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Current Issues in Minimally Invasive Esophagectomy

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Minimally invasive esophagectomy (MIE) was first introduced in the 1990s. Currently, it is a widely accepted surgical approach for the treatment of esophageal cancer, as it is an oncologically sound procedure; its advantages when compared to open procedures, including reduction in postoperative complications, reduction in the length of hospital stay, and improvement in quality of life, are well documented. However, debates are still ongoing about the safety and efficacy of MIE. The present review focuses on some of the current issues related to conventional MIE and robot-assisted MIE based on evidence from the current literature.

Keywords: Esophageal neoplasm, Minimally invasive surgical procedures, Thoracoscopy, Laparoscopy, Robotic surgical procedures

Introduction

Esophageal cancer presents a significant oncological burden globally. It is the seventh most common malignancy, and its incidence is rapidly increasing in the Western world [1,2]. Surgical treatment remains the mainstay of curative management of esophageal cancer, with a 5-year survival rate of approximately 40%–50% when preceded by chemoradiation therapy [3,4]. Esophagectomy is a highly complex surgical procedure that requires 2-field or 3-field access. Thus, it is associated with significant morbidity and mortality. With advances in thoracic surgery in the 1990s, the progress made in thoracic anesthesia, surgical instruments, and skills has enabled reduction in the surgical trauma and invasiveness. Of particular note, minimally invasive esophagectomy (MIE) has dramatically reduced the morbidity and mortality associated with esophageal surgery. Furthermore, this trend was supported by 3 prospective and randomized clinical trials that revealed the benefits of MIE even after neoadjuvant treatment [5-7]. Although several earlier studies have demonstrated that MIE is an oncologically sound procedure with some benefits for short-term outcomes, some controversies and issues still need to be clarified. This review presents an overview of some of the current issues related to MIE.

Various types of minimally invasive esophagectomy

As esophageal surgery requires 2-field or 3-field access, several different types of MIE have been reported. MIE was first introduced by Cuschieri et al. [8] in 1992. They reported a series of 5 patients who underwent thoracoscopic surgery combined with laparotomy. DePaula et al. [9] reported their experience of laparoscopic transhiatal esophagectomy in 1995. Luketich et al. [10] reported the first large series of a combined thoracoscopic and laparoscopic approach for esophageal cancer in 2003. Horgan et al. [11] and Kernstine et al. [12] reported the first case of robot-assisted MIE (RAMIE). Currently, most of the published literature uses similar terminology for MIE. However, there are still subtle differences in terminology among surgeons [13-15].

Total MIE via a transthoracic approach is currently the most common method of esophageal resection. It combines thoracoscopy with laparoscopy and creates an esophagogastric anastomosis at the intrathoracic level (Ivor Lewis) or at the cervical level (McKeown). Luketich et al. [10] reported the first large series of total MIE with 222 patients; they reported low mortality and morbidity rates, as well as short hospital stays. Moreover, they reported further improved outcomes in over 1,000 patients [16]. The Traditional Invasive versus Minimally Invasive (TIME) trial in 2012 was the first published randomized controlled trial comparing the outcomes of open esophagectomy (OE) and total MIE [5]. It demonstrated lower rates of pulmonary complications and shorter hospital stays in the MIE group, with comparable 30-day mortality and number of harvested lymph nodes (LNs).

Hybrid MIE is a combination of minimally invasive and open approaches, applying minimally invasive techniques at one level of the 2 stages. The previous literature, including 1 randomized controlled trial, has demonstrated the benefits of hybrid MIE involving a combination of laparoscopic surgery and thoracotomy [6,17,18]. Recently, results from the French randomized MIRO trial have demonstrated the benefits of laparoscopic hybrid MIE for short-term, mid-term, and long-term outcomes when compared with OE [6]. The overall major morbidity rates and pulmonary complication rates were lower in hybrid MIE than in OE, with similar 30-day mortality and oncologic parameters. A recent meta-analysis by Booka et al. [19] also demonstrated a significant reduction in pulmonary complication rate with laparoscopic hybrid MIE. Two recent reports based on big data regarding thoracoscopic hybrid MIE were published in Japan [20,21]. They reported superior perioperative outcomes of hybrid MIE when compared with OE in terms of in-hospital mortality, surgery-related mortality, and postoperative morbidity.

Traditionally, the transthoracic approach was most frequently performed in the lateral decubitus position; however, this position requires total lung collapse, which is frequently associated with pulmonary complications. Palanivelu et al. [22] reported transthoracic MIE in the prone position in a large cohort. They reported that it was technically feasible, with a low respiratory complication rate and a shorter operative time due to the excellent exposure of the operative field and the better ergonomics. However, it is difficult to perform classical thoracotomy conversion in an urgent setting. Lately, MIE in a semi-prone position has become popular among surgeons to overcome the abovementioned problem, while retaining the benefits of the prone position [23].

Transhiatal OE was first reported by Orringer and Sloan [24]. It is regarded as less invasive and less radical than transthoracic OE. Transhiatal esophagectomy with a laparoscopic abdominal procedure is also considered to be a type of MIE. Most of the previous literature regards it as a type of total MIE [13,15], as it includes only minimally invasive abdominal procedures without a transthoracic approach. A recent systematic review by Parry et al. [25] reported that transhiatal MIE showed less blood loss and shorter hospital stays than transhiatal OE with comparable postoperative morbidity rates and LN retrieval.

Although the transhiatal approach is regarded as less invasive than the transthoracic approach, mediastinal LN dissection is insufficient for the treatment of esophageal cancer. In some institutions, a video-assisted transcervical approach for dissection of the proximal and mid-esophagus has been implemented in combination with a transhiatal approach to improve the quality of mediastinal LN dissection without transthoracic dissection and one-lung ventilation [26-28]. They reported that this approach was associated with a lower pulmonary complication rate and better postoperative quality of life, with comparable numbers of retrieved mediastinal LNs compared to transthoracic esophagectomy. Larger prospective studies should be conducted to verify these results, including long-term oncologic outcomes.

RAMIE was introduced in 2003 and was found to be a safe technique with good oncologic outcomes in the first reported series [29,30]. Based on the definition by Gottlieb-Vedi et al. [13], RAMIE is technically a form of MIE. However, most surgeons who perform RAMIE consider it to be a procedure distinct from conventional MIE, as robotic surgical systems were developed to overcome the technical limitations of conventional MIE. They believe that RAMIE has several benefits over conventional MIE. Several types of RAMIE have been reported. The ROBOT trial, which compared RAMIE with OE, included patients in whom thoracic RAMIE was combined with a laparoscopic procedure [7]. Recently, our group reported the outcomes of RAMIE [31]. We defined total RAMIE as RAMIE for thoracic as well as abdominal procedures and hybrid RAMIE as RAMIE only for thoracic procedures in combination with laparotomy. There is no consensus regarding the specific terminology for various types of RAMIE. However, we believe that they should be well defined for proper comparisons to be made in future research.

Long learning period and associated problems

Although perioperative morbidity and mortality rates

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have remarkably decreased with recent advances in surgical techniques and postoperative care, esophagectomy is still associated with a high mortality rate compared to other high-risk surgical procedure and has a morbidity rate up to 60%. The previous literature, including 3 randomized controlled trials, has demonstrated improved short-term outcomes of MIE. However, it is a highly complex procedure, making it difficult to achieve proficiency. In particular, thoracoscopic surgery is technically demanding due to movement of the target anatomy, mirrored intracorporeal movements of the instruments, and nearby vital structures that need to be avoided (aorta, pulmonary artery, trachea, and vagal nerve branches). Moreover, various types of MIE with different levels of complexity (transhiatal, transthoracic with cervical, or intrathoracic anastomosis) have different learning curves.

Learning-associated morbidity is defined as morbidity during a learning curve, which could have been avoided if patients were operated on by surgeons who have completed the learning curve. It is now a recognized problem, and there is robust evidence suggesting that the implementation of MIE can have a significant effect on patients' clinical outcomes. Training in complex MIE is a long process with a reported learning curve of 50 to 119 cases [32,33]. As the reported anastomotic leakage rate dropped from 18.8% to 4.5% from the first to the fifth quintile, it is suggested that patients are exposed to an increased risk of surgical morbidity during the learning phase [32]. Moreover, early series related to MIE have reported higher rates of acute gastric conduit necrosis [33], which were attributed to a lack of proficiency in technique during the learning phase. Multiple population-based studies from several countries demonstrated higher rates of reintervention in MIE than in OE [34-37]. Some authors suggested that this finding may have reflected the learning curve of MIE experienced by surgeons and centers during the early national adaptation phase. The reported duration of the learning curve for RAMIE is 20–80 cases [38-40]. Our group analyzed the number of cases required to attain surgical proficiency for short-term postoperative outcomes [40]. We found that the rate of vocal fold palsy decreased from 36% to 17% after 60 cases, the rate of anastomotic leakage decreased from 15% to 2% after 80 cases, and the length of hospital stay decreased from 24 days to 14 days after 80 cases. Thus, it seems that the postoperative outcomes after MIE improve over time based on accumulated experience in the learning period.

According to the aforementioned results, some learning-associated morbidity is inevitable, as MIE is a surgically complex procedure. Therefore, shortening the learning curves and reducing the learning-associated morbidity remain important goals for the implementation of MIE. Gottlieb-Vedi et al. [41] reported that surgeons who performed a higher volume of cases and younger surgeons seemed to require a substantially shorter period to gain proficiency for long-term mortality and other outcomes following surgery for esophageal cancer. Moreover, some studies have demonstrated that standardized training programs were effective for surgical procedures [42]. A study by van der Sluis et al. [39] revealed that the use of a structured training pathway that involved proctoring reduced the learning curve for RAMIE from 70 to 24 cases. These findings indicate that the safe implementation of a standardized MIE training program for younger surgeons may improve patient outcomes and safety in the current surgical era.

Lymph node dissection in minimally invasive esophagectomy

The status of LNs in esophageal cancer is an important prognostic factor and has been proposed as a predictor of overall survival [43-45]. The pattern of LN metastasis of esophageal cancer relies on several factors such as tumor location, histology, depth of invasion (T-stage), and the use of neoadjuvant treatment. As many factors are associated with the pattern of LN metastasis, the optimal extent of lymphadenectomy is still under debate [46,47].

In East Asia, squamous cell carcinoma constitutes more than 90% of all resected esophageal cancers and the most frequent location of the tumor is the upper to middle esophagus. Akiyama et al. [45] investigated the distribution pattern of LN metastasis in squamous cell carcinoma and reported that the most frequent sites of LN metastasis were the upper mediastinal LNs in patients with esophageal squamous cell carcinoma in the upper thoracic esophagus, while the upper mediastinal and perigastric LNs were involved in patients with cancer in the middle thoracic esophagus. Therefore, in many centers in East Asia and especially in Japan, extensive LN dissection including abdominal, whole mediastinal, and even cervical LNs has been advocated as a standard surgical procedure with curative intent. In Western countries, a dramatic increase in the incidence of adenocarcinoma of the lower thoracic esophagus and esophagogastric junction has been reported in the past 2 decades [48,49]. Many of these cancers are associated with gastroesophageal reflux and Barrett esophagus. Some studies have indicated that only 1%–2% of Siewert type II esophagogastric adenocarcinomas showed metastasis to the LNs in the supracarinal area [50,51]. Differences in tumor characteristics (histology and the predominant location of the tumors) between Western countries and East Asian countries result in differing perspectives regarding the surgical approach for esophageal cancer, including the extent of lymphadenectomy.

Radical lymphadenectomy attempts to improve both the locoregional tumor control rate and long-term survival, though it increases postoperative morbidity. Although debates are continuing about whether the extent and the number of harvested LNs improve long-term survival, a key measurement of oncologic outcomes in esophagectomy is the extent of LN retrieval. Many researchers have reported that the number of harvested LNs was associated with good long-term survival [46,52]. Studies comparing the number of harvested LNs in MIE compared to those in OE revealed a similar extent of resection between the 2 procedures. The TIME trial and the MIRO trial showed no difference in the average number of LNs retrieved [5,6]. Some recent studies, including a meta-analysis, have confirmed these results, while others have reported a greater number of retrieved LNs in MIE [34,53,54]. The ROBOT trial reported no differences in the total number of retrieved LNs between RAMIE and OE [7]. Our group also reported that there was no difference in the number of retrieved LNs in the cervical, mediastinal, or abdominal area between the 2 groups [31].

For upper mediastinal lymphadenectomy, LN dissection along both the recurrent laryngeal nerves is a challenging procedure during MIE. Recurrent laryngeal LNs are among the most common metastatic sites in esophageal squamous cell carcinoma [55,56]. A proper and complete dissection of these LNs is important for locoregional control of the tumor. However, it is technically challenging due to the possibility of vocal fold palsy caused by nerve injury. Dissection of the left recurrent laryngeal nerve is especially challenging, as esophageal surgery is mostly performed through the right hemithorax. Cuesta [57] summarized 5 different surgical approaches for left laryngeal nerve LN dissection during MIE. The position of the patient, placement of the trocars, and the surgical platform (thoracoscopy or robot) might affect surgeons' preferences for the surgical approach during left recurrent laryngeal nerve LN dissection.

As robotic surgical platforms provide some technical advantages, such as articulating arms and ×10 magnification with 3-dimensional vision, some reports have suggested that RAMIE is feasible for upper mediastinal LN dissection, especially for recurrent laryngeal nerve LNs [58,59]. Our group compared outcomes between RAMIE and conventional MIE and reported that the total number of harvested LNs was significantly higher in RAMIE than in conventional MIE [60]. The number of harvested LNs in the upper mediastinum was higher in RAMIE than in MIE and specifically, the numbers of harvested LNs from the laryngeal nerve and the sub-aortic areas were significantly higher in RAMIE, while the rate of vocal fold paralysis was similar.

Quality of life after minimally invasive esophagectomy

Several previous studies demonstrated that MIE is associated with a rapid restoration of health-related quality of life. This benefit may be attributable to the reduction of postoperative complications in MIE. The TIME trial showed that MIE was associated with better short-term quality of life [5]. The physical component summary of the Short Form 36 Health Survey, European Organization for Research and Treatment of Cancer Quality of Life Questionnaires, and quality-of-life domains of talking and pain in the OES 18 questionnaire were significantly better in MIE. Moreover, the ROBOT trial demonstrated better health-related quality of life and physical functioning at discharge and at postoperative 6 weeks in the RAMIE group [7]. The MIRO trial assessed short- and long-term health-related quality of life of OE and hybrid MIE groups [61]. They reported that hybrid MIE reduced the incidence of short-term adverse events, with some degree of persistent improvements of health-related quality of life up to 2 years; however, at 3 years, there was no difference between the 2 groups.

Minimally invasive esophagectomy after neoadjuvant treatment

Neoadjuvant treatment has been proven to have survival benefits, especially for locally advanced esophageal cancers. The CROSS trial showed a better R0 resection rate, a lower node-positive rate, and longer overall survival in the neoadjuvant treatment group without significant postoperative mortality or morbidities [4]. Some previous studies have reported the efficacy of MIE in patients who underwent neoadjuvant treatment. The TIME trial examined the role of MIE in patients who had undergone neoadjuvant chemoradiotherapy for esophageal cancer [5]. The trial reported promising early postoperative outcomes. Some retrospective studies have also demonstrated that MIE was a

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safe procedure after neoadjuvant chemoradiation therapy [62,63]. However, MIE should be considered carefully in patients with an advanced bulky tumor before neoadjuvant treatment and in patients in whom esophagectomy was planned as salvage therapy. Moreover, possible postoperative morbidities should be carefully monitored in these patients [64].

Long-term survival after minimally invasive esophagectomy

Although many studies have revealed that MIE has benefits over OE in terms of short-term perioperative outcome and quality of life, the long-term outcomes of MIE remain to be established due to the heterogeneity of the procedure, small sample sizes, and the lack of long-term data. The most recent follow-up results of the TIME trial demonstrated 3-year overall survival rates of 40.4% and 50.5% in OE and in MIE, respectively, without a statistically significant difference [65]. The TIME trial also reported 3-year disease-free survival rates of 35.9% and 40.2% in OE and in MIE, respectively. In the MIRO trial, the 3-year and the 5-year overall survival rates were 55% and 39%, respectively, in OE and 67% and 60%, respectively, in hybrid MIE [6]. In the ROBOT trial, no statistically significant differences were observed in overall survival and disease-free survival between RAMIE and OE at a median follow-up of 40 months [7]. A recent meta-analysis by Gottlieb-Vedi et al. [13] including 14,592 patients from 55 relevant studies reported that MIE was associated with lower 5-year and 3-year all-cause mortality and disease-specific mortality rates than OE. The 3-year and 5-year all-cause mortality rates were lower by 18% and 15%, respectively, after MIE when compared with OE. Moreover, the 3-year and the 5-year disease-specific mortality rates were lower by 17% and 16%, respectively, after MIE when compared with OE. The authors concluded that MIE might be recommended as a standard surgical approach for esophageal cancer. Further studies are still warranted, as a greater number of high-quality cohort studies and randomized clinical trials would improve the status of the current evidence. Therefore, the results of the JCOG1409 study (Japan Clinical Oncology Group trial) planned in Japan (a randomized controlled trial comparing MIE and OE in terms of overall survival) are eagerly anticipated [66].

Conclusion

MIE is a valuable surgical option for the treatment of esophageal cancer. Many studies have suggested that MIE has advantages related to early postoperative outcomes, including reduced postoperative complications, early recovery, and improved quality of life. However, several debatable issues remain that should be clarified. The heterogeneity of the procedure, risks during the learning period, adequate extent of LN dissection, and long-term survival after MIE should be investigated in future studies.

Conflict of interest

C.H. Kang received proctor fees from Intuitive Surgical Korea. No potential conflict of interest relevant to this article was reported.

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