

Preserving the pulmonary vagus nerve branches during thoracoscopic esophagectomy

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Abstract

Background Pulmonary vagus branches are transected as part of a transthoracic esophagectomy and lymphadenectomy for cancer. This may contribute to the development of postoperative pulmonary complications. Studies in which sparing of the pulmonary vagus nerve branches during thoracoscopic esophagectomy is investigated are lacking. Therefore, this study aimed to determine the feasibility and pitfalls of sparing pulmonary vagus nerve branches during thoracoscopic esophagectomy.

Methods In 10 human cadavers, a thoracoscopic esophagectomy was performed while sparing the pulmonary vagus nerve branches. The number of intact nerve branches, their distribution over the lung lobes and the number and location of the remaining lymph nodes in the relevant esophageal lymph node stations (7, 10R and 10L) were recorded during microscopic dissection.

Results A median of 9 (range 5–16) right pulmonary vagus nerve branches were spared, of which 4 (0–12) coursed to the right middle/inferior lung lobe. On the left side, 10 (3–12) vagus nerve branches were spared, of which 4 (2–10) coursed to the inferior lobe. In 8 cases, lymph nodes were left behind,

at stations 10R and 10L while sparing the vagus nerve branches. Lymph nodes at station 7 were always removed.

Conclusions Sparing of pulmonary vagus nerve branches during thoracoscopic esophagectomy is feasible. Extra care should be given to the dissection of peribronchial lymph nodes, station 10R and 10L.

Keywords Thoracoscopic esophagectomy · Pulmonary nerves · Mediastinal lymphadenectomy · Pulmonary complications

Pulmonary complications are the most frequently encountered complications following esophagectomy. Many strategies have been developed to reduce these complications [1], such as minimally invasive surgery [2, 3]. However, depending on the definition used [4], pneumonia incidence rates of 12 % [2], 20 % [5] and 36 % [6] are still reported. Postoperative pneumonia increases the length of hospital stay, intensive care unit re-admissions and even mortality, emphasizing the need to refine the therapeutic strategies in order to reduce these problems [6].

The vagus nerve exerts an important regulatory role in inflammation and many pulmonary functions such as the cough reflex, bronchus diameter and mucous production [7–9]. Recently, we have demonstrated that nearly all vagus nerves to the right lung and inferior left lung lobe are transected by the mediastinal lymphadenectomy performed during transthoracic esophagectomy [10]. One clinical study has suggested that sparing the pulmonary branches of the vagus nerve during open transthoracic esophagectomy reduces the incidence of pulmonary complications and even mortality [11]. Studies which investigate whether these pulmonary vagus nerve branches can be spared during minimally invasive esophagectomy do not exist.

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An important argument not to spare vagus nerve branches is to ensure a radical and complete lymphadenectomy. A radical lymphadenectomy by a transthoracic approach is preferred for esophageal carcinoma since there is a survival benefit [12–14]. However, it is unclear whether or not the pulmonary branches of the vagus nerve can be spared during thoracoscopic esophagectomy without compromising a radical lymphadenectomy. Therefore, an experimental cadaveric study was performed to determine the feasibility of sparing the pulmonary vagus nerve branches during thoracoscopic esophagectomy with mediastinal lymphadenectomy as performed for esophageal carcinoma.

Methods

An experimental cadaveric study was performed at the Department of Anatomy of the University Medical Center Utrecht. All cadavers were obtained through a nationwide donation program in which people donate themselves after death for research and education through written consent.

Surgical procedure

In total, 10 adult, fresh-frozen cadavers without signs of previous cervical or thoracic surgery were included. Surgery was conducted by two surgeons who perform >50 minimally invasive surgery esophageal resections yearly (RvH and JR). Endoscopic surgical equipment consisted of a 30° angled rigid endoscope, Xenon® 300-W light source, 27-inch monitor and basic laparoscopic instruments (Karl Storz, Tutlingen, Germany). A right-sided thoracoscopic esophagectomy was performed as described previously with cadavers placed in a left lateral decubitus position [15]. The location where a right-sided vagotomy would normally have been performed was clipped to determine which nerve branches would have been transected during conventional *en bloc* esophagectomy, performed as described previously [15, 16]. Generally, vagotomy is performed at the upper edge of the main bronchus in our institution.

Each procedure started with division of the right pulmonary ligament and an anterior incision through the right parietal pleura from the diaphragm up to the azygos vein. The azygos vein was transected after endoclip application. Then the pleura was incised along the azygos vein, and a posterior dissection plane was created between the esophagus and the aorta. Subsequently, the esophagus was dissected from the pericardium through the anterior pleural incision. This anterior dissection plane was connected with the posterior plane, allowing retraction of the esophagus. The thoracic duct was identified at the aortic hiatus and transected following endoclip application. The anterior

plane was developed cranially, while the esophagus was retracted dorsally until the first large right pulmonary vagus nerve branch was encountered (Fig. 1A). Now the anterior pleural incision was extended cranially, exposing the trachea. The usual level of right vagotomy was identified and marked by clipping the right vagus nerve at the superior edge of the right main bronchus. All tissues overlying the right pulmonary vagus nerve branches were dissected and resected *en bloc* with the esophagus.

The posterior dissection plane was extended cranially, dissecting the esophagus from the trachea. Now the esophagus only remained fixed at the level of the carina. Distally, the right vagus nerve was transected below the level of the last large pulmonary vagus nerve branch. The right vagus nerve including pulmonary branches was carefully dissected, while the esophagus was retracted. This exposed the carinal lymph nodes which were dissected *en bloc*. Then the left vagus nerve could be transected after identification and sparing of the distal most large left pulmonary vagus nerve branch (Fig. 1B). The esophagus was dissected from the left vagus nerve, completing the thoracic phase.

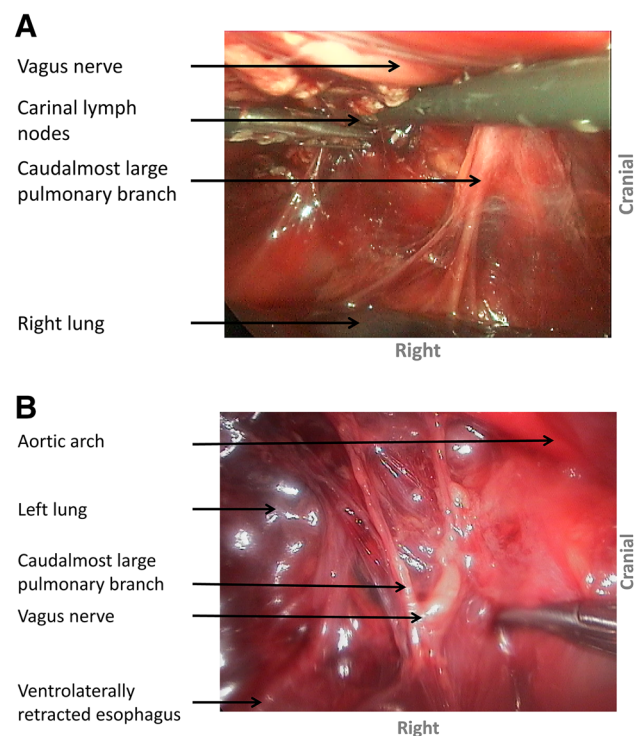


Fig. 1 Photograph from a right lateral viewpoint showing the most caudal large pulmonary branch of the right vagus nerve during minimally invasive transthoracic esophagectomy in left lateral decubitus position (A) and the distal most large pulmonary branch of the left vagus nerve (B)

Measurements

After each procedure, the surgeons graded how difficult sparing the pulmonary vagus nerve branches was, and how complete they regarded the mediastinal lymphadenectomy. A scale ranging from 0 to 10 was used. Regarding difficulty, 0 meant very easy and 10 very difficult, and for completeness, 0 meant very incomplete and 10 very complete. After the thoracoscopic esophagectomy and lymphadenectomy, the cadavers were dissected to determine the number of remaining pulmonary vagus nerve branches and lymph nodes. First, the thoracic cage was removed in total allowing for *en bloc* resection of the mediastinum. The left and right vagus nerves were identified cranially and dissected until the point of vagotomy was reached. The nerve branches posterior to the main bronchus to the right lung and left inferior lung lobe are at risk during conventional mediastinal lymphadenectomy [10]. Therefore, all intact nerve branches posterior to the main bronchus supplying the right or left lung were counted. The recurrent nerve may be at risk during the identification of the left recurrent nerve in the aortopulmonary window. Therefore, the left and right recurrent nerves were dissected to assess whether these were intact or not.

All left behind tissue next to the pulmonary vagus nerve branches was dissected with the aid of a surgical microscope (10582, Carl Zeiss, Oberkochen, Germany) and visually checked for the presence of lymph nodes. Lymph nodes at stations 10L, 10R and 7 were considered to have the highest risk of being left behind due to their location dorsal to the pulmonary vagus nerve branches [11]. Therefore, these stations were carefully examined. The lymph node stations were defined according to the guidelines of the American Joint Committee on Cancer and International Association for the study of Lung Cancer (Table 1) [17, 18]. All identified lymph nodes were individually fixed with formaldehyde 4 % and embedded in paraffin. The presence or absence of lymph nodes was confirmed by the examination of 7- μ m-thick microscopic tissue sections stained for hematoxylin and eosin (H&E). The remaining tissue, in which no lymph nodes could be identified macro- nor microscopically, was also fixed with formaldehyde and embedded in paraffin. Microscopic sections were taken randomly and H&E stained to check for missed lymph nodes.

Table 1 Investigated lymph node stations definitions

| | | |
|------------|---|--|
| Station 7 | Carinal lymph nodes | <i>Upper border:</i> tracheal bifurcation <i>Lower border:</i> upper border of right intermedium bronchus and left lower lobe bronchus |
| Station 10 | Right and left tracheobronchial lymph nodes | Immediately adjacent to main bronchi and hilar vessels. <i>Upper border:</i> inferior border of the azygos vein on the right side, upper border of the pulmonary artery on the left side. <i>Lower border:</i> interlobar region |

Statistical analysis

All analyses were performed using IBM SPSS statistics version 19. Continuous data were summarized as median (range).

Results

Feasibility

The right vagus nerve was identified in all cases and clipped where it would have been transected during conventional *en bloc* mediastinal lymphadenectomy. On the right side, a median of 9 (5–16) pulmonary vagus nerve branches posterior to the bronchus were spared (Table 2, Fig. 2A). These included 4 (0–12) branches of the right middle/inferior lung lobe. In 1 specimen, none of the right vagus nerve branches to the right middle/inferior lung lobe were spared.

The left vagus nerve was identified, and an attempt to spare it was made in 9 specimens.

On the left side, 10 (3–12) pulmonary vagus nerve branches were spared posterior to the lung hilum (Table 2, Fig. 2B). Of these nerve branches, 4 (2–10) coursed toward the left inferior lung lobe. In 1 specimen, the left lung was completely destroyed by empyema. Since the distribution of the spared pulmonary vagus nerve branches could not be determined in this specimen, it was not included in reported number of spared branches to the left inferior lung lobe.

Sparing the pulmonary vagus nerve branches was considered to be difficult by the surgeons [median difficulty score 8 (7–9)].

Pitfalls

It is difficult to identify the left vagus nerve during surgery due to its course behind the esophagus from a right posterolateral point of view. The left vagus nerve is retracted with the esophagus in order to dissect the carinal lymph nodes. This maneuver increases the risk of a proximal vagotomy, denervating the left inferior lung lobe.

The left recurrent laryngeal nerve is at risk during attempts to identify the proximal left vagus nerve stem in

Table 2 Numbers of intact pulmonary vagus nerve branches and left behind lymph nodes

| Case | Right posterior plexus | | | Left posterior plexus | | |
|----------------|------------------------|-----------------------------|----------------------------|-----------------------|---------------------|----------------------------|
| | Total | To median/ inferior lobe | Left behind lymph nodes | Total | To inferior lobe | Left behind lymph nodes |
| 1 | 16 | 8 | 7 | 3 | 0 | 0 |
| 2 | 8 | 5 | 1 | 10 | 5 | 1 |
| 3 | 8 | 4 | 0 | 10 | ? | 1 |
| 4 | 5 | 1 | 0 | 3 | 2 | 0 |
| 5 | 11 | 4 | 0 | 10 | 9 | 0 |
| 6 | 16 | 12 | 1 | 10 | 10 | 0 |
| 7 | 8 | 3 | 2 | 4 | 3 | 0 |
| 8 | 9 | 5 | 1 | 7 | 6 | 2 |
| 9 | 9 | 2 | 1 | 12 | 2 | 1 |
| 10 | 7 | 0 | 1 | 7 | 5 | 0 |
| Median (range) | 9 (5–16) | 4 (0–12) | 1 (0–3) | 10 (3–12) | 4 (2–10) | 0 (0–2) |

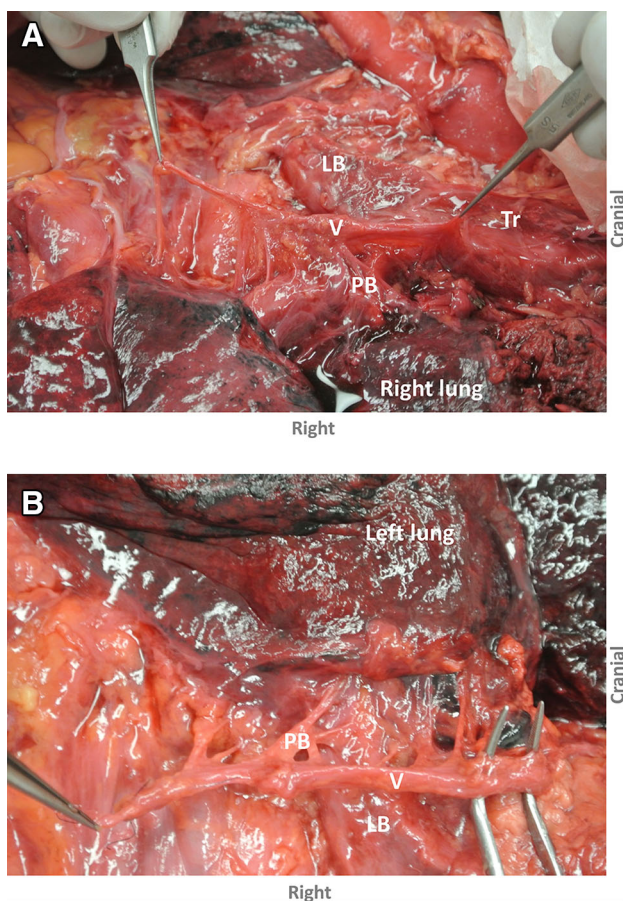


Fig. 2 Photographs from a dorsal viewpoint showing an intact right (A) and left posterior pulmonary plexus (B) following minimally invasive esophagectomy with complete mediastinal lymphadenectomy. Abbreviations *Tr* trachea, *LB* left bronchus, *V* vagus nerve, *PB* pulmonary branch

the aortopulmonary window (Fig. 3). In 1 specimen, identification of the proximal left vagus nerve stem was attempted, completely severing the left recurrent nerve. The left recurrent nerve was not injured when the left vagus nerve stem was identified by finding the most caudal large pulmonary vagus nerve branch with subsequent vagotomy distal to this branch. The right recurrent laryngeal nerve was intact in all cases.

Completeness of mediastinal lymphadenectomy as perceived by the surgeons was considered to be high [median score 9 (7–10)]. Figure 3 shows the relevant lymph node stations: 7, 10R and 10L. All lymph nodes at station 7 (subcarinal) were resected. On the right side, peribronchial (10R) lymph nodes were left behind in 7 cases [median 1 (0–3)] (Table 2). On the left side, peribronchial (10L) lymph nodes were left behind in 4 cases [median 0 (0–2)]. The specific locations of the peribronchial lymph nodes

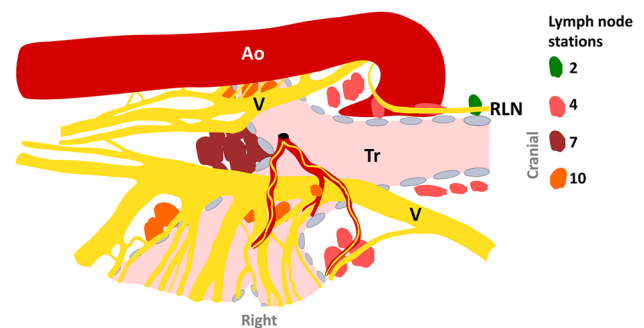


Fig. 3 Figure showing the pulmonary branches of the vagus nerve in relation to the relevant lymph node stations, those at stations 7, 10R and 10L. Abbreviations *Tr* trachea, *V* vagus nerve, *Ao* aorta, *RLN* recurrent laryngeal nerve

that were left behind were on the membranous part of the right main bronchus, in the most lateral corner between the right pulmonary vein and the right main bronchus, in the lateral most corner between a left pulmonary vein and the left main bronchus and in tissue surrounding the severed right bronchial artery (Fig. 4).

Discussion

Reduction in the severity and incidence of pulmonary complications following esophagectomy is of utmost importance and remains challenging. In the last decade, pulmonary complications following esophagectomy remain very common and significantly increase postoperative mortality [19]. Many important pulmonary functions are controlled by the vagus nerve [7–9]. Conventional mediastinal lymphadenectomy during esophagectomy significantly denervates the lungs, potentially contributing to the development of postoperative pulmonary complications

[10]. In the current study, it is shown that a significant part of the pulmonary innervation can be spared during thoracoscopic esophagectomy. The main pitfall is leaving behind lymph nodes that might have been resected otherwise.

Sparing of the entire vagus nerve during esophagectomy improves recovery [20]. For example, a vagus nerve-sparing transhiatal esophagectomy ($n = 49$) resulted in significantly lower pneumonia rates (4 versus 18 %), respiratory failure (0 versus 15 %) and length of stay (12 versus 16 days) compared to conventional transhiatal esophagectomy ($n = 39$) [20]. Unfortunately, this technique is contraindicated for stages >T1 or with lymph node metastasis since this would compromise the completeness of the resection [21]. A more selective approach, sparing the pulmonary vagus nerve branches only, may be a promising alternative and was therefore investigated by the present study.

This is the first study that evaluates the feasibility of sparing the pulmonary innervation during a thoracoscopic esophagectomy. In only one other study in open transthoracic 3-field esophagectomy, sparing of the pulmonary vagus nerve branches (and right bronchial artery) was investigated [11]. In this study, the pulmonary branches were identified and spared while retracting the vagus nerve. This seemed to prevent severe respiratory dysfunction and reduce in-hospital mortality. However, these results were not significant due to the small sample size ($n = 17$). Furthermore, it was unclear to what extent the pulmonary innervation was spared, and how this affected mediastinal lymphadenectomy. A problem were the at that time incomplete topographic descriptions of the pulmonary vagus nerve branches.

Therefore, recently the course of the pulmonary nerves has been described in detail [10] to develop and validate the here presented pulmonary nerve-sparing thoracoscopic esophagectomy. The extensive pulmonary nerve supply via the posterior pulmonary plexus consists of a median of 13 vagus nerve branches to the right lung, and a median of 12 branches to the left lung [10]. The most superior nerve branches innervate the superior lung lobe, and the most inferior nerves innervate the inferior lobe. This means that the most caudal large pulmonary branch of the vagus nerve has to be spared to preserve the inferior lung lobe innervation. This branch is located at a median of 9 mm beneath the right main bronchus, and 11 mm beneath the left main bronchus. Using the technique described in this study, most pulmonary vagus nerve branches could be spared: a median of 9 branches to the right lung and a median of 10 to the left lung. Studies should now determine whether this is beneficial.

Compromising mediastinal lymphadenectomy is the main risk of selective sparing of the pulmonary vagus

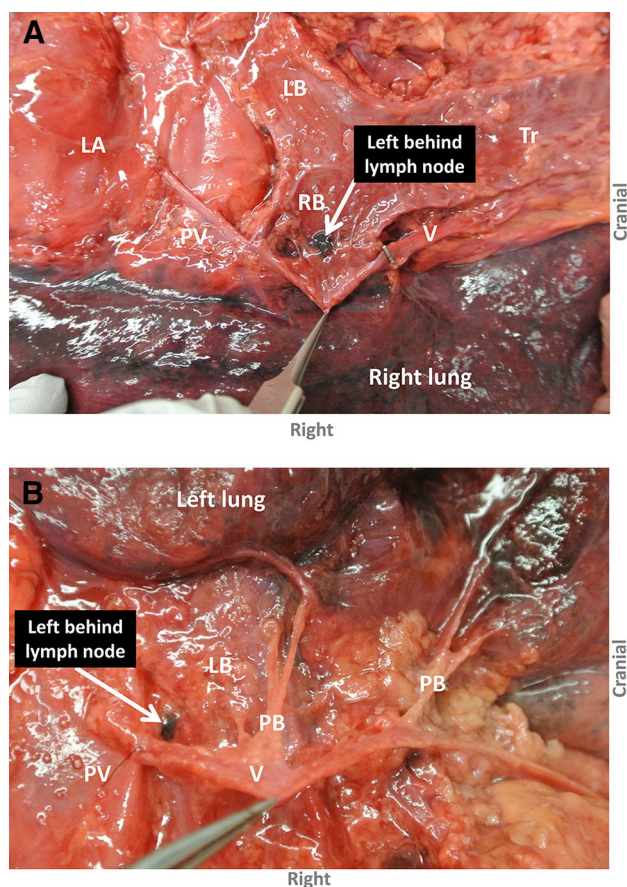


Fig. 4 Photograph from a dorsal viewpoint showing an example of a left behind lymph node at station 10R (A) and station 10L (B) following a pulmonary vagus nerve branches sparing esophagectomy. Abbreviations *Tr* trachea, *RB* right bronchus, *LB* left bronchus, *V* vagus, *LA* left atrium, *PV* pulmonary vein

nerve branches. The present study shows that lymph nodes at station 10R and 10L may remain in situ during this procedure. However, it is unclear whether these are resected during conventional mediastinal lymphadenectomy; also large variation exists between the extent of lymph node dissection worldwide [22–24]. Esophageal cancer might metastasize to peribronchial lymph node stations 10R and 10L. This is illustrated by a meta-analysis ($n = 18,415$, 93 % squamous cell carcinoma) showing a lymph node metastasis rate of 6 % in station 10R and 4 % in station 10L [25]. In esophageal adenocarcinoma ($n = 104$), the lymph node metastasis rate was 18 % in 10R and 15 % in 10L [26]. The main critic of these studies is that it is nearly impossible to correctly classify lymph nodes resected during esophagectomy. Lymph nodes ought to be classified based on their location with respect to surrounding mediastinal structures, which is impossible in a resection specimen. Furthermore, the retrieval of lymph nodes is very variable and dependent of the technique used and how an adequate lymph node dissection is locally defined. Interestingly, in the present study in most cadavers left behind lymph nodes were found, while the operating surgeon's perception was that the lymphadenectomy was very complete. This emphasizes the need for studies that aim to define the margins of an adequate mediastinal lymphadenectomy.

Hence, it is unclear whether leaving peribronchial lymph nodes behind when the pulmonary vagus nerve branches are spared will result in residual disease that would have been resected otherwise. Until this has been clarified and benefits of this technique are shown, we advocate careful removal of all lymph nodes in stations 10R and 10L. In this respect, robot assistance is interesting, since this may enable sparing of pulmonary vagus nerve branches with an adequate lymph node dissection through magnification (10x), three-dimensional vision, 7° of freedom and tremor filtering [15, 16].

Conclusions

It is feasible to spare pulmonary vagus nerve branches during thoracoscopic esophagectomy. The most important pitfall is leaving behind lymph nodes behind vagus nerve branches. Studies are needed to investigate the effect of sparing pulmonary vagus nerve branches on pulmonary complications.

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Compliance with ethical standards

Disclosures Teus J Weijs, MD; Jelle P Ruurda, MD, PhD; Misha DP Luyer, MD, PhD; Grard AP Nieuwenhuijzen, MD, PhD; Sylvia van der Horst, Ronald LAW Bleys, MD, PhD; and Richard van Hillegersberg, MD, PhD have no conflicts of interest to declare.

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