Uitgangsvraag 5: evidence tables

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Gruen 2009 [1]	• Design: SR and MA • Source of funding: Victorian Government Department of Human Services - a National Health and Medical Research Council Career Development Award • Search date: 1979-2005 • Searched databases: OVID PreMEDLINE, MEDLINE, Cochrane Library, AMI, EMBASE, EconLit, PubMed, ISI Web of Knowledge - also SRs of related topics so that reference lists could be hand-searched • Included study designs: SR, MA, RCT; other controlled trials, comparative studies, and cohort studies • Number of included studies: 28 on esophagus (patients: N=45822; hospitals: N=3405)	• Eligibility: esophageal cancer or those undergoing procedures usually undertaken to treat gastrointestinal cancers • Exclusion: non-English publications, publication types other than primary study, inappropriate study designs, studies not addressing relationship between volume and patient mortality, Sx performed for disease conditions other than cancer	Surgical interventions delivered by a high-volume clinician or in a high-volume hospital vs. Surgical interventions delivered by a low-volume clinician or in a low-volume hospital	Effect on mortality of doubling hospital case volume (N=24 studies): OR 0.81 (95%CI 0.77-0.84) (unadjusted)	Lower quartile mortality (max 3 cases/year): 16.7% Upper quartile mortality (min18 cases/year): 6.7% Patients needed to be moved from a lower quartile hospital to an upper quartile hospital to prevent 1 volume-associated death (calculated by 100/ [lower quartile mortality– upper quartile mortality]): NNT=10 2 studies reported adjusted analyses (adjusted for age, stage of disease and comorbidities) • Bachmann 2002: 30-d surgical mortality, per increase of 10 cases in surgeon volume: OR 0.60 (0.36-0.99) Overall death rate: Per increase of 10 cases in hospital volume HR 1.01 (0.96-1.05) Per increase of 10 cases in surgeon volume HR 0.92 (0.85-0.99) • Birkmeyer 2003: Surgical mortality: Hospital volume low vs high: OR 1.67 (1.02-2.73) Surgeon volume low vs high: OR 1.80 (1.13-2.87)	Level of evidence: B • High quality SR: study quality assessed, data extraction clearly described, correctly performed statistics • Studies included: Bachmann MO, Br J Surg 2002 Begg CB, JAMA 1998 Birkmeyer JD, Ann Surg 2007 Birkmeyer JD ,Cancer 2006 Birkmeyer JD, N Engl J Med 2002 Birkmeyer JD, N Engl J Med 2003 Dimick JB, Ann. Thorac. Surg. 2005 Dimick JB, Ann. Thorac. Surg. 2001 Dimick JB, Ann. Thorac. Surg. 2003 Dimick JB, Arch. Surg. 2003 Finlayson EVA, Arch Surg 2003 Gillison EW, Br J Surg 2002 Hollenbeck BK, J Clin Oncol 2007 Jensen LS, SJS 2007 Kuo EY, Ann Thorac Surg 2001 Lin HC, Ann. Surg. Oncol. 2006 Patti MG, J Gastrointest Surg 1998 Rouvelas I, Arch Surg 2007 Simunovic M, Can J Surg 2006 Swisher SG, J Thorac Cardiovasc Surg 2000 Thompson AM, Br J Surg 2007 Urbach DR, J Clin Epidemiol 2005 Urbach DR , CMAJ 2003 Urbach DR, Qual Saf Health Care 2004

Cohort studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Al-Sarira 2007 [2]	• Design: Retrospective cohort study • Source of funding: Audit Department at Leighton Hospital and UK Department of Health • Setting: Hospital Episode Statistics (HES) in England • Sample size: N=11838 esophagectomies & esophago-gastrectomies (1997-1999: N=3601; 2000-2001: N=3260; 2002-2003: N=4838) • Duration: 1997–1998 to 2003–2004 Period 1: 1997-1999= before manual; Period 2: 2000-2001= introduction of manual; Period 3: 2002-2003= after introduction manual	• Eligibility criteria: patients undergoing esophagectomy and esophago-gastrectomy for esophageal and EGJ cancers • Exclusions: not reported • Patient characteristics: Age 64 years, 75% men stable over the period under study	Introduction of manual "Improving Outcomes in Upper Gastro-intestinal Cancers" Annual hospital volume grouped into 5 categories: Very high: ≥40 High: 30–39 Medium: 20–29 Low: 10–19 Very low: ≤9	<u>In hospital mortality</u>, % Overall: Period 1: 11.7 Period 3: 7.6 p<0.001 Very high: Period 1: 6.9 Period 3: 4.5 p=0.118 High: Period 1: 9.0 Period 3: 9.0 p=0.845 Medium: Period 1: 12.7 Period: 3: 6.0 p<0.001 Low: Period 1: 13.9 Period 3: 8.3 p<0.001 Very low: Period 1: 13.0 Period 3: 11.8 p=0.801 <u>Number of hospitals</u> performing esophagectomies/esophago-gastrectomies 1997 : 180 2003: 111 (decrease: mostly very low and low volume hospitals) <u>Median annual hospital volume</u> 1997: 7 2003: 11 (p=0.030)	<u>Prolonged hospital stay</u> (longer than the 75th percentile) Overall: Period 1: 23.9 % of patients Period 3: 23.9% of patients p=0.869 Very high: Period 1: 17.6% of patients Period 3: 22.7% of patients p=0.040 High: Period 1: 16.4% of patients Period 3: 25.2% of patients p=0.001 Medium: Period 1: 20.0% of patients Period: 3: 20.9% of patients p=0.913 Low: Period 1: 26.3% of patients Period 3: 25.3% of patients p=0.212 Very low: Period 1: 30.4% of patients Period 3: 25.3% of patients p=0.109	Level of evidence: B • High quality retrospective cohort study; outcomes well defined but potential confounders not identified or taken into account in the analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Branagan 2004 [3]	• Design: Prospective cohort, compared to another prospective cohort • Source of funding: Not reported • Setting: 1 centre and 4 centres in the UK • Sample size: N=73 (cases: N=33; control group: N=40) • Duration: From May 2002, for one year and from October 1999 to September 2000.	• Eligibility: patients undergoing esophageal cancer Sx • Exclusions: not reported • Patient characteristics: Mean age 62/66 M ale: Female 25:8/ 34:6 ASA I 6/10; II 25/20; III 2/1 Site Upper third 1 /0 Middle third 0 /3 Lower third 18 /28 EGJ 14/ 9 Tumour stage Barrett's 3 /0 I 2 /3 II 4 /11 III 24 /17 Node stage 0 13/19 I 20/12 Not staged 0 /9	Centralization of esophageal cancer Sx into a single site vs. Esophageal cancer Sx in 4 hospitals before centralisation	Hospital deaths Single site: 0 cases WOCA: 5 cases p=0.022 Preoperative disease stage 1 site: 33/33 WOCA 31/40 (p=0.004) Staging failure 1 site: 0/33 WOCA 6/40 (p=0.020)	Major postoperative complications Single site: 16 cases WOCA: 15 cases Not significant Incomplete pathology reports Single site: 3 cases WOCA: 15 cases p=0.001 Duration of Sx, transfusion requirements, time spent in intensive care or high-dependency units, number of histopathologically positive nodes: similar for the two groups	Level of evidence: B • Cohort study with small sample size • Potential confounders are not taken into account for the analysis
Wouters 2009 [4]	• Design: Retrospective and prospective cohort study • Sources of funding: Not reported • Setting: 11 hospitals + 1 university hospital in the Netherlands • Sample size: 555 • Duration: 1990-2004	• Eligibility: surgically treated esophageal carcinomas with curative intent • Exclusions: not reported • Patient characteristics: stable between periods, except for neoadjuvant therapy, surgical approach and anastomoses	Voluntary centralization in 2000 (in 2 hospitals >10 surgeries annually) vs. Before centralization: 1990 -2000	In hospital mortality 1990-1994: 14.3% 1995-2000: 12.3% 2000-2004: 4.7% p=0.003 Risk of dying after Sx: (Adjusted for stage, comorbidity, surgical approach, and neoadjuvant treatment) Adjusted HR compared to 1990–1994: 1995–1999 0.85 (0.63–1.16) 2000–2004 0.61 (0.44–0.86) Risk of dying after Sx, exclusion of patients who died in- hospital (Adjusted for stage, age, gender, comorbidity, and surgical approach) Adjusted HR compared to 1990–1994: 1995–1999: 0.92 (0.66–1.29)	Hospital stay (median; range) 1990-1994: 20 (9-92) 1995-2000: 21 (9-125) 2000-2004: 17 (8-273) p=0.002 Complications (2000-2004), Low volume (<10/year): 77.5% High volume (≥10/year): 55.3% p=0.001	Level of evidence: B • Partly overlap with Wouters Ann Surg Oncol 2008 and Wouters J Surg Oncol 2009 • Primary outcome not defined; • Groups not comparable regarding stage and adjuvant treatment • Lost to follow up not presented • Adjusted analyses not including the same variables

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
				2000–2004: 0.75 (0.52–1.07)		
Birkmeyer2005 [5]	• Design: retrospective cohort study • Source of funding: National Cancer Institute and Agency for Healthcare Research and Quality • Setting: 102 centers in the USA • Sample size: 1987 Cases: N=1173 Controls: =814 • Duration: 1994-1999	• Eligibility: Medicare recipients covered by the hospital care program and undergoing cancer related esophagectomy • Exclusion criteria: Medicare patients who were enrolled in risk-bearing health maintenance organizations (approximately 10% of Medicare enrollees) ; patients who were <65 or > 99 years • Patient characteristics: Age >85 yrs (%) 1.4/ 1.6 % female 25.2/ 23.2 % black 6.2 /6.1 Charlson comorbidity score (% ≥3) 43.4 /41.0 Urban (%) 63.9/ 68.1 Low income (%) 17.9 /20.6	Cases: patients treated in 51 National cancer institute centers Controls: patients treated in 51 other hospitals with the highest volumes for each procedure.	<u>Surgical mortality</u> (before hospital discharge or within 30 days after the procedure) Adjusted OR 0.70 (0.51–0.97) (Adjusted for patient characteristics and residual procedure volume differences)	<u>Long term survival</u> (from date index surgical admission until death or the termination of the period of observation) Adjusted HR: 1.05 (0.92–1.20) (Adjusted for patient characteristics and residual procedure volume differences)	Level of evidence: B • High quality study with clearly defined primary outcome • Main confounders are taken into account
Kazui 2007 [6]	• Design: Retrospective cohort study • Source of funding: Not reported • Setting: 551 nationwide Japanese hospitals • Sample size: N=21020 Cases N=4085 Controls: 1-4: N=3114; 5-9:N=5290; 10-14:N=3141; 15-19:N=1538; 20-29:N=2022 30-39:N=1830 • Duration: Between 2000 and 2004	• Eligibility: Patients undergoing esophageal cancer Sx	Cases: patients treated in institutions with an annual number of procedures of ≥40 Controls: patients treated in institutions with an annual number of procedures of : 30-39 20-29 15-19 10-14 5-9 1-4	<u>In hospital mortality:</u> ≥40: reference group 30-39: OR 0.96 (0.62-1.49) 20-29: OR 1.20 (0.73-1.98) 15-19: OR 1.61(0.94-2.76) 10-14: OR 1.82 (1.22-2.70) 5-9: OR 2.21 (1.53-3.21) 1-4: OR 2.27 (1.54-3.33)	No other outcomes reported	Level of evidence: B • Large sample size • Potential confounders were not identified or taken into account in analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Gasper 2009 [7]	• Design: Retrospective cohort study • Source of funding: Not reported • Setting: multicenter study in California, USA • Sample size: N=2404 period B: N=1194 period C: N=1210 • Duration: Between 1995 and 2004	• Eligibility: patients who had resections for cancer of the esophagus	Cases: patients treated in period A (1990-1994) Controls: patients treated in period B (1995-1999) and C (2000-2004)	<u>In-hospital mortality</u> Adjusted OR stratified by annual hospital volume Period A: reference Period B: <6: 1.95 (1.03–3.69) 6-10:1.01 (0.50–2.06) 11-20:1.59 (0.84–3.03) 21-30: 1.29 (0.58–2.86) >30:1.0 Period C: <6: 1.65 (1.01–2.69) 6-10: 1.45(0.78–2.68) 11-20: 1.19 (0.57–2.47) 21-30: 0.94 (0.45–1.98) >30:1.0 (Adjusted for age, gender, race, insurance type, comorbities, location of the tumor)	<u>Number of hospitals- number of patients</u> Period A: <6: 72%-29% 6-10: 16%-21% 11-20: 7%-19% 21-30:3%-14% >30:2%-17% Period B: <6: 64%-23% 6-10: 19%-20% 11-20: 12%-24% 21-30:2%-8% >30:3%-25% Period C: <6: 64.5%-21% 6-10: 15.8%-14% 11-20: 10.4%-18% 21-30:4.9%-14% >30:4.4%-34%	Level of evidence: B • Moderate quality study • Clearly defined primary outcome • Potential confounders are taken into account
Gomi 2003 [8]	• Design: Retrospective cohort study • Source of funding: Not reported • Setting: 76 randomly selected institutions in Japan • Sample size: N=220 A1:N=87 A2:N=72 B:N=61 • Duration: between September 1998 and March 2001	• Eligibility: thoracic esophageal cancer treated during 1995–1997, any pathologic type, and ≥60 initial Karnofsky performance status who had undergone preoperative or postoperative RT • Exclusions: presence of distant metastasis or other active malignancies. • Patient characteristics: median age 62.3 years male 88.1% KPS 60–70 17.5% SCC 99.5% Tumour location: upper: 11.8% middle: 61.3% lower: 24.5% Stage III: 41.7% In non-academic 52.6% vs. academic 37.7%,	A1= academic institutions (mainly cancer centers and university hospitals) ≥300 patients annually; Control groups: A2= academic institutions (university hospitals) treating <300 patients annually B=non-academic institutions (national hospitals, public general hospitals, and private hospitals)	<u>Overall 2-year survival rate</u> A1: 77.9% A2: 61.6% C: 40.0% Difference A1 vs. non-academic: p=0.001 <u>Overall survival:</u> Multivariate analysis: Type of institution (p=0.0373, RR=0.588) Clinical stage (p=0.0268, RR= 0.566) Presence of macroscopic residual tumor (p=0.0040, RR= 0.461) Photon energy (p=0.0215, RR= 0.536) Use of chemotherapy (p=0.0118, RR=1.910)		Level of evidence: B • Low quality cohort study • Unclear which variables were included in multivariate analyses • Lost of follow up not presented • Small sample size

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		p=0.016				
Goodney 2003 [9]	• Design: Retrospective cohort study • Sources of funding: Agency for Healthcare Research & Quality and the VA Health Services Research & Development program • Setting: multicentre study in the USA • Sample size: Not reported • Duration: 1994-1999	• Eligibility: Medicare recipients covered by the hospital care program and undergoing cancer related esophagectomy • Exclusion criteria: Medicare patients who were enrolled in risk-bearing health maintenance organizations during the period (approximately 10% of Medicare enrollees) ; patients who were <65 or > 99 years • Patient characteristics: not reported	Exposure: annual hospital volume (average number of procedures annually)	<u>Post-operative length of stay</u>(period from the index procedure to hospital discharge); stratified by average number of procedures annually <2: mean 19.7 days 2-4: mean 20.1 days 5-7: mean 19.6 days 8-19: mean 20.0 days >19: mean 18.2 days Significantly shorter in high-volume (p-value not given)	<u>30-day readmission rate</u> (readmission to any hospital within 30 days of discharge after the index procedure); stratified by annual hospital volume quintile Overall: 18.4% Very low: 19.1% Low: 17.9% Medium: 18.2% High: 18.4% Very high: 18.7% Trend not significant	Level of evidence: B • The following potential confounders were taken into account: age, gender, race, comorbidities, admission acuity, and mean Social Security income, but were not significant • Cancer stage was not taken into account • Comparison between different groups not shown
Ioka 2007 [10]	• Design: Retrospective cohort study • Sources of funding: Not reported • Setting: Osaka, Japan • Sample size: N=2430 High volume: N=655 Medium volume: N=590 Low volume: N=588 Very low volume: N=597 • Duration: 1994-1998	• Eligibility: Patients with esophagus cancer • Exclusion: second or more tumour, carcinomas in situ • Patient characteristics: not reported	Patients treated in high volume hospital vs. Patients treated in: Medium volume hospital Low volume hospital Very low volume hospital	<u>5- year survival</u> High: reference Medium volume: Adjusted HR 1.3 (1.2-1.5) Low volume: Adjusted HR 1.3 (1.2-1.5) Very low volume: Adjusted HR 1.6 (1.4-1.9) (adjusted for sex, age and cancer stage)		Level of evidence: B • Cut-off points for categorisation volume hospitals not specified • Patients in different hospitals not from same source population • Potential confounders identified and taken into account
Jeganathan 2009 [11]	• Design: retrospective cohort study • Sources of funding: Not reported • Setting: 1 centre in Northern Ireland • Sample size: N=252 (consultants: N=5; trainees: N=17) • Duration: June 1994 and June 2006	• Eligibility: patients diagnosed with esophageal cancer who were surgically treated with curative intent at a tertiary referral centre with a total thoracic esophagectomy • Patient characteristics: mean age 63 years, 75% male	Patients operated by consultants vs. Patients operated by trainees	<u>In hospitality mortality</u> Consultants: 4.3% Trainees: 4.4% p=0.61 <u>Case volume per surgeon</u>: p=0.24	<u>Overall 1-year survival</u>: 69% <u>Overall 5-year survival</u>: 28.8% no significant difference amongst surgeons when adjusted for pathological staging (log-rank P=0.17)	Level of evidence: B • Small sample size • Potential confounders identified and taken into account

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Leigh 2009 [12]	• Design: Retrospective cohort study • Sources of funding: English NHS National Coordinating Centre for Research Capacity Development - Hanson Trust Research fellowship • Setting: nationwide data from the UK • Sample size: N=9034 Hospitals ≥100 operations: N=3791; Hospitals <100 operations: N=5243 • Duration: April 1998 to March 2003	• Eligibility: Patients treated with esophagectomy for esophageal cancer or esophago-gastric cancer • Exclusions: not reported • Patient characteristics: Mean age 64.2/ 63.5 % male 72.9/ 74.0 Deprivation score 21.4/ 21.2 % EGJ, lower third 80.7 / 80.6 % esophago-gastrectomy 61.0/ 76.3 (p<0.001)	Patients treated in low volume hospitals (<100/ 5 year) vs Patients treated in high volume hospitals (≥100/ 5 year)	<u>30-day mortality ,low volume vs high volume</u> Adjusted OR: 1.62 (1.38-1.91) <u>90-day mortality ,low volume vs high volume</u> Adjusted OR: 1.55 (1.35-.77) (Adjusted for age, sex, socio-economic deprivation score)	<u>30 day mortality, general surgical patients vs cardiothoracic Sx patients</u> Adjusted OR: 1.62 (1.34-1.96) <u>90 day mortality, general surgical patients vs cardiothoracic Sx patients</u> Adjusted OR: 1.38 (1.18-.61) (Adjusted for age, sex, socio-economic deprivation score) <u>Multivariate analysis for 30 days mortality</u>, adjusting for age, sex and socioeconomic deprivation: Low volume hospital: OR 1.43 (1.18-1.74) General Sx specialty : OR 1.30 (1.04-1.62) Multivariate analysis for 90 days mortality, adjusting for age, sex and socio-economic deprivation Low volume hospital: OR 1.49 (1.27-1.75)	Level of evidence: B • Primary outcome not well defined • Cancer stage as confounders not taken into account
Meguid 2009 [13]	• Design: Retrospective cohort study • Sources of funding: Ruth L. Kirschstein National Research Service Award • Setting: data collected from the Nationwide Inpatient Sample file (US) • Sample size: N=4080 • Duration: 1998-2003	• Eligibility: patients from the NIS database ≥17 years of age admitted with the diagnosis of esophageal cancer • Exclusions: not reported • Patient characteristics: 79.6% male, median age 64 years, 83.9% were white, median Charlson Comorbidity 3 (IQR 2 -8)	Hospital volume above or below volume threshold (=15)	<u>Mortality Rate:</u> Centers ≥ Volume Threshold: 5.30% Centers < Volume Threshold: 10.16% p<0.01 Threshold modeling adjusted for patient age, gender, race and Charlson Index of comorbidities, procedure year, and hospital teaching status		Level of evidence: B • Primary outcome not well defined • Unclear whether difference in mortality rates took account of confounders

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Milne 2000 [14]	• Design: Retrospective cohort study • Sources of funding: Not reported • Setting: 2 centres in the UK • Sample size: N=113 General Sx: N=60 Specialist Sx: N=53 • Duration: January 1993 – December 1996	• Eligibility: Patients with biopsy proven esopaheagal cancer • Exclusions: absent or incomplete data • Patient characteristics: Age 70/ 72 Male:female 34:26 / 39:17 SCC: 38/ 34%	Treated by 1general surgeon within the General district hospital vs Treated by 2 cardiothoracic surgeons in the regional cardiothoracic unit	<u>Survival at 3 months</u> General surgeon: 63% Specialist surgeons: 62%	<u>Survival at 1 year</u> Exposure: 24% Controls: 25% Survival at 2 years Exposure: 12% Controls: 8% Survival at 3 years Exposure: 7% Controls: 6% No statistical significant difference at any time point between the two groups	Level of evidence: B • Primary outcome not defined • Comparison between both groups does not indicate stage • Confounders not taken into account • Small sample size
Migliore 2007 [15]	• Design: retrospective cohort study • Sources of funding: Not reported • Setting: 1 centre in the UK • Sample size: N=195 High-volume surgeon: N=118 Low-volume surgeon: N=77 • Duration: January 1994 and December 2005	• Eligibility: patients, who underwent esophagectomy for malignant disease with palliative or curative intent • Exclusion: patients treated by endoscopic techniques • Patient characteristics: 140 males and 55 women, mean age 64 years (range 48-80)	Patients treated by a high-volume surgeon (mean ≥ 6 cases/year) vs. Patients treated by a low-volume surgeon (mean < 6 cases/year)	<u>In hospital mortality, low vs high volume</u> Adjusted OR: 4.60 (1.55- 13.60) p=0.006 (Adjusted for age, tumour stage and type)	<u>Overall survival, median</u> High volume: 16.8 months (13.8- 19.8) Low volume: 13.9 months (11.0- 17.0) p=0.48	Level of evidence: B • Small sample size • Potential confounders identified and taken into account
Rouvelas 2007 [16]	• Design: Prospective cohort study • Sources of funding: Not reported • Setting: Nationwide Swedish study • Sample size: N=607 Low volume surgeons: N=70 Medium volume surgeons: N=187 High volume surgeons: N=350 • Duration: April 2001 - December 2006	• Eligibility: Swedish residents diagnosed with esophageal or cardia cancer treated with esophagectomy • Exclusions: not reported • Patient characteristics: Mean age 66.2 Men:women 489:118 Concurrent disease None 31% One or two 59% Three or more 9.5% Type of cancer Esophageal cancer 54% Gastric cardia cancer 46%	Patients treated by low-volume surgeons (LVS) (<2 esophagectomies annually) vs Patients treated by medium-volume surgeons (MVS) performed (2- 6 esophagectomies annually) vs Patients treated by high-volume surgeons (HVS) (>6 esophagectomies annually)	<u>30-days post operative mortality</u> Adjusted OR LVS: reference MVS: 0.39 (0.09- 1.70) HVS: 0.42 (0.10- 1.80) (Adjusted for age, sex, co-morbidity, tumour stage, location, histology, preoperative oncological treatment, and curative intention)	<u>90-days post operative mortality</u> Adjusted OR LVS: reference MVS: 0.48 (0.16-1.38) HVS: 0.86 (0.31-2.38) (Adjusted for age, sex, co-morbidity, tumor stage, location, histology, preoperative oncological treatment, and curative intention)	Level of evidence: B • Potential confounders identified and taken into account

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Rutegard 2008 [17]	• Design: Prospective cohort study • Sources of funding: Swedish cancer society • Setting: multicentre study in Sweden • Sample size: N=355 LVH: N=174 HVH: N=181 LVS: N=148 HVS: N=207 • Duration: 2001-2005	• Eligibility: patients newly diagnosed with esophageal or cardia cancer who underwent macroscopically and microscopically radical resection • Exclusions: not reported • Patient characteristics: Age (yr): <60: 25.7%; 60–70: 33.5%; >70 40.8%; Male 80.7% Comorbidity: None 32.7%, 1 or 2 62.6%; 3 or more 4.6% Tumour stage: Stage 0–I 18.7%; Stage II 29.1%; Stage III 40.5%; Stage IV 11.2% Tumour location: Cardia 46.2%, Lower esophagus 38.0%; Upper or middle esophagus 15.8% SCC 24.2% Neoadjuvant treatment 11.2% Macroscopically radical 90.4%	Low volume hospitals (LVH) (0–9 operations annually) vs High volume hospitals (HVH) (≥ 9 operations annually) Low volume surgeons (LVS) (0–6 operations annually) vs High volume surgeons (HVS) (> 6 operations annually)	<u>HRQOL at 6 months</u> Mean score Per hospital: LVH: 60 (57–64) HVH: 60 (57–63) p≥0.05 Per surgeon LVS: 62 (58–65) HVS: 59 (56–62) p≥0.05		Level of evidence: B • Small sample size • Potential confounders identified and taken into account • Well defined outcome • Measure of outcome is reliable
Rutegard 2009 [18]	• Design: prospective cohort study • Sources of funding: Swedish cancer society • Setting: multicentre study in Sweden • Sample size: N=615 HVS: N=347 MVS:N=199 LVS:N=69 • Duration: 2001-2005	• Eligibility: patients diagnosed with esophageal or cardia cancer who underwent surgical resection • Exclusions: not reported • Patient characteristics: Age (yr): <60: 25.7%; 60–70: 33.5%; >70 40.8% Male 80.7% Comorbidity: None 32.7%, 1 or 2 62.6%; 3 or more 4.6% Tumour stage: Stage 0–I 18.7%; Stage II 29.1%; Stage III 40.5%; Stage IV 11.2%	Patients treated by high volume surgeons (HVS) (>6 operations annually) vs Patients treated by medium volume surgeons (MVS) (2-6 operations annually) vs patients treated by low volume surgeons (LVS) (<2 operations annually)	<u>Primary surgical complications</u> (considered to be more closely linked with the individual surgeon's efforts) HVS: reference MVS: OR 0.66 (0.38–1.17) LVS: OR 0.49 (0.19–1.24) (Adjusted for age, sex, tumor stage, location, histology, comorbidity, surgical approach, neoadjuvant therapy, macroscopic radicality, and examined lymph nodes)	<u>Secondary surgical complications</u> (less markedly related to the individual surgeon's operative performance) HVS: reference MVS: OR 0.83 (0.39–1.74) LVS: OR 1.41 (0.65–3.08) <u>Primary and secondary complications</u> HVS: reference MVS: OR 0.80 (0.45–1.42) LVS: OR 0.99 (0.49–1.98) (Adjusted for age, sex, tumor stage, location, histology, comorbidity, surgical approach, neoadjuvant therapy, macroscopic	Level of evidence: B • Potential confounders identified and taken into account • Well defined outcome • Measure of outcome is reliable • Same source population as Rutegard 2008

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		Tumour location: Cardia 46.2%, Lower esophagus 38.0%; Upper or middle esophagus 15.8% SCC 24.2% Neoadjuvant treatment 11.2% Macroscopically radical 90.4%			radicality, and examined lymph nodes)	
Smith 2008 [19]	• Design: Retrospective cohort study • Sources of funding: Not reported • Setting: Multicentre in the USA • Sample size: N=2657 (Exposure group: N=1079; Control group: 1578) • Duration: 2003-2007	• Eligibility: Patients who underwent partial or total esophagectomy for esophageal cancer • Patient characteristics: male (%) 80 / 81 Race (%): Caucasian 81/ 84 p=0.05 Black 4 /4 p=0.68 Hispanic 2 /1 p=0.02 Asian 1 /1 p=0.56 Comorbid illness (%) Moderate 24.2/28.6 p=0.01 Major 55.7 /54.5 p=0.55 Extreme 20.1 /16.9 p=0.04	Patients treated by a general surgeon vs. Patients treated by a thoracic surgeon	<u>Overall complications</u> (included those related to cardiac, pulmonary, thrombotic, hemorrhagic, iatrogenic, and wound infectious events) General surgeon: 55% Thoracic surgeon: 52% p=0.11	<u>In hospital mortality</u> General surgeon: 3.6% Thoracic surgeon: 2.9% p=0.31 <u>Length of stay (mean, days)</u> General surgeon: 16.6±11.5 Thoracic surgeon: 16.9±14.0 p=0.80 <u>ICU stay (mean, days)</u> General surgeon: 8.4 Thoracic surgeon: 9.7 p=0.29 <u>Mean number of cases /year</u> General surgeon: 216 Thoracic surgeon: 316	Level of evidence: B • Primary outcome not defined • Confounders not taken into account • Groups not comparable regarding race, comorbidity and surgical approach
Stitzenberg 2009 [20]	• Design: Retrospective cohort study • Sources of funding: the John A. Ridge Surgical Oncology Fellowship at Fox Chase Cancer Center (K.B.S.); from the National Institutes of Health (B.L.E.) • Setting: Multicentre study in the USA • Sample size: N=5273 • Duration: 1996-2006	• Eligibility: patients treated with esophagectomy for neoplasm • Exclusions: Endoscopic resections • Patient characteristics: not reported	Patients treated at low volume hospital (LVH: ≤3 surgeries/year) vs. Patients treated at greater volume hospitals	<u>Having Sx at a LVH over time</u> Per year OR: 0.87(0.85 -0.90)	<u>In hospitality mortality</u> 1996: 8.15% 2006: 3.12% p=0.038 <u>Changes in median travel distance 1996-2006</u> 72% (p<0.001) <u>Disparities</u> Patients at LVH after centralisation: Black: OR 3.22 (p<0.001) Medicare: OR 1.58 (p<0.05) 6-20% below poverty line: OR 1.61 (p<0.05) >20% below poverty line: OR 2.39 (p<0.01)	Level of evidence: B • Sample size not stratified by hospital volume • Potential confounders not identified or taken into account

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Sundelof 2008 [21]	• Design: Retrospective cohort study (subgroup of earlier case-control study) • Sources of funding: National Cancer Institute,Cancerfonden • Setting: Nationwide study in Sweden • Sample size: N=232 High hospital: N=81 Low hospital: N=151 High surgeon: N=67 Low surgeon: N=165 • Duration: December 1994 -December 1997.	• Eligibility: incident cases of ACA of the esophagus and gastric cardia and half of those with SCC of the esophagus in the native Swedish population, <80 years of age, diagnosed between 1994 and 1997, and had undergone a surgical resection • Exclusions: not reported • Patient characteristics: Age at Sx (years) <59 24%; 60-65 20%; 66-70 26%; >70 30% Gender Male 83% Tumor location: Proximal/middle: 8% Distal esophagus 41% Cardia 51% Comorbidity None 60% Prior Sx within the operating field 14% Combined co-morbidity 3% Tumour stage: Stage 1 22% Stage 2 26% Stage 3 30%) Stage 4 16% Grade of tumor differentiation High 7% Medium 33% Low 56% Treatment: Surgical resection only 77% Surgical resection and neoadjuvant therapy 23%	High volume hospital (HVH) (annual number of the resections ≥ 10) vs Low volume hospitals (LVH) High volume surgeon (HVS) (annual number of the resections ≥ 10) vs Low volume surgeons (LVS)	5 year survival, stratified by volume hospital HR, 95%CI: HVH: reference LVH: 1.3 (1.0–1.9) p=0.02 HR, 95%CI: HVS: reference LVS: 1.4 (1.0–2.0) p=0.07 30-day mortality, (%) HVH 0 LVH 3 p=0.30 HVS 0 LVS 2 p=0.33 In-hospital mortality, (%) HVH 1 LVH 3 p=0.66 HVS 1 LVS 2 P=1.00	Operating time (min), median (range) HVH: 525 (150–830) LVH 360 (145–780) p<0.001 HVS 546 (210–830) LVS 360 (145–780) p<0.001 Operative bleeding volume (ml), median (range) HVH: 1100 (250–5200) LVH: 1100 (200–6500) p=0.78 HVS 1000 (250–5200) LVS 1200 (200–6500) p=0.20 Postoperative complications, (%) HVH 28) LVH 6 p=0.31 HVS 30 LVS 35 p=0.54 Postoperative respirator support, (%) HVH 17 LVH 38 p<0.001 HVS 24 LVS 34 p=0.16 Days in ICU, median (range) HVH 1 (1–17) LVH 2 (1–72) p<0.001 HVS 1 (1–17) LVS 2 (1–72) p<0.001 Days in hospital, median (range) HVH 19 (9–57) LVH 17.5 (7–102) p=0.28 HVS 18 (9–58) LVS 18 (7–102) p=0.42	Level of evidence: B • Potential confounders not identified or taken into account • Stratified sample size small

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
					Required secondary Sx, (%) HVH 10 LVS 13 p=0.67 HVS 9 LVS 13 p=0.50	
Van Vliet 2008 [22]	• Design: retrospective cohort study • Source of funding: Erasmus MC–University Medical Center Rotterdam • Setting: 8 centres in the Netherlands • Sample size: 8 (cases: N=2; controls: N=6) • Duration: 1994-2003	• Eligibility: CT examinations (N=72) of patients diagnosed with esophageal or gastric cardia cancer (random selection) that were re-evaluated or repeated at the referral centre • Patient characteristics: N stage: N0 41 N1 31 M stage: M0 35 M1 37	Radiologists from referral centers ('expert') (centers had a volume of >100 patients with esophageal or gastric cardia cancer per year) vs Radiologists from regional non-referral centers ('non-expert') (centers < 10 cases per year)	Radiologist experience (expert versus non-expert) Lymph node metastases All CT examinations OR 0.94 (0.50–1.77) Distant metastases All CT examinations OR 2.93 (1.36–6.29) (Adjusted for origin of CT examination) Origin of CT examination (referral center versus regional center) Lymph node metastases All CT examinations OR 1.06 (0.46–2.42) Distant metastases All CT examinations OR 0.85 (0.38–1.94)	Quality of CT examination Lymph node metastases All CT examinations OR 0.93 (0.56–1.55) Distant metastases All CT examinations OR 1.94 (1.00–3.68) (Adjusted for radiologist experience and origin of CT examination)	Level of evidence: B • Primary outcome not defined • Main confounders taken into account • Partly overlap with Van Vliet AM J Gastroentero 2006
Van Vliet 2006 [23]	• Design: Retrospective cohort study • Source of funding: Erasmus MC–University Medical Center Rotterdam • Setting: 62 centres in the Netherlands • Sample size: N=573, repeated CT scan: 115 re-evaluated CT scan: 235 • Duration: 1994-2003	• Eligibility: patients diagnosed with esophageal cancer; treated at the Erasmus MC Rotterdam, after first being diagnosed in a regional center • Patient characteristics: Mean age ± SD (yr) 63 ± 10.4 Male 77% Histology of tumour at biopsy (%) SCC 35%, ACA 57% Location of tumour (%) Cervical 1%, upper 1/3 thoracic 4%, central 1/3 thoracic 15%, lower 1/3	Examinations evaluated at regional center vs Examinations evaluated at referral center	Repeated CT-scan (n = 115) Sensitivity (%) Regional lymph nodes Regional 26% Referral 52% p=0.002 Distant metastases Regional 44% Referral 84% p=0.001 Peri-esophageal lymph nodes Regional 26% Referral 48% p=0.022 Celiac lymph nodes Regional 41%	Repeated US Abdomen (n = 167) Sensitivity (%) Celiac lymph nodes Regional 7% Referral 44% p <0.001 Liver metastases Regional 6% Referral 71% p=0.001 Specificity (%) Celiac lymph nodes Regional 100% Referral 99% p=0.320 Liver metastases	Level of evidence: B • Primary outcome not defined • Potential confounders not taken into account • Both groups comparable, CT scans repeated within median of 2 weeks=time bias • Partly overlap with Van Vliet Eur Radiol 2008 and Van Vliet Gastrointestin Endosc 2006

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		thoracic 39%, gastric cardia 41%		Referral 79% p=0.001 Liver metastases Regional 30% Referral 60% p=0.250 <u>Specificity (%)</u> Regional lymph nodes Regional 94% Referral 99% p=0.375 Distant metastases Regional 99% Referral 98 p= 1.000 Peri-esophageal lymph nodes Regional 97% Referral 99% p= 1.000 Celiac lymph nodes Regional 96% Referral 99% p=0.625 Liver metastases Regional 100% Referral 97% p=0.083 <u>Re-evaluated CT-scan (n = 235)</u> <u>Sensitivity (%)</u> Regional lymph nodes Regional 19% Referral 41% p <0.001 Distant metastases Regional 18% Referral 43% p <0.001 Peri-esophageal lymph nodes Regional 18% Referral 36% p <0.001 Celiac lymph nodes Regional 13%	Regional 100% Referral 100% p=1.000 <u>Repeated US Neck (n = 153)</u> <u>Sensitivity (%)</u> Regional 26% Referral 84% p=0.001 <u>Specificity (%)</u> Regional 100% Referral 100% p=1.000 <u>Repeated Chest x-Ray (n = 270)</u> <u>Sensitivity (%)</u> Regional 9% Referral 64% p=0.031 <u>Specificity (%)</u> Regional 99% Referral 99% p=1.000	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
				Referral 45% p <0.001 Liver metastases Regional 8% Referral 31% p=0.250 <u>Specificity (%)</u> Regional lymph nodes Regional 92% Referral 90 p=0.804 Distant metastases Regional 97% Referral 95% p=0.375 Peri-esophageal lymph nodes Regional 91% Referral 91% p= 1.000 Celiac lymph nodes Regional 97% Referral 95% p=0.453 Liver metastases Regional 97% Referral 97% p= 1.000		
Van Vliet 2006 [24]	• Design: Retrospective cohort study, compared to literature data • Source of funding: Erasmus MC–University Medical Center Rotterdam • Setting: 8 centres in the Netherlands • Sample size: N=244 • Duration: 1994-2003	• Eligibility: patients diagnosed with esophageal cancer; who underwent endoscopic ultrasonography (EUS) at the Erasmus MC Rotterdam and underwent a resection without neoadjuvant chemotherapy and/or radiation therapy • Patient characteristics: Mean age 64 y Male 83% Histology of tumour at biopsy: SCC 10%, ACA 87% Location of tumour Cervical -	EUS performed at a low volume center (the Erasmus MC Rotterdam: <50 EUS/endoscopist/ year) vs EUS performed at 3 high volume centers (>50 EUS/ endoscopist/ year) (data identified by a literature search)	<u>k value= measure of agreement between the Tstage determined by EUS and the postoperative T stage</u> Low-volume center (EUS probe passage) 0.23 (0.14-0.33) Low-volume center (no EUS probe passage) -0.09 (-0.29-0.11) High-volume centers 0.58 (0.47-0.69) to 0.83 (0.77-0.89)		Level of evidence: C • Retrospective analysis comparing to data identified by literature search • Only k value reported with 95% CI, all other results crude percentages without statistical test for significant differences • Potential confounders not shown • Partly overlap with Van Vliet Am J Gastroenter 2006

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		Upper 1/3 thoracal - Central 1/3 thoracal 4% Lower 1/3 thoracal 39% EGJ 57%				
Verhoef 2007 [25]	• Design: Prospective cohort study • Sources of funding: Not reported • Setting: multicenter study in the Netherlands • Sample size: N=1149 (Initially diagnosed in the university hospital: N=85, in teaching nonuniversity hospitals: N=428; in the nonteaching hospitals: N=636) • Duration: January 1994 to January 2002	• Eligibility: primary invasive esophageal cancer in the region of the Comprehensive Cancer Centre North-Netherlands • Exclusions: Patients with a history of cancer other than nonmelanoma skin cancer • Patient characteristics: Age at diagnosis (y) <50 7.5%; 50–59 19.2%; 60–69 27.8%; 70+ 45.5% Male 69.1% 1 SCC 36.1%, ACA 51.6% Upper thoracic 7.1% Middle thoracic 18.3% Lower thoracic 67.0% Overlapping and unspecified 7.6% Stage: 1 4.5%; 2A 15.1%; 2B 6.0% ; 3 18.0%; 4 27.5	Non teaching hospital vs Teaching, non university hospital vs Treatment in university hospital	5 year survival University hospital: 49.2% Teaching non-university: 32.6% Non-teaching hospitals: 27.3% p=0.0039	Relative excess risk of death (RER) Adjusted RER Non teaching: reference Teaching: 1.32 (0.79–2.22) University: 0.57 (0.29–1.12) p=0.0126 (Adjusted for age, stage, and time since diagnosis) Multivariate analysis on RER (including age, stage, tumour location, hospital volume, frequency of referral, and time since diagnosis): stage: p<0.0001 age: p=0.0467 hospital type: p=0.0126 hospital volume: p=0.112 Odds of operation: 1.89 (1.26–2.82) for non-teaching hospital vs. teaching non-university hospital (Adjusted for age, stage, and tumor location)	Level of evidence: B • Potential confounders identified and taken into account • Different groups are not comparable
Wenger 2005 [26]	• Design: Retrospective Cohort study • Sources of funding: Not reported • Setting: Nationwide study in Sweden • Sample size: N=402 (high volume: N=300; low volume: N=102) • Duration: 1997-2000	• Eligibility: patients newly diagnosed with esophageal or cardia cancer, treated with self-expanding metal stents • Patient characteristics: Men 72%, median age 74 years (range 22±96 years)	High-volume unit (>10 procedures) Low-volume units (≤10 procedures) Definition of high/low volume: based on median number of patients in the evaluation of complications	Overall survival time p=0.001 in favour of being treated in low volume units	Overall complication rate High volume: 30% Low volume: 25% Not significant	Level of evidence: B • Clinical data of only 152 patients was available for analysis of complication rate • No comparison of demographics between the two groups is presented • Potential confounders are not identified or taken into account
Wouters 2008 [27]	• Design: Retrospective cohort study • Sources of funding: Not reported • Setting: Multicentre study in the Netherlands	• Eligibility: surgically treated esophageal carcinomas • Patient characteristics: Age (years) 65/ 64	High volume center (mean volume: 56 surgeries annually) Low volume center (≤7 surgeries annually)	In hospital mortality Adjusted OR: 3.05 (1.82–5.11) (Adjusted for age and comorbidity)	Surgical complications LVH: 42% HVH:37% p=0.01 General complications LVH: 56%	Level of evidence: B • Partly overlap with Wouters 2008 and Wouters J Surg Oncol 2009 • Primary outcome not defined

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	• Sample size: N=903 Low volume: N=342 High volume: N=561) • Duration:1990-1999	Male 73 /78% Comorbidity No 42 /49% 1 organ system 32 /32% 2 organ systems 15 /14% ‡3 organ systems 3 / 5% Histology ACA 69 /62% SCC 28 /34% Barrett's dysplasia 1 /1 Tumor localization Cervical esophagus 2 /3% Mid esophagus 15 /15% Distal esophagus 33 /36% EGJ 49 /45% Stage (pTNM) 0 and I 12 /11% II 47 /38% III 31 /33% IV 6 /17% (Neo)-adjuvant treatment None 92 /83% Chemotherapy 5 /17% RT 0 /0% CRT 1 /0%			HVH:37% p<0.01 <u>No complications</u> LVH: 26% HVH:44% p<0.01 <u>Overall survival after esophagus resection for stage I and II carcinoma:</u> (in-hospital mortality excluded) log rank p value =0.04 in favour of HVH	• Both groups not comparable regarding stage and adjuvant treatment • Lost of follow up not presented
Wouters 2009 [28]	• Design: Nested case control study • Sources of funding: Not reported • Setting: Nationwide study in the Netherlands • Sample size: N=4939 Low: N=1886; Medium: N=515; High: N=1629 • Duration: 1991-2005	• Eligibility: all esophageal resections for cancer that were performed in Dutch hospitals • Patient characteristics: 1991–1994 Age 62 year Male 75% 1995–1999 Patient age 63 years Male 76% 2000–2004 Patient age 62.6 years Male 77%	Low volume hospitals (<10 resections/year) vs Medium volume hospitals (10-20 resections/year) vs High volume hospitals (>20 resections/year)	<u>In hospital mortality</u> LVH: reference MVH: OR 1.01 (0.66-1.54) (p=0.98) HVH: OR 0.48 (0.30-0.77) (p=0.003) (Adjusted for age, gender, operation year, volume, and region)	<u>Odds of dying before and after 2000</u> 4.68 times (1.26-17.3; p<0.02) in favour of after 2000	Level of evidence: B • Partly overlap with Wouters 2008 and Wouters Ann Surg Oncol 2009 • Group comparability not shown • Cancer stage not taken into account as potential confounder

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Wright 2009 [29]	• Design: Retrospective cohort study • Sources of funding: Not reported • Setting: 73 sites in the USA • Sample size: N=2315 • Duration: 2002-2007	• Eligibility: patients treated with esophagectomies for primary esophageal cancer • Exclusions: 2 sites (49 operations) for inconsistent reporting • Patient characteristics: Age (y) <60 35.0%; 60–64 17.8; 65–69 17.2% ; 70–74 14.0%; 75–80 11.2%; >80 4.8% Male 82.0% White 90.9% Black 2.7% Other 4.6%	Hospital volume	Morbidity, for a 10-unit decrease in volume: OR: 1.09 (0.98–1.20) p=0.10 (Adjusted for age, gender, race and comorbidities)		Level of evidence: B • No comparison between high and low volume hospitals was presented • Cancer stage as potential confounder not identified and taken into account

Abbreviations: 95%CI: 95 percent confidence intervals; ACA: adenocarcinoma; ASA: American Society of Anesthesiologists; CRT: chemoradiotherapy; EGJ: esophagogastric junction; HR: hazard ratio; HVH: high volume hospital; HVS: high volume surgeon; LVH: low volume hospital; LVS: low volume surgeon; MA: meta-analysis; MVH: medium volume hospital; MVS: LVH: low volume hospital; LVS: low volume surgeon; volume surgeon; NS: not significant; OR: odds ratio; RCT: randomized controlled trial; RER: relative excess risk; RR: risk ratio; RT: radiotherapy; SCC: squamous cell carcinoma; SD: standard deviation; SR: systematic review; Sx: surgery; UK: United Kingdom; US: United States; WOCA: Wessex Oesophageal Cancer Audit.

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