

Appendix C:
Evidence Table

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

Ref #	Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
4	**Eyck BM, van Lanschot JJB, Hulshof MCCM, et al. Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial. J Clin Oncol Off J Am Soc Clin Oncol. 2021;39(18):1995-2004. doi:10.1200/JCO.20.03614	Prospective randomized Phase III	From 2004 through 2008, we randomly assigned 366 patients to either five weekly cycles of carboplatin and paclitaxel with concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week) followed by surgery, or surgery alone. Follow-up data were collected through 2018. Cox regression analyses were performed to compare overall survival, cause-specific survival, and risks of locoregional and distant relapse. The effect of neoadjuvant chemoradiotherapy beyond 5 years of follow-up was tested with time-dependent Cox regression and landmark analyses.	To assess long-term outcome of this regimen.	The median follow-up was 147 months (interquartile range, 134-157). Patients receiving neoadjuvant chemoradiotherapy had better overall survival (hazard ratio [HR], 0.70; 95% CI, 0.55 to 0.89). The effect of neoadjuvant chemoradiotherapy on overall survival was not time-dependent (P value for interaction, P = .73), and landmark analyses suggested a stable effect on overall survival up to 10 years of follow-up. The absolute 10-year overall survival benefit was 13% (38% v 25%). Neoadjuvant chemoradiotherapy reduced risk of death from esophageal cancer (HR, 0.60; 95% CI, 0.46 to 0.80). Death from other causes was similar between study arms (HR, 1.17; 95% CI, 0.68 to 1.99). Although a clear effect on isolated locoregional (HR, 0.40; 95% CI, 0.21 to 0.72) and synchronous locoregional plus distant relapse (HR, 0.43; 95% CI, 0.26 to 0.72) persisted, isolated distant relapse was comparable (HR, 0.76; 95% CI, 0.52 to 1.13).	1
8	**Coccolini F, Nardi M, Montori G, Ceresoli M, Celotti A, Cascinu S, Fugazzola P, Tomasoni M, Glehen O, Catena F, Yonemura Y, Ansaloni L. Neoadjuvant chemotherapy in advanced gastric and esophago-gastric cancer. Meta-analysis of randomized trials. Int J Surg. 2018 Mar; 51:120-127. doi:10.1016/j.ijsu.2018.01.008. Epub 2018 Feb 20. Review. PubMed PMID: 29413875.	Meta-analysis	15 RCTs have been included (2001 patients: 977 into NACT + surgery arm and 1024 into control arm).	To evaluate the effects of neoadjuvant chemotherapy (NACT) on cancer of the stomach and GEJ	NACT + Surgery reduces the overall mortality at 1, 3 and 5-year in cumulative analysis (RR = 0.78; 0.81; 0.88 respectively), at 1, 2, 3 and 5-years in GEJ (RR = 0.79; 0.83; 0.84; 0.91 respectively) and at 3 and 5-years in gastric (RR = 0.74; 0.82 respectively). Morbidity and perioperative mortality rate are not influenced by NACT. Recurrence rate is reduced by NACT + surgery in GEJ (RR = 0.80). NACT reduces the mortality in gastric and esophago-gastric cancer. Morbidity and perioperative mortality are not influenced by NACT. The overall recurrence rate is reduced by NACT in esophagogastric cancer.	M
9	**Kidane B, Coughlin S, Vogt K, Malthaner R. Preoperative chemotherapy for resectable thoracic esophageal cancer.	Meta-analysis	We identified a total of 13 RCTs involving 2362 participants. Ten trials (2122 participants) reported	To evaluate the role of preoperative	Preoperative chemotherapy improves overall survival (HR 0.88, 95% confidence interval (CI) 0.80 to 0.96) and is associated	M

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

	Cochrane Database Syst Rev. 2015 May19;(5):CD001556. doi: 10.1002/14651858.CD001556.pub3. Review. PubMed PMID:25988291.		sufficient detail on survival to be included in a meta-analysis for the primary outcome from Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to 2013), EMBASE (1988 to 2013), and CANCERLIT (1993 to 2013).	chemotherapy in the treatment of patients with resectable thoracic esophageal cancer	with a significantly higher rate of complete (R0) resection (RR 1.11, 95% CI 1.03 to 1.19). No evidence suggests that the overall rate of resection (RR 0.96, 95% CI 0.92 to 1.01), tumor recurrence (RR 0.81, 95% CI 0.54 to 1.22) or nonfatal complications (RR 0.90; 95% CI 0.76 to 1.06) was different for preoperative chemotherapy compared with surgery alone. Trials reported risks of toxicity with chemotherapy that ranged from 11% to 90%.	
10	**Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009 Oct 20; 27(30):5062-7. doi: 10.1200/JCO.2009.22.2083. Epub 2009 Sep 21. PubMed PMID: 19770374.	Prospective randomized phase III	OEO2 recruited 802 patients, 400 on CS and 402 on S.	Phase III: To compare surgery alone (S) to two cycles of combination cisplatin and fluorouracil before surgery (CS).	There were 655 deaths, 335 for S and 320 for CS. The survival benefit has been maintained with a hazard ratio (HR) of 0.84 (95% CI, 0.72 to 0.98; P = .03) which in absolute terms is a 5-year survival of 23.0% for CS compared with 17.1% for S. The treatment effect is consistent in both adenocarcinoma and squamous cell carcinoma. The first disease-free survival event was macroscopic residual disease from incomplete resection (R2) or no resection in 26.4% of the S group versus 14.3% of the CS P < .001. Three-year survival by type of resection was R0 42.4%, R1 was 18.0%, and R2 was 8.6%. Longterm follow-up confirms that preoperative chemotherapy improves survival in operable esophageal cancer and should be considered as a standard of care.	1
11	**Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med. 1998;339(27):1979–1984. doi: 10.1056/NEJM199812313392704	Prospective randomized phase III	Preoperative chemotherapy for patients randomly assigned to the chemotherapy group included three cycles of cisplatin and fluorouracil. Surgery was performed two to four weeks after the completion of the third cycle; patients also received two additional cycles of chemotherapy after the operation. Patients randomly assigned to the immediate surgery group underwent the same surgical procedure. The	To compare preoperative chemotherapy followed by surgery with surgery alone for patients with local and operable esophageal cancer.	After a median possible study time of 55.4 months, there were no significant differences between the two groups in median survival: 14.9 months for the patients who received preoperative chemotherapy and 16.1 months for those who underwent immediate surgery (P=0.53). At one year, the survival rate was 59 percent for those who received chemotherapy and 60 percent for those who had surgery alone; at two years, survival was 35 percent and 37 percent, respectively. The toxic effects of chemotherapy were tolerable, and the addition of chemotherapy did not appear to	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

			main end point was overall survival.		increase the morbidity or mortality associated with surgery. There were no differences in survival between patients with squamous-cell carcinoma and those with adenocarcinoma. Weight loss was a significant predictor of poor outcome (P=0.03). With the addition of chemotherapy, there was no change in the rate of recurrence at locoregional or distant sites.	
12	**Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. <i>N Engl J Med.</i> 2006 Jul 6;355(1):11-20. doi: 10.1056/NEJMoa055531. PMID: 16822992.	Prospective randomized phase III	N = 303 poCT + surgery (250 patients) vs. surgery alone (253 patients) Gastric: 74% Lower esophagus: 15% GEJ (Siewert unspecified): 11%	Phase III study to assess whether perioperative ECF improves outcomes among patients with potentially curable gastric cancer	ECF-related adverse effects were similar to those previously reported among patients with advanced gastric cancer. Rates of postoperative complications were similar in the perioperative-chemotherapy group and the surgery group (46 percent and 45 percent, respectively), as were the numbers of deaths within 30 days after surgery. The resected tumors were significantly smaller and less advanced in the perioperativechemotherapy group. With a median followup of four years, 149 patients in the perioperative-chemotherapy group and 170 in the surgery group had died. As compared with the surgery group, the perioperativechemotherapy group had a higher likelihood of overall survival (hazard ratio for death, 0.75; 95 percent confidence interval, 0.60 to 0.93; P = 0.009; five-year survival rate, 36 percent vs. 23 percent) and of progressionfree survival (hazard ratio for progression, 0.66; 95 percent confidence interval, 0.53 to 0.81; P<0.001).	1
13	Athauda, Avani; Nankivell, Matthew; Langley, Ruth E; Alderson, Derek; Allum, William; Grabsch, Heike I; Starling, Naureen; Chau, Ian; Cunningham, David. Impact of sex and age on chemotherapy efficacy, toxicity and survival in localised oesophagogastric cancer: A pooled analysis of 3265 individual patient data from four large randomized trials (OE02, OE05,	Meta-analysis using individual patient data from prospective randomized trials	Individual patient data from four prospective randomized controlled trials were pooled using a two-stage meta-analysis. For survival analysis, hazard ratios (HRs) were calculated for patients aged <70 and ≥ 70 years, as well as between males and females. Mandard tumour	To identify the impact of sex and age on chemotherapy efficacy, toxicity and survival in localised oesophagogastric cancer	3265 patients were included for survival analysis (2668 [82%] male, 597 [18%] female; 2627 (80%) <70 years, 638 (20%) ≥70 years). A significant improvement in overall survival (OS) (HR: 0.78; p < 0.001) and disease-specific survival (DSS) (HR: 0.78; p < 0.001) was observed in females compared with males. No significant differences in OS (HR: 1.11; p = 0.045) or DSS (HR: 1.01; p = 0.821) were observed in older patients compared	M

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

	MAGIC and ST03). European journal of cancer (Oxford, England: 1990) / 2020;137(arv, 9005373):45-56. DOI: 10.1016/j.ejca.2020.06.005		regression grade (TRG) and, $\geq$ grade III toxicities were compared using logistic regression models to calculate odds ratios. All analyses were adjusted for the type of chemotherapy received		with younger patients. For patients who underwent resection, older patients (15% vs 10%; $p = 0.03$) and female patients (14% vs 10%, $p = 0.10$) were more likely to achieve favourable Mandard TRG scores. Females experienced significantly more $\geq$ grade III nausea (10% vs 5%; $p \leq 0.001$), vomiting (10% vs 4%; $p \leq 0.001$) and diarrhoea (9% vs 4%; $p \leq 0.001$) than males.	
14	Liu, Drolaiz H W; Sefcovicova, Nina; Emmerson, Jake; Spaans, Louisa N; Saito, Yuichi; Hutchins, Gordon; Nankivell, Matthew G; Langley, Ruth E; Allum, William; Cunningham, David; Langer, Rupert; Grabsch, Heike I. Neoadjuvant chemotherapy improves survival in patients with oesophageal mucinous adenocarcinoma: Post-hoc analysis of the UK MRC OE02 and OE05 trials. European journal of cancer (Oxford, England: 1990) / 2022;170(arv, 9005373):140-148. DOI: 10.1016/j.ejca.2022.04.026	Retrospective	OeAC patients either treated by surgery alone in the OE02 trial (S-patients) or by neoadjuvant chemotherapy followed by surgery (CS-patients) in OE02 or OE05 trials were included. Cancers from 1055 resection specimens (OE02 [test cohort]: 187 CS, 185 S; OE05 [validation cohort]: 683 CS) were classified as either mucinous (more than 50% of the tumour area consists of extracellular mucin, OeACmucin) or non-mucinous adenocarcinoma (OeACnon-mucin). The relationship between histological phenotype, clinicopathological characteristics, survival and treatment was analysed.	To investigate whether patients with mucinous OeAC (OeACmucin) benefit from neoadjuvant chemotherapy.	Overall, 7.3% and 9.6% OeAC were classified as OeACmucin in OE02 and OE05, respectively. In OE02, the frequency of OeACmucin was similar in S and CS-patients. Patients with OeACmucin treated with surgery alone had poorer overall survival compared with OeACnon-mucin patients (hazard ratio: 2.222, 95% confidence interval: 1.08-4.56, $P = 0.025$). Patients with OeACmucin treated with neoadjuvant chemotherapy and surgery had similar survival as OeACnon-mucin patients in test and validation cohort. This is the first study to suggest in a post-hoc analysis of material from two independent phase III clinical trials that the poor survival of patients with mucinous OeAC can be improved by neoadjuvant chemotherapy.	3
15	**Mariette C, Dahan L, Mornex F, Maillard E, Thomas PA, Meunier B, Boige V, Pezet D, Robb WB, Le Brun-Ly V, Bosset JF, Mabrut JY, Triboulet JP, Bedenne L, Seitz JF. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2014 Aug 10;32(23):2416-22. doi:10.1200/JCO.2013.53.6532. Epub 2014 Jun 30. PubMed PMID: 24982463.	Prospective randomized phase III	From June 2000 to June 2009, 195 patients (57 adeno) in 30 centers were randomly assigned to surgery alone (group S; $n = 97$) or NCRT followed by surgery (group CRT; $n = 98$). CRT protocol was 45 Gy in 25 fractions over 5 weeks with two courses of concomitant chemotherapy composed of fluorouracil 800 mg/m ² and cisplatin 75 mg/m ² . Median follow-up of 93.6 months.	Phase III: To assess whether NCRT improves outcomes for patients with stage I or II EC. The primary end point was overall survival. Secondary end points were disease-free survival, postoperative morbidity, in-hospital	Pretreatment disease was stage I in 19.0%, IIA in 53.3%, and IIB in 27.7% of patients. For group CRT compared with group S, R0 resection rate was 93.8% versus 92.1% ($P = .749$), with 3-year overall survival rate of 47.5% versus 53.0% (hazard ratio [HR], 0.99; 95% CI, 0.69 to 1.40; $P = .94$) and postoperative mortality rate of 11.1% versus 3.4% ($P = .049$), respectively. Because interim analysis of the primary end point revealed an improbability of demonstrating the superiority of either treatment arm (HR, 1.09; 95% CI, 0.75 to 1.59; $P = .66$), the trial was stopped for anticipated futility. Compared with surgery alone, NCRT with cisplatin plus fluorouracil does not improve	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

				mortality, R0 resection rate, and prognostic factor identification.	R0 resection rate or survival but enhances postoperative mortality in patients with stage I or II EC.	
16	**Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, van Laarhoven HWM, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA, Blaisse RJB, Busch ORC, Ten Kate FJW, Creemers GM, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Sangen MJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A; CROSS study group. Noadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomized controlled trial. Lancet Oncol. 2015 Sep;16(9):1090-1098. doi:10.1016/S1470-2045(15)00040-6. Epub 2015 Aug 5. PubMed PMID: 26254683.	Prospective randomized phase III	368 patients from eight participating centres randomly assigned to the two treatment groups: 180 to surgery plus neoadjuvant chemoradiotherapy and 188 to surgery alone. Two patients in the neoadjuvant chemoradiotherapy group withdrew consent, so a total of 366 patients were analysed (178 in the neoadjuvant chemoradiotherapy plus surgery group and 188 in the surgery alone group). Eligible pts had clinically resectable, locally advanced cancer of the oesophagus or oesophagogastric junction (clinical stage T1N1M0 or T2-3N0-1M0, according to the TNM cancer staging system, sixth edition) were randomly assigned in a 1:1 ratio with permuted blocks of four or six to receive either weekly administration of five cycles of neoadjuvant chemoradiotherapy (intravenous carboplatin [AUC 2 mg/mL per min] and intravenous paclitaxel [50 mg/m(2) of body surface area] for 23 days) with concurrent radiotherapy (41.4 Gy, given in 23 fractions of 1.8 Gy on 5 days per week) followed by surgery, or surgery alone.	Phase III: To update results On ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) comparing neoadjuvant chemoradiotherapy plus surgery versus surgery alone in patients with squamous cell carcinoma and adenocarcinoma of the oesophagus or oesophagogastric junction showed a significant increase in 5-year overall survival in favour of the neoadjuvant chemoradiotherapy plus surgery group after a median of 45 months' followup. Long-term results after a minimum follow-up of 5 years reported. The primary endpoint was overall survival, analysed by intention-to-treat.	Of 171 patients who received any neoadjuvant chemoradiotherapy in this group, 162 (95%) were able to complete the entire neoadjuvant chemoradiotherapy regimen. After a median follow-up for surviving patients of 84.1 months (range 61.1-116.8, IQR 70.7-96.6), median overall survival was 48.6 months (95% CI 32.1-65.1) in the neoadjuvant chemoradiotherapy plus surgery group and 24.0 months (14.2-33.7) in the surgery alone group (HR 0.68 [95% CI 0.53-0.88]; log-rank p=0.003). Median overall survival for patients with squamous cell carcinomas was 81.6 months (95% CI 47.2-116.0) in the neoadjuvant chemoradiotherapy plus surgery group and 21.1 months (15.4-26.7) in the surgery alone group (HR 0.48 [95% CI 0.28-0.83]; log-rank p=0.008); for patients with adenocarcinomas, it was 43.2 months (24.9-61.4) in the neoadjuvant chemoradiotherapy plus surgery group and 27.1 months (13.0-41.2) in the surgery alone group (HR 0.73 [95% CI 0.55-0.98]; log-rank p=0.038).	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

17	**Noordman BJ, Verdam MGE, Lagarde SM, Hulshof MCCM, van Hagen P, van BergeHenegouwen MI, Wijnhoven BPL, van Laarhoven HWM, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA, Blaisse RJB, Busch OR, Ten Kate FJW, Creemers GM, PuntCJA, Plukker JTM, Verheul HMW, Spillenaar Bilgen EJ, van Dekken H, van der SangenMJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, TilanusHW, Steyerberg EW, van der Gaast A, Sprangers MAG, van Lanschot JJB. Effect of Neoadjuvant Chemoradiotherapy on Health-Related Quality of Life in Esophageal or Junctional Cancer: Results From the Randomized CROSS Trial. J Clin Oncol. 2018 Jan 20;36(3):268-275. doi: 10.1200/JCO.2017.73.7718. Epub 2017 Nov 21. PubMedPMID: 29161204.	Prospective randomized phase III	A total of 363 patients were analyzed from CROSS	Secondary endpoint analysis for Phase III: To compare preagreed Health-related quality of life (HRQOL) domains in patients with esophageal or junctional cancer who received neoadjuvant chemoradiotherapy (nCRT) followed by surgery or surgery alone on CROSS. Secondary aims were to examine the effect of nCRT on HRQOL before surgery and the effect of surgery on HRQOL	No statistically significant differences in postoperative HRQOL were found between treatment groups. In the nCRT group, PF, EA, GQOL, FA, and EM scores deteriorated 1 week after nCRT (Cohen's d: -0.93, P < .001; 0.47, P < .001; -0.84, P < .001; 1.45, P < .001; and 0.32, P = .001, respectively). In both treatment groups, all end points declined 3 months postoperatively compared with baseline (Cohen's d: -1.00, 0.33, -0.47, -0.34, and 0.33, respectively; all P < .001), followed by a continuous gradual improvement. EA, GQOL, and EM were restored to baseline levels during follow-up, whereas PF and FA remained impaired 1 year postoperatively (Cohen's d: 0.52 and -0.53, respectively; both P < .001). Although HRQOL declined during nCRT, no effect of nCRT was apparent on postoperative HRQOL compared with surgery alone. In addition to the improvement in survival, these findings support the view that nCRT according to the Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study-regimen can be regarded as a standard of care.	1
18	Sunde, B; Klevebro, F; Johar, A; Johnsen, G; Jacobsen, A-B; Glenjen, N I; Friesland, S; Lindblad, M; Ajengui, A; Lundell, L; Lagergren, P; Nilsson, M. Health-related quality of life in a randomized trial of neoadjuvant chemotherapy or chemoradiotherapy plus surgery in patients with oesophageal cancer (NeoRes trial). The British journal of surgery / 2019;106(11):1452-1463. DOI: 10.1002/bjs.11246	Prospective randomized phase III	In the NeoRes trial, patients were assigned randomly in a 1 : 1 ratio to receive either cisplatin 100 mg/m2 on day 1 and an infusion of 750 mg per m2 5-fluorouracil over 24 h on days 1-5 in three 21-day cycles (nCT) or the same chemotherapy regimen, but with the addition of 40 Gy radiotherapy (nCRT). HRQoL data were collected at baseline, after neoadjuvant therapy and at 1, 3 and 5 years after surgery. The European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30 and	To compare health-related quality of life (HRQoL) after neoadjuvant chemotherapy alone (nCT) compared with neoadjuvant chemoradiotherapy (nCRT) in patients with oesophageal cancer.	Of 181 patients randomized, 165 were included in the analysis of HRQoL. In a direct comparison between the allocated treatments, odynophagia after completion of neoadjuvant therapy but before surgery (P = 0.047) and troublesome coughing at 3 years' follow-up (P = 0.011) were more pronounced in the nCRT arm. In the longitudinal analyses within each treatment arm, a large deterioration in HRQoL was noted at 1 year. Some recovery was seen in both arms over time but, after 3 and 5 years, patients in the nCRT arm reported more symptoms compared with baseline than patients in the nCT arm.	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

			disease-specific modules were used			
19	**Liu B, Bo Y, Wang K, Liu Y, Tang X, Zhao Y, Zhao E, Yuan L. Concurrent neoadjuvant chemoradiotherapy could improve survival outcomes for patients with esophageal cancer: a meta-analysis based on random clinical trials. Oncotarget.2017 Mar 21;8(12):20410-20417. doi: 10.18632/oncotarget.14669. Review. PubMedPMID: 28099899; PubMed Central PMCID: PMC5386772	Meta-analysis	Twelve articles including 1756 patients from Pubmed and web of knowledge.	To determine the long-term effect of nCRT on OS vs SA	Concurrent neoadjuvant chemoradiotherapy followed by surgery was associated with significantly improved overall survival (HR=0.76, 95% CI= 0.68-0.86), progression survival (HR =0.69, 95% CI= 0.59-0.81), and R0 resection rate (RR =1.17, 95% CI= 1.03-1.33). Subgroup analysis suggested that concurrent neoadjuvant chemoradiotherapy could improve overall survival outcome for squamous cell carcinoma (HR=0.73, 95%CI=0.61-0.88) but not those for adenocarcinoma (HR=0.72, 95%CI=0.48-1.04). Findings are suggestive that concurrent neoadjuvant chemoradiotherapy was associated with a significant survival benefit in patients with esophageal cancer.	M
20	**Ajani JA, Xiao L, Roth JA, Hofstetter WL, Walsh G, Komaki R, Liao Z, Rice DC, Vaporciyan AA, Maru DM, Lee JH, Bhutani MS, Eid A, Yao JC, Phan AP, Halpin A, Suzuki A, Taketa T, Thall PF, Swisher SG. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. Ann Oncol. 2013 Nov;24(11):2844-9. doi: 10.1093/annonc/mdt339. Epub 2013 Aug 23. PubMed PMID: 23975663; PubMed Central PMCID: PMC3937600.	Prospective randomized phase III	126 pts. 122 adeno (97%)	To assess whether induction chemo would increase the rate of pathologic complete response (pathCR). No IC (Arm A) or IC (oxaliplatin/FU; Arm B) before oxaliplatin/FU/radiation. Surgery was attempted ~5-6 weeks after chemoradiation	The median actuarial OS for all patients (54 deaths) was 45.62 months [95% confidence interval (CI), 27.63-NA], with median OS 45.62 months (95% CI 25.56-NA) in Arm A and 43.68 months (95% CI 27.63-NA) in Arm B (P = 0.69). The pathCR rate in Arm A was 13% (7 of 55) and 26% (14 of 54) in Arm B (two-sided Fisher's exact test, P = 0.094). Safety was similar in both arms.	1
21	**Shimodaira Y, Slack RS, Harada K, Chen HC, Sagebiel T, Bhutani MS, Lee JH, Weston B, Elimova E, Lin Q, Amlashi FG, Mizrak Kaya D, Blum MA, Roth JA, Swisher SG, Skinner HD, Hofstetter WL, Rogers JE, Mares J, Thomas I, Maru DM, Komaki R, Walsh G, Ajani JA. Influence of induction chemotherapy in trimodality therapy-eligible oesophageal cancer patients: secondary analysis of a randomized trial. Br	Secondary analysis of prospective randomized trial	126 pts 122 adeno (97%)	To identify subsets that might benefit from IC, a secondary analysis was done.	OS was associated with tumour length (P=0.03), cT (P=0.02), cN (P=0.04), clinical stage (P=0.01), and tumour grade (P<0.001). The effect of IC differed according to tumour grade. Among patients with well or moderately differentiated (WMD) ECs (n=59), the 5-year survival rate was 74% with IC and 50% without IC, P=0.001. IC had no effect on OS of patients with poorly differentiated (PD) ECs (31% and	2

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

	J Cancer. 2018 Feb 6;118(3):331- 337. doi: 10.1038/bjc.2017.423. Epub 2017 Dec 12. PubMed PMID: 29235564; PubMed Central PMCID: PMC5808035				28%, respectively; interaction, P=0.04; IC, P=0.03). In the multivariate reduced model, WMD with IC was an independent prognosticator for better OS (HR=0.41, 95% CI, 0.25-0.67; P<0.001). The following four EC phenotypes emerged for OS: (1) very high risk (PD, cN2/N3), (2) high risk (PD, cN0/N1, stage cIII), (3) moderate risk (PD, cN0/N1, stage cI/II or WMD without IC), and (4) low risk (WMD with IC). The 5-year survival rates were 11%, 27%, 48%, and 74%, respectively (P<0.001).	
22	Yoon, Harry H; Ou, Fang-Shu; Soori, Gamini S; Shi, Qian; Wigle, Dennis A; Sticca, Robert P; Miller, Robert Clell; Leenstra, James L; Peller, Patrick J; Ginos, Brenda; Heying, Erica; Wu, Tsung-Teh; Drevyanko, Timothy F; Ko, Stephen; Mattar, Bassam Ibrahim; Nikcevic, Daniel A; Behrens, Robert J; Khalil, Maged F; Kim, George P; Alberts, Steven R. Induction versus no induction chemotherapy before neoadjuvant chemoradiotherapy and surgery in oesophageal adenocarcinoma: a multicentre randomized phase II trial (NCCTG N0849 [Alliance]). European journal of cancer (Oxford, England: 1990) / 2021;150(arv, 9005373):214-223. DOI: 10.1016/j.ejca.2021.03.025	Prospective randomized phase II	In this phase 2 trial (28 centres in the U.S. NCI-sponsored North Central Cancer Treatment Group [Alliance]), trimodality-eligible patients (T3-4N0, TanyN+) were randomized to receive induction (docetaxel, oxaliplatin, capecitabine; Arm A) or no induction chemotherapy (Arm B) followed by oxaliplatin/5-fluorouracil/radiation and subsequent surgery. The primary endpoint was the rate of pathologic complete response (pathCR). Secondary/exploratory endpoints were OS and disease-free survival (DFS)	To report primary results from the first multicentre randomized trial evaluating induction chemotherapy prior to trimodality therapy in patients with oesophageal or gastro-oesophageal junction adenocarcinoma. Notably, recent data from a single-institution randomized trial reported that induction chemotherapy prolonged overall survival (OS) in patients with well/moderately differentiated tumours	Of 55 patients evaluable for the primary endpoint, the pathCR rate was 28.6% (8/28) in A versus 40.7% (11/27) in B (P = .34). Given interim results indicating futility, accrual was terminated, but patients were followed. After a median follow-up of 60.4 months, a longer median OS in Arm A versus B was unexpectedly observed (3-year rates 57.1% versus 41.7%, respectively) driven by longer DFS after margin-free surgery. In posthoc analysis, induction (versus no induction) chemotherapy was associated with significantly longer OS and DFS among patients with well/moderately differentiated tumours, but not among patients with poorly/undifferentiated tumours (Pinteraction = 0.037). Adding induction chemotherapy prior to trimodality therapy did not improve the primary endpoint, pathCR. However, induction chemotherapy was associated with longer median OS, particularly among patients with well/moderately differentiated tumours.	1
23	Mukherjee, Somnath; Hurt, Christopher; Radhakrishna, Ganesh; Gwynne, Sarah; Bateman, Andrew; Gollins, Simon; Hawkins, Maria A; Canham, Joanne; Grabsch, Heike I; Falk, Stephen; Sharma, Ricky A; Ray, Ruby; Roy, Rajarshi; Cox, Catrin; Maynard, Nick; Nixon, Lisette; Sebag-Montefiore, David J; Maughan, Timothy; Griffiths, Gareth O;	Prospective randomized phase III	This is the first randomized study to evaluate toxicity and survival outcomes of two neoadjuvant chemoradiotherapy (CRT) regimens for patients with localised oesophageal adenocarcinoma (OAC) or	To evaluate toxicity and survival outcomes of two neoadjuvant chemoradiotherapy (CRT) regimens for patients with localised oesophageal adenocarcinoma	Eighty-five patients were recruited from 17 UK centres. The median OS was 41.7 months (95% confidence interval [CI] 19.6 to not reached) in the OxCapRT arm and was not reached in the CarPacRT arm (multivariable hazard ratio [HR] = 0.48, 95% CIs: 0.24-0.95, P = 0.035). The median PFS was 32.6 months (95% CIs: 17.1 to not reached) in the OxCapRT arm and was not	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

	Crosby, Tom D L. Oxaliplatin/capecitabine or carboplatin/paclitaxel-based preoperative chemoradiation for resectable oesophageal adenocarcinoma (NeoSCOPE): Long-term results of a randomized controlled trial. European journal of cancer (Oxford, England: 1990) / 2021;153(arv, 9005373):153-161. DOI: 10.1016/j.ejca.2021.05.020		gastro-oesophageal junction (GOJ) adenocarcinoma. The initial results showed comparable toxicity between regimens and pathological complete response (pCR) rate favouring CarPacRT. Herein, we report survival, progression patterns, and long-term toxicity after a median follow-up of 40.7 months., NeoSCOPE was an open-label, UK multicentre, randomized, phase II trial. Eighty-five patients with resectable OAC or GOJ adenocarcinoma, $\geq$cT3 and/or $\geq$cN1 (TNM v7), suitable for neoadjuvant CRT, were recruited between October 2013 and February 2015. Patients were randomized to OxCapRT (oxaliplatin 85 mg/m² on Days 1, 15, and 29; capecitabine 625 mg/m² orally twice daily on days of radiotherapy [RT]) or CarPacRT (carboplatin AUC2; paclitaxel 50 mg/m² on Days 1, 8, 15, 22, and 29). RT dose was 45 Gy/25 fractions/5 weeks. Both arms received induction chemotherapy (two cycles oxaliplatin 130 mg/m² on Day 1, capecitabine 625 mg/m² orally twice daily on Days 1-21) before CRT. Surgery was performed 6-8 weeks after CRT. The primary end-point was pCR. Secondary end-points were toxicity, progression-free survival (PFS), overall survival (OS), and patterns of progression	(OAC) or gastro-oesophageal junction (GOJ) adenocarcinoma.	reached in the CarPacRT arm (multivariable HR = 0.54, 95% CIs: 0.29-1.01, P = 0.053). In both arms, the distant progression was twice as common as locoregional progression. OS and PFS favoured neoadjuvant CarPacRT over OxCapRT. Distant was more common than locoregional progression; therefore, priority should be given to optimising the systemic treatment compone	
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American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

24	Goodman, Karyn A; Ou, Fang-Shu; Hall, Nathan C; Bekaii-Saab, Tanios; Fruth, Briant; Twohy, Erin; Meyers, Michael O; Boffa, Daniel J; Mitchell, Kisha; Frankel, Wendy L; Niedzwiecki, Donna; Noonan, Anne; Janjigian, Yelena Y; Thurmes, Paul J; Venook, Alan P; Meyerhardt, Jeffrey A; O'Reilly, Eileen M; Ilson, David H. Randomized Phase II Study of PET Response-Adapted Combined Modality Therapy for Esophageal Cancer: Mature Results of the CALGB 80803 (Alliance) Trial. <i>Journal of clinical oncology: official journal of the American Society of Clinical Oncology</i> / 2021;39(25): 2803-2815.DOI: 10.1200/JCO.20.03611	Prospective randomized phase III	After baseline PET, patients were randomly assigned to an induction chemotherapy regimen: modified oxaliplatin, leucovorin, and fluorouracil (FOLFOX) or carboplatin-paclitaxel (CP). Repeat PET was performed after induction; change in maximum standardized uptake value (SUV) from baseline was assessed. PET nonresponders (< 35% decrease in SUV) crossed over to the alternative chemotherapy during chemoradiation (50.4 Gy/28 fractions). PET responders (>= 35% decrease in SUV) continued on the same chemotherapy during chemoradiation. Patients underwent surgery at 6 weeks postchemoradiation. Primary end point was pathologic complete response (pCR) rate in nonresponders after switching chemotherapy	To evaluate the use of early assessment of chemotherapy responsiveness by positron emission tomography (PET) imaging to tailor therapy in patients with esophageal and esophagogastric junction adenocarcinoma.	Two hundred forty-one eligible patients received Protocol treatment, of whom 225 had an evaluable repeat PET. The pCR rates for PET nonresponders after induction FOLFOX who crossed over to CP (n = 39) or after induction CP who changed to FOLFOX (n = 50) was 18.0% (95% CI, 7.5 to 33.5) and 20% (95% CI, 10 to 33.7), respectively. The pCR rate in responders who received induction FOLFOX was 40.3% (95% CI, 28.9 to 52.5) and 14.1% (95% CI, 6.6 to 25.0) in responders to CP. With a median follow-up of 5.2 years, median overall survival was 48.8 months (95% CI, 33.2 months to not estimable) for PET responders and 27.4 months (95% CI, 19.4 months to not estimable) for nonresponders. For induction FOLFOX patients who were PET responders, median survival was not reached., CONCLUSION: Early response assessment using PET imaging as a biomarker to individualize therapy for patients with esophageal and esophagogastric junction adenocarcinoma was effective, improving pCR rates in PET nonresponders. PET responders to induction FOLFOX who continued on FOLFOX during chemoradiation achieved a promising 5-year overall survival of 53%.	1
25	Safran, Howard P; Winter, Kathryn; Ilson, David H; Wagle, Dennis; DiPetrillo, Thomas; Haddock, Michael G; Hong, Theodore S; Leichman, Lawrence P; Rajdev, Lakshmi; Resnick, Murray; Kachnic, Lisa A; Seaward, Samantha; Mamon, Harvey; Diaz Pardo, Dayssy Alexandra; Anderson, Carryn M; Shen, Xinglei; Sharma, Anand K; Katz, Alan W; Salo, Jonathan; Leonard, Kara L; Moughan, Jennifer; Crane, Christopher H. Trastuzumab with trimodality treatment for oesophageal adenocarcinoma with HER2 overexpression (NRG Oncology/RTOG 1010): a multicentre, randomized, phase 3 trial. <i>The Lancet. Oncology</i> / 2022; 23(2):259-269. DOI: 10.1016/S1470-2045(21)00718-X	Prospective randomized phase III	NRG Oncology/RTOG-1010 was an open label, randomized, phase 3 trial for which patients were accrued from 111 NRG-affiliated institutions in the USA. Eligible patients were adults (aged >=18 years) with newly diagnosed pathologically confirmed oesophageal adenocarcinoma, American Joint Committee on Cancer 7th edition T1N1-2 or T2-3N0-2 stage disease, and a Zubrod performance status of 0-2. Patients were stratified by adenopathy (no vs yes [coeliac absent] vs yes [coeliac present <=2 cm]) and randomly assigned	To establish whether trastuzumab improves disease-free survival when combined with trimodality treatment (paclitaxel plus carboplatin and radiotherapy, followed by surgery) for patients with untreated HER2-overexpressing oesophageal adenocarcinoma.,	606 patients were entered for HER2 assessment from Dec 30, 2010 to Nov 10, 2015, and 203 eligible patients who were HER2-positive were enrolled and randomly assigned to chemoradiotherapy plus trastuzumab (n=102) or chemoradiotherapy alone (n=101). Median duration of follow-up was 2.8 years (IQR 1.4-5.7). Median disease-free survival was 19.6 months (95% CI 13.5-26.2) with chemoradiotherapy plus trastuzumab compared with 14.2 months (10.5-23.0) for chemoradiotherapy alone (hazard ratio 0.99 [95% CI 0.71-1.39], log-rank p=0.97). Grade 3 treatment-related adverse events occurred in 41 (43%) of 95 patients in the chemoradiotherapy plus trastuzumab group versus 52 (54%) of 96 in the chemoradiotherapy group and grade 4 events occurred in 20 (21%) versus 21 (22%). The most common grade 3 or worse treatment-related	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

			(1:1) to receive weekly intravenous paclitaxel (50 mg/m ² intravenously over 1 h) and carboplatin (area under the curve 2, intravenously over 30-60 min) for 6 weeks with radiotherapy 50.4 Gy in 28 fractions (chemoradiotherapy) followed by surgery, with or without intravenous trastuzumab (4 mg/kg in week one, 2 mg/kg per week for 5 weeks during chemoradiotherapy, 6 mg/kg once presurgery, and 6 mg/kg every 3 weeks for 13 treatments starting 21-56 days after surgery). The primary endpoint, disease-free survival, was defined as the time from randomisation to death or first of locoregional disease persistence or recurrence, distant metastases, or second primary malignancy. Analyses were done by modified intention to treat. This study is registered with Clinicaltrials.gov, NCT01196390; it is now closed and in follow-up.,		adverse events for both groups were haematological (53 [56%] of 95 patients in the chemoradiotherapy plus trastuzumab group vs 55 [57%] of 96 patients in the chemotherapy group) or gastrointestinal disorders (28 [29%] vs 20 [21 %]). 34 (36%) of 95 patients in the chemoradiotherapy plus trastuzumab group and 27 (28%) of 96 patients in the chemoradiotherapy only group had treatment-related serious adverse events. There were eight treatment-related deaths: five (5%) of 95 patients in the chemoradiotherapy plus trastuzumab group (bronchopleural fistula, oesophageal anastomotic leak, lung infection, sudden death, and death not otherwise specified), and three (3%) of 96 in the chemoradiotherapy group (two multiorgan failure and one sepsis)	
26	Hoepfner, Jens; ; Brunner, Thomas; Schmoor, Claudia; Bronsert, Peter; Kulemann, Birte; Claus, Rainer; Utzolino, Stefan; Izbicki, Jakob Robert; Gockel, Ines; Gerdes, Berthold; Ghadimi, Michael; Reichert, Benedikt; Lock, Johan F; Bruns, Christiane; Reitsamer, Ernst; Schmeding, Maximilian; Benedix, Frank; Keck, Tobias; Folprecht, Gunnar; Thuss-Patience, Peter; Neumann, Ulf Peter; Pascher, Andreas; Imhof, Detlef; Daum, Severin; Strieder, Tanja; Krautz, Christian; Zimmermann, Simone; Werner, Jens; Mahlberg, Rolf; Illerhaus, Gerald; Grimminger, Peter;	Prospective randomized phase III	In this phase 3, multicenter, randomized trial, we assigned in a 1:1 ratio patients with resectable esophageal adenocarcinoma to receive perioperative chemotherapy with FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) plus surgery or preoperative chemoradiotherapy (radiotherapy at a dose of 41.4 Gy and carboplatin and paclitaxel) plus surgery.	To investigate whether perioperative chemotherapy is preferable to preoperative chemoradiotherapy in advanced esophageal adenocarcinoma	From February 2016 through April 2020, we assigned 221 patients to the FLOT group and 217 patients to the preoperative-chemoradiotherapy group. With a median follow-up of 55 months, overall survival at 3 years was 57.4% (95% confidence interval [CI], 50.1 to 64.0) in the FLOT group and 50.7% (95% CI, 43.5 to 57.5) in the preoperative-chemoradiotherapy group (hazard ratio for death, 0.70; 95% CI, 0.53 to 0.92; P = 0.01). Progression-free survival at 3 years was 51.6% (95% CI, 44.3 to 58.4) in the FLOT group and 35.0% (95% CI, 28.4 to 41.7) in the preoperative-chemoradiotherapy group (hazard ratio for disease progression or death, 0.66; 95%	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

	Lordick, Florian. Perioperative Chemotherapy or Preoperative Chemoradiotherapy in Esophageal Cancer. The New England journal of medicine / 2025;392(4):323-335. DOI: 10.1056/NEJMoa2409408		Eligibility criteria included a primary tumor with a clinical stage of cT1 cN+, cT2-4a cN+, or cT2-4a cN0 disease, in which T indicates the size and extent of the tumor (higher numbers indicate a more advanced tumor), and N indicates the presence (N+) or absence (N0) of cancer spread to the lymph nodes, without evidence of metastatic spread. The primary end point was overall survival		CI, 0.51 to 0.85). Among the patients who started the assigned treatment, grade 3 or higher adverse events were observed in 120 of 207 patients (58.0%) in the FLOT group and in 98 of 196 patients (50.0%) in the preoperative-chemoradiotherapy group. Serious adverse events were observed in 98 of 207 patients (47.3%) in the FLOT group and in 82 of 196 patients (41.8%) in the preoperative-chemoradiotherapy group. Mortality at 90 days after surgery was 3.1% in the FLOT group and 5.6% in the preoperative-chemoradiotherapy group. Perioperative chemotherapy with FLOT led to improved survival among patients with resectable esophageal adenocarcinoma as compared with preoperative chemoradiotherapy.	
27	Barbour, A P; Walpole, E T; Mai, G T; Barnes, E H; Watson, D I; Ackland, S P; Martin, J M; Burge, M; Finch, R; Karapetis, C S; Shannon, J; Nott, L M; Varma, S; Marx, G; Falk, G L; GebSKI, V; Oostendorp, M; Wilson, K; Thomas, J; Lampe, G; Zalcberg, J R; Simes, J; Smithers, B M. Preoperative cisplatin, fluorouracil, and docetaxel with or without radiotherapy after poor early response to cisplatin and fluorouracil for resectable oesophageal adenocarcinoma (AGITG DOCTOR): results from a multicentre, randomized controlled phase II trial. Annals of oncology: official journal of the European Society for Medical Oncology / 2020;31(2):236-245. DOI: 10.1016/j.annonc.2019.10.019	Prospective randomized phase II	Patients with resectable EAC were enrolled and randomized into two single-arm, multicentre phase II trials. After induction cisplatin and 5-fluorouracil (CF), all were assessed by day 15 positron emission tomography (PET). Patients with an EMR [maximum standardised uptake values (SUVmax) >=35% reduction from baseline to day 15 PET] received a second CF cycle then oesophagectomy. Non-responders were randomized 1 : 1 to two cycles of CF and docetaxel (DCF, n = 31) or DCF + 45 Gy radiotherapy (DCFRT, n = 35) then oesophagectomy. The primary end point was major histological response (<10% residual tumour) in the oesophagectomy specimen; secondary end points were overall survival (OS), progression-free survival (PFS), and locoregional recurrence (LR).	To investigate whether tailoring neoadjuvant therapy can improve outcomes in oesophageal/ gastro-oesophageal junction adenocarcinoma (EAC) not showing early metabolic response (EMR) to chemotherapy	Of 124 patients recruited, major histological response was achieved in 3/45 (7%) with EMR, 6/30 (20%) DCF, and 22/35 (63%) DCFRT patients. Grade 3/4 toxicities occurred in 12/45 (27%) EMR (CF), 13/31 (42%) DCF, and 25/35 (71%) DCFRT patients. No treatment-related deaths occurred. LR by 3 years was seen in 5/45 (11%) EMR, 10/31 (32%) DCF, and 4/35 (11%) DCFRT patients. PFS [95% confidence interval (CI)] at 36 months was 47% (31% to 61%) for EMR, 29% (15% to 45%) for DCF, and 46% (29% to 61%) for DCFRT patients. OS (95% CI) at 60 months was 53% (37% to 67%) for EMR, 31% (16% to 48%) for DCF, and 46% (29% to 61%) for DCFRT patients. EMR is associated with favourable OS, PFS, and low LR. For non-responders, the addition of docetaxel augmented histological response rates, but OS, PFS, and LR remained inferior compared with responders. DCFRT improved histological response and PFS/LR outcomes, matching the EMR group. Early PET/CT has the potential to tailor therapy for patients not showing an early response to chemotherapy	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

28	von Döbeln, Gabriella Alexandersson; Wagenius, Gunnar; Holtved, Eva; Jacobsen, Anne-Birgitte; Nilsson, Magnus; Yu, Jingru; Baeksgaard, Lene. Definitive chemoradiotherapy plus cetuximab for cancer in the oesophagus or gastro-oesophageal junction. Cancer treatment and research communications / 2020;24(101694651):100187. DOI: 10.1016/j.ctarc.2020.100187	Prospective nonrandomized phase II	This non-randomized multicentre phase II trial recruited patients aged 18-75 with WHO performance status 0-2 having squamous cell carcinoma or adenocarcinoma in the oesophagus or gastro-oesophageal junction, T2-4, N0-3, M0 not suitable for surgery. Chemotherapy was three 21-day cycles of fluorouracil 750 mg/m² D1-5 and oxaliplatin D1 (cycle 1:130mg/m², cycle 2-3:85 mg/m²). Radiotherapy was 50Gy in 2Gy/fraction, 5 days a week, concurrent with cycle 2 and 3 and weekly cetuximab. The primary objective was loco-regional control at one year	To evaluate the efficacy of cetuximab in combination with chemoradiotherapy	52 patients were included. 51 were eligible for toxicity and survival analysis and 46 for recurrence analysis. Full radiotherapy dose was delivered to 80%, 75% received all three cycles of chemotherapy and 75% received four or more doses of cetuximab. The most common related grade III-IV adverse events were gastro-intestinal (16), hypersensitivity (6) and infection (5). There were two drug-related deaths. Within six months from the end of treatment, six patients died from complications from fistulas. The loco-regional control rate at one year was 47.3% (95%CI 30.9%-62.1%). Overall survival at three years was 29.1% (95% CI 17.4-41.9%). Oxaliplatin and fluorouracil given concurrent with radiotherapy and cetuximab had an acceptable safety profile and showed a clinical response in patients with locoregionally advanced oesophageal cancer unsuitable for surgery. However, the primary end-point was not met, and the addition of cetuximab to definitive chemoradiotherapy cannot be recommended	2
29	Sunde, B; Johnsen, G; Jacobsen, A-B; Glenjen, N I; Friesland, S; Lindblad, M; Rouvelas, I; Wang, N; Lundell, L; Lagergren, P; Nilsson, M. Effects of neoadjuvant chemoradiotherapy vs chemotherapy alone on the relief of dysphagia in esophageal cancer patients: secondary endpoint analysis in a randomized trial. Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus / 2019;32(2): DOI: 10.1093/dote/doy069	Prospective randomized phase III	Patients completed dysphagia questionnaires before the start and after neoadjuvant therapy, using the European Organization for Research and Treatment of Cancer (EORTC) esophageal cancer modules QLQ-OES24/OG25. Chiriac tumor regression grade (TRG) was used to assess the histological response.	To compare the effects on dysphagia of neoadjuvant chemotherapy (nCT) versus neoadjuvant chemoradiotherapy (nCRT) and further to study the association between dysphagia response and histological response. Patient reported swallowing function was a secondary endpoint in the NeoRes trial, in which patients were randomized between neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy.	Out of 181 patients were randomized, of whom 87% completed the dysphagia questionnaires before and 73% after neoadjuvant treatment. Patient characteristics were similar between the treatment arms. Among patients reporting dysphagia at baseline, neoadjuvant therapy improved dysphagia in both arms. The mean dysphagia score after neoadjuvant treatment was significantly lower after nCT compared to after nCRT (P = 0.022). The reported dysphagia did not differ between those with a complete histological response (TRG 1) and those without any response at all (TRG 4) (P = 0.583).	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

30	**Burmeister BH, Thomas JM, Burmeister EA, Walpole ET, Harvey JA, Thomson DB, Barbour AP, Gotley DC, Smithers BM. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. <i>Eur J Cancer.</i> 2011 Feb;47(3): 354-60.doi: 10.1016/j.ejca.2010.09.009. PubMed PMID: 21084184.	Prospective randomized phase II	75 patients were enrolled on the study: 36 received preoperative CT and 39 preoperative CRT. Chemo: 5-FU+cisplatin RT: 35 Gy/15 fx	To compare preoperative CT and CRT for resectable adenocarcinoma of the oesophagus and gastroesophageal junction.	Toxicity was similar for CT and CRT. Eight patients (11%) did not proceed to resection. The histopathological response rate (CRT 31% versus CT 8%, $p = 0.01$) and R1 resection rate (CRT 0% versus CT 11%, $p = 0.04$) favoured those receiving CRT. The median PFS was 14 and 26 months for CT and CRT respectively ($p = 0.37$). The median OS was 29 months for CT compared with 32 months for CRT ($p = 0.83$). Despite no difference in survival, the improvement from preoperative CRT with respect to margin involvement makes this treatment a reasonable option for bulky, locally advanced resectable adenocarcinoma of the oesophagus.	1
31	**Stahl M, Walz MK, Riera-Knorrenschild J, Stuschke M, Sandermann A, Bitzer M, Wilke H, Budach W. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. <i>Eur J Cancer.</i> 2017 Aug; 81:183-190. doi: 10.1016/j.ejca.2017.04.027. PubMed PMID: 28628843	Prospective randomized phase III	119 patients with locally advanced adenocarcinomas of the oesophagogastric junction (Siewert types I-III) were randomized to nCT (group A) or iCT-nCRT (group B) followed by S. CRT: 30 Gy in 15 fx with cisplatin & etoposide. Chemo alone: 5-Fu/Leucovorin/Cisplatin	To compare nCT vs. iCT-nCRT in the treatment of EC	Update of 2009 report. Local progression-free survival after tumour resection was significantly improved by CRT (hazard ratio [HR] 0.37; 0.16-0.85, $p = \text{value } 0.01$) and 20 versus 12 patients were free of local tumour progression at 5 years ($p = 0.03$). Although the rate of postoperative in-hospital mortality was somewhat higher with CRT (10.2% versus 3.8%, $p = 0.26$), more patients were alive at 3 and 5 years after CRT (46.7% and 39.5%) compared with chemotherapy (26.1% and 24.4%). Thus, overall survival showed a trend in favour of preoperative CRT (HR 0.65, 95% confidence interval [CI] 0.42-1.01, $p = 0.055$). Although the primary end-point overall survival of the study was not met, our long-term follow-up data suggest a benefit in local progression-free survival when radiotherapy was added to preoperative chemotherapy in patients with locally advanced adenocarcinoma of the oesophagogastric junction.	1
32	**Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, Kopp HG, Mayer F, Haag GM, Luley K, Lindig U, Schmiegel W, Pohl M, Stoecklacher J, Folprecht G, Probst S, Prasnikar N, Fischbach W, Mahlberg R, Trojan	Prospective randomized phase III	716 patients with histologically confirmed advanced clinical stage cT2 or higher or nodal positive stage (cN+), or both, resectable tumours, with no evidence of distant metastases,	Phase III: The primary outcome of the trial was overall survival (superiority)	Overall survival was increased in the FLOT group compared with the ECF/ECX group (hazard ratio [HR] 0.77; 95% confidence interval [CI]; 0.63 to 0.94; median overall survival, 50 months [38-33 to not reached] vs 35 months [27-35 to 46-26]). The number	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

	J,Koenigsmann M, Martens UM, Thuss-Patience P, Egger M, Block A, Heinemann V, Illerhaus G, Moehler M, Schenk M, Kullmann F, Behringer DM, Heike M, Pink D, Teschendorf C, Löhner C, Bernhard H, Schuch G, Rethwisch V, von Weikersthal LF, Hartmann JT, Kneba M, Daum S, Schulmann K, Weniger J, Belle S, Gaiser T, Oduncu FS, Güntner M, Hozaeel W, Reichart A, Jäger E, Kraus T, Mönig S, Bechstein WO, Schuler M, Schmalenberg H, Hofheinz RD; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomized, phase 2/3 trial. Lancet. 2019 May 11;393(10184):1948-1957. doi:10.1016/S0140-6736(18)32557-1. Epub 2019 Apr 11. PubMed PMID: 30982686		via central interactive web based-response system, to receive either three pre-operative and three postoperative 3-week cycles of 50 mg/m ² epirubicin and 60 mg/m ² cisplatin on day 1 plus either 200 mg/m ² fluorouracil as continuous intravenous infusion or 1250 mg/m ² capecitabine orally on days 1 to 21 (ECF/ECX; control group) or four preoperative and four postoperative 2-week cycles of 50 mg/m ² docetaxel, 85 mg/m ² oxaliplatin, 200 mg/m ² leucovorin and 2600 mg/m ² fluorouracil as 24-h infusion on day 1 (FLOT; experimental group).	analysed in the intention-to-treat population.	of patients with related serious adverse events (including those occurring during hospital stay for surgery) was similar in the two groups (96 [27%] in the ECF/ECX group vs 97 [27%] in the FLOT group), as was the number of toxic deaths (two [$<1\%$] in both groups). Hospitalisation for toxicity occurred in 94 patients (26%) in the ECF/ECX group and 89 patients (25%) in the FLOT group. In locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma, perioperative FLOT improved overall survival compared with perioperative ECF/ECX	
33	Reynolds, John V; Preston, Shaun R; O'Neill, Brian; Lowery, Maeve A; Baeksgaard, Lene; Crosby, Thomas; Cunningham, Moya; Cuffe, Sinead; Griffiths, Gareth O; Parker, Imelda; Risumlund, Signe Lenora; Roy, Rajarshi; Falk, Stephen; Hanna, George B; Bartlett, Frederick R; Alvarez-Iglesias, Alberto; Achiam, Michael P; Nilsson, Magnus; Piessen, Guillaume; Ravi, Narayanasamy; O'Toole, Dermot; Johnston, Ciaran; McDermott, Raymond S; Turkington, Richard C; Wahed, Shajahan; Sothi, Sharmila; Ford, Hugo; Wadley, Martin S; Power, Derek. Trimodality therapy versus perioperative chemotherapy in the management of locally advanced adenocarcinoma of the oesophagus and oesophagogastric junction (Neo-AEGIS): an open-label, randomized, phase 3 trial. The lancet. Gastroenterology & hepatology / 2023;8(11):1015-1027. DOI: 10.1016/S2468-1253(23)00243-1	Prospective randomized phase III	Neo-AEGIS (CTRIAL-IE 10-14) was an open-label, randomized, phase 3 trial done at 24 centres in Europe. Patients aged 18 years or older with clinical tumour stage T2-3, nodal stage N0-3, and M0 adenocarcinoma of the oesophagus and oesophagogastric junction were randomly assigned to perioperative chemotherapy (three preoperative and three postoperative 3-week cycles of intravenous 50 mg/m ² epirubicin on day 1 plus intravenous 60 mg/m ² cisplatin or intravenous 130 mg/m ² oxaliplatin on day 1 plus continuous infusion of 200 mg/m ² fluorouracil daily or oral 625 mg/m ² capecitabine twice daily up to 2018, with four	To compare trimodality therapy (preoperative radiotherapy with carboplatin plus paclitaxel [CROSS regimen]) with optimum contemporaneous perioperative chemotherapy regimens (epirubicin plus cisplatin or oxaliplatin plus fluorouracil or capecitabine [a modified MAGIC regimen] before 2018 and fluorouracil, leucovorin, oxaliplatin, and docetaxel [FLOT] subsequently).	Between Jan 24, 2013, and Dec 23, 2020, 377 patients were randomly assigned, of whom 362 were included in the intention-to treat population (327 [90%] male and 360 [99%] White): 184 in the perioperative chemotherapy group and 178 in the trimodality therapy group. The trial closed prematurely in December, 2020, after the second interim futility analysis (143 deaths), on the basis of similar survival metrics and the impact of the COVID-19 pandemic. At a median follow-up of 38.8 months (IQR 16.3-55.1), median overall survival was 48.0 months (95% CI 33.6-64.8) in the perioperative chemotherapy group and 49.2 months (34.8-74.4) in the trimodality therapy group (3-year overall survival 55% [95% CI 47-62] vs 57% [49-64]; hazard ratio 1.03 [95% CI 0.77-1.38]; log-rank p=0.82). Median disease-free survival was 32.4 months (95% CI 22.8-64.8) in the perioperative chemotherapy group and 24.0 months (18.0-40.8) in the trimodality therapy group [hazard ratio 0.89 [95% CI 0.68-1.17]; log-rank p=0.41). The pattern of	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

			preoperative and four postoperative 2-week cycles of 2600 mg/m² fluorouracil, 85 mg/m² oxaliplatin, 200 mg/m² leucovorin, and 50 mg/m² docetaxel intravenously on day 1 as an option from 2018) or trimodality therapy (41.4 Gy in 23 fractions on days 1-5, 8-12, 15-19, 22-26, and 29-31 with intravenous area under the curve 2 mg/mL per min carboplatin plus intravenous 50 mg/m² paclitaxel on days 1, 8, 15, 22, and 29). The primary endpoint was overall survival, assessed in all randomly assigned patients who received at least one dose of study drug, regardless of which study drug they received, by intention to treat. Secondary endpoints were disease-free survival, site of treatment failure, operative complications, toxicity, pathological response (complete [ypTONO] and major [tumour regression grade 1 and 2]), margin-free resection (R0), and health-related quality of life. Toxicity and safety data were analysed in the safety population, defined as patients who took at least one dose of study drug, according to treatment actually received. The initial power calculation was based on superiority of trimodality therapy (n=366 patients); it was adjusted after FLOT became an option to a non-inferiority design with a margin of 5% for perioperative chemotherapy (n=540).		recurrence, locoregional or systemic, was not significantly different (odds ratio 1.35 [95% CI 0.63-2.91], p=0.44). Pathological complete response (odds ratio 0.33 [95% CI 0.14-0.81], p=0.012), major pathological response (0.21 [0.12-0.38], p<0.0001), and R0 rates (0.21 [0.08-0.53], p=0.0003) favoured trimodality therapy. The most common grade 3-4 adverse event was neutropenia (49 [27%] of 183 patients in the perioperative chemotherapy group vs 11 [6%] of 178 patients in the trimodality therapy group), followed by diarrhoea (20 [11%] vs none), and pulmonary embolism (ten [5%] vs nine [5%]). One (1%) patient in the perioperative chemotherapy group and three (2%) patients in the trimodality therapy group died from serious adverse events, two (one in each group) of which were possibly related to treatment. No differences were seen in operative mortality (five [3%] deaths in the perioperative chemotherapy group vs four [2%] in the trimodality therapy group), major morbidity, or in global health status at 1 and 3 years. Although underpowered and incomplete, Neo-AEGIS provides the largest comprehensive randomized dataset for patients with adenocarcinoma of the oesophagus and oesophagogastric junction treated with perioperative chemotherapy (predominantly the modified MAGIC regimen), and CROSS trimodality therapy, and reports similar 3-year survival and no major differences in operative and health-related quality of life outcomes. We suggest that these data support continued clinical equipoise	
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American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

34	Leong, Trevor; Smithers, B Mark; Michael, Michael; Haustermans, Karin; Wong, Rebecca; GebSKI, Val; O'Connell, Rachel L; Zalcbberg, John; Boussioutas, Alex; Findlay, Michael; Willis, David; Moore, Alisha; Murray, William K; Lordick, Florian; O'Callaghan, Chris; Swallow, Carol; Darling, Gail; Miller, Danielle; Strickland, Andrew; Liberman, Moishe; Mineur, Laurent; Simes, John. Preoperative Chemoradiotherapy for Resectable Gastric Cancer. The New England journal of medicine / 2024;391(19):1810-1821. DOI: 10.1056/NEJMoa2405195	Prospective randomized phase III	We conducted an international, phase 3 trial in which patients with resectable adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to receive preoperative chemoradiotherapy plus perioperative chemotherapy or perioperative chemotherapy alone (control). In both groups, patients received either epirubicin, cisplatin, and fluorouracil or fluorouracil, leucovorin, oxaliplatin, and docetaxel both before and after surgery; the preoperative-chemoradiotherapy group also received chemoradiotherapy (45 Gy in 25 fractions of radiation, plus fluorouracil infusion). The primary end point was overall survival, and secondary end points included progression-free survival, pathological complete response, toxic effects, and quality of life	To investigate whether the addition of preoperative chemoradiotherapy to perioperative chemotherapy improves overall survival as compared with perioperative chemotherapy alone among patients with resectable gastric and gastroesophageal junction adenocarcinoma.	A total of 574 patients underwent randomization at 70 sites in Australasia, Canada, and Europe: 286 to the preoperative-chemoradiotherapy group and 288 to the perioperative-chemotherapy group. A higher percentage of patients in the preoperative-chemoradiotherapy group than in the perioperative-chemotherapy group had a pathological complete response (17% vs. 8%) and greater tumor downstaging after resection. At a median follow-up of 67 months, no significant between-group differences in overall survival or progression-free survival were noted. The median overall survival was 46 months with preoperative chemoradiotherapy and 49 months with perioperative chemotherapy (hazard ratio for death, 1.05; 95% confidence interval, 0.83 to 1.31), and the median progression-free survival was 31 months and 32 months, respectively. Treatment-related toxic effects were similar in the two groups. The addition of preoperative chemoradiotherapy to perioperative chemotherapy did not improve overall survival as compared with perioperative chemotherapy alone among patients with resectable gastric and gastroesophageal junction adenocarcinoma.	1
35	Goetze, Thorsten O; Hofheinz, Ralf-Dieter; Gaiser, Timo; Schmalenberg, Harald; Strumberg, Dirk; Goekkurt, Eray; Angermeier, Stefan; Zander, Thomas; Kopp, Hans G; Pink, Daniel; Siegler, Gabriele; Schenk, Michael; de Vita, Ferdinando; Galizia, Gennaro; Maiello, Evaristo; Bechstein, Wolf O; Elshafei, Moustafa; Loose, Maria; Sookthai, Disorn; Brulin, Tanita; Pauligk, Claudia; Homann, Nils; Al-Batran, Salah-Eddin. Perioperative FLOT plus ramucirumab for resectable esophagogastric adenocarcinoma: A randomized phase II/III trial of the German AIO and Italian GOIM. International journal of cancer / 2023;153(1): 153-163.DOI: 10.1002/ijc.34495	Prospective randomized phase II/III	Patients received either FLOT alone (Arm A) or combined with ramucirumab followed by ramucirumab monotherapy (Arm B). The primary endpoint for the phase II portion was the pathological complete or subtotal response (pCR/pSR) rate. Baseline characteristics were comparable between both arms with a high rate of tumors signet-ring cell component (A:47% B:43%).	To evaluate the addition of the vascular endothelial growth factor receptor-2 inhibitor ramucirumab to FLOT as perioperative treatment for resectable esophagogastric adenocarcinoma.	No between-arm difference in pCR/pSR rate was seen (A:29% B:26%), therefore the transition to phase III was not pursued. Nevertheless, the combination was associated with a significantly increased R0-resection rate compared with FLOT alone (A:82% B:96%; P = .009). In addition, the median disease-free survival was numerically improved in Arm B (A:21 months B:32 months, HR 0.75, P = 0.218), while the median overall survival was similar in both treatment arms (A:45 months B:46 months, HR 0.94, P = 0.803). Patients with Siewert type I tumors receiving transthoracic esophagectomy with intrathoracic anastomosis showed an increased risk of serious postoperative complications after ramucirumab treatment, therefore recruitment of those patients was stopped after the first-third of the	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

					study. Overall, surgical morbidity and mortality was comparable, whereas more non-surgical grade ≥ 3 adverse events were observed with the combination, especially anorexia (A:1% B:11%), hypertension (A:4% B:13%) and infections (A:19% B:33%). The combination of ramucirumab and FLOT as perioperative treatment shows efficacy signals, particularly in terms of R0 resection rates, for a study population with a high proportion of prognostically poor histological subtypes, and further evaluation in this subgroup seems warranted	
36	Taberno J, Hoff PM, Shen L, Ohtsu A, Chah MA, Siddiqui A, Heeson S, Kiermaier A, Macharia H, Restuccia E, Kang Y-K. Pertuzumab, trastuzumab, and chemotherapy in HER2-positive gastric/gastroesophageal junction cancer: end-of-study analysis of the JACOB phase III randomized clinical trial. Gastric Cancer. 2022 Sep 6;26(1):123–131. doi: 10.1007/s10120-022-01335-4	Prospective randomized phase III	Eligible patients were randomized 1:1 to pertuzumab/placebo plus trastuzumab and chemotherapy every 3 weeks. Primary endpoint: overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), and safety.	To evaluate the safety and efficacy of pertuzumab/placebo plus trastuzumab and chemotherapy in patients with gastric/GEJ cancer	The intention-to-treat population comprised 388 patients in the pertuzumab arm and 392 in the placebo arm. The safety population comprised 385 and 388 patients, respectively. Median follow-up was ≥ 44.4 months. Median OS was increased by 3.9 months (hazard ratio 0.85 [95% confidence intervals, 0.72–0.99]) and median PFS by 1.3 months (hazard ratio 0.73 [95% confidence intervals, 0.62–0.85]) in the pertuzumab vs. the placebo arm. ORR was numerically higher (57.0% vs. 48.6%) and median DoR 1.8 months longer with pertuzumab treatment. There was a trend for more favorable hazard ratios in certain subgroups related to HER2 amplification/overexpression. Safety was comparable between arms, except for serious and grade 3–5 adverse events, and any-grade diarrhea, which were more frequent with pertuzumab. JACOB did not meet its primary endpoint. Nonetheless, the study continues to demonstrate some, albeit limited, evidence of treatment activity and an acceptable safety profile for pertuzumab plus trastuzumab and chemotherapy in previously untreated HER2-positive metastatic gastric or gastroesophageal junction cancer after long-term follow-up.	1
37	Shitara, Kohei; Rha, Sun Young; Wyrwicz, Lucjan S; Oshima, Takashi; Karaseva, Nina; Osipov, Mikhail; Yasui, Hisateru; Yabusaki, Hiroshi; Afanasyev, Sergey; Park, Young-Kyu; Al-Batran, Salah-Eddin; Yoshikawa, Takaki; Yanez, Patricio; Dib Bartolomeo,	Prospective randomized phase III	The KEYNOTE-585 study is a multicentre, randomized, placebo-controlled, double-blind, phase 3 study done at 143 medical centres in 24 countries. Eligible patients were aged 18	To assess the antitumor activity of neoadjuvant and adjuvant pembrolizumab plus chemotherapy in	Between Oct 9, 2017, and Jan 25, 2021, of 1254 patients screened, 804 were randomly assigned to the main cohort, of whom 402 were assigned to the pembrolizumab plus cisplatin-based chemotherapy group and 402 to the placebo plus cisplatin-based chemotherapy group, and 203 to	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

	Maria; Lonardi, Sara; Tabernero, Josep; Van Cutsem, Eric; Janjigian, Yelena Y; Oh, Do-Youn; Xu, Jianming; Fang, Xiao; Shih, Chie-Schin; Bhagia, Pooja; Bang, Yung-Jue. Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): an interim analysis of the multicentre, double-blind, randomized phase 3 study. The Lancet. Oncology / 2024;25(2):212-224. DOI: 10.1016/S1470-2045(23)00541-7		years or older with untreated, locally advanced, resectable gastric or gastro-oesophageal adenocarcinoma, and an Eastern Cooperative Oncology Group performance status 0-1. Patients were randomly assigned (1:1) by an interactive voice response system and integrated web response system to neoadjuvant pembrolizumab 200 mg intravenously or placebo (saline) plus cisplatin-based doublet chemotherapy (main cohort) every 3 weeks for 3 cycles, followed by surgery, adjuvant pembrolizumab or placebo plus chemotherapy for 3 cycles, then adjuvant pembrolizumab or placebo for 11 cycles. A small cohort was also randomly assigned (1:1) to pembrolizumab or placebo plus fluorouracil, docetaxel, and oxaliplatin (FLOT)-based chemotherapy (FLOT cohort) every 2 weeks for four cycles, followed by surgery, adjuvant pembrolizumab, or placebo plus FLOT for four cycles, then adjuvant pembrolizumab or placebo for 11 cycles. Patients were stratified by geographic region, tumour stage, and chemotherapy backbone. Primary endpoints were pathological complete response (reviewed centrally), event-free survival (reviewed by the investigator), and overall survival in the intention-to-treat population, and safety assessed in all patients who received at	patients with locally advanced resectable gastric or gastro-oesophageal adenocarcinoma	the FLOT cohort, of whom 100 were assigned to the pembrolizumab plus FLOT group and 103 to placebo plus FLOT group. In the main cohort of 804 participants, 575 (72%) were male and 229 (28%) were female. In the main cohort, after median follow-up of 47.7 months (IQR 38.0-54.8), pembrolizumab was superior to placebo for pathological complete response (52 [12.9%; 95% CI 9.8-16.6] of 402 vs eight [2.0%; 0.9-3.9] of 402; difference 10.9%, 95% CI 7.5 to 14.8; p<0.00001). Median event-free survival was longer with pembrolizumab versus placebo (44.4 months, 95% CI 33.0 to not reached vs 25.3 months, 20.6 to 33.9; hazard ratio [HR] 0.81, 95% CI 0.67 to 0.99; p=0.0198) but did not meet the threshold for statistical significance (p=0.0178). Median overall survival was 60.7 months (95% CI 51.5 to not reached) in the pembrolizumab group versus 58.0 months (41.5 to not reached) in the placebo group (HR 0.90, 95% CI 0.73 to 1.12; p=0.174). Grade 3 or worse adverse events of any cause occurred in 312 (78%) of 399 patients in the pembrolizumab group and 297 (74%) of 400 patients in the placebo group; the most common were nausea (240 [60%] vs 247 [62%]), anaemia (168 [42%] vs 158 [40%]), and decreased appetite (163 [41%] vs 172 [43%]). Treatment-related serious adverse events were reported in 102 (26%) and 97 (24%) patients. Treatment-related adverse events that led to death occurred in four (1%) patients in the pembrolizumab group (interstitial ischaemia, pneumonia, decreased appetite, and acute kidney injury [n=1 each]) and two (<1%) patients in the placebo group (neutropenic sepsis and neutropenic colitis [n=1 each]). Although neoadjuvant and adjuvant pembrolizumab versus placebo improved the pathological complete response, it did not translate to significant improvement in event-free survival in patients with untreated, locally advanced resectable gastric or gastro-oesophageal cancer	
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American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

			least one dose of study treatment.			
38	Janjigian, Yelena Y; Van Cutsem, Eric; Muro, Kei; Wainberg, Zev; Al-Batran, Salah-Eddin; Hyung, Woo Jin; Molena, Daniela; Marcovitz, Michelle; Ruscica, Dario; Robbins, Scott H; Negro, Alejandra; Tabernero, Josep. MATTERHORN: phase III study of durvalumab plus FLOT chemotherapy in resectable gastric/gastroesophageal junction cancer. Future oncology (London, England) / 2022;18(20):2465-2473. DOI: 10.2217/for-2022-0093	Prospective randomized phase III	Phase III study investigating the efficacy and safety of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy followed by adjuvant durvalumab monotherapy in patients with resectable gastric/gastroesophageal junction cancer. The planned sample size is 900 patients, the primary end point is event-free survival and safety and tolerability will be evaluated	To describe the rationale for and the design of MATTERHORN, a randomized, double-blind, placebo-controlled, phase III study investigating the efficacy and safety of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy followed by adjuvant durvalumab monotherapy in patients with resectable gastric/gastroesophageal junction cancer.	Results pending	1
39	Kelly, RJ; Ajani, JA; Kudzal, J; Zander, T; Van Cutsem, E; Piessen, G; Mendez, G; Moehler, MH. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): First results of overall survival (OS) from CheckMate 577. Journal of Clinical Oncology. 43(16s). doi: 10.1200/JCO.2025.43.16_suppl.400	Prospective randomized phase III	Adults with resected (R0) stage II/III EC/GEJC who received neoadjuvant CRT and had residual pathologic disease were randomized 2:1 to nivolumab 240 mg or placebo Q2W for 16 weeks, followed by nivolumab 480 mg or placebo Q4W. Maximum treatment duration was 1 year. The primary endpoint was DFS. OS was a secondary endpoint, and exploratory endpoints included safety, distant metastasis-free survival (DMFS), and progression-free survival on subsequent systemic therapy (PFS2).	To report the final analysis of the hierarchically tested secondary endpoint of OS along with longer follow-up of DFS	794 pts were randomized (nivolumab, n = 532; placebo, n = 262). With a median follow-up of 78.3 (range, 60.1–96.6) mo, adjuvant nivolumab continued to show DFS benefit vs placebo (HR 0.76 [95% CI 0.63–0.91]; Table). Median OS was numerically longer with nivolumab vs placebo (51.7 vs 35.3 mo), although the difference was not statistically significant (HR 0.85 [95.87% CI 0.70–1.04]; P = 0.1064; Table). OS rates at 3 and 5 years with nivolumab vs placebo were 57% vs 50% and 46% vs 41%, respectively. OS subgroup analyses will be presented. Clinically meaningful improvement in DMFS with nivolumab vs placebo was maintained (Table). PFS2 favored nivolumab vs placebo (HR 0.81 [95% CI 0.67–0.98]). In the nivolumab group, 46% of pts received subsequent therapy vs 60% in the placebo group; 5% vs 15% received subsequent immunotherapy. No new safety signals were identified. Adjuvant nivolumab demonstrated sustained long-term DFS benefit and numerical improvement in OS vs placebo in pts with resected EC/GEJC and residual pathologic disease following neoadjuvant CRT.	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

					The safety profile of adjuvant nivolumab remained well-tolerated with longer follow-up. These results further support the use of adjuvant nivolumab in this pt population.	
40	Lordick, F; ; Mauer, M E; Stocker, G; Cella, C A; Ben-Aharon, I; Piessen, G; Wyrwicz, L; Al-Haidari, G; Fleitas-Kanonnikoff, T; Boige, V; Lordick Obermannova, R; Martens, U M; Gomez-Martin, C; Thuss-Patience, P; Arrazubi, V; Avallone, A; Shiu, K K; Artru, P; Brenner, B; Buges Sanchez, C; Chau, I; Lorenzen, S; Daum, S; Sinn, M; Merelli, B; van Grieken, N C T; Nilsson, M; Collienne, M; Giraut, A; Smyth, E. Adjuvant immunotherapy in patients with resected gastric and oesophagogastric junction cancer following preoperative chemotherapy with high risk for recurrence (ypN+ and/or R1): European Organisation of Research and Treatment of Cancer (EORTC) 1707 VESTIG. Annals of oncology : official journal of the European Society for Medical Oncology / 2025;36(2):197-207. DOI: 10.1016/j.annonc.2024.10.829	Prospective randomized phase II	VESTIGE was an academic international, multicentre, open-label, randomized phase II trial evaluating the efficacy of adjuvant nivolumab/ipilimumab versus chemotherapy in gastro-oesophageal adenocarcinoma at high risk of recurrence. Patients were randomized 1 : 1 to receive standard adjuvant chemotherapy (same regimen as neoadjuvant) or nivolumab 3 mg/kg intravenously (i.v.) every 2 weeks plus ipilimumab 1 mg/kg i.v. every 6 weeks for 1 year. Key inclusion criteria included ypN+ and/or R1 status after neoadjuvant chemotherapy plus surgery. The primary endpoint was disease-free survival in the intent-to-treat population. Secondary endpoints included overall survival, locoregional and distant failure rates, and safety according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0	To investigate if nivolumab/ipilimumab would be more effective than adjuvant chemotherapy in high-risk (ypN+ and/or R1) patients with gastro-oesophageal adenocarcinoma following neoadjuvant chemotherapy and resection	The independent Data Monitoring Committee reviewed data from 189 of the planned 240 patients in June 2022 and recommended stopping recruitment due to futility. At the time of final analysis, median follow-up was 25.3 months for 195 patients (98 nivolumab/ipilimumab and 97 chemotherapy). Median disease-free survival for the nivolumab/ipilimumab group was 11.4 months [95% confidence interval (CI) 8.4-16.8 months] versus 20.8 months (95% CI 15.0-29.9 months) for the chemotherapy group, hazard ratio 1.55 (95% CI 1.07-2.25, one-sided P = 0.99). The 12-month disease-free survival rates were 47.1% and 64.0%, respectively. There were no toxicity concerns or excess early discontinuations. Nivolumab/ipilimumab did not improve disease-free survival compared with chemotherapy in patients with ypN+ and/or R1 gastro-oesophageal adenocarcinoma following neoadjuvant chemotherapy and surgery.	1
41	de Steur, W O; van Amelsfoort, R M; Hartgrink, H H; Putter, H; Meershoek-Klein Kranenbarg, E; van Grieken, N C T; van Sandick, J W; Claassen, Y H M; Braak, J P B M; Jansen, E P M; Sikorska, K; van Tinteren, H; Walraven, I; Lind, P; Nordmark, M; van Berge Henegouwen, M I; van Laarhoven, H W M; Cats, A; Verheij, M; van de Velde, C J H. Adjuvant chemotherapy is superior to chemoradiation after D2 surgery for gastric cancer in the per-protocol analysis of the randomized CRITICS trial. Annals of	Prospective randomized phase III	The CRITICS trial was a randomized, controlled trial in which 788 patients with stage Ib-Iva resectable gastric or esophagogastric adenocarcinoma were included. Before start of preoperative CT, patients from the Netherlands, Sweden and Denmark were randomly assigned to receive post-operative CT or CRT. For the current analysis, only	To report results from the per-protocol (PP) analysis of the CRITICS trial.	Of the 788 patients, 478 started post-operative treatment according to protocol, 233 (59%) patients in the CT group and 245 (62%) patients in the CRT group. Patient and tumor characteristics between the groups before start of the post-operative treatment were not different. After a median follow-up of 6.7 years since the start of post-operative treatment, the 5-year overall survival was 57.9% (95% confidence interval: 51.4% to 64.3%) in the CT group versus 45.5% (95% confidence interval: 39.2% to 51.8%) in the CRT group (adjusted hazard ratio CRT	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

	oncology: official journal of the European Society for Medical Oncology / 2021;32(3):360-367. DOI: 10.1016/j.annonc.2020.11.004		patients who started their allocated post-operative treatment were included. Since it is uncertain that the two treatment arms are balanced in such PP analysis, adjusted proportional hazards regression analysis and inverse probability weighted analysis were used to minimize the risk of selection bias and to estimate and compare overall and event-free survival.		versus CT: 1.62 (1.24-2.12), P = 0.0004). Inverse probability weighted analysis resulted in similar hazard ratios. After adjustment for all known confounding factors, the PP analysis of patients who started the allocated post-operative treatment in the CRITICS trial showed that the CT group had a significantly better 5-year overall survival than the CRT group	
42	**Kachnic LA, Winter K, Wasserman T, et al. Longitudinal Quality-of-Life Analysis of RTOG 94-05 (Int 0123): A Phase III Trial of Definitive Chemoradiotherapy for Esophageal Cancer. Gastrointest Cancer Res. 2011;4(2):45–52.	Prospective randomized phase III	236 patients with cT1-4NxM0 esophageal cancer were randomized to CD CRT (50.4 Gy and concurrent 5-fluorouracil and cisplatin) vs. HD CRT (64.8 Gy and the same chemotherapy). QoL was assessed using the Functional Assessment of Cancer Therapy, Head & Neck (version 2) at baseline, after CRT, at 8 months from the start of CRT, and at 1 year.	To compare longitudinal quality of life (QoL) was compared for patients with esophageal cancer receiving definitive chemoradiotherapy (CRT) with conventional dose (CD) vs. high-dose (HD) radiotherapy as used in the RTOG phase III 94-05 trial (Intergroup 0123).	Of 218 eligible patients, 166 participated in pretreatment QoL assessments (82 HD, 84 CD). Patients with ≥10% weight loss and Karnofsky Performance Status 60-80 were less likely to participate (P = .02 and P = .002, respectively). Pretreatment characteristics for participating patients were similar in both arms. At CRT completion, 96 patients completed QoL (46 HD, 50 CD) assessment. Total mean QoL was significantly lower in the HD arm (P = .02) and remained lower at 8 and 12 months after the start of CRT, but these values did not reach statistical significance. Change in mean QoL from baseline to each of the three subsequent assessment time points did not differ significantly between the two treatment arms.	1
43	**Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol. 2002;20(5):1167–1174. doi:10.1200/JCO.2002.20.5.1167	Prospective randomized phase III	236 patients (31 with adeno) with clinical stage T1 to T4, N0/1, M0 squamous cell carcinoma or adenocarcinoma selected for a nonsurgical approach, after stratification by weight loss, primary tumor size, and histology, were randomized to receive combined-modality therapy consisting of four monthly cycles of fluorouracil (5-FU) (1,000 mg/m ² /24 hours for 4 days) and cisplatin (75	To compare the local/regional control, survival, and toxicity of combined modality therapy using high-dose (64.8 Gy) versus standard-dose (50.4 Gy) radiation therapy for the treatment of patients with esophageal cancer.	For the 218 eligible patients, there was no significant difference in median survival (13.0 v 18.1 months), 2-year survival (31% v 40%), or local/regional failure and local/regional persistence of disease (56% v 52%) between the high-dose and standard dose arms. Although 11 treatment-related deaths occurred in the high-dose arm compared with two in the standard-dose arm, seven of the 11 deaths occurred in patients who had received 50.4 Gy or less.	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

			mg/m(2) bolus day 1) with concurrent 64.8 Gy versus the same chemotherapy schedule but with concurrent 50.4 Gy.			
44	**Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA. 1999;281(17):1623–1627. doi:10.1001/jama.281.17.1623	Prospective randomized phase III	129 Patients had squamous cell (n=106) or adenocarcinoma (n=23) of the esophagus, T1-3 N0-1 M0, adequate renal and bone marrow reserve, and a Karnofsky score of at least 50. Interventions Combined modality therapy (n = 134): 50 Gy in 25 fractions over 5 weeks, plus cisplatin intravenously on the first day of weeks 1, 5, 8, and 11, and fluorouracil, 1 g/m2 per day by continuous infusion on the first 4 days of weeks 1, 5, 8, and 11. In the randomized study, combined therapy was compared with RT only (n = 62): 64 Gy in 32 fractions over 6.4 weeks.	To report the long-term outcomes of a previously reported trial designed to determine if adding chemotherapy during RT improves the survival rate of patients with esophageal carcinoma.	Combined therapy significantly increased overall survival compared with RT alone. In the randomized part of the trial, at 5 years of follow-up the overall survival for combined therapy was 26% (95% confidence interval [CI], 15%-37%) compared with 0% following RT. In the succeeding nonrandomized part, combined therapy produced a 5-year overall survival of 14% (95% CI, 6%-23%). Persistence of disease (despite therapy) was the most common mode of treatment failure; however, it was less common in the groups receiving combined therapy (34/130 [26%]) than in the group treated with RT only (23/62 [37%]). Severe acute toxic effects also were greater in the combined therapy groups. There were no significant differences in severe late toxic effects between the groups. However, chemotherapy could be administered as planned in only 89 (68%) of 130 patients (10% had life-threatening toxic effects with combined therapy vs 2% in the RT only group).	1
45	**Suntharalingam M, Winter K, Ilson D, et al. Effect of the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation Therapy for Patients With Esophageal Cancer: The NRG Oncology RTOG 0436 Phase 3 Randomized Clinical Trial [published correction appears in JAMA Oncol. 2017 Nov 1;3(11):1589]. JAMA Oncol. 2017; 3(11):1520–1528. doi:10.1001/jamaoncol.2017.1598	Prospective randomized phase III	Patients were well matched between the treatment arms for patient and tumor characteristics: 263 (80%) with T3 or T4 disease, 215 (66%) N1, and 62 (19%) with celiac nodal involvement.	To evaluate the benefit of cetuximab added to concurrent chemoradiation therapy for patients undergoing nonoperative treatment of esophageal carcinoma. Overall survival (OS) was the primary endpoint. Patients were randomized to weekly concurrent cisplatin (50 mg/m2),	Incidence of grade 3, 4, or 5 treatment-related adverse events at any time was 71 (46%), 35 (23%), or 6 (4%) in the experimental arm and 83 (50%), 28 (17%), or 2 (1%) in the control arm, respectively. A clinical complete response (cCR) rate of 81 (56%) was observed in the experimental arm vs 92 (58%) in the control arm (Fisher exact test, P = .66). No differences were seen in cCR between treatment arms for either histology (adenocarcinoma or squamous cell). Median follow-up for all patients was 18.6 months. The 24- and 36-month local failure for the experimental arm was 47% (95% CI, 38%-57%) and 49% (95% CI, 40%-59%) vs 49% (95% CI, 41%-58%) and 49% (95% CI, 41%-58%) for the	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

				paclitaxel (25 mg/m ²), + RT (50.4 Gy/28fx) with/without weekly cetuximab (400 mg/m ² on day 1 then 250 mg/m ² weekly).	control arm (HR, 0.92; 95% CI, 0.66-1.28; P = .65). The 24- and 36-month OS rates for the experimental arm were 45% (95% CI, 37%-53%) and 34% (95% CI, 26%-41%) vs 44% (95% CI, 36%-51%) and 28% (95% CI, 21%-35%) for the control arm (HR, 0.90; 95% CI, 0.70-1.16; P = .47).	
46	van der Wilk, Berend J; Eyck, Ben M; Wijnhoven, Bas P L; Lagarde, Sjoerd M; Rosman, Camiel; Noordman, Bo J; Valkema, Maria J; Bisseling, Tanya M; Coene, Peter-Paul L O; van Det, Marc J; Dekker, Jan Willem T; van Dieren, Jolanda M; Doukas, Michail; van Esser, Stijn; Fiets, W Edward; Hartgrink, Henk H; Heisterkamp, Joos; Holster, I Lisanne; Klarenbeek, Bastiaan; van Klaveren, David; Kouw, Eva; Kouwenhoven, Ewout A; Luyer, Misha D; Mostert, Bianca; Nieuwenhuijzen, Grard A P; Oostenbrug, Liekele E; Pierie, Jean-Pierre; van Sandick, Johanna W; Sosef, Meindert N; Spaander, Manon C W; Valkema, Roelf; van der Zaag, Edwin S; Steyerberg, Ewout W; van Lanschot, J Jan B. Neoadjuvant chemoradiotherapy followed by active surveillance versus standard surgery for oesophageal cancer (SANO trial): a multicentre, stepped-wedge, cluster-randomized, non-inferiority, phase 3 trial. The Lancet. Oncology / 2025;26(4):425-436. DOI: 10.1016/S1470-2045(25)00027-0	Prospective randomized phase III	We performed a multicentre, stepped-wedge, cluster-randomized, non-inferiority, phase 3 trial in 12 Dutch hospitals. Individuals with locally advanced oesophageal cancer and a clinical complete response after neoadjuvant chemoradiotherapy (ie, no tumour detected with endoscopic biopsies, ultrasound, and PET-CT) underwent active surveillance or standard surgery (ie, oesophagectomy within 2 weeks after reaching clinical complete response). There were no inclusion restrictions regarding comorbidities or performance status, but participants had carcinoma, were age 18 years or older, and were treated with curative intent. Randomisation of hospitals was performed using computer-generated sequences without stratification methods, after an initial phase of all hospitals performing standard surgery. The primary endpoint was overall survival, analysed according to a modified intention-to-treat principle (allowing crossover at time of clinical complete response) and an intention-to-treat principle. Non-inferiority was defined as 2-year survival rate for active	To investigate whether active surveillance could be an alternative for individuals with a clinical complete response after neoadjuvant chemoradiotherapy	Between Nov 8, 2017, and Jan 17, 2021, 1115 individuals were screened, of whom 309 were included. 198 underwent active surveillance and 111 underwent standard surgery. 242 (78%) participants were male and 67 (22%) were female. Median follow-up was 38 months (IQR 32-48). 2-year overall survival for active surveillance (74% [95% CI 69-78]) was non-inferior to standard surgery (71% [62-78]) after modified intention-to-treat analysis (one-sided 95% boundary: 7% lower). It remained non-inferior in the intention-to-treat analysis (75% [68-80] vs 70% [63-77], one-sided 95% boundary: 6% lower). There were no significant differences in overall survival according to modified intention-to-treat analysis (hazard ratio 1.14, two-sided 95% CI 0.74-1.78) or intention-to-treat analysis (0.83, 0.53-1.31). The frequency of postoperative complications and postoperative mortality after standard surgery or postponed surgery after active surveillance was similar between groups. Overall survival after active surveillance for oesophageal cancer was non-inferior compared with standard surgery after 2 years. For the long-term efficacy of active surveillance, extended follow-up is required. The results of the present trial could be used for patient counselling and shared decision making	1

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma

			surveillance of 15% or less below that for standard surgery.			
47	Hulshof MCCM, Geijssen ED, Rozema T, et al. Randomized Study on Dose Escalation in Definitive Chemoradiation for Patients With Locally Advanced Esophageal Cancer (ARTDECO Study). J Clin Oncol Off J Am Soc Clin Oncol. 2021;39(25):2816-2824. doi:10.1200/JCO.20.03697	Prospective randomized phase III	Patients with medically inoperable and/or irresectable esophageal carcinoma, referred for dCRT, were randomly assigned between a standard dose (SD) of 50.4 Gy/1.8 Gy for 5.5 weeks to the tumor and regional lymph nodes and a high dose (HD) up to a total dose of 61.6 Gy to the primary tumor. Chemotherapy consisted of courses of concurrent carboplatin (area under the curve 2) and paclitaxel (50 mg/m2) in both arms once a week for 6 weeks. The primary end point was LPFS	To analyze the effect of radiation dose escalation to the primary tumor on local tumor control in definitive chemoradiation (dCRT) for patients with esophageal cancer.	Between September 2012 and June 2018, 260 patients were included. Squamous cell carcinoma (SCC) was present in 61% of patients, and 39% had adenocarcinoma (AC). Radiation treatment was completed by 94%, and 85% had at least five courses of chemotherapy. The median follow-up time for all patients was 50 months. The 3-year local progression-free survival (LPFS) was 70% in the SD arm versus 73% in the HD arm (not significant). The LPFS for SCC and AC was 75% versus 79% and 61% versus 61% for SD and HD, respectively (not significant). The 3-year locoregional progression-free survival was 52% and 59% for the SD and HD arms, respectively (P = .08). Overall, grade 4 and 5 common toxicity criteria were 12% and 5% in the SD arm vs 14% and 10% in the HD arm, respectively (P = .15).	1

Article Key:

Of the 47 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, 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 evidence or they were no longer cited in the revised narrative text. Six 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 25 citations from bibliographies, websites, or books not found in the literature search. Of the 41 references used as evidence, 41 are categorized as therapeutic references including 34 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 4 references that are meta-analysis studies.

Study Quality Category Definitions

Category 1 The study is well-designed and accounts for common biases.

Category 2 The study is moderately well-designed and accounts for most common biases.

Category 3 There are important study design limitations.

Category 4 The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

- a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
- b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
- c) the study is an expert opinion or consensus document.

Category M The study is a meta-analysis and has not been rated for quality because the method is designed to evaluate individual studies only.

Abbreviations Key:

** Reference retained from original 2021 Executive Summary of the American Radium Society Appropriate Use Criteria for Operable Esophageal and Gastroesophageal Junction Adenocarcinoma: Systematic Review and Guidelines bibliography if they were more than 10 years old and significantly contributed to the evidence.