American Radium Society™ (ARS) Appropriate Use Criteria (AUC) Systematic Review and Guidelines for Operable Esophageal and Gastroesophageal Junction Adenocarcinoma

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INTRODUCTION
While 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 account 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, led to the evolution of multidisciplinary therapeutic strategies. It is notable that the 5-yr overall survival (OS) improved from 5% to about 20% over 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 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 radiation therapy (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 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, Timing, Setting (PICOTS) framework. For the population of operable patients with adenocarcinoma of the esophagus or gastroesophageal junction, we sought to evaluate how any neoadjuvant or adjuvant treatment compared to each other, surgery alone, or definitive chemoradiation in terms of response to therapy, quality of life (QoL), or oncologic outcomes. Trial size required for inclusion was ≥50 for phase IIR and III randomized controlled trials (RCTs), and ≥100 for meta-analyses, of which at least 20 patients were required to be adenocarcinoma. With librarian (N.B.) assistance we developed literature search strategies using subject headings and combinations of keyword search terms (Appendix A) to address our PICOTS question. An extensive analysis of current medical literature covering January 1, 2009 - 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 guidelines (PRISMA) yielded a comprehensive set of relevant articles. Two authors (C.A. and J.D.) independently screened the studies and full text articles to determine the final studies included in this review as detailed in the Figure. Data was extracted from the final publications to create the Evidence Table (online supplemental document). 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 meeting all inclusion criteria except publication date (3 were published before 2009). Forward citation chaining via Web of Science was then performed on the selected documents to determine if
any eligible articles published no later than May 28, 2019 had been missed by the searches, and one was discovered. The literature was reviewed for quality of study design, cohort size, selection bias, variability of evaluation of participants in regard to time from exposure, and methods of assessments. A well-established consensus methodology (modified Delphi) was used by the expert panel to rate the appropriateness of the treatment procedures (6). Disagreement was defined as >1/3 votes occurring outside the main rating category. Studies within the introduction and future directions sections are referenced only to provide context but are not included in the Evidence Table or as the supporting evidence for oncologic interventions. For the radiation therapy section, evidence from the literature search was supplemented by recommendations from an expert contouring guidelines atlas(7). The expert panel is a group composed of radiation oncologists with expertise in the management of esophageal cancer.

SUMMARY OF LITERATURE REVIEW

TOPIC 1.

NEoadjuvant TREATMENT

Subtopic 1. Neoadjuvant chemotherapy (nCT) or Peri-operative chemotherapy (poCT) vs. Surgery alone

In the meta-analysis of RCTs comparing neoadjuvant chemotherapy (nCT) or perioperative CT (poCT) to surgery alone by Coccolini et al., a subset analysis of gastroesophageal junction (GEJ) adenocarcinoma patients noted that the addition of chemotherapy improved OS(8). However, it should be noted that the three studies included within this analysis did not distinguish between Siewert grades, thus limiting the generalizability to the more proximal Siewert I & II patients who are typically regarded as falling within the esophageal cancer paradigm(9–11). Subset analysis for adenocarcinoma (67% of the patients) also showed improved OS with the 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 while the overall resection rate, tumor recurrence, and nonfatal complication rates were not found to be different(12). The potential for increased toxicity with chemotherapy was noted. However, the OS benefit was no longer significant on subset analysis of adenocarcinoma patients, 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 this meta-analysis (2/3 adenocarcinoma), esophageal cancer patients were randomized to neoadjuvant cisplatin and fluorouracil (5-FU) vs surgery alone, noting an improvement in OS and DFS as well as R0 resections with chemotherapy(13). The next largest proportion of patients within this meta-analysis were from the Intergroup 0113 study that involved adenocarcinoma in just over half the population, which did not show any OS benefit to nCT with cisplatin and 5-FU(14). 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 in OS.
Subtopic 2.

**Neoadjuvant chemoradiation (nCRT) vs 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 operable patients as noted in the National Comprehensive Cancer Network (NCCN) guidelines(2). However, long-term outcomes are still suboptimal with surgery alone, suggesting a possible utility with neoadjuvant therapy(15–19). In the randomized, controlled phase III trial Francophone de Cancerologie Digestive (FFCD) 9901, 195 patients (29% adenocarcinoma) with Union for International Cancer Control (UICC) 5th edition Stage I or II disease (i.e. T1-2 N0-1 M0 or T3 N0 M0) were randomized to receive surgery alone vs. nCRT with 45 Gy in 25 fractions and 2 cycles of concomitant 5-FU and cisplatin(19). 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<0.049). No difference in distant metastases was noted. Subset analyses showed no differences in outcomes between adenocarcinoma and squamous cell carcinoma (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 is 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 +/- chemotherapy) or upfront surgery leads to optimal outcomes for T2N0 patients(20–22). Although the R0 resection rate increased with neoadjuvant therapy in the largest series which involved 5433 patients in 9 retrospective studies(20), this sample size did not translate to improved OS(20–22) or recurrence free survival (20, 22) for either adenocarcinoma or SCC patients in any of the 3 meta-analyses. Of note, over 80% of the patients in these series had adenocarcinoma. No differences in anastomotic leak rates or perioperative mortality were noted(20, 22). Kidane et al. noted 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. As 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 (FNA) biopsy specimens but may be evaluated in endoscopic mucosal or submucosal resection specimens. The authors also noted that neoadjuvant therapy could be considered for patients with dysphagia despite T2N0 disease on EUS, as retrospective data indicates that the greater the extent of dysphagia the higher the likelihood of ≥T3 disease with very high (>90%) specificity but low sensitivity(23). None of the studies within the meta-analyses included a quality of life (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(20).

In the Phase III ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS), locoregionally advanced patients (81% T3, 64% node positive) were randomized to surgery alone vs. nCRT with
carboplatin/paclitaxel concurrent with RT to 41.4 Gy/23 fractions (16). OS was significantly improved with nCRT for adenocarcinoma (median OS: 43.2 vs. 27.1 mos, p=0.038) and SCC patients (81.6 vs. 21.1 mos, p=0.008), and no differences in post-operative mortality or complications were noted. In a subsequent secondary analysis of the patients on the CROSS trial, although health-related QoL (HRQoL) declined during nCRT, no persistent degradation of HRQoL due to nCRT was identified compared to surgery alone on further follow-up (17). Contemporary meta-analyses of RCTs have found that nCRT provides significant improvements compared to surgery alone in OS, R0 resection rate, and locoregional control with similar postoperative mortality (15, 18). 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 for the analysis by Liu et al. that included several fewer adenocarcinoma studies, the benefit only trended towards 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 survival benefit found with nCRT. Therefore, nCRT followed by surgery appears to provide a survival benefit compared to surgery alone for locoregionally advanced (i.e. ≥T3 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) and/or symptoms of dysphagia, as these factors are associated with clinical understaging.

Subtopic 3.
Neoadjuvant chemoradiation (nCRT) with or without Induction Chemotherapy
When compared to standard nCRT, in a randomized phase II trial Ajani et al. reported no significant increase in the primary endpoint of pathologic complete response (pCR) rate with or without induction chemotherapy involving 5-FU/oxaliplatin followed by nCRT to 50.4 Gy with further 5-FU/oxaliplatin. Secondary endpoints including OS and complications were all similar (24). In a secondary subset analysis, it was found that 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 (25). In addition, in the phase IIR NEOSCOPE (Neo-adjuvant Study of Chemoradiotherapy in Oesophageal Cancer) study, with a primary endpoint of pCR, patients were randomized to either carboplatin/paclitaxel vs. capecitabine/oxaliplatin with RT to 45 Gy/25 fractions following 6 weeks of induction capecitabine/oxaliplatin, with only the carboplatin/paclitaxel arm achieving a pCR rate worthy of further investigation (29.3% vs 11.1%, respectively) (26). Induction chemotherapy is a promising approach for patients with esophageal cancer.

Subtopic 4.
Neoadjuvant chemotherapy (nCT) vs. Neoadjuvant chemoradiation (nCRT)
Although results are mixed regarding differences in outcomes between nCT and nCRT, overall RT appears beneficial when added to chemotherapy in the neoadjuvant setting for esophageal/GEJ adenocarcinoma patients. Although
contemporary meta-analyses addressing adenocarcinoma have shown that adding RT significantly increases the pCR and R0 resection rates for esophageal and GEJ patients compared to nCT alone, this addition has not translated to an improvement in OS(27–29). As might be expected, RT decreased the risk of locoregional relapse, but distant metastases-free survival (DMFS) was not improved. Although the network meta-analysis of RCTs by Cai et al. found peri-operative 5-fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT) to be superior to all other neoadjuvant regimens, it included all patients from the FLOT4-AIO study in the analysis even though the majority of patients had either gastric or Siewert III disease, limiting the generalizability of their findings to esophageal or Siewert I-II GEJ adenocarcinoma (30, 31). Long-term results of the initial report of the Phase IIR 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 as compared to nCT was not associated with an improvement in progression-free survival (PFS) or OS (32). 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 following nCRT (9%) compared to nCT (1%) (p=0.02)(32, 33). A secondary analysis of the NeoRes I trial that evaluated QoL found a significant improvement in the dysphagia score following nCT vs. nCRT, with the authors hypothesizing RT-induced esophagitis led to worse dysphagia(34). Also driving the results of these meta-analyses were the phase IIR and III trials by Burmeister et al. and Stahl et al., respectively. Burmeister et al. found an improvement in their primary endpoint of increased R0 resections and pCR with nCRT (involving 35 Gy/15 fx) as compared to nCT, making the addition of RT reasonable for locoregionally advanced disease(35). In the phase III POET (PreOperative therapy in Esophagogastric adenocarcinoma Trial) study, although the primary endpoint of OS was not met, value was noted by the improved PFS with nCRT (both overall & within RT field involving 30 Gy/15 fx) compared to nCT(36).

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 vs. surgery alone with or without any of the other neoadjuvant therapies, including nCT(37). 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 post-operative mortality. Although the OS benefit with nCRT only remained significant for SCC, the adenocarcinoma analysis was limited by small patient numbers. Of note, compared to surgery alone, none of the neoadjuvant therapies led to a significant increase in post-operative mortality in direct pairwise comparisons. Neoadjuvant CRT was also found to provide the optimal OS relative to other treatments in the network meta-analysis performed by Cheng et al.(38). Although they specifically excluded the FLOT4-AIO study due to 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 to nCT for esophageal adenocarcinoma.
TOPIC 2. ADJUVANT THERAPY

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

Subtopic 1. Adjuvant Chemoradiation (aCRT) vs. Surgery Alone

Adjuvant CRT has been inconsistently described in prospective and retrospective literature. Recent contemporary meta-analyses have included RCTs as well as prospective and retrospective studies (39, 40). The meta-analysis by Luo et al. compared aCRT to surgery alone, and it demonstrated an OS benefit on subset analysis for lymph node positive 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 to a group that consisted of surgery alone, adjuvant chemotherapy (aCT), or adjuvant radiation therapy (aRT). Treatment within the aCRT group was associated with a significant OS and loco-regional control benefit without an increase in severe complications. Only about 5% of the patients included 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, aRT, or aCRT(41). The aggregate of neoadjuvant regimens was associated with increased OS vs. 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 is likely minimized by the suboptimal treatment completion rates, noted to be only 48-64% in the following combined gastric and GEJ trials. Results from a small phase IIIR study involving Siewert II/III patients suggests nCRT followed by surgery may be a better tolerated treatment sequence (42). For INT-0116 (approximately 20% GEJ patients), aCRT as compared to surgery alone provided a benefit to OS, relapse-free survival, and locoregional control, but not DMFS(43). The CRITICS trial (17% GEJ) did not show a benefit to aCRT compared to aCT for patients receiving nCT before surgery.(44) Following upfront surgery, CALGB 80801 (22% GEJ) found no benefit to adjuvant epirubicin, cisplatin, fluorouracil (ECF) as opposed to 5-FU and leucovorin given before and after aCRT(45). It should be noted that none of these studies differentiated between Siewert III and Siewert I/II locations. No studies meeting our selection criteria evaluated aCT following nCRT and surgery, and therefore no high level evidence exists to support this approach but based on the limited data, aCRT has been used with apparent success in the general GEJ setting.
TOPIC 3.
DEFINITIVE CHEMORADIATION (dCRT)

Subtopic 1.
dCRT vs Surgery Alone or nCRT

In a meta-analysis by Ma et al. comparing dCRT to surgery alone for potentially resectable patients, only 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(46). 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 was significantly lower for dCRT(47). 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 due 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 protocol of this study.

RTOG 8501 and later the Intergroup 0123 trial established chemotherapy concurrent with 50-50.4 Gy as a potentially curative RT dose in the definitive treatment of esophageal cancer, with long term OS (i.e. 10-year) at approximately 20% for the predominately squamous cell (82-86%) populations of patients(48–50). However, when broken down by histology OS dropped below 20% for adenocarcinoma 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 noted regardless of histology(51). None of these three 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.

TOPIC 4.
CHEMOTHERAPY

Subtopic 1.
Chemotherapy regimens (nCT/nCRT/poCT)

Regarding neoadjuvant chemotherapy alone, in the phase III United Kingdom Medical Research Council Oesophageal 05 (MRC OE05) trial for esophageal adenocarcinoma patients, randomization to the more intensive 4 cycles of neoadjuvant epirubicin, cisplatin and capecitabine (ECX) versus 2 cycles of cisplatin and 5-FU (CF) did not improve
the primary endpoint of OS, and ECX is therefore not recommended(52). In the phase IIR ECOG 1201 trial for adenocarcinoma patients assessing two novel concurrent chemotherapy regimens with RT to 45 Gy, neither arm (neither paclitaxel/cisplatin nor irinotecan/cisplatin) was found to be superior to historic controls involving 5-FU and platinum (53). In a network meta-analysis of 10 RCTs involving nCRT versus surgery alone, the authors compared two common concurrent chemotherapy regimens and found paclitaxel plus platinum to be significantly better than 5-FU plus platinum, but only for SCC and not adenocarcinoma (54). 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 also provided improved response rates, disease control rates, and pathologic response rates (55). However, taxane-based regimens were significantly associated with toxicities including grade 3-4 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 vs. ECF/ECX, making peri-operative FLOT the regimen of choice in gastric cancer the location of which comprised 45% of the patients in this trial. Although 23% of the patients had Siewert I disease, the applicability of the results of the trial to the GEJ is in question due to the grouping of Siewert II and III patients and the lack of subset analyses for the GEJ vs gastric locations(31). Therefore, there is no clear optimal chemotherapy regimen, and regimens involving paclitaxel plus platinum and 5-FU plus platinum are reasonable when combined with RT, and perioperative chemotherapy including FLOT may carry promise in the setting of GEJ cancers but studies have not examined it in the setting of RT.

Subtopic 2.

Targeted therapy

There have been several studies investigating the addition of targeted therapy in the treatment of esophageal/GEJ cancer including bevacizumab, panitumumab, and cetuximab(56–58). In the UK 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(56). There was no difference in the primary endpoint of OS, and there were significantly more wound healing complications in the bevacizumab group. In the phase IIR German Cancer Society study reported by Stahl et al. involving 43% GEJ patients (Siewert undefined), the addition of panitumumab to perioperative chemotherapy 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 that could benefit from epidermal growth factor receptor (EGFR)-directed therapy(57). 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/25 fractions(58). 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 time to locoregional failure for R0 patients was significantly improved. On subset analysis the OS for adenocarcinoma was improved albeit non-significantly 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 with surgery in the treatment plan.(51, 59). As of now, there is no clear indication for targeted therapy in esophageal adenocarcinoma.

TOPIC 5.
RADIATION THERAPY

Simulation, treatment technique, and radiation dose
In modern radiotherapy practice, treatment volumes are defined based on the International Commission on Radiation Units (ICRU) definitions of clinical target volume (CTV) and planning target volume (PTV), utilizing 3D conformal techniques or intensity-modulated radiation therapy (IMRT) techniques(16, 26, 36). These techniques allow for greater sparing of normal tissues, particularly the lungs and heart. Highly conformal radiation techniques require the radiation oncologist to define target volumes with greater specificity, utilizing CT-derived images and PET imaging (7, 26).

Subtopic 1.
Simulation

As a first step in radiation treatment planning, CT simulation is done using appropriate immobilization (e.g. vac-lok or alpha cradle), in a supine position with the arms raised(26). Narrowing of the esophageal lumen with dilation superiorly can be noted with small volume oral contrast and may assist with primary tumor localization. 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 (7, 26).

Subtopic 2.
Radiation volumes

For neoadjuvant RT, the gross tumor volume (GTV) is based on the extent of disease (pre-chemotherapy if induction chemotherapy was given) using the initial PET/CT scan, endoscopy report, and CT scan(2, 16, 26, 36). The entire esophageal wall, including any disease that has extended through the wall should be contoured as the GTV as well as any PET/CT-avid or enlarged lymph nodes. For creation of the CTV, trials included in this review have delineated the superior extent between 2-4 cm margin above the proximal edge of the GTV, or 0.5-1 cm above any grossly involved paraesophageal nodes, whichever is more cephalad, and the panel favors a 3-4 cm expansion superiorly. The nodal CTV should involve a 0.5-1 cm expansion past the grossly involved node, respecting anatomic boundaries(16, 26, 36). For distal esophageal or GEJ tumors, a 2-3 cm margin along clinically uninvolved gastric mucosa is recommended(16, 26, 36). For radial borders the CTV should include the esophagus and GTV with a 1 cm margin in all directions to cover the paraesophageal nodal region. The CTV expansion should be ≤0.5 cm into uninvolved organs (e.g. heart,
lungs, liver, etc.) given the low likelihood of microscopic extension in the absence of gross invasion(26). For distal tumors involving or approaching the GEJ, the CTV should include the celiac and subdiaphragmatic/paracardial nodes. To respect the proximal margin on gross tumor for distal tumors in which the CTV extends superiorly to the mediastinum only, it is not mandatory 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 (7, 26). However, for tumor extending proximally to the carina, in addition to supraclavicular nodes upper mediastinal (prevascular/para-aortic/aorta-pulmonary window/paratracheal/subcarinal) nodes may be considered for inclusion as well(7). Splenic nodes are not typically included for esophageal or GEJ Siewert I-II tumors. In a single trial that notes targeting splenic nodes, it was defined as the region adjacent to the proximal 2 cm of the splenic artery, and they may be incidentally included for tumors with a large amount of gastric involvement(36).

In the CROSS trial, most patients had either distant failure or combined distant and locoregional recurrence. Elective nodal coverage was not required, and the exact details of coverage was not described. Under 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 esophageal tumors with the overall location breakdown also including 13% middle thoracic and 82% distal thoracic/GEJ. This findings suggest that inclusion of the supraclavicular area appears unnecessary for most middle and distal tumors, and the panel recommends including the supraclavicular regions for tumors extending superior to the carina. Only 7% (n=11) of the surgery alone arm vs. 4% (n=8) of the radiation group experienced a celiac axis failure (p = non-significant), of which 90% involved distal tumors, and most patients had experienced concurrent systemic metastasis. Thirty-eight percent (n=3) of the celiac failures in the nCRT group were at the edge of the RT field. Mediastinal recurrences occurred in 21% vs. 7% of the surgery alone vs. nCRT patients, although it is not clear whether the term mediastinum refers to anterior non-paraesophageal nodal stations. Also in the CROSS trial, as compared to SCC in the surgery alone arm, adenocarcinoma was less likely to experience a locoregional relapse (30% vs. 47%, respectively) than SCC, but this finding did not hold true for nCRT patients (13% vs. 14%). For patients undergoing nCRT, 91% of the recurrences involved a distant component.

For PTV delineation, an expansion of the CTV by 0.5-1cm in all directions is used(26, 36). For tumors involving the distal esophagus and GEJ, it is important that respiratory motion be considered especially when using highly conformal techniques (IMRT). This should include, at a minimum, fluoroscopic or 4-dimensional CT imaging to estimate the degree of superior-inferior motion due to respiration, which can then be incorporated into the PTV expansion(26). Daily image guided radiation therapy (IGRT) should be strongly considered, especially for PTV expansions <0.7 cm, and because GEJ tumors can vary in location due to diaphragmatic motion.

Subtopic 3.

Dose
For preoperative radiation therapy doses of 41.4-50.4 Gy (1.8–2 Gy fractions) are recommended, delivered to ≥95% of the PTV with the planning objectives placing the highest priority on achieving PTV coverage and minimizing the doses to normal lung and heart(16, 19, 26, 32). The well-tolerated neoadjuvant dose of 41.4 Gy used in the CROSS protocol allowed a 94% resection rate, with only 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 50-50.4 Gy at the start of CRT, with the option 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, radiation doses higher than 50.4 Gy have not been shown to increase survival, local/regional control or QoL, and so 50-50.4 Gy in 25-28 fractions is typically preferred (48–50). Although the literature involves doses ranging from 45-60 Gy in the postoperative setting, typically adjuvant radiation is given 3 to 4 weeks after the operation, with a dose in the range of 45-50.4 Gy due to inconclusive evidence of a benefit with higher doses(40, 43, 44). Given the potential for increased toxicity with no benefit to higher doses in the definitive setting, there does not appear to be any indication for escalating the dose beyond 54 Gy to the anastamosis. An initial treatment volume to 41.4-45 Gy followed by a boost to a planning volume including gross disease to 50.4 Gy can be considered to reduce doses to adjacent organs. If dose limits to organs at risk cannot be respected with 3D conformal therapy, IMRT should be considered and may carry benefit for cardiac sparing(7).

TOPIC 6.
LIMITATIONS
Although the literature search limited its results to papers published between 2009-2019, 22 meta-analyses were included, many of which included papers published before this time period. This introduced heterogeneity in staging practices and tumor location categorization, and with PET/CT becoming part of the standard workup stage migration has occurred over time. Although a strength of this manuscript is the inclusion of only Phase III or randomized Phase II 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 the squamous cell carcinoma 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.

TOPIC 7.
FUTURE DIRECTIONS
Outcomes for esophageal adenocarcinoma remain suboptimal, and ongoing clinical trials are exploring different fields of research such as 1) the comparison of a more intensive neoadjuvant/perioperative CT with CRT; 2) the introduction of immunotherapy into classical nCRT platforms of preoperative trials; 3) the early assessment of tumor
responsiveness by PET imaging to direct subsequent therapies, and 4) the addition of targeted agents or radiosensitizers into the neoadjuvant regimen. 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. 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 IIR study that randomized patients to 6 weeks of either induction FOLFOX or carboplatin/paclitaxel (NCT01333033)(60). Responders based on PET scan reassessment continued the same regimen, whereas non-responders changed to the other regimen during concurrent RT to 50.4 Gy/28 fractions. Initial results showed that the pCR rate for non-responders was high enough to be considered a positive trial, but there was no head to head comparison with non-responders who continued the same regimen. We await the results of RTOG 1010, A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma (NCT01196390). Research efforts to help avoid the morbidity of surgery includes the ESOSTRATE study: Comparison of Systematic Surgery Versus Surveillance and Rescue Surgery in Operable Oesophageal Cancer With a Complete Clinical Response to Radiochemotherapy (NCT02551458). These various investigations provide hope towards improving clinical outcomes.

SUMMARY OF PANEL RECOMMENDATIONS/CONCLUSIONS

- For a medically operable patient with a cT3 or N+ and M0 adenocarcinoma of the esophagus or gastroesophageal junction (Siewert I-II) the panel:
  1. Recommends strongly that neoadjuvant chemoradiation is usually appropriate.
  2. Recommends that induction chemotherapy followed by neoadjuvant chemoradiation may be appropriate.
  3. Recommends with reservations neoadjuvant chemotherapy alone or perioperative chemotherapy 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 gastroesophageal junction (Siewert I-II) with high risk features including length >3 cm, high grade pathology, symptoms of dysphagia, or if pathology from EMR shows lymphovascular invasion, the panel recommends that neoadjuvant chemoradiation is usually appropriate.

- For a patient with adenocarcinoma of the esophagus or gastroesophageal junction (Siewert I-II) found to have pathologically involved nodes (pN+) who did not receive any neoadjuvant therapy, the panel recommends that adjuvant chemoradiation is usually appropriate.
- In the setting of neoadjuvant chemoradiation for adenocarcinoma of the esophagus or gastroesophageal junction (Siewert I-II), the panel strongly recommends that a radiation dose between 40-50.4 Gy in daily fractions sizes between 1.8-2.0 Gy to involved disease and elective nodal areas is usually appropriate.

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

**Summary of Evidence (pending final reference Evidence Table)**

Of the 51 references that are cited in the ARS Appropriateness Criteria Esophageal Adenocarcinoma document that were found through the search strategy, all 51 of them are categorized as therapeutic references including 31 well-designed studies (Phase III and IIR) and 20 references that are meta-analysis studies. These 51 references published from 1998 to 2019 formed the Evidence Table found in the Supplemental Materials.

1     (esophag* or oesophag* or gastroesophag* or gastro-esophag* or "gastro-oesophag*").ti,ab,kf. (176096)
2     (cancer* or carcinoma* or neoplas* or adenocarcinoma* or malignan* or tumor* or tumour*).ti,ab,kf. (3163127)
3     1 and 2 (69644)
4     exp *Esophageal Neoplasms/ (40889)
5     exp *Neoplasms/ (2780090)
6     exp *Esophagus/ (31869)
7     5 and 6 (5498)
8     3 or 4 or 7 (74581)
9     (resect* or esophagectom* or oesophagectom* or surg* or opera* or adjuvant* or neoadjuvant*).ti,ab,kf. (2754273)
10    exp Esophagectomy/ (9218)
11    su.fs. (1905698)
12    9 or 10 or 11 (3577588)
13    (radiotherap* or radiat* or irradiat* or chemoradi* or chemotherap* or adjuvant* or neoadjuvant*).ti,ab,kf. (1035545)
14    exp Radiotherapy/ (176454)
15    exp antineoplastic agents/ or exp antineoplastic protocols/ (1094704)
16    exp combined modality therapy/ (249945)
17    rt.fs. (184745)
18    th.fs. (1774289)
19    or/13-18 (3547253)
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. (768147)
21    clinical trial, phase II/ or clinical trial, phase III/ or clinical trial, phase IV/ (464443)
22    exp Meta-Analysis/ (102077)
23    validation studies/ (95475)
24    exp controlled clinical trial/ (573006)
25    or/20-24 (1151901)
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. (70983)
30    28 not 29 (805)

******************************************************************************
Records Identified through database searching:
Ovid Medline: n = 805
Embase: n = 1888
Cochrane Central: n = 1265
Total: n = 3958

Figure: Selection flow chart for the systematic review
Clinical Condition: Operable Esophageal Cancer

Variant 1: 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 para-esophageal nodes and 3 gastrohepatic nodes measuring up to 2.5 cm in size noted on EUS and PET/CT.

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<th>Final Tabulations</th>
<th>Group Median Rating</th>
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<td>3</td>
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<td>3</td>
<td>L</td>
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<td>(37, 38, 46, 47)</td>
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<td>S</td>
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If RT: Dose to Involved Primary/Nodes (if Neoadjuvant)‡

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<td>40–41.4 Gy / 20-23 fx</td>
<td>A</td>
<td>3 3 3 8</td>
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<tr>
<td>50–50.4 Gy / 25-28 fx</td>
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<td>S</td>
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<td>54 Gy / 30 fx</td>
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<td>59.4–60 Gy / 33-30 fx</td>
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If RT: Dose to Elective nodes‡

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<td>U</td>
<td>2 2 3 1 1</td>
<td>3</td>
<td>(36, 47)</td>
<td>1</td>
<td>L</td>
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<td>36 Gy / 18-20 fx</td>
<td>M*</td>
<td>1 5 3 2 5*</td>
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<td>L</td>
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<td>40–41.4 Gy / 20-23 fx</td>
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<td>45–46 Gy / 25-23 fx</td>
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<td>(26)</td>
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<td>S</td>
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<td>50–50.4 Gy / 25-28 fx</td>
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<td>(24, 47)</td>
<td>1</td>
<td>S</td>
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If RT: Elective nodal regions‡

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<th>Final Tabulations</th>
<th>Group Median Rating</th>
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<td>U</td>
<td>7 3</td>
<td>1</td>
<td>(16, 32)</td>
<td>1</td>
<td>M</td>
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<tr>
<td>Mediastinal pre-vascular &amp; paraortic/Paratracheal/AP Window</td>
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<td>(16)</td>
<td>1</td>
<td>L</td>
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<td>Subcarinal</td>
<td>M</td>
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<td>(16)</td>
<td>1</td>
<td>L</td>
<td></td>
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<tr>
<td>Para-esophageal</td>
<td>A</td>
<td>1 1 8 9</td>
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<tr>
<td>Celiac/Paracardial/Subdiaphragmatic</td>
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<td>1 2 7 9</td>
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<tr>
<td>Gastrohepatic ligament</td>
<td></td>
<td>1 3 6 9</td>
<td>(16, 26, 36)</td>
<td>1</td>
<td>S</td>
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</table>
Clinical Condition: Operable Esophageal Cancer

Variant 2: Clinical Stage III, T3 N0 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 para-esophageal node noted on EUS and PET/CT in a medically operable patient. Bronchoscopy was negative for trachea-esophageal fistula.

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<tr>
<td>nCRT</td>
<td>A</td>
<td></td>
<td>2</td>
<td>8</td>
<td>(15, 16, 27–29, 37, 38)</td>
<td>1</td>
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<td>↑</td>
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<tr>
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<td>A</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>7</td>
<td>(24, 26)</td>
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<td>M*</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>5*</td>
<td>X</td>
<td>(44)</td>
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<tr>
<td>dCRT</td>
<td>M*</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>5*</td>
<td>X</td>
<td>(46, 48–51)</td>
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<td>4</td>
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<td>4</td>
<td>(8, 9, 11, 13, 14, 20, 32, 37, 38)</td>
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<tr>
<td>poCT</td>
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<td>4</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>(8, 10)</td>
<td>1</td>
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<tr>
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<td>2</td>
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<td>2</td>
<td>1</td>
<td>1</td>
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**If RT: Dose to Primary/Involved Nodes (if neoadjuvant)**†

<table>
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<th>Final Tabulations</th>
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<tr>
<td>30-30.6 Gy / 15-17 fx</td>
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<td>2</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>(36)</td>
<td>1</td>
</tr>
<tr>
<td>40-41.4 Gy / 20-23 fx</td>
<td>A</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>(16, 32, 47)</td>
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</table>

† NOTE: Based on encouraging initial results from CALGB 80803.

‡ Key Radiation points:
1. In the neoadjuvant setting, 40-50.4 Gy in fraction sizes between 1.8-2.0 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.

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

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

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

**Disagree:**
- Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

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

**SO:**
- Study Quality: (1, 2, 3, or 4) of the references listed

**SOE:**
- Strength of Evidence: S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

**SOR:**
- Strength of Recommendation (of Rating Category): ↑ Strong; ↓ Weak; - Additional considerations do not strengthen or weaken the panel’s recommendation

**SQ:** Study Quality: (1, 2, 3, or 4) of the references listed

**SOE:**
- Strength of Evidence: S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

**SOR:**
- Strength of Recommendation (of Rating Category): ↑ Strong; ↓ Weak; - Additional considerations do not strengthen or weaken the panel’s recommendation
### Key Radiation Points:
- Neoadjuvant doses of 40-50.4 Gy in fraction sizes between 1.8-2.0 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.
- Elective radiation of the paraesophageal, supraclavicular, mediastinal pre-vascular and para-aortic, paratracheal, AP 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.

### References:
- Lists the references associated with the recommendation.
- Study Quality (1, 2, 3, or 4) of the references listed
- Strength of Evidence: S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion
- Strength of Recommendation (of Rating Category): ↑ Strong; ↓ Weak; - Additional considerations do not strengthen or weaken the panel’s recommendation

### Variant 3:
Clinical Stage IIB, cT2 cN0 M0 high grade‡ (signet-ring) adenocarcinoma of the lower thoracic esophagus noted on EUS, extending from 32-36 cm‡ from the incisors in a medically operable patient. No dysphagia§ present. No elevated FDG uptake noted on PET.
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<td>3</td>
<td>1</td>
<td>5</td>
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<td>Surgery alone</td>
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<td>M*</td>
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<td>3</td>
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<td>1</td>
<td>1</td>
<td>3</td>
<td>5*</td>
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| If RT: Dose to Primary (if neoadjuvant)         |                 |                   |                     |          |           |    |     |     |
| 30–36.6 Gy / 15-17 fx                          | U               | 4                 | 1                   | 3        | 1         | 2   | (36) | 1   | L   | †   |
| 40–41.4 Gy / 20-23 fx                          | A               | 2                 | 4                   | 3        | 8         | (16, 32) | 1   | S   | †   |
| 45–46 Gy / 25-23 fx                            | A               | 1                 | 2                   | 9        | 2         | (19–22) | 1   | S   | †   |
| 50–50.4 Gy / 25-28 fx                          | A               | 1                 | 2                   | 5        | 1         | 8   | (20–22) | 3   | M   | †   |
| 54 Gy / 30 fx                                  | M*              | 1                 | 2                   | 4        | 3         | 1   | 5*  |     |
| 59.4–60 Gy / 33-30 fx                          | U               | 5                 | 3                   | 1        | 1         | N/A | N/A | EO  | †   |

| If RT: Dose to Elective nodes                  |                 |                   |                     |          |           |    |     |     |
| Supraventricular                               | U               | 6                 | 1                   | 2        | 1         | 1   | (16, 32) | 1   | M   | †   |
| Mediastinal pre-vascular & para-aortic/Paratracheal/AP Window | M* | 1 | 6 | 1 | 1 | 1 | 5* | (16) | 1 | L | - |
| Subcarinal                                      | M*              | 1                 | 1                   | 2        | 3        | 2   | 5*  | (16) | 1 | L | - |
| Para-esophageal                                 | A               | 1                 | 3                   | 6        | 9         | (16, 26, 32, 36) | 1 | S | † |
| Celiac/Paracardial/Subdiaphragmatic             | A               | 1                 | 2                   | 3        | 4         | 8   | (16, 26, 32, 36) | 1 | S | † |
| Gastrohepatic ligament/ Lesser Curvature        | A               | 1                 | 4                   | 2        | 3         | 8   | (16, 26, 36) | 1 | S | † |
| Splenic *                                       | U               | 4                 | 5                   | 1        | 3         | (36) | 1   | L   | †   |

| Key points:                                    |                 |                   |                     |          |           |    |     |     |
| † Tumor size >3 cm, poor differentiation, and LVI 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).

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Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.  
Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate
**Final Tabulations:** A histogram of the number of panel members who rated the recommendation as noted in the column heading (i.e. 1, 2, 3, etc.)

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

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

**SQ:** Study Quality: (1, 2, 3, or 4) of the references listed

**SOE:** Strength of Evidence: S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

**SOR:** Strength of Recommendation (of Rating Category): \(\uparrow\) Strong; \(\downarrow\) Weak; - Additional considerations do not strengthen or weaken the panel’s recommendation
**Clinical Condition:** Operable Esophageal Cancer

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

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<td>45-46 Gy / 25-23 fx</td>
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<td>M</td>
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<td>M*</td>
<td>2 1 4 4</td>
<td>5*</td>
<td>X</td>
<td>(16)</td>
<td>1</td>
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<td>-</td>
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<td>(16, 26, 32, 36)</td>
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‡Key Radiation point:
- Adjuvant radiation doses between 45-50.4 Gy in fraction sizes between 1.8-2.0 Gy to the anastomosis & elective nodal areas are preferred in the adjuvant setting. Doses to the anastomosis of 54 Gy and above are not preferred.

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APPENDIX B:

Abbreviation Key

SCC = squamous cell carcinoma
GEJ = gastroesophageal junction
CRT = concurrent chemoradiation therapy
RT = radiation therapy
IGRT = image guided radiation therapy
Fx = fractions
GTV = Gross Tumor Volume
CTV = Clinical Target Volume
PTV = Planning Target Volume
nCRT = neoadjuvant concurrent chemoradiation therapy
nCT = neoadjuvant chemotherapy
nRT = neoadjuvant RT
aRT = adjuvant radiation therapy
aCT = adjuvant chemotherapy
aCRT = adjuvant concurrent chemoradiation therapy
dCRT = definitive concurrent chemoradiation therapy
iCT = induction chemotherapy given before CRT
poCT = perioperative chemotherapy
TTO = total thoracic esophagectomy
MIO = minimally invasive esophagectomy
EMR = Endoscopic mucosal resection
OS = overall survival
pCR = pathological complete response
cCR = clinical complete response
PFS = progression free survival
RCT = randomized controlled trial
RR = risk ratio
OS = overall survival
PFS = progression-free survival
DFS = disease-free survival
DMFS = distant metastases free survival
QoL = Quality of Life
EUS = Endoscopic ultrasound
CT = Computed Tomography
FNA = fine needle aspiration
PET/CT = Positron Emission Tomography/Computed Tomography
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting
CALGB = Cancer and Leukemia Group B
RTOG = Radiation Therapy Oncology Group
ECOG = Eastern Cooperative Oncology Group
MRC OE02 = Medical Research Council Oesophageal 02
MRC OE05 = Medical Research Council Oesophageal 05
FFCD = Francophone de Cancerologie Digestive
NCCN = National Comprehensive Cancer Network
UICC = Union for International Cancer Control
LVI = lymphovascular invasion
FOLFOX = Folinic acid, 5-Fluorouracil, and oxaliplatin
5-FU = 5-fluorouracil
FLOT = 5-fluorouracil, leucovorin, oxaliplatin, docetaxel
ECX = Epirubicin, cisplatin and capecitabine
ECF = epirubicin, cisplatin, fluorouracil
EOF = epirubicin, oxaliplatin fluorouracil
EOX = epirubicin, oxaliplatin, capecitabine
CF = cisplatin, fluorouracil
HRQoL = health related quality-of-life
EGFR = epidermal growth factor receptor
IMRT = Intensity Modulated Radiation Therapy
ICRU = International Commission on Radiation Units
NEOSCOPE: NEO-adjuvant Study of Chemoradiotherapy in OesoPhagEal Cancer
NEORES: Neoadjuvant Chemotherapy Versus Radiochemotherapy for Cancer of the Esophagus or Cardia
POET: PreOperative therapy in Esophagogastric adenocarcinoma Trial
CRITICS: ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach
CROSS: ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study
REFERENCES


