2015-03-11

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Gut 2014. 63: 1393-1400

http://doi.org/10.1136/gutjnl-2013-306074

http://hdl.handle.net/10616/44567

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Hospital and surgeon volume in relation to long-term survival after oesophagectomy: Systematic review and meta-analysis

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Word count: 2784

Keywords: Hospital volume; surgeon volume; centralization; oesophageal cancer; prognosis; outcome.

Abbreviations (used in manuscript, tables and/or figures)

AdenoCa: Adenocarcinoma

CI: Confidence interval

HRs: Hazard ratios

MeSH: Medical subject headings

N: Number of studies

n: Number of patients

NCI: National Cancer institute (United States)

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SCC: Squamous cell carcinoma

ABSTRACT (word count: 250)

Objective: Centralization of health care has been a matter of debate, especially for advanced cancer surgery. Clear short-term mortality benefits were described for oesophageal cancer surgery conducted at high-volume hospitals and by high-volume surgeons. However, the impact of volume on long-term survival after oesophagectomy remains unclear.

Design: The systematic literature search included PubMed, Web of Science, Cochrane library, EMBASE, and Science Citation Index, and considered the period 1990-2013. Eligible articles were those which reported survival (time to death) as hazard ratios (HRs) after oesophagectomy for cancer by hospital volume, surgeon volume, or hospital type. The fully adjusted HRs for the longest follow-up were the main outcomes. Results were pooled by means of meta-analysis, and reported as HRs and 95% confidence intervals (CIs).

Results: Sixteen studies from seven countries met the inclusion criteria. These studies reported hospital volume (N=13), surgeon volume (N=4) or hospital type (N=4). A survival benefit was found for high-volume hospitals (HR 0.82, CI 0.75-0.90), and possibly also for high-volume surgeons (HR 0.87, CI 0.74-1.02) compared to their low-volume counterparts. No association with survival remained for hospital volume after adjustment for surgeon volume (HR 1.01, CI 0.97-1.06; N=2), while a survival benefit was found in favour of high-volume surgeons after adjustment for hospital volume (HR was 0.91, CI 0.85-0.98; N=2).

Conclusion: This meta-analysis demonstrated better long-term survival (even after excluding early deaths) after oesophagectomy with high-volume surgery, and surgeon volume might be more important than hospital volume. These findings support centralization to fewer surgeons working at large centres.

SUMMARY BOX

What is already known about this subject?

- Oesophageal cancer has a very poor prognosis, with a 5-years survival of only 30% after complete oesophageal cancer resection (oesophagectomy).
- Oesophagectomy is one of the most complex surgical procedures, entailing a substantial risk of severe postoperative complications.
- Short-term mortality (in-hospital and 30-day postoperative) has shown to be lower if operated in high volume hospitals and/or by high volume surgeons. Yet, 95% of all patients survive the first 30 days after surgery.
- Based on these differences in short-term mortality, centralisation of oesophagectomy within centres of excellence has been recommended and adopted in many countries.

What are the new findings?

- This meta-analysis demonstrated a better long-term survival after oesophagectomy with high-volume surgery.
- Surgeon volume seems to be more important than hospital volume.

How might it impact on clinical practice in the foreseeable future?

- Differences in long-term survival imply an ever greater benefit of centralisation in number of patient years than already presumed based on short-term mortality, since the mortality followed by such surgery is strongly dominated by deaths from tumour recurrence rather than procedure-related complications.

INTRODUCTION

Centralization of complex cancer surgery is a topic of debate in several countries. Such centralization can improve care by collating multidisciplinary expertise and experience, as well as specialized equipment within centres of excellence, and will impact the health care budget. Treating more patients should improve the skills of the medical team, and adapting specific treatment procedures should facilitate and improve patient-tailored care. However, the benefit of such centralization should be weighed up against the potential disadvantages for patients, e.g. long travel times and social isolation.[1] Oesophageal cancer surgery is one of the most complex surgical procedures, entailing a substantial risk of severe postoperative complications, and a convincing benefit of centralization of has been shown for short-term mortality (in-hospital and 30-day post-operatively) for this surgery.[2-7] However, the existing data addressing oesophageal cancer surgery volume in relation to long-term survival is limited, and the results from individual studies are contradictory.[7] Moreover, the influence of tumour stage has not always been taken into account in previous research, which is of major concern whenever long-term mortality is the outcome. Thus, the impact of surgery volume on long-term survival after oesophageal cancer remains to be established. Such knowledge would be of clinical importance since tumour recurrence in oesophageal cancer is common, resulting in an approximately 60-70% risk of death within 5 years of surgery.[8, 9] The objective of this study was to clarify the association between hospital volume, surgeon volume and hospital type in relation to long-term survival after oesophagectomy for cancer, by means of a meta-analysis.

METHODS

This was a systematic review and meta-analysis analysing differences in long-term survival between high-volume and low-volume hospitals and surgeons after oesophagectomy for cancer. The available literature was identified and examined by means of a systematic review and survival meta-analysis. The results are reported in accordance with the PRISMA guidelines ('Preferred Reporting Items for Systematic Reviews and Meta-Analyses').[10] The study followed an a priori established study protocol.

Exposure and outcome

The main exposure was surgery performed in either low- or high-volume hospitals, as defined by the authors of the included studies. Other examined exposures were surgeon volume (low or high) and type of hospital (e.g. university or non-university). Both surgeon and hospital volume were measured as the average annual number of oesophagectomies per year (e.g. more or less than 10 procedures/per year). The group with the lowest volume or non-university was used as reference category. If an included study reported hazard ratios (HRs) for different surgical volume groups, only the lowest and highest volume group were compared and reported in the forest plots. The study outcome was the time to death after the oesophagectomy, defined by a minimal period of follow-up of the study cohort of three months.

Data sources and searches

The primary data sources screened were PubMed and the Web of Science. The search string in these databases consisted of four parts: (1) the anatomical location of interest (i.e. oesophagus, oesophagectomy, and oesophageal), (2) surgery,

surgical or cancer, (3) outcome, mortality, survival or prognosis, and (4) volume, determinants or predictors. Different spelling was accounted for, and medical subheadings (MeSH) were incorporated in the PubMed search. Complementary searches were performed through analyses of reference lists, the Science Citation index, Cochrane library, EMBASE, and searching for relevant publications of 'expert' authors (known or identified to have published in the field of surgery volume).

Study selection

The time period for publications was limited to January 1990 to September 2013, a period which we considered to represent modern oesophageal cancer management. The search method to identify all relevant articles was discussed and developed by 2 authors (NB and JL) and the final search string was approved by all authors. The initial search was performed by one reviewer (N.B.) who eliminated clearly irrelevant articles based on the title and abstract as defined by the pre-set selection criteria. The final selection of the articles was made by mutual consideration of all authors, based on the reporting of all necessary data and in accordance with the pre-defined inclusion and exclusion criteria.

Inclusion and exclusion criteria

Studies that provided original data on survival of patients who underwent oesophagectomy for malignancy were included. Abstracts or other conference proceedings, case reports, case series, intervention studies and review articles were excluded. Both prospective and retrospective studies were eligible. Articles describing oesophagectomy for non-malignant reasons were excluded, as well as studies only reporting a subgroup of oesophagectomy patients. If studies also

reported survival after gastric cancer surgery, survival for oesophageal cancer needed to be reported separately, otherwise the study was excluded. A language restriction was only applied in the end-stage of the search, to enable assessment of language selection bias. The languages selected a priori as eligible were English, French, Dutch, German, Spanish, Swedish and Chinese. Studies were eligible only if HRs comparing survival after oesophagectomy by hospital or surgeon volume groups, or by hospital type were reported. The minimum reported follow-up time was three months.

Data extraction and quality assessment

The following data were collected (if available): study and population characteristics, type of surgery and hospital characteristics. Assessment of quality and generalizability was based on the key domains considered fundamental for observational studies.[11] From each article, the crude HRs were extracted (if reported), as well as the HRs based on the most fully-adjusted regression models for the longest duration of follow-up. If several volume groups were reported, the most extreme comparison, i.e. highest versus lowest reported volume, was considered the primary result. If possible, the HR for hospital volume adjusted for surgeon volume was extracted as well as the most fully-adjusted model without adjustment for surgeon volume. The same approach was taken for surgeon volume and adjustment for hospital volume. If HRs were reported including and excluding “early” mortality, defined as within three months of surgery, both HRs were extracted, but the HR including the full follow-up period was considered the main result.

Data synthesis and analysis

This survival meta-analysis pooled the HRs based on hospital volume, surgeon volume and hospital type. Sub-analysis was based on duration of follow-up, inclusion or exclusion of early mortality, and reported regression models. Random-effect meta-analyses were performed with STATA (StataCorp, version 12·1/MP4), and were based on the HRs and standard errors. The values were reported by means of forest plot, and uncertainty of the pooled estimates was quantified by 95% confidence intervals (95% CI). If no standard error was reported, it was calculated based on the 95% CI, number of patients or reported p-values.[12, 13] The presence of small study effects and publication bias was evaluated by funnel plots and Egger´s regression asymmetry analysis.[14] Statistical heterogeneity was assessed by means of Cochran's Q test and I-squared test. The I-squared represents the percentage of variation attributable to heterogeneity, which is usually categorized as low (25-50%), moderate (51-75%), or high (>75%).[15]

RESULTS

Description of the included studies

The search was finalized on September 10th 2013, and included a total of 2392 publications as shown in the Appendix. The search resulted in 16 eligible studies. Only 1 potentially eligible Japanese study was excluded because of the language restriction.[16] These were from the United States (N=4),[1, 17-19] Sweden (N=4),[20-23] the Netherlands (N=3),[24-26] the United Kingdom (N=2),[27, 28] Australia (N=1),[29] Canada (N=1)[30] and Japan (N=1).[31] The longest reported follow-up was 23 years.[20] Thirteen studies reported HRs for survival by hospital volume groups (n= 39,761),[1, 17, 20-24, 26-31] four by surgeon volume (n= 2,874),[20, 22, 26, 27] and four by hospital type (n= 13,433).[18, 19, 25, 26] Two of the three Dutch studies described the same nationwide cohort, once for hospital volume and once for hospital type,[24, 25] and there was some overlap with the third (regional) study.[26] The studies from the United Kingdom did not overlap.[27, 28] Some overlap was possible in the four American studies.[1, 17-19] The study periods of the three oldest (nationwide) Swedish studies partly overlapped.[21-23] An overview of the main study characteristics is presented in Table 1, and a quality assessment is shown in Figure 1. All but three studies [17, 18, 27] were population-based, and 10 studies were nationwide. Eight studies also described other cancer types. Mean or median age of operated patients ranged from 63 to 66 years, as reported in four studies.[1, 20, 21, 30] The proportion of male patients, as reported in nine studies, ranged from 71 to 83%. Four studies reported the proportion of the main histological types: adenocarcinoma (26-75%) and squamous cell carcinoma (22-66%).[20, 21, 24, 25]

Hospital volume and long-term survival

All 13 studies addressing hospital volume reported adjusted HRs. One study considered hospital volume as a continuous variable (HR for an increase of 10 oesophagectomies per year) and reported only HRs adjusted for surgeon volume.[27] Another study reported HRs both including and excluding adjustment for surgeon volume.[20] Ten studies reported HRs for the complete survival period, two of which also reported HRs excluding mortality within the first two months of surgery,[1] or as "survived surgery" (not specified).[17] Three studies reported only HRs excluding early mortality, i.e. the first two,[23] three,[20] or six[24] postoperative months.[20] Six studies adjusted for tumour stage.[1, 17, 20, 22, 24, 31]

The pooled adjusted HRs of mortality in 12 studies (excluding the study adjusting for surgeon volume)[27] was 0.82 (95% CI 0.75-0.90) in favour of high-volume hospitals (Figure 2). The statistical heterogeneity was moderate (I^2= 68.0%). Sub-analyses are presented in Table 2, showing a pooled HR of 0.76 (95% CI 0.68-0.84) in studies adjusting for tumour stage. The seven studies with the longest complete follow-up (over 3 years) showed an HR of 0.77 (95% CI 0.69-0.87), and a survival benefit remained after exclusion of early mortality (HR 0.85, 95% CI 0.75-0.95) (Table 2). In the two studies reporting complete follow up, and follow-up without early mortality,[1, 17] the HRs were 0.75 (95% CI 0.69-0.81) and 0.78 (95% CI 0.71-0.85), respectively, and I^2=0%. In the two studies that adjusted for surgeon volume, the HR was 1.01 (95% CI 0.97-1.06, I^2=0%) (Figure 2).

There was no evidence of publication bias or small-study effects bias (p=0.313) (funnel plot not shown).

Surgeon-volume and long-term survival

The four studies that reported HRs for surgeon volume also reported hospital volume.[20, 22, 26, 27] In one study, surgeon and hospital volume were equivalent since all oesophagectomies were performed by one surgical team led by one surgeon per specialized regional centre.[26] One study reported the HR for surgeon volume adjusted for hospital volume as a continuous variable.[27] Another study reported HRs with and without adjustment for hospital volume.[20] One study reported both hospital and surgeon volume, but did not conduct any mutual adjustment for these variables.[22] Only one study excluded early mortality (within three months of surgery).[20] The follow-up time ranged from 2 to 23 years.[20, 22, 26, 27] Only two studies adjusted for tumour stage.[20, 22]

As presented in Figure 3, the pooled adjusted HR for surgeon volume was 0.87 (95% CI 0.74-1.02) in favour of high surgeon volumes. After further adjustment for hospital volume, the pooled HR was 0.91 (95% CI 0.85-0.98). Statistical heterogeneity in both analyses was low (I^2=0%).

There was no evidence for publication bias or small-study effects bias (p=0.150) (funnel plot not shown).

Hospital type and long-term survival

Four studies analysed hospital type in relation to survival after oesophagectomy.[18, 19, 25, 26] It was not possible to calculate a pooled HR because of clinical heterogeneity between these studies (Figure 4).

DISCUSSION

This meta-analysis indicates a survival benefit in favour of high-volume hospitals and high-volume surgeons compared to the low-volume equivalents. No independent risk reduction remained for high hospital volume after adjustment for surgeon volume, while high surgeon volume remained beneficial after adjustment for hospital volume. Strengths of meta-analyses include the fact that they facilitate objective evaluation and pooling of different study populations, enable analyses of large and diverse cohorts of patients, and summarize the available evidence up to a certain time point. Inherent limitations of meta-analyses are that results depend on the availability, quality and methods of the published studies, and they might be hampered by publication bias as well as clinical and statistical heterogeneity. However, there was no evidence of publication bias in this study, and the statistical heterogeneity was low to moderate. Language bias cannot be ruled out completely since we based our search on English-language dominated sources. Only one potentially eligible study was excluded because of the language, [16] but this Japanese study was conducted by the same group of an included study.[31] Moreover, even after implementing strict inclusion criteria, a considerable clinical heterogeneity remained between study populations. Moreover, meta-analyses assessing long-term survival are more complex than those evaluating short-term mortality, because of the need to take duration of survival and variation in follow-up time into account.

Despite the heterogeneity between studies, this study provides evidence of improved long-term survival when the oesophagectomy is conducted at high-volume hospitals and by high-volume surgeons. This distinction of early mortality from long-term mortality enables comparison of the underlying mechanisms; when patients die early

after surgery it is usually due to complications, while later deaths are typically related to cancer recurrence. This study showed that even after excluding the first months after surgery, a 15% benefit in favour of high-volume hospitals remained, indicating that surgery volume influences the risk of tumour recurrence. These findings support centralization of oesophageal cancer surgery to fewer surgeons working at centres of excellence in this field.[32-34] The discussion on which hospital and surgeon volume should be recommended cannot be answered by this study. As in other meta-analyses [2, 6] we compared the largest volume group with the lowest volume group when different thresholds were used, so based on this study design we cannot define a recommended quantity of annual oesophagectomies by hospital or surgeon. The findings of the present study complement previous meta-analyses evaluating short-term mortality after oesophagectomy, with pooled odds ratios of 0.20-0.40 for high-volume hospitals compared to low-volume hospitals.[2, 4, 6, 35] However, deaths from tumour recurrence after oesophageal cancer surgery are far more common (60-70%) than deaths occurring during the initial postoperative period (<5%), stressing the relevance of evaluating surgery volume in relation to longer-term survival. Yet, this issue has been addressed only in a few systematic reviews,[4, 6, 36-38] and one meta-analysis based on four studies.[6] The previous meta-analysis showed an odds ratio of survival of 1.17 (95% CI 1.05-1.31) in favour of high-volume hospitals, but it did not take time to death into account.[6] Nevertheless, the finding of that meta-analysis is in line with the results of the present study.

An important, yet complex, question is the underlying mechanism of the findings of this study, and if hospital and surgeon volumes should be considered separate entities or merely proxies of each other. The surgery volume effect might be due to

the total package of multidisciplinary teams, advanced diagnostics, treatment and care, or alternatively, it might mainly be due to the experience and expertise of the surgeon and the surgical team. This study found no association between hospital volume and survival when considering only the two studies adjusting for surgeon volume, but interestingly, the influence of surgeon volume remained after adjusting for hospital volume. Although based on a small number of studies, this might suggest a more important role of surgeon volume than hospital volume.

It is important to point out that survival not only depends on surgery volume.[39] Substantial logistical and case-mix differences exist between countries, especially considering geographical distances and tumour incidence. A related question is if the patient population and case-mix, particularly regarding tumour stage and socio-economic status, are similar between volume groups.[40, 41] In an attempt to adjust for such confounding, we only included the most adjusted regression models. The six studies including adjustment for tumour stage, the strongest prognostic factor, showed a larger effect than those which did not adjust (24% versus 9%), which indicates robustness of the findings of the present study.

The size of the effect of high surgery volume in relation to long-term survival after oesophageal cancer surgery is not negligible. The effect size is similar to the effect of pre-operative oncological therapy that has been demonstrated in recent large meta-analyses,[42] and neoadjuvant therapy has therefore become routine clinical practice in the treatment of these patients in most countries. It therefore seems logical that centralization of this surgery should be a prioritized measure to improve the prognosis in oesophageal cancer.

To conclude, this meta-analysis of long-term survival after oesophageal cancer surgery showed an 18-25% and 9-13% improved survival for high-volume hospitals and high-volume surgeons respectively, compared to their low-volume counterparts. This difference in survival was not solely due to a decreased early postoperative mortality, since even after exclusion of early deaths, a 15% benefit was observed. Surgeon volume appears to be more strongly related to survival than hospital volume.