



The amount of mediastinal lymph nodes dissected in robot-assisted cervical esophagectomy—an experimental cadaver study

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Background: Transthoracic esophagectomy (TTE) is the preferred approach for curative esophageal cancer. However, concomitant single-lung ventilation limits its use in patients with compromised cardio-pulmonary function. Transhiatal esophagectomy (THE) grants two-lung ventilation yet offers a limited mediastinal lymphadenectomy and is only suitable for distal tumors. A promising alternative is robot-assisted cervical esophagectomy (RACE). Initial studies show its feasibility, yet, the mediastinal lymph node yield (LNY) is unknown. The aim of this study is to describe the accessibility of the lymph node stations (LNS) and to analyze to which extent the mediastinal LNS can be resected during the cervical phase of RACE.

Methods: Experienced robotic upper-gastrointestinal (GI) surgeons performed cervical esophagectomy and mediastinal lymphadenectomy on 4 cadavers using a “da Vinci Xi” surgical system through a left cervical approach. Target LNS were 4R, 4L, 5 and 7, as defined by Naruke. Resected tissues were categorized as primary—esophagus and lymph nodes (LNs) resected through RACE- or secondary—residual LNs post-RACE- resected tissue and were analyzed by experienced pathologists. LNs were counted for every station.

Results: Station 4R yielded a median of 16 LNs primarily and 12 secondarily; station 4L: 17 primarily, 0 secondarily; station 5: 4 primarily, 7 secondarily; and for station 7: 9 primarily and 5 secondarily.

Conclusions: This study shows that the RACE procedure delivers a limited mediastinal lymphadenectomy. LNS 4L can be fully resected. Stations 4R, 5 and 7 could be partially resected. The RACE procedure may, however, be a viable alternative for patients who cannot undergo a TTE.

Keywords: Cervical esophagectomy; mediastinal esophagectomy; robot-assisted; lymph node yield (LNY); lymph node station (LNS)

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Introduction

Esophageal cancer is one of the most common cancers worldwide and ranks 7th in oncologic mortality (1). Esophagectomy is the mainstay treatment for curative esophageal cancer (2). Minimally invasive transthoracic esophagectomy (TTE) is the best surgical approach to date as it provides the best accessibility to the mediastinum in order to obtain the highest possible lymph node yield (LNY), and is associated with less postoperative anastomotic complications and morbidity compared to an open approach (3). An extended lymphadenectomy is considered standard of care because of the unpredictable nature of lymph node (LN) metastasis in esophageal cancer, regardless of the location of the primary tumor (4,5), and because a higher LNY is associated with improved overall survival (6,7). The downside of TTE is the associated increased risk of pneumonia due to post-operative right sided chest pain, which can lead to an increased morbidity and short-term mortality (3). Moreover, TTE requires intraoperative single-lung ventilation. Patients with distal esophageal cancer with comorbidities refraining them from the TTE procedure may undergo transhiatal esophagectomy (THE) (3). Due to the limited access to the mediastinum, THE does not allow for lymphadenectomy in the mid to upper mediastinum. To overcome these limitations, the robot-assisted cervical esophagectomy (RACE) was developed. RACE combines a transhiatal with a transcervical approach. Initial studies demonstrated the

safety and feasibility of RACE (8-11) and presented the first clinical series (12-16). It is yet unknown to what extent the mediastinal lymphadenectomy can be performed in the RACE procedure. This study aims to identify the amount of resected and residual LNs per lymph node station (LNS) in the mid-upper mediastinum and to describe the accessibility of each LNS during RACE.

Methods

Cadaver study

An experimental cadaveric study was performed at the Department of Anatomy of the University Medical Center (UMC) Utrecht. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. All cadavers were obtained through a regional donation program in which people donate their entire bodies after death for research and educational purposes through written informed consent. Four fresh-frozen cadavers without signs of previous cervical, thoracic or abdominal surgery were included. The age and sex of cadavers one to four were 90 (male), 89 (female), 69 (male) and 91 (female) years old, respectively. Measurements of the thorax and neck extension were similar in all four cadavers.

Surgical team

The surgical experiment was conducted by a team of surgeons (J.P.R., R.v.H.) and a physician assistant (S.v.d.H.) of the UMC Utrecht, The Netherlands; and a surgeon (P.P.G.) of the UMC of the Johannes Gutenberg University Mainz, Germany. All surgeons are highly experienced in robotic esophagectomy, having performed >100 procedures individually and trained and proctored many surgeons. The RACE procedure was already being implemented in Mainz and not yet in Utrecht. All surgeons have previously performed cadaveric RACE procedures (10) and did extensive research into the anatomic point-of-view for this procedure (17,18). First assistant during the procedures was a physician assistant who is highly experienced in assisting robotic upper gastrointestinal (GI) tract surgery.

Intervention

Robotic equipment consisted of two “da Vinci Xi” surgical systems (Intuitive Surgical Incorporate, Sunnyvale, California, USA). Corresponding with the aim of the study, we performed only the cervical phase of RACE. For this, the

Highlight box

Key findings

- Robot-assisted cervical esophagectomy (RACE) delivers a limited mediastinal lymphadenectomy.

What is known and what is new?

- If a patient cannot undergo a transthoracic esophagectomy (TTE) due to comorbidities, the standard care for patients with a distal esophageal carcinoma is a transhiatal esophagectomy (THE); whereas patients with mid-upper carcinomas are deemed inoperable.
- The RACE procedure can be offered to patients with a malignancy located in the mid-upper esophagus who cannot undergo a TTE and the RACE procedure can yield a higher lymph node count compared to a THE.

What is the implication, and what should change now?

- The RACE procedure could be superior to the transhiatal approach and could be applied to a wider patient group. Safety and feasibility should be researched next.

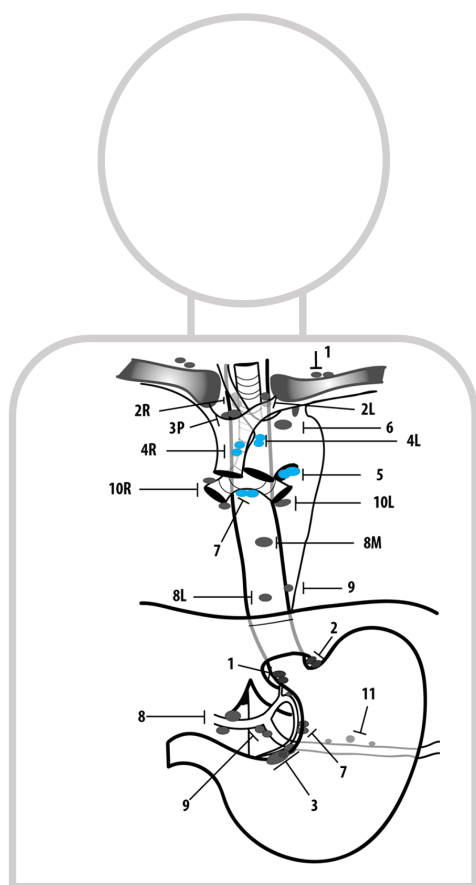


Figure 1 Schematic anterior overview of the thoracic and abdominal lymph node stations relevant for oncologic esophagectomy, according to the 7th edition of the AJCC cancer staging manual (19) and the 3rd edition of JGCA (20). The four lymph node stations marked blue are the stations of the mid-upper mediastinum of interest for this study: station 4R/L (lower paratracheal right and left), 5 (aortopulmonary window) and 7 (subcarinal). AJCC, American Joint Committee on Cancer; JGCA, Japanese Gastric Cancer Association.

anatomic area of interest was the mid-upper mediastinum, containing the LNS 4R/L, 5, and 7 as defined by Naruke, according to the 7th edition of the American Joint Committee on Cancer (AJCC) cancer staging manual (19), displayed in *Figure 1*. High paratracheal LNS 2R/L were not examined because they are not part of the standard lymphadenectomy in TTE. Tracheobronchial LNS 10R/L were not examined as they are pulmonary LNS and not part of the standard extensive lymphadenectomy in esophagectomy. The transhiatal dissection of RACE was not included because it is similar to THE which is extensively

researched and reported on. The tracheal bifurcation was used as the anatomical landmark to distinguish the lower and mid-upper mediastinum. The intervention consisted of five steps:

- (I) **Cervical port:** the body was positioned in a supine position with the head tilted backwards. At the left side of the neck, a 4 cm long incision along the medial border of the sternocleidomastoid muscle was made, after which the carotid sheath was approached (*Figure 2A*). Dissection medially of the carotid sheath was continued to reach the esophagus, which was looped. An Alexis wound retractor, or Gel port mini (Applied Medical, Rancho Santa Margarita, California, USA) was inserted and a GelSeal cap was used for the installation of the robotic system. Three 8 mm robot trocars were inserted in the GelSeal Cap, with the camera-port (300 up) anterior, cadierre forceps at the left lateral and a monopolar cautery hook at the right lateral port, as seen in *Figure 2B*. A posterior port was used for suction and irrigation by the physician assistant at the table (*Figure 2C*). The Gel port facilitated air pressurization of the mediastinum through carbon dioxide insufflation.
- (II) **Mobilization primary tissue:** using the previously defined anatomical landmarks (18), dissection was performed of the mid-upper esophagus (supracarinal esophagus) and corresponding mediastinal LNs. A plane between the vertebrae and the esophagus was created, using the prevertebral fascia as a posterior landmark. Lateral landmarks were the parietal pleura on both sides. Anteriorly, a plane between the esophagus and trachea was created. The dissection of the esophagus and LNS was performed up until below the tracheal bifurcation and the subcarinal LNS (LNS 7). Caution was made of vital anatomic structures including the recurrent laryngeal nerves and the membranous part of the trachea and main bronchi. The cervical dissection was video recorded for quality control of the technique. All tissue that was mobilized and removed through cervical dissection was marked as the “primary tissue”. LNs were collected in separate boxes corresponding to their LNS.
- (III) **Conversion to thoracotomy:** after mobilization of the primary tissue, the robotic system was removed. The cadaver was turned into a left semi-prone position and the thoracic cavity was opened through

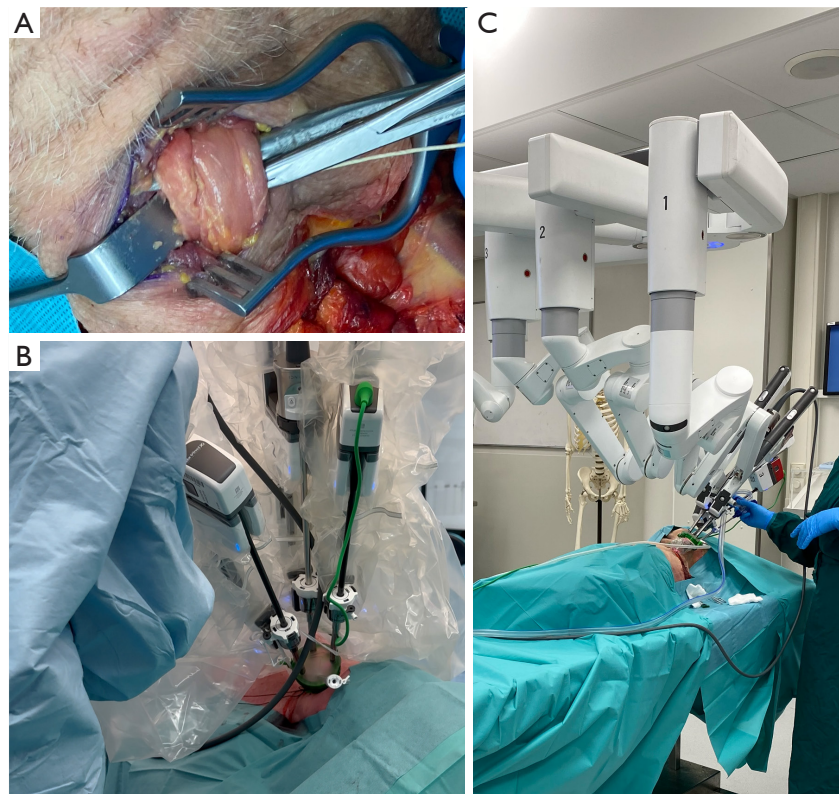


Figure 2 Cadaver torso and da Vinci Xi surgical system setup at the anatomy department. Access to the mediastinum is gained through a cervical incision at the left side of the neck, after looping the esophagus (A) the wound retractor is inserted and a gel cap is placed for the installation of the three robotic arms (B), a caudal port is used by the table assistant for suction and irrigation (C).

a right posterolateral thoracotomy (*Figure 3*).

- (IV) Resection primary tissue: the robotically mobilized esophagus was removed (primary tissue) by one of the surgeons and the PhD-student, guided by the pathologist (J.E.F.).
- (V) Resection secondary tissue: the mid-upper mediastinum was checked for residual LNs as would have been dissected during a formal TTE (*Figure 4*) by one of the experienced upper GI surgeons. When present, the residual LNs were resected according to the standard lymphadenectomy performed for (transthoracic) esophagectomy and collected in separate boxes corresponding to their LNS, marked as “secondary tissue”.

Outcome measures

The resected ‘primary’ and ‘secondary’ tissues were analyzed according to the standard clinical protocol for LN assessment in esophageal cancer at the pathology department of the

UMC Utrecht by an experienced pathologist (J.E.F.). All resected tissues were analyzed completely at macroscopic and microscopic level for the presence of nodes and an LN count was performed for each box. LNs on the resected esophagus specimen were labelled as “paraesophageal lymph nodes”. The microscopic analysis was blindly double-checked by another experienced pathologist (L.A.B.). Outcomes were reported as amount of LNs per LNS in the primary and secondary tissue. Adequate lymphadenectomy was defined as 0 LNs left *in situ* after primary resection. If no secondary resection was performed of a primarily resected LNS, we assume that no LNs were left *in situ* for that station based on the experience of the surgeons.

Statistical analysis

Descriptive statistics were calculated to summarize the data. Means and ranges were used to report the amount of LNs identified. These measures provided an overview of the distribution and variability of the found LNs per LNS.

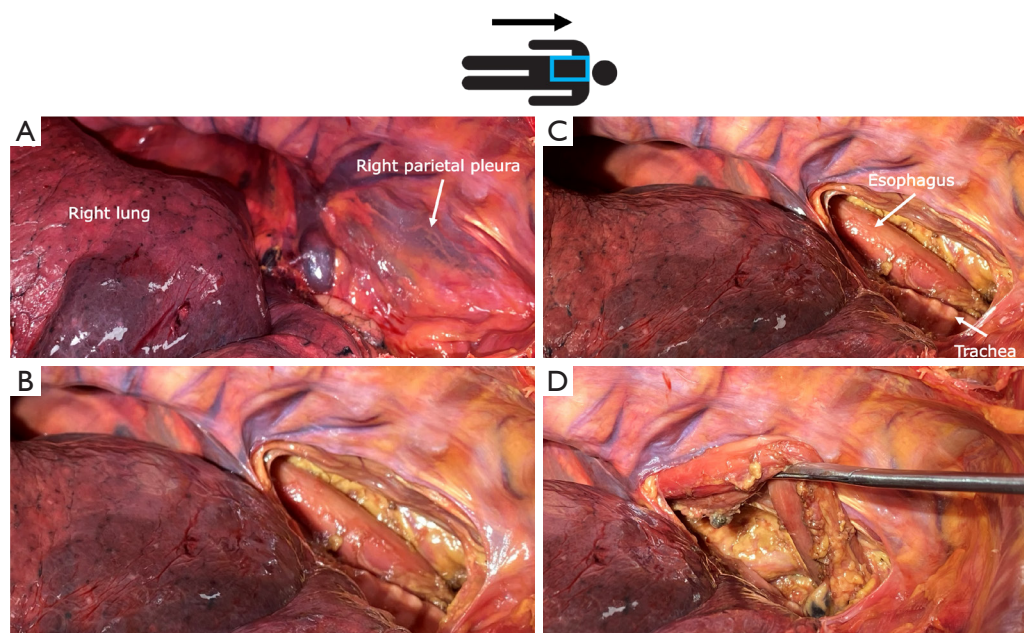


Figure 3 View after right thoracotomy, semiprone positioning. After mobilization of the upper esophagus and midthoracic lymph nodes (primary tissue), the da Vinci system was removed, and the thorax was opened through a right thoracotomy (A). After the right parietal pleura was dissected (B), the upper mediastinum comes into view, with the mobilized supracarinal esophagus (C,D).

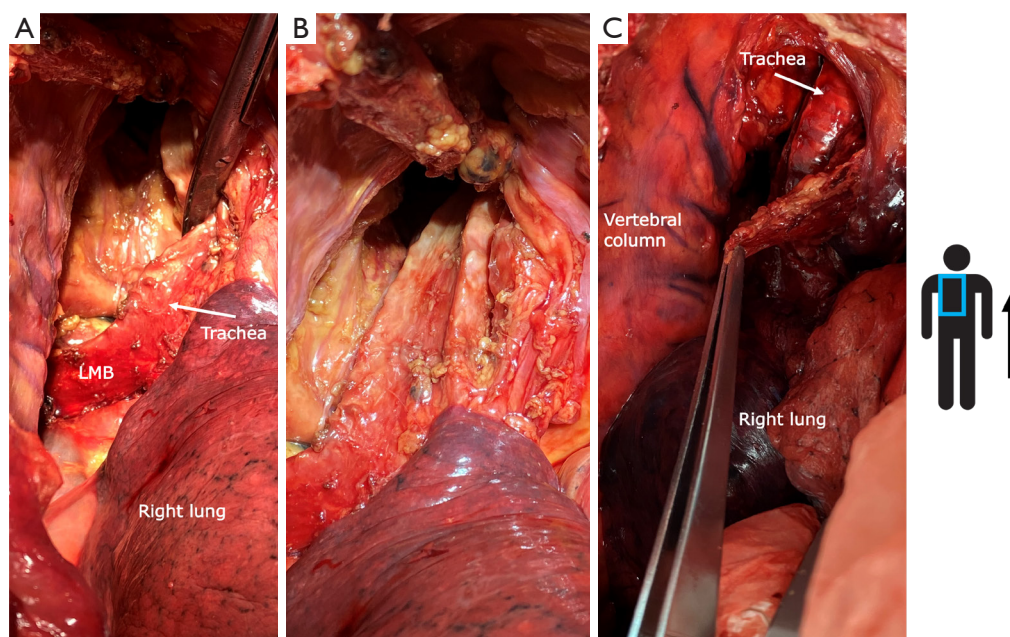


Figure 4 After the dissection of the esophagus, the midthoracic mediastinum is checked for residual lymph nodes (A,B); if found, the lymph nodes were resected and marked as “secondary tissue” (C). LMB, left main bronchus.

Table 1 All resected tissue, lymph node count per lymph node station of the primary and secondary resected tissues

Cadaver	LN station	Primary tissue, amount of LN	Secondary tissue, amount of LN
1	4R	–	5
	4L	6	0
	5	–	1
	7	0	5
	Paraesophageal	1	–
2	4R	–	–
	4L	5	–
	5	–	2
	7	5	–
	Paraesophageal	3	–
3	2L	5	–
	4R	1	5
	4L + paraesophageal	6	–
	5	4	–
	7	2	–
4	10L	–	4
	4R	15	2
	4L	–	–
	5	–	4
	7	2	–
	Paraesophageal	1	–

Paraesophageal: i.e., paraesophageal tissue and fat. “–”, no resection. LN, lymph node.

Results

In *Table 1*, all resected LNs are reported per LNS in the primary and secondary tissue. In cadaver 3, LNS 2L could be accessed during the primary resection and was resected as well. Only in cadaver 3, all four LNS were accessible. All primary resected LNs per LNS are shown in *Table 2*. The mean number of primarily resected LNs were 8 for LNS 4R, 5.7 for LNS 4L, 4 for LNS 5 and 2.3 for LNS 7, as would be the LNY per station for cervical esophagectomy. The total mean LNY was 25 (range, 7–18) in the upper thoracic mediastinum. The amount of LNs per LNS that were resected secondarily and would have been left *in situ* are also shown in *Table 2*. The mean number of secondarily resected LNs were 4 for LNS 4R, 0 for LNS 4L, 2.3 for LNS 5 and 5 for LNS 7. *Table 3* shows the adequacy of the cervical lymphadenectomy per LNS for each cadaver. Adequate resection of the left lower paratracheal station 4L and subcarinal station 7 was achieved in three out of the four cadavers. The LNs in the aortopulmonary window,

Table 3 Adequacy of lymphadenectomy in the mid-upper mediastinum of cervical esophagectomy

Cadaver/LNS	4R	4L	5	7
1	×	√	×	×
2	–	√	×	√
3	×	√	√	√
4	×	–	×	√

√, adequate resection; all lymph nodes of lymph node station primarily resected; ×, inadequate resection; >1 lymph node(s) left *in situ*; –, lymph node station not resected primarily and secondarily. LNS, lymph node station.

Table 2 Mean amount of lymph nodes resected per lymph node station through cervical (primary) resection, and left *in situ* per lymph node station as discovered through secondary resection

LN station	LN resected in total [n] [†]	LN resected, mean [range] [†]	LN <i>in situ</i> in total [n] [‡]	LN <i>in situ</i> , mean [range] [‡]
4R	16 [2]	8 [1–15]	12 [3]	4 [2–5]
4L	17 [3]	5.7 [5–6]	0 [1]	0
5	4 [1]	4	7 [3]	2.3 [1–4]
7	9 [4]	2.3 [0–5]	5 [1]	5

[†], primary resection; [‡], secondary resection. LN, lymph node; n, number of cadavers.

LNS 5, were completely resected in one out of four cadavers. As for the right lower paratracheal LNS 4R, the LNs could not or only partially be resected.

Technical challenges

Due to the confined space in the mediastinum during cervical esophagectomy, instrument collision incidentally occurred during the peri-esophageal dissection. Retracting the camera to the level of the thoracic inlet allowed visualization and resolution of these conflicts. Optimal port placement is of the utmost importance to minimize the chance of collision.

During cervical esophagectomy, the surgeon needs to be aware of the vital structures in surrounding tissues (17,18). In this experiment, the left recurrent laryngeal nerve was transected in 2 cadavers. In 1 cadaver, the right parietal pleura was damaged, leading to a more challenging intervention due to loss of pneumomediastinum.

Discussion

RACE seems to originate three decades ago in Germany and Japan. In search of alternative, less invasive techniques for TTE, in 1993 a mediastinoscope was developed specially for endodissection of the thoracic esophagus under direct vision (21), by a left cervical approach in combination with open THE [mediastinoscope-assisted THE (MATHE)]. Later, carbon dioxide insufflation was added for improved exposure (22). Reasons to perform mediastinoscopy were to reduce the risks associated with blunt dissection in THE and enabling LN dissection in cases with LN metastasis around the left recurrent laryngeal nerve (23). To this day, different MATHE operation modes have been developed (24,25), and keep improving (26). MATHE has been compared to THE, showing reduced morbidity and mortality in MATHE, as well as a greater mean number of resected LNs in MATHE (12 *vs.* 8) (27). In 2021, the MATHE operation has been adapted and altered and was called the minimally invasive transcervical esophagectomy (MICE). Recent work shows a median LNY of 29 LNs per patient in MICE, including both abdominal and mediastinal lymphadenectomy (28).

MATHE and MICE was adapted in robot-assisted surgery in 2019. Five articles have been published on the lymphadenectomy of transcervical robot-assisted esophagectomy (10-14). In three studies, a complete mobilization of the esophagus and LN dissection of the

whole mediastinum was performed (10,11,14). Nakauchi *et al.* (13), looked into LN dissection of the upper and middle mediastinum, they showed a median LNY of 20.5 nodes in the thoracic mediastinum. Mori *et al.* (12), compared the total LNY of robotic transthoracic and robotic nontransthoracic esophagectomy and found no difference in the amount of retrieved LNs (29 *vs.* 30, respectively) throughout the entire mediastinum. A recent study reported a novel approach, robot-assisted bilateral transcervical esophagectomy and reported a median of 37.2 retrieved LNs (29). Including the aforementioned literature, no reports have been found on the LNY for each mediastinal LNS, or the amount of residual LNs that remain in each LNS postoperatively.

In our study, the accessibility of the upper thoracic mediastinal LNS was poor. Only LNS 7 could be reached in all cadavers. LNS 4R was reached in 2 cadavers, LNS 4L in 3, and LNS 5 in only 1 cadaver. The resulting LNY of the mid-upper mediastinum that could be acquired through robotic cervical esophagectomy was very limited, as the median LNY per cadaver was 15.5 (range, 7–18). The median LNs left *in situ* per cadaver was 7.5 (range, 2–11). None of the mediastinal LNS could be fully dissected in all four cadavers. In two cadavers, 2 LNS were not resected primarily nor secondarily because no nodes were detectable to the surgeons. The cadavers did not show any presence of esophageal malignancy nor having received chemoradiotherapy, possibly affecting the size and number of LNs present. The inferior accessibility could be based on a decreased recognizability of LNs in fresh-frozen fatty tissue and connective tissue, as these are one of the first tissues to be affected postmortem by an increase of extracellular fluids. During the procedure there was difficulty to reach the low paratracheal LNS on the right (LNS 4R) due to the limited angulation towards this area and collision of the robotic instruments. The surgical tools that were used in this experiment are widely used in robotic TTE. However, the transcervical approach might require different technical approach as the LNS are positioned deep and behind unresectable tissue such as the trachea and the main bronchi. Technical solutions are needed to further improve RACE. The da Vinci Single Port surgical robotic system could possibly improve the accessibility and thus the LNY in RACE (16).

Intra-operative damage to the recurrent laryngeal nerve is a feared complication of esophagectomy and especially during RACE. Recent results of the MICE procedure showed a postoperative hoarseness in 48% of the patients,

of whom 91% recovered 1 year after the surgery (27). In our study, the left recurrent laryngeal nerve was damaged in two cadavers (50%). Decreased recognizability or increased fragility of the nerve tissue due to post-mortem changes could have attributed to this. Nonetheless, this area must be handled with much caution to prevent any palsy.

With a predicted increased incidence rate of esophageal carcinoma and a low 5-year survival, the surgical field aims to improve treatments and surgical outcomes (30). TTE is preferred due to the highest possible LNY and lower anastomotic leak rates. For patients who cannot undergo this approach, the RACE procedure could be the most fitting alternative approach. Compared to a solely transhiatal approach, the RACE procedure has a higher LNY, which could lead to improved survival. On top of that, while THE is suitable for patients with distal esophageal carcinoma, consisting mostly of adenocarcinomas (AC), RACE can be applied for tumors located in the mid-upper esophagus as well, which may include both AC and squamous cell carcinomas (SCC). RACE could offer a viable curative surgical treatment to the patient group with mid-upper esophageal carcinomas who have a contra-indication for TTE and are currently inoperable.

Conclusions

We described the accessibility of each mid-upper mediastinal LNS in RACE, as well as the LNY and the amount of residual LNs postoperatively per station. Our results show that stations 4L and 7 could be fully dissected in 3/4 cadavers. LNS 4R and 5 were not accessible enough to dissect properly or could not be reached at all. Still, RACE offers a higher LNY than solely a transhiatal approach and RACE could be a relevant technique for patients who are not suitable for a TTE with a mid-upper located tumor. As techniques are improving, the LNY in RACE will likely improve as well.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Informed consent was obtained from all individuals by registering for the regional donation program.

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