



Reducing pulmonary complications after esophagectomy for cancer

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Abstract: The cornerstone of curative care for esophageal cancer is neoadjuvant chemoradiotherapy followed by esophagectomy with a radical lymphadenectomy. An esophagectomy is a major and complex surgical procedure and is often followed by postoperative morbidity, especially pulmonary complications. These complications may lead to an increase in hospital stay, intensive care unit admission rate and mortality. Therefore, perioperative strategies to reduce these complications have been investigated and implemented in clinical practice. In this review we highlight the influence of minimally invasive surgery, postoperative pain management, early identification of complications and the usage of uniform definitions on (pulmonary) complications after esophagectomy. Finally, we will discuss some future perspectives.

Keywords: Esophagectomy; surgery; postoperative morbidity; ERAS

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Introduction

Esophageal cancer has a fast-growing incidence. Currently it is the eight most common cancer worldwide, with 456,000 patients diagnosed each year. Moreover, it is an aggressive disease, illustrated by the annual worldwide cancer-related mortality rate of approximately 406,800. The cornerstone of curative care for esophageal cancer is neoadjuvant chemoradiotherapy followed by esophagectomy with a two-field lymphadenectomy. Although many advances in surgical techniques have already been made, postoperative morbidity remains high, with morbidity and mortality incidences reported up to 65% and 15% respectively. Especially pulmonary complications are frequently observed after esophagectomy, leading to an increased hospital- and intensive care unit stay. In this paper we review the influence of minimally invasive surgery, postoperative pain management, early identification of complications and the usage of uniform definitions on (pulmonary) complications

after esophagectomy. Finally, we discuss some future perspectives.

Minimally invasive surgery

Minimally invasive surgery has become the standard of care in many surgical procedures. The use of minimally invasive techniques may reduce blood loss, postoperative pain and complications. This generally leads to a shorter hospital stay and an improved quality of life. Nevertheless, the standard surgical approach for esophagectomy has always been by means of a laparotomy or a combined laparotomy and thoracotomy (1). The first thoracoscopic esophagectomy was performed in 1992 by Sir Alfred Cuschieri, a pioneer in minimally invasive surgery (2). Subsequently, the safety and feasibility of MIE were demonstrated by case series (3,4). The only randomized controlled trial comparing open and conventional minimally invasive esophagectomy published to date (TIME trial) demonstrated a shorter hospital stay,

a reduction of postoperative pulmonary infections and a better short-term quality of life in favor of the minimally invasive group, without compromising radicality and lymph node yield (5). Also a hybrid approach may reduce postoperative complications after esophagectomy when compared to an open approach (6). Although several studies demonstrated comparable short-term benefits of minimally invasive esophagectomy when compared to the open approach, some population-based studies were unable to identify a difference in the pulmonary complication rate and even showed increased rates of anastomotic leakage and reintervention in patients who underwent a minimally invasive esophagectomy (7-10). A possible explanation for these findings might be the rapid introduction and wide implementation of minimally invasive esophagectomy, which carries a significant learning curve. A multicenter retrospective study showed that the learning curve of minimally invasive esophagectomy with an intrathoracic anastomosis was over 100 cases to reach a plateau incidence of anastomotic leakage, despite the fact that all participating surgeons were already experienced in minimally invasive esophagectomy with a cervical anastomosis before transiting (11). These outcomes warrant more dedicated proctor programs and additional research to investigate how learning associated morbidity may be further reduced and preferably eliminated. The benefits of minimally invasive surgery will expectantly start to show after learning curve completion.

Within minimally invasive esophagectomy, a variety of performance shaping factors may influence postoperative outcomes. The first thoroscopic esophagectomy was performed with the patient in left lateral decubitus position. To improve the exposure of the posterior mediastinum and obtain better ergonomic results, some surgeons suggested changing the left lateral decubitus position to a prone position. Nevertheless, conversion to open surgery may be easier in left lateral decubitus position. The semiprone position, combining “the best of both worlds”, has been proposed as an alternative and was found to be at least comparable to a prone positioning in terms of oncological quality and occurrence of postoperative complications (12). Minimally invasive esophagectomy may be further facilitated by using robotic assistance (13,14). Besides its ergonomic benefits, robotic assistance enables the surgeon to reach the upper mediastinum and thoracic aperture with more ease (15). This facilitates an extended lymphadenectomy along the recurrent laryngeal nerves, which may increase the chances of long-term

disease-free survival. The recently published ROBOT trial, a randomized controlled trial comparing open esophagectomy versus robot-assisted minimally invasive esophagectomy (RAMIE), clearly demonstrates the benefits of the robotic approach (16). RAMIE was associated with less intraoperative blood loss, a lower overall postoperative complication rate, a shorter length of hospital stay, better short-term quality of life, and a faster functional recovery when compared to open esophagectomy (16). In combination with comparable lymph node yield, radicality, and survival, one can conclude that RAMIE is effective in reducing postoperative complications while maintaining high oncological standards (16). The use of RAMIE may also open new indications for curative surgery in patients with T4b tumors, high mediastinal tumors and lymph node metastases after neoadjuvant treatment (15,17).

Perioperative care

Over 50% of all patients will develop one or more complications after esophagectomy, which frequently involves pulmonary complications. To reduce the risk of developing postoperative pulmonary complications, adequate breathing and early mobilization should be facilitated. Effective postoperative pain management is essential context (18). Epidural analgesia is the current gold standard following esophageal surgery, as it was associated with better pain control, less pneumonia, and a lower mortality rate when compared to intravenous opioids in patients who underwent open transthoracic esophagectomy (19). However, due to the inherent bilateral block of sympathetic nerves, epidural analgesia can cause hypotensive events that may hamper mobilization and thereby counteract an important benefit of adequate pain control. Paravertebral analgesia has been suggested as an alternative, as it can conceptually induce a satisfactory unilateral sensory block while avoiding bilateral block of sympathetic nerves. In a Cochrane review that compared epidural versus paravertebral analgesia in patients who underwent thoracotomy procedures, pain control was comparable between these techniques and paravertebral analgesia was associated with less hypotension, nausea, urinary retention, and itch (20). Although prospective series are lacking for patients undergoing esophageal surgery, a retrospective study found that paravertebral analgesia was associated with less need for inotropic support and shorter length of stay on the intensive care unit when compared to epidural analgesia for pain control after open

esophagectomy (21). The implementation of paravertebral analgesia in the context of an enhanced recovery protocol has also been described (22). As these results are promising, more research is warranted to investigate the potential merits of paravertebral block in esophageal surgery, preferably in the setting of a randomized prospective trial.

Besides pulmonary complications, other problems such as anastomotic leakage, atrial fibrillation, and chylothorax are common after esophagectomy. Once complications occur, early identification and treatment is essential to minimize the failure to rescue rate. Early recognition of complications limits the development of the systemic inflammatory response syndrome, consequently reducing the severity of encountered complications (23). Postoperative complications may have linked pathophysiology, and therefore can also function as an early warning sign. For example, atrial fibrillation is a frequently encountered complication after esophagectomy and is rarely seen in isolation. Atrial fibrillation is frequently associated with pneumonia and anastomotic leakage (24-27). This implies that, atrial fibrillation may be of predictive value and it therefore seems advisable to have a low threshold for initiation of additional diagnostic work-up in case signs of cardiac arrhythmia are observed after esophagectomy. Also, recurrent laryngeal nerve injury and pulmonary complications have a linked pathophysiology. It has been demonstrated that recurrent laryngeal nerve injury increases the chance of aspiration pneumonia and therefore requires extra attention (28,29). In addition, recurrent laryngeal nerve injury has a relatively high impact on long-term outcomes (30). Up to a quarter of all patients who suffer from recurrent laryngeal nerve paralysis after esophagectomy require vocal cord surgery within a year after esophagectomy (30). This is an extra argument to make a serious effort to minimize recurrent laryngeal nerve injury during esophagectomy.

Outcome definitions

Before 2015, no widely accepted system existed for the documentation of complications that are associated with esophagectomy. As a result, widely varying definitions for complications were used, making comparisons between studies difficult (31). Although the publication by Low *et al.*, in which the most frequently encountered postoperative complications were standardized, has been a major step in developing standardized and uniformly used definitions for complications after esophagectomy for cancer, it still

does not cover all definitions (32). An uniform definition for post esophagectomy pneumonia, which is highly frequent observed, is lacking. The Uniform Pneumonia Score fills this gap (33). The Uniform Pneumonia Score is the only objective to precisely define pneumonia after esophagectomy and was validated in Europe and North-America (34,35). Taking this into account, it remains questionable whether the Uniform Pneumonia Score will also function in an Asian population. Patients in Western society are usually older and have a different set of comorbidities, such as those associated with obesity (36). Furthermore, squamous cell carcinoma is more frequent in Asia and patients more often present with early stage cancer as a result of active screening programs (36,37). This affects decision making regarding neoadjuvant regimens, which consequently affects the postoperative course. Next to tumor- and patient related factors, the health care system and the clinical decision making in Asian society is different from western society. Validation of the Uniform Pneumonia Score in an Asian population would therefore be most valuable and should preferably be carried out by independent researchers. However, despite lacking validation studies for Asian populations, the Uniform Pneumonia Score is the best available definition for pneumonia after esophagectomy that has been published to date and is therefore strongly recommended for use in future research.

Conclusions and future perspectives

Several important aspects of perioperative care in esophageal cancer surgery are addressed in this review. As already pointed out above, it would be valuable to validate the Uniform Pneumonia Score in an Asian population. If the Uniform Pneumonia Score is indeed also valid in Asian populations and will be used as a standard definition in research worldwide, this may reveal the true effectiveness of intra- and perioperative strategies to reduce pneumonia after esophagectomy by allowing fair comparison of literature.

The next step for minimally invasive esophagectomy will be its further implementation and centralization. The outcomes of minimally invasive esophagectomy may be improved by centralization of esophageal cancer care (38). One may compare surgery to sports: extended experience and practice will lead to better results. This applies not only to the surgeon, but to all health care professionals involved in the esophageal cancer care chain. In order to achieve safe implementation of minimally invasive esophagectomy it is

pivotal to follow strict guidelines and proctor programs (39). At the same time, further improvement of minimally invasive esophagectomy may be achieved with robotic assistance. Although robotic assistance may improve outcomes for both the surgeon (ergonomics) and the patient, costs are currently high. Not many companies produce surgical robots at this moment, which hinders healthy forces of supply and demand. More competition on this market will decrease costs and facilitate the further implementation and development of robotic surgery. In terms of future developments in robotic surgery, one could think of augmented reality. Augmented reality allows you to still keep in touch with the real world, while at the same time adding an extra layer. This technique can be used to construct a virtual image, like a CT-scan or MRI that may overlap a real-time camera feed. For example, this may enable the surgeon to visualize the location and extent of a tumor in relationship to its surrounding structures. In addition, the creation of a three-dimensional panorama by the stereoscopic camera is expected in new robotic surgical system, which can enhance the surgeon's view of the surgical field.

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Footnote

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