Review Article

Minimally invasive esophagectomy—should we improve the evidence?

Sonia Fernández-Ananín, Carmen Balagué

Department of Digestive Surgery, Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Barcelona, España

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Correspondence to: Sonia Fernandez-Ananín; Carmen Balagué. Department of Digestive Surgery, Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Barcelona, España. Email: SFernandezA@santpau.cat; cbalague@santpau.cat.

Abstract: Since the first minimally invasive esophagectomy (MIE) for esophageal cancer was introduced in the 1990s, a multitude of articles have been published in relation to this issue. However, the great heterogeneity according to the location of the tumor, histological type, approach route, oncological outcomes, and the scarcity of randomized controlled trials (RCT) lead to a weak scientific evidence. It is unquestioned that minimally invasive surgery provides a better postoperative recovery with a shorter hospital stay and an early return to normal activities of daily living. Concerning MIE is a marked decrease in pulmonary complications have been described. The ongoing point of discussion is the oncological equivalence of the MIE compared to the open approach. Even though, an RCT (TIME trial) demonstrated no differences in disease-free and overall 3-year survival between both approaches, we still lack long-term outcomes that support this affirmation. The aim of the article presented here is to assess the current scientific evidence of the specific aspects of interest concerning to MIE, in order to define criteria and clarify concepts.

Keywords: Esophageal cancer; minimally invasive surgery; laparoscopy; thoracoscopy; technical approach; surgical complications; surgical outcomes

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Introduction

Esophageal cancer is a disease in increasing prevalence worldwide, whose main axis of curative treatment is surgical resection with radical lymphadenectomy (1). Although this is considered a complex intervention, therapeutic advances, refinement of surgical procedures, standardization of minimally invasive approach and the centralization in specialized centers have contributed to reduce the morbidity and mortality of this procedure.

However, pulmonary complications after esophageal resection are the major cause of postoperative morbidity and mortality. Almost half of the patients undergoing open esophagectomy (OE) will develop postoperative severe respiratory complications, that increase the need for intensive care unit, global hospital stay and overall mortality. In addition, these complications condition a severe concerning in the health-related quality of patient life (2,3).

Firts minimally invasive esophagectomy (MIE) was introduced by Cuschieri *et al.* (4) in 1992 with a series of five patients. They described the video-assisted thoracoscopic mobilization combined with a laparotomy. Subsequently, several studies worldwide reported different hybrid techniques combining minimally invasive surgery with open surgery (laparoscopy/thoracotomy, laparotomy/thoracostomy) for esophageal resection, in benign or malignant conditions, demonstrating its feasibility and good outcomes (5,6).

Over the years, several systematic reviews suggesting the benefits of MIE have been published. But these systematic reviews are based mostly on observational studies, so these conclusions should be taken with prudence (7-13) (*Table 1*).

Table 1 Systematic reviews and meta-analysis in MIE

Author	Year	Type of study	n	Endpoint	Outcomes
Van Workum (7)	2017	SR and meta-analysis	1,681	Comparation MIE and HIE Ivor-Lewis *vs.* McKeown	Ivor_lewis is associated with less recurrent laryngeal nerve trauma, hospital length stay and blood loss
Zhou (8)	2015	SR and meta-analysis	5,537	To explore superiority of MIE reducing AL	Moore proofs are needed to clarify the strengths or weaknesses of MIE in preventing AL
Zhou (9)	2015	Meta-analysis	14,311	To explore effect of MIE *vs.* OE on the occurrence of in-hospital mortality	MIE is superiority over OE in-hospital mortality
Koyanagi (10)	2016	SR		To assess its benefits of MIE in prone position	Studies have not verified this
Markar (11)	2013	SR and meta-analysis		To examine the main technical parameters that impact on anastomotic integrity	No significant difference in the incidence of anastomotic lea kwas demonstrated for technical factors
Hanna (12)	2012	SR	50	To assess the use of MIE for cancer	There is need to reach a consensus regarding surgical approaches in MIE
Biere (13)	2009	SR and meta-analysis	1,061	To evaluate the effects of MIE *vs.* OE on outcome	A faster postoperative recovery and reduction in morbidity can be achieved with MIE

MIE, minimally invasive esophagectomy; AL, anastomotic leakage; OE, open esophagectomy.

Nowadays, around ten RCT have been published analyzing surgical outcomes, morbidity (mostly respiratory complications) mortality and quality of life comparing the different approaches (open, hybrid, minimally invasive, Robot). Topics such as aspects of surgical technique (patient position, anastomosis, pre-conditioning of gastric conduit), oncology therapeutics and antithrombolic prophylaxis, as well as nutritional issues were also discussed (*Table 2*).

The common characteristic of these RCTs is the low number of patients included, which limits the reliability of the conclusions. Surgery is an area where RCTs are complex to perform. The usual difficulties of the design of this type of study are added those of the surgical patients. For this reason, a group of authors (ROMIO study group) designed a study to establish efficient methods to perform a main trial of MIE versus OE, defining a list of feasibility objectives (20).

The aim of this article is to assess the current scientific evidence of the different points of interest concerning to MIE, such as surgical techniques, approach, patient position, morbidity, mortality and oncological outcomes available in the medical literature, in order to clarify concepts.

Open vs. introduction of minimal invasive surgery

Pathological examination and oncological outcomes

Two considerations must be taken into account in oncological surgery when a new surgical procedure is evaluated; pathological analysis of the specimen must be comparable between the different surgical techniques, as well as the biological evolution of the tumor (oncological outcomes).

Of the 7 randomized, controlled trials, published, only 2 reported the histopathologic findings of examinations of the resected specimens. Mariette *et al.* found no significant differences between hybrid minimally invasive esophagectomy (HMIE) and OE according to the pathological characteristics of the tumor, its relationship with the resection margins or with the total number of lymph nodes harvested or their involvement. Also, TIME-trial demonstrated similar results in relation to R0 resection (MIE 54 *vs.* OE 47; P=0.106) and the total number of lymph nodes retrieved in both approaches (MIE 20 *vs.* OE 21; P=0.469) (21).

Long-term 3-year follow-up from TIME-trial, showed similar rates for overall and disease-free survival in patients who underwent MIE or OE (37.3%; 95% CI, 23.5–49% *vs.* 42.9%; 95% CI, 28.6–55.4%), even when the analysis was stratified for age, gender and disease-stage. The overall survival and the disease-free survival at 5 years between HIE and OE did not differ significantly in Mariette's RCT (22) although it should be noted that tumor recurrence and overall survival were not part of primary end points.

Table 2 Randomized controlled trials related to minimal invasive esophagectomy for cancer

Author	Year	Groups	n	Endpoint	Follow-up	Outcomes
Maas (14)	2015	MIE/OE	144/115	Primary: postop pulmonary infection Secondary: other postoperative complications, quality of life	1 year	MIE is associated with better quality of life compared to OE
Mariette (11)	2019	OE/HIE	104/103	Primary: major complications during surgery or within 30 days after surgery Secondary: postoperative death within 30 days, intraoperative and postoperative overall complications	3-year	HIE is associated with a 77% lower risk of major intraoperative and postoperative complications than OE
Biere (15)	2017	MIE/OE	55/52	Post-operative respiratory infections	Post-operative (not exactly specified)	BMI ≥26 and open approach are independent predictive factors for post-operative respiratory infections
Straatman (16)	2017	MIE/OE	59/56	Primary: 3-year disease-survival Secundary: operative and post-operative data, overall survival	3-year	Equally outcomes regarding survival and disease-free survival
Tao (17)	2019	JF/NF	58/62	Perioperative complications, major nutritional status, survival rates, length of hospital stay	Mean: 19 months	JF more economical, safer, long-lasting, better QOL and nutritional rates
Berkelmans (NUTRIENT II) (18)	2019	OF/JF	65/67	Primary outcome: time to functional recovery Secondary outcomes: anastomotic leakage, pneumonia rate and other surgical complications	–	OF does not affect functional recovery and does not increase complications
Sun (19)	2018	EOF/LOF	140/140	Primary outcomes: postoperative complications Secondary outcomes: bowel function recovery, QOL	24 weeks after surgery	EOF group had a quicker recovery of bowel function and improved short-term QOL

MIE, minimally invasive esophagectomy; OE, open esophagectomy; HE, hybrid minimally invasive esophagectomy; QOL, quality of life; JF, jejunostomy feeding; NF, nasogastric feeding; OF, oral feeding; EOF, early oral feeding; LOF, later oral feeding.

Overall complication

Recently, Mariette group published a multicenter and randomized controlled trial (RCT) that compared patients with resectable cancer of middle or lower third esophagus submited to transthoracic OE or HMIE. Hybrid esophagectomy consisted of a laparoscopic gastric mobilization and open right thoracotomy. The primary endpoint was major complication during surgery or in the 30 days later. They found that HIE was associated with a 77% lower risk of major intraoperative and postoperative complications than OE. Furthermore, HIE showed a 50% lower risk of major pulmonary complications than open surgery (22), interestingly, at the expense of laparoscopic approach in abdominal field.

Pulmonary complications

As in most areas of foregut cancer surgery, minimally invasive approach for esophageal cancer provides a faster postoperative recovery and fewer rate of complications, specially in the respiratory tract (15). MIE associates a lower overall morbidity and a shorter hospital stay, with an equivalent oncological result to those of OE.

Different cohort studies have proven that both HIE and MIE are associated with a significant lower incidence of

postoperative pulmonary morbidity compared to OE. The minor trauma surgical-access thoracoscopy related added with the best ventilation and oxygenation of prone position would contribute to produce a less basal lung atelectasis than consequently causing lower lung infections (14,23).

In this way, Biere *et al.* compared postoperative pulmonary complications after MIE and OE, verifying that the rate is higher in patients undergoing open surgery. The same working group in order to identify those predictive factors responsible for respiratory infections performed a multivariate analysis. This showed that the patients who underwent OE and who had a body mass index ≥26 had a threefold higher incidence of pneumonia (16). This data is still interesting given the underlying positive association between obesity and esophageal adenocarcinoma, whose incidence is increasing (17).

Pain

Moreover, up to 30–50% of patients undergoing thoracotomy may suffer post-thoracotomy pain syndrome (18,19). It is a widely described disturbance that consists in the presence of pain along the thoracotomy scar that persists 2 months after surgery. It results from the combination of neuropathic (intercostal nerve damage) and nociceptive components (myofascial damage). Postoperative pain affects the quality of life of patients, so this would be one of the reasons that would explain better results in these terms in patients undergoing MIE. With MIE myofascial damage and wounds length are circumscribed.

Recurrent laryngeal nerve injury

Biere *et al.* demonstrated that there was significantly more recurrent nerve palsy in patients undergoing OE than those operated by MIE (15% *vs.* 2% P=0.012), without being related to lung infections (16). The same results in relation to this complication were observed by Maas *et al.* (24).

Explanations for these results could be the use of the double lumen tube in OE, although some authors also use it in MIE, and that the diffusion of carbon dioxide from the thoracic cavity in the MIE to the neck would facilitate the dissection.

Nutrition

Early nutrition in patients undergoing esophageal resection surgery is one of the key points for faster recovery and the decrease of postoperative complications. Advantages of enteral nutrition over parenteral nutrition have been broadly described.

However, in recent years, concepts such as the access route of enteral nutrition (direct oral, nasogastric tube, jejunostomy) and the beginning of it have been the objective of study. Three RCT assessed these parameters. While Tao *et al.* (25) focused on determining the best method of enteral nutrition administration, between jejunostomy and nasogastric tube, Berkelmans *et al.* in their study introduced, in the context of the ERAS protocol, the onset of direct oral nutrition after esophageal surgery (26). Along the same lines, Sun *et al.* showed that patients who started oral diet early (1st day after surgery), did not present a greater number of complications compared to those who started the seventh day after surgery (25.0% *vs.* 27.9%; 95% CI, −13.2% to 7.4%). In addition, this group presented a faster recovery of bowel transit (median of 3 *vs.* 4 days, P<0.001) and a better short-term QOL (27).

Mortality

While it is true that esophageal resection is still considered a technique that implies high morbidity and mortality, the associated rates have decreased considerably thanks to the implementation of minimally invasive surgery, the standardization of surgical techniques and perioperative clinical care protocols (28) and their development in specialized centers.

Biere *et al.* demonstrated no statistically differences in relation to hospital mortality between both approaches (MIE/OE). Nor did Mariette and collaborators found differences between groups (HIE/OE) in relation to mortality 30 days after surgery. However, in this same study, at 5 years the percentage of patients who lived was higher in the hybrid group (60% *vs.* 40%), but the difference was not significant (16).

Quality of life

The term quality of life includes a wide range of concepts, meaning in the medical setting, as the perceived quality of an individual's daily life. In general terms, it is well known that minimally invasive treatments lead to promote improvements in the postoperative quality of patient life.

In 2015, Maas *et al.* in a multicenter randomized trial, showed that MIE is associated with a better mid-term 1 year quality of life than OE. They examined three

domains in health-related quality in patients' life (physical activity, global health and pain) and MIE was superior in all three, especially regarding physical health and pain, compared to OE. Thus, the influence of the approach in relation to the quality of life goes beyond the first postoperative months (24). An explanation for these results could be the lower aggression produced by minimally invasive approach that would be responsible for a lower rate of post-thoracotomy syndrome.

However, a systematic review and a meta-analysis, published 2 years later by Kauppila *et al.* (29) that involve a total of 2,064 patients, demonstrated that those who underwent MIE showed better global outcomes in quality of life tests compared who were subjected to OE only in the first 3 months after surgery, matching after 6 months and 1 year of follow-up.

Other technical aspects

Thoracoscopic approach: lateral vs. prone position

Right thoracoscopic access for mobilization and resection of the thoracic esophagus can be done in two positions: lateral or prone.

Traditionally, MIE was carried out with the patient placed in the left lateral decubitus with double tracheal intubation and lung block. Subsequently, thoracoscopy in prone position gained popularity given its less invasion and better exposure of the operative field, achieving the partial collapse of the lung due to the effect of gravity and the insufflation of carbon dioxide at 8 mmHg or double-lumen endotracheal tube.

Hence, two retrospective studies showed that prone thoracoscopy shows less blood loss, less operative time and less post-operative respiratory infections. This approach allows a better ventilation and oxygenation of the right lung which is blocked in the lateral position, with a consequent lower rate of atelectasis (30,31).

Robotics & esophagectomy

Since in the 2000s, van Hillegersberg (32) and Kernstine (33) published the initial experiences of robotic-assisted surgery in esophagectomy (RAMIE) for esophageal cancer, several specialized high-volume centers have contributed their knowledge to demonstrate their safety and feasibility.

It is true that in centers with wide experience, the results that the robot provides are still motivating. Favorable RAMIE outcomes reported in terms of morbidity and mortality (34,35). However, high cost of Da Vinci robotic system and its annual maintenance makes the implementation of robotic technique difficult in most hospitals.

In the last year, a RCT have been carried out that include the robotic approach for esophageal cancer resection. van der Sluis *et al.* (36), in a single-center randomized trial, compared 112 patients with intrathoracic esophageal cancer who underwent RAMIE or OE. The primary endpoint was complications related to surgery. Overall, patients undergoing RAMIE had fewer postoperative complications (59%) compared those underwent OE (80%) (RR with RAMIE 0.74; 95% CI, 0.57–0.96; P=0.02), with lower percentage of cardiopulmonary complications and better recovery. In oncological terms, both techniques were comparable, with an average follow-up of 40 months. In order to establish solid conclusions, we will have to wait for the long-term results of the study designed by Yang *et al.*, which compares RAMIE *vs.* MIE and which was started in 2017 (37).

Conclusions

Regarding to short-term results, although it seems that MIE is superior in certain aspects such as lower intraoperative risk, lower number of postoperative complications and better quality of life than the open approach, the heterogeneity of the studies and the low sample number, do not allow reach robust conclusions with a high level of evidence.

In the same way, the oncological outcomes between MIE/HIE and open surgery seem comparable, but data is still lacking in relation long-term survival rates.

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Footnote

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