



Effects of improving outcomes after esophagectomy on the short- and long-term: a review of literature

Laura F. C. Fransen, Misha D. P. Luyer

Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands

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Correspondence to: Laura F. C. Fransen, MD; Misha D. P. Luyer, MD, PhD. Department of Surgery, Catharina Hospital, 5623 EJ, Eindhoven, The Netherlands. Email: laura.fransen@catharinaziekenhuis.nl; misha.luyer@catharinaziekenhuis.nl.

Abstract: An esophagectomy is still correlated with a high morbidity rate, despite advances made in minimally invasive surgery, enhanced recovery after surgery (ERAS) and centralization of this type of surgery. The short-term benefits are clearly described for esophageal cancer surgery patients, however, the long-term effects are yet to be determined. In colorectal cancer, the association between complications, especially anastomotic leakage, shows detrimental effects on long-term survival and cancer recurrence. In esophageal cancer surgery, current evidence is scarce and the described results are conflicting. Optimization of perioperative care by introduction of minimally invasive surgery, ERAS programs and patient prehabilitation is promising and shows a clear effect on short-term outcomes. Potentially, this may also result in better outcomes on the long-term, although current evidence is insufficient to infer definite conclusions. Reduction of anastomotic leakage seems important to reduce risk of cancer recurrence and improve long-term outcome.

Keywords: Esophagectomy; enhanced recovery after surgery (ERAS); minimally invasive surgery; complications; long-term survival

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Introduction

An esophagectomy is the cornerstone for curative treatment of esophageal cancer, however, the procedure is technically challenging and associated with postoperative morbidity and mortality (1,2). Many advancements have been made over the past decade, such as implementation of enhanced recovery after surgery (ERAS) programs and minimally invasive surgery, leading to a reduction of postoperative complications (3-6). Nevertheless, postoperative morbidity remains substantial with anastomotic leakage and pulmonary complications being the most frequent and feared complications (7).

In colorectal cancer surgery has been found that postoperative complications not only result in impaired short-term outcomes, but are also associated with increased

local recurrence and reduced long-term survival rates, especially for postoperative anastomotic leakage (8,9). Similar to the effect found in colorectal cancer surgery, anastomotic leakage after an esophagectomy seems to lead to an increased risk of cancer recurrence (10).

Although this indicates that postoperative complications following esophagectomy affect long-term survival and early cancer recurrence, the overall evidence is scarce and has conflicting results (11-15). Furthermore, most available literature has been published before introduction of minimally invasive esophagectomy (MIE) and implementation of ERAS programs (3,5,6).

Here, we describe the effects of recent advancements in perioperative care on short- and long-term outcome following esophagectomy.

Improvements on short-term outcomes and survival

Improvement in perioperative care

After successful implementation of ERAS programs in colorectal cancer patients, ERAS has been widely implemented in different types of major abdominal surgery with comparable beneficial results (6,16-20). The described gains in short-term outcomes include similar or decreased complication and mortality rates, reduction in length of hospital stay, less intensive care unit (ICU) (re)admission, similar or decreased hospital readmission and reduction of hospital costs (16-19). Also in patients undergoing an esophagectomy, introduction of an ERAS program resulted in a reduction of overall complications, reduced length of ICU stay and length of hospital stay, and a reduction of hospital costs without an increase in readmission rate or a decrease in patient satisfaction (5,6,20).

The combination of all elements in the ERAS program, such as early mobilization, short acting pain medication and adherence to the ERAS program, are key factors for success (5,16). Early start of oral intake is an important part of ERAS programs, but remains a matter of debate for patients that underwent an esophagectomy (5,6). In many types of abdominal surgery has been found that early enteral or oral feeding reduces the risk of any type of infection and decreases mean length of hospital stay when compared with nil-by-mouth (16). However, following an esophagectomy, patients are often kept nil-by-mouth due to the fear of increasing anastomotic leakage and pulmonary complication rate.

The above-mentioned short-term benefits of ERAS programs for esophagectomy patients are evident, however, the potential effects on the long-term remain to be investigated. Adherence to an ERAS program of 70% or more in colorectal cancer surgery patients was found to lower the risk of 5-year cancer-specific death by 42% when compared with patients that were less adherent (21). Though, the current available evidence is insufficient to determine whether the favorable short-term outcomes of ERAS after major abdominal surgery will also be applicable on the long-term (22).

In colorectal cancer patients undergoing surgery it is suggested that the number and severity of complications are not only related to perioperative care, but are also largely influenced by the preoperative performance status of patients (23). Prehabilitation is aimed to improve preoperative performance status, thereby enabling patients

to better withstand the upcoming surgical stress (24,25). A systematic review on prehabilitation in major abdominal surgery showed an overall reduction in postoperative complication rates with a greater effect of multimodal prehabilitation programs (26). Although prehabilitation has been shown to result in a significant reduction of pulmonary complications and length of hospital stay in patients undergoing a pancreatoduodenectomy, the benefit in improved clinical outcomes for esophagectomy patients has not yet been demonstrated (25,27,28).

Currently, the efficacy of prehabilitation in patients scheduled to undergo an esophagectomy is lacking. New studies in esophageal cancer patients investigating the effect of prehabilitation on postoperative outcomes have to be awaited (29).

Finally, introduction of MIE has been shown to reduce pulmonary complications, surgical stress and pain, and results in less blood loss and less vocal-cord paralysis while improving quality of life on the short-term (3). In this study, no differences were shown in disease-free and overall 3-year survival in the MIE group compared with the open esophagectomy group (30).

Surgical volume and complications

Surgical volume per center may also be directly related to postoperative outcome. Centralization of a different type of complex abdominal surgery showed significant improvement in survival rates for patients operated in high-volume centers (>20 procedures yearly) (31). For esophagectomy patients, a significant decrease in mortality was found when they were operated on in a high-volume center (32). Also, a significant independent association was found between the development of severe anastomotic leakage with low hospital procedural volume (10). Interestingly, only when annual hospital volume was increased up to 60 esophagectomies per year a plateau in mortality was found (33). Also, centralization of emergency esophageal perforation to high volume centers showed a reduction in 30- and 90-day mortality (34). This might be related to the need for a sufficient amount of surgeon volume to progress through the learning curve (35). Hospital readmission within 30 days, assessed in patients that underwent a colectomy, was inversely associated with hospital procedural volume, but not surgeon volume (36). Since early readmission is a potentially modifiable factor and significantly associated with worsened short- and long-term survival in patients undergoing major abdominal surgery (i.e., colectomy and esophagectomy patients), it emphasizes the

importance of reducing complications (36-38).

Effect of complications on long-term survival

Although the negative effect of complications on short-term outcome has received a lot of attention, the question remains whether the presence of postoperative complications also influence long-term outcomes.

In colorectal cancer it has been described that postoperative complications lead to a reduced long-term survival and might lead to a higher (local) recurrence rate, especially for postoperative anastomotic leakage (9,39,40). However, the available evidence of the influence of postoperative complications following esophagectomy on long-term survival and cancer recurrence is scarce and results are conflicting (11-15,41). Previously, a meta-analysis in major surgery showed postoperative complications to be related with overall survival (42). However, this meta-analysis included two esophagectomy cohort studies (of which one study was not analyzed due to poor methodological quality) showing no relation between postoperative complications and survival (12,42,43). Next, two subsequent trials in esophagectomy patients concluded that perioperative complications did not influence long-term survival (13,14).

On the other hand, several studies found that postoperative complications following esophagectomy predicted a worsened long-term survival for surgical patients (15,44,45), adding to the ambiguity of the relation between these two variables. It is yet unknown what factors are important in the found differences.

Pulmonary complications are the main contributor to postoperative morbidity in esophagectomy patients, accounting for up to 31% of all postoperative complications (1,20). In a cohort of 118 patients undergoing an extended esophagectomy for squamous cell carcinoma, Kinugasa *et al.* found a correlation between pneumonia and increased in-hospital mortality and poorer 5-year overall survival; respectively 26.7% and 53.4% for patients with and without pneumonia (46). However, a single-center study of 341 patients undergoing a radical, open transthoracic esophagectomy for both adenocarcinoma and squamous cell carcinoma found no association between Clavien-Dindo classified pulmonary complications and disease free survival (47).

Whereas effects of pulmonary complications after an esophagectomy on long-term survival are conflicting, anastomotic leakage has consistently been found to have

a negative impact long-term survival (48). Kofoed *et al.* described a significantly lower long-term survival after intrathoracic anastomotic leakage, even when patients fully recovered after the leakage (49). Another study showed a similar negative prognostic effect of anastomotic leakage after curative resection for gastric or esophageal cancer, together with an independently associated high risk of recurrence (50). A large multicenter study showed that severe esophageal anastomotic leakage (Clavien-Dindo grade III or IV leak) adversely impacts cancer prognosis, leading to a significant reduction in median overall and disease-free survival (10). Only one small, single center study from 2010 found no influence of anastomotic leakage on long-term survival (51). However, the absence of a uniform complication grading system, such as the Clavien-Dindo classification, makes it difficult to compare these results with other studies (52).

It has to be noted that most available literature on long-term effects of complications has been published before introduction of MIE and implementation of ERAS programs (3,5,6). If these improvements are effective and would further decrease complication rate, it might be possible that effects of postoperative complications are smaller than previously expected. Also, the large variety between studies due to difference in investigated histology (squamous cell and/or adenocarcinoma), potential difference in surgeon experience by low institutional volume (44), lack of predefined definitions for complications (44,46) and a period of at least 5 years for patient inclusion (12-14,43-48,50-52), make it more difficult to interpret the results of complications on long-term outcomes.

Conclusions

Optimization of perioperative care by introduction of minimally invasive surgery, ERAS programs and patient prehabilitation is promising and shows a clear effect on short-term outcomes. Potentially, this may also result in better outcomes on the long-term, although current evidence is insufficient to infer definite conclusions. Reduction of anastomotic leakage seems important to reduce risk of cancer recurrence and improve long-term outcome.

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Footnote

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