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Executive Summary of the American Radium Society Appropriate Use Criteria for Operable Esophageal and Gastroesophageal Junction Adenocarcinoma: Systematic Review and Guidelines

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Critical Review

Executive Summary of the American Radium Society Appropriate Use Criteria for Operable Esophageal and Gastroesophageal Junction Adenocarcinoma: Systematic Review and Guidelines

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Purpose: Limited guidance exists regarding the relative effectiveness of treatment options for nonmetastatic, operable patients with adenocarcinoma of the esophagus or gastroesophageal junction (GEJ). In this systematic review, the American Radium Society (ARS) gastrointestinal expert panel convened to develop Appropriate Use Criteria (AUC) evaluating how neoadjuvant and/or adjuvant treatment regimens compared with each other, surgery alone, or definitive chemoradiation in terms of response to therapy, quality of life, and oncologic outcomes.
Methods and Materials: Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology was used to develop an extensive analysis of peer-reviewed phase 2R and phase 3 randomized controlled trials as well as meta-analyses found within the Ovid Medline, Cochrane Central, and Embase databases between 2009 to 2019. These studies were used to inform the expert panel, which then rated the appropriateness of various treatments in 4 broadly representative clinical scenarios through a well-established consensus methodology (modified Delphi).
Results: For a medically operable nonmetastatic patient with a cT3 and/or cN+ adenocarcinoma of the esophagus or GEJ (Siewert I-II), the panel most strongly recommends neoadjuvant chemoradiation. For a cT2N0M0 patient with high-risk features, the panel recommends neoadjuvant chemoradiation as usually appropriate. For patients found to have pathologically involved nodes (pN+) who did not receive any neoadjuvant therapy, the panel recommends adjuvant chemoradiation as usually appropriate. These guidelines assess the appropriateness of various dose-fractionating schemes and target volumes.
Conclusions: Chemotherapy and/or radiation regimens for esophageal cancer are still evolving with many areas of active investigation. These guidelines are intended for the use of practitioners and patients who desire information about the management of operable esophageal adenocarcinoma. © 2020 Published by Elsevier Inc.

Introduction

Although esophageal cancer is the 20th most common cancer in the United States, its high lethality and much higher prevalence worldwide demand attention.[1,2] Adenocarcinoma of the distal esophagus accounts for approximately two-thirds of all esophageal cancers in the United States, and approximately half of these are stage III or IV. Radical resection, in the form of esophagectomy, is the mainstay of curative therapy, but overall outcomes for patients with esophageal adenocarcinoma remain poor.[2,3] Advancements in nonsurgical modalities, including systemic therapy and radiation therapy (RT), led to the evolution of multidisciplinary therapeutic strategies. It is notable that the 5-year overall survival (OS) improved from 5% to about 20% during the last 30 years, suggesting small yet measurable improvements in diagnosis, staging, treatment, and supportive care.[4] The 5-year survival rates for localized, regional, and distant disease are 47%, 25%, and 5%, respectively, highlighting the importance of early diagnosis. Geographic variability in esophageal cancer (preponderance of squamous cell carcinoma (SCC) in the East vs adenocarcinoma in the West) has led to differences in the management of this disease around the world.[2,3,5] Except for in situ or early-stage disease, which can be managed with esophagectomy alone or endoscopic resection, multimodality therapy integrating neoadjuvant and/or adjuvant chemotherapy and RT with surgery is widely accepted based on high-level evidence.[2,3] Despite these advances, there remains little guidance regarding the relative effectiveness of the various treatment options for patients with operable esophageal adenocarcinoma. Herein, this systematic review and guidelines intend to provide insights and direction to practitioners based on the available evidence.

Methodology

The evidence regarding treatment outcomes was assessed using the Population, Intervention, Comparator, Outcome, and Study design (PICOS) framework. For the population of operable patients with adenocarcinoma of the esophagus or gastroesophageal junction (GEJ), we sought to evaluate how neoadjuvant or adjuvant treatment compared with each other, surgery alone, or definitive chemoradiation in terms of response to therapy, quality of life (QoL), or oncologic outcomes through the assessment of data from randomized controlled trials (RCTs) and meta-analyses. Trial size required for inclusion was $\geq$50 patients for phase 2R and 3 RCTs and $\geq$100 patients for meta-analyses, of whom at least 20 patients were required to have adenocarcinoma. With librarian assistance we developed literature search strategies using medical subject headings (MeSH) and combinations of keyword search terms (Table 1) to address our PICOS question.

An extensive analysis of current medical literature covering January 1, 2009 to May 28, 2019, from peer-reviewed journals indexed in the Ovid Medline, Cochrane Central, and Embase databases and using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines yielded a comprehensive set of relevant articles. The literature was reviewed for quality of

Table 1 Literature search strategy for 2020 American Radium Society (ARS) Appropriate Use Criteria (AUC) for operable esophageal adenocarcinoma

Set number	Search text	No. of references retrieved
1	(esophag* or oesophag* or gastroesophag* or "gastro-esophag*" or "gastro-oesophag*").ti,ab,kf.	176,096
2	(cancer* or carcinoma* or neoplas* or adenocarcinoma* or malignan* or tumor* or tumour*).ti,ab,kf.	3,163,127
3	1 and 2	69,644
4	exp *Esophageal Neoplasms/	40,889
5	exp *Neoplasms/	2,780,090
6	exp *Esophagus/	31,869
7	5 and 6	5498
8	3 or 4 or 7	74,581
9	(resect* or esophagectom* or oesophagectom* or surg* or opera* or adjuvant* or neoadjuvant*).ti,ab,kf.	2,754,273
10	exp Esophagectomy/	9218
11	su.fs.	1,905,698
12	9 or 10 or 11	3,577,588
13	(radiotherap* or radiat* or irradiat* or chemoradi* or chemotherap* or adjuvant* or neoadjuvant*).ti,ab,kf.	1,035,545
14	exp Radiotherapy/	176,454
15	exp antineoplastic agents/ or exp antineoplastic protocols/	1,094,704
16	exp combined modality therapy/	249,945
17	rt.fs.	184,745
18	th.fs.	1,774,289
19	or/13-18	3,547,253
20	("phase II*" or "phase 2*" or "phase III*" or "phase 3*" or "meta-analys*" or "metaanalys*" or "randomi*" or "phase IV*" or "phase 4*").ti,ab,kf.	768,147
21	clinical trial, phase II/ or clinical trial, phase III/ or clinical trial, phase IV/	46,443
22	exp Meta-Analysis/	102,077
23	validation studies/	95,475
24	exp controlled clinical trial/	573,006
25	or/20-24	1,151,901
26	8 and 12 and 19 and 25	1698
27	limit 26 to yr="2009 - 2019"	892
28	limit 27 to English language	839
29	("non-small cell lung ca*" or "non small cell lung ca*" or "small cell lung ca*" or "NSCLC" or "SCLC").ti,ab,kf.	70,983
30	28 not 29	805

Key: Sets 1-8, esophageal adenocarcinoma; sets 9-12, treatment addresses surgery; sets 13-19, treatment addresses systemic therapy and/or radiation; lines 20-25, limits search to phase 2-4 trials or meta-analyses; set 26, selects for studies contained in each of the 4 prior groups of set themes; sets 27-30, additional limitations on search including date range and English language, and excluding lung cancer.

Literature search date range: January 1, 2009 to May 28, 2019.

Database: Ovid MEDLINE(R) without revisions.

study design, cohort size, selection bias, and methods of assessments. Two authors independently screened the studies and full-text articles to determine the final studies included in this review, as detailed in Figure 1. Any discrepancies between the reviewers were resolved by consensus. We reviewed the bibliographies of full articles for a comprehensive survey, and 8 additional studies were included; these met all inclusion criteria except publication date (3 published before 2009). Forward citation chaining via Web of Science was then performed on the selected documents to determine whether any eligible articles published no later than May 28, 2019, had been missed by the searches, and 1 was found, resulting in 52 references.[6-57] Study type and quality were assessed via American Radium Society (ARS) Appropriate Use Criteria (AUC) methodology (Appendix A).[58] The checklist confirming completion of all essential elements for a PRISMA systematic review may be found in Appendix B, and Appendix C contains a list of abbreviations. A well-established consensus methodology (modified Delphi) was used by the expert panel; panel members had expertise in the management of esophageal cancer and could rate the appropriateness of the treatment procedures.[59] Disagreement was defined as more than one-third of votes occurring

Table 2 Clinical condition: Operable esophageal adenocarcinoma

Variant 1: Clinical stage IIB, cT2 cN0 M0 high-grade* (signet-ring) adenocarcinoma of the lower thoracic esophagus noted on EUS, extending 32-36 cm from the incisors in a medically operable patient. No dysphagia† present. No elevated FDG uptake noted on PET.

Treatment	Rating category	Group median rating	Relevant references	SOE	SOR
Planned treatment					
nCRT	A	8	17-20	S	↑
nCT	M	5	6,7,9,11,12,18,34,35	S	↑
Surgery alone	M§	5§	17-20	S	↑
S → aCRT	M	5	36,37,40	M	↑
S → aCT	M§	5§	37	L	-
dCRT	M§	5§	43,44	L	↑
S → aRT	U	3	37	L	↑
If RT: Dose to primary (if neoadjuvant)					
30- 30.6 Gy/15-17 fx	U	2	33	L	↑
40-41.4 Gy/20-23 fx	A	8	14,29	S	↑
45-46 Gy/25-23 fx	A	7	17-20	S	↑
50-50.4 Gy/25-28 fx	A	8	18-20	M	↑
54 Gy/30 fx	M§	5§	18-20,45-47	L	-
59.4-60 Gy/33-30 fx	U	1	N/A	EO	↑
If RT: Dose to elective nodes					
30- 30.6 Gy/15-17 fx	U	2	N/A	EO	↑
36 Gy/18-20 fx	U	3	N/A	EO	-
40-41.4 Gy/20- 23 fx	A	8	44	S	↑
45-46 Gy/25-23 fx	A	8	44	S	↑
50-50.4 Gy/25-28 fx	M§	5§	43,44	S	-
If RT: Elective nodal regions					
Supraclavicular	U	1	14,29	M	↑
Mediastinal prevascular and paraortic/ paratracheal/aortopulmonary window	M§	5§	14	L	-
Subcarinal	M§	5§	14	L	-
Paraesophageal	A	9	14,23,29,33	S	↑
Celiac/paracardial/subdiaphragmatic	A	8	14,23,29,33	S	↑
Gastrohepatic ligament/lesser curvature	A	8	14,23,33	S	↑
Splenic‡	U	3	33	L	↑

Rating: U, usually not appropriate (1-3); M, may be appropriate (4-6); A, usually appropriate (7-9).

Strength of evidence (SOE): S: strong; M: moderate; L: limited; EC: expert consensus; EO: expert opinion.

Strength of recommendation (SOR) of rating category: ↑: strong; ↓: weak; "-": additional considerations do not strengthen or weaken the panel's recommendation.

Abbreviations: aCT = adjuvant chemotherapy; aCRT = adjuvant concurrent chemoradiation therapy; aRT = adjuvant radiation therapy; dCRT = definitive concurrent chemoradiation therapy; EUS = endoscopic ultrasound; FDG = fluorodeoxyglucose; fx = fractions; nCT = neoadjuvant chemotherapy; nCRT = neoadjuvant concurrent chemoradiation therapy; PET/CT = positron emission tomography/computed tomography; poCT = perioperative chemotherapy; S = surgery.

* Tumor size >3 cm, poor differentiation, and/or lymphovascular invasion found on endoscopic resection specimens are associated with higher risk of upstaging to T3 and/or N+[20] and neoadjuvant therapy should be considered.

† Complete solid food dysphagia is associated with increased likelihood of pT3 disease.[23]

‡ Proximal 2 cm of splenic artery region.

§ Disagreement (ie, the variation of the individual ratings from the median rating) indicates panel disagreement on the final recommendation (see narrative text for definition). Group median rating is set automatically to 5.

outside the rating category. Categories included (1) usually not appropriate (U, score 1-3); (2) may be appropriate (M, score 4-6); and (3) usually appropriate (A, score 7-9). Studies within the introduction and future directions sections are referenced only to provide context but are not included as the supporting evidence for oncologic interventions. For the RT section, evidence from the literature search was supplemented by recommendations from an expert contouring guidelines atlas.[60]

Summary of Literature Review

Neoadjuvant treatment

Neoadjuvant chemotherapy or perioperative chemotherapy versus surgery alone

In the meta-analysis of RCTs comparing neoadjuvant chemotherapy (nCT) or perioperative chemotherapy (poCT) to surgery alone by Coccolini et al, a subset analysis of

Table 3 Clinical condition: Operable esophageal adenocarcinoma

Variant 2: Clinical stage IVA, T3 N2 M0 moderately differentiated adenocarcinoma of the gastroesophageal junction (Siewert II) located 38-43 cm from the incisors in a medically operable patient. Two distal paraesophageal nodes and 3 gastrohepatic nodes measuring up to 2.5 cm in size noted on EUS and PET/CT.

Treatment	Rating category	Group median rating	Relevant references	SOE	SOR
Planned treatment					
nCRT	A	9	13,14,24-26,34,35	S	↑
iCT → nCRT → S*	A	7	21,23	M	↑
nCT	M	5	6,7,9,11,12,18,29,34,35	S	↑
poCT	M	5	6,8	M	↑
dCRT	M†	5†	43,45-48	M	↑
nCT and aCRT	M	4	41	M	-
S → aCRT	U	3	36,37,40	M	↑
S → aCT	U	2	37	L	↑
S → aRT	U	1	37	L	↑
Surgery alone	U	1	34,35,43,44	S	↑
If RT: Dose to involved primary/nodes (if neoadjuvant)‡					
30-30.6 Gy/15-17 fx	U	2	33	M	↑
40-41.4 Gy/20-23 fx	A	8	14,29,44	S	↑
45-46 Gy/25-23 fx	A	7	23,44	S	↑
50-50.4 Gy/25-28 fx	A	8	21,44	S	↑
54 Gy/30 fx	M	4	44	L	↑
59.4-60 Gy/33-30 fx	U	2	44	L	↑
If RT: Dose to elective nodes‡					
30-30.6 Gy/15-17 fx	U	3	33,44	L	↑
36 Gy/18-20 fx	M†	5†	44	L	-
40-41.4 Gy/20-23 fx	A	7.5	14,29,44	S	↑
45-46 Gy/25-23 fx	A	7	23	S	↑
50-50.4 Gy/25-28 fx	A	7	21,44	S	↑
If RT: Elective nodal regions‡					
Supraclavicular	U	1	14,29	M	↑
Mediastinal prevascular and paraortic/paratracheal/aortopulmonary window	U	3	14	L	↑
Subcarinal	M	5	14	L	↑
Paraesophageal	A	9	14,23,29,33	S	↑
Celiac/paracardial/subdiaphragmatic	A	9	14,23,29,33	S	↑
Gastrohepatic ligament/lesser curvature	A	9	14,23,33	S	↑
Splenic§	U	3	33	L	↑

Rating: U, usually not appropriate (1-3); M, may be appropriate (4-6); A, usually appropriate (7-9).

Strength of evidence (SOE): S: strong; M: moderate; L: limited; EC: expert consensus; EO: expert opinion.

Strength of recommendation (SOR) of rating category: ↑: strong; ↓: weak; "-": additional considerations do not strengthen or weaken the panel's recommendation.

Abbreviations: aCT = adjuvant chemotherapy; aCRT = adjuvant concurrent chemoradiation therapy; aRT = adjuvant radiation therapy; dCRT = definitive concurrent chemoradiation therapy; EUS = endoscopic ultrasound; fx = fractions; iCT = induction chemotherapy given before CRT; nCT = neoadjuvant chemotherapy; nCRT = neoadjuvant concurrent chemoradiation therapy; PET/CT = positron emission tomography/computed tomography; poCT = perioperative chemotherapy; S = surgery.

* Based on encouraging initial results from CALGB 80803.

† Disagreement (ie, the variation of the individual ratings from the median rating) indicates panel disagreement on the final recommendation (see narrative text for definition). Group median rating is set automatically to 5.

‡ Key radiation points:

1. In the neoadjuvant setting, 40-50.4 Gy in fraction sizes between 1.8 and 2.0 Gy to involved disease and elective nodal areas is preferred. This may involve a reduced field size to include just the primary tumor after an elective dose to 40-45 Gy.
2. Elective radiation of the paraesophageal, celiac, paracardial, subdiaphragmatic, gastrohepatic ligament, and lesser curvature nodes is preferred for distal tumors. Subcarinal nodes should be included if paraesophageal nodes extend superiorly to the same axial plane.

§ Proximal 2 cm of splenic artery region.

patients with GEJ adenocarcinoma found that the addition of chemotherapy improved OS.[6] However, it should be noted that the 3 studies included within this analysis did not distinguish between Siewert grades, thus limiting the generalizability to the more proximal Siewert I and II patients, who are typically regarded as falling within the esophageal cancer paradigm.[7-9] Subset analysis for adenocarcinoma (67% of the patients) also showed improved OS with the

Table 4 Clinical condition: Operable esophageal adenocarcinoma

Variant 3: Clinical stage III, T3 N1 M0 adenocarcinoma of the middle thoracic esophagus extending 25-30 cm from the incisors with its proximal extent just superior to the carina. One adjacent paraesophageal node noted on EUS and PET/CT in a medically operable patient. Bronchoscopy was negative for trachea-esophageal fistula.

Treatment	Rating category	Group median rating	Relevant references	SOE	SOR
Planned treatment					
nCRT	A	9	13,14,24-26,34,35	S	↑
iCT → nCRT → S*	A	7	21,23	M	↑
nCT and aCRT	M†	5†	41	L	-
dCRT	M†	5†	43,45-48	M	↑
nCT	M	4	6,7,9,11,12,18,29,34,35	S	↑
poCT	M	4	6,8	L	↑
S → aCRT	U	3	36,37,40	L	↑
S → aCT	U	3	37	L	↑
S → aRT	U	3	37	L	↑
Surgery alone	U	1	34,35,43,44	S	↑
If RT: Dose to primary/involved nodes (if neoadjuvant)‡					
30-30.6 Gy/15-17 fx	U	3	33	M	↑
40-41.4 Gy/20-23 fx	A	8	14,29,44	S	↑
45-46 Gy/25-23 fx	A	8	23,44	S	↑
50-50.4 Gy/25-28 fx	A	8	21,44	S	↑
54 Gy/30 fx	M†	5†	44	L	↑
59.4-60 Gy/33-30 fx	U	2	44	L	↑
If RT: Dose to elective nodes‡					
30-30.6 Gy/15-17 fx	U	2	33,44	L	↑
36 Gy/18-20 fx	U	3	44	L	↑
40-41.4 Gy/20-23 fx	A	8	14,29,44	S	↑
45-46 Gy/25-23 fx	A	8	23	S	↑
50-50.4 Gy/25-28 fx	M†	5†	21,44	S	↑
If RT: Elective nodal regions‡					
Supraclavicular	M†	5†	14,29	M	↑
Mediastinal prevascular and paraortic/paratracheal/ aortopulmonary window	A	8	14	L	↑
Subcarinal	A	8	14	L	↑
Paraesophageal	A	9	14,23,29,33	S	↑
Celiac/paracardial/ subdiaphragmatic	M†	5†	14,23,29,33	M	-
Gastrohepatic ligament/lesser curvature	M†	5†	14,23,33	M	-
Splenic§	U	1	33	L	↑

Rating: U, usually not appropriate (1-3); M, may be appropriate (4-6); A, usually appropriate (7-9).

Strength of evidence (SOE): S: strong; M: moderate; L: limited; EC: expert consensus; EO: expert opinion.

Strength of recommendation (SOR) of rating category: ↑: strong; ↓: weak; "-": additional considerations do not strengthen or weaken the panel's recommendation.

Abbreviations: aCT = adjuvant chemotherapy; aCRT = adjuvant concurrent chemoradiation therapy; aRT = adjuvant radiation therapy; dCRT = definitive concurrent chemoradiation therapy; EUS = endoscopic ultrasound; fx = fractions; iCT = induction chemotherapy given before CRT; nCT = neoadjuvant chemotherapy; nCRT = neoadjuvant concurrent chemoradiation therapy; PET/CT = positron emission tomography/computed tomography; poCT = perioperative chemotherapy; S = surgery.

* Based on encouraging initial results from CALGB 80803.

† Disagreement (ie, the variation of the individual ratings from the median rating) indicates panel disagreement on the final recommendation (see narrative text for definition). Group median rating is set automatically to 5.

‡ Key radiation points

1. Neoadjuvant doses of 40-50.4 Gy in fraction sizes between 1.8 and 2.0 Gy to involved disease and elective nodal areas is preferred. This may involve a reduced field size to include just the primary tumor after an elective dose to 40-45 Gy.
2. Elective radiation of the paraesophageal, supraclavicular, mediastinal prevascular and paraortic, paratracheal, aortopulmonary window, and subcarinal nodes is preferred in the setting of neoadjuvant concurrent chemoradiation for adenocarcinoma of the middle thoracic esophagus extending above the carina.Elective radiation of the celiac, paracardial, subdiaphragmatic, gastrohepatic ligament, and lesser curvature nodes may be omitted in the setting of neoadjuvant concurrent chemoradiation for adenocarcinoma of the middle thoracic esophagus extending above the carina with minimal to no involvement of the distal thoracic esophagus.

§ Proximal 2 cm of splenic artery regiony.

Table 5 Clinical condition: Operable esophageal cancer

Variant 4: After surgery for clinical stage II, T2 N0 M0 moderately differentiated adenocarcinoma of the lower thoracic esophagus located 30-35 cm from the incisors staged via EUS and PET/CT, final pathology revealed 2 positive nodes indicating pathologic stage IIIA, pT2 pN1 M0 disease.

Treatment	Rating category	Group median rating	Relevant references	SOE	SOR
Planned treatment					
aCRT	A	8	36,37,40	S	↑
aCT	M	5	37	M	↑
aRT	M*	5*	37	M	-
Observation	U	3	37	S	↑
If RT: Dose to operative bed†					
40-41.4 Gy/20-23 fx	U	3	36,37	L	↑
45 Gy/25 fx	A	8	36,37,40	L	↑
50-50.4 Gy/25-28 fx	A	8	36,37	M	↑
54 Gy/30 fx	M	5	36,37	L	↑
59.4-60 Gy/33-30 fx	U	2	36,37	L	↑
If RT: Dose to elective nodes†					
30-30.6 Gy/15-17 fx	U	1	N/A	L	↑
36 Gy/18-20 fx	U	3	N/A	L	↑
41.4 Gy/23 fx	M	4	36,37	S	↑
45-46 Gy/25-23 fx	A	8	36,37,40	S	↑
50-50.4 Gy/25-28 fx	A	7	36,37	S	↑
If RT: Elective regions					
Supraclavicular	U	1	14,29	M	↑
Mediastinal prevascular and paraortic/ paratracheal/aortopulmonary window	U	3	14	L	-
Subcarinal	M*	5*	14	L	-
Paraesophageal	A	8.5	14,23,29,33	S	↑
Celiac/paracardial/subdiaphragmatic	A	8	14,23,29,33	S	↑
Gastrohepatic ligament/lesser curvature	A	7.5	14,23,33	S	↑
Splenic‡	U	2	33	L	↑
Anastomosis	A	9	36,37,40	S	↑

Rating: U, usually not appropriate (1-3); M, may be appropriate (4-6); A, usually appropriate (7-9).

Strength of evidence (SOE): S: strong; M: moderate; L: limited; EC: expert consensus; EO: expert opinion.

Strength of recommendation (SOR) of rating category: ↑: strong; ↓: weak; "-": additional considerations do not strengthen or weaken the panel's recommendation.

Abbreviations: aCT = adjuvant chemotherapy; aCRT = adjuvant concurrent chemoradiation therapy; aRT = adjuvant radiation therapy; EUS = endoscopic ultrasound; fx = fractions; PET/CT = positron emission tomography/computed tomography.

* Disagreement (ie, the variation of the individual ratings from the median rating) indicates panel disagreement on the final recommendation (see narrative text for definition). Group median rating is set automatically to 5.

† Key radiation point: Adjuvant radiation doses between 45 and 50.4 Gy in fraction sizes between 1.8 and 2.0 Gy to the anastomosis and elective nodal areas are preferred in the adjuvant setting. Doses to the anastomosis of 54 Gy and higher are not preferred.

‡ Proximal 2 cm of splenic artery region.

addition of chemotherapy. In a Cochrane review of 13 randomized trials assessing nCT for resectable thoracic esophageal cancer, Kidane et al noted an OS and R0 resection rate benefit with chemotherapy, although the overall resection rate, tumor recurrence, and nonfatal complication rates were not found to be different.[10] The potential for increased toxicity with chemotherapy was noted. However, the OS benefit was no longer significant on subset analysis of patients with adenocarcinoma, leading to uncertainty of the potential benefit for this population. In the United Kingdom Medical Research Council Oesophageal 02 (MRC OE02) trial, which comprised the largest population of patients in the Kidane et al meta-analysis (two-thirds adenocarcinoma), esophageal cancer patients were randomized to neoadjuvant cisplatin and fluorouracil (5-FU) versus surgery alone; an improvement in OS and disease-free survival (DFS) as well as R0 resections was noted with chemotherapy.[11] The next largest proportion of patients within this meta-analysis was from the Intergroup 0113 study, which involved adenocarcinoma in just over half the population; this study did not show any OS benefit to nCT with cisplatin and 5-FU.[12] Locoregional failure was equivalent between groups, with a numerically but not significantly higher number of distant failures in the surgery alone group. Therefore, nCT appears of borderline benefit given the mixed results regarding OS.

Neoadjuvant chemoradiation versus surgery alone

Early stage esophageal cancer invading into the muscularis propria (T2) is not suitable for endoscopic therapies, so upfront esophagectomy is the preferred therapy for

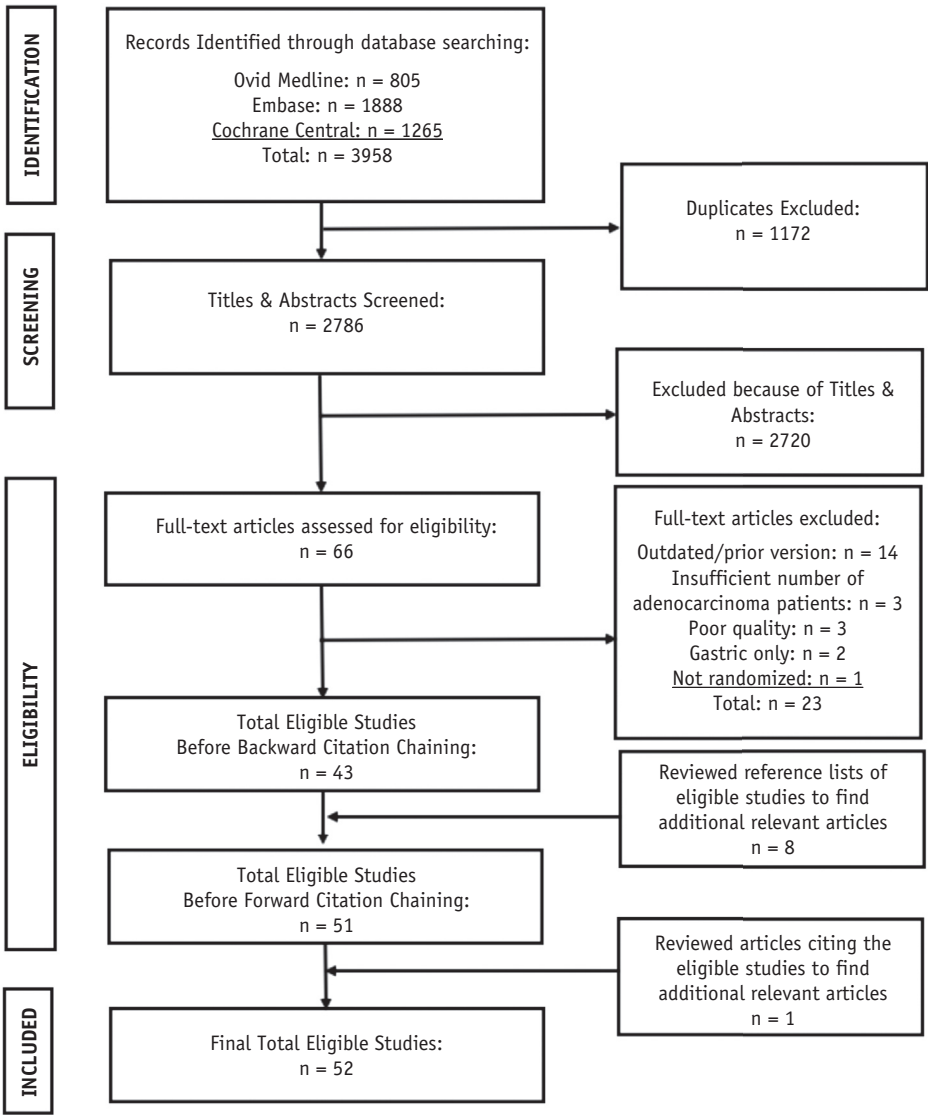

Fig. 1. Study selection flow chart for the systematic review.

operable patients as noted in the National Comprehensive Cancer Network guidelines.[2] However, long-term outcomes are still suboptimal with surgery alone, suggesting a possible use of neoadjuvant therapy.[13-17] In the randomized, controlled phase 3 trial Federation Francophone de Cancerologie Digestive (FFCD) 9901, 195 patients (29% adenocarcinoma) with Union for International Cancer Control 5th edition stage I or II disease (ie, T1-2N0-1M0 or T3N0M0) were randomized to receive surgery alone versus neoadjuvant concurrent chemoradiation therapy (nCRT) with 45 Gy in 25 fractions and 2 cycles of concomitant 5-FU and cisplatin.[17] No difference was seen in OS or R0 resection rate, but the postoperative mortality rate was significantly worse in the nCRT arm (11.1% vs 3.4%, $P < .049$). No difference in distant metastases was noted. Subset analyses showed no differences in outcomes between adenocarcinoma and SCC patients. Although the majority of the patients in this trial were T2 (56.4%) and N0 (72.3%), the number of patients who were both T2 and N0 was not specified and subset analyses were not performed; thus, definitive conclusions on this patient population cannot be made.

Three contemporaneous meta-analyses were published investigating whether neoadjuvant therapy (RT with or without chemotherapy) or upfront surgery leads to optimal outcomes for T2N0 patients.[18-20] Although the R0 resection rate increased with neoadjuvant therapy in the largest series, which involved 5,433 patients in 9 retrospective studies,[18] this sample size did not translate to improved OS[18-20] or recurrence-free survival[18,20] for either adenocarcinoma or SCC patients in any of the 3 meta-analyses. Of note, more than 80% of the patients in these series had adenocarcinoma. No differences in anastomotic leak rates or perioperative mortality were noted.[18,20] Kidane et al found that, in patients proceeding to surgery without neoadjuvant therapy, the N-stage was upstaged in 33.4% of cases and either T- or N- stage was upstaged in 41.5% of cases, although positive emission tomography (PET) and

endoscopic ultrasound (EUS) use was inconsistent. Because larger tumor size (>3 cm) and lymphovascular invasion (LVI) were significant predictors of pathologic upstaging, the authors suggested these factors, along with high-grade histology, could help identify patients who could benefit from neoadjuvant therapy. Of note, LVI is not available on conventional fine needle aspiration biopsy specimens but may be evaluated in endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) specimens. The authors also noted that neoadjuvant therapy could be considered for patients with dysphagia despite T2N0 disease on EUS; retrospective data indicate that the greater the extent of dysphagia, the higher the likelihood of ≥T3 disease, with very high (>90%) specificity but low sensitivity.[61] None of the studies within the meta-analyses included a QoL component, and as noted by Kidane et al, QoL assessments need to be a focus of future investigations in this population to help guide shared-decision making.[18]

In the phase 3 ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS), locoregionally advanced patients (81% T3, 64% N+) were randomized to surgery alone versus nCRT with carboplatin/paclitaxel concurrent with RT to 41.4 Gy/23 fractions.[14] OS was significantly improved with nCRT for adenocarcinoma (median OS: 43.2 vs 27.1 months, $P = .038$) and SCC patients (81.6 vs 21.1 months, $P = .008$), and no differences in postoperative mortality or complications were noted. In a subsequent secondary analysis of the patients on the CROSS trial, although health-related QoL declined during nCRT, no persistent degradation of health-related QoL due to nCRT was identified compared with surgery alone on further follow-up.[15] Contemporary meta-analyses of RCTs have found that nCRT provides significant improvements compared with surgery alone in OS, R0 resection rate, and locoregional control, with similar postoperative mortality.[13,16] On subset analysis by histology, Feng et al performed a meta-analysis including the initial report of the CROSS study and found that OS was significantly improved for adenocarcinoma, whereas in the analysis by Liu et al that included fewer adenocarcinoma studies, the benefit only trended toward significance. It should also be noted that each of these meta-analyses included FFCD 9901, and the early stage patients in that series may have dampened the magnitude of the overall OS benefit from nCRT. Therefore, nCRT followed by surgery appears to provide an OS benefit compared with surgery alone for locoregionally advanced (ie, T3 and/or N+) patients. Neoadjuvant chemoradiation has the potential to benefit T2N0 adenocarcinoma patients with high-risk features (length >3 cm, high grade, LVI on EMR/ESD) and/or symptoms of dysphagia, as these factors are associated with clinical understaging (Table 2, Variant 1).

nCRT with or without induction chemotherapy

In a randomized phase 2 trial, Ajani et al reported no significant increase in the primary endpoint of pathologic complete response (pCR) rate when using treatment with or without induction chemotherapy involving 5-FU/oxaliplatin followed by nCRT to 50.4 Gy with concurrent 5-FU/oxaliplatin compared with standard nCRT. Secondary endpoints including OS and complications were similar.[21] In a secondary subset analysis, induction chemotherapy led to significantly improved OS for those with well- to moderately differentiated adenocarcinoma but had no effect on those with poor differentiation, leading to the hypothesis that certain patients might still benefit from an induction approach.[22] In addition, in the phase 2R NEO-adjuvant Study of Chemoradiotherapy in OesoPhagEal cancer (NEOSCOPE) study, with a primary endpoint of pCR, patients were randomized to either carboplatin/paclitaxel or capecitabine/oxaliplatin with RT to 45 Gy in 25 fractions after 6 weeks of induction capecitabine/oxaliplatin; only the carboplatin/paclitaxel arm achieved a pCR rate worthy of further investigation (29.3% vs 11.1%, respectively).[23] Induction chemotherapy is a promising approach for esophageal cancer patients.

nCT versus nCRT

Although results are mixed regarding differences in outcomes between nCT and nCRT, RT appears beneficial overall when added to chemotherapy in the neoadjuvant setting for esophageal/GEJ adenocarcinoma patients. While contemporary meta-analyses addressing adenocarcinoma have shown that adding RT significantly increases the pCR and R0 resection rates for esophageal/GEJ patients compared with nCT alone, this addition has not translated to an improvement in OS.[24-26]

As might be expected, RT decreased the risk of locoregional relapse, but distant metastases-free survival (DMFS) was not improved. Although a network meta-analysis of RCTs found perioperative 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) to be superior to all other neoadjuvant regimens, it included all patients from the FLOT4-AIO study in the analysis even though most patients had either gastric or Siewert III disease, limiting the generalizability to esophageal or Siewert I-II GEJ adenocarcinoma.[27,28] Long-term results of the initial report of the phase 2R NeoRes I (NEOadjuvant chemotherapy versus Radiochemotherapy for cancer of the ESophagus or cardia) contained within these meta-analyses also noted that the higher pCR found with nCRT versus nCT was not associated with an improvement in progression-free survival (PFS) or OS.[29] Patients on the nCRT arm received cisplatin/5-FU concurrent with 40 Gy/20 fractions. Overall treatment-related complications were similar, but fatal postoperative complications were more common after nCRT (9%) compared with nCT (1%) ($P = .02$).[29,30] A secondary QoL analysis of the NeoRes I trial found a significantly greater improvement in the dysphagia score after nCT compared with nCRT, with the authors hypothesizing that RT-induced esophagitis led to worse dysphagia.[31] Also driving the results of these meta-analyses were the phase 2R and 3 trials by Burmeister et al and Stahl et al, respectively. Burmeister et al found an improvement

in their primary endpoints of increased R0 resections and pCR with nCRT (involving 35 Gy in 15 fractions) versus nCT, making the addition of RT reasonable for locoregionally advanced disease.[32] In the phase 3 PreOperative therapy in Esophagogastric adenocarcinoma Trial (POET), although the primary endpoint of OS was not met, value was noted in the improved PFS with nCRT (both overall and within the RT field involving 30 Gy in 15 fractions) compared with nCT.[33]

Other authors have tried to increase the power of their comparisons by performing network meta-analyses. Using this technique, Chan et al found a significant OS and locoregional control benefit with nCRT versus surgery alone or with any of the other neoadjuvant therapies, including nCT.[34] There was a 97.5% probability on Bayesian analysis that nCRT was the best regimen to maximize OS; however, this came at a marginally significant risk for increased risk of postoperative mortality. Although the OS benefit with nCRT only remained significant for SCC, the adenocarcinoma analysis was limited by small patient numbers. Of note, compared with surgery alone, none of the neoadjuvant therapies led to a significant increase in postoperative mortality in direct pairwise comparisons. Neoadjuvant chemoradiation was also found to provide the optimal OS relative to other treatments in the network meta-analysis performed by Cheng et al.[35] Although they specifically excluded the FLOT4-AIO study because of a lack of subgroup OS data on GEJ cases, they did hypothesize that it might be worthwhile to assess FLOT further in the treatment of esophageal cancer. In sum, nCRT provides a benefit in local control, PFS, and pCR, at the risk of a slight increase in postoperative complications compared with nCT for esophageal adenocarcinoma (Tables 3-5, Variants 2-4).

Adjuvant therapy

CROSS and associated meta-analyses demonstrate the superiority of nCRT for locoregionally advanced esophageal cancer (T3/N+).[5] Consideration of adjuvant therapy may occur when patients are upstaged after esophagectomy for what is thought to be early stage disease. Although prospective data are sparse to guide adjuvant therapy when no neoadjuvant therapy was already given, a growing body of literature including meta-analyses helps guide practice.

Adjuvant chemoradiation versus surgery alone

Adjuvant CRT (aCRT) has been inconsistently described in prospective and retrospective literature. Contemporary meta-analyses included RCTs as well as prospective and retrospective studies.[36,37] The meta-analysis by Luo et al compared aCRT with surgery alone and demonstrated an OS benefit on subset analysis for N+ patients. Local control was improved with aCRT, but not DMFS. Toxicity was noted to be similar with no increase in pneumonitis, anastomotic stenosis, or hematologic toxicities, and the esophagitis experienced was mild and easily managed. In the meta-analysis by Kang et al, aCRT was compared with a group that consisted of surgery alone, adjuvant chemotherapy (aCT), or adjuvant RT. Treatment within the aCRT group was associated with a significant OS and locoregional control benefit without increased severe complications. About 5% had adenocarcinoma (n = 117), bringing into question the applicability of the overall results to this histology.

Pasquali et al performed a network meta-analysis of 33 RCTs comparing surgery alone to surgery plus nCT, neoadjuvant RT (nRT), nCRT, aCT, adjuvant RT, or aCRT.[38] The aggregate of neoadjuvant regimens was associated with increased OS versus surgery alone, with nCRT being the only regimen also independently associated with improved OS, but the adjuvant regimens were not associated with improved OS. The potential benefit to adjuvant therapy was likely minimized by the suboptimal treatment completion rates, noted to be only 48% to 64% in the following combined gastric and GEJ trials. Results from a small phase 2R study involving Siewert II/III patients suggest nCRT followed by surgery may be a better tolerated treatment sequence than surgery followed by aCRT.[39] For INT-0116 (approximately 20% GEJ), aCRT compared with surgery alone provided a benefit to OS, relapse-free survival, and locoregional control, but not DMFS.[40] The ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach (CRITICS) trial (17% GEJ) did not show a benefit to aCRT compared with aCT for patients receiving nCT before surgery.[41] After upfront surgery, Cancer And Leukemia Group B (CALGB) 80801 (22% GEJ) found no benefit to adjuvant epirubicin, cisplatin, and 5-fluorouracil (ECF) as opposed to 5-FU and leucovorin given before and after aCRT.[42] None of these studies differentiated Siewert III versus I/II locations. No studies meeting our selection criteria evaluated aCT after nCRT and surgery, and therefore no high-level evidence exists to support this approach. Based on the limited data, however, aCRT has been used with apparent success in the general GEJ setting.

Definitive chemoradiation

Definitive chemoradiation versus surgery alone or nCRT

In a meta-analysis by Ma et al comparing definitive chemoradiation (dCRT) to surgery alone for potentially resectable patients, 2 of the 13 included studies included an appreciable number (56% on average) of adenocarcinoma patients, thus lowering the confidence of conclusions from this analysis.[43] For these Western studies that included adenocarcinoma, the odds ratio favored surgery alone. In a meta-analysis of 32 RCTs and observational studies comparing dCRT vs nCRT followed by surgery, 2-, 3-, and 5-year OS were significantly lower for dCRT.[44] When analyzing studies with similar baseline patient prognostic characteristics, no statistically significant differences at any time point were found, but numerically the 5-year OS was almost twice as high in the nCRT group. No OS subgroup

analysis was possible for adenocarcinoma owing to the lack of studies involving this histology. The authors noted that many studies were published before the establishment of the effective regimen used in CROSS, and they proposed that contemporary nCRT patients might have better outcomes when treated according to the CROSS protocol.

Radiation Therapy Oncology Group (RTOG) 8501 and later the Intergroup 0123 trial established chemotherapy concurrent with 50 to 50.4 Gy in 25 to 28 fractions as a potentially curative RT dose in the definitive treatment of esophageal cancer, with long-term OS (ie, 10-year) at approximately 20% for the predominately squamous cell (82%-86%) populations of patients.[45-47] However, for adenocarcinoma, OS decreased to less than 20% by 3 years, with 5-year OS at 13% and only 1 of 23 patients alive at long-term follow-up. Higher RT doses did not result in improved QoL or oncologic outcomes. Although with shorter follow-up, the predominantly adenocarcinoma RTOG 0436 trial involving dCRT showed essentially equivalent 2-year OS regardless of histology.[48] None of these 3 trials required patients to be unresectable for enrollment, and the number of medically and technically operable patients was not defined. Given these data, both dCRT and nCRT remain options, although for optimal outcomes, surgery should be strongly considered.

Chemotherapy

Chemotherapy regimens (nCT/nCRT/poCT)

Regarding nCT alone, in the phase 3 United Kingdom Medical Research Council Oesophageal 05 (MRC OE05) trial for adenocarcinoma patients, randomization to the more intensive 4 cycles of neoadjuvant epirubicin, cisplatin, and capecitabine (ECX) versus 2 cycles of cisplatin and 5-FU did not improve the primary endpoint of OS, and ECX is therefore not recommended.[49] In the phase 2R Eastern Cooperative Oncology Group (ECOG) 1201 trial for adenocarcinoma patients assessing 2 novel concurrent chemotherapy regimens with RT to 45 Gy, neither the paclitaxel/cisplatin nor irinotecan/cisplatin arm was found to be superior to historic controls involving 5-FU/platinum.[50] In a network meta-analysis of 10 RCTs involving nCRT versus surgery alone, the authors compared 2 common concurrent chemotherapy regimens and found paclitaxel/platinum to be significantly better than 5-FU/platinum, but only for SCC and not adenocarcinoma.[51] In a meta-analysis of 31 RCTs and observational studies, Wang et al found that taxane-based regimens resulted in better OS than 5-FU/platinum in the settings of nCT, nCRT, and dCRT, and they provided improved response, disease control, and pathologic response rates.[52] However, taxane-based regimens were significantly associated with toxicities including grade 3 to 4 leukopenia, neutropenia, and diarrhea, and there was no breakdown in benefit by histology.

For chemotherapy-alone regimens, the FLOT4-AIO trial demonstrated significantly improved OS with FLOT versus ECF/ECX, making perioperative FLOT the regimen of choice in gastric cancer, a location that comprised 45% of the patients in this trial. Although 23% were Siewert I, the applicability of the trial results to the GEJ is in question owing to the combined grouping of Siewert II and III patients and lack of subset analyses for the GEJ vs gastric locations.[28] Therefore, there is no clear optimal chemotherapy regimen, and regimens involving paclitaxel/platinum and 5-FU/platinum are reasonable when combined with RT. Perioperative chemotherapy including FLOT may carry promise in the setting of esophageal or Siewert I/II GEJ cancers, but studies have not isolated outcomes for these tumor locations in the setting of RT.

Targeted therapy

Several studies have investigated the addition of targeted therapy in the treatment of esophageal/GEJ cancer including bevacizumab, panitumumab, and cetuximab.[53-55] In the United Kingdom MRC ST03 trial, patients with adenocarcinoma anywhere from the distal esophagus to stomach (44% lower esophageal or Siewert I-II) were randomized to 3 cycles of perioperative ECX with or without bevacizumab.[53] There was no difference in the primary endpoint of OS, and there were significantly more wound healing complications with bevacizumab. In the phase 2R German Cancer Society study involving 43% GEJ patients (Siewert undefined), the addition of panitumumab to poCT did not improve the primary endpoint involving downstaging, but the authors noted that plasma levels of pathway-associated proteins might identify a group of patients who could benefit from epidermal growth factor receptor−directed therapy.[54] In the SAKK 75/08 trial, locoregionally advanced patients (63% adenocarcinoma) received induction cisplatin/docetaxel, which was then also given concurrently with nRT to 45 Gy in 25 fractions.[55] Although the experimental arm involving cetuximab given during induction and concurrent chemotherapy as well as adjuvantly did not improve the primary endpoint of DFS, the secondary endpoint of locoregional failure for R0 patients was significantly improved. On subset analysis, the OS for adenocarcinoma was improved, albeit nonsignificantly, from 3.2 to 5.1 years. The authors of the SAKK 75/08 trial recognized that the RTOG 0436 and SCOPE-1 studies did not find a benefit to cetuximab in the definitive setting, so they hypothesized that a benefit might be limited to those receiving surgery.[48,56] As of now, there is no clear indication for targeted therapy in esophageal adenocarcinoma.

Radiation therapy

Simulation, treatment technique, and radiation dose

In modern RT practice, treatment volumes are defined based on the International Commission on Radiation Units definitions of clinical target volume (CTV) and planning target volume (PTV), using 3D conformal or intensity modulated RT (IMRT) techniques.[14,23,33] Highly conformal radiation techniques integrating computed tomography (CT)−derived images and PET imaging allow for greater

sparing of normal tissues, particularly the lungs and heart, while defining target volumes with greater specificity.[23,60]

Simulation

As a first step in radiation treatment planning, CT simulation is done using appropriate immobilization (eg, Vac-Lok), supine with arms raised.[23] Primary tumor localization may be assisted by small-volume oral contrast showing esophageal lumen narrowing with dilation superiorly. A 4-dimensional CT simulation should be obtained if available to assess excursion of the target areas over time, especially for more distal tumors that might extend to the more mobile GEJ and stomach.[23,60]

Radiation volumes

For neoadjuvant RT, the gross tumor volume (GTV) is based on the extent of disease (prechemotherapy if induction chemotherapy was given) using the initial PET/CT scan, endoscopy report, and CT scan.[2,14,23,33] The entire circumference of the esophageal wall, including any disease that extended through the wall, should be contoured as GTV, including any PET-avid or enlarged lymph nodes. Regarding CTV creation, trials included in this review have delineated the margin between 2 and 4 cm beyond the proximal and distal edges of the esophageal GTV, or 0.5 to 1 cm beyond any grossly involved paraesophageal nodes, whichever expansion is larger. The panel favors a 3- to 4-cm longitudinal expansion from the esophageal GTV, except for distal esophageal or GEJ tumors, where a 2- to 3-cm margin caudally along clinically uninvolved gastric mucosa is recommended.[14,23,33] The CTV should include the esophageal GTV with a 1-cm margin radially to cover the paraesophageal nodal region, including a 0.5- to 1-cm expansion past any grossly involved node, respecting anatomic boundaries.[14,23,33] The CTV expansion should be $\leq$0.5 cm into uninvolved organs (eg, heart, lungs, liver), given the low likelihood of microscopic extension in the absence of gross invasion.[23] For distal tumors involving or approaching the GEJ, the CTV should include the celiac and subdiaphragmatic/paracardial nodes. For distal tumors in which the CTV but not the GTV extends superiorly to the mediastinum, it is not necessary to deliberately include the anteriorly located superior mediastinal nodal stations electively other than would be encompassed by a 1-cm radial expansion of the esophagus.[23,60] However, for primary tumors extending proximally to the carina, in addition to supraclavicular nodes, upper mediastinal (prevascular/paraortic/aortopulmonary window/paratracheal/subcarinal) nodes may be considered for inclusion.[60] Splenic nodes are not typically included for esophageal or GEJ Siewert I-II tumors. In a single trial that involved radiating splenic nodes, the target was defined as the region adjacent to the proximal 2 cm of the splenic artery; this area might be incidentally included for tumors with a large amount of gastric involvement.[33]

In the CROSS trial, most patients had either distant failure or combined distant and locoregional recurrence.[57] Elective nodal coverage was not required, and the exact details of coverage were not described. Less than 5% of patients recurred in the supraclavicular fossa in both the surgery alone and nCRT groups despite infrequent coverage, but only 2% of the patients had proximal thoracic esophagus tumors, with the overall location breakdown also including 13% middle thoracic and 82% distal thoracic/GEJ. This finding suggests that inclusion of the supraclavicular area appears unnecessary for most middle and distal tumors, and the panel thus recommends limiting elective radiation of the supraclavicular regions to tumors extending superiorly to the carina. Only 7% (n = 11) of the surgery-alone arm versus 4% (n = 8) of the nCRT group experienced a celiac axis failure (P = nonsignificant), of which 90% involved distal tumors, and most patients had experienced concurrent systemic metastases. A total of 38% (n = 3) of the celiac failures in the nCRT group were at the edge of the RT field. Mediastinal recurrences occurred in 21% versus 7% of the surgery-alone versus nCRT patients, although it is not clear whether the term *mediastinum* refers to anterior nonparaesophageal nodal stations. Also, in the CROSS trial, compared with SCC in the surgery-alone arm, adenocarcinomas were less likely to experience a locoregional relapse (30% vs 47%, respectively), but this difference between histologies did not exist in the setting of nCRT (13% vs 14%). For patients undergoing nCRT, 91% of the recurrences involved a distant component.

For PTV delineation, an expansion of the CTV by 0.5 to 1 cm in all directions is typical.[23,33] For tumors involving the distal esophagus and GEJ, it is important that respiratory motion be considered, especially when using highly conformal techniques (eg, IMRT). This should include, at a minimum, fluoroscopic or 4-dimensional CT imaging to evaluate the degree of superior-inferior motion due to respiration, which can then be incorporated into the PTV margin.[23] Daily image guided RT should be strongly considered, especially for PTV expansions <0.7 cm, and because GEJ tumors can vary in location owing to diaphragmatic motion.

Dose

For preoperative RT doses of 41.4 to 50.4 Gy (1.8-2 Gy/fraction) are recommended, delivered to $\geq$95% of the PTV, with the planning objectives placing the highest priority on achieving PTV coverage and minimizing the doses to the heart and lungs.[14,17,23,29] The well-tolerated neoadjuvant dose of 41.4 Gy used in the CROSS protocol allowed a 94% resection rate, with 1% of patients having grade 3 esophagitis. Only 5% of patients experienced an in-field failure, indicating that this dose is effective, with no improved outcomes noted with higher doses. However, significant caution must be exercised to ensure patients receiving <50 Gy proceed to surgery as planned, so consider devising a radiation plan for 50 to 50.4 Gy at the start of nCRT, with the goal of stopping at 41.4 Gy if surgery is assured. Although long-term QoL in the CROSS study was similar with and without nCRT, this reassuring finding has not yet been reported with higher RT doses. In the definitive setting, RT doses higher than 50.4

Gy have not been shown to increase OS, locoregional control, or QoL; thus, 50 to 50.4 Gy in 25 to 28 fractions is typically preferred.[45-47] Although the literature involves doses ranging from 45 to 60 Gy in the postoperative setting, typically adjuvant radiation is given 3 to 4 weeks after the operation, with a dose in the range of 45 to 50.4 Gy because of inconclusive evidence of a benefit with higher doses.[37,40,41] Given the potential for increased toxicity with no benefit to higher doses in the definitive setting, there also does not appear to be any indication for escalating the dose beyond 54 Gy to the anastomosis when given adjuvantly. An initial dose of 41.4 to 45 Gy to a target including elective regions followed by a boost to a reduced volume focused on gross disease to 50.4 Gy can be considered to reduce doses to adjacent organs at risk. If organ at risk dose limits cannot be respected with 3D conformal therapy, IMRT should be considered and may carry benefit particularly for cardiac sparing.[60]

Limitations

Although the literature search limited its results to papers published between 2009 and 2019, 20 meta-analyses were included, many of which included papers published before this period. This increased the heterogeneity in staging practices and tumor location categorization, and stage migration occurred over time with PET/CT becoming part of the standard workup. Although a strength of this manuscript is the inclusion of only phase 3 or randomized phase 2 experimental trials, many meta-analyses also included observational studies, thereby decreasing the overall study quality of those manuscripts. The majority of patients in many series, especially those with predominately Eastern populations, had SCC histology. Despite enforcing a minimum number of adenocarcinoma patients required for inclusion (n = 20), often the number of adenocarcinoma patients was too small for subset analyses, thus potentially limiting the generalizability of the results.

Future Directions

Outcomes for esophageal adenocarcinoma remain suboptimal, and ongoing clinical trials are exploring different fields of research such as (1) the early assessment of tumor responsiveness by PET imaging to direct subsequent therapies; (2) the comparison of more intensive neoadjuvant/perioperative systemic therapy with nCRT; (3) novel radiation techniques including proton beam therapy; and (4) integration of immunotherapy/targeted agents/radiosensitizers into classical nCRT platforms of preoperative trials. Although pCR has been found to be prognostic, a meta-analysis found that both DFS and pCR do not reliably correlate with OS for GEJ cancers undergoing neoadjuvant therapy.[62] Therefore, OS remains the gold standard primary endpoint, and it should be evaluated when feasible.

With the goal of learning the optimal radiosensitizing chemotherapy regimen to use during nCRT, CALGB 80803 was a phase 2R study that randomized patients to 6 weeks of either induction folinic acid, 5-FU, and oxaliplatin (FOLFOX) or carboplatin/paclitaxel (NCT01333033).[63] Responders based on PET scan reassessment continued the same regimen, whereas nonresponders changed to the other regimen during concurrent RT to 50.4 Gy/28 fractions. Initial results showed that the pCR rate for nonresponders was high enough to be considered a positive trial, but there was no head-to-head comparison with nonresponders who continued the same regimen. Research efforts to help avoid the morbidity of surgery include the Comparison of Systematic Surgery Versus Surveillance and Rescue Surgery in Operable Oesophageal Cancer With a Complete Clinical Response to Radiochemotherapy study (NCT02551458). With perioperative FLOT now established as a standard of care option for gastric cancer, the Preoperative Chemotherapy vs. Chemoradiation in Esophageal/GEJ Adenocarcinoma (POWERRANGER) trial seeks to investigate whether this regimen or perioperative ECF/ECX offers any advantages versus nCRT with concurrent carboplatin/paclitaxel for esophageal or Siewert I-II GEJ adenocarcinomas (NCT01404156).[28] A randomized phase 2B trial identified decreased side effects with proton beam therapy versus IMRT as measured by the metric "total toxicity burden,"[64] leading to the phase 3 NRG GI-006 trial comparing these modalities (NCT03801876). Preliminary results from phase 3 RTOG 1010 (NCT01196390) did not find any benefit to DFS when trastuzumab was added both concurrently with nCRT and adjuvantly for operable HER2-overexpressing esopahgeal adenocarcinoma.[65] More encouraging are initial results of the Phase 3 CheckMate 577 study (NCT02743494), which showed that PD-1 inhibitor nivolumab given adjuvantly for esophageal/GEJ patients who had residual disease following nCRT and surgery improved the primary endpoint of DFS.[66] These various investigations provide hope toward further improving clinical outcomes.

Conclusions: Summary of Panel Recommendations

- For a medically operable nonmetastatic patient with a cT3 and/or cN+ adenocarcinoma of the esophagus or GEJ (Siewert I-II) the panel:

1. Recommends strongly that nCRT is usually appropriate.
2. Recommends that induction chemotherapy followed by nCRT may be appropriate.
3. Recommends with reservations nCT alone or poCT may be appropriate.
4. Does not recommend definitive chemoradiation without surgery unless surgery is declined.

- For a medically operable patient with cT2N0M0 adenocarcinoma of the esophagus or GEJ (Siewert I-II) with high-risk features including length >3 cm, high-grade

pathology, symptoms of dysphagia, and/or if pathology from EMR/ESD shows lymphovascular invasion, the panel recommends that nCRT is usually appropriate.

- For a patient with adenocarcinoma of the esophagus or GEJ (Siewert I-II) found to have pathologically involved nodes (pN+) who did not receive neoadjuvant therapy, the panel recommends that adjuvant chemoradiation is usually appropriate.

- In the setting of nCRT for adenocarcinoma of the esophagus or GEJ (Siewert I-II), the panel strongly recommends that a radiation dose between 40 and 50.4 Gy in daily fractions sizes between 1.8 and 2.0 Gy to involved disease and elective nodal areas is usually appropriate.

- In the setting of adjuvant chemoradiation for adenocarcinoma of the esophagus or GEJ (Siewert I-II), the panel strongly recommends that a radiation dose between 45 and 50.4 Gy in daily fraction sizes between 1.8 and 2.0 Gy to involved disease, the anastomosis, and elective nodal areas is usually appropriate.

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