Author: Wouters, M.W.J.M
Title: Measuring and improving quality of care in surgical oncology
Issue Date: 2013-05-23

Chapter 2

The volume-outcome relationship in the surgical treatment of esophageal cancer: a systematic review and meta-analysis

M.W.J.M. Wouters[1,2], G.A. Gooiker[2], J.W. van Sandick[1], R.A.E.M. Tollenaar[2]

[1] Department of Surgical Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek hospital, Amsterdam, The Netherlands

[2] Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands

Cancer. 2012 Apr 1; 118(7):1754-63.

ABSTRACT

Aims:
To conduct a systematic review and meta-analysis of the literature on the relationship between procedural volume and outcome of esophagectomies.

Methods:
A systematic search to identify articles investigating effects of hospital (HV) or surgeon volume (SV) on short- and long-term outcomes, published between 1995 and 2010. Articles were scrutinized on methodological quality and after inclusion of only high-quality studies a meta-analysis assuming a random effects model was done to estimate the effect of higher volume on patient outcome. Heterogeneity in study results was evaluated with an I^2-test and risk of publication bias with an Egger's regression intercept.

Results:
Forty-three studies were found. Sixteen studies met the strict inclusion criteria for the meta-analysis on HV and postoperative mortality and 4 studies on HV and survival. The pooled estimated effect size was significant for high-volume providers in the analysis of postoperative mortality (OR 2.30; CI 1.89-2.80) and in the survival analysis (OR 1.17; CI 1.05-1.30). The meta-analysis on SV and outcome showed no significant results.
Studies in which the results were adjusted not only for patient characteristics, but also for tumor characteristics and urgency of the operation, showed a stronger correlation between HV and mortality. Also, studies performed on data from the United States showed higher effect sizes.

Conclusions:
The evidence for HV as an important determinant of outcome in esophageal cancer surgery is strong. Concentration of procedures in high volume hospitals with a dedicated setting for the treatment of esophageal cancer, might lead to an overall improvement in patient outcome.

INTRODUCTION

Improving quality and effectiveness of health care is one of the priorities of health policies. In surgical oncology there has been a continuous debate about how to assure that every patient gets the optimal treatment for his or her cancer. Despite improvements in targeted therapies and adjuvant treatments, surgery is still the key to cure cancer patients with solid malignancies. In the past, surgical outcomes and causes of variation were largely unknown, but since the beginning of this century there are an increasing number of population-based studies evaluating differences in practice patterns and outcomes between providers.

Many studies suggest that procedural volume is an important determinant of outcome in cancer surgery[1]. Especially for high-risk, low-volume surgical procedures, like esophagectomies and pancreatectomies, differences in outcomes between high- and low-volume providers have been reported[2,3]. Though the number of volume-outcome studies in the literature is high and continues to increase, there is solid criticism on the methodological quality of these studies. The vast majority of volume-outcome studies in cancer surgery is observational and based on administrative data collected for other purposes. Moreover, potential differences in case mix between high- and low-volume hospitals are not always accounted for and postoperative mortality is often presented as the sole outcome measure. Inadequate reporting of volume-outcome studies restricts the generalizability and credibility of study results, feeds a fruitless debate and hampers the introduction of minimal volume standards for cancer surgery in several countries, for example in the Netherlands[4].

Esophagectomy for cancer is a high-risk, low-volume surgical procedure for which the volume-outcome relationship could be important. In many countries esophagectomies are performed in a low-volume setting. For example, until 2007 approximately 350 of these operations were performed annually in the Netherlands, shared by more than 50 different hospitals[5]. It is believed that concentration of these procedures with high-volume providers could improve overall patient outcome.

The aim of this study was to inform the debate on the volume-outcome relationship in esophageal cancer surgery, by conducting a systematic review of the literature on this subject. The methodological quality of the studies in this review was scrutinized and only high-quality volume-outcome studies were included in a meta-analysis.

METHODS

Systematic Search Strategy

We performed a systematic search to identify all articles describing the association between hospital or surgeon volume of esophagectomies and clinical outcomes (morbidity, mortality, survival, quality of life), published after January 1st 1995. The search was conducted in the

Table 1. Search terms used in the search in the Medline database

Medline (Pubmed)
("Esophagectomy"[MAJR] OR "Esophageal Neoplasms/surgery"[MAJR] OR ("Surgical Procedures, Operative"[MAJR:NoExp] AND "Neoplasms"[MAJR:NoExp])) AND ("hospital volume" OR "surgeon volume" OR "provider volume" OR "Outcome Assessment (Health Care)"[MAJR] OR regionalization[ti] OR regionalization[ti] OR "Health Facility Size"[majr] OR "Workload"[majr] OR (outcome*[ti] AND volume*[ti]) OR (outcome*[ti] AND complication*[ti]) OR (outcome*[ti] AND mortality*[ti]) OR (outcome*[ti] AND morbidity*[ti]) OR (outcome*[ti] AND survival*[ti]) OR (outcome*[ti] AND quality of life*[ti]))

electronic Medline database (Pub med) with a combination of MESH terms and text words (Table 1). Because volume is not well indexed in the electronic databases, we formulated the search terms as sensitive as possible to ensure no publications were missed. The last search was done on July 1st 2010.

Study selection

Two reviewers (MW, GG) independently screened titles and abstracts of all retrieved articles. Studies were selected using the following inclusion criteria:

- The article was in the English language
- The study used primary data (i.e., letters, editorials, and reviews were excluded)
- The subject of the study was the surgical treatment of esophageal cancer.
- The study did not describe the results of a single hospital or surgeon.

After this first selection on titles and abstracts, the remaining articles were obtained in full text and were further selected by the same two reviewers using the following exclusion criteria:

- Lack of comparisons between providers (hospitals or surgeons).
- No definition for procedural volume as a distinct number or cut-off value (i.e., studies that defined volume as 'specialization' were excluded)
- No postoperative morbidity, mortality, survival or quality of life among outcome parameters.

Any discrepancies regarding inclusion or exclusion of a study were solved by consulting a third investigator (RT). In addition, reference lists of relevant articles and recent reviews were hand-searched to identify additional articles, which could have been missed in the initial search[6,7]. We also used the "related articles" function in Pub med.

Assessment of study quality

Two authors (MW, GG) critically appraised each study in the review on methodological quality and risk of bias. Data of the included studies were gathered in a data-extraction form, which was based on the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) criteria (www.strobe-statement.org). From each study, characteristics were collected regarding the unit of analysis (hospital or surgeon), the data source (administrative

or clinical data), study period, the study design (prospective or retrospective), the country of origin, the number of analyzed patients, hospitals and surgeons, volume categories for hospitals and surgeons, outcome parameters (morbidity, mortality, survival, quality of life) and results regarding these outcome parameters (statistically significant or not significant) and the degree of risk adjustment. We noted the case mix factors for which statistical adjustment was done. Case mix factors were categorized as demographic parameters (age, gender, race and income); co morbidities; tumor characteristics (stage, grade, location); treatment characteristics (neo-adjuvant treatments) and urgency of the operation. In addition, some studies adjusted for in-hospital mortality in the survival analyses.
Study inclusion criteria were checked to verify if there was a probability of selection bias. Cut-off values for high- and low-volume were noted per volume group, along with how these cut-off points were determined. The study results were recorded separately for each unit (surgeon or hospital) and for each outcome parameter (postoperative morbidity, postoperative mortality, 2- or 5-year survival and quality of life). The crude outcomes for each volume group were noted (if reported). Subsequently, we noted for each volume group and outcome parameter the estimated effect size after adjustment, expressed as odds ratio's (OR), hazard ratio's (HR) or risk rates (RR) with confidence intervals (CI) and measures of significance.

Synthesis of the data for meta-analysis

A meta-analysis was performed for the relationship between hospital volume and surgeon volume on the one hand and postoperative mortality and survival on the other. No meta-analysis was performed for postoperative morbidity because this outcome parameter was defined too heterogeneous among the included studies. For quality of life, only one study was available.
Only high quality studies were included in the meta-analyses. A high quality study was defined as a multicenter study in which a multivariate analysis was performed including casemix factors, such as demographic parameters (age, gender, race and income); comorbidities; tumor characteristics (stage, grade, location); treatment characteristics (neo-adjuvant treatments) and urgency of the operation. Studies without a multivariate analysis and/or no reporting of OR, HR or RR were excluded from the meta-analysis. The reference category varied between studies. Therefore, we had to convert the effect sizes so that the highest volume group was the reference in all studies. As a result, the OR of mortality or the HR of survival reflected the odds of mortality in the lowest volume group compared to the odds of mortality in the highest volume group.
To determine a pooled estimated effect, we used the random effect model for meta-analyses. The random effects model accounts for expected heterogeneity, which is more appropriate with pooling of observational studies.
Heterogeneity was quantified by the I^2 test. An $I^2 < 40$ was considered homogeneous, between 40 and 60 moderately heterogeneous and > 60 very heterogeneous[8]. We conducted a sensitivity analysis to further explore heterogeneity and to assess the impact

of subgroups. A subgroup analysis was done by data source (administrative versus clinical), adjustments for urgency of the operation (adjusted versus not adjusted), adjustments for tumor characteristics (adjusted versus not adjusted) and by study country (United States versus non-United States). No subgroup analysis by patient characteristics was performed, because all studies were adjusted for age, gender and co morbidities.

Publication bias was assessed with an Egger's regression intercept and shown in a funnelplot[9].

The meta-analysis was conducted with Comprehensive Meta Analysis, professional version 2.2 (©2006, Biostat inc. Englewood, USA).

RESULTS

Search results

Our initial search identified 97 potentially relevant articles regarding the volume-outcome relationship in the surgical treatment of esophageal cancer (figure 1). After the first screening on titles and abstracts we excluded 37 studies. The other 60 articles were retrieved for more detailed evaluation. Among these 35 articles were excluded: in 27 studies, comparisons were made between treatment techniques or patient groups, instead of comparing the outcome between providers (hospitals or surgeons). In 3 studies, degree of specialization (board-certified vs. non-certified surgeons, academic vs. non-academic hospitals) or nurse-to-patient ratio was evaluated, instead of procedural volume[10-12]. And in 5 studies, other outcome parameters than morbidity, mortality, survival or quality of life were evaluated[13-17]. The remaining 25 papers were selected. After this first selection, the related articles feature in Pub med was used and the reference lists of retrieved articles were hand-searched. We identified 18 additional articles which met the predefined criteria for our systematic review.

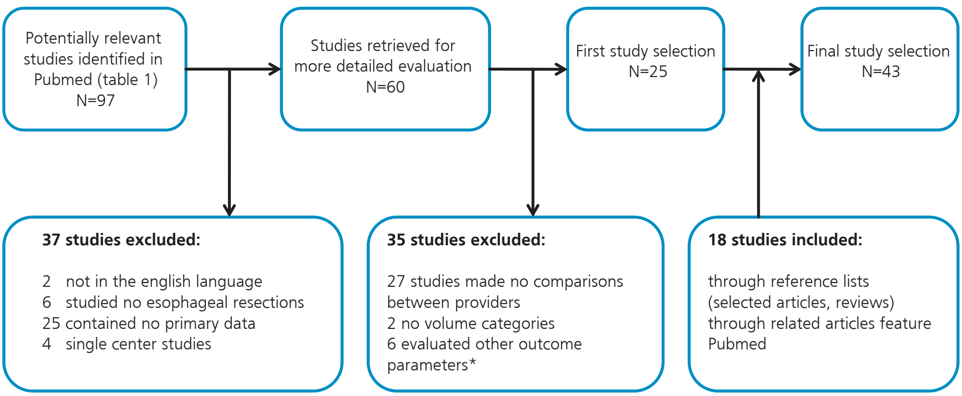

Figure 1. Selection of reviewed studies

Systematic review

Table 2 shows the characteristics of the 43 studies included in the review. Most studies are from the United States and Canada, though the number of European studies has been growing. Study data have been obtained frequently from insurance companies' databases (Medicare, National Inpatient Sample). The number of patients, hospitals and surgeons varied widely between the included studies. In most studies, results were adjusted for differences in case mix between high- and low-volume providers, but the parameters used for adjustments differed largely among studies. In some studies, data were corrected for differences in age and gender only. In other studies, adjustments were made for race, income, co morbidities, ASA-classification, tumor characteristics (stage, grade and location), urgency of the operation, (neo-adjuvant) treatments and (other) hospital characteristics. There was a considerable variation in the cut-off values for the volume groups in the included studies. For hospital volume, cut-off values of the highest volume strata varied between 3 and 87 procedures annually. The cut-off values of the lowest hospital volume strata varied between 1 and 20 procedures per year. The rationale for the cut-off values used was seldom explained in the methodological paragraph of the articles.

Hospital volume

In 36 studies, the relationship between hospital volume and outcome was evaluated. Postoperative mortality was used as an outcome parameter in 32 studies, and in 24 of these studies, a significant inverse relationship between hospital volume and postoperative mortality was found. In 9 studies, hospital volume and postoperative morbidity were investigated; in 4 studies, a statistically significant association was found, favoring high volume. Differences in survival between high- and low-volume hospitals were evaluated in 7 studies of which 4 were positive. Quality of life was evaluated in only one study; in this study, there was no correlation between hospital volume and quality of life[18].

Meta-analysis: hospital volume & postoperative mortality

Of the 32 studies evaluating the relationship between *hospital volume* and *postoperative mortality,* 16 met the inclusion criteria for the meta-analysis. All of these studies had an observational design and only three studies were based on clinical data, often collected in regional or national cancer registries. The other 13 studies were based on administrative data. In all but one study, the results of the multivariate analysis were adjusted for age, gender and co morbidities and in 9 studies the results were adjusted for urgency of the operation. A few studies adjusted for other confounding factors like stage of the disease, type of resection and neo-adjuvant treatments.

Figure 2a shows the forest plot of the included studies regarding hospital volume and postoperative mortality. The pooled estimated effect size was significant in favor of high-volume providers (OR 2.30; CI 1.89-2.80). There was moderate heterogeneity between the studies (I^2=60).

Table 2. Studies included in the systematic review of the literature on the relationship between volume and outcome of esophagectomies for cancer (adjusted from Gruen et al.6).

Study	Country	Data	Patients	Hospitals	Surgeons	Casemix adjustment	Hospital volume
							Volume categories
Leigh 2009 [27]	UK	Adm	9034	n.r.	n.r.	D	<20>
Meguid 2009 [28]	US	Adm	4080	1506	n.a.	D, C, V	<15>
Rutegard 2009 [29]	Swe	Clin	615	n.a.	n.a.	D, C, S, T	-
Gasper 2009 [30]	US	Adm	1210	183	n.a.	D, C	<1-2-4-6>
Yasunaga 2009 [31]	Jap	Adm	642	n.a.	183	n.r.	-
Sundelöf 2008 [32]	Swe	Clin	232	33	n.r.	D, C, S, T	<10>
Reavis 2008 [33]	US	Adm	5236	107	n.a.	n.r.	<6-13>
Wouters 2008 [34]	Neth	Clin	903	12	n.a.	D, C, U, S, T, M	<7>
Ra 2008 [35]	US	Adm	1172	361	n.a.	D, C, S	<.68-2.33>
Rutegard 2008 [18]	Swe	Clin	355	n.a.	n.a.	D, C, S, T	<10>
Hollenbeck 2007 [36]	USA	Adm	421	151	n.a.	D, C, U, S	n.r.
Thompson 2007 [37]	UK	Clin	1079	53	n.a.	D, C, U, S	<13-20-35>
Jensen 2007 [38]	Den	Adm	1152	26	n.a.	none	<5-21>
Allareddy 2007 [20]	US	Adm	2437	717	n.a.	D, C, U, V	<13>
Rodgers 2007 [21]	US	Adm	8075	995	1651	D, C, V	<5-10>
Rouvelas 2007 [39]	Swe	Clin	1199	53	n.a.	D, C, S, T	<10>
Birkmeyer 2007 [19]	US	Adm	822	206	n.a.	D, C, U, S, T, M	<4-14>
Rouvelas 2007 [39]	Swe	Clin	328	n.a.	n.r.	D, C, S, T	-
Simunovic 2006 [40]	Can	Clin	629	n.r.	n.a.	D, C	<8-20-44>
Lin 2006 [41]	Tai	Adm	6674	111	n.a.	D, C	<20-34-59-87>
Urbach 2005 [42]	Can	Adm	613	58	93	D, C	<2.2-7.1-12.1>
Wenner 2005 [43]	Swe	Clin	1429	74	n.a.	D	<5-16>
Birkmeyer 2004 [44]	US	Adm	4350	n.r.	n.a.	none	<13>
Ward 2004 [45]	US	Adm	44	14	n.a.	D, C	<13>
Goodney 2003 [46]	US	Adm	n.r.	n.r.	n.a.	D, C, U	<2-5-8-20>
Elixhauser 2003 [47]	US	Adm	1623	710	n.a.	none	<7>
Dimick 2003 [48]	US	Adm	3023	192	n.a.	D, C, U, T	<3-6-17>
McCulloch 2003 [49]	UK	Clin	955	32	n.a.	D, C, S, T	<11-21>
Dimick 2003 [50]	US	Adm	1226	n.r.	n.a.	D, C, U	<median>
Birkmeyer 2003 [3]	US	Adm	n.r.	n.a.	n.r.	D, C, U	-
Dimick 2003 [51]	US	Adm	366	52	n.a.	D, C, U, T	<8.5>
Urbach 2003 [52]	Can	Adm	613	47	n.a.	D, C	quartiles
Finlayson 2003 [53]	US	Adm	5282	603	n.a.	D, C, U	<4-10>
Gillison 2002 [54]	UK	Clin	1125	n.a.	64	D, U, S	-
Bachmann 2002 [55]	UK	Clin	322	n.a.	23	D, C, U, S	-
Birkmeyer 2002 [2]	US	Adm	6337	1575	n.a.	D, C, U	<2-5-8-20>
Kuo 2001 [56]	US	Adm	1193	64	n.a.	D, C, U	<6>
Dimick 2001 [57]	US	Adm	1136	62	n.a.	D, C, U	<4-16>
vLanschot 2001 [58]	Neth	Adm	1792	100	n.a.	D, S	<11-20>
Swisher 2000 [59]	US	Adm	340	25	n.a.	D,C, U	<5>
Begg 1998 [60]	US	Adm	503	190	n.a.	D, C, S	<6-11>
Patti 1998 [61]	US	Adm	1561	273	n.a.	D, C	<1-2-4-6>
Miller 1997 [62]	Can	Clin	74	n.a.	20	none	-

QoL = Quality of life; Adm = based on administrative data ; Clin = based on clinical data; n.r. = not reported; n.a. =not applicable; D = adjusted for demographic data (e.g. patient age, gender, race, income); C = adjusted for comorbidities (including ASA-classification); U = adjusted for urgency of the operation; S = adjusted for tumor characteristics (e.g. stage, grade, location); T = adjusted for treatment differences (e.g. surgical approach;

				Surgeon volume				
Morbidity	Mortality	Survival	QoL	Volume categories	Morbidity	Mortality	Survival	QoL
-	S	-	-	-	-	-	-	-
-	S	-	-	-	-	-	-	-
-	-	-	-	<2-7>	NS	-	-	-
-	S	-	-	-	-	-	-	-
-	-	-	-	<50-100>	S	-	-	-
NS	NS	S	-	<10>	NS	NS	S	-
S	S	-	-	-	-	-	-	-
-	S	S	-	-	-	-	-	-
-	S	-	-	-	-	-	-	-
-	-	-	NS	<7>	-	-	-	NS
-	NS	-	-	-	-	-	-	-
-	-	NS	-	-	-	-	-	-
-	NS	-	-	-	-	-	-	-
-	S	-	-	-	-	-	-	-
-	NS	-	-	<2-7>	-	S	-	-
-	NS	NS	-	-	-	-	-	-
-	-	S	-	-	-	-	-	-
-	-	-	-	<2-7>	-	NS	-	-
-	NS	NS	-	-	-	NS	NS	-
-	S	-	-	-	-	-	-	-
-	NS	-	-	<2.4-4.6-6.9>	-	NS	-	-
-	S	S	-	-	-	-	-	-
-	S	-	-	-	-	-	-	-
-	NS	-	-	-	-	-	-	-
NS	-	-	-	-	-	-	-	-
-	S	-	-	-	-	-	-	-
-	S	-	-	-	-	-	-	-
NS	S	-	-		-	-	-	-
S	S	-	-		-	-	-	-
-	-	-	-	<2-6>	-	S	-	-
S	S	-	-		-	-	-	-
-	S	-	-		-	-	-	-
-	S	-	-		-	-	-	-
-	-	-	-	<4-12>	-	S	NS	-
-	-	-	-	continuous	-	S	S	-
-	S	-	-	-	-	-	-	-
-	S	-	-	-	-	-	-	-
S	S	-	-	-	-	-	-	-
-	S	-	-	-	-	-	-	-
NS	S	-	-	-	-	-	-	-
-	S	-	-	-	-	-	-	-
NS	S	-	-	S				
-	-	-	-	<6>	NS	S	-	-

(neo)adjuvant treatments); M = survival analysis adjusted for postoperative mortality; V = adjusted for other hospital characteristics (e.g., teaching or academic status); <10-20> = low-volume group less than 10, medium-volume group 10-19 and high-volume 20 or more esophageal resections a year; S = statistically significant; NS = statistically not significant.

Hospital mortality

Study name	Year	Low	High	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Allareddy	2007	12	13	1.980	1.279	3.066	3.061	0.002
Birkmeyer	2002	2	20	2.778	2.003	3.852	6.124	0.000
Dimick, Cataneo	2001	4	16	4.762	2.324	9.759	4.263	0.000
Dimick, Cowan	2003		16	2.900	1.708	4.923	3.943	0.000
Dimick, Pronovost	2003	2	7	5.700	2.015	16.122	3.281	0.001
Finlayson	2003	4	10	2.632	1.637	4.230	3.996	0.000
Gasper	2009	1	6	1.650	1.011	2.693	2.004	0.045
Kuo	2001	5	6	4.300	2.350	7.868	4.732	0.000
Leigh	2009		20	1.620	1.377	1.906	5.818	0.000
Lin	2006	20	87	1.538	1.024	2.311	2.076	0.038
McCulloch	2003		20	2.041	1.015	4.103	2.002	0.045
Ra	2008	1	2	1.810	1.179	2.778	2.714	0.007
Simunovic	2006		44	0.900	0.312	2.598	-0.195	0.846
Swisher	2000	4	5	3.970	1.141	13.813	2.167	0.030
Urbach	2003	3	19	1.900	0.988	3.655	1.923	0.054
Wouters	2008	6	7	3.050	1.820	5.111	4.234	0.000
				2.300	1.890	2.799	8.308	0.000

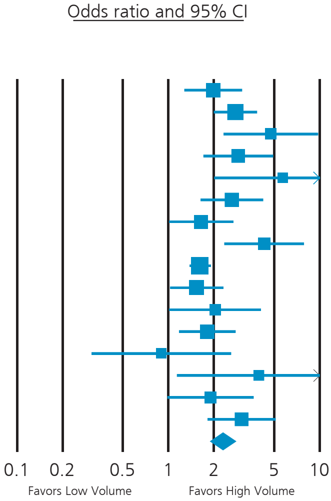

Figure 2a. Forest plot of the included studies in the meta-analysis on hospital volume and postoperative mortality for esophageal resections for cancer. Year = year of publication; Low = highest annual volume of low volume category; High = lowest annual volume of high volume category; CI = confidence interval

Hospital Survival

Study name	Year	Low	High	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Rouvelas	2007	1	7	1.110	0.968	1.273	1.490	0.136
Sundelöf	2008	9	10	1.300	0.943	1.792	1.602	0.109
Simunovic	2006	7	44	1.200	0.849	1.697	1.031	0.303
Birkmeyer	2007	3	14	1.320	1.000	1.742	1.962	0.050
				1.170	1.049	1.305	2.824	0.005

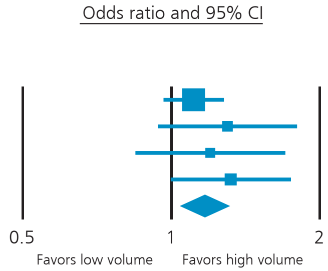

Figure 2b. Forest plot of the included studies in the meta-analysis on hospital volume and survival of esophageal resections for cancer. Year = year of publication; Low = highest annual volume of low volume category; High = lowest annual volume of high volume category; CI = confidence interval

In table 3 the results of the sensitivity analysis of the 16 included studies are depicted. A larger effect size was noted in studies from the United States (OR 2.56; P<0.001), in studies based on clinical data (OR 2.29; P<0.001), in studies with data that were adjusted for urgency of the operation (OR 2.84; P<0.001) and in studies with data that were adjusted for tumor characteristics (OR 2.20; P<0.001).

Figure 4 shows the qualitative analysis of publication bias of all studies regarding hospital volume and postoperative mortality using OR’s. The results were suggestive for publication

Table 3. Sensitivity analysis of the 16 included studies on hospital volume and postoperative mortality with Odds ratios as effect size.

Factor	Subgroup	N	OR	CI	P-value
Country	US	10	2.56	2.17-3.00	<0.001
	other countries	6	1.70	1.48-1.94	<0.001
Datasource	Administrative	13	1.99	1.79-2.22	<0.001
	Clinical	3	2.29	1.56-3.37	<0.001
Urgency	Not adjusted	7	1.69	1.49-1.92	<0.001
	Adjusted	9	2.84	2.37-3.40	<0.001
Tumor stage	Not adjusted	13	1.99	1.78-2.22	<0.001
	Adjusted	3	2.20	1.63-2.97	<0.001

N = number of studies; OR = Odds ratio; CI = confidence interval; I2 = result of I square test on heterogeneity of study results8. US = United States

bias, which indicates that smaller negative studies are missing, which to some degree could have influenced the results of this meta-analysis.

Meta-analysis: hospital volume & survival

Of the seven studies evaluating the relationship between *hospital volume* and *survival,* four met the criteria for the meta-analysis. All four studies were observational, though three studies used clinical instead of administrative data. Adjustments for age, gender and co morbidities were made in all four studies; three of them adjusted for tumor characteristics (e.g. stage and grade) and two studies corrected also for (neo)adjuvant treatments in their survival analysis. Figure 2b shows the forest plot of the included studies on hospital volume and survival. Again, the meta-analysis showed a significant pooled estimated effect size in favor of high-volume hospitals (HR 1.17; CI 1.05-1.31). This result was very homogeneous (I^2=0.0).

Surgeon volume

In 12 studies, the relationship between surgeon volume and outcome was investigated. Nine of these studies used postoperative mortality as an outcome parameter and 5 of them showed a significant result favoring high volume. In 4 studies, postoperative morbidity was an outcome parameter; only one study was positive. The relationship between surgeon volume and survival was investigated in 4 studies; in two of them, a significant relationship was found. Quality of life was evaluated in one study; again the result was negative.

Meta-analysis: surgeon volume & postoperative mortality

Of the nine studies evaluating *surgeon volume* and *postoperative mortality,* only three met the inclusion criteria for the meta-analysis. In all three studies age, gender and co morbidities were included in the multivariate analysis. Figure 3a shows the forest plot of the included studies regarding the effect of surgeon volume on postoperative mortality. In the meta-analysis a pooled estimated effect size was detected in favor of high-volume

Surgeon Mortality

Study name	Year	Low	High	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bachmann	2002	.	.	7.690	1.104	53.579	2.060	0.039
Birkmeyer	2003	1	6	1.800	1.129	2.869	2.472	0.013
Rodgers	2007	1	7	1.110	1.062	1.160	4.598	0.000
				1.551	0.876	2.745	1.506	0.132

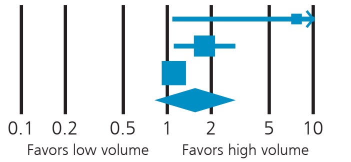

Figure 3a. Forest plot of the included studies in the meta-analysis on surgeon volume and postoperative mortality of esophageal resections for cancer. Year = year of publication; Low = highest annual volume of low volume category; High = lowest annual volume of high volume category; CI = confidence interval

Surgeon Survival

Study name	Year	Low	High	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bachmann	2002	.	.	1.090	1.008	1.178	2.168	0.030
Sundelöf	2008	9	10	1.400	0.990	1.980	1.903	0.057
				1.164	0.938	1.445	1.379	0.168

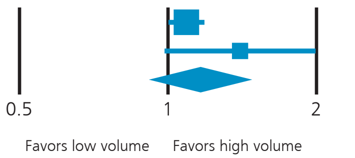

Figure 3b. Forest plot of the included studies in the meta-analysis on surgeon volume and survival of esophageal resections for cancer. Year = year of publication; Low = highest annual volume of low volume category; High = lowest annual volume of high volume category; CI = confidence interval

surgeons, but this effect did not reach statistical significance (OR 1.55; 0.88-2.75) and was very heterogeneous (I^2=75).

Meta-analysis: surgeon volume & survival

Two out of four studies evaluating *surgeon volume* and *survival* were included in the meta-analysis and both adjusted for tumor characteristics in their survival analyses. Figure 3b shows the forest plot of the two included studies regarding the effect of surgeon volume on survival. In the meta-analysis there was a pooled estimated effect size in favor of high-volume surgeons (HR 1.16; 0.94-1.45), which was not significant. The result was moderately heterogeneous (I^2=48).

DISCUSSION

The present study contains the first meta-analysis on the relationship between procedural volume and outcome of esophageal resections for cancer, with strict criteria for

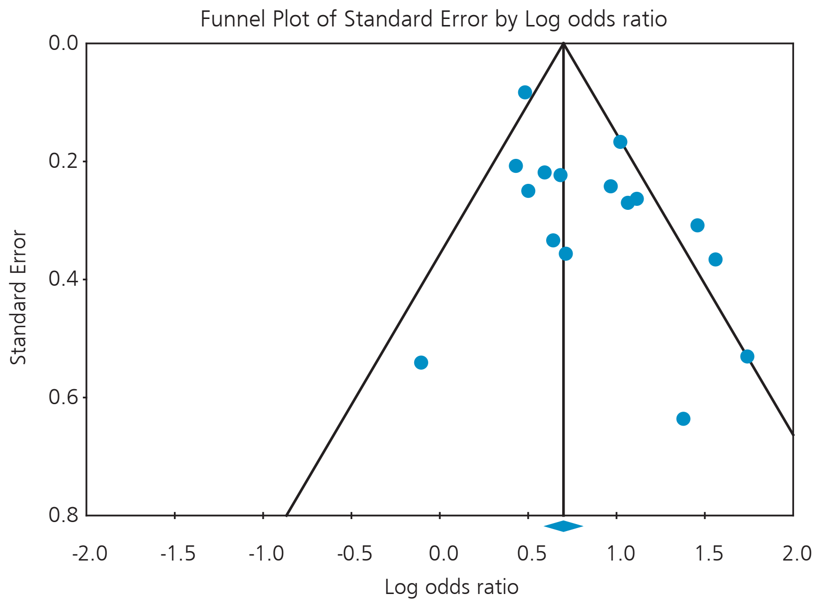

Figure 4. Analysis of risk of publication bias: funnel plot of studies included in the meta-analysis on hospital volume and postoperative mortality using odds ratio's. The funnel plot is asymmetric, missing smaller negative studies, suggesting publication bias. Quantitative analysis with the Egger's regression intercept showed an intercept of 1.7 with a two-sided P value of 0.03, confirming the suggestion of publication bias.

methodological quality. Our systematic review shows that there is an increasing number of studies on this subject originating from different parts of the world and evaluating hospitals' as well as surgeons' procedural volume. Not only short-term outcomes like postoperative morbidity and mortality have been evaluated, but also long-term outcomes like survival and quality of life. Only a minority of these studies met the methodological inclusion criteria for our meta-analysis. We found that hospital volume has a strong inverse relationship with postoperative mortality and that patients operated in high-volume centers have a better survival. This relationship is much stronger than that between surgeon volume and outcome of esophageal cancer resections.

There is solid criticism on the level of evidence for a volume-outcome relationship regarding low-volume, high-risk surgical procedures, like esophagectomies for cancer[10]. Our review confirms that most studies are observational, retrospective and based on administrative data collected for other purposes, instead of carefully designed comparative studies (Table 2). Moreover, studies originate from different health care systems all over the world introducing a large variety in demographical, geographical and epidemiological factors as well as standards of care. For example, our analyses showed larger differences in postoperative mortality between high- and low-volume hospitals identified in the United States than in other countries. In the evaluation of the methodological quality of the available studies substantial heterogeneity was identified. Especially, the choice of volume categories was extremely diverse among all studies. The rationale for specific volume cut-offs was seldom explained in the methodological paragraphs suggesting a potential selection bias. In addition, the risk of publication bias was calculated for the studies on hospital volume and postoperative mortality, missing the smaller negative studies, which obviously had little chance for publication in peer-reviewed medical journals.

Only high-quality comparative studies were included in our meta-analyses. All but one study included at least age, gender and co morbidity in the multivariate analysis on the relationship between hospital volume and postoperative mortality. Several studies used additional parameters as potential confounders (e.g., neo-adjuvant treatments, urgency of the operation, tumor characteristics). This led to higher effect sizes and less heterogeneity in results between properly adjusted studies, as was shown in our sensitivity analyses (Table 3). Because of these robust effect sizes, the risk of publication bias detected in our analyses (Figure 4), is expected to have influenced the results of this meta-analysis insignificantly.
Adjustments for tumor characteristics not only gave higher effect sizes in studies on hospital volume and postoperative mortality. Also, in three out of four studies on hospital volume and survival in which results were adjusted for tumor stage, a significantly better outcome was found in high-volume hospitals (Table 2).

In the meta-analysis on surgeon volume and outcome, the correlations between volume and postoperative mortality and volume and survival were not significant. This suggests that outcome of esophageal cancer surgery is not only dependent on the experience and skills of individual surgeons. The hospital setting in which they perform their operations seems more important. The above results indicate that - for high-quality of care - experience with esophageal cancer surgery is important on a hospital's level rather than on an individual surgeon's level.

Apart from the methodological shortcomings mentioned above, volume-outcome studies have other important limitations. First, surgery is not the only treatment used in esophageal cancer patients. Differences in treatment patterns, like the use of (neo)adjuvant chemo- and/or radiotherapy may also influence long-term survival. In our meta-analysis on the relationship between hospital volume and survival, data in three out of four studies have been adjusted for differences in the use of (neo)adjuvant therapies. Especially in the study of Birkmeyer, based on the SEER-Medicare database, it is shown that the percentage of patients that receives chemo- and / or radiotherapy besides surgical treatment is not different between low-, medium- and high-volume hospitals[19].
In addition, in only few studies, data have been corrected for (other) provider characteristics[20,21], such as the available infrastructure, teaching or academic status, inner city or private hospital status, experience with other high-risk operations, expertise in multimodality cancer treatments, a hospital's budget, focus and/or referral bias. These factors are often related to, but not identical with procedural volume. In a recent study, Courrech-Staal et al. have reported the results of esophageal cancer surgery in a tertiary

referral center, with a mean annual hospital volume of more than 100 esophageal cancer patients a year[22]. Due to selective referral of patients with higher tumor stages only 20% of them had potentially curable disease, an unfavorable tumor mix when compared to the 50% reported in most series. Nevertheless, the authors have shown excellent results of esophageal cancer surgery despite a low procedural volume (<10 resections/year). The use of procedural volume as the sole measure of quality of care might fall short in identifying high-leverage processes of care in individual institutions. In our opinion policy makers should bare this in mind when efforts are made to centralize complex high-risk surgical procedures.

In the Netherlands, the Quality of Cancer Care taskforce of the Dutch Cancer Society has recently proposed to concentrate specific cancer treatments in those hospitals that meet a set of criteria. These criteria do not only focus on procedural volume, but also on the available infrastructure, specialization of medical professionals and outcome measures, that should be reported by individual institutions[23]. From a patients' perspective outcome information might be more interesting and informative than volume alone. However, also from a professional perspective too much focus on proxy variables like 'volume' is not preferable. Volume standards do have little ability to move the medical field forward[24]. Identifying 'best practices' in patient selection, treatment strategies, technical procedures and peri-operative care is much more important and the central issue in outcomes research and surgical audits[25,26]. Careful analysis of data retrieved from different hospitals, that vary in patterns of care and outcomes, might identify ways to improve the whole field of esophageal cancer treatment.

In conclusion, this meta-analysis has shown that procedural volume is associated with less postoperative mortality and better survival in esophageal cancer surgery. A hospital's annual volume seems more important than the experience of individual surgeons. Although there is no evidence for a specific volume cut-off in the literature, centralization of esophageal cancer surgery in dedicated high-volume centers could lead to better outcome in this patient group.

REFERENCES

1. Killeen SD, O'Sullivan MJ, Coffey JC et al. Provider volume and outcomes for oncological procedures. Br J Surg 2005; 92:389-402.
2. Birkmeyer JD, Siewers AE, Finlayson EV et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002; 346:1128-1137.
3. Birkmeyer JD, Stukel TA, Siewers AE et al. Surgeon volume and operative mortality in the United States. N Engl J Med 2003; 349:2117-2127.
4. van Heek NT, Kuhlmann KF, Scholten RJ et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. Ann Surg 2005; 242:781-8, discussion.
5. Smolders KHA. Minstens tien keer per jaar. Medisch Contact 2007; 23.
6. Gruen RL, Pitt V, Green S et al. The effect of provider case volume on cancer mortality: systematic review and meta-analysis. CA Cancer J Clin 2009; 59:192-211.
7. Lauder CI, Marlow NE, Maddern GJ et al. Systematic review of the impact of volume of esophagectomy on patient outcome. ANZ J Surg 2010; 80:317-323.
8. Higgins JP, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557-560.
9. Egger M, Davey SG, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629-634.
10. Amaravadi RK, Dimick JB, Pronovost PJ et al. ICU nurse-to-patient ratio is associated with complications and resource use after esophagectomy. Intensive Care Med 2000; 26:1857-1862.
11. Dimick JB, Goodney PP, Orringer MB et al. Specialty training and mortality after esophageal cancer resection. Ann Thorac Surg 2005; 80:282-286.
12. Verhoef C, van de Weyer R, Schaapveld M et al. Better survival in patients with esophageal cancer after surgical treatment in university hospitals: a plea for performance by surgical oncologists. Ann Surg Oncol 2007; 14:1678-1687.
13. Al-Sarira AA, David G, Willmott S et al. Esophagectomy practice and outcomes in England. Br J Surg 2007; 94:585-591.
14. Birkmeyer JD, Siewers AE, Marth NJ et al. Regionalization of high-risk surgery and implications for patient travel times. JAMA 2003; 290:2703-2708.
15. Dimick JB, Wainess RM, Upchurch GR, Jr. et al. National trends in outcomes for esophageal resection. Ann Thorac Surg 2005; 79:212-216.
16. Kohn GP, Galanko JA, Meyers MO et al. National trends in esophageal surgery--are outcomes as good as we believe? J Gastrointest Surg 2009; 13:1900-1910.
17. Steyerberg EW, Neville BA, Koppert LB et al. Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. J Clin Oncol 2006; 24:4277-4284.
18. Rutegard M, Lagergren P. No influence of surgical volume on patients' health-related quality of life after esophageal cancer resection. Ann Surg Oncol 2008; 15:2380-2387.
19. Birkmeyer JD, Sun Y, Wong SL et al. Hospital volume and late survival after cancer surgery. Ann Surg 2007; 245:777-783.
20. Allareddy V, Allareddy V, Konety BR. Specificity of procedure volume and in-hospital mortality association. Ann Surg 2007; 246:135-139.
21. Rodgers M, Jobe BA, O'Rourke RW et al. Case volume as a predictor of inpatient mortality after esophagectomy. Arch Surg 2007; 142:829-839.
22. Courrech Staal EF, van Coevorden F, Cats A et al. Outcome of low-volume surgery for esophageal cancer in a high-volume referral center. Ann Surg Oncol 2009; 16:3219-3226.
23. Wouters MW, Jansen-Landheer ML, van de Velde CJ. The Quality of Cancer Care initiative in the Netherlands. Eur J Surg Oncol 2010; 36 Suppl 1:S3-S13.
24. Birkmeyer JD, Dimick JB, Birkmeyer NJ. Measuring the quality of surgical care: structure, process, or outcomes? J Am Coll Surg 2004; 198:626-632.
25. van Gijn W, van de Velde CJ. Improving quality of cancer care through surgical audit. Eur J Surg Oncol 2010; 36 Suppl 1:S23-S26.
26. Wouters M. Outcome-based referral to improve quality of care in upper GI surgery. J Surg Oncol 2008; 98:307-308.
27. Leigh Y, Goldacre M, McCulloch P. Surgical specialty, surgical unit volume and mortality after esophageal cancer surgery. Eur J Surg Oncol 2009; 35:820-825.
28. Meguid RA, Weiss ES, Chang DC et al. The effect of volume on esophageal cancer resections: what constitutes acceptable resection volumes for centers of excellence? J Thorac Cardiovasc Surg 2009; 137:23-29.
29. Rutegard M, Lagergren J, Rouvelas I et al. Surgeon volume is a poor proxy for skill in esophageal cancer surgery. Ann Surg 2009; 249:256-261.
30. Gasper WJ, Glidden DV, Jin C et al. Has recognition of the relationship between mortality rates and hospital volume for major cancer surgery in California made a difference?: A follow-up analysis of another decade. Ann Surg 2009; 250:472-483.
31. Yasunaga H, Matsuyama Y, Ohe K. Effects of hospital and surgeon case-volumes on postoperative complications and length of stay after esophagectomy in Japan. Surg Today 2009; 39:566-571.
32. Sundelof M, Lagergren J, Ye W. Surgical factors influencing outcomes in patients resected for cancer of the esophagus or gastric cardia. World J Surg 2008; 32:2357-2365.

33. Reavis KM, Smith BR, Hinojosa MW et al. Outcomes of esophagectomy at academic centers: an association between volume and outcome. Am Surg 2008; 74:939-943.
34. Wouters MW, Wijnhoven BP, Karim-Kos HE, et al. High-volume versus low-volume for esophageal resections for cancer: the essential role of case- mix adjustments based on clinical data. Ann Surg Oncol. 2008;15:80-87.
35. Ra J, Paulson EC, Kucharczuk J et al. Postoperative mortality after esophagectomy for cancer: development of a preoperative risk prediction model. Ann Surg Oncol 2008; 15:1577-1584.
36. Hollenbeck BK, Hong J, Zaojun Y et al. Misclassification of hospital volume with Surveillance, Epidemiology, and End Results Medicare data. Surg Innov 2007; 14:192-198.
37. Thompson AM, Rapson T, Gilbert FJ et al. Hospital volume does not influence long-term survival of patients undergoing surgery for esophageal or gastric cancer. Br J Surg 2007; 94:578-584.
38. Jensen LS, Bendixen A, Kehlet H. Organisation and early outcomes of major upper gastrointestinal cancer surgery in Denmark 1996-2004. Scand J Surg 2007; 96:41-45.
39. Rouvelas I, Lindblad M, Zeng W et al. Impact of hospital volume on long-term survival after esophageal cancer surgery. Arch Surg 2007; 142:113-117.
40. Simunovic M, Rempel E, Theriault ME et al. Influence of hospital characteristics on operative death and survival of patients after major cancer surgery in Ontario. Can J Surg 2006; 49:251-258.
41. Lin HC, Xirasagar S, Lee HC et al. Hospital volume and inpatient mortality after cancer-related gastrointestinal resections: the experience of an Asian country. Ann Surg Oncol 2006; 13:1182-1188.
42. Urbach DR, Austin PC. Conventional models overestimate the statistical significance of volume-outcome associations, compared with multilevel models. J Clin Epidemiol 2005; 58:391-400.
43. Wenner J, Zilling T, Bladstrom A et al. The influence of surgical volume on hospital mortality and 5-year survival for carcinoma of the esophagus and gastric cardia. Anticancer Research 2005; 25:419-424.
44. Birkmeyer JD, Dimick JB. Potential benefits of the new Leapfrog standards: effect of process and outcomes measures. Surgery 2004; 135:569-575.
45. Ward MM, Jaana M, Wakefield DS et al. What would be the effect of referral to high-volume hospitals in a largely rural state? J Rural Health 2004; 20:344-354.
46. Goodney PP, Stukel TA, Lucas FL et al. Hospital volume, length of stay, and readmission rates in high-risk surgery. Ann Surg 2003; 238:161-167.
47. Elixhauser A, Steiner C, Fraser I. Volume thresholds and hospital characteristics in the United States. Health Aff (Millwood) 2003; 22:167-177.
48. Dimick JB, Cowan JA, Jr., Ailawadi G et al. National variation in operative mortality rates for esophageal resection and the need for quality improvement. Arch Surg 2003; 138:1305-1309.
49. McCulloch P, Ward J, Tekkis PP. Mortality and morbidity in gastro-esophageal cancer surgery: initial results of ASCOT multicentre prospective cohort study. BMJ 2003; 327:1192-1197.
50. Dimick JB, Pronovost PJ, Cowan JA, Jr. et al. Variation in postoperative complication rates after high-risk surgery in the United States. Surgery 2003; 134:534-540.
51. Dimick JB, Pronovost PJ, Cowan JA et al. Surgical volume and quality of care for esophageal resection: do high-volume hospitals have fewer complications? Ann Thorac Surg 2003; 75:337-341.
52. Urbach DR, Bell CM, Austin PC. Differences in operative mortality between high- and low-volume hospitals in Ontario for 5 major surgical procedures: estimating the number of lives potentially saved through regionalization. CMAJ 2003; 168:1409-1414.
53. Finlayson EV, Goodney PP, Birkmeyer JD. Hospital volume and operative mortality in cancer surgery: a national study. Arch Surg 2003; 138:721-725.
54. Gillison EW, Powell J, McConkey CC et al. Surgical workload and outcome after resection for carcinoma of the esophagus and cardia. Br J Surg 2002; 89:344-348.
55. Bachmann MO, Alderson D, Edwards D et al. Cohort study in South and West England of the influence of specialization on the management and outcome of patients with esophageal and gastric cancers. Br J Surg 2002; 89:914-922.
56. Kuo EY, Chang Y, Wright CD. Impact of hospital volume on clinical and economic outcomes for esophagectomy. Ann Thorac Surg 2001; 72:1118-1124.
57. Dimick JB, Cattaneo SM, Lipsett PA et al. Hospital volume is related to clinical and economic outcomes of esophageal resection in Maryland. Ann Thorac Surg 2001; 72:334-339.
58. van Lanschot JJ, Hulscher JB, Buskens CJ et al. Hospital volume and hospital mortality for esophagectomy. Cancer 2001; 91:1574-1578.
59. Swisher SG, Deford L, Merriman KW et al. Effect of operative volume on morbidity, mortality, and hospital use after esophagectomy for cancer. J Thorac Cardiovasc Surg 2000; 119:1126-1132.
60. Begg CB, Cramer LD, Hoskins WJ et al. Impact of hospital volume on operative mortality for major cancer surgery. JAMA 1998; 280:1747-1751.
61. Patti MG, Corvera CU, Glasgow RE et al. A hospital's annual rate of esophagectomy influences the operative mortality rate. J Gastrointest Surg 1998; 2:186-192.
62. Miller JD, Jain MK, de Gara CJ et al. Effect of surgical experience on results of esophagectomy for esophageal carcinoma. J Surg Oncol 1997; 65:20-21.