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Review

Minimally Invasive Transcervical Esophagectomy With Mediastinal Lymphadenectomy for Cancer. A Comparison With Standardized Techniques

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Abstract. *Pulmonary complications remain the most common problem following transthoracic esophagectomy. Minimally invasive approach has significantly improved clinical outcomes; however, respiratory distress is still significant. Minimally invasive transcervical esophagectomy with mediastinal lymphadenectomy avoids thoracic access, which may decrease pulmonary complications. Transcervical esophagectomy refers to transcervical esophageal mobilization and mediastinal lymphadenectomy followed by a transhiatal gastric and distal-esophageal mobilization, abdominal and lower mediastinal lymphadenectomy. Adoption of innovative minimally invasive techniques for the transcervical or transhiatal approach, such as laparoscopy or robotic-assisted mediastinoscopy have made possible transmediastinal approach for radical esophagectomy. This novel approach with avoidance of thoracotomy or thoracoscopy can omit one lung ventilation as in transthoracic esophagectomy. Patients with previous thoracic surgery, impaired respiratory system, and major comorbidities, who are unable to undergo transthoracic esophagectomy, become candidates for radical esophagectomy with promising results. Minimally invasive transcervical esophagectomy for esophageal cancer is a safe and feasible approach and may be a valuable alternative with promising clinical and oncological outcomes.*

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The mainstay of treatment for esophageal cancer is surgery. Esophageal surgery carries high rates of post-operative morbidity and mortality. For the treatment of distal esophageal and gastro-esophageal junction Siewert type I-II tumors, 2-stage or Ivor Lewis esophagectomy, with 2-field lymphadenectomy is considered the gold standard approach (1). On the other hand, for tumors of the mid or upper esophagus, 3-stage or McKeown esophagectomy with 2-field or 3-field lymphadenectomy can be performed (2).

Two-stage transthoracic (TTE) esophagectomy consists of abdominal phase followed by a right thoracotomic phase, while 3-stage TTE constitutes of a right thoracotomic phase followed by abdominal and cervical phase. Transhiatal esophagectomy (THE), which does not include a thoracic phase was the treatment of choice more than twenty years ago; however, nowadays, its clinical implementation is limited due to lack of mediastinal lymphadenectomy and compromised oncological outcomes compared to Ivor Lewis or McKeown esohagectomy (3).

Minimally invasive esophagectomy (MIE), executed as hybrid-MIE consisting either of laparoscopic phase and open

thoracotomy or thoracoscopic followed by laparotomic and cervical phases (4-6), or as totally minimally invasive approach, which was first introduced in the 90's (7), is associated with significantly reduced respiratory complications and improved clinical outcomes compared to open esophagectomy (8-10). Totally-MIE, which combines laparoscopic and thoracoscopic techniques, offers all the advantages of minimally invasive surgery both in abdominal and thoracic cavities, thus further minimizing the rate of post-operative complications and providing favorable outcomes (11). Robotic-assisted MIE (RAMIE) was introduced in the past decade as a valuable alternative to open esophagectomy, for improving the pitfalls of laparoscopic/thoracoscopic MIE (12).

Minimally invasive transhiatal esophagectomy with robotic transervical mediastinal lymphadenectomy is gaining popularity over the past years among esophageal surgeons. Combining total esophageal resection as in THE with mediastinal lymphadenectomy (13), aims to achieve the same oncological outcomes with open or minimally invasive transthoracic approaches, with no mediation of thoracotomy and further reduction of pulmonary complications comparing even to MIE (14). It may be the procedure of choice in patients with impaired pulmonary and cardiac functions or in patients with significant previous thoracic surgery, unfit for transthoracic surgery.

Herein, we aimed to present all data regarding transmediastinal esophagectomy for the treatment of esophageal cancer compared to open or minimally invasive transthoracic approaches, which may lead to a paradigm shift towards further reduction of pulmonary related complications and comparable clinical and oncological outcomes.

Transthoracic Esophagectomy

Ivor Lewis or 2-stage esophagectomy was first introduced in 1946 (15), while 3-stage esophagectomy was first presented by McKeown in 1972 (3). Both these transthoracic approaches have long been utilized in clinical practice for the treatment of esophageal and gastro-esophageal junction cancer. They combine gastric and esophageal resection, alongside abdominal and mediastinal lymphadenectomy (standard 2-field lymphadenectomy).

Mediastinal lymphadenectomy includes all the lower mediastinal, paraesophageal, and subcarinal lymph nodes; for mid or upper esophageal tumors, upper mediastinal or cervical lymph nodes can be included (extended 2-field or 3-field lymphadenectomy, respectively) (16).

The burden of open TTE is the significantly high rate of post-operative pulmonary and cardiac complications, that can reach as high as 30% and 14%, respectively, even in the hand of experts. Furthermore, accumulated mortality rate can reach as high as 6% (17).

Minimally Invasive Transthoracic Esophagectomy

Minimally invasive esophagectomy is on the rise worldwide (10) and refers to hybrid transthoracic esophagectomy combining laparoscopy and open thoracotomy (9), totally minimally invasive esophagectomy combining thoracoscopic and laparoscopic techniques (10) or robotic-assisted esophagectomy.

MIE in the form of HE and TMIE or RAMIE, were introduced gradually, with the purpose of reducing post-operative pulmonary and cardiac complications and surgical trauma, shortening length of hospital stay, improving quality of life, and inducing earlier post-operative systemic therapies (17). All these were the considering factors alongside equal if not improved oncological results compared to open esophagectomy (17).

Transhiatal Esophagectomy

THE consists of a transhiatal and transcervical approach, with blunt and blind dissection of the thoracic esophagus. It was reported by Turner in 1933 (18). Turner performed the first successful THE for carcinoma and reestablished continuity of the alimentary tract using an antethoracic skin tube at a second operation. However, after the introduction of safe open thoracotomy and transthoracic esophagectomy took more than 40 years for THE to be established as an esophageal surgery practice by Orringer *et al*. in 1978 (19).

THE is considered less invasive than TTE because it avoids thoracotomy (14). However, it offers a limited surgical view and less extensive lymphadenectomy compared to TTE.

Transcervical Esophagectomy

Transcervical esophagectomy was first reported by Bumm *et al*. in 1993 (20); Bumm described his technique as 'endo-dissection of the thoracic esophagus'. It refers to combination of transhiatal and transcervical approaches. They concluded in their study, that utilization of their technique can be especially useful for esophageal dissection at or above the trachea, allowing proper identification of mediastinal structures, while offering access to mediastinal lymph nodes. Additionally, they showed that recurrent nerve damage and pulmonary distress were reduced compared to THE (20).

Laparoscopic THE was first described by DePaula *et al*. in 1995 (21). A decrease in intra-operative blood loss has been observed in clinical studies compared to open THE, however, operative time and extend of lymph node dissection were similar. Mediastinoscopy was initially used for transcervical procedures, such as mediastinal dissection, lymph node sampling, lung biopsies and mediastinal tumor resection. It engages a specialized set configuration for procedures in the narrow space around the scope tip (22). For the treatment of

esophageal cancer, mediastinoscopy was combined with THE to improve visibility and tissue manipulation in the narrow cervical space; it can provide a safe and effective esophageal and lymph node handling without blind dissection. Following that, mediastinoscopy-assisted transhiatal esophagectomy (MATHE) was first reported by Buess *et al*. in 1997 (23).

Ever since, reports from the West were published and from 2004, reports from the East and especially Japan and China have shed light on this new approach of esophagectomy (24-28). This approach is combining a laparoscopic THE and transcervical mediastinoscopy for the treatment of distal esophageal or gatro-esophageal junction Siewert type I-II adenocarcinoma in Western countries, while it is performed for the treatment of clinical T1-T2 or stage I-II esophageal squamous cell carcinoma, regardless of the primary tumor locations, in patients unfit for thoracotomy in Asia (24-28).

Reports on short-term outcomes have showed a great profile of safety and feasibility of the approach, whereas regarding long-term outcomes, Feng *et al*. compared MATHE and 2-stage TMIE in a double arm comparative study (n=27 patients in each arm) and presented that MATHE was associated with reduced operative times, similar rates of pulmonary complications and lesser mediastinal resected lymph nodes; however, survival was similar among the two study groups (29). Subsequently, Okumura *et al*. (24) studied a cohort of patients that underwent MATHE (n=63), and based on the clinical and oncological outcomes, they concluded that MATHE is a useful operation for the treatment of mid-esophageal or distal-esophageal cancers without clinical lymph node metastasis, in patients with serious comorbidities that are unable to undergo a transthoracic esophagectomy. As a result, MATHE is considered safe and feasible, with improved outcomes compared to THE, but can apply to specific surgical candidates (24).

Robotic-assisted mediastinoscopic esophagectomy (RAME) combined with transhiatal and trancervical approaches could overcome the difficulties of conventional laparoscopic THE and mediastinoscopic-assisted trancercival lymphadenectomy (MATHE) (30). The technical benefits of robotic system can further improve upper mediastinal lymphadenectomy (31).

Introduction of minimally invasive (mediastinoscopic) transcervical approach, can offer extended mediastinal lymphadenectomy, allowing a radical lymph node dissection of the superior mediastinum, while eluding the need for transthoracic approach with the theoretic possibility to further reduce pulmonary complications after major esophageal surgery (32).

Technique of Transcervical Esophagectomy

Transervical esophagectomy is considered challenging due to altered anatomical view compared to transthoracic approach, as well as due to limited available working space in the mediastinum. It is essential for esophageal surgeons to have deep knowledge of the thoracic and mediastinal surgical anatomy.

Patients are routinely placed in supine position, with right shift of their head. A collar incision is performed in the left neck. Cervical esophagus is dissected and taped (umbilical tape), while lymphadenectomy along the left recurrent laryngeal nerve (LRLN) can be performed. With the development and adoption of single incision laparoscopic surgery (SILS), cervical access is gained through utilization of a single port. A 30-degree endoscope and two laparoscopic instruments are inserted via the cervical access ports for mediastinal dissection.

At the beginning, the left side of the cervical and thoracic esophagus is dissected. All adipose tissue along the left carotid artery can be dissected free reaching up to the aortic arch. The para-tracheal and para-esophageal lymph nodes can then be dissected, with meticulous care to avoid injury to the LRLN. The upper thoracic esophagus is then mobilized with identification of the thoracic duct on the left side of the esophagus. The dissection can then be continued to the mid-thoracic esophagus, mobilizing it from the membranous part of the trachea and carina; exposure of the tracheal wall can be advanced to the left main bronchus until the trunk of the pulmonary artery is identified.

Tracheobronchial lymph nodes between the previously exposed aortic arch and left pulmonary artery can then be harvested. Exposure of the right parietal pleura and the carina can then be completed, followed by dissection of the subcarinal lymph nodes down to the right tracheobronchial angle. The vagii nerves are then isolated and divided, with preservation of their pulmonary branches.

Lymph node dissection along the right RLN and the right cervical esophagus can be performed with an open method using bilateral neck incision and before reconstruction. At this point, a transhiatal mobilization of the lower thoracic esophagus, abdominal lymphadenectomy, gastric mobilization, and gastric conduit formation is then completed. Gastric pull-up is then performed, and reconstruction of the gastro-intestinal continuity is achieved, with construction of the esophago-gastric anastomosis in the neck.

Discussion

Esophageal cancer is one of the most lethal malignancies, being the sixth cause of cancer related mortality worldwide (4). Squamous cell carcinoma is the predominant histological subtype in Asia, while adenocarcinoma is the most common subtype in Western countries, with constantly increasing incidence. Esophagectomy remains the mainstay of treatment for esophageal adenocarcinoma and squamous cell carcinoma (10). Over the past years, transthoracic esophagectomy, either

by open or by minimally invasive procedures has been established as the gold-standard approach over transhiatal esophagectomy, mainly due to the limited lymphadenectomy offered by the THE approach (4).

However, transthoracic approach is associated with high morbidity and mortality and to reduce pulmonary complication rate, minimally invasive TTE has been increasingly utilized, offering significantly reduced post-operative morbidity compared to open TTE (22).

Transthoracic esophagectomy, open or minimally invasive, is performed with one lung ventilation either with double lumen endotracheal tube and blocked right lung or with single lumen endotracheal tube and right bronchial blocker to achieve blockage of the right lung and adequate surgical operating field. While respiratory complications after esophagectomy are abridged by minimally invasive surgery, it remains one of the most common post-operative problems. Single lung ventilation and collapse of one lung (right) accompanied with chest trauma (thoracotomy or thoracoscopy/mini thoracotomy) have been associated with acute respiratory distress syndrome (ARDS) and severe oxidative stress (33).

Transmediastinal esophagectomy consists of a minimally (laparoscopic or robotic-assisted) invasive transhiatal gastric and lower thoracic esophagus mobilization, as well as by abdominal lymphadenectomy and conduit formation, followed by minimally invasive (mediastinoscopic or robotic-assisted mediastinoscopic) transcervical middle and upper thoracic esophagus dissection and mid- and upper-mediastinal lymphadenectomy. This approach can lead to reduced respiratory complications by emitting thoracotomy or thoracoscopy related to TTE, without compromising the mediastinal lymph node dissection related to THE.

Mediastinoscopic-assisted THE can offer precise mediastinal lymphadenectomy and has been considered as radical surgery for the treatment of esophageal and gastro-esophageal tumors. Introduction of minimally invasive approach to esophageal surgery has increased the spectrum of patients able to undergo major resection. As proposed by Wang *et al*. in 2021, MATHE can broaden the indications for esophagectomy, including patients with compromised pulmonary function, previous thoracic procedures, as well as patients with early-stage esophageal cancer (34).

Thus far, MATHE has been performed only in few institutions and especially in Asia. This is a result of complexity, limited and narrow working space and requirement of excellent knowledge of the mediastinal anatomy under mediastinoscopy. Daiko *et al*., have presented an alternative to single neck incision and SILS port implemented by others, with a bilateral transcervical mediastinoscopy-assisted method, that can resolve these difficulties by using both operator's hands and simultaneously inserting surgical devices into the mediastinum via each of the bilateral cervical incisions and ports. This technique can provide not only improved handling but also a more stable operative field even in patients with narrow mediastinum, improving the extend and quality of mediastinal lymph node dissection (33).

Subsequently, advances in surgical instruments and adoption of robotic surgery have established the role of robotic-assisted mediastinoscopy for radical transcervical esophagectomy. Mori *et al*. in 2017 were the first to present their experience of MATHE in a cadaveric model, showing the feasibility and benefits of this technique for mediastinal dissection and robotic system use (35).

Development of the robotic single port system allowed the introduction of 3-dimensional (3D) endoscope and 3 robotic arms within a narrow space. Utilization of this method in a cadaveric model was first described in 2019 by Chiu *et al*. (36). Following that, Grimminger *et al*. compared the two robotic systems, the da Vinci Xi versus the Single Port (SP) system, in cadavers and found that the SP system made possible esophageal dissection up to the level of the distal-esophagus (diaphragm) comparing to the mid-mediastinum from the classical robotic method (37).

The first to successfully perform a MATHE in clinical practice were Nakauchi *et al*. in 2019 (13); in a cohort of n=6 patients, they completed esophageal mobilization and lymph node dissection up to the middle-esophagus, while in the lower mediastinum a transhiatal approach was utilized. Clinical outcomes were promising, with no reported mortality and acceptable morbidity. Egberts *et al*. followed and reported favorable outcomes and radical resection in 4 cases operated with MATHE that combined transcervical and transhiatal approach using the Da Vinci Xi robotic system (38).

Conclusion

To date, only limited data exist regarding minimally invasive transcervical esophagectomy, which reflect the novelty of this surgical technique. Consequently, and while it is too early to draw conclusions about the feasibility and safety of the approach, it can be considered a valuable alternative to well established surgical procedures for esophageal and gastro-esophageal cancer, such as open or minimally invasive transthoracic esophagectomy, and may become the new norm in the near future with the expansion of surgical innovation. Patients with contraindications to thoracic access, patients with early tumors or with metastasis to the upper mediastinal lymph nodes may be candidates and benefit from this approach. Taking all these into consideration, further studies are needed to better elucidate the role of minimally invasive transcervical esophagectomy and create a standardized, step-by-step, safe, and feasible technique, which may lead to a paradigm shift in esophageal cancer surgery.

Conflicts of Interest

All Authors declare no potential conflicts of interest in relation to this study.

Authors' Contributions

SD and AC equally contributed to study conception and design, the acquisition of data and drafting the manuscript. EK contributed to drafting the manuscript and the analysis and interpretation of data. PS, GT and DD contributed to the analysis and interpretation of data and drafting the manuscript. NK contributed to study conception and design, the acquisition of data, and the drafting and critical revision of the manuscript. All Authors read and approved the final manuscript.

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