

# Impact of Hospital Volume on Long-term Survival After Esophageal Cancer Surgery

Ioannis Rouvelas, MD; Mats Lindblad, MD, PhD; Wenyi Zeng, PhD; Pernilla Viklund, RN; Weimin Ye, MD, PhD; Jesper Lagergren, MD, PhD

**Hypothesis:** The improved survival after esophageal cancer surgery in Sweden during recent years may be attributable to the increased centralization of such surgery.

**Design:** Population-based study.

**Setting:** All Swedish residents undergoing esophageal cancer surgery from January 1, 1987, through December 31, 2000, were identified from the inpatient and cancer registers and were followed up until October 18, 2004, through nationwide registers. Hospital, tumor, and patient characteristics and preoperative oncological treatment were assessed through the registers and histopathological records.

**Patients:** Among 4904 patients with esophageal cancer, 1199 patients (24.4%) who underwent resection constituted the study cohort.

**Main Outcome Measure:** Survival rates and hazard ratios (HRs) relative to hospital volume. Low-volume hospitals (LVHs) conducted fewer than 10 esophagec-

tomies annually, while high-volume hospitals (HVHs) conducted 10 or more. Hazard ratios were adjusted for several potential confounders.

**Results:** Thirty-day survival was 96% at HVHs and 91% at LVHs ( $P = .09$ ). Survival rates 1, 3, and 5 years after surgery at HVHs were nonsignificantly higher (58%, 35%, and 27%, respectively) compared with those at LVHs (55%, 30%, and 24%, respectively). The adjusted HR was nonsignificantly 10% decreased at HVHs (HR, 0.90; 95% confidence interval, 0.79-1.04). In an analysis restricted to 764 patients (64%) without preoperative oncological treatment (in which the tumor stage was also adjusted for), survival was similar at HVHs and at LVHs (HR, 0.99; 95% confidence interval, 0.84-1.18).

**Conclusions:** This study revealed no effect of hospital volume on long-term survival after esophageal cancer surgery. Tumor biology apparently has a greater effect on the chances of long-term survival than hospital volume.

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**I**N THIS STUDY, WE ADDRESSED 2 hypotheses regarding esophageal cancer surgery that hospital volume affects (1) long-term survival and (2) short-term mortality. The anatomical location of the esophagus explains why esophagectomy for esophageal cancer is one of the

10% in Western societies.<sup>6</sup> Because the tumor stage is often already advanced when the diagnosis is first confirmed, few patients are eligible for treatment with curative intent.<sup>7</sup> Moreover, even after successful esophageal resection, less than 40% of the patients are cured.<sup>1,2,4</sup> It is encouraging that the short-term and long-term population-based survival after esophagectomy has improved considerably in recent years.<sup>8</sup> This

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**Author Affiliations:** Unit of Esophageal and Gastric Research, Department of Molecular Medicine and Surgery (Drs Rouvelas, Lindblad, and Lagergren and Ms Viklund), and Department of Medical Epidemiology and Biostatistics (Drs Zeng and Ye), Karolinska Institutet, Stockholm, Sweden; and Department of Mathematics, Beijing Normal University, Beijing, China (Dr Zeng).

most demanding and traumatic surgical procedures undertaken in general surgery. The operation often involves combined extensive surgery of the neck, chest, and abdomen, and the postoperative in-hospital mortality is considerable.<sup>1-5</sup> However, esophagectomy remains the only established curative treatment for patients with resectable esophageal cancer.<sup>1,2</sup> The prognosis associated with this cancer is worse than that associated with most malignant diseases, with an overall 5-year survival of less than

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improvement is probably explained by developments in preoperative risk evaluation, advances in operative techniques, and improved postoperative care.<sup>8</sup> Regarding the group of patients deemed suitable for surgery, there has been much debate on whether specialization and an increased hospital operative volume may improve the outcome. Population-based studies<sup>9-17</sup> have addressed the effect of annual hospital and

surgeon volume on the outcome of major cancer surgery and have consistently demonstrated lower short-term postoperative mortality and complications associated with higher hospital and surgeon volumes. This effect seems to be particularly marked after esophagectomy.<sup>10,13,14</sup> To our knowledge, only in 2 studies<sup>18,19</sup> have attempts been made to investigate the long-term prognosis after esophagectomy relative to surgical volume, and the results have been conflicting. Hence, the potential effect of hospital volume on long-term survival after esophageal cancer surgery, a question of obvious clinical relevance, remains uncertain. Therefore, we conducted a nationwide study in Sweden with the aim of assessing the population-based effect of hospital volume on long-term survival after esophageal cancer surgery with curative intent, as well as comparing it with the effect of tumor biology. We hypothesized that the improved survival after esophageal cancer surgery in Sweden during recent years may be attributable to the increased centralization of such surgery.<sup>8</sup>

## METHODS

### DESIGN

The design of this Swedish nationwide population-based study has been described in detail elsewhere.<sup>8</sup> In brief, all residents in Sweden diagnosed as having esophageal cancer and treated with esophagectomy from January 1, 1987, through December 31, 2000, were included. Patients were identified through linkage of the national cancer register to the inpatient register using the patient's national registration number, a unique 10-digit identification number assigned to every resident in Sweden. Only primary adenocarcinomas and squamous cell carcinomas of the esophagus were included. Through information collected in the inpatient register, we assessed data regarding the operating hospital, type and date of surgery, and any concurrent diseases. Comorbidity was defined as any disease treated in-hospital that the patient may have experienced before surgery or at the time of surgery. Because the inpatient register has had complete nationwide coverage since January 1, 1987, this date was chosen as the starting date for the study. Information on preoperative oncological treatment and on tumor characteristics (ie, stage, histopathological type, and specific site within the esophagus) was collected through a scrutiny of histopathological records. The tumor stage was determined by a reviewer (I.R.) blinded to the patients' survival time and hospital in patients treated with esophagectomy alone (ie, without preoperative oncological treatment). This classification was conducted according to recommendations by the *Union Internationale Contre le Cancer, Sixth Edition*. Information regarding the tumor stage before preoperative oncological treatment was unavailable. Follow-up of all cohort members was made possible through linkages to the nationwide registers of death, emigration, and total population. The patients were followed up from the date of surgery until death, emigration, or the end of the study period (October 18, 2004), whichever occurred first. The completeness and quality of the data collected in the registers used were high.<sup>20,21</sup> The most common surgical approach was a trans-thoracic esophageal resection with a pulled-up gastric tube as the esophageal substitute and an intrathoracic anastomosis.<sup>8</sup> The ethics committee at Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, approved the study.

## STATISTICAL ANALYSIS

The hospitals performing esophageal cancer surgery were divided into 2 predefined categories based on the annual number of esophagectomies conducted. Low-volume hospitals (LVHs) were defined as hospitals that performed fewer than 10 esophageal resections annually during the 14-year study period from 1987 to 2000, and high-volume hospitals (HVHs) were defined as hospitals that performed 10 or more esophageal resections annually during that period. The outcome measure was survival. Observed survival was assessed as short-term survival, defined as survival up to 30 days after surgery, and as long-term survival, defined as survival up to 1, 3, and 5 years after surgery. The 30-day definition of short-term survival was preferred over in-hospital mortality because it was considered less susceptible to different discharge policies and to inequalities regarding the availability of suitable intermediate-care facilities in our population-based study design. Moreover, we measured tumor stage-specific survival rates among patients treated with esophagectomy without preoperative oncological treatment in the 2 hospital volume categories. Survival rates were estimated using the Kaplan-Meier method, and survival curves were compared by means of the log rank test. A Cox proportional hazards regression model was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for estimating differences in survival between patients treated with esophagectomy in HVHs and those treated in LVHs. The basic model included adjustment for sex and age categorized into 4 groups (<55, 55-65, 66-75, and >75 years). The adjusted model included adjustment for sex, age, preoperative oncological treatment (yes or no), comorbidity categorized into 3 groups (no concurrent disease, 1, and >1), calendar period categorized into 3 periods (1987-1991, 1992-1996, and 1997-2000), tumor site categorized into 4 sites (upper esophagus, middle, lower, and undefined), and tumor type categorized into 3 types (adenocarcinoma, squamous cell carcinoma, and cancer in which the distinction between these histological types was uncertain). In the adjusted model that also included the tumor stage, this variable was categorized into 5 stages (I, II, III, IV, and undefined). All statistical analyses were performed using SAS software version 8.2 (SAS Institute, Cary, NC), and the SAS PHREG procedure was used for the Cox proportional hazards regression model.

## RESULTS

### PATIENT AND TUMOR CHARACTERISTICS

During the study period, we identified 4904 patients with esophageal cancer in the Swedish Cancer Register. Among these, 1199 patients (24.4%) treated with esophagectomy constituted our study cohort. We received the pathologists' reports on the surgical specimens in 1135 (95%) of the study patients. Among 53 hospitals that contributed data on esophagectomies, 2 hospitals were classified as HVHs (ie, conducted  $\geq 10$  resections annually during the study period). Some characteristics of the study patients operated on at LVHs and at HVHs are given in **Table 1**. Seven hundred thirty-one patients (61%) underwent surgery at an LVH. The sex and age distributions were similar at LVHs and at HVHs. The proportion of surgically treated patients operated on without any concurrent disease was slightly higher in the HVH group (363 patients [78%]) than in the LVH group (472 patients [65%]). There were no clear differences in the

**Table 1. Characteristics of 1199 Study Patients With Resectable Esophageal Cancer by Hospital Volume Category\***

Characteristic	Low-Volume Hospital (n = 731)	High-Volume Hospital (n = 468)
Age, mean ± SD, y	65 ± 9	66 ± 10
Sex		
Male	528 (72.2)	334 (71.4)
Female	203 (27.8)	134 (28.6)
Concurrent disease		
None	472 (64.6)	363 (77.6)
1	132 (18.1)	57 (12.2)
>1	118 (16.1)	26 (5.6)
Missing data	9 (1.2)	22 (4.7)
Tumor stage†		
I	67 (14.8)	50 (16.1)
II	180 (39.7)	112 (36.0)
III	142 (31.3)	112 (36.0)
IV	50 (11.0)	37 (11.9)
Undefined	14 (3.1)	0
Tumor location in esophagus		
Upper	31 (4.2)	28 (6.0)
Middle	144 (19.7)	121 (25.9)
Lower	506 (69.2)	309 (66.0)
Missing data	50 (6.8)	10 (2.1)
Tumor histology		
Squamous cell carcinoma	429 (58.7)	308 (65.8)
Adenocarcinoma	215 (29.4)	123 (26.3)
Uncertain‡	87 (11.9)	37 (7.9)
Preoperative oncological treatment		
No	453 (62.0)	311 (66.5)
Yes	243 (33.2)	148 (31.6)
Missing data	35 (4.8)	9 (1.9)
Calendar period		
1987-1991	224 (30.6)	164 (35.0)
1992-1996	290 (39.7)	153 (32.7)
1997-2000	217 (29.7)	151 (32.3)

\*Data are given as number (percentage) unless otherwise indicated. Percentages may not total 100 because of rounding. Low-volume hospitals performed fewer than 10 resections annually; high-volume hospitals, 10 or more resections annually.

†Tumor stage could be assessed in 764 patients treated with surgery alone (453 at low-volume hospitals and 311 at high-volume hospitals).

‡Uncertain distinction between adenocarcinoma and squamous cell carcinoma.

calendar periods, distribution of tumor characteristics, or frequency of preoperative oncological treatment between the 2 hospital volume categories.

### SURVIVAL RELATIVE TO HOSPITAL VOLUME

The observed survival rates in the 2 hospital volume groups are summarized in **Table 2** and in the **Figure**. The 30-day mortality rate was more than twice as high at LVHs (9%) compared with that at HVHs (4%), but this difference ( $P = .09$ ) did not reach the level of statistical significance. The overall observed postoperative survival was about 3% to 5% better among the patients operated on at HVHs, but none of the differences were statistically significant (Table 2). The observed 5-year survival after surgery at HVHs was 27.4% compared with 23.8% at LVHs. The observed tumor stage-specific survival was calculated among

**Table 2. Short-term and Long-term Survival by Hospital Volume Category Among 1199 Study Patients Who Underwent Esophageal Cancer Surgery\***

Hospital Volume Category	No. of Patients (Survival Rate, %)			
	30 d†	1 y‡	3 y§	5 y
Low (n = 731)	667 (91.2)	402 (55.0)	221 (30.2)	174 (23.8)
High (n = 468)	448 (95.7)	272 (58.1)	163 (34.8)	128 (27.4)

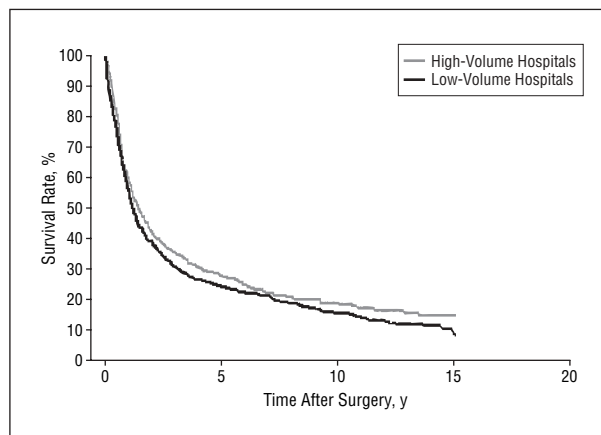
\*All  $P$  values were determined using a Cox proportional hazards regression crude model.

† $P = .09$ .

‡ $P = .46$ .

§ $P = .15$ .

|| $P = .10$ .



**Figure.** Observed survival relative to hospital volume in 1199 study patients having esophageal cancer treated with esophagectomy. High-volume hospitals performed 10 or more resections per year; low-volume hospitals, less than 10 resections per year.

764 patients treated with surgery alone (ie, in the subgroup of patients for whom information regarding the tumor stage was available). The 1-year and 5-year survival rates in patients with stage III tumor treated at LVHs were 38.7% and 6.5%, respectively, compared with 45.4% and 9.6%, respectively, at HVHs, but the differences were not statistically significant (**Table 3**). The adjusted HRs are given in **Table 4**. The basic HRs (adjusted for sex and age only) showed a statistically significant decreased overall mortality among patients operated on at HVHs (HR, 0.88; 95% CI, 0.77-0.99), but after additional adjustment for calendar period, comorbidity, tumor location, tumor histology, and preoperative oncological treatment, this difference was attenuated and was no longer statistically significant (HR, 0.90; 95% CI, 0.79-1.04;  $P = .16$ ). In the analysis when the full model (including the tumor stage) was available and restriction was made to patients without preoperative oncological treatment, the adjusted HR of long-term mortality was similar in the 2 hospital volume groups (HR, 0.99; 95% CI, 0.84-1.18).

### COMMENT

In this nationwide population-based study, no differences in long-term survival after esophageal cancer sur-

**Table 3. Tumor Stage–Specific Short-term and Long-term Survival Among 764 Patients Treated With Surgery Alone at Low-Volume Hospitals (LVHs) and at High-Volume Hospitals (HVHs)\***

Tumor Stage	No. of Patients (Survival Rate, %)							
	30 d		1 y		3 y		5 y	
	LVHs	HVHs†	LVHs	HVHs‡	LVHs	HVHs§	LVHs	HVHs
All stages	411 (90.7)	297 (95.5)	246 (54.3)	179 (57.7)	138 (30.4)	105 (34.0)	110 (24.4)	81 (26.3)
I	64 (94.4)	48 (95.4)	57 (84.0)	43 (84.3)	49 (72.4)	34 (67.2)	43 (63.2)	31 (61.3)
II	163 (90.6)	106 (93.8)	115 (63.5)	72 (64.2)	66 (36.3)	45 (39.7)	54 (30.0)	33 (29.8)
III	131 (91.8)	107 (95.0)	55 (38.7)	51 (45.4)	16 (10.7)	19 (16.7)	10 (6.5)	11 (9.6)
IV	43 (85.2)	36 (96.2)	15 (29.2)	13 (35.5)	6 (11.4)	7 (18.6)	2 (4.0)	6 (15.1)
Undefined	10 (67.9)	0	4 (28.6)	0	1 (7.1)	0	1 (7.1)	0

\*All *P* values were determined using a Cox proportional hazards regression crude model.

†*P* = .71.

‡*P* = .90.

§*P* = .68.

||*P* = .68.

**Table 4. Basic and Adjusted Hazard Ratios (HRs) of Mortality After Esophagectomy by Hospital Volume**

Hospital Volume Category	All Patients (n = 1199)		Patients Without Preoperative Oncological Treatment (n = 764)	
	HR (95% CI)	<i>P</i> Value	HR (95% CI)	<i>P</i> Value
Low	1.00	...	1.00	...
High				
Crude model	0.89 (0.78-1.01)	.08	0.92 (0.78-1.08)	.30
Basic model	0.88 (0.77-0.99)*	.047	0.91 (0.77-1.07)*	.26
Adjusted model	0.90 (0.79-1.04)†	.16	0.99 (0.84-1.18)‡	.99

Abbreviation: CI, confidence interval.

\*Included adjustments for age and sex.

†Included adjustments for age, sex, comorbidity, tumor location, tumor histology, calendar period, and preoperative oncological treatment.

‡Included adjustments for age, sex, comorbidity, tumor location, tumor histology, calendar period, and tumor stage.

gery were found between hospitals with a higher surgical volume compared with those with a lower volume after adjustment for clinically relevant covariates. Previous studies<sup>9-14,22</sup> demonstrated an inverse correlation between hospital volume and postoperative mortality, expressed as in-hospital mortality or as 30-day mortality, after esophageal cancer surgery. Most of these studies were selected series that revealed striking operative mortality differences between HVHs and LVHs. A meta-analysis by Metzger et al<sup>23</sup> confirmed this beneficial association between hospital volume and surgical outcome. These findings are strengthened by the results of our population-based study regarding 30-day mortality in which patients operated on at HVHs seemed to be at reduced risk compared with those operated on at LVHs.

To our knowledge, only 2 studies<sup>18,19</sup> have addressed the association between hospital volume and long-term prognosis after esophageal cancer surgery. In a retrospective case study<sup>18</sup> in the West Midlands region of England, no inverse relation was found between increasing surgeon volume or hospital volume and long-term survival after resection for esophageal or cardia cancer. Patient and tumor characteristics such as age and stage were more likely than the annual workload to predict the outcome from surgical resection. Problems of that study<sup>18</sup>

included failure to retrieve all the required hospital notes and a high 30-day mortality (10% overall) compared with the reported mortality in other Western studies.<sup>2,4,8,24</sup> In another Swedish study,<sup>19</sup> the overall in-hospital mortality was lower and the 5-year survival was higher among patients operated on at HVHs vs LVHs. Although that study<sup>19</sup> partly included the same patients as in the present study, the 2 studies differed considerably in design with regard to study period, tumor types, tumor classification, and efforts at case validation. Moreover, the previous study<sup>19</sup> lacked data on the tumor stage, comorbidity, and preoperative oncological treatment. These differences may explain the divergent results.

The main hypothesis proposed in the present study was that esophageal cancer surgery at a HVH may increase the chance of cure compared with surgery at an LVH, a hypothesis that was not proven. Although the HR adjusted only for sex and age showed a statistically significant lower overall mortality among patients operated on at HVHs, no difference remained after additional adjustments for potential confounders. When the tumor stage, the single most important prognostic factor in esophageal cancer,<sup>25</sup> was added to the model, the HR was confidently close to unity.

Advantages of our study include the population-based and nationwide design with a long and complete follow-

up. All patients in Sweden who were diagnosed as having esophageal cancer and who underwent esophagectomy during the 14-year study period were included. This design reduces the risk of selection bias and facilitates generalizability. The availability of updated and complete registers in combination with the personal identification numbers in Sweden enabled complete follow-up. Furthermore, the results were adjusted for several potentially important confounders. We identified the following 4 limitations of the study: the inability to assess the tumor stage in all patients, the lack of data regarding individual surgeon volume, the sparse details of the surgical procedures, and the missing information on any treatment given after esophageal resection. However, these limitations should not have strongly affected our results. First, the tumor stage was available for a large subset of patients, which made it possible to evaluate the effect of this important prognostic variable. Second, surgeon volume should be well mirrored by hospital volume. Third, details of the surgical procedure were not included in the hypothesis of our study and could not have explained our overall negative finding. Fourth, postoperative oncological treatment for esophageal cancer was virtually never used in Sweden during the study period because of the absence of any proven effect of such therapy.<sup>1,26</sup>

The lack of association between hospital volume and long-term cure deserves a cautious interpretation. More studies are needed to address this issue further. If our finding is true, an interpretation is that tumor biology seems to have a greater effect on the chances of long-term survival than hospital volume. It is important to stress that high-volume surgery must still be recommended for surgical treatment of esophageal cancer because it has been well established that short-term mortality is higher at LVHs.<sup>9-11,13,14</sup> Moreover, the occurrence of severe complications, including anastomotic leakage, is more prevalent at LVHs,<sup>5</sup> and finally, the quality of life and remaining symptoms after esophageal cancer surgery seem to be improved among patients undergoing procedures at HVHs.<sup>27</sup>

In conclusion, this nationwide and population-based study did not reveal any overall survival benefit among patients with esophageal cancer who underwent esophagectomy at HVHs compared with those operated on at LVHs. Further research to evaluate the effects of different individual surgeon techniques and surgeon volumes on long-term survival is needed. A high volume (ie, centralization) of esophageal cancer surgery is still warranted because it has been established that this reduces the risk of short-term mortality and morbidity.

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**Correspondence:** Ioannis Rouvelas, MD, Unit of Esophageal and Gastric Research, Department of Molecular Medicine and Surgery, Karolinska Institutet, Solna, SE-171 76 Stockholm, Sweden (ioannis.rouvelas@ki.se). **Author Contributions:** Study concept and design: Rouvelas, Lindblad, Ye, and Lagergren. Acquisition of data: Rouvelas, Lindblad, and Viklund. Analysis and interpretation of data: Rouvelas, Lindblad, Zeng, Ye, and Lagergren. Drafting of the manuscript: Rouvelas, Lindblad, Zeng, Ye, and Lagergren. Critical revision of the manuscript for important intellectual content: Rouvelas, Viklund, and Lagergren. Statistical analysis: Zeng and Ye. Obtained funding:

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