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EDITORIAL

Natural orifice transesophageal thoracoscopic surgery: A review of the current state

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Abstract

Since the concept of Natural Orifice Translumenal Endoscopic Surgery (NOTES) was introduced, it has continued to gain significantly in popularity and enthusiasm for its potential clinical applications. The ability to perform conventional laparoscopic and thoracoscopic procedures without the creation of scars and perhaps faster and less painful recovery has prompted a worldwide devotion to further this field. While intra-abdominal NOTES has rapidly transitioned from animal models to human trials, applying the NOTES concept to perform thoracic procedures has been slower to gain momentum. The goal of this review is to summarize the current state of transesophageal NOTES thoracoscopy by looking at its potential for diagnostic and therapeutic interventions as well as the challenges in transitioning to human trials.

Key words: Natural orifice translumenal endoscopic surgery; Transesophageal; Thoracoscopy; Mediastinoscopy; Esophagotomy; Natural orifice; Endoscopy

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INTRODUCTION

The initial introduction of Natural Orifice Translumenal Endoscopic Surgery (NOTES) by Kalloo *et al*[1] prompted significant interest in what has become a new frontier of endoscopic surgeries through natural orifices. Specifically, NOTES refers to surgical procedures that involve the passage of a flexible endoscope through a natural orifice, including the mouth and rectum, where subsequent incisions are made in intra-abdominal or intra-thoracic viscera. To permit a safe and controlled introduction of this new concept, a White Paper was drafted describing natural orifice surgery and potential barriers to clinical practice[2,3].

Since the introduction of NOTES, many transgastric NOTES procedures have been developed including tubal ligation and oophorectomy[4,5], cholecystectomy[6], gastrojejunostomy[7], splenectomy[8], and pancreatectomy[9]. The field then moved beyond transgastric exploration and intervention to crossing other visceral boundaries resulting in transvaginal[10], transcolonic[11], and transvesicular[12] access. In addition, several hybrid approaches have been explored combining NOTES with laparoscopy and transanal endoscopic microsurgery (TEM) in swine[13,14] and humans[15,16]. NOTES quickly moved from swine models to clinical experiments in humans. In 2004, the first human NOTES operation was reported when an appendix was removed through the mouth. In the United States, currently reported studies

have included the use of diagnostic peritoneoscopy[17] and transvaginal[18] and transgastric cholecystectomy[19]. Internationally, use of NOTES in humans continues in countries such as India, Japan, Turkey, Japan, South America, and France.

Despite the relatively rapid evolution of NOTES to human trials, entry into the thoracic cavity *via* a transesophageal route has been slower to gain attention. Presently, access to the chest with conventional thoracoscopic and mediastinoscopic approaches has become routine for staging of oncologic disease, biopsy of pathologic tissues, and lung resection, among other uses. Unfortunately, even minimally invasive techniques can result in significant pain and prolonged recovery. A recent study of patients undergoing video-assisted thoracoscopic surgery (VATS) and thoracotomy found the prevalence of chronic pain was 40% and 47% after thoracotomy and VATS, respectively[20]. As a potential means to reduce post-operative and chronic pain from conventional thoracoscopic techniques, a transesophageal approach with NOTES evolved. The purpose was to develop a NOTES technique capable of accomplishing similar diagnostic studies and therapeutic interventions as conventional mediastinoscopy and thoracoscopy. In fact, it is felt that that access to the mediastinum via the esophagus would eliminate the need to dissect pre-tracheal fascia (as required in mediastinoscopy) and provide a better view of the lung hila with a flexible endoscope.

Initial results showed the feasibility of this approach in both sacrificed and survived swine models[21,22]. Identification and visualization of mediastinal and intrathoracic structures was accomplished and short-term survival with limited infectious complications was demonstrated. The development of a transesophageal platform could lead to less pain and scarring than occurs with conventional thoracoscopy and transcervical mediastinoscopy. The field of NOTES has permitted us to embark on the development of new approaches to laparoscopic and thoracoscopic techniques. The purpose of this article is to provide an overview of the currently available animal study data on trans-esophageal NOTES. In addition, we discuss potential barriers to the evolution of these techniques and speculate on future work and advancements needed to bring such innovative endoscopic surgeries to human trials.

TRANSESOPHAGEAL ACCESS TECHNIQUES

As with the transgastric approach, techniques continue to be developed that permit safe and controlled transesophageal access to the mediastinum and thorax. Using endoscopic ultrasound (EUS) to identify an appropriate esophageal entry site, Fritscher-Ravens *et al*[23] performed an esophageal incision using a needle-knife and exited directing into the mediastinum (Figure 1). EUS permitted identification of large vessels and positioning near the heart for planned procedures. After marking the site of entry into the esophagus by suctioning the esophageal wall and leaving an imprint, a standard gastroscope was introduced to perform an esophagotomy for mediastinal entry. However, the use of EUS was later abandoned due to lack of necessity and a standard gastroscope only was used along with a needle-knife to create a 2-cm full thickness incision in the esophageal wall.

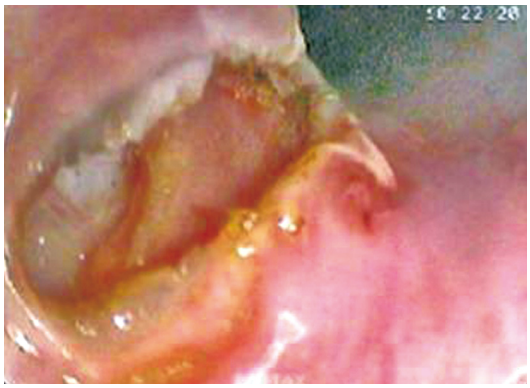


Figure 1 Endoscopic view showing access to the mediastinum following a full thickness incision with a needle knife alone. Reproduced with permission from Fritscher-Ravens *et al*[23].

Sumiyama *et al*[24] reported a new technique, called submucosal endoscopy, with a mucosal flap safety valve (SEMF). In this approach, saline injection into the esophageal wall was used to confirm entry into the submucosa, and high-pressure gas was used to perform a submucosal dissection. A biliary catheter was then inserted into the submucosal layer and a 10-cm long submucosal tunnel was created. Subsequently, an endoscopic mucosal resection (EMR) cap device (Olympus Optical Co, Ltd, Tokyo, Japan) was used to create a defect in the muscularis propria and the mediastinum was entered after removal of the EMR cap from the endoscope (Figure 2). The goal of this technique is to provide an offset closure of the defect with the overlying mucosal flap.

A similar approach was reported by Willingham *et al*[22], in which mediastinal access was demonstrated via submucosal tunneling. This technique employed a needle-knife, prototype flexible carbon dioxide laser fiber (OmniGuide Inc., Cambridge, MA, USA) or Duette multiband mucosectomy device (Cook Medical Inc) to incise the esophageal mucosal layer (Figure 3A). In this method, a long submucosal tunnel (Figure 3B) of at least 10-cm was created using air and blunt dissection with the endoscope and the aid of closed forceps. The tunnel was extended to the gastroesophageal junction. Unlike Sumiyama *et al*[24], a needle-knife was used to directly incise the muscular layer and provide a portal to the mediastinum (Figure 3C).

Each of these techniques provides relatively safe and efficient access to the mediastinum. In the three studies combined, major complications were limited to

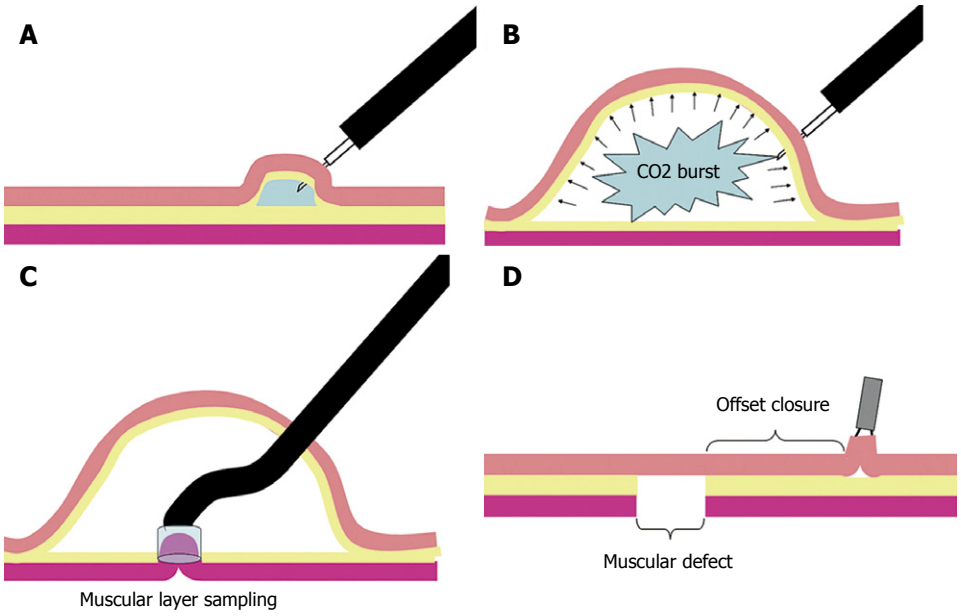
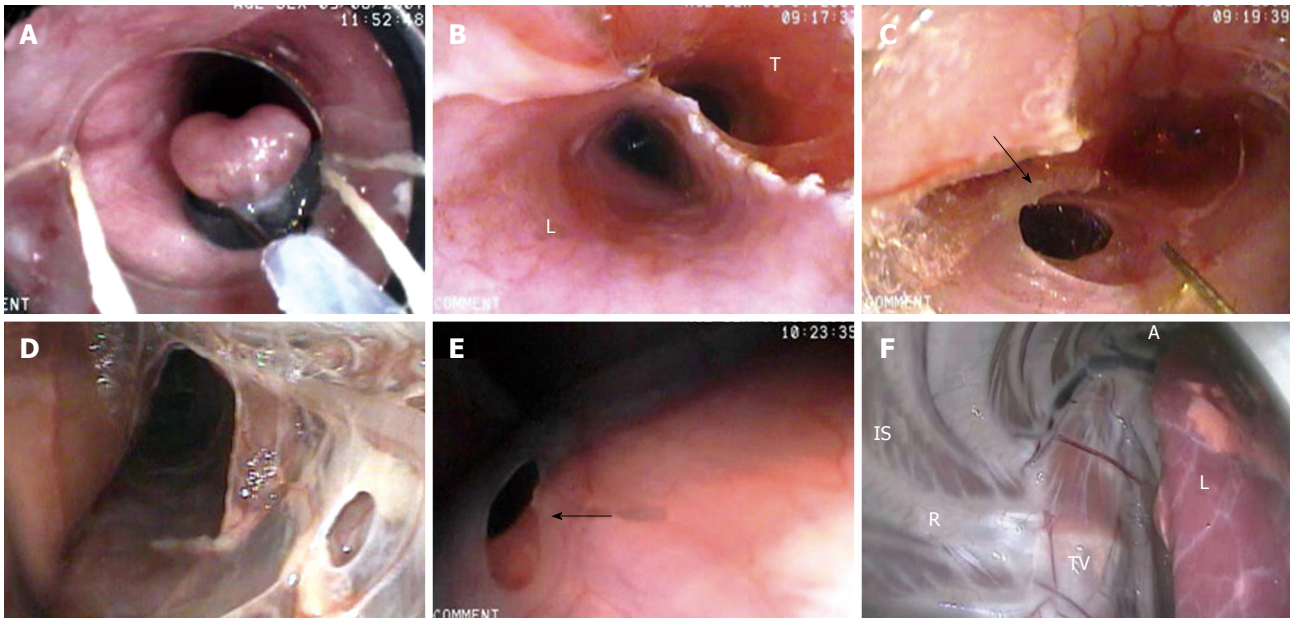


Figure 2 Transesophageal mediastinoscopy technique. A: Saline-solution-injection test to confirm needle-tip entry into the submucosa; B: Gas submucosal dissection with high-pressure CO2; C: Muscular-layer resection with cap-EMR technique inside of the submucosal space; D: Offset closure of the muscular defect with overlying mucosal flap. Reproduced with permission from Sumiyama *et al*[24].



Figures 3 This figure outlines the process of transesophageal entry into the mediastinum and shows representative flexible endoscopic views. A: Endoscopic view of the Duette Band Mucosectomy device. A band is placed around a small segment of esophageal mucosa and a snare is placed around the entrapped mucosa. Electrocautery is applied through the snare to accomplished resection of the mucosa; B: Endoscopic view of the esophageal lumen (L) and the submucosal tunnel (T); C: Endoscopic view from within the submucosal tunnel. A needle knife, pictured in the lower right corner of the image, is used to create and esophageal exit site (indicated by the black arrow); D: View of the mediastinum with the lateral esophageal wall on the left and pleura on the right; E: Endoscopic view of the lung and pleura. The black arrow shows a tear in the pleura created by biopsy forceps, which permits entry into the chest cavity; F: Endoscopic view of the chest cavity structures including the lung apex (A), lung (L), thoracic vertebra (TV), rib (R), and intercostal space (IS). Figure 3A-C and 3E are reproduced with permission from Gee *et al*[21] Figure 3D is reproduced with permission from Willingham *et al*[22].

one animal requiring immediate euthanization due to respiratory distress from pleural injury.

TRANSESOPHAGEAL NOTES MEDIASTINOSCOPY AND THORACOSCOPY

In clinical practice, transesophageal access remains limited to the sampling of lymph nodes with EUS. Studies in swine suggest that the new frontier of transesophageal access to perform minimally invasive procedures is feasible. Gee *et al*[21] published a study that looked at the feasibility of transesophageal mediastinoscopy and thoracoscopy in a swine model. These results reported excellent visualization of mediastinal structures (Figure 3D). Following entry into the mediastinum, a small tear in the pleura was made to enter the chest cavity (Figure 3E). Thoracic structures were then easily identified (Figure 3F). In this study, all animals thrived and had no

Table 1 Access techniques and interventions performed in swine transesophageal NOTES studies

Study	Year	Number of subjects (*n*)	Survival study (Yes/No), (*n*)	Days survived, (*n*)	Esophagotomy method	Intervention (s) performed
Fritscher-Ravens *et al*[23]	2007	9	Yes[2], *n* = 3 Yes, *n* = 4 No, *n* = 2	14, (*n* = 3) 28, (*n* = 1) 42, (*n* = 3)	Needle-knife	Mediastinoscopy, thoracoscopy, myocardial and left atrium saline injection, pericardial fenestration, lymphadenectomy
Sumiyama *et al*[24]	2007	4	Yes[2]	14	SEMF	Mediastinoscopy
Gee *et al*[21]	2008	4	Yes[1]	8, (*n* = 2) 12, (*n* = 2)	m-SEMF	Pleural biopsy, Mediastinoscopy, thoracoscopy
Sumiyama *et al*[34]	2008	5	Yes[2]	7	SEMF	Mediastinoscopy, thoracoscopy, pericardial window, epicardial ablation
Willingham *et al*[22]	2008	5	No[1]	0	m-SEMF	Mediastinoscopy, thoracoscopy, pleural biopsy

[1]Denotes administration of pre-operative antibiotics only (1 g Ancef); [2]Represents post-operative antibiotics (5-7 d enrofloxacin). SEMF: Submucosal endoscopy with mucosal flap safety valve; m-SEMF: Modified SEMF.

Table 2 Closure techniques and associated complications in swine transesophageal NOTES studies

Study	Esophageal closure strategy	Early complications	Late complications	Morbidity (*n*)	Mortality (%), (*n*)
Fritscher-Ravens *et al*[23]	Prototype T-tag device (*n* = 6) EndoClip (*n* = 3)	Pericardial hematoma (acute animal)	None	1	None
Sumiyama *et al*[24]	SEMF	Pleural injury resulting in death	None	None	25 (*n* = 1)
Gee *et al*[21]	m-SEMF + Endoclip (*n* = 2), m-SEMF only (*n* = 2)	None	Subclinical esophageal abscess	1	None
Sumiyama *et al*[34]	SEMF + EndoClip	Descending aorta injury	Esophageal mucosal ulceration at SEMF site	1	20 (*n* = 1)
Willingham *et al*[22]	m-SEMF + EndoClip	Pneumothorax requiring angiocatheter decompression	N/A	1	None

EndoClip: Metal clip applied to esophageal mucosa; N/A: Not applicable in this non-survival study.

clinical evidence of mediastinitis or thoracic contamination. EUS has also been used to identify small mediastinal lymph nodes that could be targeted for sampling and complete removal[23]. In cases where fine needle aspirates do not provide sufficient information, the preserved lymph node architecture obtained with this technique could provide a more definitive pathologic sample.

The use of transesophageal access to perform diagnostic and therapeutic interventions in the mediastinum and chest seems to be a growing possibility. To date, interventions in swine models have included lymph node biopsies and lymphadenectomy, pericardial fenestration, myocardial saline injections, pleural biopsy, and the creation of a pericardial window among others[21,23]. A current summary of experience with transesophageal access to the mediastinum and thoracic cavity is detailed in Tables 1-2. Overall, the results are promising and propose an array of intrathoracic interventions that could be accomplished with less post-operative and chronic pain. While several factors prevent large studies being carried out in swine models, larger, randomized studies are needed to compare procedure times and outcomes to standard thoracoscopic interventions.

ESOPHAGOTOMY CLOSURE

An important part of performing NOTES procedures in humans lies in the esophagotomy closure technique and the ability to prevent infectious complications. Sumiyama *et al*[24] and Gee *et al*[21] have performed survival studies in swine without the use of a closure device. Both studies included the creation of a submucosal tunnel. Perhaps unexpectedly, these studies demonstrated good clinical outcomes and no evidence of large abscesses or mediastinitis. One group has experimented with endoscopic suturing devices for the closure of transesophageal entry sites[23]. While the endoscopic sutures successfully closed the mucosal defects in the esophagus, there were remaining defects in the esophageal muscular wall on necropsy. More recently, a group reported the first use of resorbable sutures at transgastric NOTES access sites, which could have applicability to esophageal sites as well[25]. It is unclear whether the use of endoscopic sutures or the submucosal tunneling technique will be superior in allowing proper healing of the transesophageal exit conduit without infectious complications. Animal trials comparing the outcomes of these different techniques have not yet been published.

It is possible that placement of an esophageal stent may prove useful in some cases and produce better outcomes than endoscopic suturing or the tunneling techniques. In humans, observational studies have looked at the utility of esophageal stent placement following

esophageal perforations. One such study looked at 15 patients with non-malignant spontaneous or iatrogenic esophageal perforations treated with self-expandable metal stents[26]. The study demonstrated excellent outcomes in one group (7 patients) undergoing immediate stent placement following identification of the perforation. This group had a mean delay of 45 min from the time the perforation was identified to placement of the stent. The second group (8 patients) had poorer outcomes, including one death, and a median delay of 123 h to stent placement. In the setting of transesophageal procedures, stents could be immediately placed following procedures resulting in significantly better outcomes. A second study in a series of 9 patients with non-malignant gastrointestinal perforations of the esophagus and colon, as well as anastomotic leaks and complete disunion, suggested that covered stents might support a new concept of "stent-guided regeneration and re-epithelialization" that would aid in healing. Though observational evidence for stents seems promising, randomized trials remain to be performed to better assess their utility to treat luminal perforations as opposed to traditional surgical interventions.

BARRIERS TO CLINICAL PRACTICE

Problems with esophageal closure techniques, the risk of esophageal leaks, and infections including mediastinitis, pneumonia, and bacteremia are major concerns when attempting to access the chest cavity with a transesophageal route. Large studies investigating infectious complications have not been reported and are challenging to complete due to the limitations of animal models. The trials summarized in Table 2 suggest the rate of infectious complications could be low. Human trials investigating transgastric instrumentation of the peritoneal cavity do report contamination of the peritoneal cavity, but the contamination was found to be clinically insignificant[17, 27, 28].

Other adverse events including bleeding and pneumothoraces are significant complications in human thoracoscopic procedures[29,30]. These complications have also been observed in swine NOTES thoracic studies. Conventional interventions such as needle decompression or use of chest tubes can be performed, though there has never been a need for chest tube placement in the animal studies reviewed in Table 2. Researchers have also turned their attention to improving methods of hemostasis. Fritscher-Ravens *et al*[31] conducted a randomized controlled study comparing different methods of obtaining endoscopic hemostasis following artificially induced hemorrhage in the peritoneal cavity. The study assessed several methods of hemostasis including an endoscopic suturing device, prototype monopolar electrocautery forceps, and forced argon plasma coagulation (FAPC). In the end, FAPC was found to have significantly faster times in controlling bleeding and in achieving complete cessation of blood loss when compared to the other methods. It will be important to extend these studies to look at hemostatic methods in the chest since vessels within the chest, including intercostal arteries and veins, can be difficult to access due to surrounding bony structures (i.e. ribs and vertebral bodies).

In a systematic review of thoracic NOTES procedures, mortality was found to be 5% and morbidity 19% when combining all published studies of thoracic-related studies using a NOTES technique[32]. This review included two studies in which thoracic procedures were accomplished with a transvesicular, transdiaphragmatic, or transgastric approach, while the remaining five studies were transesophageal. The morbidity and mortality found in the combined studies represent one of the major challenges in creating a new, minimally invasive technique and underscores the technological improvements that are necessary to move transesophageal NOTES to human clinical applications.

FUTURE DIRECTIONS

A foundation for potential transesophageal NOTES thoracic procedures has been established. Moving forward, there is a need for studying the hemodynamic and physiologic consequences of these transesophageal interventions. In the literature, studies have been performed on the effects of carbon dioxide insufflation during transthoracic thoracoscopy[33]. This study of 32 consecutive patients demonstrated that intrapleural pressures of 2-14 mmHg did not have significant adverse hemodynamic consequences and that insufflation at pressures of < 10 mmHg were safe. Studies will need to be performed examining the consequences of controlled endoscopic insufflation with room air versus the use of carbon dioxide regulated insufflation and other potential consequences of an esophageal entry site.

Future work will continue to focus on potential infectious complications and how to best prevent these occurrences. The field will also need continued instrument development to improve hemostatic ability when bleeding complications occur or when transesophageal surgical resections are performed. Finally, a closure device and/or technique permitting full thickness closure of the esophageal wall without the development of an esophageal wall abscess, stricturing, or discontinuous muscular wall closure needs further development.

CONCLUSION

Transesophageal NOTES is a promising platform that may offer hope for a less invasive means of accessing the mediastinum and chest cavity. The continued relationships of surgeons, gastroenterologists, and researchers in industry are crucial for the development of devices that will permit better endoscopic control

and precision during planned operative procedures. Technological advances remain to be made that will make transesophageal NOTES a viable approach in humans, however, preliminary studies suggest this technique is of great potential to the field of thoracic surgery.

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