

American Radium Society Appropriate Use Criteria for a Multidisciplinary Treatment Approach to the Management of Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

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Conflict of Interest Disclosure Statement

All panelists were required to declare all conflicts of interest for the previous 36 months prior to initiating work on this document. These complete disclosure forms are retained by the American Radium Society™ in perpetuity. The ARS Appropriate Use Criteria Steering Committee reviewed the

disclosures with the chair and co-chair of this document and approved participation of the panelists prior to starting development of this work. Disclosures potentially relevant to the content of this guideline are provided:

Dr. Attallah reports consulting fees from Aptitude Health, Curio Science, GLG, Targeted Oncology, ZoomRx.

Dr. Donington reports personal fees from Amgen, AstraZeneca, BMS, Merck, Roche/Genentech

Dr. Edelman reports personal fees from AstraZeneca, Takeda, Glaxo Smith Kline, Omega Therapeutics, Novocure, InterVenn, WindMil, Seattle Genetics, Regeneron/Sanofi, Flame Consulting, Proventus Consulting, GE Healthcare Consulting, BioAlta Consulting, Replimmune Consulting, Coherus Consulting, and AnHeart

Dr. Jaboor reports grant support from Merck, Belgene, Guardant, and Haystack, consulting fees from Merck, AstraZeneca, JNJ, Radialogica, IMX Medical, travel/meeting support from Merck, AstraZeneca, and payment for expert testimony from Deichert

Dr. Jethwa reports honoraria from RadOncQuestions.com, LLC.

Dr. Jin reports grant support from Lilly, GlaxoSmithKline, Daiichi Sankyo/Astra Zeneca, Exelis, Elvar

Dr. Lee reports honoraria from Varian, ViewRay, AstraZeneca; consulting fees from Varian, ViewRay, AstraZeneca, Genentech, Johnson & Johnson, Roche, RTOG foundation, and travel/meeting support from Radiosurgery Society

Dr. Miller reports honoraria from Horizon CME

Dr. Park reports grant support from Merck Sharp & Dohme, personal fees from AstraZeneca, BMS, Daiichi Sankyo, G1 Therapeutics, Galera Medical, RefleXion Medical, Regeneron, and other support from Incyte and AstraZeneca

Dr. Rimner reports grant support from Varian Medical Systems, AstraZeneca, Merck, Boehringer Ingelheim, Pfizer, and NIH, and personal fees from AstraZeneca, Merck, and MoreHealth

Dr. Small reports personal fees from Carl Zeiss; and travel/meeting support for ACR, NRG Oncology, Carl Zeiss.

Dr. Tao reports honoraria from Total Health and Henry Ford Hospital, and travel/meeting support from Total Health and the American Board of Radiology (ABR)

Acknowledgements

Ellie See, Talley Management Group for her attention to detail and diligence in this project.

Introduction

Globally, esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer-related death. In the United States, esophageal cancer ranks 14th in incidence and 13th in mortality among all cancers^{1,2}. The majority of global cases are squamous cell carcinoma (SCC), but in Western countries, esophageal adenocarcinoma (EAC) has become the predominant subtype. In the United States, its incidence has increased markedly over the past several decades, rising from 0.42 per 100,000 in 1975 to 3.6 cases per 100,000 in 2020, but with incidence plateauing in recent years^{1,2}. Esophageal cancer is typically defined as that of the upper, middle, and distal thoracic esophagus, as well as Siewert I and II locations of the gastroesophageal junction (GEJ). 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) is widely accepted for locoregionally advanced disease.

In 2021, the American Radium Society (ARS) published Appropriate Use Criteria (AUC) for Operable Esophageal and Gastroesophageal Junction Adenocarcinoma³, at which time the predominant standard approach for patients with advanced EAC who are medically operable and deemed to have technically resectable disease was neoadjuvant chemoradiation (nCRT) followed by surgical resection, as established by the CROSS trial⁴. Noted in those guidelines was a network meta-analysis of RCTs that found perioperative 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) to be superior to all other neoadjuvant regimens, but it included all patients from the FLOT4-AIO study even despite most of those patients having either gastric or Siewert III disease, limiting the generalizability to esophageal or Siewert I-II GEJ adenocarcinoma. Since the publication of those initial guidelines, multiple landmark randomized controlled trials (RCTs) have been published directly comparing perioperative systemic therapy approaches with nCRT or adjuvant chemoradiation (CRT). Additional practice-changing trials integrating immunotherapy into various treatment regimens have also since been reported. Furthermore, active surveillance has been investigated as an option for patients with resectable disease who want to avoid a potentially morbid procedure such as esophagectomy. Despite these advances, long-term survivors are rare, with 5-year overall survival (OS) rates around 20%¹. Therefore, a strong knowledge of the literature is essential to obtain the current best outcomes and improve on them in this rapidly evolving clinical landscape.

With these advances resulting in evolving treatment options, the ARS multidisciplinary panel sought to update their guidelines of medically operable and technically resectable EAC. Oncologic outcomes and quality of life were assessed. Due to the publication of high-quality RCTs to address major prior gaps in our knowledge, this update no longer relies on meta-analyses involving retrospective studies or network analyses with indirect comparisons. These timely and novel guidelines were developed with a multidisciplinary committee, including surgeons, medical oncologists, radiation oncologists and gastroenterologists, critical in the era of modern systemic therapy. The key questions

associated with our Population, Intervention, Comparator, and Outcome (PICO) based methods included: 1) What is the appropriate neoadjuvant treatment strategy for patients with resectable locally advanced EAC or GEJ cancers based on various clinical and stage presentations?; 2) What is the role for adjuvant therapy following surgical resection for patients with resectable EAC or GEJ cancers based on pathologic findings?; and 3) What is the optimal treatment strategy in patients with technically operable EAC or GEJ cancers that ultimately become medically inoperable after neoadjuvant systemic therapy?

These updated guidelines incorporate recent changes to esophageal adenocarcinoma treatments which integrates immunotherapy into first-line and perioperative settings, often combined with chemotherapy, and a focus on perioperative systemic therapy which has replaced the standard neoadjuvant chemoradiation approach. A non-operative approach with close surveillance for select patients with complete clinical response following neoadjuvant therapy is also discussed.

Methodology

This ARS AUC multidisciplinary committee was comprised of all key specialties (thoracic and gastrointestinal radiation and medical oncologists, gastroenterologists, and thoracic surgeons). Using the Population, Intervention, Comparator, and Outcome (PICO) framework, the evidence regarding treatment outcomes was assessed using Cochrane and PRISMA 2020 methodology^{5, 6}. Eligible studies included randomized Phase 2 and 3 trials, meta-analyses of RCTs, and retrospective secondary analyses of RCTs published between January 1, 2019 and July 7, 2025 in the Ovid Medline database. Trial size required for inclusion was >25 patients with EAC or GEJ (Siewert I & II). Appendix A contains the database search strategy designed by a librarian-trained information specialist (CJA). Two authors independently screened the comprehensive list of articles, and one assessed the full text articles to determine the final studies included in the Summary of the Literature Review that advised our recommendations (Appendix B). Discrepancies between the reviewers were resolved by consensus. Of the 861 articles identified using the search strategy, 22 were selected for inclusion that met all inclusion criteria. Of the 52 citations in the original bibliography, 19 citations were retained in the final document. Articles were removed from the original bibliography if they were more than 10 years old and did not contribute to the updated key question evidence or they were no longer cited in the revised narrative text. In total, 41 references were selected for inclusion as evidence (Appendix C). Study type and quality for these references were assessed via ARS AUC methodology (Appendix C). The systematic review PRISMA 2020 checklist confirms the completion of essential elements (Appendix D). Well-established RAND-UCLA consensus methodology (modified Delphi) was used by the expert panel to rate the appropriateness of the treatment options⁷, with a total of 2 rounds of voting employed by the group. 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 referenced outside the “Summary of Literature Review” are included to provide context, but unless they are also cited within the “Summary of Literature Review,” they were not used by the committee to guide recommendations. The project proposal as well as this executive summary were reviewed and approved by the ARS AUC Steering Committee, which includes a librarian with expertise in systematic reviews. For further details on ARS AUC methodology guidelines, see <https://www.americanradiumsociety.org/page/aucmethodology>.

Summary of Literature Review

TOPIC 1. NEOADJUVANT TREATMENT

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

In meta-analyses of randomized controlled trials, perioperative (poCT) or neoadjuvant chemotherapy (nCT) for gastric and GEJ adenocarcinoma has demonstrated a survival benefit over surgery alone, although this benefit appears heterogeneous and influenced by tumor location, chemotherapy regimen, and patient-specific prognostic factors. In the meta-analysis by Coccolini et al., a subset analysis of patients with GEJ adenocarcinoma showed improved overall survival (OS) with the addition of chemotherapy⁸. However, the three studies included in this analysis did not distinguish between Siewert subtypes, limiting generalizability to more proximal Siewert I and II tumors, which are typically considered within the esophageal cancer paradigm. Although a subset analysis comprising 67% adenocarcinoma also demonstrated an OS benefit with chemotherapy, the magnitude and consistency of this benefit remain uncertain across studies. This uncertainty is further highlighted by prior trials, included in a Cochrane review by Kidane et al., which reported an improvement in OS and R0 resection rates with nCT for resectable thoracic esophageal cancer, but no differences in overall resection rates, tumor recurrence, or nonfatal complications⁹. Notably, in a subset analysis limited to patients with adenocarcinoma, the OS benefit was no longer statistically significant. The Medical Research Council (MRC) OE02 trial, the largest study included in the Kidane analysis and consisting of approximately two-thirds adenocarcinoma, demonstrated improved OS, disease-free survival (DFS), and R0 resection rates with neoadjuvant cisplatin and 5-fluorouracil (5-FU) compared to surgery alone¹⁰. In contrast, the Intergroup 0113 trial, which also included a majority of adenocarcinoma patients, did not show an OS benefit from the same chemotherapy regimen. Locoregional failure rates were equivalent between groups, with a numerically higher, although not statistically significant, incidence of distant failure in the surgery-alone arm¹¹. A clear OS benefit to chemotherapy versus surgery was reported in the MRC Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial with ECF given perioperatively, although only a

quarter of the patients had disease in the distal esophagus or GEJ, and the remaining patients had gastric cancer¹².

An individual patient data meta-analysis of 4 RCTs involving systemic therapy has underscored the importance of prognostic factors¹³. The authors found that older patients achieved comparable OS and disease specific survival (DSS) to younger patients, and dependent on performance status should be offered the same treatment options. While women experience more grade ≥ 3 gastrointestinal side effects than men (e.g. nausea, vomiting, and diarrhea, all approximately 5% to 10%), there was no difference in the number of women going to surgery. Even after adjusting for baseline stage, women still had superior OS compared to men. Another post-hoc analysis of 2 of the same trials analyzed by Athauda et al. revealed that patients with esophageal mucinous adenocarcinoma have improved OS from chemotherapy vs surgery alone¹⁴. Taken together, poCT appears superior to nCT, which showed mixed results regarding an OS benefit.

Subtopic 2. Neoadjuvant Chemoradiation (nCRT) versus Surgery alone

Early-stage esophageal cancer invading into the muscularis propria (clinical T2) is generally not considered suitable for endoscopic therapy; for operable patients the preferred therapy remains esophagectomy. However, long-term outcomes with surgery alone remain suboptimal, especially given risks of occult nodal disease and recurrence, suggesting a role for neoadjuvant or combined-modality therapy. In the French Federation of Digestive Oncology (FFCD) 9901 randomized phase 3 trial, 195 patients (29% adenocarcinoma) with stage I–II disease (i.e. T1-2 N0-1 or T3 N0) were randomly assigned to surgery alone vs nCRT (45 Gray [Gy]/25 fractions [fx] with two cycles of 5-FU and cisplatin)¹⁵. The trial showed no differences in OS or R0 resection rate, but there was higher postoperative mortality in the nCRT arm (11.1% vs 3.4%, $P < .049$). Most patients had T2 (56.4%) and N0 (72.3%), but the subgroup of patients who had both T2 and N0 were not separately analyzed, thus limiting definite conclusions of nCRT for that population.

In the phase 3 ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS), T2-3 and/or node-positive (N+) patients (81% T3, 64% N+) were randomized to surgery alone versus nCRT with carboplatin/paclitaxel (CP) concurrent with radiation therapy (RT) to 41.4 Gy/23 fx^{4, 16}. While Eastern Cooperative Oncology Group performance status (ECOG) 2 patients were allowed on the trial, the enrolled population consisted only of ECOG 0 (81%) and 1 (19%) patients. OS was improved with nCRT for patients with adenocarcinoma (median OS: 43.2 vs 27.1 months, $P = .038$) and squamous cell carcinoma (SCC) (81.6 vs 21.1 months, $P = .008$), and no differences in postoperative mortality or complications were noted. At a median follow-up of 12.3 years, long-term results show that the 10% benefit in OS seen at 5 years (43% vs 33%) was maintained at 10

years (36% vs 26%). This OS benefit appears to be driven by an improvements in locoregional control, with less isolated locoregional relapse (8% vs 18%) and combined locoregional/distant relapse (13% vs 22%). However, similar distant relapse rates (27% vs 28%) highlight a need for further optimizing systemic therapy. In both the nCRT and surgery alone groups, at least 85% of locoregional and distant recurrences occurred by 5 years, with no locoregional recurrences after 6 years, and no distant progression after 8 years. In a secondary analysis of the patients on the CROSS trial, although health-related quality of life (QoL) declined during nCRT, no persistent degradation of health-related QoL due to nCRT was identified compared with surgery alone on further follow-up, and no excess deaths due to nCRT were noted¹⁷. This contrasts with the findings of NEOadjuvant chemotherapy versus Radiochemotherapy for cancer of the ESophagus or cardia (NeoRes I), which found worse long-term effects from the addition of RT compared to chemotherapy alone, including worse long-term cough, possibly because of less intense chemotherapy and lower RT dosing used in CROSS¹⁸. Contemporary meta-analyses of RCTs have similarly found that nCRT provides improvements compared with surgery alone in OS, R0 resection rate, and locoregional control, with similar postoperative mortality¹⁹. Therefore, nCRT followed by surgery appears to provide an OS benefit compared with surgery alone for locoregionally advanced (ie, T3 and/or N+) patients. nCRT has the potential to benefit T2N0 adenocarcinoma patients with high-risk features (length ≥ 3 cm, high grade, or lymphovascular invasion (LVI) on endomucosal resection or endoscopic submucosal dissection) and/or symptoms of dysphagia, as these factors are associated with clinical understaging. In summary, nCRT results in superior outcomes compared to surgery alone for patients with EAC/GEJ adenocarcinoma.

Subtopic 3. Neoadjuvant Chemoradiation (nCRT) with or without Induction Chemotherapy

In a randomized phase 2 trial, Ajani et al reported no increase in the primary endpoint of pathologic complete response (pCR) rate for 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 nCRT²⁰. Secondary endpoints, including OS and complications, were similar. In a secondary subset analysis, induction chemotherapy led to 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 approach²¹. North Central Cancer Treatment Group (NCCTG) N0849 was a randomized phase 2 trial that closed early due to a futility analysis showing a lack of improvement in the primary endpoint of improved pCR with induction versus no induction chemotherapy before nCRT²². However, in a post hoc analysis, similar to Ajani et al, induction chemotherapy was associated with longer OS and DFS among patients with well/moderately differentiated tumors, but not among patients with poorly/undifferentiated tumors. 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 CP or capecitabine/oxaliplatin with RT to 45 Gy/25 fx after 6 weeks of induction capecitabine/oxaliplatin; only the CP arm achieved a pCR rate worthy of further investigation (29.3% vs 11.1%, respectively)²³.

Cancer and Leukemia Group B (CALGB) 80803 was a randomized phase 2 trial that did not seek to directly evaluate the benefit of induction therapy directly, but rather sought to optimize neoadjuvant therapy for resectable EAC by using positron emission tomography (PET) response to make an early change in systemic therapy²⁴. A response on PET was defined as $\geq 35\%$ decrease in standard uptake value (SUV). The trial hypothesized that making an early change after induction chemotherapy for PET nonresponders would increase pCR rates after nCRT (50.4 Gy/28 fx from historic values of $< 5\%$ to a value of 20%. There was no difference in PET responders with folinic acid (leucovorin), fluorouracil (5-FU), and oxaliplatin (FOLFOX) (64.9%) versus CP (56.1%) ($P = .22$). The pCR rates for PET nonresponders after induction FOLFOX who crossed over to CP or after induction CP who changed to FOLFOX was 18.0% and 20%, respectively. For PET responders who continued on FOLFOX, the pCR rate was 40.3%, whereas responders receiving CP only had a pCR of 14.1% ($P = .001$). While it is not clear whether switching chemotherapy regimens is what led to pCR rates comparable to other contemporary trials (23-29%)^{4, 25, 26}, the 53% 5-year OS rate for the FOLFOX group that responded is one of the highest reported 5-year OS rates for locoregionally advanced EAC. Australasian Gastro-Intestinal Trials Group (AGITG) DOCTOR is another trial that evaluated PET response after induction chemotherapy (cisplatin/5-FU), also defining a response as $\geq 35\%$ decrease in SUV²⁷. Poor responders, randomized to intensified therapy with docetaxel/cisplatin/5-fluorouracil (DCF) or DCF plus RT (DCFRT), achieved higher rates of major histological response (63% for DCFRT vs. 20% for DCF alone), and DCFRT improved progression-free survival and locoregional control to levels comparable to early responders. However, intensified regimens were associated with increased grade 3/4 toxicity, especially with DCFRT. In CALGB 80803²⁴, quality of life was most impacted during CRT but generally returned to baseline six months after surgery, mirroring the long-term recovery seen after 2 years in AGITG DOCTOR²⁷. Both CALGB 80803 and AGITG DOCTOR indicate this imaging-based adaptive approach may represent a rational platform to further evaluate neoadjuvant regimens with the goal of tailoring therapy for patient subsets. In summary, induction chemotherapy is a reasonable approach for esophageal cancer patients, particularly as part of a response-adapted plan.

Subtopic 4. Comparison of concurrent chemotherapy options during CRT

Given success with gastric cancer, Radiation Therapy Oncology Group (RTOG) 1010 investigated

whether trastuzumab improved outcomes when combined with nCRT for operable EAC patients with untreated human epidermal growth factor receptor 2 (HER2)-overexpressing adenocarcinoma. While trastuzumab did not increase toxicity, it also did not provide any oncologic benefits²⁵. Therefore, there are no data supporting the addition of this targeted agent to CRT.

Subtopic 5. Neoadjuvant (nCT)/perioperative chemotherapy (poCT) versus Neoadjuvant chemoradiotherapy (nCRT)

CROSS definitively showed a benefit to nCRT over surgery alone⁴, leading to randomized studies examining the role of nCRT versus systemic therapy while building a more effective systemic therapy regimen. Common among earlier studies were the findings of improved pCR rates with nCRT that did not translate to an OS benefit, with more recent data showing superior OS with perioperative FLOT vs. nCRT. Included among these studies was the phase 2R NeoRes I²⁸. Patients received cisplatin/5-FU with or without concurrent RT to 40 Gy/20 fx. A secondary QoL analysis of the NeoRes I trial found a greater improvement in the dysphagia score after nCT compared with nCRT, with the authors hypothesizing that RT-induced esophagitis led to worse dysphagia²⁹. Additional 2R and 3 trials by Burmeister et al.³⁰ and Stahl et al.³¹ (POET), respectively, also showed improvements in pCR with nCRT versus nCT, but without an OS benefit.

The FLOT4- Arbeitsgemeinschaft Internistische Onkologie (AIO) study showing superiority of perioperative FLOT over epirubicin, cisplatin, and 5-FU (ECF) involved mainly gastric or Siewert III disease, limiting its generalizability to EAC or Siewert I-II GEJ adenocarcinoma³². However, it led to the development of landmark nCRT versus poCT trials. Neoadjuvant trial in Adenocarcinoma of the Oesophagus and Oesophago-Gastric Junction International Study (NEO-AEGIS) was a multi-institution phase 3 trial for patients with T2-3 and/or N+ EAC that compared the CROSS regimen (preoperative RT (41.4 Gy/23 fx) with concurrent CP) with neoadjuvant chemotherapy alone (either the MAGIC regimen [epirubicin plus cisplatin or oxaliplatin plus fluorouracil used before 2018] or the FLOT4-AIO regimen [fluorouracil, leucovorin, oxaliplatin, and docetaxel]³³. However, most patients received the modified MAGIC regimen (86%), and the study was closed early due to an interim futility analysis showing no benefit to OS with poCT. While the study was underpowered and incomplete, the authors concluded that poCT and nCRT had continued clinical equipoise.

TOPGEAR was an international study evaluating poCT with or without nCRT to 45 Gy/25 fx³⁴. In both groups, poCT was epirubicin, cisplatin, and capecitabine or 5-Fluorouracil (ECF/ECX) until the publication of FLOT4-AIO, and thereafter, similar to NEO-AEGIS, a switch to FLOT was allowed, with 1/3 of patients ultimately receiving the newer regimen. While 2/3 of the patients in NEO-AEGIS had a tumor of the lower esophagus or Siewert I location, in TOPGEAR, the most proximal tumors were Siewert II or III making up 1/3 of the overall total, with the exact split unspecified. While pCR

and R0 rates favored trimodality therapy, there was no difference in OS, operative mortality, or quality of life measures.

The ESOPEC trial was the first to use FLOT (4 cycles pre- and post-operatively) as the sole peri-operative regimen, which was compared to the CROSS regimen of weekly CP and 41.4 Gy/23 fx²⁶. While T2-4 and/or N+ pts of the esophagus or GEJ were eligible, patients were predominantly T3 (74%) and N+ (80%). Most patients had tumors of the esophagus/Siewert I location (46%) or Siewert II (31%), with only 2% Siewert III. With a median f/u of 55 months, 3-year OS and PFS were superior for FLOT vs nCRT at 57% vs 51% and 52% vs 35%, respectively. The OS benefit was driven by a decrease in those with isolated distant metastases for FLOT (crude rate, 20%) versus nCRT (crude rate, 33%). Simultaneous locoregional and distant metastases occurred in about 12% of each group. There was only a marginal improvement in locoregional recurrences with nCRT (4% vs 8%), less than that seen in other studies. While supplementary data shows that a non-mandatory PET revealed a larger number of patients enrolled with M1 disease on the CRT arm, given that FLOT prevented distant metastases more than CRT prevented locoregional recurrences, the results showing the superior OS with FLOT still stand. Rates of R0 resection were similar between groups (~95%), and this was the first randomized trial to show a lower pCR with nCRT (10.1%) versus the chemotherapy arm (17%). Postoperative complications were similar, with a 90-day mortality estimate of 3.1% with FLOT vs 5.6% with nCRT. Yet, toxicity concerns with FLOT are valid. Serious adverse events were common in each group, 47% for FLOT and 42% for nCRT. The only serious AE with an incidence of ≥5% was pneumonia (5.3% FLOT vs 8.7% CRT). It should be noted that both groups included patients up to age 80 years (CRT) and even above (maximum of 86 years old for FLOT), with a median age of 63 years old. For the FLOT group, to receive clinical benefit it was not necessary to receive all of the planned chemotherapy, as 87% received all 4 planned preoperative cycles, but only 53% received all 4 postoperatively. For the nCRT group, 89% received the full planned RT dose, and 67% and a further 17% received all 5 or 4 of the planned cycles of chemotherapy, respectively. In summary, ESOPEC established perioperative FLOT as the neoadjuvant treatment of choice over nCRT in the treatment of EAC or GEJ adenocarcinoma for ECOG 0-1 patients expected to be able to tolerate this poCT regimen [**Variants 1 & 2**].

Subtopic 6. Optimizing perioperative systemic therapy options

Targeted therapy

In a randomized phase 2/3 trial evaluating the addition of vascular endothelial growth factor receptor-2 inhibitor ramucirumab to poCT for GEJ and gastric patients, no improvement in the primary endpoint of pCR was found, so the transition to phase 3 was not pursued³⁵. Notably, patients with Siewert type I tumors receiving transthoracic esophagectomy with intrathoracic

anastomosis showed an increased risk of serious postoperative complications after ramucirumab, so recruitment was stopped for those patients early in the study's progress. For HER-2 positive resectable gastric cancer, a phase 2 trial found improved pCR rates without improvement in survival outcomes in patients with HER-2 positive resectable gastric cancer, but with higher rates of diarrhea and leukopenia with the addition of trastuzumab and pertuzumab³⁶. In summary, there are no data supporting the addition of targeted agents to perioperative systemic therapy.

Immunotherapy

KEYNOTE-585 was a phase 3 study evaluating whether pembrolizumab added to poCT improved outcomes in resectable gastric or gastroesophageal adenocarcinoma³⁷. About 20% of the 804 patients had GEJ adenocarcinoma, but the authors did not specify how many were Siewert Type II versus III. Notably, most patients received cisplatin-based chemotherapy, with a FLOT cohort being developed after FLOT-AIO. Although neoadjuvant and adjuvant pembrolizumab versus placebo increased the pCR, it did not improve oncologic outcomes such as event-free survival (EFS) or OS. More recently, MATTERHORN, a phase 3, international trial, evaluated FLOT with or without durvalumab for GEJ/gastric patients (T3-4 91%, 70% N+)³⁸. Tumor location was 2/3 gastric & 1/3 GEJ, and Siewert I and II patients comprised 9% and 15% of the total patient population, respectively. The primary endpoint was met showing an improvement in event-free survival with durvalumab, and there was a numerically improved OS at 2-years as well (76% vs 70%). The trial included 5% microsatellite instability-High (MSI-H) and 90% programmed cell death ligand 1 (PD-L1) ≥1% patients, with all subgroups benefiting from the addition of immunotherapy to poCT [see **Variants 1 & 3**]. Grade 3 or 4 adverse events were not increased with durvalumab (72% vs 71%), and grade 5 events were likewise similar (5% vs 4%). Similar to ESOPEC²⁶, the only non-hematologic grade 3 or 4 toxicity occurring in either group was diarrhea (6% for each group). Durvalumab was just as likely to be completed as placebo in the neoadjuvant (97% vs 95%) and adjuvant settings (52% vs 52%). Similar to ESOPEC, the vast majority of patients completed all assigned neoadjuvant FLOT (95% vs 92%), and about half completed all cycles of adjuvant FLOT (48% vs 52%). Subset analyses showed all groups benefited from durvalumab when added to perioperative FLOT. While there are currently no data for adding immunotherapy to perioperative FLOT for esophageal tumors that do not involve the GEJ, for patients with Siewert I-II GEJ adenocarcinoma, outcomes may be improved by adding durvalumab to FLOT.

TOPIC 2. ADJUVANT THERAPY

Subtopic 1. Adjuvant Chemotherapy versus Surgery alone

While there are multiple phase 3 trials for the use of poCT as discussed above, no studies met our search criteria requiring a RCT or meta-analysis of RCTs involving the use of adjuvant

chemotherapy alone in patients with resected EAC or GEJ adenocarcinoma who did not receive neoadjuvant therapy. Given the preponderance of evidence for neoadjuvant therapy in patients with locally advanced disease, the question of adjuvant RT commonly arises when patients are pathologically upstaged (either because of N+ or based on T stage) after undergoing upfront resection or if an emergent surgery is performed. As the majority (~80%) of patients in the poCT trials involved cT3 or N+ patients, patients found to have more advanced disease than expected could be reasonably offered adjuvant FLOT depending on performance status^{26, 34}. **[Variant 4]**

Subtopic 2. Adjuvant Immunotherapy versus Surgery alone

The CheckMate 577 phase 3 trial evaluated the role of adjuvant immunotherapy in patients for whom neoadjuvant therapy failed to achieve a pCR after nCRT and resection³⁹. Eligible patients had stage II and III esophageal or GEJ cancer and residual disease after nCRT followed by an R0 resection were randomized 2:1 to receive nivolumab or placebo for a year. The median DFS was 22.4 months in those patients receiving adjuvant nivolumab versus 11.0 months with placebo (hazard ratio [HR] 0.69, p<0.001), meeting the primary endpoint. The use of adjuvant immunotherapy led to both improvements in locoregional control as well as a decrease in distant metastasis. The DFS benefit persists across histological subtypes and PD-L1 expression levels in pre-specified subgroup analyses. The effect in adenocarcinoma (HR 0.75; 0.59 – 0.96) was certainly attenuated as compared to SCC (HR 0.61; 0.42 – 0.88) **[Variant 5]**. Grade 3+ adverse event rates were 13% in the nivolumab arm and 6% with placebo, and overall safety was in line with immune-related adverse event rates seen across multiple immunotherapy trials across drug type, indication, and solid tumor histology. Importantly, as discussed in prior sections, the MATTERHORN³⁸ and ESOPEC²⁶ trials have introduced new standards of care into the neoadjuvant treatment, offering perioperative FLOT or FLOT/durvalumab as potentially superior options to CRT. Thus, the CheckMate 577³⁹ paradigm of adjuvant immunotherapy based on pathologic findings are no longer as widely applicable. Patients being treated on the MATTERHORN paradigm typically receive immunotherapy after surgery per the regimen; however, there are currently no data to support the use of immunotherapy-based adjuvant treatment in patients who did not receive neoadjuvant therapy.

The VESTIGE phase 2R trial specifically examined the role of adjuvant dual checkpoint immunotherapy in patients who underwent nCT that were deemed to be at high risk of recurrence based on poor pathologic features (R1 resection or ypN-positive disease)⁴⁰. The study randomized patients to adjuvant chemotherapy (same regimen given neoadjuvantly) versus 1 year of ipilimumab and nivolumab, and failed to show a benefit with IO for the primary endpoint of DFS. Therefore, while evidence exists for poCT with immunotherapy for patients with Siewert I GEJ and adjuvant immunotherapy following nCRT if there is residual disease at esophagectomy for esophageal/GEJ

patients, there is no proven role to adjuvant immunotherapy in the setting of nCT, even among patients with high-risk features.

Subtopic 3. Adjuvant Radiation/CRT

Similar to with adjuvant chemotherapy, there are no RCTs evaluating adjuvant RT or CRT for patients with resected EAC or GEJ adenocarcinoma who did not receive neoadjuvant systemic therapy. However, the phase 3 CRITICS trial involved neoadjuvant capecitabine/oxaliplatin or epirubicin/cisplatin followed by resection (D2 in 84%), after which patients were then randomized to adjuvant chemotherapy or CRT⁴¹. The randomization occurred pre-resection, and resultingly only about 60% of patients in each arm were able to receive their intended assigned adjuvant regimen. While the intention-to-treat analysis did not show an OS between the 2 arms, a subsequent per-protocol analysis showed that for those patients who started the allocated post-operative treatment, OS was improved for the adjuvant chemotherapy group over adjuvant CRT. This finding remained even in subgroup analyses for those with R1 disease (present in 10% of adjuvant CRT and 7% of adjuvant chemotherapy groups) and pathologically node-positive patients. A major limitation of this trial is that only 15% of the patients in each arm (72 patients total) had adenocarcinoma involving the GEJ, of which a substantial proportion likely had Siewert III disease, as only 10% of all patients had an esophago-cardiac resection rather than a gastrectomy. These data suggest that adjuvant CRT may not provide a clear benefit over adjuvant CT for R1 or node-positive patients [**Variant 6**].

TOPIC 3. DEFINITIVE CHEMORADIATION (dCRT)

Subtopic 1. dCRT +/- active surveillance versus nCRT

While the typical standard of care for EAC is trimodality therapy, there may be patients who ultimately do not undergo surgical resection. Reasons for this may be due to patient preference, development of metastatic disease, or a decline in patient performance status after neoadjuvant therapy. With a true neoadjuvant approach, the likelihood of proceeding to surgery is high. In CROSS, nCRT was very well tolerated, with 94% proceeding to surgery as compared to 99% in the surgery alone group^{4, 16}. Of the 10 nCRT patients who did not proceed to surgery, 7 had disease progression, 1 developed a second cancer, and 2 patients declined surgery, with no patient considered medically unfit for surgery. In ESOPEC, just 7% of patients in both the nCRT and perioperative FLOT groups did not proceed to surgery, and the reasons for not doing so were nearly equivalent in each group (split evenly between developing metastases, having an adverse event, and withdrawing from the study)²⁶. In MATTERHORN, surgery was completed in 87%, with adverse events as the cause for surgery not being performed very rare in the durvalumab (0.6%) vs. placebo (0.4%) groups³⁸. A surgical delay from adverse events occurred in only 2.3% vs 2.6% of the durvalumab vs placebo arms, respectively.

For those patients unable to undergo or hoping to avoid surgery, there are data involving the use of dCRT. RTOG 8501 and subsequently the Intergroup 0123 trial established chemotherapy concurrent with 50 to 50.4 Gy/25 to 28 fx as a potentially curative regimen in the definitive treatment of esophageal cancer, with long-term OS (ie, 10-year) at approximately 20% of patients who were predominately SCC (82%-86%)⁴²⁻⁴⁴. However, for adenocarcinoma, in RTOG 8501 OS decreased to less than 20% by 3 years, with 5-year OS at 13% and only 1 of 23 patients alive with at least 5 years of follow-up⁴⁴. Higher RT doses did not result in improved QoL or oncologic outcomes^{42, 43}. The predominantly adenocarcinoma RTOG 0436 phase 3 trial (79% T3-4, 66% N+) evaluated dCRT with 50.4 Gy/28 fx and concurrent cisplatin and paclitaxel with or without cetuximab⁴⁵. No benefit to cetuximab versus the control arm was noted for any outcome, including 2- and 3-year OS (45% & 34% vs 44% & 28%), complete clinical response (cCR) rate for adenocarcinoma (54% vs 53%), and quality of life measures. For all patients, the 3-year local failure rate was approximately 50%. None of these 3 trials required patients to be unresectable for enrollment, and the number of medically and technically operable patients was not described.

More recently, the SANO trial evaluated active surveillance versus standard surgery for locoregionally advanced esophageal cancer (73% T3-4, 54% N+) including both adenocarcinoma and SCC⁴⁶. While ECOG 0-2 were allowed on trial, only 3 patients (1%) were ECOG 2. Notably, due to concerns for fibrosis making surgical resection more challenging, only 41.4 Gy/23 fx was used along with weekly CP, as per the CROSS regimen. Of the 776 patients included in the study, only 35% had a complete clinical response (cCR), and that subgroup was randomized to active surveillance versus standard surgery. Active surveillance included clinical evaluation (PET/CT, endoscopic ultrasound [EUS] with fine needle aspiration [FNA] of suspicious lymph nodes, and EGD with at least four bite-on-bite biopsies) every 3 months for the first year, every 4 months in year 2, every 6 months in year 3, and once annually in years 4 and 5. Histology did not affect cCR rates, with this rate comparable to the pCR rate of 23% seen for adenocarcinoma patients in the CROSS trial. Notably, 27% of those randomized to surgery that declined and crossed over to the active surveillance group, defined as the “modified intention-to-treat (ITT) population.” The trial met its non-inferiority goal of <15% worse OS in the active surveillance group, with 2-year OS actually slightly higher for the experimental arm (74% vs 71% for the modified ITT group and 75% vs 70% for the original ITT group). Of those going onto active surveillance, just over one-third had persistent cCR, and over 10% developed an early distant metastasis by 6 months. With the sum of these groups totaling about 50%, the authors concluded that about half of those undergoing active surveillance avoided unnecessary surgery due to the presence of micrometastatic disease already present at the time surgery. Complications related to the surgery were similar, with a perioperative

mortality of 4% versus 5% for the active surveillance and standard surgery groups, respectively. However, with a durable cCR only occurring in just over 10% of patients, there is need for improved outcomes. With a cCR rate of nearly 50% that was durable in RTOG 0436, a dose of 50.4 Gy/28 fx may be more likely to provide successful locoregional control in an active surveillance plan, although the safety of surgical salvage has not been defined in this population in a randomized trial⁴⁵. It should be noted that the high crossover rate indicates a strong interest in avoiding surgery among esophageal patients. Global quality of life questionnaires indicated superior outcomes at 6 and 9 months for the active surveillance group, but from 12 months onward there were no differences seen. Therefore, active surveillance following dCRT with a definitive RT dose in the range of 40-50.4 Gy via 1.8-2 Gy/fx is an appropriate option.

For patients that start as esophagectomy candidates but become medically inoperable due to systemic therapy toxicity, the RT dose could potentially be further advised from the ARTDECO trial⁴⁷. In this phase 3 trial, medically inoperable or unresectable patients were randomized to one of two 28-fraction courses: 50.4 Gy (1.8 Gy/fx; standard dose, SD) versus 61.6 Gy (2.2 Gy/fx). No difference was observed in 3-year local PFS for the entire cohort (70% for SD vs 73% for HD, p = nonsignificant [NS]), nor was there any observed local PFS difference for adenocarcinoma that made up 38% of the patients (61% for SD vs 61% for HD, p = NS). There was no OS difference observed between arms (3-year OS 42% vs 39% for SD and HD, respectively). There were no differences in toxicities, with Grade 4 at 12% for SD versus 14% HD. However, grade 5 toxicities were numerically higher in the HD arm at 10% vs 5% for SD. Therefore, caution should be applied when using definitive RT doses >50-50.4 Gy outside of a clinical trial.

Given the advances in poCT, it is possible that induction or consolidation chemotherapy could increase the chance of a sustained cCR. However, with a pCR rate of 16% for TOPGEAR (poCT followed by nCRT) as compared to a pCR rate of 23% for CROSS adenocarcinoma patients, improvement cannot be assumed or assured^{4, 16, 46}. One of the best phase 2R or 3 pCR rate reported is 40% as noted on CALGB 80803, indicating response directed induction chemotherapy followed by CRT should be studied prospectively as a non-operative approach²⁴. CROSS and SANO were the only 2 trials (see Table 1) that allowed up to ECOG 2 versus all of the nCT/poCT options that are available are for ECOG 0-1 patients, but it should be noted that only 1% of the patients in SANO had an ECOG 2. Therefore, if a patient's ECOG worsens to 2 from 0-1 during poCT, it is reasonable to offer that patient CRT as the next step. If surgery is definitely not going to be pursued, a dose of 50-50.4/25-28 fx should be employed. A dose of 41.4 Gy/23 fx could be used if salvage surgery remains a possibility as it did for SANO. Given these data, dCRT with or without

active surveillance remain an option, although data are more limited for the active surveillance approach for patients who start with a plan for resection [**Variant 7**].

Limitations

A strength of the manuscript is the requirement of the data to come from phase 3 or randomized phase 2 trials, but some interpretations were based on unplanned retrospective analyses of patient subsets to help guide practice. There remain many studies that inconsistently used PET for initial staging, leading to potential errors in staging, but presumptively this was balanced between arms. There remain several trials where SCC made up a significant portion of the patient population, limiting the direct applicability to adenocarcinoma patients. Additionally, while our inclusion criteria included only Siewert I-II GEJ AC, many papers did not specify the Siewert classification, or they combined Siewert II and III. Thus, low numbers of Siewert I and II in what are likely predominantly Siewert III GEJ populations could limit the applicability of the data.

Future Directions

Despite the flurry of advances in recent years, much work remains left to be done to improve the quality of life and OS for patients with EAC. ESOPEC and MATTERHORN clearly demonstrate the importance of perioperative systemic therapy with multiagent chemotherapy and with immunotherapy, respectively, in this patient population. Notably, at a median follow-up of 43 months, the final analysis of the MATTERHORN study revealed an OS benefit to durvalumab added to FLOT regardless of PD-L1 status (HR 0.78, $P < 0.0001$) [ESMO 2025]. However, it remains an open question as to whether there is a role for neoadjuvant RT along with intensified multi-agent chemotherapy +/- immunotherapy to further improve outcomes. The RACE trial (NCT04375605) is a phase 3 trial randomizing patients to neoadjuvant FLOT or FLOT followed by CRT (45 Gy with concurrent 5-FU and oxaliplatin) prior to surgical resection and further adjuvant systemic therapy, with a primary endpoint of 5-year progression free survival. Should this trial show an improvement in outcomes, it may also facilitate improved clinical complete response rates and further consideration of active surveillance per a SANO approach. In the interim, the SANO-2 study (NCT05491616) is a nationwide prospective cohort study for active surveillance in clinical complete responders after nCRT to gain more data in a larger sample size to further support this strategy. Among many efforts to further investigate the incorporation of immunotherapy into management of locoregional disease, the KEYNOTE 975 trial (NCT04210115) is a phase 3 randomized control trial of definitive CRT with either placebo or pembrolizumab. While designed for inoperable patients, this study will inform the safety and efficacy of a triple therapy CRT/immunotherapy approach that may improve the long term clinical complete response rates for those considering active surveillance. Further, immunotherapy alone options for non-operative management are being evaluated, such as

the INFINITY study (NCT06644781). The ongoing NRG GI006 (NCT03801876) phase 3 study aims to determine if proton therapy can improve OS compared to intensity-modulated radiation therapy (IMRT).

Variant Cases and Treatment Algorithm

Variant cases and a Treatment Algorithm were developed as examples for these guidelines to illustrate practical applications of consensus recommendations.

Summary of Recommendations

1. The panel strongly recommends that perioperative chemotherapy +/- immunotherapy followed by surgery is usually appropriate for the typical case of operable locally-advanced and/or node-positive non-metastatic adenocarcinoma of the esophagus/GEJ [**Variant 1**].
2. The panel strongly recommends that neoadjuvant chemoradiation followed by surgery is usually appropriate for the typical case of operable locally advanced and/or node-positive non-metastatic adenocarcinoma of the esophagus/GEJ. Alternatively, definitive chemoradiation followed by response assessment and non-operative management with close surveillance can be considered for cases achieving a complete clinical response [**Variant 2**].
3. The panel strongly recommends that either perioperative chemoimmunotherapy followed by surgery or immunotherapy alone followed by response assessment and non-operative management with close surveillance for those achieving a complete clinical response are usually appropriate for the typical case of non-metastatic, microsatellite unstable adenocarcinoma of the esophagus/GEJ [**Variant 3**].
4. The panel strongly recommends that adjuvant chemotherapy is usually appropriate for the typical case of clinically node-negative non-metastatic esophageal adenocarcinoma/GEJ found to have lymph node involvement following neoadjuvant chemoradiation and surgery [**Variant 4**].
5. The panel strongly recommends that adjuvant immunotherapy is usually appropriate for the typical case of non-metastatic esophageal adenocarcinoma/GEJ with residual disease noted following neoadjuvant chemoradiation and surgery [**Variant 5**].
6. The panel strongly recommends that adjuvant chemotherapy is usually appropriate for the typical case of locally advanced and/or node-positive non-metastatic adenocarcinoma of the esophagus/GEJ with a poor pathologic response to neoadjuvant chemotherapy followed by surgery. The addition of immunotherapy may also be considered, although the strongest data exist for patients who also receive immunotherapy in the neoadjuvant setting. The addition of adjuvant (chemo)radiation can be considered for patients who are at a high risk of locoregional recurrence following surgery (i.e. positive margin) [**Variant 6**].

7. The panel recommends that continued systemic therapy may be appropriate for the typical case for patients with locally advanced and/or node-positive non-metastatic adenocarcinoma/GEJ of the esophagus who experience a decline in performance status during perioperative therapy and become inoperable. Definitive chemoradiation should be considered for such patients deemed able to tolerate this treatment. Best supportive care also may be appropriate for patients who are unable to receive or decline further treatment [**Variant 7**].

Summary of Evidence

Of the 46 references cited in the American Radium Society® Appropriate Use Criteria for Operable Esophageal and Gastroesophageal Junction Adenocarcinoma, 22 were identified through the search strategy. Of the 52 citations in the original bibliography, 18 citations were retained in the final document. Articles were removed from the original bibliography if they were more than 10 years old and did not contribute to the evidence or they were no longer cited in the revised narrative text. Seven additional studies referenced outside the “Summary of Literature Review” are included to provide context and were not used by the committee to guide recommendations. In sum the authors added 24 citations from bibliographies, websites, or books not found in the literature search.

Of the 40 references used as evidence, 40 are categorized as therapeutic references including 32 well-designed studies (Phase II randomized and Phase III), 2 moderately well-designed studies that account for most common biases (matched cohort and Phase II studies), 1 study with design limitations (retrospective reviews), and 5 references that are meta-analysis studies.

Supporting Documents

For additional information on the ARS Appropriate Use Criteria methodology and other supporting documents go to <http://www.americanradiumsociety.org/page/aucmethodology>.

The American Radium Society™ Appropriate Use Criteria and its expert panels have developed criteria for determining appropriate procedures for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide treating and referring physicians in making decisions regarding diagnosis and treatment of cancers and related or associated conditions. Generally, the complexity and severity of a patient’s clinical condition should dictate the selection of appropriate diagnostic procedures or treatments. Only those examinations or treatments generally used for evaluation of the patient’s condition are ranked. Other procedures necessary to evaluate or treat other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate procedures or treatments. Procedures, techniques, or other interventions classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment, applications, and treatment protocols should be encouraged. The ultimate decision regarding the appropriate use of any specific examination or treatment must be made by the referring physician and oncologist in light of all the circumstances presented in an individual examination.

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Abbreviation Key

5-FU = 5-fluorouracil

CALGB = Cancer and Leukemia Group B

cCR = clinical complete response

CRT = concurrent chemoradiation therapy

CT = Computed Tomography

CTV = Clinical Target Volume

dCRT = definitive concurrent chemoradiation therapy

DFS = disease-free survival

DMFS = distant metastases free survival

EAC = esophageal adenocarcinoma

ECOG = Eastern Cooperative Oncology Group

EFS = Event Free Survival

EMR = Endoscopic mucosal resection

EUS = Endoscopic ultrasound

FDA = Food and Drug Administration

FFCD = Francophone de Cance´rologie Digestive

FLOT = 5-fluorouracil, leucovorin, oxaliplatin, docetaxel

FNA = fine needle aspiration

FOLFOX = Folinic acid, 5-Fluorouracil, and oxaliplatin

Fx = fractions

GEJ = gastro-esophageal junction

GTV = Gross Tumor Volume

Her2 = human epidermal growth factor receptor 2

iCT = induction chemotherapy given before CRT

IUCC = International Union Against Cancer

IMRT = intensity modulated radiation therapy

LVI = lymphovascular invasion

MAGIC = MRC Adjuvant Gastric Infusional Chemotherapy

MIO = Minimally invasive esophagectomy

MRC = Medical Research Council

NCCN = National Comprehensive Cancer Network

nCR = neoadjuvant chemotherapy

nCRT = neoadjuvant concurrent chemoradiation therapy

NeoRes = NEOadjuvant chemotherapy versus Radiochemotherapy for cancer of the ESophagus or cardia

OS = overall survival

pCR = pathological complete response

PET/CT = Positron Emission Tomography/Computed Tomography

PFS = progression free survival

PFS = progression-free survival

PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting

poCT = perioperative chemotherapy including surgery

poCT & IO = perioperative chemotherapy and immune-oncology therapy including surgery

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis

PTV = Planning Target Volume

QOL = Quality of Life

RCT = randomized controlled trial

RR = risk ratio

RT = radiation therapy

RTOG = Radiation Therapy Oncology Group

SCC = squamous cell carcinoma

TTO = total thoracic esophagectomy

Table 1: Characteristics & Outcomes of Key Esophageal Studies

Trial	Author (Year)	Number of Patients	Study Design (Years)	Randomization	Eligibility	Cancer Location	Stage	Radiation (Gy / fx)	Chemotherapy	Median Follow-up (years)	Pathologic Complete Response	2-year LRFS (%)	2-year DMFS (%)	PFS/EFS	OS	Toxicity
CROSS	Eyck (2021) Shapiro (2015) Van Hagen (2012)	366	Phase 3 (2004-2008)	+/- nCRT → surgery	Resectable, locally advanced EC or GEJ cancer ECOG 0-2	75% EC, 25% GEJ (Siewert I/II); Siewert III excluded	cT1N1M0 or cT2-3 N0-1M0 81% T3+ 64% N+	41.4 Gy/ 23 fx regional nodes optional	Carbo- platin AUC 2 mg/mL/min + Paclitaxel (50 mg/m ²) weekly x 5	12.3	29% (47/161) SCC (49%) AC (23%)	10-year isolated LRR HR 0.40 reduced with CRT	NR	NS	3-year OS: CRT+Surgery: 58% Surgery alone: 44% CRT+Surgery: 48.6-49.4 mo Surgery alone: 24.0 mo	CRT+Surgery: Grade ≥3 leukopenia (6%) neutropenia (2%) anorexia (5%) fatigue (3%) Surgery alone similar postoperative complications 4% in-hospital mortality in both arms
SANO	Van der Wilk (2025)	309	Phase 3 (2017-2021)	nCRT & Surgery vs. nCRT & active surveillance	cCR after nCRT for locally advanced EC ECOG 0-2	100% EC Siewert not specified	cT1-4a N0-3 M0 72% T3+ 52% N+	41.4 Gy/23 fx	Carboplatin + Paclitaxel (CROSS)	3.2	NA	NR	NR	DFS Surveillance 35 mo Surgery 49 mo	2-year OS Surveillance 74% Surgery 71%	Postop complications similar; no new safety signals
MATTER-HORN	Jenizian (2025)	948	Phase 3 double blind (2020-2023)	FLOT +/- Durva	Resectable gastric/GEJ AC ECOG 0-1	80% EC Siewert I/II/III not specified 20% GEJ, Siewert II/III	cT2-4 and/or N+ 91%T3+ 80% N+	NA	FLOT +/- Durva	2.6	19.2% Durva Placebo 7.2%	NR	NR	2-year EFS Durva 67.4% Placebo 58.5%	2-year OS Durva 75.7% Placebo 70.4%	Grade 3-4 Durva 71.6% Placebo 71.2%
KEY NOTE-588	Shitara (2024)	1007	Phase 3 double blind (2017-2021)	poCT +/- Pembro	Locally advanced, resectable gastric/ GEJ AC ECOG 0-1	EC not included GEJ included 20% GEJ, Siewert II/III	cT2-4 and/or N+ ~80% T3/4 ~80% N+	N/A	Cisplatin-based or FLOT ± Pembro	4.0	12.9% Pembro + poCT 2.0% placebo + poCT	NR	NR	EFS Pembro 44.4 mo Placebo 25.3 mo	3-year OS Pembro 67.2% Placebo 65.1% Pembro 60.7 mo Placebo 58.0 mo	Grade ≥ 3 Pembro 78% Placebo 74%

CheckMate 577	Kelly (2021)	794	Phase 3 double blind (2016-2019)	+/- adjuvant Nivo	Resected stage II/III EC/GEJ cancer following nCRT with residual disease ECOG 0-1	70% EC 30% GEJ Siewert not specified	ypT1+ and/or ypN1+ 95% T3+ 83% N+	nCRT: 41.4 Gy/23 fx	Carboplatin + Paclitaxel (CROSS)	2.0	NA	LRR: 12% Nivo 17% placebo	DM: 29% Nivo 39% placebo DMFS: 28.3 mo Nivo 17.6 mo placebo	DFS: Nivo 22.4 mo Placebo 11.0 mo	NR	Grade 3-4: Nivo 13% Placebo 6%
CALGB 80803	Goodman (2021)	241	Phase 2R (2013-2016)	Chemo switch with CRT based on PET response (defined as $\leq 35\%$ reduction in SUVmax)	Resectable locally advanced EC/GEJ AC ECOG 0-1	100% EC/GEJ Siewert not specified	cT1N+ or cT2-4 Nany 81% T3+ 74% N+	CRT: 50.4 Gy/28 fx	Induction FOLFOX or Carboplatin + Paclitaxel then CRT with same or alternate	5.2	40.3% PET response FOLFOX 14.1% PET response Carbo taxol 18-20% PET non-response switch	NR	NR	NR	3-year OS: PET responders 62%, nonresponders 38% Median OS PET responders 48.8 mo, nonresponders 27.4 mo	Grade 3-4: 54% during CRT all arms
TOPGEAR	Leong (2024)	574	Phase 3 (2013-2020)	poCT +/- nCRT	Resectable gastric/GEJ adenocarcinoma AC ECOG 0-1	EC not included GEJ included 20% GEJ, Siewert II/III	cT2-4 and/or N+ 88% T3+ 62% N+	CRT: 45 Gy/25 fx (preop)	ECX or FLOT	5.6	16% poCT + nCRT 8% poCT	NR	NR	PFS CRT 31 mo, Chemo 32 mo	3-year OS CRT 59%, Chemo 62% Median OS CRT 46 mo, Chemo 49 mo	Grade 3-4: CRT 66%, Chemo 65%
ESOPEC	Hoepfner (2025)	438	Phase 3 (2016-2020)	poCT vs nCRT	Resectable EC AC ECOG 0-1	EC or Siewert I 32% Siewert II 32% Siewert III 18% not classifiable 18%	cT1cN+, cT2-4a Nany cM0 80% T3+ 80% N+	CRT: 41.4 Gy/23 fx	FLOT or CROSS	4.6	10.1% nCRT 16.7% FLOT	Isolate d LRR: 17 pts FLOT: 9 pts	Isolate d DM: 45 pts FLOT: 71 pts	3-year PFS: FLOT 51.6%, nCRT 35.0%	3-year OS: FLOT 57.4%, nCRT 50.7% Median OS: FLOT 66 mo, nCRT 37 mo	Grade ≥ 3 : FLOT 58%, nCRT 50%

ABBREVIATION KEY: Gy/fx, Gray/number of fractions; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; EC, esophageal cancer; GEJ, gastroesophageal; ECOG, Eastern Cooperative Oncology Group; AUC, area under curve; mg, milligram; mL, milliliter; min, minute; m², meter squared; SCC, squamous cell carcinoma; AC, adenocarcinoma; LRR, locoregional recurrence; HR, hazard ratio; CRT, chemoradiation; NR, not reported; NS, not significant; mo, months; nCRT, neoadjuvant chemoradiation; cCR, complete clinical response; NA, not applicable; DFS, disease-free survival; FLOT, 5-fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel; Durva, Durvalumab; poCT, perioperative chemotherapy; Pembro, pembrolizumab; Nivo, nivolumab; DM, distant metastases; PET, positron emission tomography; SUVmax, maximum standard uptake value; FOLFOX, Leucovorin, 5-fluorouracil and Oxaliplatin; preop, preoperative; ECX, Epirubicin, Cisplatin, capecitabine; pts, patients

VARIANT CASES

Variant 1: Node-positive middle thoracic adenocarcinoma, operative candidate

65 year-old male (ECOG performance status 1) presents with a 3-month history of progressive dysphagia to solids and semisolids (Blazeby dysphagia grade 3) and a 12% unintentional weight loss. Upper endoscopy demonstrates a near obstructing ulcerative mass mid-esophagus extending 24 – 30 cm from the incisors. Biopsy demonstrates moderately differentiated adenocarcinoma (microsatellite stable). EUS reveals invasion through the muscularis propria with penetration of the adventitia and 3 enlarged distal paraesophageal lymph nodes measuring up to 2 cm in size. Staging PET-CT demonstrates no evidence of distant metastatic disease. The patient was clinically staged as Stage IVA (cT3N2M0). He is evaluated by a multidisciplinary team and is deemed an operative candidate.

Procedure	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
nCRT → S	M	0	0	0	1	0	20	3	0	0	6		S	↑
iCT → nCRT → S	M	0	0	1	3	8	5	4	0	0	5		S	↑
dCRT	M	1	1	4	8	5	2	0	0	0	4		S	↑
nCT → S	M	0	0	1	21	1	1	0	0	0	4		S	↑
poCT with S	A	1	1	1	0	1	1	8	6	2	7		S	↑
poCT & IO with S	A	0	0	0	0	1	0	12	11	0	7		S	↑
S → Adjuvant therapy based on pathology†	U	3	7	8	1	1	0	1	0	0	3		S	↑

†Adjuvant therapy based on final surgical pathology; adjuvant chemotherapy is generally recommended for $\geq$ pT2 and/or pN+.

Variant Discussion:

For ECOG 0-1 patients with resectable esophageal adenocarcinoma expected to tolerate perioperative FLOT, ESOPEC showed that poCT resulted in superior outcomes than nCRT. Further improvements in outcomes were seen with adding IO to perioperative FLOT in MATTERHORN. Considering the similar disease biology comparing adenocarcinoma of locations other than mid-esophagus, the results of MATTERHORN may be generalized to those with mid-esophageal adenocarcinoma despite not being included in the trial. Induction chemotherapy is a reasonable approach for esophageal cancer patients, particularly as part of a response-adapted plan involving nCRT. While surgical resection remains the crux of curative therapy, definitive CRT followed by active surveillance is an option for patients who decline surgery. While neoadjuvant approaches are favored, if surgery is performed first, adjuvant CT is generally favored for $>$ pT2 and/or pN+. Adjuvant IO is typically delivered to patients who receive nCRT with residual tumor found at the time of surgery.

Key Radiation Points:

1. Neoadjuvant and definitive doses of 40-50.4 Gy in fraction sizes between 1.8 and 2.0 Gy to involved disease and elective nodal areas are 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 paraaortic, 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.

Variant 2: Elderly, moderate comorbidities, node-positive adenocarcinoma, operative candidate

75 year-old male (ECOG performance status 1 with diabetes-related peripheral neuropathy) presents with a 4-month history of progressive dysphagia to solids and semisolids (Blazeby dysphagia grade 3) and a 15% unintentional weight loss. Upper endoscopy demonstrates a near obstructing mass at the gastroesophageal junction (Siewert type II). Biopsy demonstrates moderately differentiated adenocarcinoma (microsatellite stable). EUS reveals invasion through the muscularis propria with penetration of the adventitia and 2 abnormal appearing paraesophageal and 1 abnormal appearing gastrohepatic lymph node, all measuring approximately 1 cm in size. Staging PET-CT demonstrates no evidence of distant metastatic disease. The patient was clinically staged as Stage IIIA (cT3N1M0). He is evaluated by a multidisciplinary team and is deemed an operative candidate, although he is interested in considering non-operative options.

Procedure	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
nCRT → S	A	0	0	0	0	1	3	10	6	1	7		S	↑
iCT → nCRT → S	M	0	0	1	4	7	5	2	2	0	5		S	↑
dCRT*	A	0	0	0	0	3	3	10	4	1	7		S	↑
nCT → S	M	0	0	1	7	7	4	2	0	0	5		S	↑
poCT with S	M	0	0	1	4	6	5	5	0	0	5		S	↑
poCT & IO with S	M	0	0	1	3	6	6	4	1	0	6		S	↑
S → Adjuvant therapy based on pathology†	U	4	7	9	0	0	0	1	0	0	2		S	↑

*followed by response assessment

†Adjuvant therapy based on final surgical pathology; adjuvant chemotherapy is generally recommended for $\geq$ pT2 and/or pN+.

Variant Discussion:

For this patient with moderate co-morbidities for whom quality of life is a particular focus, a definitive CRT followed by surveillance is particularly appropriate pending adequate response. However, optimal oncologic outcomes have been shown for perioperative systemic therapy approaches. As this patient is interested in non-operative options, surgery first is not preferred.

Key Radiation Points:

1. Neoadjuvant and definitive doses for a patient who is interested in non-operative approach of 41.4 - 50.4 Gy in fraction sizes between 1.8 and 2.0 Gy to involved disease and elective nodal areas are preferred. Doses of 50 Gy may be preferred in a patient hoping for non-operative approach. 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.

Variant 3: Node-negative middle thoracic esophageal adenocarcinoma (with microsatellite instability), operative candidate

55 year-old male (ECOG performance status 0) presents with a 2-month history of dysphagia to solids unless they are pureed (Blazeby dysphagia grade 2) and a 3% unintentional weight loss. Upper endoscopy demonstrates a partially obstructing mass in the mid-esophagus extending 24 – 30 cm from the incisors. Biopsy demonstrates poorly differentiated adenocarcinoma (with microsatellite instability). EUS reveals invasion into the adventitia and no evidence of abnormal or enlarged paraesophageal lymph nodes. Staging PET-CT demonstrates no evidence of nodal or distant metastatic disease. The patient is clinically staged as Stage III (cT3N0M0). He is evaluated by a multidisciplinary team and is deemed an operative candidate.

Procedure	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
nCRT → S	M	0	0	0	3	16	5	0	0	0	5		S	↑
iCT → nCRT → S	M	0	0	1	17	4	2	0	0	0	4		S	↑
dCRT	U	1	1	21	1	0	0	0	0	0	3		S	↑
nCT → S	M	0	0	6	18	0	0	0	0	0	4		S	↑
poCT with S	M	0	0	1	21	0	1	1	0	0	4		S	↑
poCT & IO with S	A	0	0	0	0	0	1	16	7	0	7		S	↑
IO → Response assessment to determine further therapy*	A	0	0	1	2	0	2	18	1	0	7		EO	↑
S → Adjuvant therapy based on pathology†	U	4	3	11	0	3	0	0	0	0	3		S	↑

*If incomplete response to IO alone, consider poCT or nCRT approaches.

†Adjuvant therapy based on final surgical pathology; adjuvant chemotherapy is generally recommended for ≥pT2 and/or pN+.

Variant Discussion:

For ECOG 0-1 patients with resectable esophageal adenocarcinoma expected to tolerate perioperative FLOT, ESOPEC showed that poCT resulted in superior outcomes than nCRT. Further improvements in outcomes were seen with adding IO to perioperative FLOT in MATTERHORN. Considering the similar disease biology comparing adenocarcinoma of locations other than mid-esophagus, the results of MATTERHORN may be generalized to those with mid-esophageal adenocarcinoma despite not being included in the trial. Patients with MSI-high tumors do not respond well to induction chemotherapy, however still derive a response from radiation. While surgical resection remains the crux of curative therapy, definitive CRT followed by active surveillance is an option for patients who decline surgery. While randomized data does not exist showing the utility of IO alone followed by response assessment, non-randomized data suggests this approach may be appropriate for MSI-H patients on extrapolation from other studies. While neoadjuvant approaches are favored, if surgery is performed first, adjuvant CT is generally favored for >pT2 and/or pN+. Adjuvant IO is typically delivered to patients who receive nCRT with residual tumor found at the time of surgery.

Key Radiation Points:

1. Neoadjuvant and definitive doses of 40-50.4 Gy in fraction sizes between 1.8 and 2.0 Gy to involved disease and elective nodal areas are 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 paraaortic, 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.

Variant 4: Pathologically node-positive disease noted after esophagectomy in cT2N0 patient who did not receive pre-operative therapy

55 year-old female (ECOG performance status 0) undergoes multidisciplinary evaluation for EUS-staged II (cT2N0M0) 2 cm non-obstructing well differentiated adenocarcinoma (microsatellite stable) of the GEJ (Siewert type I). PET-CT demonstrates no evidence of distant metastatic disease. She undergoes the recommended esophagectomy, and final pathology demonstrates pT2N1 disease with metastases in 2 of 16 paraesophageal lymph nodes measuring up to 3 mm without evidence of extranodal invasion and negative margins. The patient is recovering well and gaining weight with ECOG performance status 1.

Procedure	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Observation	U	4	7	7	0	2	1	0	0	0	2		S	↑
Adjuvant CRT	M	0	0	5	7	6	3	0	0	0	4		S	↑
Adjuvant CT	A	0	0	0	0	1	1	11	8	0	7		S	↑
Adjuvant IO & CT		0	1	6	2	7	1	3	1	0	5	X	EO	-

Variant Discussion:

As the majority (~80%) of patients in the peri-operative systemic therapy trials involved cT3 or N+ patients. Patients found to have more advanced disease than expected could be reasonably offered adjuvant FLOT depending on performance status (TOPGEAR, ESOPEC, MATTERHORN). In the CRITICS trial that included GEJ patients, there was no benefit to adjuvant CRT compared to adjuvant CT, but this was a secondary analysis.

Key Radiation Point:

1. Adjuvant radiation doses between 40 - 45 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 >50.4 Gy and higher are not preferred.

Variant 5: Residual disease noted on resection after neoadjuvant chemoradiotherapy

65 year-old female (ECOG performance status 1) undergoes multidisciplinary evaluation for EUS-staged III (cT2N1M0) moderately differentiated adenocarcinoma (microsatellite stable) of the lower esophagus, not involving the GEJ. PET-CT demonstrates no evidence of distant metastatic disease. She completes the recommended long-course chemoradiation with weekly concurrent carboplatin/paclitaxel, which she tolerates well and proceeds to planned surgical resection. Final pathology demonstrates residual ypT1N1 disease with negative margins (1 of 17 nodes positive). Restaging contrast-enhanced CT of the chest and abdomen shows no evidence of distant metastases. The patient is recovering well and gaining weight with ECOG performance status 1.

Procedure	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Observation	U	5	4	7	3	2	0	0	0	0	3		S	↑
Adjuvant IO	A	0	0	0	0	0	0	6	11	4	8		S	↑
Adjuvant IO & CT		0	1	9	14	0	0	0	0	0	5	X	EO	-

Variant Discussion:

For patients without a pCR after nCRT and resection, CheckMate 577 found improved outcomes with adjuvant IO as compared to observation. Although there are no data specifically supporting adjuvant chemo-IO in the postoperative setting after receipt of neoadjuvant CRT, the MATTERHORN trial demonstrated improved outcomes with perioperative chemo-IO compared to perioperative chemotherapy alone. The lack of complete consensus on this recommendation is driven by ATTRACTION-5 which demonstrated no improvement in outcomes with the delivery of postoperative chemo-IO when compared with postoperative chemo alone for resected stage III gastric cancer.

Variant 6: Poor pathologic response to neoadjuvant chemotherapy with a positive margin

60 year-old female (ECOG performance status 1) presents with a 3-month history of progressive dysphagia to solids and a 5-pound unintentional weight loss. Upper endoscopy demonstrates a partially obstructing mass in the GEJ (Siewert type I). Biopsy demonstrates poorly differentiated adenocarcinoma (with microsatellite stability). EUS reveals invasion into the muscularis propria with penetration of the adventitia and 3 enlarged paraesophageal lymph nodes measuring up to 20 mm in size. Staging PET-CT demonstrates no evidence of distant metastatic disease. The patient is clinically staged as Stage IVA (cT3N2M0). She is evaluated by a multidisciplinary team and is recommended to undergo peri-operative chemotherapy and surgical resection. She undergoes four cycles of FLOT chemotherapy, which she tolerates well with resolution of dysphagia, followed by planned esophagectomy. Pathology demonstrates poor response with significant residual disease, ypT3N2 with 5 of 17 paraesophageal lymph node metastases measuring up to 10 mm and a microscopically positive resection margin (R1).

Procedure	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Observation	U	6	7	6	0	2	0	0	0	0	2		S	↑
Adjuvant CRT	M	0	0	1	3	5	13	1	0	0	6		S	↑
Adjuvant CT	A	0	0	0	0	2	3	12	4	0	7		S	↑
Adjuvant IO & CT	M	0	0	5	9	8	0	1	0	0	4		S	↑

Variant Discussion:

While the MAGIC trial demonstrated benefit of poCT over observation, further benefit of continuing the same chemotherapy is unclear. The VESTIGE trial demonstrated superior outcomes with continuing chemotherapy over switching to IO in the postoperative setting. In the CRITICS trial which included 15% GEJ patients and only 8% with positive margins, there was no benefit to adjuvant CRT compared to adjuvant CT. Further improvements in outcomes were seen with adding IO to perioperative FLOT in MATTERHORN study however this patient did not receive chemo-IO in the neoadjuvant setting.

Key Radiation Point:

1. Adjuvant radiation doses between 40 - 45 Gy in fraction sizes between 1.8 and 2.0 Gy to the anastomosis and elective nodal areas are preferred in the adjuvant setting. A boost up to 50.4 Gy to the positive margin could be considered, but no data exists to show this improves outcomes. Doses to the anastomosis >50.4 Gy and higher are not preferred.

Variant 7: Planned peri-operative chemotherapy, unable to receive surgery

60 year-old male (ECOG performance status 0) presents with a 3-month history of mild dysphagia to solids (Blazeby dysphagia grade 1) and a 2% unintentional weight loss. Upper endoscopy demonstrates a partially obstructing mass at the gastroesophageal junction (Siewert type 2). Biopsy demonstrates moderately differentiated adenocarcinoma (microsatellite stable). EUS reveals invasion into the muscularis propria without penetration of the adventitia and 2 abnormal appearing paraesophageal lymph nodes measuring up to 1 cm. Staging PET-CT demonstrates no evidence of nodal or distant metastatic disease. The patient is staged clinically as Stage IIIA (cT2N1M0). He is evaluated by a multidisciplinary team and is recommended to undergo peri-operative chemotherapy and surgical resection. He undergoes four cycles of FLOT chemotherapy and is noted to have a decline in performance status making him medically inoperable.

Procedure	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
dCRT*		0	0	0	0	0	8	8	3	2	5	X	S	↑
continue systemic therapy†	M	0	0	2	3	12	4	0	0	0	5		EO	↑
Best supportive care	M	0	0	2	11	3	3	2	0	0	4		EO	↑

*if patient deemed able to tolerate

†Adjust chemotherapy based on patient tolerance

Variant Discussion:

SANO, RTOG 8501 and INT 0123 demonstrated that dCRT is a reasonable option in this setting. While continuing the same chemotherapy may result in further worsening of the patient's performance status, switching to another systemic therapy or lower intensity chemotherapy can be considered. However, if the patient has more comfort-directed goals, transitioning to best supportive care may be a reasonable option as well.

Key Radiation Points:

1. Neoadjuvant and definitive doses of 40-50.4 Gy in fraction sizes between 1.8 and 2.0 Gy to involved disease and elective nodal areas are 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 definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

Key:

ECOG: Eastern Cooperative Oncology Group

cm: centimeter

EUS: endoscopic ultrasound

PET-CT: positron emission tomography-computed tomography

nCRT: neoadjuvant chemoradiation

S: surgery

iCT: induction chemotherapy

dCRT: definitive chemoradiation

nCT: neoadjuvant chemotherapy

poCT: perioperative chemotherapy

IO: immunotherapy

pN+: pathologically involved lymph nodes

FLOT: 5- Fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel

MSI: microsatellite instability

Gy: Gray

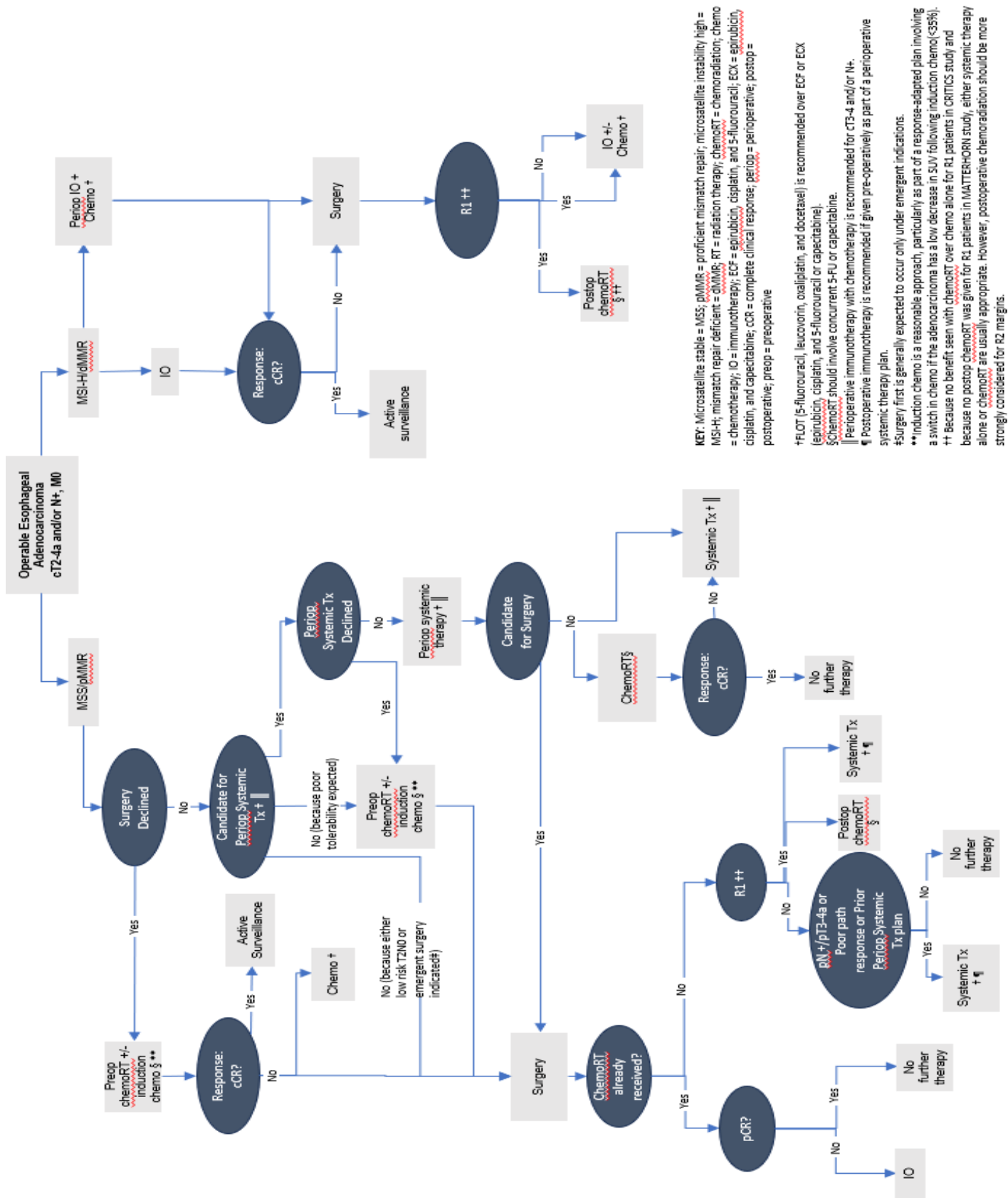
GEJ: gastroesophageal junction

CT: chemotherapy

pCR: pathologic complete response

R1: positive resection margin

TREATMENT ALGORITHM



Appendix A: ARS AUC Management of Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

Performed on July 7, 2025

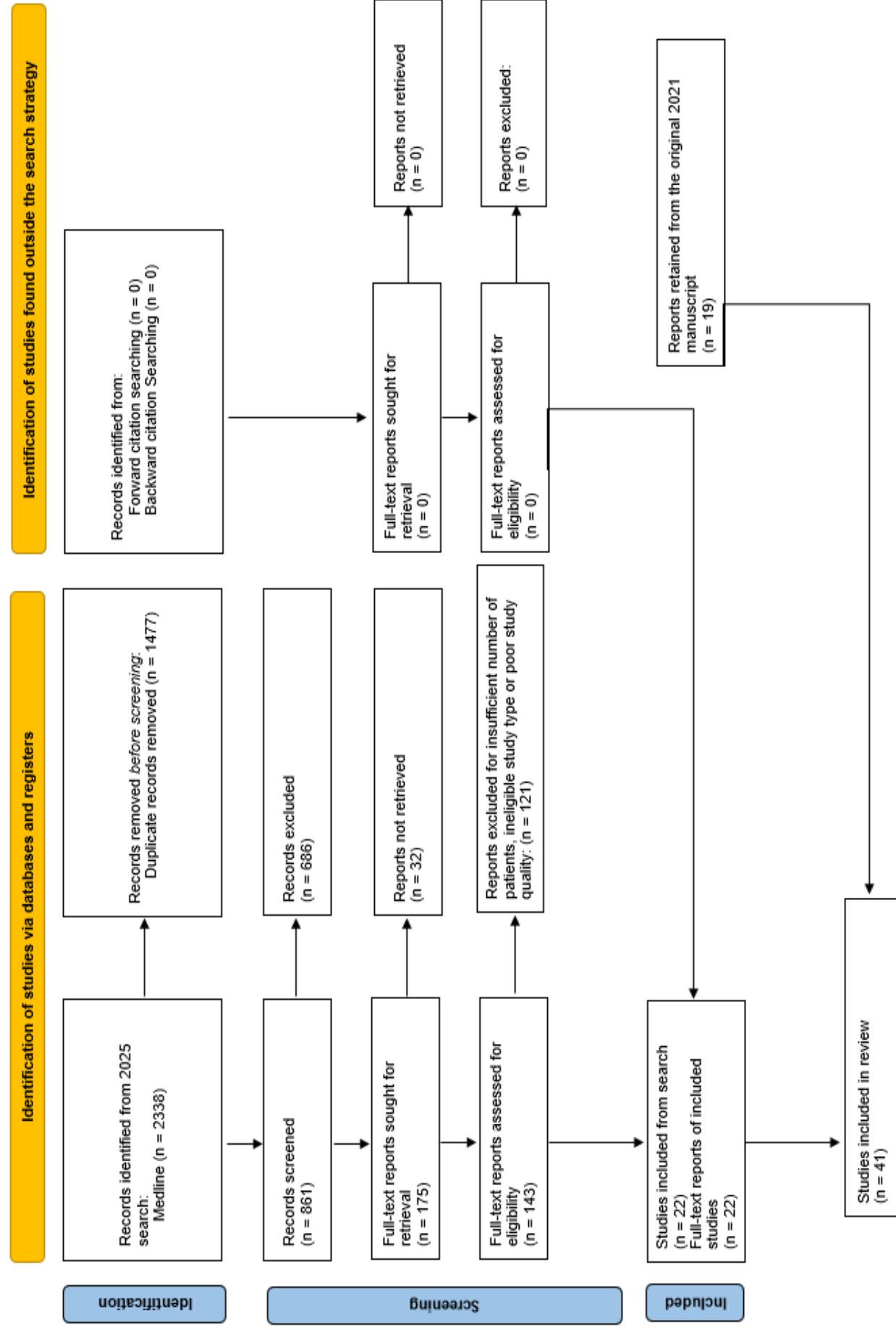
Search Strategy:

Database: Ovid MEDLINE(R) All

Search Strategy:

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- 2 (cancer* or carcinoma* or neoplas* or adenocarcinoma* or malignan* or tumor* or tumour*).ti,ab,kf. (4492454)
- 3 1 and 2 (98973)
- 4 exp *Esophageal Neoplasms/ (55975)
- 5 exp *Neoplasms/ (3681024)
- 6 exp *Esophagus/ (34572)
- 7 5 and 6 (6429)
- 8 3 or 4 or 7 (105048)
- 9 (resect* or esophagectom* or oesophagectom* or surg* or opera* or adjuvant* or neoadjuvant*).ti,ab,kf. (3961052)
- 10 exp Esophagectomy/ (13790)
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- 14 exp Radiotherapy/ (218689)
- 15 exp antineoplastic agents/ (1326187)
- 16 exp combined modality therapy/ (314975)
- 17 rt.fs. (223217)
- 18 th.fs. (2294035)
- 19 or/13-18 (4638441)
- 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. (1294996)
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- 22 exp Meta-Analysis/ (223109)
- 23 validation studies/ (119059)
- 24 exp controlled clinical trial/ (734797)
- 25 or/20-24 (1730439)
- 26 8 and 12 and 19 and 25 (2527)
- 27 limit 26 to yr="2019 -Current" (888)
- 28 limit 27 to english language (865)
- 29 ("non-small cell lung ca*" or "non small cell lung ca*" or "small cell lung ca*" or "NSCLC" or "SCLC").ti,ab,kf. (121211)
- 30 28 not 29 (854)

Appendix B: PRISMA 2020^{5,6} Study Selection Flow Diagram: Management of Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma



Appendix D: PRISMA 2020 Checklist for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	INTRODUCTION/BACKGROUND ¶2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	¶2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	METHODOLOGY ¶1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	¶1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix A: Search Strategy
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	¶1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	¶1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	¶1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	¶1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Appendix C: Evidence Table
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as	N/A

Appendix D: PRISMA 2020 Checklist for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

Section and Topic	Item #	Checklist item	Location where item is reported
		handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Variants 1-7 via Strength of Evidence (SOE)
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Appendix B: Flow Diagram
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix B: Flow Diagram
Study characteristics	17	Cite each included study and present its characteristics.	Appendix C: Evidence Table
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix C: Evidence Table
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Variants 1-7 via Strength of Evidence (SOE) and Strength of Recommendation (SOR), & section "SUMMARY OF



Appendix D: PRISMA 2020 Checklist for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	SUMMARY OF LITERATURE REVIEW Topics 1 - 3
	23b	Discuss any limitations of the evidence included in the review.	N/A
	23c	Discuss any limitations of the review processes used.	N/A
	23d	Discuss implications of the results for practice, policy, and future research.	N/A
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title Page
Competing interests	26	Declare any competing interests of review authors.	Title Page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	https://www.americanradiology.org/page/aucmethodology

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
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