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CHAPTER 7

Centralization of esophagectomy: how far should we go?

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ABSTRACT

Objective: To define a statistically sound and clinically meaningful cutoff point for annual hospital volume for esophagectomy.

Background: Higher hospital volumes are associated with improved outcomes after esophagectomy. However, reported optimal volumes in literature vary, and minimal volume standards in different countries show considerable variation. So far, no research was done on studying the non-categorical, non-linear volume-outcome relationship in esophagectomy.

Methods: Data were derived from the Netherlands Cancer Registry. Restricted cubic splines were used to investigate the non-linear effects of annual hospital volume on 6-month and 2-year mortality rates. Outcomes were adjusted for year of diagnosis, case-mix and (neo)adjuvant treatment.

Results*:* Between 1989 and 2009, some 10,025 patients underwent esophagectomy for cancer in the Netherlands. Annual hospital volumes varied between 1/year to 83/year, increasing over time. Increasing annual hospital volume showed a continuous, non-linear decrease in HR (Hazard Ratio) for mortality along the curve. Increasing hospital volume from 20/year (baseline, HR = 1.00) to 40/year and 60/year was associated with decreasing 6-month mortality, with a HR of 0.73 (95% Confidence Interval (0.65-0.83) and 0.67 (0.58-0.77) respectively. Beyond 60/year, no further decrease was detected. Higher hospital volume was also associated with decreasing 2-year mortality until 50 esophagectomies/year with a HR of 0.86 (0.79-0.93).

Conclusions: Centralization of esophagectomy to a minimum of 20 resections/year has been effectively introduced in the Netherlands. Increasing annual hospital volume was associated with a non-linear decrease in mortality up to 40-60 esophagectomies/year,

after which a plateau was reached. This finding may guide quality improvement efforts worldwide.

INTRODUCTION

Surgical resection is the cornerstone of curative treatment for esophageal cancer. Postoperative mortality remains a challenge with reported mortality rates as high as 8.9% in the Western world[1], with a 5-year survival rate after esophagectomy of around 50%[2].

There is compelling evidence that patients have better short- and long-term outcomes when operated in hospitals with a high annual caseload of esophagectomies[3,4,5].

To improve outcomes after esophagectomy, many countries introduced minimum hospital volume standards [1,6,7], but it remains unclear, how high this minimum volume standard should be. Many different definitions of a 'high-volume hospital' have been proposed in the recent literature, ranging from more than 5 to over 86 esophageal cancer resections annually[1,3,8-34]. Consequently, there is no consensus what should be considered a 'high-volume' hospital and minimum volume standards for esophagectomies vary per country or region. The American Leapfrog group set the standard at a minimum of 13 esophagectomies per hospital annually[35,36], whereas in the Netherlands, the minimum was recently set at 20 esophagectomies per year[37]. In Great Britain and Ireland, AUGIS advises at least 60 esophagogastric cancer resections per unit per year[38].

The majority of volume-outcome studies in esophagectomy analyze hospital volume as a categorical variable. Hospitals are grouped in volume categories and casemix adjusted outcomes are compared between the highest and the lowest group. Therefore, the definition of a 'high-volume' hospital is based on the predefined hospital volume categories, based on the available data or are chosen arbitrarily. Non-linear statistical modeling techniques allow analysis of annual hospital volume as a continuous variable, thus providing support in defining a meaningful cutoff point. So far, these statistics have not been used for volume-outcome studies in esophagectomy.

The purpose of this study is to define a meaningful cutoff point for annual hospital volume for esophagectomy, using non-linear statistical modeling techniques on a large dataset with a broad range in annual hospital volumes.

METHODS

Dataset

Data were derived from the Netherlands Cancer Registry (NCR), which routinely collects information on all newly diagnosed malignancies in all Dutch hospitals 6-18 months after diagnosis. Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O)[39]. ICD-O morphology codes were used to classify tumors as adenocarcinoma (8140-8145, 8190, 8201-8211, 8243, 8255-8401, 8453-8520, 8572, 8573, 8576), squamous cell carcinoma (SCC) (8032, 8033, 8051-8074, 8076-8123), and other/unknown histology (8000-8022, 8041-8046, 8075, 8147, 8153, 8200, 8230- 8242, 8244-8249, 8430, 8530, 8560, 8570, 8574, 8575). Staging was according to the International Union Against Cancer (UICC) Tumor Node Metastases (TNM) classification in use in the year of diagnosis. Vital status was initially obtained from municipal registries, and from 1994 onwards from the nationwide population registries network, which provides complete coverage of all deceased Dutch citizens. Follow-up was complete for all patients until 31st December 2009. The study was approved by the NCR Review Board.

Patients

Between January 1989 and December 2009, 37,560 patients with esophageal or gastric cardia cancer were diagnosed in the Netherlands. Esophagectomies were defined as resections for cancers of the esophagus (C15.0-15.9) and gastric cardia (C16.0). Patients who did not undergo surgery (N = 26,521) were excluded, leaving 11,039 resections available to calculate annual hospital volumes. Annual hospital volumes, defined as the number of esophagectomies per hospital per year, were determined for each year of surgery and may have changed per year for individual hospitals.

Subsequently, patients with in situ and M1 disease (N = 1,014) were excluded, leaving 10,025 patients with non-metastatic invasive carcinoma available for volume–outcome analyses.

Statistical analyses

Differences in baseline characteristics between hospital volume categories were calculated with the Chi-square test. The main outcomes were 6-month and 2-year overall mortality (OM). These were calculated using Cox regression, adjusted for sex, age, socioeconomic status, tumor stage, morphology, preoperative therapy use, postoperative therapy use (only for 2-year mortality) and year of diagnosis. To adjust for possible correlation due to clustering of patients in hospitals, robust standard errors were obtained using sandwich estimators. Frailty models with random hospital effects were used as sensitivity analysis. OM was calculated from the day of diagnosis until death, because the date of surgery was not available before 2005. Six-month OM was calculated unconditionally, while 2-year OM was calculated conditionally on surviving the first 6 months after diagnosis.

The relationship between annual hospital volume and outcomes was calculated using Cox regression with annual hospital volume modeled through restricted cubic splines[40], adjusted for the above-mentioned patient and treatment factors. Restricted cubic splines statistics allow investigation of non-linear effects of continuous covariates and have been described as a method for threshold identification [41,42]. The current Dutch minimum volume standard of 20 esophagectomies per year was taken as a reference and given a hazard ratio (HR) of 1.

Analyses were performed with SPSS (version 17.0.2) and R (version 2.12.2).

RESULTS

Patient characteristics

Patient, tumor, and treatment characteristics are displayed in table 1. The majority of patients were males (76%). The median age was 64 years. Hospitals in the higher volume categories (>40/year) operated a slightly lower percentage of patients aged 75 years and older. Pre-operative therapy use was significantly different between the volume categories.

Hospital volumes

From 1989 to 2009, the annual number of esophagectomies performed in the Netherlands doubled from 352 to 723. The percentage of esophagectomies performed in hospitals with an annual volume of more than 20 esophagectomies per year increased from 7% to 64%. From 1998 on, 18.2% of patients were operated in hospitals performing more than 60 esophagectomies per year. Overall, throughout the study period the mean hospital volume was 20.7 esophagectomies per year. In 2009, 44 of 92 Dutch hospitals performed esophagectomies.

Table 1. Patient characteristics for patients treated in different annual hospital volume categories. SES= socio-economic status; SCC= squamous cell carcinoma; pTNM= pathological tumor, nodal, metastasis staging. * χ^2 test

Patient characteristics		Total patient group		Hospital volume category 1-20/year		21-40/year		41-60/year		>60/year		P-value*
	Total	10025	100%	7103	100%	865	100%	890	100%	1167	100%	
Gender	male	7650	76%	5401	76%	684	79%	669	75%	896	77%	0.193
Age category	<60 years	3439	34%	2407	34%	292	34%	337	38%	403	35%	0.007
	60-75 years	5532	55%	3900	55%	486	56%	481	54%	665	57%	
	>75 years	1054	11%	796	11%	87	10%	72	8%	99	8%	
SES	Low	1006	10%	747	11%	105	12%	69	8%	85	7%	<0.001
	Medium	7878	79%	5747	81%	592	68%	775	87%	764	65%	
	High	426	4%	311	4%	29	3%	44	5%	42	4%	
	Unknown	715	7%	298	4%	139	16%	2	0%	276	24%	
Tumor morphology	Adenocarcinoma	7541	75%	5407	76%	679	78%	610	69%	845	72%	<0.001
	SCC	2255	22%	1523	21%	177	20%	260	29%	295	25%	
	Other	229	2%	173	2%	9	1%	20	2%	27	2%	
pTNM stage	I	1941	19%	1419	20%	146	17%	137	15%	239	20%	<0.001
	II	3898	39%	2830	40%	328	38%	325	37%	415	36%	
	III	3575	36%	2463	35%	316	37%	367	41%	429	37%	
	IV	108	1%	83	1%	4	0%	9	1%	12	1%	
	Unknown	503	5%	308	4%	71	8%	52	6%	72	6%	
Preoperative therapy	Yes	1704	17%	766	11%	347	40%	182	20%	409	35%	<0.001
Postoperative therapy	Yes	531	5%	380	5%	53	6%	54	6%	44	4%	0.053

Volume outcome analysis

The results of the cubic splines analyses are shown in Table 2 and in Figures 1 and 2. In Figure 1, the volume-outcome curve for 6-month mortality showed a steep decrease in HR in volumes above 20. At 40 resections per year, the HR was 0.73 (95% confidence interval 0.65-0.83). From this point, the curve became less steep but the HR decreased to 0.68 (0.60-0.78) at 50 resections per year and to a HR of 0.67 (0.58-0.77) at 60 per year. Beyond this point, no further decrease in HR was observed. Figure 2 displays the volume-outcome curve for 2-year conditional mortality. The curve was similar to Figure 1: the HR for death after 2 years strongly decreased between 20 and 40 esophagectomies per year, with a HR of 0.88 (0.83-0.93) at 40 resections per year. At 50 resections per year, the HR was 0.86 (95% CI 0.79-0.93)- similar to the HR at 60 resections per year (HR 0.85 (0.75-0.97)). Sensitivity analyses using frailty models did not qualitatively change these hazard ratios or confidence intervals (data not shown).

Table 2. Volume-outcome analyses

6-months mortality			**Conditional 2-year mortality**		
Annual hospital volume	HR	95% CI	Annual hospital volume	HR	95% CI
20	1	REFERENCE	20	1	REFERENCE
30	0.83	(0.76-0.91)	30	0.92	(0.89-0.96)
40	0.73	(0.65-0.83)	40	0.88	(0.83-0.93)
50	0.68	(0.60-0.78)	50	0.86	(0.79-0.93)
60	0.67	(0.58-0.77)	60	0.85	(0.75-0.97)
70	0.67	(0.54-0.83)	70	0.86	(0.71-1.05)
80	0.68	(0.49-0.94)	80	0.88	(0.66-1.16)

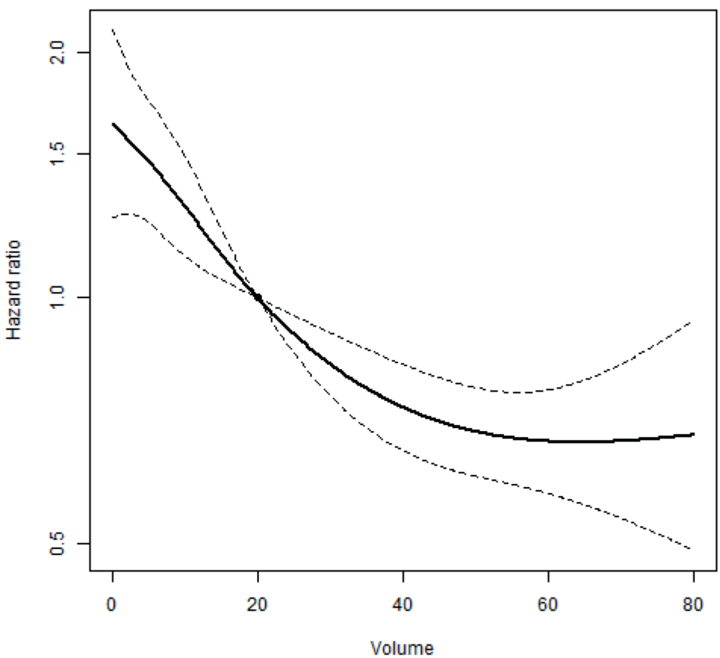

Figure 1: Volume-outcome curve for 6-month mortality (black line) with 95 percent confidence intervals (dotted line). Note that the vertical axis has a logarithmic scale.

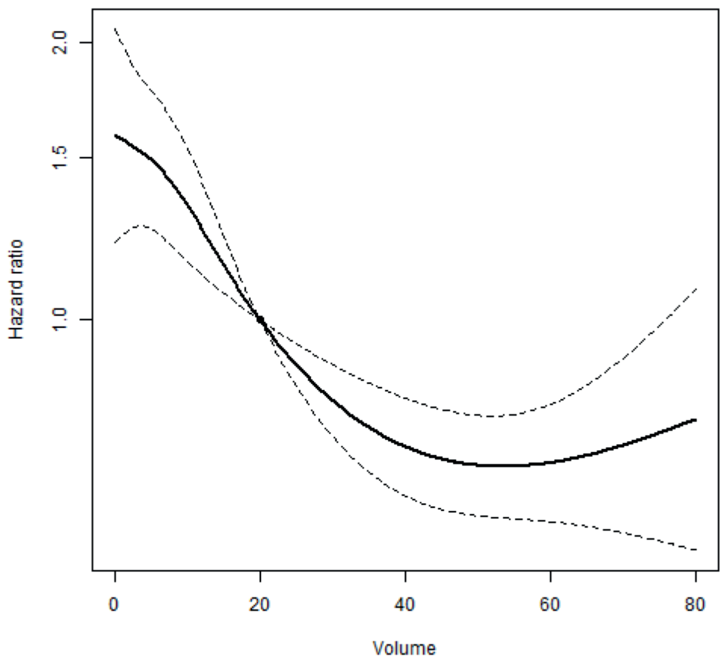

Figure 2: Volume-outcome curve for conditional 2-year mortality (black line) with 95 percent confidence intervals (dotted line). Note that the vertical axis has a logarithmic scale.

DISCUSSION

In the current study, the volume-outcome relationship in esophagectomy was assessed in a non-categorical fashion, using non-linear statistical modeling techniques on a large dataset with reliable case-mix information. It was found that further centralization of esophagectomy beyond the current Dutch minimum volume standard of 20 resections per year can have a beneficial effect on mortality rates. A continuous decrease in HRs for 6-month and 2-year mortality was observed until hospital volumes of up to 40-60 esophagectomies per year. Beyond this point, no further improvement was detected.

Increasing annual hospital volume is associated with better outcomes after esophagectomy[1,3,4,5,34,43]. So far, little research has been performed on defining the optimal hospital volume threshold for esophagectomy. In an American study, analyzing 4080 esophagectomy patients from the Nationwide Inpatient Sample, a cutoff point of 15 resections per year showed the largest difference in postoperative mortality between hospitals with a volume below and above this threshold[44]. However, mean and maximum hospital volumes were small with 4 and 33 esophagectomies per year respectively.

Another study, investigating 1634 esophagectomies from the 1999-2000 UHC clinical database found the greatest difference in mortality between hospitals at the volume threshold of 22 esophagectomies per year [45]. However, this analysis did not go beyond a threshold of 25.

A meta-analysis of relevant literature available between 1990 and 2003[46] showed that differences in postoperative mortality after esophagectomy were best discriminated using a volume threshold of at least 20 esophagectomies. However, no analyses were performed for hospital volumes above 20. In contrast to the abovementioned studies, the current study aimed to define the annual hospital volume above which no further improvement in outcomes can be detected.

A potential bias when analyzing outcomes over a long period is that preoperative staging and (perioperative) care generally improved over time, while at the same time most high-volume resections were performed in the more recent years. Therefore, high volume resections may be intrinsically associated with better outcomes. To offset this effect, we adjusted for year of diagnosis among other covariates. The surgery hospital was not available for part of the patients treated before 2005. Instead, the hospital of diagnosis was used in this case. Although referral of esophageal cancer patients to another hospital for surgery was uncommon in the earlier years of the study period, it may have influenced the analyses in the time period between 2000 and 2004.

The results of the current study are representative for the entire population as case ascertainment of the Netherlands Cancer Registry is high[47].

Due to the high number of registered variables, case-mix adjustments could be made, in all survival analyses, although it is possible that some confounding factors not available in the dataset may have influenced differences in outcomes between hospitals. However, after adjusting for age, tumor stage and SES, the added value of other confounding factors like comorbidity may be limited, especially in more aggressive types of cancer.

Worldwide, programs to concentrate esophageal cancer surgery towards high-volume hospitals take place, which has led to decreasing mortality rates in, for instance, the United States,[1, 35,] and the United Kingdom [9, 43].

Because of the minimum volume standard in the Netherlands (10 per hospital per year as of 2006, 20 per year as of 2011), the majority of Dutch patients are currently operated in centers performing 20 or more resections per year[48]. The current results suggest that further centralization up to 40-60 esophagectomies per hospital per year may further improve both short-term mortality and long-term survival. The recent increase in hospital volumes can mainly be attributed to hospitals performing 20-40 procedures per year as of 2005, whereas the highest volume category remained the same size since approximately 2000. Therefore, the learning curve of the hospitals that became referral centers after 2005 might have influenced results: it may have taken some time for these hospitals to arrange care in such a way that they could achieve results similar to the higher volume centers (performing >60 resections/year) that existed already a longer time. However, by adjusting for year of diagnosis, there is also adjusted for the potential presence of learning curves.

Moreover, it is possible that a greater effect of volumes above 60 resections/year would have been detected with more hospitals in this higher end of the spectrum.

In the Netherlands, a small country with a good infrastructure, further centralization will not likely lead to unreasonable travel burdens or problems in continuity of post-surgical care. The right number for a small, densely populated country might differ from that of larger countries with less densely populated areas.

Hospital volume may be a reflection of a variety of factors in the process of care, such as multidisciplinary approach, patient selection, and protocols; as well as resources. Arguably, lower volume hospitals may achieve excellent results with a similar approach and environment. Volume-based referral carries the risk that high-volume hospitals with unfavorable outcomes are selected as referral centers[34,36] but identification of the processes and structural factors that account for superior results remains challenging [49]. Outcome-based referral avoids this problem by selecting referral centers based on outcomes[50]. Identification of centers of excellence requires valid, reliable, complete, and adequate risk-adjusted registration of outcomes through audits[51,52], which provide insight in care patterns, and allow clinicians to benchmark their hospital on outcomes, thereby stimulating improvement[53].

In conclusion, the current study showed a continuous, non-linear decrease in HRs for 6-month and 2-year mortality, until hospital volumes of up to 40-60 esophagectomies per year, implicating that centralization of esophageal cancer resections to hospitals performing 40-60 resections per year may lead to an improved 6-month mortality and 2-year survival. These findings may guide national and regional centralization efforts worldwide.

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