Uitgangsvraag 1: evidence tables

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Fiorica 2004 [1]	• SR and MA • Supported by Universities and a cancer centre • Search date – until December 2002 • Search included MEDLINE & CANCERLIT, (also non- English), manual searches of reference lists, review articles, primary studies, meeting abstracts, bibliographies from books, contact with investigators • Included study designs: RCTs • Number of included studies = 6 (N=764)	Patients with resectable histologically proven SCC or ACA of the esophagus without metastatic disease	Preoperative CRT + Sx vs. Sx alone	3-year mortality, CRT + Sx vs.Sx alone: OR 0.53, 95%CI 0.31–0.93; p = 0.03 (NNT = 10) Subgroup analysis: - ACA: OR 0.24, 95%CI 0.07–0.78; p=0.018 - SCC: OR 0.81, 95%CI 0.55–1.19; p=0.29	• Downstaging, CRT + Sx vs. Sx alone: OR 0.43, 95%CI 0.26–0.72; p = 0.001 • Postoperative mortality, CRT + Sx vs. Sx alone: OR 2.10, 95%CI 1.18–3.73;p = 0.01 (NNH = 25) • Overall rate of postoperative adverse events: 39.4% (137/348) in the CRT group vs. 34.3% (123/358) in the surgery alone group; p=0.16	Level of evidence: B • Good methodological quality • Includes some small trials, but this has been adjusted for
Graham 2007 [2]	• SR • No funding source declared • Search date – until October 2004 • MEDLINE, Pubmed, EMBASE, CINHAL, Cochrane CT &SR Cross referencing bibliographies and consultation with experts • Included study designs: RCTs • Number of studies included = 14 (Sx alone N=1359; CT + Sx N=737; CRT + Sx N=372; Sx + CRT N=281)	Patients with locally advanced esophageal cancer	• Sx alone • CRT+ Sx • CT + Sx • Sx + CRT	CRT followed by Sx appears to be associated with the best survival and the largest expected gain in QALYs. For the first year, the RR (95%CI) of death for treatments compared with Sx were: • CRT + Sx: 0.87 (0.75 to 1.02) • CT + Sx: 0.94 (0.82 to 1.08) • Sx + CRT: 1.33 (0.93 to 1.93) The QALYs gained: • Sx alone: 2.07 • CRT + Sx: 2.18 • CT + Sx: 2.14 • Sx + CRT: 1.99	If reduction in utility for multimodality treatment increased to 21%, QALYs gained became: • Sx alone: 2.07 • CRT + Sx: 2.03 • CT + Sx: 1.99 • Sx + CRT: 1.85	Level of evidence: A2 • Good search method • Documented trial quality assessment, which was not used • The survival times are drawn from studies examining differing histologies, chemotherapeutic regimens, and radiation doses • The estimates of utility needed to be obtained from an observational study with a limited number of patients (64) divided between the therapies. It therefore might be unreliable • Resectability was not a specific inclusion criteria in this review which specifies “locally advanced esophageal cancer”

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Jin 2009 [3]	• SR and MA • No funding source declared • Search date: 1980-2008 • Search included MEDLINE, EMBASE, manual searches • Included study designs: RCTs • Number of included studies = 11 (N= 1308)	Patients with resectable esophageal cancer	Neoadjuvant CRT + Sx vs. Sx alone	Overall survival, neoadjuvant CRT + Sx vs. Sx alone: OR (95%CI) • 1.28 (1.01-1.64, p=0.05) for 1-year survival, • 1.78 (1.20-2.66, p=0.004) for 3-year survival, • 1.46 (1.07-1.99, p=0.02) for 5-year survival	• Postoperative mortality increased in patients treated by neoadjuvant CRT (OR 1.68, 95%CI 1.03-2.73, p=0.04) • Incidence of postoperative complications was similar in two groups (OR 1.14, 95%CI 0.88-1.49, p=0.32) • Neoadjuvant CRT lowered the locoregional cancer recurrence (OR 0.64, 95%CI 0.41-0.99, p=0.04), • Incidence of distant cancer recurrence was similar (OR 0.94, 95%CI 0.68-1.31, p=0.73). • Subgroup analyses showed that patients benefited from concurrent CRT: (survival rate estimates by schedule) ○ Sequential: OR (95%CI) at 1 yr 1.12 (0.77-1.64), p=0.56; 3 yr 1.24 (0.82-1.88), p=0.31; 5 yr 1.24 (0.81-1.91), p=0.32 ○ Concurrent: OR (95%CI) at 1 yr 1.41 (1.03-1.94), p=0.03; 3 yr 2.12 (1.20-3.76), p=0.011; 5 yr 1.72 (1.10-2.71), p=0.02 • Histological subgroup analysis indicated that esophageal SCC did not benefit from neoadjuvant CRT: OR (95%CI) 1.16 (0.85-1.57, p=0.34) for 1-year survival, 1.34 (0.98-1.82, p=0.07) for 3-year survival and 1.41 (0.98-2.02, p=0.06) for 5-year survival	Level of evidence: B • Good quality, explicit and clear methodology, search , selection, QA of studies, meta-analysis, and testing appropriately for heterogeneity

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Lv 2009 [4]	• SR and MA • Source of funding not declared, no COI declared • Search date - June 2009 • Searched databases: PubMed and manual searches, independently and in duplicate • Included study designs: RCT • Number of included studies = 14 (N=1737), but see comment	Patients with resectable esophageal carcinoma	Neoadjuvant CRT + Sx vs. Sx alone	Overall survival, CRT + Sx vs. Sx: OR (95%CI) • 1.19 (0.94-1.48) for 1-year survival, • 1.33 (1.07-1.65) for 2-year survival, • 1.76 (1.42-2.19) for 3-year survival, • 1.41 (1.06-1.87) for 4-year survival, • 1.64 (1.28-2.12) for 5-year survival	CRT + Sx vs. Sx: OR (95%CI) • rate of resection 0.82 (0.39-1.73), • rate of complete resection 1.53 (1.33-2.84), • operative mortality 1.78 (1.14-2.78), • all treatment mortality 1.12 (0.89-2.48), • rate of adverse treatment 1.33 (0.94-1.88), • locoregional cancer recurrence 1.38 (1.23-1.63), • distant cancer recurrence 1.28 (0.85-1.58), • all cancer recurrence 1.27 (0.86-1.65) • The 5-year survival benefit was most pronounced when CT and RT were given concurrently (OR 1.45, 95%CI 1.26-1.79) instead of sequentially (OR 0.85, 95%CI 0.64-1.35)	Level of evidence: B • Moderate quality • Limited search - PubMed only although manual search done • Good quality appraisal of studies and testing for heterogeneity, but no detail of primary research • Wrong reporting of p-values! • Study of Walsh is used twice in the analysis.
Malthaner 2006 [5]	• SR and MA • Source of funding: no External support supplied, Cochrane Review • Search date: 2006 • Searched databases CENTRAL, MEDLINE, EMBASE, CANCERLIT; no language restrictions • Included study designs: RCT • Number of included studies = 11(N=2019); 8 trials were used for primary outcome survival (N=1729)	Patients with localized potentially resectable thoracic esophageal carcinoma Trials involving patients with carcinomas of the cervical esophagus were excluded	Preoperative CT + Sx vs. Sx alone	Survival: 12% risk reduction of mortality for patients given CT + Sx compared to Sx alone Evidence for treatment effect inconclusive (HR 0.88, 95%CI 0.75-1.04; p=0.15)	• Overall rate of resections: RR 0.96, 95%CI 0.92-1.01 • Rate of complete resections (R0): RR 1.05, 95%CI 0.97-1.15 • Tumour recurrence: RR 0.81, 95%CI 0.54-1.22 • Non-fatal complication rates: RR 0.90, 95%CI 0.76-1.06 • Risk of toxicity with chemotherapy ranged from 11%- 90%	Level of evidence: A2 • Good quality SR with meta-analysis • Quality of studies and heterogeneity clearly presented and taken into account • Hazard ratio used for primary outcome in this study to summarise complete survival experience in one analysis

Randomised controlled trials

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Allum 2009 [6]	• RCT • Supported by Medical Research Council, COI declared • Setting: UK and European cancer centres • Sample size: N=802 (CT + Sx: N=400; Sx N=402) • Duration – 5 yr survival data (median follow up 6.1 yrs for Sx and 5.9 yrs for CT)	• Histologically confirmed, previously untreated, esophageal cancer • Suitable for radical surgery with curative intent • SCC, ACA and undifferentiated carcinoma were included • Tumor location: upper, middle,& lower thirds of the esophagus, gastric cardia • Excluded: postcricoid cancer; comorbid contraindications to Sx or CT • Groups were comparable	CT + Sx vs. Sx alone **CT + Sx:** 2 cycles of cisplatin 80mg/m² IV on day 1, fluorouracil 1000 mg/m² daily as a continuous infusion over 96 hours repeated every 3 weeks; Sx within 3 to 5 weeks of completing chemotherapy **Sx alone:** Sx as soon as possible. Sx procedure was selected by the surgeon according to tumour site and local practice Preoperative RT was permitted (25 Gy in 5 fractions over 1 week, 325 Gy in 10 fractions over 2 weeks, or a biologically equivalent dose)	• Overall survival, CT+ Sx vs. Sx: HR 0.84, 95%CI 0.72-0.98; p=0.03 • 5-year survival: 23.0% for CT + Sx vs. 17.1% for Sx alone • The treatment effect is consistent in both ACA and SCC, with no evidence of heterogeneity of treatment effect (p=0.81): 5-year survival for ACA 22.6% (CT + Sx) vs. 17.6% (Sx alone), SCC 25.5% (CT + Sx) vs. 17.0% (Sx alone)	• Disease-free survival, CT + Sx vs. Sx: HR 0.82, 95%CI 0.71-0.95; p=0.003 • The first disease-free survival event was macroscopic residual disease from incomplete resection (R2) or no resection in 26.4% of the Sx alone group vs. 14.3% of the CT + Sx group (p<0 .001) • Three-year survival by type of resection was R0 42.4%, R1 18.0%, and R2 8.6%	Level of evidence: A2 • This paper updates the long term results (5 yr) of the MRC OE02 trial which is included in the Malthaner Cochrane SR • Not blinded • The possible effect of some patients receiving RT was not discussed (9% of patients in both arms)
Cao 2009 [7]	• RCT • Funding source not disclosed • Setting: Oncology centre, University, China • Sample size: N=473 (RT n=118, CT n=119, CRT n=118, Sx n=118) • 3 year study	• Patients with esophageal SCC stage II or later • Recruited from an ongoing clinical trial that was evaluating neoadjuvant CRT for esophageal cancer • Comparable groups	Neoadjuvant RT vs. CT vs. CRT vs. Sx alone **RT group**: Daily fractions of 2 Gy (days 1–5, 8–12, 15–19, and 22–26) to a total dose of 40 Gy **CT group:** PFM regimen: Mitomycin 10 mg/m²/day on day 1, cisplatin 20 mg/m²/ day and 5-fluorouracil 500 mg/m²/day as continuous infusion over 24 h on days 1–5 **CRT group:** CT was carried out at the first 2 weeks, in the	• 1-year survival: no statistical differences among groups • 3-year survival: RT (69.5%) and CRT (73.3%) statistically different from Sx group (53.4%) (p=0.005 and p<0.005); CT (57.1%) not • 5-year survival: statistically significant difference among groups, no details reported	• 1-year morbidity rate: CRT 87.28% vs. Sx alone 88.98% (p>0.05) • Radical resection rate: RT 97.5%, CT 86.6%, CRT 98.3%, significantly different from Sx alone (73.3%) (p<0.001) • Clinical complete response rate: RT 27.2% and CRT 33.89%, significantly higher than that in CT group (1.7%) (p<0.05) • The pathological complete response rates were RT 15.2%, CT 1.7%, and CRT 22.3%	Level of evidence: B • The paper states the patients have been randomized. However, there is no description of how and there is also no description of when, as 473 patients who have been randomized seem to form part of a group who have been recruited for another trial. • Method of selection is not clear, there are no dropouts and no operative deaths • There does not seem to be *a priori* selection criteria

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			same way as in CT group. Combination with concomitant RT in 4 weeks (the same way as in RT group) **Sx group:** Esophagectomy through left thoracotomy with two-field lymphadenectomy			
Cunningham 2006 [8]	• RCT • Supported by Pharmacia for reimbursement of cost of epirubicin and a grant from the MRC; no COI • Setting: hospitals in UK, the Netherlands, New Zealand, Germany, Singapore and Brazil • Sample size: N=503 (perioperative CT N=250, Sx alone N=253) • Median follow up 4 years	• Histologically proven ACA of the stomach or lower third of the esophagus, stage II or higher; no evidence of distant metastases or locally advanced inoperable disease • Patients of any age who had a World Health Organization (WHO) performance status of 0 or 1 • Exclusion criteria: previous cytotoxic CT or RT, uncontrolled cardiac disease, or creatinine clearance of 60 ml per minute or less • Group comparability: no significant differences between groups	Perioperative CT vs. Sx alone **Perioperative CT:** 3 cycles preoperatively + 3 cycles postoperatively; epirubicin (50 mg/m² IV bolus on day 1) + cisplatin (60 mg/m² IV on day 1) + fluorouracil (200 mg/m² daily for 21 days by continuous IV infusion); Sx 3-6 weeks after completion of the 3rd cycle of CT; postoperative CT to be initiated 6 to 12 weeks after Sx **Sx alone:** within 6 weeks after randomization in the Sx group	• Overall survival, perioperative CT vs. Sx alone: HR for death 0.75; 95%CI 0.60-0.93; p=0.009 • 5-year survival rate: 36% vs. 23% • Progression-free survival: HR for progression 0.66; 95%CI 0.53-0.81; p<0.001 • No clear evidence of heterogeneity of treatment effect according to the site of the primary tumor (HR not provided with numeric data)	• Postoperative complications: perioperative CT 46% vs. Sx 45% • Postoperative mortality: perioperative CT 5.6% vs. Sx alone 5.9%	Level of evidence: A2 • Central randomization • No blinding • The treatment arm includes both preoperative and postoperative CT • Authors state that they cannot attribute the favourable outcome to preoperative or postoperative CT • This trial was originally for gastric cancer , but eligibility was extended and included esophageal cancer (N=65 in perioperative CT +Sx arm and N=66 in Sx alone arm) • MAGIC trial
Kelsen 2007 [9]	• RCT • Supported by grants from National Cancer institute Bethesda • Setting: cancer centres in US, UK and Canada • Sample size: N=467 (443 with adequate follow up: CT + Sx N=216, Sx alone N=227) • Study duration: median 5 years	• Histologically confirmed epidermoid or ACA of the esophagus, including the EGJ (stage I, II, or III, any nodal stage, and no metastasis) • At least 18 years old • Adequate hepatic, renal, and bone marrow function • Could tolerate the planned surgical procedure • Not received prior therapy for their esophageal cancer	CT + Sx vs. Sx alone **CT + Sx group:** 3 cycles of CT using cisplatin and fluorouracil; Patients randomly assigned to CT who had stable or responding disease, and in whom an R0 resection was performed, were to receive two cycles of CT after resection **Sx alone group:** Immediate Sx with agreed surgical	• Overall survival: HR for death relative to R0 resection: R1 2.42, R2 4.18, and R3 4.45 • 3-year survival: R0 39%, R1 12%, R2 and R3 4% • 32% of patients with R0 resections were alive and free of disease at 5 years, only 5% of patients undergoing an R1 resection survived for longer than 5 years • Median survival for patients still alive at time of analysis: R0 8.9 yrs, R1 7 yrs, R2 5.8 yrs, R3 1.7 yrs (for R1, R2, or R3 not	• Although no difference in overall survival for patients receiving preoperative CT compared with the Sx only group, patients with objective tumour regression after preoperative CT had improved survival • Only 19% of patients randomly assigned to preoperative CT had major objective regressions (7% complete radiographic regression and12% partial radiographic regression)	Level of evidence: B • This paper updates the long term results (5 yr) of the RTOG trial included in the Malthaner Cochrane SR • Concealment of randomization not mentioned • Not blinded • The possible effect of some patients receiving RT or additional postoperative CT is not discussed

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		• Exclusion criteria: patients with tumours in the cervical esophagus, supraclavicular/ distant metastasis, or T4 tumours	techniques For patients undergoing an R1or R2 resection, RT could be considered (in most cases, CT was given concurrently)	significantly different) • 59% of Sx only and 63% of CT + Sx underwent R0 resections (p=0.51)		
Stahl 2009 [10]	• RCT • Supported by grants from Ortho-Biotech and Baxter Deutschland • Setting: Oncology and Surgery University departments Germany • Sample size: N=126 randomly assigned, N=119 evaluated (CT + Sx N=59, CRT + Sx N=60) • 3 yr follow up	• Histologically proven ACA of the EGJ (type I to III) • Untreated patients • Up to 70 yrs • Locally advanced disease (T3-T4 NX M0) • WHO performance status grade 0 to 1, allowing major surgery • Normal liver, renal and bone marrow function	CT + Sx vs. CRT + Sx **CT + Sx group:** Induction CT with 2.5 courses of PLF: 1 course comprised a 6-wk schedule of weekly fluorouracil (2 g/m², 24-hour infusion) + leucovorin (500 mg/m², 2-hour infusion) + biweekly cisplatin (50mg/m², 1-hour infusion) **CRT + Sx:** 2 courses of the same induction CT (PLF) + 3 weeks of combined CRT: cisplatin (50 mg/m², 1-hour infusion IV) on day 1 + 8, etoposide (80 mg/m², 1-hour infusion IV) days 3 – 5; RT 30 Gy in fractions of 2 Gy, 5 fractions per week Sx was performed 3 to 4 weeks after the end of CT or CRT	• 3-year survival: CT 27.7% (95%CI 14.7-42.3%) vs. CRT 47.4% (95%CI 32.8-60.7%), p=0.07; HR 0.67, 95%CI 0.41-1.07 • Postoperative mortality was non-significantly increased in the CRT group (10.2% vs. 3.8%; p=0 .26)	• The number of patients undergoing R0 resection was not different between treatment groups (CT 69.5% vs. CRT 71.5%). • Patients treated with CRT had a significant higher probability of showing pathologic complete response (15.6% vs. 2.0%) or tumor-free lymph nodes (64.4% vs. 37.7%) at resection	Level of evidence: B • Probable central randomization • No blinding • The trial was originally designed as a two-stage adaptive design to recruit > 100 patients per arm to prove a hypothesis of a superiority of 10% in 3 yr survival in the CRT arm. There was low recruitment, amendment was made to the protocol and the trial was closed

Abbreviations: 95%CI: 95 percent confidence intervals; ACA: adenocarcinoma; COI: conflict of interest; CRT: chemoradiotherapy; CT: chemotherapy; EGJ: esophagogastric junction; Gy: gray; HR: hazard ratio; MA: meta-analysis; NNH: number needed to harm; NNT: number needed to treat; OR: odds ratio; QA: quality appraisal; QALY: quality-adjusted life years; RCT: randomized controlled trial; RR: risk ration; RT: radiotherapy; SCC: squamous cell carcinoma; SR: systematic review; Sx: surgery; UK: United Kingdom; US: United States.

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