Introduction

For patients with locally advanced esophageal cancer, neoadjuvant chemoradiotherapy followed by esophagectomy can achieve a 5-year survival rate of approximately 40–50% (1-3). However, esophagectomy is traditionally associated with considerable postoperative morbidity and mortality (4). Over the last decades, advancements such as centralization of care, development of enhanced recovery protocols, and application of minimally invasive techniques have improved the perioperative outcomes for surgically treated esophageal cancer patients (5-7). Nonetheless, esophagectomy is traditionally associated with considerable postoperative morbidity and mortality (4).

Over the last decades, advancements such as centralization of care, development of enhanced recovery protocols, and application of minimally invasive techniques have improved the perioperative outcomes for surgically treated esophageal cancer patients (5-7). Nonetheless, esophagectomy is traditionally associated with considerable postoperative morbidity and mortality (4). To improve the outcome for patients undergoing esophagectomy for cancer, each perioperative facet needs to be optimized. One of the most recent developments is the introduction of robot-assisted minimally invasive esophagectomy (RAMIE) (9,10). The aim of this review was to describe how RAMIE could contribute to improving perioperative care and outcomes for esophageal cancer patients.

Conventional minimally invasive esophagectomy (MIE)—benefits and limitations

MIE was first described in the 1992 and has since then been increasingly applied for the treatment of patients with esophageal cancer, aiming to improve patient outcome by reducing surgical trauma and its sequelae in terms of immunosuppression (7,11). In the only randomized controlled trial so far (i.e., the TIME trial), MIE was found to be superior to open esophagectomy in terms of intraoperative blood loss, acute immunological response, postoperative pulmonary infections, length of hospital stay, postoperative pain scores, and quality of life (12,13). Furthermore, in contrast to initial concerns regarding the oncological quality of MIE, lymph node yield and 3-year survival were equivalent when compared to open esophagectomy (12,14). These findings were in line with meta-analyses, indicating that MIE provides short-term
advantages and preserves oncological quality (15).

Although MIE seems to improve at least short-term patient outcome, it is a highly complex procedure to master. Especially the thoracoscopic part of MIE is technically demanding when using conventional minimally invasive techniques, which is mostly due to the combination of two-dimensional vision, mirrored intracorporeal movements of the instruments, moving target anatomy, and nearby vital structures that need to be avoided (e.g., aorta, pulmonary veins, trachea, main bronchi). The technical complexity of MIE is emphasized by a recent multicenter study that investigated the learning curve when transiting from MIE with a cervical anastomosis to MIE with an intrathoracic anastomosis (16). Even though all participating centers where experienced in performing MIE with a cervical anastomosis, the learning curve of a minimally invasive intrathoracic anastomosis was found to be as much as 119 cases when taking anastomotic leakage as the parameter of proficiency (16). As the anastomotic leakage rate dropped from 18.8% (first time quintile) to 4.5% (fifth time quintile), the authors concluded that patients are exposed to an increased risk of surgical morbidity during such a learning phase (16). The learning phase of MIE was also considered to be a likely explanation of the higher re-operation rates that were found when compared to open esophagectomy in multiple population-based studies in Japan, the United Kingdom, The Netherlands, and the United States (17–20). Considering these findings, it appears that the technical complexity of MIE requires a substantial learning phase, which may take several years to complete for centers with a relatively low caseload. Effective training programs and the centralization of esophageal surgical care to ensure sufficient case load are probably key to optimize the learning curve. Nonetheless, other technical limitations will remain when using conventional minimally invasive techniques in MIE, such as the fulcrum effect and the limited range of motion of the instrument tips, which might limit the global spread of this technique. This may explain the findings from a survey amongst esophageal surgeons in 2014, which indicated that only 43% of the respondents had reported MIE as their preferred approach (7). A hybrid procedure, which combines a laparoscopic abdominal phase with a conventional thoracotomy for the most challenging part, has been suggested as an alternative to MIE. A randomized controlled trial comparing hybrid versus open esophagectomy has been conducted and its full results are expected to be published soon (21).

**RAMIE vs. open esophagectomy**

Robotic surgical systems were developed to aid in overcoming the technical limitations of conventional minimally invasive surgery. Such systems create an enhanced three-dimensional vision of the surgical field and can translate the surgeon’s natural hand movements into corresponding tremor-less actions of the intracorporeal instruments. RAMIE was introduced in 2003 and found to be a safe technique with good oncological outcomes in the first reported case series (9,10,22). Although these results were confirmed in a systematic review, the available evidence was limited to retrospective and prospective case series at that moment (23). Therefore, the ROBOT trial was conducted, which compared RAMIE to open esophagectomy regarding postoperative morbidity, mortality, and survival (24). A total of 112 patients were randomized in a high-volume tertiary referral center that was experienced in both techniques (24). The primary endpoint was the percentage of overall surgery-related postoperative complications, with complications being defined as those with a modified Clavien-Dindo classification (MCDC) of 2 or higher (24). The overall complication rate was significantly lower in the RAMIE group (59% vs. 80%), which was likely attributable to significantly lower rates of pulmonary complications (32% vs. 58%) and cardiac complications (47% vs. 22%) (25). Furthermore, RAMIE was associated with less intraoperative blood loss, lower postoperative pain scores, faster functional recovery, and better quality of life when compared to open esophagectomy (25). Radicality, lymph node yield, and overall survival did not differ between the groups, indicating that RAMIE offers short-term benefits while maintaining the high oncological standards of an open esophagectomy (25). As these results are in line with the findings from the TIME-trial, one can conclude that RAMIE is superior to open esophagectomy and a good alternative to MIE (12,25). Furthermore, it was reported that RAMIE can safely be performed with the patient in semiprone position (26), which can reduce the incidence of postoperative pulmonary complications (27). The duration of the learning curve for RAMIE has been reported to take 20–70 cases (28–30). One study found that the use of a structured training pathway that involved proctoring reduced the learning curve for RAMIE from 70 to 24 cases (30). In light of the increasing centralization of care, this seems to be a feasible number of cases in order to complete the learning curve within an acceptable time frame.
Despite the positive results from trials in favor of MIE and RAMIE, opponents of using minimally invasive techniques in esophagectomy surgery may emphasize the longer operating time when compared to open esophagectomy (12,25). Although the operating times are indeed longer when compared to open esophagectomy, the short term postoperative outcomes of RAMIE and MIE were found to be superior regardless (12,25). Literature is sparse and controversial regarding the relationship between the duration of surgery and outcomes after MIE (31,32). It therefore seems that limited evidence exists to support the hypothesis that the duration of surgery alone increases the risk of complications after esophagectomy. In combination with clear evidence of superiority of both RAMIE and MIE when compared to open esophagectomy (12,25), a longer duration of surgery should not be the argument to refrain from using minimally invasive techniques from patient outcome perspective.

**Anastomotic technique in RAMIE**

While the construction of a cervical anastomosis is identical for all surgical approaches to esophagectomy, many surgeons experience difficulties when creating an intrathoracic anastomosis during conventional MIE. Although some small case series have reported satisfactory results with a conventional minimally invasive hand-sewn intrathoracic esophagogastric anastomosis, this technique is exceedingly difficult and therefore MIE with a stapled intrathoracic anastomosis has become common practice (33,34). A stapled anastomosis can be made entirely mechanically in circular direction or semi-mechanically in linear direction. Currently available literature suggests that these stapling techniques are comparable regarding anastomotic leakage, while linear stapling might be associated with less benign stricture formation (35). Benign stricture formation is a troublesome long-term complication and prevention of this complication is important, since it can seriously impact the patient’s ability to eat and often requires multiple endoscopic dilatations to resolve (36). Hand-sewing of the esophagogastric anastomosis has been suggested to reduce the incidence of benign stricture formation when compared to stapling, which was demonstrated by two meta-analyses (37,38). As no clear difference was found regarding anastomotic leakage and mortality in these studies (37,38), it could be justified to prefer a hand-sewn anastomosis for the restoration of gastro-intestinal continuity during esophagectomy. Robotic assistance can be of great use in this context, as it diminishes the difficulty of performing an intrathoracic hand-sewn anastomosis. By translating the surgeon’s natural hand movements on the console to the surgical instruments with endo-wrists, a robotic system can achieve a large range of motion that enables manual suturing. Several case series have been published, which suggest that a robot-assisted hand-sewn intrathoracic anastomosis is safe and feasible for RAMIE (39-41). Prospective randomized studies are warranted to investigate hand-sewing versus stapling in terms of anastomotic leakage and benign stricture formation after RAMIE with an intrathoracic anastomosis.

**Lymphadenectomy in RAMIE**

Although the extent of nodal dissection in esophagectomy is well-studied, practice varies worldwide (42). The therapeutic value of a high nodal yield was recently demonstrated in a population-based study in the Netherlands that included 2,698 patients, which found that harvesting at least 15 lymph nodes was significantly associated with improved overall survival after esophagectomy (43). This was found across all subgroups of patients, including both squamous cell carcinoma and adenocarcinoma, both transthoracic and transhiatal approaches, both cN0 and cN+, and both ypN0 and ypN+ (43). A meta-analysis confirmed that a high lymph node yield significantly increases survival after esophagectomy in both Western and Eastern patient populations, regardless of whether neoadjuvant therapy has been administered or not (44). The ROBOT trial showed that a mean of 27 and 25 lymph nodes were harvested in RAMIE and open esophagectomy, respectively (not significantly different), demonstrating that robotic surgery is at least comparable to open surgery in retrieving of a sufficient amount of lymph nodes (25).

The routine performance of lymphadenectomy in the paratracheal regions (levels 2, 3 and 4) is still under debate and is considered to be technically challenging in esophageal cancer surgery. Although many surgeons prefer to only perform a paratracheal dissection for proximal or mid-esophageal tumors, it should not be underestimated that upper mediastinal lymph node metastases are found in a substantial part of patients who undergo esophagectomy for more distal tumors (45). In a recent study in patients who underwent esophagectomy for mid- to distal esophageal tumors, it was found that dissection of the paratracheal
lymph nodes has a high therapeutic value in terms of long-term survival (46). However, the balance between oncological principles and the risk of iatrogenic damage is important and may have twofold consequences for the patient. Nearby vital structures such as the superior vena cava, recurrent laryngeal nerves, and the membranous part of the trachea and main bronchi all must be spared during dissection. Damage to these structures can result into severe complications such as severe bleeding with hemodynamic shock, permanent vocal cord paralysis, and fistulas between gastric conduit and major airway structures. However, the technical advantages of RAMIE enable a meticulous and safe dissection in these anatomical areas. More research is needed to investigate the benefits and risks of performing a paratracheal lymphadenectomy during esophagectomy in general and for the different surgical approaches.

The extent of nodal dissection can be further improved by near-infrared (NIR) fluorescent imaging modalities that are standardly integrated into the latest robotic platforms. This visual support can identify lymph nodes when a patient's tumor is injected preoperatively with labeled colloid or also preoperatively with indocyanine green (ICG) dye (47). Of course, it should be mentioned that conventional minimally invasive cameras are also available with NIR fluorescent imaging modes.

**Extended indications and future developments in RAMIE**

The use of RAMIE can be especially helpful in extended oncological indications. The thoracic aperture is notoriously difficult to access especially in open surgery, due to the scapula and transverse direction of the thoracotomy that hamper the reach of the instruments and view on this area. MIE achieves better vision and access to the upper thoracic structures by the placement of trocars in more proximal intercostal spaces. Conventional minimally invasive techniques, however, are hindered by straight instruments and a relatively great distance between the trocars and the target anatomy, which reduces the level of control. RAMIE can provide advantages in this regard, as better overview and an increased range of motion can be achieved. A recent study demonstrated that RAMIE can be applied to achieve adequate oncological results (i.e., lymph node yield and radicality rate) for patients with proximal tumors and lymph node involvement in the superior mediastinum, although an increased preoperative mortality (7–10%) and recurrent nerve injury rate (17%) were reported (48). Acute respiratory distress syndrome (ARDS) seemed to contribute to the increased mortality rate, which could possibly be explained by the combination of extended irradiation fields and the surgical trauma along the trachea and vagal nerve in the superior mediastinum. It must furthermore be noted that most cases of recurrent laryngeal nerve injury were classified as grade 1.

In addition to better access to the superior mediastinum, RAMIE can facilitate the resection of cT4b tumors that have been down-staged by chemoradiotherapy (49). The extended irradiation scheme [50 Gy, compared to 41.4 Gy for < cT4b tumors according the CROSS regimen (1)] frequently induces severe fibrosis, which can make dissection of the anatomical planes between the esophagus and the surrounding structures (i.e., main bronchus, aorta, atrium) very challenging. However, the stability of the robotic instruments and a zoomed-in three-dimensional view allow very precise exploration of the structures and could help in preventing damage with preservation of the resection margins. The first small case series shows that RAMIE can achieve a radical resection in 90% of the down-staged cT4b cases (49). Larger series and long-term results are still awaited.

The future opportunities of RAMIE probably reside in the fact that a surgical robot is a platform that can be developed further to keep up with technical developments such as artificial intelligence. Surgical literature is increasingly addressing the possibilities of machine learning in the context of surgical navigation and to enhance surgical training (50,51). Moreover, in the future it might be possible to interconnect robotic systems and thereby allow assistance from a peer surgeon in a remote center. The possibilities are expected to be explored further in the near future.

**Costs perspectives of RAMIE**

Cost-effectiveness is an important aspect when implementing new techniques in health care. RAMIE is frequently challenged in this context, since it requires the capital investment of a surgical robot and the relatively high costs of maintenance. However, postoperative complications are known to significantly increase the total treatment costs of esophagectomy and RAMIE is associated with less postoperative complications and shorter length of hospital stay when compared to open esophagectomy.
The necessary investments for RAMIE are therefore expected to be at least partially counterbalanced by the saving of costs that would be associated with the complications after open esophagectomy. Unfortunately, insight is lacking with regard to the cost-effectiveness of RAMIE when compared to conventional MIE, as no clear evidence is available to support clinical benefits of either technique that might be translated to a difference in treatment costs, apart from higher investment costs for RAMIE. This implies that RAMIE is probably a more expensive treatment modality when compared to conventional MIE at this moment. However, the additional possibilities that RAMIE offers over conventional MIE (e.g., hand-sewn intrathoracic anastomosis, operating on high mediastinal tumors, developments in the context of artificial intelligence) should not be overlooked in the discussion on cost-effectiveness. In addition, robotic assistance has been suggested to improve the surgeon’s ergonomic conditions when operating. Musculoskeletal complaints are reported in 74% of conventional minimally invasive surgeons and a survey amongst urologists found that shoulder and neck complaints are significantly less common when performing robot-assisted surgery (53). As work-related musculoskeletal complaints can result in sick leave of surgeons and the costs attached to that (54), improving the ergonomic conditions in the operating room could positively contribute to the overall costs balance of surgical treatment. Lastly, the current situation is that only one manufacturer is producing surgical robotic systems that are permitted for use on human patients (i.e., Intuitive Surgical Inc.), which creates a monopoly position. The future arrival of competing companies on this marked will expectantly decrease the required investments for robotic surgical systems, which will likely result in altered costs perspectives for RAMIE.

**Summary**

Robotic systems can facilitate minimally invasive surgery by improving the view of the surgical field and increasing the range of motion of the instruments. A recent randomized controlled trial showed that RAMIE is superior to open esophagectomy in terms of postoperative complications, length of hospital stays, and quality of life. However, the clinical benefits of RAMIE over conventional MIE are not entirely clear yet and in this light the cost-effectiveness of RAMIE is frequently challenged. However, the technical advantages of robotic assistance provide opportunities that might lead to improvements in perioperative care. One potential technical advantage of RAMIE is the possibility to construct a hand-sewn instead of a stapled intrathoracic anastomosis, which might be less prone to developing benign strictures. Additionally, a meticulous dissection along the recurrent laryngeal nerves can be performed during RAMIE and the upper thoracic inlet can easily be reached to operate on tumors and involved lymph nodes located in the upper mediastinum. Furthermore, an important advantage of robotic systems is that they provide a computerized platform that can be developed further towards image guided surgery. More high-quality prospective studies are needed to provide more clarity regarding the advantages and opportunities of RAMIE in the treatment of esophageal cancer.

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**Footnote**

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**References**


