systematic reviews[5,9,10,12,13] and used them as a source of outcomes data wherever possible. Data from studies included in the NICE[11] review that met the inclusion criteria outlined in the Methods section were extracted, and two more recent eligible studies identified in the ASCO systematic review were added to the evidence base.[17,35]

Study Characteristics

Seventeen studies met the inclusion criteria for this systematic review. Studies were conducted in the United Kingdom,[15,36] France,[24,37] Australia,[38,39] the Netherlands,[40] China,[35,41,42] Korea,[43,44] Japan,[45] United States,[46] Germany,[25,48] and Norway and Sweden.[17,47] Most studies included patient populations that were accrued before the mid-2000s; three studies included more recent patient populations.[35,40,42]

In patients with adenocarcinoma, surgery alone was compared with preoperative CT,[15] perioperative CT,[36,37] and preoperative CRT.[39,40,42,46] Preoperative CRT was compared with preoperative CT,[38,47,48] and preoperative CRT was compared with CRT alone[24] (Table 1).

In patients with squamous cell carcinoma, surgery alone was compared with preoperative CT,[15] postoperative CRT,[44] and preoperative CRT.[35,39,40,43,44,46] Preoperative CRT was compared with preoperative CT.[47] Other comparisons included preoperative compared with perioperative CT[41] and postoperative CT[45] as well as preoperative CRT compared with CRT alone[24,25] (Table 1).

Outcomes of interest were extracted where available. All comparisons included an estimate for overall survival, while the reporting of other outcomes of interest varied across comparisons (Tables 2-10).

Different regimens of CT/CRT were used, and surgical approach varied according to the location of the tumor or other factors. Sample sizes of the studies ranged from to 56[46] to 802 patients.[15] Details related to study characteristics are included in Data Supplement Tables 1-7.

Assessment of Data Quality

Risk-of-bias assessments for study outcomes were adopted from a previous review.[11] In addition to the risk-of-bias concerns identified by the previous review,[11] this review identified concerns with the directness of the evidence. Many studies included patient populations that were accrued in the 1990s to early 2000s and/or patients who were not staged with modern techniques or staged using older versions of the AJCC/Union for International Cancer Control staging system.[4] The studies included a mix of histologic types; some had a large percentage of patients with gastric cancer and/or other study limitations. In addition, for many comparisons, the evidence base consisted of only a single study. More details regarding the reasons for downgrading the quality (ie, certainty) of the evidence are included in the footnotes in Tables 2-10.

Study Outcomes

Preoperative CT versus surgery alone in adenocarcinoma and squamous cell carcinoma. Preoperative CT versus surgery alone was compared in a study by the UK Medical Research Council that accrued 802 patients between 1992 and 1998[16] (Table 2). This study included a population of 66% adenocarcinoma, 31% squamous cell carcinoma, and 2% undifferentiated. Longer-term (6-year) follow-up results for this study were published in 2009.[15] Five-year overall survival was 14% in the surgery-alone group *v* 19% (95% CI, 15% to 24%) in the preoperative CT group with an HR of 0.84 (95% CI, 0.72 to 0.98).[11] There was no evidence of heterogeneity of treatment effects between squamous cell and adenocarcinoma ($P = .81$). No significant differences were found for complications, postoperative mortality, or complete tumor resection.

Perioperative CT versus surgery alone in adenocarcinoma. In Ychou et al,[37] perioperative cisplatin and fluorouracil (CF) were compared with surgery alone in 224 patients with adenocarcinoma of the lower esophagus (11%), gastroesophageal junction (64%), or stomach (25%). A study of patients with adenocarcinoma by Cunningham et al[36] included mostly patients with gastric cancer (74%; Table 3). In a meta-analysis of these two studies, a significant benefit was found with perioperative CT for overall survival (HR, 0.73; 95% CI, 0.61 to 0.88). Ychou et al and Cunningham et al also found improvements in disease-free survival (HR, 0.65; 95% CI, 0.48 to 0.89) and progression-free survival (HR, 0.66; 95% CI, 0.53 to 0.81) with perioperative CT versus surgery alone, respectively. There were no significant differences between groups for rate of complete tumor resection[37] or complications.[36,37]

Preoperative CRT versus surgery alone in adenocarcinoma. Four RCTs met the inclusion criteria for the comparison of preoperative CRT versus surgery alone in patients with locally advanced adenocarcinoma[26,39,40,42,46] (Table 4). It was possible to extract results for patients with nonsquamous cell carcinoma or adenocarcinoma from studies by Burmeister et al[39] (73% of patients with adenocarcinoma) and van Hagen et al[40]/Shapiro et al[26] (77% of patients with adenocarcinoma), respectively. Results for overall survival, where reported, were combined in a meta-analysis, resulting in a nonsignificant HR favoring CRT (0.87; 95% CI, 0.63 to 1.20). Complication rates for both groups were similar (Table 4), although a higher rate of treatment-related mortality with CRT was reported previously in a meta-analysis that included older studies.[11]

In addition, there was a significantly better rate of complete tumor resection in the CRT plus surgery group compared with surgery alone (RR, 1.32; 95% CI, 1.21 to 1.43). Results for Tepper et al[46] could not be extracted separately by histologic type (adenocarcinoma, 75% of 56 patients),

TABLE 1. Included Studies

Histologic Type	First Author							
	Preoperative CT *v* Surgery (Table 2)	**Perioperative CT *v* Surgery (Table 3)**	**Preoperative CRT *v* Surgery (Tables 4 and 5)**	**Preoperative CRT *v* Preoperative CT (Table 6)**	**Perioperative CT *v* Preoperative CT (Table 7)**	**Preoperative CT *v* Postoperative CT (Table 8)**	**Preoperative CRT *v* CRT Alone (Table 9)**	**Postoperative CRT *v* Surgery (Table 10)**
Adenocarcinoma	Allum[15,16] (MRC)	Cunningham[36] (MAGIC) Ychou[37]	Table 4: van Hagen[40] (CROSS) Shapiro[26] (CROSS) Burmeister[39] Tepper[46] Zhao[42]	Burmeister[38] Klevebro[47] (NeoResI) von Döbeln[17] (NeoResI) Stahl[48,49] (POET)			Bedenne[24]	
Squamous cell carcinoma	Allum[15,16] (MRC)		Table 5: van Hagen[40] (CROSS) Shapiro[26] (CROSS) Burmeister[39] Lee[43] Lv[44] Tepper[46] Yang[35] (NeoResII)	Klevebro[47] (NeoResI) von Döbeln[17] (NeoResI)	Zhao[41]	Ando[45]	Bedenne[24] Stahl[25]	Lv[44]

Abbreviations: CRT, chemoradiation therapy; CT, chemotherapy.

TABLE 2. Patients With Locally Advanced Esophageal Cancer Adenocarcinoma and Squamous Cell Carcinoma—Preoperative CT Versus Surgery Alone (Allum[15,16])

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain-Text Summary
		Surgery Alone	Preoperative CT		
Overall survival	HR, 0.84 (95% CI, 0.72 to 0.98)[16] Based on data from 802 patients in 1 study Follow-up: 5 years Median follow-up: 6 years	829 deaths per 1,000	770 deaths per 1,000 Difference: 59 fewer per 1,000 (95% CI, 109 fewer to 6 fewer)	Low (1, 2)	Preoperative CT may improve overall survival
Postoperative complications	RR, 0.98 (95% CI, 0.82 to 1.16) Based on data from 739 patients in 1 study Follow-up: postoperative period	420 per 1,000	410 per 1,000 Difference: 10 fewer per 1,000 (95% CI, 76 fewer to 63 more)	Low (1, 2)	No important benefit or harm with preoperative CT
Postoperative mortality	RR, 0.9 (95% CI, 0.59 to 1.39) Based on data from 802 patients in 1 study Follow-up: 30 days postsurgery	100 per 1,000	90 per 1,000 Difference: 10 fewer per 1,000 (95% CI, 41 fewer to 39 more)	Low (1, 2)	No important benefit or harm with preoperative CT

NOTE. (1) Downgrade: risk of bias[11]; indirectness: differences between the population of interest and those studied (older study population accrued 1992-1998; mixed histology population, 66% adenocarcinoma/31% squamous cell carcinoma); only one study; (2) upgrade: consistent with previous systematic review.[9]

Abbreviations: CT, chemotherapy; HR, hazard ratio; RR, relative risk.

but HR for overall survival significantly favored the CRT plus surgery group (HR, 0.38; 95% CI, 0.20 to 0.70) with a median survival of 4.48 versus 1.79 years ($P = .002$). Tepper et al reported no significant differences in complications.[46]

Preoperative CRT versus surgery alone in squamous cell carcinoma. Six RCTs of CRT followed by surgery versus surgery alone were included for patients with squamous cell carcinoma[35,39,40,43,44,46]. Overall survival (HR, 0.68; 95% CI, 0.55 to 0.84) and disease-free survival (HR, 0.59; 95% CI, 0.45 to 0.79) favored the CRT plus surgery group (Table 5).[35,39,40,43]

For patients with squamous cell carcinoma within the CROSS RCT, median survival was 21.1 months with surgery alone compared with 81.6 months with preoperative CRT (HR, 0.48; 95% CI, 0.28 to 0.83).[26] In the most recently published study,[35] which accrued 451 patients with locally advanced squamous cell carcinoma in China between June 2007 and December 2014, median survival was 66.5 months with surgery alone compared with 100.1 months with preoperative CRT (HR, 0.71; 95% CI, 0.53 to 0.96; $P = .025$). There were no significant differences in peritreatment mortality (2.2% preoperative CRT *v* 0.4% surgery only; $P = .212$) or adverse events, with the exception of arrythmia (13% preoperative CRT *v* 4% surgery only; $P = .001$).[35] The remainder of the studies did not find any significant differences in treatment-related or postoperative mortality; a meta-analysis for complications was not conducted due to inconsistent definitions of outcome measures across studies.

Preoperative CRT versus preoperative CT in adenocarcinoma. Three studies that compared preoperative CRT to preoperative CT met the inclusion criteria (Table 6). NeoResI included patients with adenocarcinoma (73%) and squamous cell carcinoma (27%),[47] Burmeister et al[38] included only patients with adenocarcinoma of the esophagus or gastroesophageal junction, and Stahl and colleagues[48,49] included patients with adenocarcinoma of the gastroesophageal junction.

In NeoResI, a higher rate of complete pathologic response in the primary tumor in the CRT group was reported (28% *v* 9%, respectively), which was the primary study outcome; however, there were no significant differences in 5-year overall survival (42.2% in the CRT group *v* 39.6% in the CT group; $P = .60$) or 5-year progression-free survival (38.9% in the CRT group *v* 33% in the CT group; $P = .82$). There was no significant difference in overall survival within the patients with adenocarcinoma ($P = .83$). In the overall study population, significantly more patients died as a result of postoperative complications in the CRT group (8 *v* 1; $P = .02$).[47]

Burmeister et al[38] reported a significant difference in histopathological response rate favoring CRT (31% *v* 8%; $P = .01$) but no difference in progression-free or overall survival, CT toxicity, or surgical complications. In Stahl and colleagues,[48,49] local progression-free survival (HR, 0.37; 95% CI, 0.16 to 0.85) after tumor resection was significantly improved with CRT; however, there was no significant difference in overall survival after 3 years (HR, 0.65; 95% CI, 0.42 to 1.01).

Preoperative CRT versus preoperative CT in squamous cell carcinoma. For the small number of patients with squamous cell esophageal carcinoma (50 patients; 28% of study sample) within the NeoResI trial, no differences in 3-year survival were found (RR, 1.08; 95% CI, 0.65 to 1.80); updated results indicated no difference in 5-year survival (42.2 *v* 39.6%; $P = .60$).[47]

TABLE 3. Patients With Locally Advanced Esophageal Adenocarcinoma—Perioperative CT Versus Surgery Alone (Ychou et al[37] and Cunningham et al[36])

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain-Text Summary
		Surgery Alone	Perioperative CT		
Overall survival	HR, 0.73 (95% CI, 0.61 to 0.88) Based on data from 727 patients in 2 studies Follow-up: 5 years	780 deaths per 1,000	669 deaths per 1,000 Difference: 111 fewer per 1,000 (95% CI, 177 fewer to 44 fewer)	Moderate (1, 3)	Perioperative CT may improve overall survival
Disease-free survival[a37]	HR, 0.65 (95% CI, 0.48 to 0.89) Based on data from 224 patients in 1 study Follow-up: 5 years	810 per 1,000	660 per 1,000 Difference: 150 fewer per 1,000 (95% CI, 261 fewer to 38 fewer)	Moderate (1, 2, 3)	Perioperative CT may improve disease-free survival
Progression-free survival[b36]	HR, 0.66 (95% CI, 0.53 to 0.81) Based on data from 503 patients in 1 study Follow-up: 5 years	810 per 1,000	666 per 1,000 Difference: 144 fewer per 1,000 (95% CI, 225 fewer to 70 fewer)	Moderate (1, 2, 3)	Perioperative CT may improve progression-free survival
Complete tumor resection rate[36]	RR, 1.15 (95% CI, 1.00 to 1.32) Based on data from 224 patients in 1 study	740 per 1,000	851 per 1,000 Difference: 111 more per 1,000 (95% CI, 0 fewer to 237 more)	Low (1, 2)	Perioperative CT may improve complete tumor resection rate
Postoperative morbidity/ complications	RR, 1.05 (95% CI, 0.88 to 1.26) Based on data from 727 patients in 2 studies	191 per 1,000	201 per 1,000 Difference: 10 more per 1,000 (95% CI, 23 fewer to 50 more)	Moderate (1)	Perioperative CT may have little or no difference on any complications

NOTE. (1) Downgrade: risk of bias[11]; indirectness: differences between the population of interest and those studied (Cunningham et al included 74% gastric cancer patients); (2) only one study; (3) upgrade: large magnitude of effect.

Abbreviations: CT, chemotherapy; HR, hazard ratio; RR, relative risk.

[a]Disease-free survival: patients with incomplete tumor resection, local and/or distant recurrence, or death.[37]

[b]Progression-free survival: patients with local recurrence or progression, distant recurrence, or death from any cause.[36]

Data for both histologic types are combined in Table 6 due to the small number of patients with squamous cell histology.

Perioperative CT versus preoperative CT in squamous cell carcinoma. One RCT of 343 patients with squamous cell carcinoma included a comparison of perioperative CT versus preoperative CT[41] (Table 7). Both groups had 2 preoperative cycles of cisplatin plus paclitaxel CT and esophagectomy through left thoracotomy/transhiatal/Ivor Lewis approach depending on site, while the perioperative CT group also received 2 additional cycles of postoperative CT. The rate of relapse-free survival was significantly higher in the perioperative CT group (HR, 0.62; 95% CI, 0.49 to 0.73), as was overall survival (HR, 0.79; 95% CI, 0.59 to 0.95). The authors reported no significant increase in toxic effects with the addition of postoperative CT to preoperative CT.

Preoperative CT versus postoperative CT in squamous cell carcinoma. In a study of patients with stage II and III esophageal squamous cell carcinoma, there was no difference in progression-free survival or complete tumor resection rate but significantly fewer deaths with preoperative CT compared with postoperative CT[45] (Table 8)

Preoperative CRT versus CRT alone in squamous cell carcinoma. Stahl et al[25] studied preoperative CRT versus CRT without surgery in a population of patients with squamous cell carcinoma with T3 and T4 tumors. Patients were treated in German centers between June 1994 and May 2002; 82% had complete tumor resections. All patients received induction CT prior to other treatment. CRT and surgery consisted of intrathoracic esophagectomy with two-field lymphadenectomy in most patients. The CRT plus surgery group experienced an improvement in local control but higher toxicity and no difference in survival. A high in-hospital mortality rate was noted (11.3%), which declined in later years of the study. Bedenne et al[24] also studied this comparison in patients with locally advanced thoracic esophageal cancer (89% squamous cell carcinoma) in centers in France, 94% of whom had transthoracic and 4% of whom had transhiatal esophagectomy. Patients who experienced tumor response with CRT were randomized to continued CRT or surgery. They found no significant difference in survival rates, fewer early deaths, and shorter hospital time but a higher rate of locoregional relapse in the surgery group. Meta-analysis results for overall survival and treatment-related mortality are presented in Table 9.

Surgery followed by CRT versus surgery alone in squamous cell carcinoma. One RCT of patients with squamous cell carcinoma included a comparison of surgery (left or right open esophagectomy) followed by CRT (concomitant) versus surgery alone (left or right open esophagectomy)[44] (Table 10). In an analysis of 158 patients, there was a significant

TABLE 4. Patients With Locally Advanced Esophageal Adenocarcinoma—Preoperative CRT Versus Surgery Alone (Burmeister et al,[39] van Hagen et al[40]/Shapiro et al,[26] and Zhao et al[42])

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain-Text Summary
		Surgery Alone	Preoperative CRT		
Overall survival[26,39]	HR, 0.87 (95% CI, 0.63 to 1.20) Based on data from 343 patients in 2 studies Follow-up: 5 years	670 deaths per 1,000	619 deaths per 1,000 Difference: 51 fewer per 1,000 (95% CI, 167 fewer to 66 more)	Low (1, 2)	Preoperative CRT may have little or no effect in patients with adenocarcinoma
Postoperative pulmonary complications[40]	RR, 1.05 (95% CI, 0.84 to 1.33) Based on data from 354 patients in 1 study Follow-up: min 2 years	449 per 1,000	471 per 1,000 Difference: 22 more per 1,000 (95% CI, 72 fewer to 148 more)	Very low (1, 2, 3)	Preoperative CRT may have little or no effect on pulmonary complications
Postoperative cardiac complications[40]	RR, 1.29 (95% CI, 0.83 to 1.98) Based on data from 354 patients in 1 study Follow-up: min 2 years	170 per 1,000	219 per 1,000 Difference: 49 more per 1,000 (95% CI, 29 fewer to 167 more)	Very low (1, 2, 3)	Preoperative CRT may have little or no effect on cardiac complications
Postoperative anastomotic leakage[40]	RR, 0.75 (95% CI, 0.52 to 1.09) Based on data from 322 patients in 1 study Follow-up: min 2 years	298 per 1,000	224 per 1,000 Difference: 74 fewer per 1,000 (95% CI, 143 fewer to 27 more)	Very low (1, 2, 3)	Preoperative CRT may have little or no effect on anastomotic leakage
R0 resection rate[39,40,42]	RR, 1.32 (95% CI, 1.21 to 1.43) Based on data from 654 patients in 3 studies	690 per 1,000	911 per 1,000 Difference: 221 more per 1,000 (95% CI, 145 more to 297 more)	Moderate (1, 3)	Preoperative CRT probably improves complete resection rate

NOTE. (1) Downgrade: risk of bias[11]; indirectness: differences between the population of interest and those studied (Burmeister et al older data 1994-2000, Zhao et al only gastroesophageal junction, van Hagen et al 45% transhiatal resection); (2) only one study; (3) indirectness: mixed histology.

Abbreviations: CRT, chemoradiation therapy; HR, hazard ratio; min, minimum; RR, relative risk.

improvement in the primary outcome, which was progression-free survival (RR, 2.87; 95% CI, 1.09 to 7.59), with surgery followed by CRT compared with surgery alone; however, there was no significant difference in 10-year overall survival (RR, 1.95; 95% CI, 0.97 to 3.92). This trial also included a third preoperative CRT arm and found no significant differences in overall and progression-free survival between the preoperative CRT and postoperative CRT arms ($P > .05$).

RECOMMENDATIONS

CLINICAL QUESTION 1

For patients with locally advanced (≥ T2 or N+, M0) esophageal carcinoma, is neoadjuvant or adjuvant therapy in addition to surgery recommended compared with surgery alone?

Recommendation 1. Multimodality therapy should be offered to patients with locally advanced esophageal carcinoma

TABLE 5. Locally Advanced Esophageal Squamous Cell Carcinoma—Preoperative CRT Versus Surgery Alone (Burmeister et al,[39] van Hagen et al[40]/Shapiro et al,[26] Lee,[43] and Yang[35])

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain-Text Summary
		Surgery Alone	Preoperative CRT		
Overall survival	HR, 0.68 (95% CI, 0.55 to 0.84) Based on data from 700 patients in 4 studies Follow-up: 5 years	670 deaths per 1,000	529 deaths per 1,000 Difference: 141 fewer per 1,000 (95% CI, 213 fewer to 64 fewer)	High (1)	Preoperative CRT improves overall survival in patients with squamous cell esophageal carcinoma
Disease-free survival	HR, 0.59 (95% CI, 0.45 to 0.79) Based on data from 700 patients in 4 studies Follow-up: 5 years	730 events per 1,000	431 events per 1,000 Difference: 299 fewer per 1,000 (95% CI, 401 fewer to 153 fewer)	High (1)	Preoperative CRT improves disease-free survival in patients with squamous cell esophageal carcinoma

NOTE. (1) Downgrade: risk of bias[11]; upgrade: large magnitude of effect.

Abbreviations: CRT, chemoradiation therapy; HR, hazard ratio; RR, relative risk.

TABLE 6. Patients With Locally Advanced Esophageal Adenocarcinoma and Squamous Cell Carcinoma—Preoperative CRT Versus Preoperative CT (Klevebro et al[47]/von Döbeln et al,[17] Burmeister et al,[38] Stahl et al,[48] and Stahl et al[49])

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain-Text Summary
		Preoperative CT	Preoperative CRT		
Overall survival[47,49]	HR, 0.85 (95% CI, 0.51 to 1.44) Based on data from 300 patients in 2 studies Follow-up: 3 years	510 deaths per 1,000	455 deaths per 1,000 Difference: 55 fewer per 1,000 (95% CI, 205 fewer to 132 more)	Moderate (1)	Preoperative CRT has little or no difference on overall survival compared with preoperative CT
Any treatment-related complications[47]	RR, 1.21 (95% CI, 0.86 to 1.71) Based on data from 181 patients in 1 study Follow-up: 3 years	385 per 1,000	466 per 1,000 Difference: 81 more per 1,000 (95% CI, 54 fewer to 273 more)	Moderate (1, 2)	Preoperative CRT may have little or no difference on treatment complications compared with preoperative CT
Any treatment-related mortality[11,38,47]	RR, 2.53 (95% CI, 0.5 to 12.69) Based on data from 256 patients in 2 studies	16 per 1,000	40 per 1,000 Difference: 24 more per 1,000 (95% CI, 8 fewer to 187 more)	Very low (1, 2, 3)	Preoperative CRT may have little or no difference on treatment-related mortality compared with preoperative CT
Complete tumor resection rate[38,47]	RR, 1.13 (95% CI, 1.00 to 1.28) Based on data from 231 patients in 2 studies	738 per 1,000	827 per 1,000 Difference: 89 more per 1,000 (95% CI, 52 fewer to 258 more)	Moderate (1)	Preoperative CRT may have little or no difference on rate of complete tumor resection compared with preoperative CT
Histologic complete response[38,47]	RR, 3.30 (95% CI, 1.71 to 6.37) Based on data from 231 patients in 2 studies	90 responses per 1,000	298 responses per 1,000 Difference: 208 more per 1,000 (95% CI, 69 more to 470 more)	High (1, 4)	Preoperative CRT improves histologic complete response compared with preoperative CT
Deaths due to postoperative complications[47]	RR, 8.09 (95% CI, 1.03 to 63.4) Based on data from 181 patients in 1 study	11 per 1,000	89 per 1,000 Difference: 78 more per 1,000 (95% CI, 0 fewer to 686 more)	Very low (1, 2, 3)	Preoperative CRT may result in more deaths due to postoperative complications compared with preoperative CT

NOTE. (1) Downgrade: risk of bias[11]; indirectness: differences between the populations of interest and those studied (histologic types combined in meta-analysis, induction CT received in CRT group of Stahl et al); (2) only one study; (3) wide CI; (4) upgrade: large magnitude of effect.

Abbreviations: CRT, chemoradiation therapy; CT, chemotherapy; HR, hazard ratio; RR, relative risk.

(Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Key evidence. Significant improvements in overall survival without significant increases in toxicity have been found with preoperative CT, perioperative CT, and preoperative CRT compared with surgery alone for patients with locally advanced esophageal adenocarcinoma and/or squamous cell carcinoma (Tables 2-5).

In addition, although outside the scope of recommendations for locally advanced esophageal cancer, the Expert

TABLE 7. Patients With Locally Advanced Esophageal Squamous Cell Carcinoma—Perioperative CT Versus Preoperative CT (Zhao et al[41])

Outcome	Study Results and Measurements	Absolute Effect Estimates: Preoperative CT	Absolute Effect Estimates: Perioperative CT	Certainty of the Evidence (quality of evidence)	Plain-Text Summary
Overall survival	HR, 0.79 (95% CI, 0.59 to 0.95) Based on data from 343 patients in 1 study Follow-up: 5 years	780 deaths per 1,000	698 deaths per 1,000 Difference: 82 fewer per 1,000 (95% CI, 189 fewer to 17 fewer)	Low (1)	Perioperative CT may improve overall survival compared with preoperative CT
Relapse-free survival	HR, 0.62 (95% CI, 0.49 to 0.73) Based on data from 343 patients in 1 study Follow-up: 5 years	830 relapses per 1,000	667 relapses per 1,000 Difference: 163 more per 1,000 (95% CI, 250 fewer to 104 fewer)	Moderate (1, 2)	Perioperative CT may improve relapse-free survival compared with preoperative CT

NOTE. (1) Downgrade: risk of bias[11]; only one study; (2) upgrade: large magnitude of effect.
Abbreviations: CT, chemotherapy; HR, hazard ratio.

Panel notes that for patients diagnosed with early esophageal cancer (T2, N0), the results of staging are frequently inaccurate.[50] For this group of patients, surgery alone may be considered after discussion within a multidisciplinary team,[6,13] and may be more appropriate for patients with low-risk cT2N0 lesions (ie, well-differentiated, < 2 cm)[14] where there is a sufficient degree of confidence in the staging results. Additionally, for early-stage esophageal cancer (T1-T2, N0), preoperative CRT is inferior to surgery alone.[6]

CLINICAL QUESTION 2

What is the preferred modality of neoadjuvant or adjuvant therapy for patients with locally advanced esophageal adenocarcinoma?

Recommendation 2. Preoperative CRT or perioperative CT should be offered to patients with locally advanced esophageal adenocarcinoma (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Key evidence.

- Significant improvements in survival were demonstrated with preoperative CT and perioperative CT compared with treatment with surgery alone in patients with locally advanced adenocarcinoma (Tables 2 and 3).
- Preoperative CT demonstrated improvement in survival compared with treatment with surgery in an older

TABLE 8. Patients With Locally Advanced Esophageal Squamous Cell Carcinoma—Preoperative CT Versus Postoperative CT (Ando et al[45])

Outcome	Study Results and Measurements	Absolute Effect Estimates: Postoperative CT	Absolute Effect Estimates: Preoperative CT	Certainty of the Evidence (quality of evidence)	Plain-Text Summary
Overall survival	HR, 0.73 (95% CI, 0.54 to 0.99) Based on data from 330 patients in 1 study Follow-up: 5 years	570 deaths per 1,000	460 deaths per 1,000 Difference: 110 fewer per 1,000 (95% CI, 204 fewer to 4 fewer)	Low (1)	Postoperative CT may worsen overall survival slightly compared with preoperative CT
Complete tumor resection rate	RR, 1.05 (95% CI, 0.99 to 1.12) Based on data from 330 patients in 1 study	910 per 1,000	956 per 1,000 Difference: 46 more per 1,000 (95% CI, 9 fewer to 109 more)	Low (1)	Postoperative CT may have little or no difference on complete tumor resection rate compared with preoperative CT
Progression-free survival	HR, 0.84 (95% CI, 0.63 to 1.11) Based on data from 330 patients in 1 study Follow-up: 5 years	610 events per 1,000	547 events per 1,000 Difference: 63 fewer per 1,000 (95% CI, 163 fewer to 38 more)	Low (1)	Postoperative CT may have little or no difference on progression-free survival compared with preoperative CT

NOTE. (1) Downgrade: risk of bias[11]; only one study.
Abbreviations: CT, chemotherapy; HR, hazard ratio; RR, relative risk.

TABLE 9. Patients With Locally Advanced Esophageal Cancer—Preoperative CRT Versus CRT Alone (Stahl et al[25] and Bedenne et al[24])

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain-Text Summary
		CRT Alone	Preoperative CRT		
Overall survival[11]	HR, 0.99 (95% CI, 0.79 to 1.24) Based on data from 431 patients in 2 studies Follow-up: 5 years or last year available	820 deaths per 1,000	817 deaths per 1,000 Difference: 3 fewer per 1,000 (95% CI, 78 fewer to 61 more)	Moderate (1)	Surgery in addition to CRT may have little or no difference on survival compared with CRT alone
Treatment-related mortality[11]	RR, 3.67 (95% CI, 1.06 to 12.68) Based on data from 172 patients in 1 study	35 per 1,000	128 per 1,000 Difference: 93 more per 1,000 (95% CI, 2 more to 409 more)	Low (1, 2)	Surgery in addition to CRT may worsen treatment related mortality compared with CRT alone

NOTE. (1) Risk of bias[11]; indirectness: differences between the populations of interest and those studied (older study data: 1993-2000,[24] 1994-2002[25]); (2) only one study; wide CI, upgrade: large magnitude of effect.

Abbreviations: CRT, chemoradiation therapy; HR, hazard ratio; RR, relative risk.

study with mixed histology (Table 2) and should be considered in patients who are not candidates for preoperative CRT or postoperative CT.

- For the meta-analysis of the effect of preoperative CRT compared with surgery alone on overall survival in patients with adenocarcinoma (Table 4), the Expert Panel considered the strengths and limitations of both studies contributing to the analysis.[26,39,40] One study contributing nonsignificant results included an earlier patient population (1994-2000) and used a lower-than-standard radiation dosage of 35 Gy.[39] The other trial (CROSS) included a more recently accrued patient population (2004-2008) and demonstrated an HR of 0.75 (95% CI, 0.56 to 1.01; $P = .059$) in an analysis that was underpowered to detect differences in histologic subgroups.[26,40] Overall, a lower-quality evidence rating was assigned to this outcome, indicating lower certainty of the results. The Expert Panel also considered the significant benefit of preoperative CRT to rate of complete resection within the adenocarcinoma subgroup. Based on these factors, the Expert Panel chose to recommend preoperative CRT for patients with locally advanced esophageal adenocarcinoma, particularly for bulky tumors with more proximal extension, taking into account the subgroup considerations outlined subsequently.
- There was no significant difference in overall survival or treatment-related mortality for the comparison of preoperative CRT versus preoperative CT (Table 6).
- No studies of postoperative CT compared with surgery alone met the inclusion criteria.

Subgroup considerations.

- For the subgroup of patients for whom surgery is not feasible, CRT without surgery is recommended.
- Preoperative CT should be considered for patients who are not candidates for radiation or postoperative CT.[15,16]
- Postoperative complications may be more severe with CRT compared with CT.[17] Consider the potential for

TABLE 10. Patients With Locally Advanced Esophageal Squamous Cell Carcinoma—Surgery Followed by CRT Versus Surgery Alone (Lv[44])

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain-Text Summary
		Surgery Alone	Surgery Followed by CRT		
10-Year overall survival	RR, 1.95 (95% CI, 0.97 to 3.92) Based on data from 158 patients in 1 study Follow-up: 10 years	125 per 1,000	244 per 1,000 Difference: 119 more per 1,000 (95% CI, 4 fewer to 365 more)	Very low (1)	Surgery followed by CRT may have little or no difference on 10-year overall survival
10-Year progression free survival	RR, 2.87 (95% CI, 1.09 to 7.59) Based on data from 158 patients in 1 study Follow-up: 10 years	62 per 1,000	178 per 1,000 Difference: 116 more per 1,000 (95% to 6 more to 409 more)	Very low (1)	Surgery followed by CRT may improve 10-year progression free survival

NOTE. (1) Downgrade: risk of bias[11]; indirectness: differences between the populations of interest and those studied (older study data: 1997-2004); only one study.

Abbreviations: CRT, chemoradiation therapy; RR, relative risk.

patient tolerance of the addition of RT based on tumor location and other factors.[18]

- The addition of RT is expected to be more beneficial in the setting of less optimal or less extensive surgery. Adequate quality and extent of surgery includes clear surgical margins and adequate nodal dissection within appropriate nodal fields (eg, abdominal and thoracic), with a goal of obtaining at least 16-18,[19] and preferably > 20, lymph nodes.[20] Lymphadenectomy fields and extent of surgery will be affected by tumor location. Detailed recommendations for surgical approach are beyond the scope of this guideline.

Note: The recommendation for perioperative CT over surgery alone is based on data from the MAGIC phase III RCT (2006),[36] which demonstrated an overall survival benefit with epirubicin-based perioperative CT compared with surgery alone. Recent findings from the FLOT4 phase III RCT (2019) demonstrated a significant overall survival advantage with the docetaxel, oxaliplatin, leucovorin, and fluorouracil (FLOT) regimen compared with the MAGIC regimen.[22] Thus, while this question was outside the scope of our systematic review, the Expert Panel recognizes FLOT as the standard of care for perioperative CT in esophageal adenocarcinoma. The FLOT regimen includes 4 preoperative and 4 postoperative 2-week cycles of 50 mg/m^2 docetaxel, 85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin, and 2,600 mg/m^2 fluorouracil as 24-hour infusion on day 1.[22] Where the FLOT regimen is not available or feasible, the Expert Panel suggests CF (2 3-weekly cycles of cisplatin [80 mg/m^2 intravenously on day 1] and fluorouracil [1 g/m^2 per day intravenously on days 1-4])[23] or a similar platinum-based regimen.

Example clinical scenarios: adenocarcinoma. For a patient with a large bulky tumor that extends more proximally, one would consider preoperative CRT in order to increase the likelihood of a complete surgical resection. For example, a patient who has been staged using computed tomography and endoscopic ultrasound and diagnosed with a large T3, node-positive esophageal adenocarcinoma located in the distal esophagus 32 cm to 42 cm from the incisors (Siewert I tumor center located 1 cm to 5 cm above the gastroesophageal junction), for whom a transthoracic (ie, incisions via abdomen and chest with or without neck incision) esophagectomy is planned, might have an increased risk of positive surgical margins because of the larger size and location of the tumor. In this scenario, preoperative CRT would be preferred. By contrast, for a patient with a relatively smaller tumor located at the gastroesophageal junction without significant proximal extension, where complete surgical resection is more feasible, the addition of RT may offer less benefit to complete surgical resection; perioperative CT (without RT) is more likely to be the preferred option.

Note: (1) In a meta-analysis comparing differing surgical approaches among patients with distal esophagus and gastroesosphageal junction tumors (Siewert I/II) in the setting of surgery alone, the number of retrieved lymph nodes was found to be significantly lower with a transhiatal approach compared to transthoracic.[64] In the CROSS RCT of preoperative CRT compared to surgery alone, in which 45% underwent a transhiatal resection, the total number of resected lymph nodes was positively associated with overall survival in the surgery-alone group, but not in the preoperative CRT group.[21,40] While this topic is controversial–with a transhiatal approach, which implies a less extensive lyphadenectomy–CRT is preferred over perioperative CT. (2) This recommendation may be altered in the future based on the results of the ongoing trials (see Discussion).

CLINICAL QUESTION 3

What is the preferred modality of neoadjuvant or adjuvant therapy for patients with locally advanced esophageal squamous cell carcinoma?

Recommendation 3. Preoperative CRT or CRT without surgery should be offered to patients with locally advanced esophageal squamous cell carcinoma (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Key evidence.

- Both patients with locally advanced adenocarcinoma and squamous cell carcinoma have been shown to benefit from CRT; however, studies have found a more pronounced effect of preoperative CRT in patients with squamous cell carcinoma (Tables 4 and 5).
- One study found a significant improvement in overall and relapse-free survival with perioperative CT compared with preoperative CT (Table 7).
- Meta-analysis of two studies found no difference in overall survival but found an increase in treatment-related mortality with preoperative CRT compared with CRT alone in patients with squamous cell carcinoma (Table 9).

Subgroup considerations.

- Historical studies suggested that in patients who respond completely to CRT, the addition of surgery may offer minimal benefit.[24,25] In patients with squamous cell carcinoma who appear to have a complete response to CRT, the option of surveillance and salvage surgery upon progression may be considered where salvage esophagectomy is practiced.[26] At this time, an RCT is exploring the question of surveillance and salvage surgery after CRT compared with planned surgery after CRT[27] using the clinical assessment criteria established in the pre-SANO trial[28]; a similar study is under way in France (Esostrate-Prodige 32).[29]
- In patients for whom radiation is not an option, preoperative CT (without radiation) may be considered.[15,16]
- Definitive CRT is recommended for patients with tumors located in the cervical esophagus; surgery should

be considered in the event of persistent or recurrent disease.
- While CRT and surgery are preferred, definitive CRT is an option for patients who cannot tolerate or choose not to undergo surgery.

Example clinical scenarios: squamous cell carcinoma. For a patient with squamous cell carcinoma who is surgically fit and willing to have surgery, and where the tumor is not in close proximity to the larynx, the Expert Panel would consider CRT followed by surgery to be the preferred option with a high likelihood of recovering well after surgery. By contrast, for a patient with a higher burden of comorbidities who is less likely to tolerate surgery and/or has a less favorable tumor location, definitive CRT without surgery immediately following neoadjuvant therapy may be preferred; where there is persistent or recurrent disease after CRT, the option of surgery should be considered.

Literature review and analysis. The results of the systematic review were consistent with previously published systematic reviews on preoperative therapies for esophageal carcinoma, showing a benefit of preoperative CT, preoperative CRT, and perioperative CT in patients with esophageal adenocarcinoma as well as recommendations for preoperative CRT or CRT without surgery in patients with squamous cell carcinoma. The included subgroup considerations are intended to assist with implementation, and the clinical interpretation of the evidence base in the context of prognostic and other factors is discussed in greater detail subsequently.

Type and extent of surgery. Surgical mortality following transthoracic esophagectomy has decreased from up to 10% to < 5% over the past few decades.[3] In the setting of surgery alone, transthoracic surgery has been associated with more favorable oncological outcomes relative to a transhiatal approach,[64] although not necessarily with better quality of life.[51] RT would be expected to be more beneficial in the setting of less optimal or less extensive surgery (outlined previously). Fewer locoregional recurrences have been noted among those who received RT in the setting of less extensive lymph node dissection.[25]

Metastases. Complete tumor resection is associated with improved long-term survival[52]; however, even after complete tumor resection, patients with squamous cell carcinoma have a poorer prognosis after surgery alone than patients with adenocarcinoma, potentially due to the higher prevalence of micrometastases in the former group.[3]

Tumor location. Esophageal adenocarcinoma is more likely than squamous cell carcinoma to present in the lower esophagus. Depending on tumor location, other organs may be at risk for radiation, including a higher risk of lung exposure with middle-third tumors and risk of gastric conduit exposure with tumors involving the upper stomach.[18] There are surgical challenges in squamous cell carcinoma with location of the tumor in the upper thoracic esophagus.[10] For patients with squamous cell carcinoma who are more amenable to resection, neoadjuvant CRT and esophagectomy may be appropriate.[18] Cervical esophageal tumors are not typically treated with surgery due to the risk of major complications, high morbidity and mortality, and negative impact on quality of life.[54]

Responders with squamous cell carcinoma to CRT. Complete pathologic response in the primary tumor or minimal residual disease are important prognostic factors in squamous cell carcinoma.[55] After CRT, surgery is beneficial in the subset of patients who have remaining locally advanced disease but would not have value for patients harboring undetected metastatic disease or for those who have experienced a complete pathologic response after CRT.[56,57] In the CROSS trial, approximately 50% of patients with squamous cell carcinoma had a complete pathologic response after CRT, meaning no viable tumor cells were detected on histologic examination in the primary tumor or resected regional lymph nodes. Therefore, in patients with squamous cell carcinoma who respond to CRT, a selective surgery approach may be considered[24,58] where there are no signs of distant dissemination.[26] In the two included trials comparing preoperative CRT to definitive CRT (Table 9), clinical complete response was defined by the absence of dysphagia and of visible tumor on esophagogram and by no dysphagia, normal barium esophagogram and esophagoscopy, and normal computed tomography scan, respectively. In the pre-SANO trial, the results of clinical response evaluations were compared with pathologic response rates in resected specimens. Clinical response evaluations included endoscopic ultrasound with bite-on-bite biopsies and fine-needle aspiration of suspicious lymph nodes for detection of locoregional disease as well as positron emission tomography-computed tomography scans for detecting interval metastases.[28] For this optimal combination of modalities for detecting response, a tumor regression grade of 3 or 4 was missed in 10% of cases. At this time, an RCT is exploring the question of surveillance and salvage surgery after CRT compared with planned surgery after CRT[27] using the clinical assessment criteria established in the pre-SANO trial.[28]

DISCUSSION

The management of locally advanced esophageal cancer has evolved with the changing epidemiology of the disease (eg, rise in adenocarcinoma), improvements in staging, surgery, and radiation techniques. As a result, the management is often complex and confusing, with multiple acceptable treatment strategies. Using a more selective evidence base, this systematic review and meta-analyses are supportive of the conclusions of previous reviews[11] showing the significant benefit associated with neoadjuvant and adjuvant therapies; however, some controversy remains regarding the balance of benefits and harms associated with

these treatment options. Thus, the Expert Panel advocates for an individualized approach to therapy among patients with locally advanced esophageal cancer, taking into consideration factors such as histologic type, likelihood of metastatic disease and/or nodal involvement, tumor size and location, surgical approach, response to neoadjuvant therapy, and overall health and performance status. A multidisciplinary team management approach should be applied.

There are several limitations associated with this systematic review. The Expert Panel attempted to overcome an issue with indirectness by limiting the inclusion of studies to more recent literature; however, many included studies have patient populations that were accrued up to 15-20 years ago. Since that time, staging systems have changed; selection of patients for curative treatments, including surgery, have improved; and surgical outcomes have improved due to centralization. Studies have historically included relatively few older patients or patients with poor performance status. In addition, many studies with smaller sample sizes lack statistical power to detect differences between treatment and control groups.

While a systematic literature review of specific CT or RT doses or regimens was outside the scope of the guideline protocol, the Expert Panel notes the recent publication of results from the FLOT4 phase II-III randomized trial. Previously, a significant overall survival benefit had been demonstrated in the MAGIC trial, published in 2006, with perioperative CT (epirubicin and cisplatin plus fluorouracil or capecitabine [ECF/ECX]) compared with surgery alone.[36] In the FLOT4 RCT, perioperative ECF/ECX was administered to the control group and compared with FLOT in a study population of 716 patients with locally advanced resectable gastric or gastroesophageal adenocarcinoma. A significant overall survival advantage was found for the FLOT regimen (HR, 0.77; 95% CI, 0.63 to 0.94), with a median survival of 50 months (95% CI, 38.3 months to not reached) in the FLOT group and 35 months (95% CI, 27.35 to 46.26 months) in the ECF/ECX group.[22] Thus, a note summarizing this result is provided within the Bottom Line Box as well as direction where this combination of CT is not available.

Several current studies explore the research questions of interest in this guideline, including:

- The German ESOPEC study of perioperative CT (FLOT regimen[22]) compared with preoperative CRT (CROSS regimen[26]) in patients with adenocarcinoma. ESOPEC investigators hypothesize that perioperative CT will result in "better overall survival due to comparable local control and better control of micrometastatic disease."[59]
- Neo-AEGIS is a study of CT (FLOT[22] or MAGIC regimen[36]) and surgery, compared with CRT and surgery (CROSS regimen[26,40]) in gastroesophageal junction adenocarcinoma.[60]
- The correlation between clinical complete response and pathologic complete response after neoadjuvant CRT was explored in the pre-SANO study.[28] The optimal combination of diagnostic modalities to detect locoregional residual disease after CRT is being used in the current SANO trial of active surveillance in high-volume centers.[27] The Esostrate trial is also exploring this comparison.[29]
- The Japanese NExT trial (JCOG1109) is a three-arm phase III trial comparing CF versus docetaxel and cisplatin plus fluorouracil versus RT with CF as preoperative therapy for locally advanced esophageal cancer.[61]

PATIENT AND CLINICIAN COMMUNICATION

Given the number of potential therapeutic options that have been reviewed in this guideline, it is vitally important that the harms and benefits of each option are presented to patients and that patients' values and preferences for treatment are explored and discussed. A practice statement has been provided following recommendation 3, detailing that for patients with esophageal squamous cell carcinoma, the decision to undertake surgery should be considered in the context of shared decision making, taking into account age, comorbidities, patient preference, caregiver support, and other factors. A discussion of these factors also applies to decision making for the other treatment options included in this guideline. For further recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[62]

OPEN COMMENT

The draft recommendations were released to the public for open comment from October 14 through October 28, 2019. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree–See comments" were captured for every proposed recommendation, with one written comment received. All 3 respondents agreed with the recommendations as written; therefore, no revisions to the recommendations were made based on feedback from the open comment process.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners, survivors of cancer, and caregivers and to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate the implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO website and are most often published in *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care Into Standard Oncology Practice[63] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[62] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

AFFILIATIONS

[1]New York Hospital/Weill Cornell Medical Center, New York, NY
[2]American Society of Clinical Oncology, Alexandria, VA
[3]University of Chicago Medicine, Chicago, IL
[4]Alexandria, VA
[5]Icahn School of Medicine at Mount Sinai, New York, NY
[6]Yolanda G. Barco Cancer Institute, Meadville, PA
[7]Duke Cancer Center, Durham, NC
[8]University of Kansas School of Medicine and VAMC, Kansas City, KS
[9]Memorial Sloan Kettering Cancer Center, New York, NY
[10]Erasmus University Medical Center, Rotterdam, the Netherlands
[11]The University of Texas MD Anderson Cancer Center, Houston, TX

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org

EQUAL CONTRIBUTION

M.A.S. and W.L.H. were Expert Panel co-chairs.

EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/gastrointestinal-cancer-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.00866.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The Expert Panel thanks Nishin Bhadkamkar, MD; Matthew Katz, MD; and the Clinical Practice Guidelines Committee for their thoughtful reviews and insightful comments on this guideline.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Treatment of Locally Advanced Esophageal Carcinoma: ASCO Guideline

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

APPENDIX

TABLE A1. Locally Advanced Esophageal Cancer Guideline Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Manish A. Shah, MD (co-chair)	New York Hospital/Weill Cornell Medicine, New York, NY	Medical Oncology
Wayne L. Hofstetter, MD (co-chair)	The University of Texas MD Anderson, Houston, TX	Surgical Oncology
Daniel V. Catenacci, MD	University of Chicago Medicine, Chicago, IL	Medical Oncology
Dana C. Deighton	Alexandria, VA	Patient Representative
Karyn A. Goodman, MD	Icahn School of Medicine at Mount Sinai, New York, NY	Radiation Oncology
Narinder K. Malhotra, MD	Yolanda G. Barco Cancer Institute, Meadville, PA	Practice Guidelines Implementation Network Representative
Christopher Willett, MD	Duke Cancer Center, Durham, NC	Radiation Oncology
Brendon Stiles, MD	New York Hospital/Weill Cornell Medicine, New York, NY	Thoracic Surgery
Prateek Sharma, MD	University of Kansas School of Medicine and VAMC, Kansas City, KS	Gastroenterology
Laura Tang, MD, PhD	Memorial Sloan Kettering Cancer Center, New York, NY	Pathology
Bas P. L. Wijnhoven, MD, PhD	Erasmus University Medical Center, Rotterdam, the Netherlands	Surgical Oncology
Erin B. Kennedy, MHSc	ASCO, Alexandria, VA	ASCO Practice Guidelines Staff (health research methods)