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Short-term Outcomes of Robot-assisted Minimally Invasive Esophagectomy Compared With Thoracoscopic or Transthoracic Esophagectomy

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Abstract. *Background/Aim: There is no study comparing open esophagectomy (OE), video-assisted thoracic surgery (VATS), and robot-assisted minimally invasive esophagectomy (RAMIE) in a single institution. Patients and Methods: This study included 272 patients who underwent subtotal esophagectomy divided into three groups: OE (n=110), VATS (n=127), and RAMIE (n=35) groups. Moreover, short-term outcomes were compared. Results: Overall complications (CD≥II) were significantly less in the RAMIE than the OE and VATS groups. Recurrent laryngeal nerve paralysis (CD≥II) was significantly lower in the RAMIE than the OE group (p=0.026) and tended to be lower than that in the VATS group (p=0.059). The RAMIE group had significantly less atelectasis (CD≥I and II), pleural effusion (CD≥I and II), arrhythmia (CD≥II), and dysphagia (CD≥II), than both the OE and VATS groups. Conclusion: RAMIE reduced overall postoperative complications after esophagectomy compared with both OE and VATS.*

Esophageal cancer is the sixth leading cause of cancer-related mortality worldwide because of its high malignant potential and poor prognosis (1). The postoperative 5-year survival rate in patients with American Joint Committee on Cancer stage I esophageal cancer is approximately 90%. This rate decreases to 45%, 20%, and 10% in patients with stages II, III, and IV diseases, respectively (2). Esophagectomy remains the most efficient treatment option, although chemoradiotherapy may effectively treat esophageal cancer (3). Despite advances in extended lymph node (LN) dissection and perioperative management of esophagectomy, it remains a highly invasive procedure associated with serious postoperative complications (4). The Japanese national database, including 5,354 esophagectomy patients in 713 hospitals in 2011, reported an overall morbidity rate of 41.9% and a 30-day and surgery-related mortality of 1.2% and 3.4%, respectively (5).

Thoracoscopic esophagectomy constitutes an attractive and less invasive alternative because esophagectomy with radical lymphadenectomy is one of the most invasive gastrointestinal surgeries (6). Of the patients, 4,209 (66.8%) underwent video-assisted thoracoscopic surgery (VATS). According to a Japanese national database, the ratio increases annually, including 6,298 esophagectomy patients in 2019 (7). Robot assistance provides an enlarged, three-dimensional field of view and improves the surgeon's dexterity due to surgical wrists and tremor filtration (8). Multiple retrospective studies have investigated the surgical outcomes of robot-assisted minimally invasive esophagectomy (RAMIE) compared to VATS since its development in 2003 (9-12). A randomized controlled trial reported the benefits of RAMIE over conventional open esophagectomy (OE) in terms of short-term outcomes, and comparable long-term results to OE were found (13).

However, there is no study comparing the three techniques of OE, VATS, and RAMIE in a single institution. This study hypothesized that VATS reduced postoperative complications compared to OE. Moreover, RAMIE reduced postoperative complications compared to VATS. Therefore, this study

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Key Words: Transthoracic esophagectomy, thoracoscopic esophagectomy, robot-assisted minimally invasive esophagectomy.

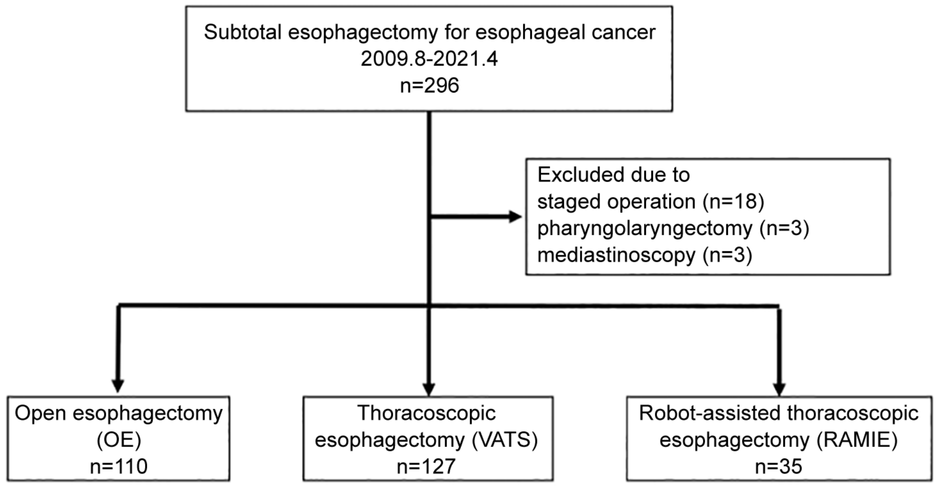

Figure 1. *Study design diagram.*

investigated the safety, feasibility, and short-term clinical outcomes of RAMIE for esophageal cancer.

Patients and Methods

Patients. This study retrospectively analyzed the records of 296 patients who underwent subtotal esophagectomy for esophageal cancer at the Department of Surgery, Hamamatsu University School of Medicine, Shizuoka, Japan, between August 2009 and April 2021. Of the 296 patients who underwent subtotal esophagectomy, eighteen who underwent staged operations, three who underwent pharyngolaryngectomy with total esophagectomy and three who underwent mediastinoscopic esophagectomy were excluded. The remaining 272 patients were divided into three groups according to the thoracic approach: OE group (*n*=110), VATS group (*n*=127), and RAMIE group (*n*=35; Figure 1). According to the tumor–node–metastasis (TNM) 8th classification system, all cancers were staged as reported by the International Union against Cancer (14).

Surgical procedure. An epidural cannula was inserted into each patient to administer intraoperative and postoperative analgesia per routine clinical protocol. All surgeries were performed under general anesthesia with selective intubation to block the right lung.

Most operations in the hospital included three-field LN dissection with an anastomosis in the neck (76.1%). This operation includes a right transthoracic subtotal esophagectomy and dissection of cervical (bilateral supraclavicular region), mediastinal (periesophagus and around the trachea, including the bilateral recurrent laryngeal nerve), and abdominal (perigastric and around the celiac axis) LNs. The other procedures in this study were two-field LN dissection (2FLND) with an anastomosis in the neck (23.9%). This operation includes a right transthoracic subtotal esophagectomy and dissection of mediastinal and abdominal LNs. All patients underwent LN dissection of the bilateral recurrent laryngeal nerves regardless of the procedures. The anastomosis was hand-sewn in the neck for all cases.

The thoracic procedures were performed through a right thoracic incision in the left decubitus position (40.4%) by VATS (46.7%) in the prone or the hybrid position (15, 16) or by RAMIE in the prone position (12.9%). Moreover, RAMIE was performed with the da Vinci Xi system (Intuitive Surgical Inc., Sunnyvale, CA, USA). The trocars for the thoracic RAMIE approach were placed as shown in Figure 2. One 8-mm port was inserted into the ninth or tenth intercostal space (ICS) on the scapular line in RAMIE. Three 8-mm ports were inserted into the seventh, fifth, and third ICSs between the anterior and the posterior axillary lines. Meanwhile, an assistant port was inserted into the fifth ICS on the anterior axillary line. The chest cavity was inflated using carbon dioxide insufflation at an 8-mmHg pressure. The upper mediastinal lymphadenectomy along the bilateral recurrent laryngeal nerves (numbers 106recR and 106recL) was mainly performed using scissors (Figure 3A and B).

The abdominal procedures were performed through an upper midline abdominal incision (37.5%) or by laparoscopic surgery (62.5%). Laparoscopic procedures were performed through a minilaparotomy (9 cm) with five trocars. Each patient was admitted to the intensive care unit (ICU) after surgery, and mechanical ventilation continued overnight. The patients were extubated on postoperative day (POD) 1 and admitted to the general surgical ward on POD 2 if their cardiopulmonary condition was stable.

Morbidity and mortality following esophagectomy. Postoperative complications were categorized using the Clavien-Dindo (CD) classifications as follows (17): grade I was any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, or radiologic intervention; grade II required pharmacologic treatment with drugs; grade III required surgical, endoscopic, or radiologic intervention; grade IV was life-threatening complications that required ICU management, and grade V was mortality. Postoperative mortality was defined as expiry within 30 days of operation or mortality during the initial hospitalization.

Statistical analysis. Statistical analysis was performed using IBM SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Demographic and surgical data (pre-, peri-, and postoperative) were compared

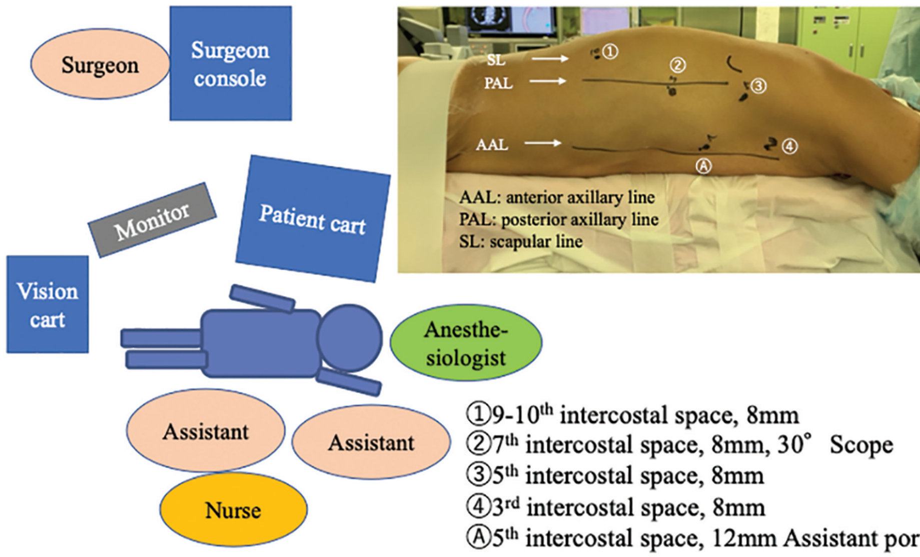

Figure 2. *Intraoperative position and port placement for robot-assisted minimally invasive esophagectomy.*

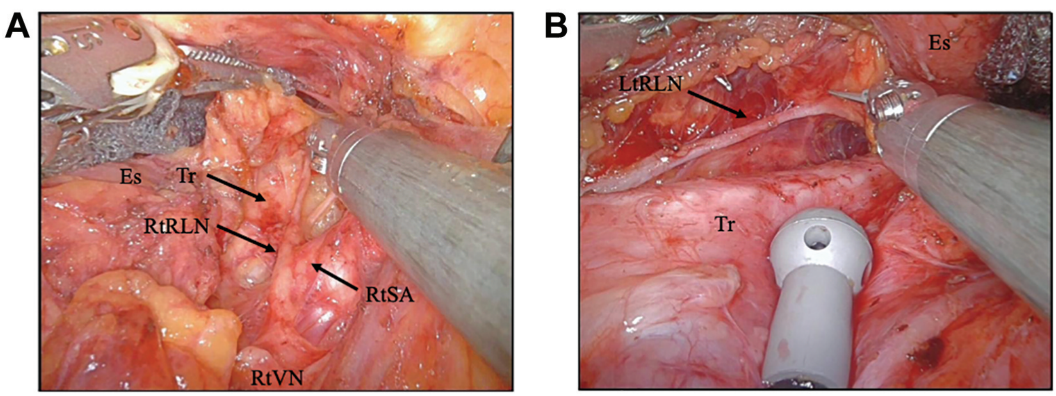

Figure 3. *Lymphadenectomy along the right recurrent laryngeal nerve (A) and left recurrent laryngeal nerve (B). Es: Esophagus; Tr: trachea; RtRLN: right recurrent laryngeal nerve; RtSA: right subclavian artery; RtVN: right vagus nerve; LtRLN: left recurrent laryngeal nerve.*

between OE and VATSs, OE and RAMIE groups, and VATS and RAMIE groups. Categorical data were analyzed using Fisher's exact test or the chi-square test, as appropriate. Quantitative data were analyzed using unpaired Student's *t*-tests. Moreover, $p<0.05$ was considered statistically significant for all analyses.

Results

Patient characteristics. Table I shows the clinicopathological characteristics of all patients. The median age was 67 years (range=32-85 years). Most patients were male (87.9%) and had squamous cell carcinoma (85.7%), followed by adenocarcinoma (12.1%). All patients in this study had undergone one-stage operations and reconstructed by gastric conduits. The patients were staged using the International Union against Cancer (UICC 8th edition) TNM classification system (14). According to the clinical staging of the esophageal cancers, 92 (33.8%), 73 (26.8%), 99 (36.4%), and 8 (2.9%) patients were cStages I, II, III, and IV, respectively. The RAMIE group included significantly more 2FLNDs and adenocarcinomas because it had more esophagogastric junction adenocarcinomas. Clinical trials comparing VATS with OE for squamous cell carcinoma (JCOG1409) (18) tended to include nontarget esophagogastric adenocarcinoma in the RAMIE group.

Perioperative outcomes. The intraoperative and postoperative outcomes are shown in Table II. In the OE group, the operation time was shorter, and the amount of blood loss was significantly higher than that in the VATS and

Table I. *Clinicopathological characteristics*.

Characteristics	All patients	OE	VATS	RAMIE	*p*-Value		
					OE *vs*. VATS	OE *vs*. RAMIE	VATS *vs*. RAMIE
Total	272	110 (40.4%)	127 (46.7%)	35 (12.9%)			
Age (years)	67 (32-85)	67 (40-79)	68 (40-82)	67 (32-85)	0.688	0.367	0.235
Gender					0.201	0.052	0.329
Male	239 (87.9%)	101 (91.8%)	110 (86.6%)	28 (80.0%)			
Female	33 (12.1%)	9 (8.2%)	17 (13.4%)	7 (20.0%)			
BMI (kg/m^2)	21.4 (14.2-33.1)	21.2 (14.3-31.2)	21.5 (14.2-33.1)	21.3 (15.5-28.4)	0.676	0.625	0.396
ECOG PS					0.747	0.782	0.962
0	210 (77.2%)	82 (74.5%)	100 (78.7%)	28 (80.0%)			
1	55 (20.2%)	25 (22.7%)	24 (18.9%)	6 (17.1%)			
2	7 (2.6%)	3 (2.7%)	3 (2.4%)	1 (2.9%)			
cStage (UICC TNM 8th)					<0.001	0.131	0.072
1	92 (33.8%)	20 (18.2%)	60 (47.2%)	12 (34.3%)			
2	73 (26.8%)	37 (33.6%)	30 (23.6%)	6 (17.1%)			
3	99 (36.4%)	48 (43.6%)	36 (28.3%)	15 (42.9%)			
4	8 (2.9%)	5 (4.5%)	1 (0.8%)	2 (5.7%)			
Surgical procedure					<0.001	<0.001	0.008
3FLND	207 (76.1%)	102 (92.7%)	89 (70.1%)	16 (45.7%)			
2FLND	65 (23.9%)	8 (7.3%)	38 (29.9%)	19 (54.3%)			
Reconstructed organ					1.000	1.000	1.000
Gastric conduit	272 (100%)	110 (100%)	127 (100%)	35 (100%)			
Others	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Reconstructed route					0.980	0.557	0.617
Posterior mediastinal	243 (89.3%)	97 (88.2%)	113 (89.0%)	33 (94.3%)			
Retrosternal	27 (9.9%)	12 (10.9%)	13 (10.2%)	2 (5.7%)			
Antesternal	2 (0.7%)	1 (0.9%)	1 (0.8%)	0 (0%)			
Laparotomy					<0.001	0.070	0.332
Laparoscopy	170 (62.5%)	53 (48.2%)	94 (74.0%)	23 (65.7%)			
Open	102 (37.5%)	57 (51.8%)	33 (26.0%)	12 (34.3%)			
Tumor location					0.074	0.131	0.823
Ut	32 (11.8%)	14 (12.7%)	15 (11.8%)	3 (8.6%)			
Mt	134 (49.3%)	63 (57.3%)	56 (44.1%)	15 (42.9%)			
Lt	106 (39.0%)	33 (30.0%)	56 (44.1%)	17 (48.6%)			
Histology					0.005	<0.001	0.069
SCC	233 (85.7%)	104 (94.5%)	106 (83.5%)	23 (65.7%)			
Adenocarcinoma	33 (12.1%)	3 (2.7%)	19 (15.0%)	11 (31.4%)			
Others	6 (2.2%)	3 (2.7%)	2 (1.6%)	1 (2.9%)			
pStage (UICC TNM 8th)					0.002	0.298	0.499
0	10 (3.7%)	5 (4.5%)	4 (3.1%)	1 (2.9%)			
1	73 (26.8%)	17 (15.5%)	45 (35.4%)	11 (31.4%)			
2	60 (22.1%)	25 (22.7%)	30 (23.6%)	5 (14.3%)			
3	88 (32.4%)	39 (35.5%)	37 (29.1%)	12 (34.3%)			
4	41 (15.1%)	24 (21.8%)	11 (8.7%)	6 (17.1%)			

Age and BMI are presented as median (range). OE: Open esophagectomy: VATS video-assisted thoracoscopic surgery; RAMIE: robot-assisted minimally invasive esophagectomy; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; PS: performance status; UICC: International Union against Cancer; TNM: tumor-node-metastasis; FLND: field lymph node dissection; Ut: upper thoracic esophagus (from the superior margin of the sternum to tracheal bifurcation); Mt: middle thoracic esophagus (superior half between tracheal bifurcation and esophagogastric junction); Lt: lower thoracic esophagus (thoracic esophagus from the inferior half between the tracheal bifurcation and esophagogastric junction); SCC: squamous cell carcinoma; 3FLND: three-field lymph node dissection.

Table II. *Intraoperative and postoperative outcomes.*

Characteristics	All patients	OE	VATS	RAMIE	*p*-Value		
					OE *vs*. VATS	OE *vs*. RAMIE	VATS *vs*. RAMIE
Total	272	110 (40.4%)	127 (46.7%)	35 (12.9%)			
Operation time (min)	558 (318-1,008)	536 (318-927)	578 (402-1008)	561 (455-671)	<0.001	0.440	0.014
Blood loss (ml)	250 (10-16,340)	455 (80-16,340)	178 (10-3,070)	150 (30-1,130)	0.003	0.062	0.345
Mortality	2 (0.7%)	2 (1.8%)	0 (0%)	0 (0%)	0.127	0.422	1.000
Overall complications (CD≥II)	181 (66.5%)	77 (70.0%)	93 (73.2%)	11 (31.4%)	0.582	<0.001	<0.001
Anastomotic leakage (CD≥II)	42 (15.4%)	22 (20.0%)	17 (13.4%)	3 (8.6%)	0.171	0.119	0.443
RLNP (CD≥I)	60 (22.1%)	24 (21.8%)	32 (25.2%)	4 (11.4%)	0.541	0.175	0.083
RLNP (CD≥II)	26 (9.6%)	14 (12.7%)	12 (9.4%)	0 (0%)	0.421	0.026	0.059
Wound infection (CD≥II)	23 (8.5%)	5 (4.5%)	16 (12.6%)	2 (5.7%)	0.030	0.779	0.251
Atelectasis (CD≥I)	81 (29.8%)	33 (30.0%)	46 (36.2%)	2 (5.7%)	0.311	0.003	<0.001
Atelectasis (CD≥II)	59 (21.7%)	29 (26.4%)	30 (23.6%)	0 (0%)	0.626	0.001	0.001
Pneumonia (CD≥II)	55 (20.2%)	26 (23.6%)	24 (18.9%)	5 (14.3%)	0.373	0.240	0.529
Pleural effusion (CD≥I)	128 (47.1%)	47 (42.7%)	80 (63.0%)	1 (2.9%)	0.002	<0.001	<0.001
Pleural effusion (CD≥II)	85 (31.3%)	36 (32.7%)	48 (37.8%)	1 (2.9%)	0.416	<0.001	<0.001
Chylothorax (CD≥I)	12 (4.4%)	6 (5.5%)	6 (4.7%)	0 (0%)	0.798	0.158	0.190
Chylothorax (CD≥II)	8 (2.9%)	3 (2.7%)	5 (3.9%%)	0 (0%)	0.607	0.324	0.233
Arrhythmia (CD≥II)	28 (10.3%)	12 (10.9%)	16 (12.6%)	0 (0%)	0.688	0.041	0.027
Dysphagia (CD≥II)	67 (24.6%)	22 (20.0%)	45 (35.4%)	0 (0%)	0.009	0.004	<0.001
Postoperative hospital stays (days)	25 (13-388)	29.5 (13-287)	25 (14-388)	24 (16-104)	0.076	0.058	0.467

Operation time, blood loss, number of resected mediastinal lymph nodes and postoperative hospital stays are presented as median (range). OE: Open esophagectomy; VATS: video-assisted thoracoscopic surgery; RAMIE: robot-assisted minimally invasive esophagectomy; CD: Clavien-Dindo classification; RLNP: recurrent laryngeal nerve paralysis.

RAMIE groups. Mortality was observed in two patients in the OE group. However, there was no significant difference. Overall complications (CD≥II) were significantly less in RAMIE (31.4%) compared with OE (70.0%) and VATS (73.2%). Recurrent laryngeal nerve paralysis (RLNP; CD≥I) occurred in less than half of VATS (25.2%) in RAMIE (11.4%), although the difference was not significant (p=0.083). RLNP (CD≥II) was significantly lower in the RAMIE (0%) than in the OE (12.7%; p=0.026) group and tended to be lower than in the VATS group (9.4%; p=0.059). The RAMIE group had significantly less atelectasis (CD≥I and II) and pleural effusion (CD≥I and II) compared to the OE and VATS groups. Arrhythmia (CD≥II) was significantly lower in the RAMIE (0%) than in the OE (10.9%; p=0.041) and VATS (12.6%; p=0.027) groups. Dysphagia (CD≥II) was significantly lower in the RAMIE (0%) than in the OE (20.0%; p=0.004) and VATS (35.4%; p<0.001) groups. Remarkably, there was no RLNP (CD≥II), atelectasis (CD≥II), chylothorax (CD≥I), arrhythmia (CD≥II), and dysphagia (CD≥II) in the RAMIE group. In the OE group, postoperative hospital stays (median, 29.5 days) tended to be longer compared with those in the VATS (median, 25 days; p=0.076) and RAMIE (median, 24 days; p=0.058) groups. However, the differences were not significant. Comparing the OE with the VATS group, wound infection (CD≥II; 4.5% *vs*. 12.6%), pleural effusion (CD≥I; 42.7% *vs*. 63.0%), and dysphagia (CD≥II; 20.0% *vs*. 35.4%) in the OE group were significantly less compared with the VATS group.

Discussion

Several single institution studies have currently demonstrated acceptable short-term outcomes of VATS for thoracic esophageal cancer in terms of operating time, blood loss, and postoperative complications, which are comparable with those of conventional OE (19, 20). Regarding operating time, most studies have reported that VATS has a longer operating, and involved less blood loss than OE (20). The current study also significantly demonstrated the longer operation time and less blood loss of VATS than OE.

Concerning postoperative complications, several studies investigated pulmonary complications, anastomotic leakage, and RLNP (20). Most studies have reported that the incidence of pulmonary complications was lower in VATS than in OE. However, there were no significant differences between VATS and OE concerning the incidence of anastomotic leakage and RLNP (20). Several studies comparing the short-term outcomes of VATS and OE based on nationwide or prospective data have been recently published (21-25). Those studies reported that the overall rate of surgical complications was higher for VATS than for OE, although VATS was associated with lower rates of respiratory complications than OE. In the current study, VATS did not reduce the incidence of pulmonary complications compared with OE and did not demonstrate the usefulness over OE.

Only one randomized controlled trial (RCT) regarding RAMIE has been conducted, which compared RAMIE to OE in patients with esophageal cancer (13). This study revealed that RAMIE resulted in a lower percentage of surgery-related overall complications, a better postoperative functional recovery, and similar oncologic outcomes than OE, concluding that RAMIE could improve short-term postoperative outcomes. Some retrospective reports exist according to the RAMIE comparison with VATS (9-11, 26). These reports showed only the safety of RAMIE and not its efficacy. Oshikiri *et al.* recently reported that RAMIE was superior to VATS in the prone position in decreasing left RLNP (27). The current study demonstrated that RAMIE reduced the incidence of overall (CD≥II) and pulmonary (atelectasis and pleural effusion) complications, and arrhythmias were significantly compared with both OE and VATS. Compared to OE and VATS, RAMIE had a stronger grip on the esophagus and LNs to be excised. Thus, strongly excluding the lung and heart to gain a good surgical field is not needed. Reducing the strain on the lung and heart may have led to reduced pulmonary complications and arrhythmias. Moreover, VATS has been reported to significantly reduce the incidence of arrhythmias compared to OE (28). However, the current study is the first to report that RAMIE significantly reduced the incidence of arrhythmias compared to OE and VATS. In addition, RLNP (C–D≥II) was significantly lower in RAMIE than in OE (p=0.026) and tended to be lower than in VATS (p=0.059). Furthermore, the area around the recurrent laryngeal nerve was dissected with scissors to avoid heat damage caused by energy devices in all three procedures. However, RLNP was lower, especially in RAMIE, because it can facilitate magnified three-dimensional imaging and seven degrees of freedom in ambidexterity due to using a manipulator with a wrist and tremor filtration. Therefore, surgeons can accurately perform a procedure and protect the RLN, which must be preserved. Moreover, Otsuka *et al.* showed that touching or stretching the recurrent laryngeal nerve can be a risk factor for palsy (29). Furthermore, the current study suggested that RAMIE reduced touching or stretching the recurrent laryngeal nerve compared to OE and VATS. These advantages of RAMIE over OE and VATS could also reduce pulmonary complications or arrhythmias.

Remarkably, no dysphagia (CD≥II) was noted in the RAMIE group. In addition, dysphagia was significantly lower in the RAMIE than in OE and VATS. Furthermore, RAMIE had less dysphagia because RAMIE had less RLNP than OE and VATS. Dysphagia leads to the deterioration of the swallowing function. Thus, patients with dysphagia had longer postoperative hospital stay. In addition, RAMIE may reduce aspiration pneumonia, because dysphagia can lead to aspiration pneumonia after the start of food intake. Patients with dysphagia had low food intake even after discharge, which led to weight loss. RAMIE has the potential to improve long-term prognosis by preventing weight loss and maintaining postoperative nutritional status. Thus, RAMIE proved useful in various aspects of the current study.

This study is believed to be the first to compare RAMIE with both VATS and OE in a single institution. For the first time, the difference in postoperative complications after esophagectomy between the three groups in a single institution was reported. Postoperative complications did not gradually decrease from OE to VATS and VATS to RAMIE. In an institution where VATS has already reduced postoperative complications compared to OE, RAMIE may not reduce the incidence of postoperative complications compared to VATS. Thus, institutions that did not reduce postoperative complications with the introduction of VATS could benefit from postoperative complication reduction with the introduction of RAMIE.

Postoperative complications were previously reported to significantly negatively impact long-term outcomes after esophagectomy in a single institution study and a meta-analysis (4, 30). Efforts to reduce postoperative complications are mandatory for improving long-term outcomes, suggesting that the introduction of RAMIE may lead to improvement in long-term outcomes.

This study has some limitations, the most important being that it was a retrospective investigation performed at a single institution. Second, the number of patients that underwent RAMIE was small compared with OE and VATS. An external validation study involving a sufficient number of patients is needed to confirm the current study's findings.

In conclusion, RAMIE could reduce postoperative overall and pulmonary complications after esophagectomy compared with OE and VATS. The introduction of RAMIE could lead to the improvement of long-term outcomes.

Conflicts of Interest

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

Authors' Contributions

E.B. and H.T. drafted and wrote the manuscript. E.B., H.K., and H.T. were involved in the study design and data interpretation. E.B., R.H., W.S., S.K., T.M., T.M. and Y.H. were involved in data acquisition. E.B. analyzed the data. All Authors read and approved the manuscript.

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