

## High-Volume versus Low-Volume for Esophageal Resections for Cancer: The Essential Role of Case-Mix Adjustments based on Clinical Data

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**Background:** Most studies addressing the volume–outcome relationship in complex surgical procedures use hospital mortality as the sole outcome measure and are rarely based on detailed clinical data. The lack of reliable information about comorbidities and tumor stages makes the conclusions of these studies debatable.

The purpose of this study was to compare outcomes for esophageal resections for cancer in low- versus high-volume hospitals, using an extensive set of variables concerning case-mix and outcome measures, including long-term survival.

**Methods:** Clinical data, from 903 esophageal resections performed between January 1990 and December 1999, were retrieved from the original patients' files. Three hundred and forty-two patients were operated on in 11 low-volume hospitals (<7 resections/year) and 561 in a single high-volume center.

**Results:** Mortality and morbidity rates were significantly lower in the high-volume center, which had an in-hospital mortality of 5 vs 13% ( $P < .001$ ). On multivariate analysis, hospital volume, but also the presence of comorbidity proved to be strong prognostic factors predicting in-hospital mortality (ORs 3.05 and 2.34). For stage I and II disease, there was a significantly better 5-year survival in the high-volume center. ( $P = .04$ ).

**Conclusions:** Hospital volume and comorbidity patterns are important determinants of outcome in esophageal cancer surgery. Strong clinical endpoints such as in-hospital mortality and survival can be used as performance indicators, only if they are joined by reliable case-mix information.

**Key Words:** Esophageal cancer—Esophagectomy—Surgical outcomes—High-volume hospitals—Case-mix—Comorbidity.

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Since Luft published his study about the inverse relationship between surgical volume and hospital

mortality in 1979, a plethora of studies has demonstrated an improvement of clinical outcome with increased hospital volume.<sup>1</sup> Most of these studies use hospital mortality as the sole outcome measure. Often, data are obtained from insurance company's databases, and few studies use clinical data for risk-adjustment.<sup>2</sup>

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The surgical treatment of esophageal cancer is often mentioned as one of the procedures for which concentration in high-volume centers might improve outcome.<sup>3,4</sup> Nevertheless, a clear volume cut-off point at which a cancer center is justified to perform esophageal resections can hardly be defined.<sup>5,6</sup> Also, the volume–outcome literature for esophageal resections is limited to postoperative mortality as the sole determinant of outcome.

Considering the growing evidence for this volume–outcome relationship for esophageal cancer surgery, we decided to investigate the outcome of these procedures in our region from 1990 until 1999. During this study period none of the 11 hospitals affiliated with the Comprehensive Cancer Center Leiden (CCCL) in the Netherlands performed more than seven esophageal resections a year; all are considered low-volume hospitals (LVH).

In contrast to most volume–outcome studies, we decided to use clinical data obtained from the original patients' files. We retrieved information about comorbid diseases, tumor characteristics, treatment, and outcome. Next to hospital mortality, several determinants of outcome were examined, such as the number of tumor-free margins and complication rates. Assuming that survival is an essential indicator for quality in cancer surgery, we included a 5-year follow-up. To put our data in the right perspective, we compared these outcomes to the results of the topographically nearest high-volume referral center (HVH).

## PATIENTS AND METHODS

All surgically treated esophageal carcinomas in the period 1990–1999 were retrospectively identified through the Leiden Cancer Registry (LCR) of the Comprehensive Cancer Center Leiden (CCCL), in which all cancer patients treated in the midwestern part of the Netherlands are registered (1.7 million inhabitants). All 11 hospitals gave consent to participate in this audit and were visited by two investigators to retrieve the original patient files. Patient demographics, pathological notes, data on the surgical and (neo)adjuvant treatments, comorbidity as well as postoperative morbidity, mortality, length of stay, radicality of the resection, and long-term survival could all be retrieved from the patient's files.

All tumors were staged according to the UICC TNM classification of 1997. This was done by two independent researchers. The obtained pTNM stages were checked with the pTNM stages registered in the LCR. Any discrepancies were discussed between the

researchers and a trained data manager from the CCCL. If consensus could not be reached, the pTNM stage was registered as “unknown.”

To make a comparison with the outcomes of the nearest high-volume center, data were categorized according to the database of this center. In this hospital, data of patients operated on for an esophageal carcinoma are prospectively collected by a trained data manager.

Differences in patient, tumor, and treatment characteristics as well as outcome measurements were assessed using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. Logistic regression was used to determine prognostic factors of in-hospital mortality. Variables were entered in the multivariate model as a prognostic factor when  $P$  values  $< .10$ .

Survival was calculated as the difference between date of surgery and either the date of death or the date of last patient follow-up. For both groups, follow-up of the patients was completed until December 31, 2005. Observed survival rates were estimated by using the Kaplan–Meier method. The log-rank test was used to assess differences in survival between patients who were operated in LVHs and the HVH. All analyses were conducted using SPSS software (version 12.0; SPSS Inc., Chicago, IL).

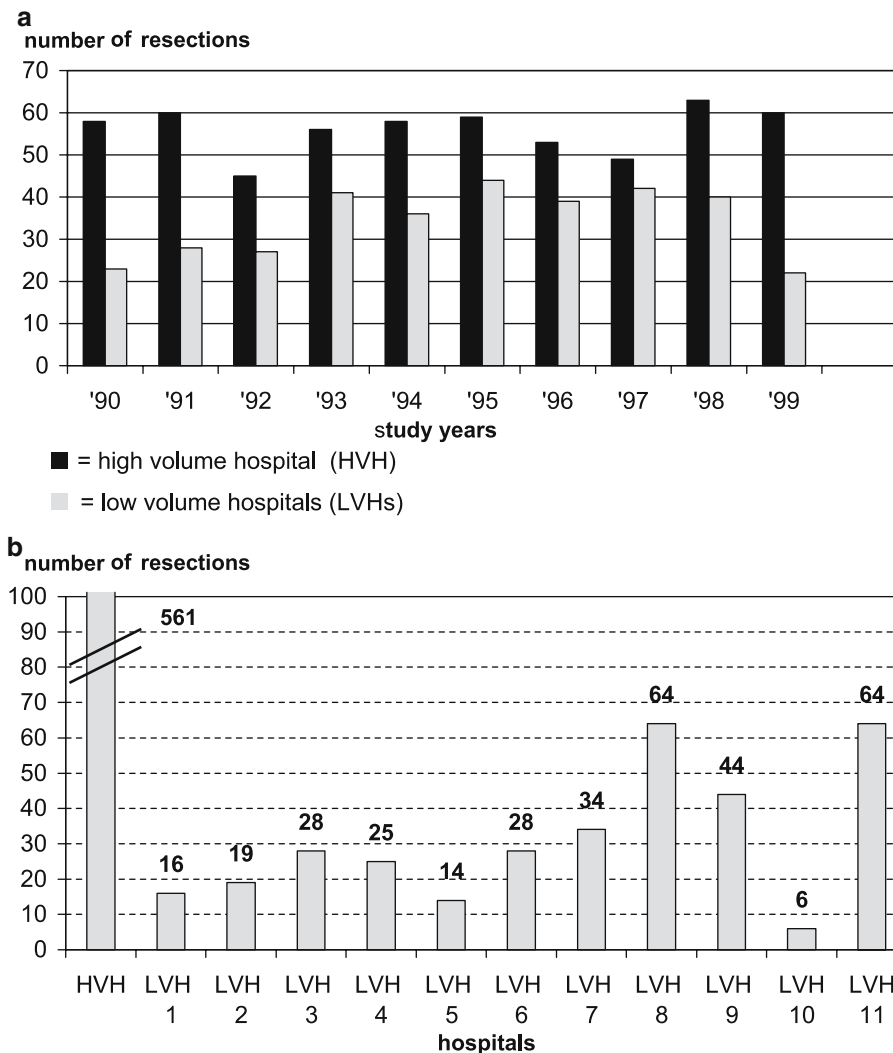
## RESULTS

### Hospital Volume

In 1990–1999 the evaluation and treatment of patients with an esophageal carcinoma were performed in 11 hospitals in the region of the CCCL (one university hospital, five teaching hospitals, and five general hospitals). In 342 patients the tumor was resected with curative intent. Figures 1A and B illustrate the distribution of surgical procedures within the studied time period and between the different hospitals. None of the CCCL hospitals performed more than seven esophageal resections a year, which makes them low-volume hospitals (LVHs).<sup>7</sup> In the same period, 561 esophageal resections were performed in the nearest high-volume referral center (HVH); a mean volume of 56 resections a year.

### Patient, Tumor, and Treatment Characteristics

Table 1 shows the patient, tumor, and treatment characteristics of both groups. More patients from the HVH had a squamous cell carcinoma and an advanced stage of the disease. Operative strategy as well as



**FIG. 1.** (A) Number of esophageal resections per year in HVH versus LVH group (1990–1999). (B) Total number of esophageal resections per hospital for HVH and LVHs (1990–1999).

adjuvant or neoadjuvant treatment varied widely between the groups. The vast majority of resections in the HVH was performed according to the transhiatal technique, with a gastric tube reconstruction and anastomosis to the cervical remnant esophagus. In the LVH group a substantial number of anastomoses were located in the thoracic cavity, after a (partial) gastroesophagectomy with either a gastric tube reconstruction or esophagojejunostomy. In the pathology, clear surgical margins (R0) were reported in 72 % and 67 %, respectively for the LVHs and the HVH group.

### Morbidity and Mortality

A significantly higher postoperative morbidity rate was found in the LVH group, which probably is also

reflected by the longer hospital stay (Table 2). The clinical anastomotic leakage rate differed between both groups: LVHs 17% versus HVH 5%. The mortality rate was almost three times higher for patients treated in the LVHs than those who had their operation in the HVH: 13% vs 5%, respectively ( $P < .001$ ). None of the LVHs had a mortality rate lower than the 5% of the HVH (Table 3). Univariate analysis showed that hospital volume, age, and comorbidity are prognostic factors for mortality (Table 4). The mortality risk increased with higher age and the number of organ systems affected. Especially cardiac (OR 3.22, CI 1.91–5.44), vascular (OR 2.49, CI 1.45–4.27), and respiratory (OR 1.90 CI 1.09–3.33) comorbidity were risk factors for postoperative mortality.

**TABLE 1.** Patient, tumor, and treatment characteristics of esophageal resections in LVH<sup>a</sup> and HVH<sup>b</sup>

Characteristics	LVH		HVH		P value
	No. of patients	%	No. of patients	%	
Age (years)	65		64		.240
Range (years)	33–87		31–83		
Gender					.072
Male	249	73	438	78	
Female	93	27	123	22	
Comorbidity					.078
No	142	42	273	49	
1 organ system	111	32	179	32	
2 organ systems	51	15	80	14	
≥3 organ systems	11	3	27	5	
Unknown	27	8	2	0	
Histology					.039
Adenocarcinoma	238	69	347	62	
Squamous	96	28	193	34	
Barrett's dysplasia	4	1	6	1	
Other	2	1	14	3	
Unknown	2	1	1	0	
Tumor localization					.740
Cervical esophagus	7	2	14	3	
Mid esophagus	53	15	86	15	
Distal esophagus	114	33	204	36	
Gastroesophageal junction	166	49	251	45	
Unknown	2	1	6	1	
Stage (pTNM)					< .001
0 and I	43	12	61	11	
II	162	47	214	38	
III	107	31	186	33	
IV	21	6	94	17	
Unknown	9	3	6	1	
(Neo)-adjuvant treatment					< .001
None	316	92	464	83	
Chemotherapy	17	5	93	17	
Radiotherapy	0	0	2	0	
Chemoradiation	4	1	0	0	
Unknown	5	2	1	0	
Surgical approach					< .001
Abdomino-cervical	150	44	466	83	
Thoraco-abdominal	97	28	60	11	
Abdomino-thoraco-cervical	43	13	17	3	
Abdominal	52	15	18	3	
Anastomoses					< .001
Cervical	195	57	541	96	
Thoracic	91	27	8	2	
Abdominal	56	16	8	2	
Unknown	0	0	4	0	
Total No. of patients	342		561		

<sup>a</sup> LVH, low-volume hospitals.  
<sup>b</sup> HVH, high-volume hospital.

Multivariate analysis showed that both hospital volume and comorbidity were independent prognostic factors for hospital mortality (Table 5).

**Survival**

Figure 2 shows the crude 10-year overall survival rate of all patients, in which an esophageal resection for cancer was performed. Survival rates for patients

**TABLE 2.** Outcome after resection of esophagus for cancer in LVH<sup>a</sup> and HVH<sup>b</sup>

Outcome	LVH		HVH		P value
	No. of patients	%	No. of patients	%	
Margins					.93
R0	248	72	377	67	
R1	55	16	161	28	
R2	35	11	21	4	
Unknown	4	1	2	1	
Complications					
Surgical complications	144	42	207	37	.01
General complications	191	56	207	37	< .001
No complications	89	26	247	44	< .001
Hospital stay					
Median (days)	21		14		< .001
In-hospital					
Mortality	45	13	28	5	< .001
Survival					
Median (months)	21		22		.90
Range (months)	(1–171)		(1–158)		
Total No. of patients	342		561		

<sup>a</sup> LVH, low-volume hospitals.  
<sup>b</sup> HVH, high-volume hospital.

**TABLE 3.** Mortality after resection of esophagus for cancer in LVH<sup>a</sup> and HVH<sup>b</sup>

Hospitalism	In-hospital mortality		
	No. of patients	No. of deaths	%
HVH	561	28	5.0
LVH 1	16	2	12.5
LVH 2	19	2	10.5
LVH 3	28	2	7.1
LVH 4	25	3	12.0
LVH 5	14	1	7.1
LVH 6	28	2	7.1
LVH 7	34	2	5.9
LVH 8	64	12	18.7
LVH 9	44	10	22.7
LVH 10	6	2	33.3
LVH 11	64	7	10.9
Total No. of patients	903	73	8

<sup>a</sup> LVH, low-volume hospitals.  
<sup>b</sup> HVH, high-volume hospital.

treated in the HVH are significantly better ( $P = .01$ ). This survival benefit loses its statistical significance, after exclusion of patients who died postoperatively of complications of the surgical procedure (Fig. 3). Only, when we select patients with stage I and II disease do we see a better survival in the HVH (Fig. 4), meaning that its overall results are worsened by the poor survival in the higher stages of the disease, stage III and IV. This can be explained by the unfavorable tumor mix, with significantly more stage IV disease treated in the HVH, than in the LVHs (16.7 vs 6.1%).

**TABLE 4.** Univariate analysis of in-hospital mortality

	Univariate analysis		
	OR	95% CI	P value
Region			<.001
HVH	1.00	Ref <sup>a</sup>	
LVH	2.88	1.76–4.72	
Age (years)			.01
< 50	0.19	0.04–0.79	
50–59	0.51	0.25–1.04	
60–69	1.00	Ref <sup>a</sup>	
> 70	1.20	0.70–2.04	
Gender			.20
Male	1.00	Ref <sup>a</sup>	
Female	0.67	0.36–1.24	
Comorbidity			<.001
No	1.00	Ref <sup>a</sup>	
1 organ system	2.02	1.06–3.86	
2 organ systems	4.51	2.30–8.85	
≥3 organ systems	4.97	1.92–12.83	
Histology			.97
Adenocarcinoma	1.00	Ref <sup>a</sup>	
Squamous	0.99	0.60–1.65	
Stage			.24
I	1.00	Ref <sup>a</sup>	
II	0.50	0.24–1.04	
III	0.80	0.39–1.63	
IV	0.65	0.26–1.61	
Tumor localization			.33
Cervical/mid esophagus	1.00	Ref <sup>a</sup>	
Distal esophagus/ gastroesophageal junction	1.41	0.71–2.80	
Neoadjuvant treatment			.14
No	1.00	Ref <sup>a</sup>	
Yes	0.49	0.20–1.25	
Surgical approach			.31
Transhiatal	1.00	Ref <sup>a</sup>	
Transthoracic	1.51	0.90–2.54	
Anastomosis			.46
Cervical	1.00	Ref <sup>a</sup>	
Thoracic	1.52	0.77–3.01	
Abdominal	1.26	0.52–3.04	

<sup>a</sup> Ref, reference category.

**DISCUSSION**

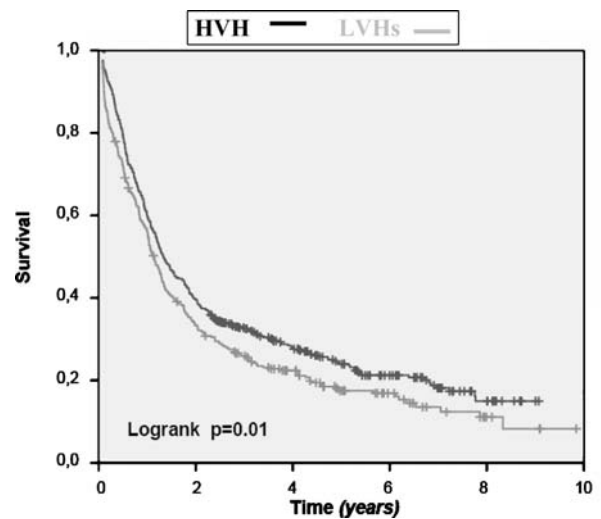
Currently, there is extensive interest in comparing outcome of complex surgical procedures between high- and low-volume providers. Most of the studies are registry-based or relatively small. Our series offers additional proof to the volume–outcome relationship, because it is based on clinical data, retrieved from the original patient files. This allows us to make reliable comparisons for comorbidities and tumor stage, which proved to be important prognostic factors for in-hospital mortality and survival.

A review of the evidence for a volume–outcome relationship was published by Dudley in 2000<sup>8</sup> and Halm in 2002.<sup>2</sup> In the latter publication 135 studies were reviewed, of which only five were not from the United States or Canada. The majority of reports

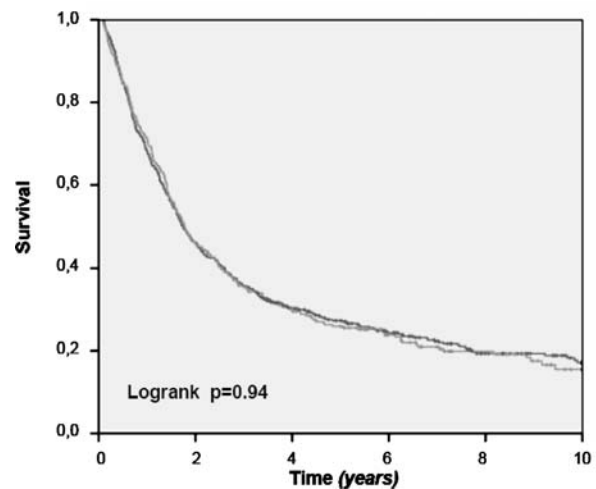
**TABLE 5.** Multivariate analysis of in-hospital mortality

	Multivariate analysis		
	OR	95% CI	P value
Region			<.001
HVH	1.00	Ref <sup>a</sup>	
LVHs	3.05	1.82–5.11	
Age (years)			.10
< 50	0.22	0.05–0.96	
50–59	0.60	0.29–1.25	
60–69	1.00	Ref <sup>a</sup>	
> 70	1.07	0.61–1.88	
Comorbidity			.004
No	1.00	Ref <sup>a</sup>	
Yes	2.34	1.30–4.19	

<sup>a</sup> Ref, Reference category.



**FIG. 2.** Overall survival after esophagus resection for cancer: LVHs vs HVH (*in-hospital mortality included*).



**FIG. 3.** Overall survival after esophagus resection for cancer: LVHs vs HVH (*in-hospital mortality excluded*).

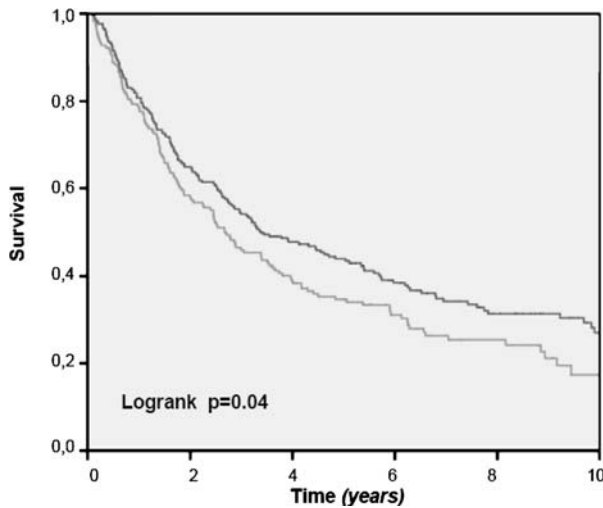


FIG. 4. Overall survival after esophagus resection for stage I and II carcinoma: LVHs vs HVH (*in-hospital mortality excluded*).

were based on state or national hospital discharge databases, where only a few studies used clinical data for risk adjustment. The outcome measure was “death” in 79% of the studies, without analyzing other dimensions of “outcome,” such as morbidity, length of hospital stay, reoperations, et cetera. For cancer-related procedures, long-term survival was not mentioned. Higher-level methodological issues were rarely addressed. Only five studies concerning cancer treatment adjusted for (neo)-adjuvant therapies or the type of surgical resection, but without any adjustment for tumor stage.

Since 2002, more extensive studies on hospital or surgeon volume appeared in the international literature. Birkmeyer reported a total number of 2.5 million operations concerning 14 different surgical procedures derived from the MEDICARE database.<sup>9</sup> Mortality was the only outcome measure. Even after risk adjustment, which decreased the outcome differences between high- and low-volume hospitals, the differences in results for esophageal and pancreatic resections were highly significant, favoring surgery in a high-volume center. Two more recently published reviews of the volume–outcome relationship for esophagectomies came up with 12 papers addressing this subject.<sup>4,5</sup> Only two of these studies were based on clinical data. Although both showed a decrease in mortality, they failed to show a statistically significant relationship of operative mortality with hospital volume.<sup>10,11</sup> In our own review of the literature we identified another study from the United Kingdom using clinical data, in which hospital case volume independently predicted operative mortality<sup>2</sup> (Table 6).

In the present study, independent data managers collected data retrospectively from the patient files. Not only the (in-hospital) mortality rate was obtained, but also a range of other outcome data, such as complication rates, resection margins, length of stay, and long-term survival. In our opinion the latter is an important performance indicator in surgical oncology, surprisingly sporadically mentioned in the volume–outcome literature.

The results of patients treated in 11 low-volume hospitals were compared with the results of patients treated in the nearest high-volume referral center. Significant differences in outcome could be revealed. In-hospital mortality was significantly higher in the low-volume hospitals. The retrieved information about comorbidity and stage of the disease made an extensive preoperative risk and tumor load comparison possible. Risk adjustment is an important issue in outcome research, because patients with severe comorbidity may be unequally distributed between (groups of) hospitals. Especially, when only administrative data are used to assess hospital performances, a selection-bias could lead to inadvertently penalizing those surgeons who provide excellent care to patients with more severe comorbid disease.<sup>7,13</sup> Administrative data sets were never designed to predict risk and should probably not be used as such.<sup>14</sup> Therefore, the validity of studies that fail to make case-mix adjustments based on clinical data, has to be questioned.

Nevertheless, a multivariate analysis of our data shows hospital volume to be an independent prognostic factor for in-hospital mortality. Although differences in surgical technique could be detected, with more transthoracic esophagectomies and intrathoracic anastomoses in the low-volume group, these factors are not significantly related to mortality. These findings are confirmed by earlier reports.<sup>15–18</sup> Also, there is little evidence for a beneficial role of neoadjuvant therapies.<sup>19–22</sup> However, above all, choices made concerning diagnostic strategy, neoadjuvant treatments, and surgical technique are related to the knowledge, experience, and judgment of the (team of) specialists.

After exclusion of in-hospital mortality, the survival of patients in the HVH was equal to those treated in the LVHs. However, the results of the HVH were negatively influenced by its case-mix. More patients with stage IV disease were treated in the HVH, corresponding with its status as a tertiary referral center. The very poor survival in this group of patients influences the overall results significantly. Only when we are informed about differences in tu-

**TABLE 6.** Volume–outcome articles for in-hospital mortality after esophagectomy 1998–2006

Author	Journal/Year	Data	Volume “cut-off”	Conclusion
Dimick et al. <sup>32</sup>	<i>Ann Thorac Surg</i> 2005	Adm	< 6 >	S
Urbach and Baxter <sup>33</sup>	<i>BMJ</i> 2004	Adm	< 9 >	NS
McCulloch et al. <sup>12</sup>	<i>BMJ</i> 2003	Clin	< 10–20 >	S
Christian et al. <sup>34</sup>	<i>Ann Surg</i> 2003	Adm	< 22 >	S
Finlayson et al. <sup>35</sup>	<i>Arch Surg</i> 2003	Adm	< 4–9 >	S
Urbach et al. <sup>36</sup>	<i>CMAJ</i> 2003	Adm	<sup>a</sup>	S
Dimick et al. <sup>37</sup>	<i>Surgery</i> 2003	Adm	< 7 >	S
Birkmeyer et al. <sup>9</sup>	<i>N Engl J Med</i> 2002	Adm	< 2–4–7–19 >	S
Gillison et al. <sup>11</sup>	<i>Br J Surg</i> 2002	Clin	< 19 >	NS
Bachmann et al. <sup>10</sup>	<i>Br J Surg</i> 2002	Clin	<sup>a</sup>	NS
Dimick et al. <sup>38</sup>	<i>Ann Thorac Surg</i> 2001	Adm	< 4–15 >	S
van Lanschot et al. <sup>7</sup>	<i>Cancer</i> 2001	Adm	< 10–20 >	S
Kuo et al. <sup>39</sup>	<i>Ann Thorac Surg</i> 2001	Adm	< 6 >	S
Swisher et al. <sup>40</sup>	<i>J Thorac Cardiovasc Surg</i> 2000	Adm	< 5 >	S
Gordon et al. <sup>41</sup>	<i>J Am Coll Surg</i> 1999	Adm	< 10–20–50 >	S
Begg et al. <sup>42</sup>	<i>JAMA</i> 1998	Mixed	< 5–10 >	S
Patti et al. <sup>43</sup>	<i>J Gastrointest Surg</i> 1998	Adm	< 1–2–4–6 >	S

<sup>a</sup> Urbach and Bachmann used equally sized groups and reported only median volumes of these groups.

Adm denotes administrative data; Clin denotes clinical data; S denotes significant; NS denotes not significant.

mor stage, we are able to detect real differences in survival between patients treated in different hospitals. Although in this study, all pathology reports were reviewed, and the number of lymph nodes resected was equal for both groups, we still have to be cautious suggesting a survival benefit for high-volume surgery. Only when a uniform pathologic evaluation is guaranteed, can we be sure that observed differences in tumor stages are truly characteristic for patient groups. This could be the reason that few studies have attempted to examine the influence of hospital volume on long-term survival in cancer surgery, only one of them concerning esophagectomies.<sup>23–27</sup> A recent study from the Netherlands failed to show a survival benefit in high-volume hospitals (> 20 resections a year), but did show an improved survival for esophagectomies performed in university compared to non-university hospitals.<sup>28</sup> On the other hand, for pancreatectomies and hepatectomies registered in the MEDICARE-database, Fong showed a significantly better survival for procedures performed in high-volume centers.<sup>25</sup> In his study, administrative data about age, gender, comorbidity, and extent of the resection were included in a univariate and multivariate analysis, but stages of the disease, radicality, and intent of the resection (palliative or curative) were not reported.

In conclusion, our study shows that hospital volume is an important determinant of perioperative morbidity and mortality in esophageal cancer surgery. Nevertheless, volume in itself is no guarantee for high quality of surgical care in a specific institution. Selecting (only) favorable patients can be the basis of superior results. Therefore, case-mix adjust-

ments are essential in the assessment of surgical performance of different institutions.

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