Peer Review File

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Reviewer A

Comment 1: This there any concern between the technique and anastomotic leakage or anastomotic stenosis?

Reply 1: Thank you for your numerous valuable comments. Regrettably, I didn't comprehend the meaning of comment 1.

Comment 2: McKeown operation requires more manipulations than Ivor Lewis. Why did the surgeon select former in early phase?

Reply2: Thank you for mentioning this important point. In the Ivor Lewis operation, the anastomosis is performed thoracoscopically within the thoracic cavity, whereas in the McKeown operation, the anastomosis is performed using an open technique, making it easier to manipulate. When dealing with anastomotic leakage, cervical anastomosis is simpler to drain and manage compared to intrathoracic anastomosis. Hence, beginners often lean towards the McKeown operation as their preferred choice.

Comment 3: (line 208) Sakari et al. → Sarkaria et al?

Reply 3: Thank you for pointing this out. We have revised it to Sarkaria et al.

Changes in the text: Previously, there have been excellent studies on the learning curve and surgical outcomes of RAMIE. Sarkaria et al. demonstrated tips that were useful during surgery and management of critical complications from 100 cases of totally minimally invasive RAMIE. (line 256)

Comment 4: (Table 2) I think that "relatively short" conduit length is obscure. Did you establish the standard about it?

Reply 4: Thank you for mentioning this important point. There is no specific definition for

"relatively short" in terms of a precise length. When a surgeon pulls up the conduit to the anastomosis site and there is a lack of length and a tight sensation, it is described as "relatively short." When the surgeon perceived the conduit to be "relatively short," we documented this in the surgical records. We added a definition of "relatively short conduit" to the Methods section.

Changes in the text: For anastomosis, the 25mm sized circular stapler was routinely considered first, while manual suture anastomosis was considered for relatively short conduits. There is no specific definition for "relatively short" in terms of a precise length. When a thoracic surgeon pulls up the conduit to the anastomosis site and there is a lack of length and a tight sensation, it is described as "relatively short." When the surgeon perceived the conduit to be "relatively short," we documented this in the surgical records. (line 139-142)

Reviewer B

Comment 1: This review describes a single-center study of RAMIE 500 by the same surgeon, comparing short-term results over time. It is noteworthy that 500 cases is the largest number of studies reported to date.

The author's explanation is consistent with the gradual increase in the use of Ivor Lewis as a

technique, since Ivor Lewis is relatively complicated to suture.

The author's explanation is consistent with the fact that Ivor Lewis is relatively complicated to suture, and if there is sufficient experience with conventional MIE, the same should be true for nCRT.

The changes in operative time and postoperative complication rates are also noteworthy, and I agree with the author that the experience of the entire team, as well as the surgeon, has improved.

Overall, the analysis of 500 cases and the possible influence of changes in surgical techniques due to the accumulation of experience are more in line with previous reports.

Reply 1: Thank you for your valuable comments.

Reviewer C

Comment 1: Drs. Jeon and Yun present a single surgeon experience of 500 robotic minimally invasive esophagectomies, outlining the changes in technique and outcomes over a 13-year period. The authors should be commended on the volume of cases performed and the number of patients they have treated over this interval. As a scholarly endeavor, the manuscript suffers from excessive heterogeneity in surgical approaches and a lack of a compelling finding that would contribute to the literature. Breaking down their experience into learning, developing and stable phases seems to employ arbitrary case number cutoffs without substantive differences in demonstrated outcomes. Other concerning factors include the frequency of cervical node dissections, the high rate of vocal cord paralysis, and low rate of

neoadjuvant chemoradiation administered given the clinical stage of the patient population.

Reply 1: Thank you for the positive comments. The majority of our patients are clinical stage I patients, which has led to a lower frequency of cervical lymph node dissection and neoadjuvant CTx. The high rate of vocal cord palsy is considered an area in our technique that requires improvement, and we are currently making efforts to perform a more meticulous recurrent laryngeal nerve lymph node dissection. We have mentioned these findings in the discussion and limitation sections of our study.

Changes in the text: Third, the number of patients receiving CND in the stable phase increased, which was associated with the increased number of patients with locally advanced esophageal cancer described above. This is the reason why the rate of VCP increased in the stable phase. However, when it comes to long-term outcome, the permanent VCP rate decreased in the stable phase, suggesting that most nerve injuries were transient palsy due to traction or thermal injury (*Table 5*). However, in terms of long-term outcomes, the rate of permanent vocal cord palsy (VCP) decreased during the stable phase, suggesting that the majority of nerve injuries were transient and likely caused by traction or thermal injury (Table 5). The relatively high rate of vocal cord palsy in our technique highlights an area that requires improvement, and we are currently making efforts to perform a more meticulous recurrent laryngeal nerve lymph node dissection. (line 316-320)

Fifth, we do not have data on the learning curve or surgical outcomes specifically related to robotic-sewn anastomosis. However, a recent study by Huscher et al. demonstrated excellent results with an AL rate of 10% in 40 patients who underwent intrathoracic robotic-sewn anastomosis (28). This indicates that as proficiency with RAMIE increases, complete robotic Ivor Lewis esophagectomy becomes feasible. Lastly, it should be noted that the patient population in our study consisted predominantly of early-stage patients who did not receive nCRT. It is important to recognize that as the proportion of patients receiving nCRT increases, the learning curve may be longer, and the surgical outcomes may not be as favorable. (line 356-369)

Reviewer D

Comment 1: In the methods section it describes that a separate surgeon performed the abdominal mobilization of the gastric conduit, and then another separate surgeon would be involved for the neck dissection if that was felt to be necessary. I would wonder if the involvement or training or learning curve of these surgeons could have played some role in the outcomes of this study.

Reply 1: A stomach surgeon with experience in over 500 cases of laparoscopic, robotic, and open stomach surgeries participated in the first RAMIE procedure. He performed conduit formation robotically or laparoscopically, following the guidance and requests of the thoracic surgeon, in a manner consistent with the thoracic surgeon's procedure. Therefore, it is believed that there are minimal aspects influencing the learning curve for stomach conduit formation in the RAMIE procedure. However, in the early stages, there were often cases where problems occurred with the conduit itself, such as conduit fistula and necrosis, rather than anastomotic leakage. Consequently, it was deemed necessary to improve the gastric conduit formation strategy. The collaborative approach using a minimally invasive technique was discontinued, and the thoracic surgeon performed conduit formation through an open laparotomy while making changes to the conduit formation strategy. The current strategy was finalized in 2014. According to this strategy, 2cm of omentum is preserved from the right gastroepiploic artery (RGEA), efforts are made to prevent serosa injury to the conduit, and the width of the conduit is requested to be set at 5cm by the stomach surgeon. From the 82nd

case onwards, the stomach surgeon has been performing the procedure using a minimally invasive technique with the same strategy, resulting in a decrease in severe conduit problems. Cervical node dissection was conducted by a single ENT surgeon in collaboration. It is deemed that the impact on the learning curve is minimal due to the extensive experience of the ENT surgeon. We have added this information to the limitations section.

Changes in the text: This study had notable limitations. First, selection bias is inherent in a retrospective study conducted at a single institution. Second, RAMIE was conducted by a single surgeon, and the operative outcomes might have been influenced by 'surgeon bias'. Third, the clinical outcomes in this study were obtained through a well-established collaborative system involving highly experienced surgeons in their respective fields. Therefore, we believe that the impact of collaboration on the learning curve in our study is likely to be minimal. However, it may be challenging to generalize our learning curves to surgeons who do not have access to a similar collaborative system. (line 345-349)

Comment 2: The lower leak rate from the neck anastomosis compared to the chest anastomosis is especially interesting to me, as this goes against just about every single prior published study on esophageal cancer surgery, and a more robust explanation of a theory behind these findings would be appreciated.

Reply 2: In our study, the rate of intrathoracic anastomotic leakage was observed to be higher than that of cervical anastomosis. During the learning phase, the implementation rate of RAMIE Ivor-Lewis was low due to a lack of proficiency, resulting in a higher incidence of anastomotic leakage. However, the cervical procedure of RAMIE McKeown, which was similar to open McKeown, was performed with proficiency, leading to a lower incidence of anastomotic leakage This was the underlying reason for the higher rate of anastomotic leakage in intrathoracic anastomotic leakage. We also found a significant association between the administration of neoadjuvant chemoradiotherapy (nCRT) and anastomotic leakage in our study. As a majority of the 113 patients who underwent nCRT also had intrathoracic anastomosis (64.6%, 73/113), we believe that this increased the occurrence of intrathoracic anastomotic leakage. Nonetheless, we consider the 7.8% rate of intrathoracic anastomotic leakage to be an acceptable outcome. We have included this information in the Discussion section, and we have also added Table S6 to provide further details.

Changes in the text: In this study, as the rate of the Ivor Lewis operation increased, conduit related complications decreased. Intra-thoracic anastomosis has a benefit in terms of the

length of the conduit, which can reduce the incidence of stricture. In contrast to general expectations, our study revealed a higher rate of intrathoracic AL compared to cervical anastomosis. Performing intrathoracic anastomosis in the context of RAMIE can be a challenging procedure. During the learning phase, the implementation rate of RAMIE Ivor-Lewis was low due to a lack of proficiency, resulting in a higher incidence of AL. However, the cervical procedure of RAMIE McKeown, which was similar to open McKeown, was performed with proficiency, leading to a lower incidence of AL. As the proficiency in RAMIE increased, we observed a gradual increase in the number of intrathoracic anastomoses and a decrease in the incidence of intrathoracic AL. This finding was evident in the stable phase, where despite a rise in the proportion of Ivor-Lewis RAMIE (67%), there was a decrease in the overall occurrence of AL. Nevertheless, we consider the 7.8% rate of intrathoracic AL to be an acceptable outcome (Table S6). (line 283-294)

Table S6 Anastomotic leakage rates for intrathoracic and cervical anastomosis according to the learning period

Intrathoracic anastomosis	Anastomotic leakage Event/Total
Learning phase	3/6 (50.0%)
Developing phase	2/25 (8.0%)
Stable phase	17/251 (6.8%)
Total	22/282 (7.8%)
Cervical anastomosis	
Learning phase	2/44 (4.5%)
Developing phase	0/73 (0.0%)
Stable phase	6/85 (7.1%)
Total	8/202 (4.0%)

Values were presented as numbers (%).

Comment 3: The percentage of vocal cord paralysis seems to be incredibly high in this study, with other reports indicating a risk of about 10-20 percent, but a rate of almost 40% for cervical anastomosis seems exceedingly high, do the authors have an explanation for this finding?

Reply 3: Thank you for your insightful comment. Compared to previous studies, the rate of vocal cord palsy in this study is higher at 29.6%. This elevated rate can be attributed to the extensive en bloc lymph node dissection in the superior mediastinum. The improved accessibility afforded by RAMIE enables surgeons to reach deeper regions of the thoracic cavity, which would not have been possible with conventional surgery. As a result, we performed nearly 35 lymph node harvesting procedures during RAMIE, a significantly higher number compared to other studies where the average ranged from 18 to 30 lymph nodes [1,2]. Similar findings have been reported in other studies, where vocal cord palsy occurred in 26% and 29% of cases after 44 and 38 lymph node harvesting procedures, respectively [3,4]. We have included this information in the Discussion section.

1. Cerfolio RJ, Wei B, Hawn MT, Minnich DJ. Robotic Esophagectomy for Cancer: Early Results and Lessons Learned. Semin Thorac Cardiovasc Surg. 2016;28(1):160-9.
2. Sarkaria IS, Rizk NP, Finley DJ, Bains MS, Adusumilli PS, Huang J, et al. Combined thoracoscopic and laparoscopic robotic-assisted minimally invasive esophagectomy using a four-arm platform: experience, technique and cautions during early procedure development. Eur J Cardiothorac Surg. 2013;43(5):e107-15.
3. Park SY, Kim DJ, Yu WS, Jung HS. Robot-assisted thoracoscopic esophagectomy with extensive mediastinal lymphadenectomy: experience with 114 consecutive patients with intrathoracic esophageal cancer. Dis Esophagus. 2016;29(4):326-32.
4. Kim DJ, Hyung WJ, Lee CY, Lee JG, Haam SJ, Park IK, et al. Thoracoscopic esophagectomy for esophageal cancer: feasibility and safety of robotic assistance in the prone position. J Thorac Cardiovasc Surg. 2010;139(1):53-9 e1.

Changes in the text: The VCP rate was 23.4% for intra-thoracic anastomosis and 37.8% for anastomosis at cervical level or above, with the intra-thoracic anastomosis rate being significantly lower (p=0.001). Compared to previous studies, the rate of vocal cord palsy in this study is higher at 29.6%. This elevated rate can be attributed to the extensive en bloc lymph node dissection in the superior mediastinum. The improved accessibility afforded by RAMIE enables surgeons to reach deeper regions of the thoracic cavity, which would not have been possible with conventional surgery. As a result, we performed nearly 35 lymph node harvesting procedures during RAMIE, a significantly higher number compared to other studies where the average ranged from 18 to 30 lymph nodes (18,19). Similar findings have been reported in other studies, where vocal cord palsy occurred in 26% and 29% of cases

after 44 and 38 lymph node harvesting procedures, respectively (20,21). (line 271-279)

Comment 4: Finally, and most concerning, the overall patient population is very difficult to generalize to the other patient populations. 97% squamous carcinoma, with a BMI of 24, excellent pulmonary function tests, the majority not receiving neoadjuvant therapy, and having 67% T1 and 75% N0 is not reflective of the esophageal cancer population that most of the western world is responsible for treating.

Overall, I enjoyed reading this well written article, and I would like to thank the authors for their manuscript and contribution to the treatment of this challenging disease process.

Reply 4: Thank you for pointing this out. The patient population in our study has different characteristics compared to esophageal cancer patients in the Western world. Therefore, it may be challenging to generalize our research findings. We have mentioned this as a limitation in our study.

Changes in the text: This study had notable limitations. First, selection bias is inherent in a retrospective study conducted at a single institution. Second, RAMIE was conducted by a single surgeon, and the operative outcomes might have been influenced by 'surgeon bias'. Third, the clinical outcomes in this study were obtained through a well-established collaborative system involving highly experienced surgeons in their respective fields. Therefore, we believe that the impact of collaboration on the learning curve in our study is likely to be minimal. However, it may be challenging to generalize our learning curves to surgeons who do not have access to a similar collaborative system. Forth, the patient population in our study has different characteristics compared to esophageal cancer patients in the Western world. Therefore, it may be challenging to generalize our research findings. (line 349-351)

Reviewer E

Comment 1: In the section Introduction the authors did not even mention one of the main problems of minimally invasive and robotic esophagectomy, which is the increased anastomotic leak rate reported by almost all the recent papers. For instance, in one of the first publication by the UGIRA study group "Worldwide Techniques and Outcomes in Robot-

assisted Minimally Invasive Esophagectomy (RAMIE). Results From the Multicenter International Registry", a quite discouraging AL rate as high as 30% is reported for hand-sewn robotic Ivor-Lewis anastomosis, with an overall leak rate of about 20%. A comment, in my opinion, is required.

Reply 1: We have added information about intrathoracic robot-sewn anastomosis to the Introduction section.

Changes in the text:

It also enables dissection of the entire mediastinum through a superior surgical view at the hiatus and thoracic inlet level in esophageal cancer surgery, which is helpful especially for upper mediastinal lymph node (LN) dissection involving the recurrent laryngeal nerve (RLN) (3). Additionally, it enables robot-sewn anastomosis within the thoracic cavity. However, intrathoracic robot-sewn anastomosis is a highly challenging procedure, and a multicenter study demonstrated a disappointing anastomotic leakage rate of 33% (4). (line 83-86)

Comment 2: Moreover, even if the Authors correctly stated that RAMIE demonstrated to be equivalent to open procedures in terms of oncologic outcomes, the most recent Literature suggests that the robotic approach might improved some of the short term oncological outcomes. For instance, in a paper published by Weindelmayer et al., "Robotic versus open Ivor–Lewis esophagectomy: A more accurate lymph node dissection without burdening the leak rate" it seems that the robotic approach allowed to improve the lymph nodes retrieval rate, even in the lower mediastinum. This or similar studies should be cited.

Reply 2: As the proficiency in RAMIE increases, there has been an increase in performing RAMIE for patients with higher staging. This is attributed to the ease of accessing and the improved accuracy in performing mediastinal lymph node harvest during RAMIE. Weindelmayer et al. demonstrated that RAMIE allows for a more accurate lymphadenectomy, resulting in a higher number of thoracic lymph nodes compared to open esophagectomy (OE), without an increase in other complications.

Changes in the text: As the surgeon's experience grew, the number of challenging cases with RAMIE also increased. In patients with suspected T4 invasion, if there was a therapeutic response after nCRT and the tumor was deemed resectable, open esophagectomy (OE) was initially recommended to address the injury to the surrounding structures during dissection when the experience with RAMIE was insufficient. As experience with RAMIE increased,

the ability to perform meticulous and precise dissection improved, thanks to the magnified surgical view and articulated surgical arm, which minimized damage to surrounding structures. This can be attributed to the ease of accessing and the enhanced accuracy in performing mediastinal lymph node harvest during RAMIE. Weindelmayer et al. demonstrated that RAMIE allows for a more accurate lymphadenectomy, resulting in a higher number of thoracic lymph nodes compared to open esophagectomy (OE), without an increase in other complications (23). Therefore, based on these experiences, it can be concluded that RAMIE is a feasible approach for locally advanced esophageal cancer. (line 302-310)

Comment 3: My main critic to your work regards, however, the little homogeneity of your study group. The patients treated in the learning phase and in stable phase are quite different, and the results of the comparison of these two groups are difficult to interpret. In an effort to homogenize the groups, I believe that you should exclude from the statistical analysis all procedures other than Ivor-Lewis and Mc Kewon esophagectomy with gastric conduit reconstruction. The fact that you started to perform more complex operation, such as colon interposition or esophago-jejunostomy is a clear sign that your proficiency actually improved, but it is not correct to compare results of a first group in which there is only 1 patient with a colonic interposition with a group with 17 colonic interpositions. So, you probably should report the changing of the type of operations but focus the analysis only on similar operations. Moreover, instead of reporting the patients characteristic for the whole population, for more clarity I believe you should report the characteristics of the patients divided according to the phase group.

Reply 3: Thank you for highlighting this important point. The learning curves and surgical outcomes of RAMIE-McKeown and RAMIE-Ivor Lewis have already been extensively analyzed in previous studies [1,2,3]. In our study, we also conducted a separate analysis of RAMIE-Ivor Lewis and RAMIE-McKeown to compare their respective learning curves and surgical outcomes, resulting in our own set of findings.

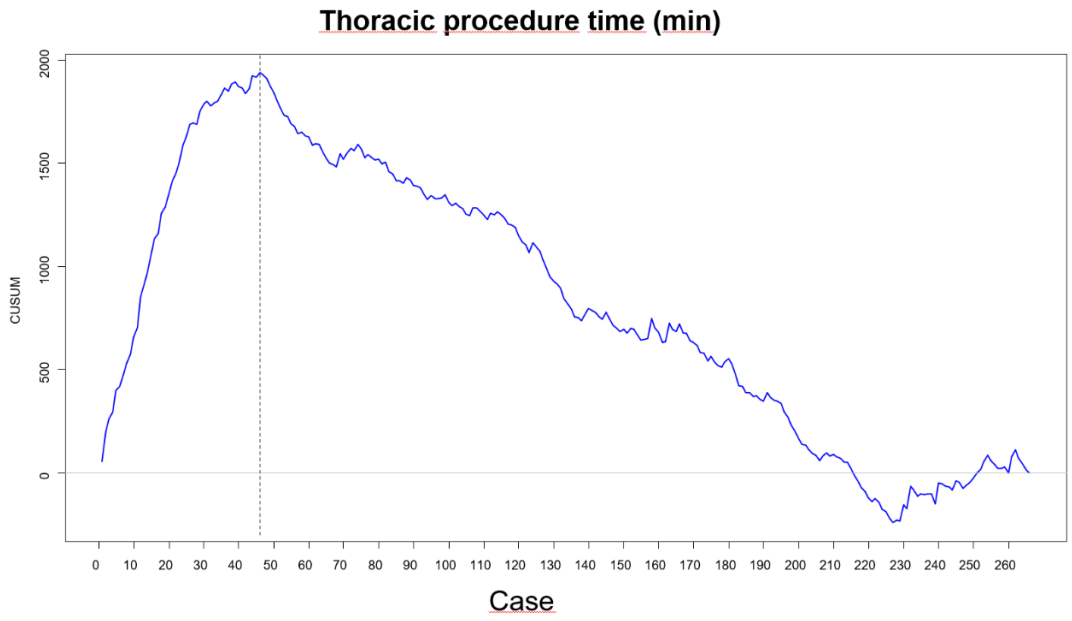

Figure. The learning curve of thoracic procedure time for RAMIE-Ivor Lewis.

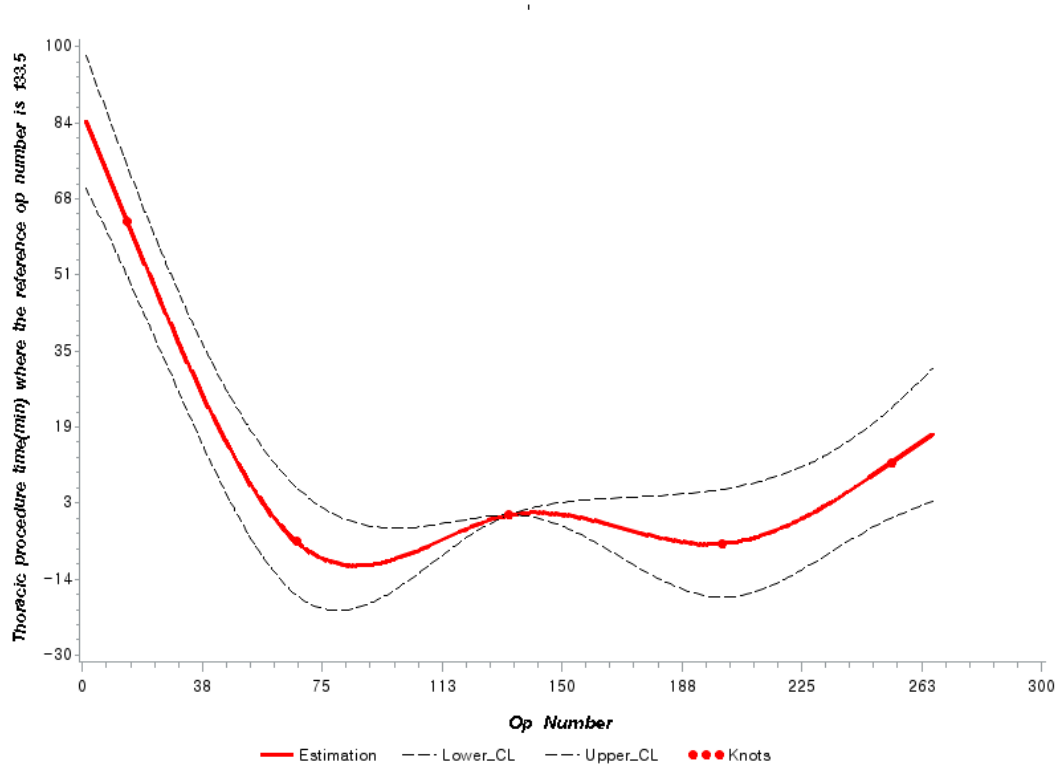

Figure. The restricted cubic spline of thoracic procedure time for RAMIE-Ivor Lewis showed a plateau phase after 44th case.

The change point in our learning curve for lymph node harvesting in RAMIE-Ivor Lewis was observed at the 30th case, and a plateau was reached after approximately the 70th case.

Han et al. also analyzed the learning curve for lymph node yield in RAMIE-Ivor Lewis and found that the number of harvested lymph nodes gradually increased until the 73rd case and then plateaued [1].

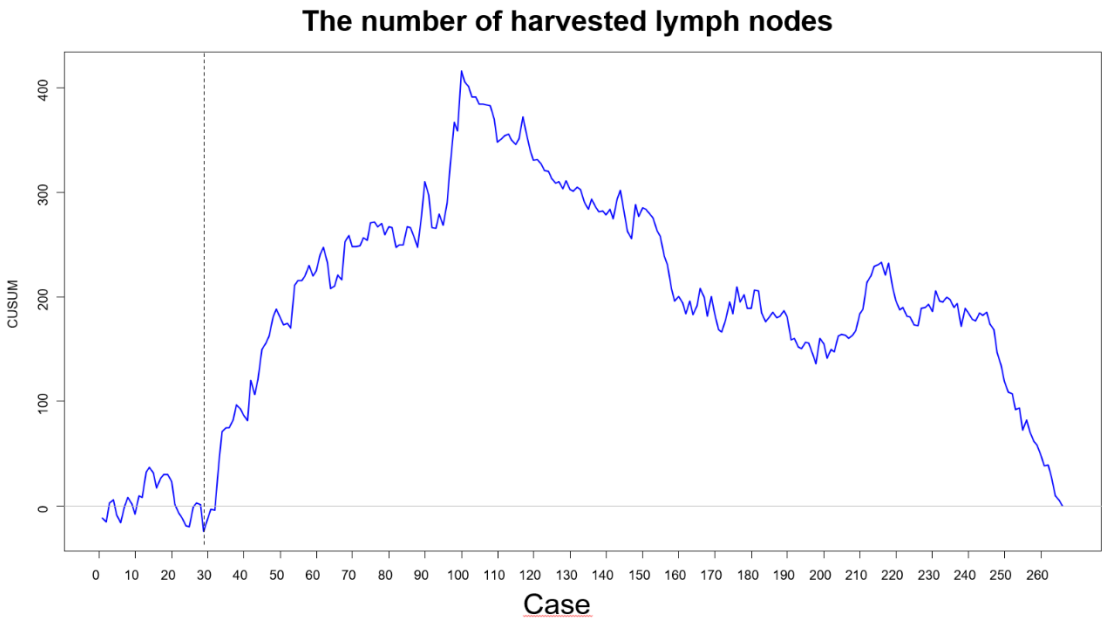

Figure. The learning curve of lymph node harvesting for RAMIE-Ivor Lewis.

The change point of our learning curve of lymph node harvesting for RAMIE-Ivor Lewis was the 30th case, and the plateau was shown after about the 70th case. Han et al. also analyzed the learning curve for lymph node yield for RAMIE-Ivor Lewis. The number of harvested LNs gradually increased up to 73rd case, and then showed a plateau pattern [1].

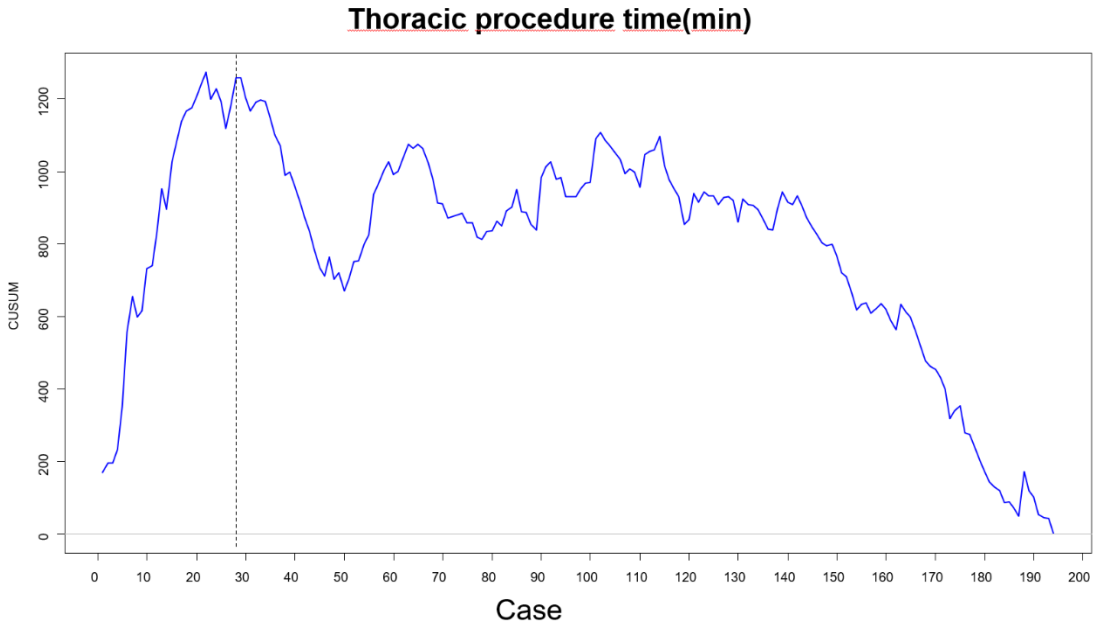

Figure. The learning curve of thoracic procedure time for RAMIE-McKeown.

The change points for the learning curve of thoracic procedure time in RAMIE-McKeown were observed at the 30th case and the 140th case in our study. In a study conducted by Yang et al., they also analyzed the learning curve of thoracic procedure time for RAMIE-McKeown and found the change points to be at the 40th case and the 215th case [2].

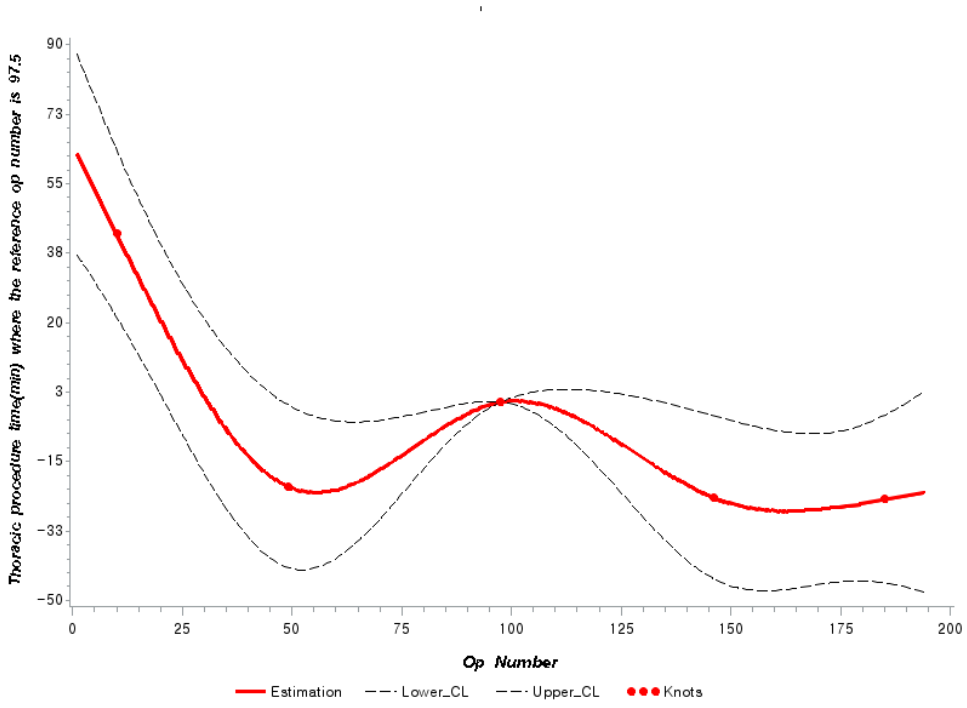

Figure. The restricted cubic spline of thoracic procedure time for RAMIE-McKeown

showed a plateau phase after 30th case.

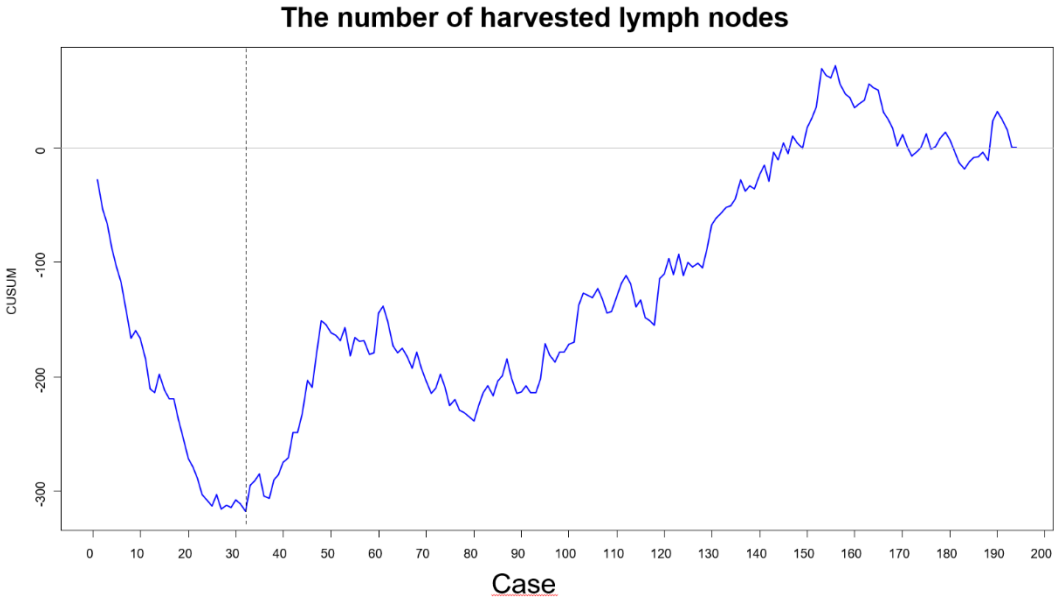

Figure. The learning curve of lymph node harvesting for RAMIE-McKeown.

The change point for the learning curve of lymph node harvesting in RAMIE-McKeown was observed at the 32nd case in our study. In a study conducted by Yang et al., they also analyzed the learning curve for lymph node harvesting in RAMIE-McKeown and found the change points to be at the 40th case [2].

Our study separately analyzed the learning curves and surgical outcomes for RAMIE-Ivor Lewis and RAMIE-McKeown. However, as these aspects have been extensively studied in previous research, we did not include detailed descriptions in this study due to limitations in word count. In our study, as the surgeon gained more experience, they employed various surgical approaches and conduits based on tumor location and patient condition. These trends were reflected in the surgical outcomes and learning curves observed in our study. We believe that this aspect differentiates our study from others and could be considered meaningful.

1. Han Y, Zhang Y, Zhang W, et al. Learning curve for robot-assisted Ivor Lewis esophagectomy. Dis Esophagus 2021.
2. Yang Y, Li B, Hua R, et al. Assessment of Quality Outcomes and Learning Curve for Robot-Assisted Minimally Invasive McKeown Esophagectomy. Ann Surg Oncol 2021; 28(2): 676-84.

Zhang H, Chen L, Wang Z, et al. The Learning Curve for Robotic McKeown Esophagectomy in Patients With Esophageal Cancer. Ann Thorac Surg 2018; 105(4): 1024-30.

Comment 4: Besides that, you report a decrease in the AL with the growing surgical experience. Again, there are other factors that can explain this reduction, first the different anastomosis location. It is quite known, and recently confirmed by the ICAN trial, that cervical anastomosis has a rate of leak almost 3 times higher than thoracic anastomosis (even if in your experience you showed a different result). As in your learning phase group only 12% of patients had an Ivor Lewis esophagectomy, versus the 67% of the stable phase group, in the discussion you should try to explain how this change of operation might have influenced the leak rate.

Reply 4: Thank you for mentioning this important point. It has been reported that the rate of leakage in intrathoracic anastomosis is generally lower compared to cervical anastomosis. Performing intrathoracic anastomosis in the context of RAMIE can be a challenging procedure. This may lead to a preference for McKeown RAMIE over Ivor-Lewis RAMIE. In our study, initially, there were more cases of cervical anastomosis than intrathoracic anastomosis. As the proficiency in RAMIE increased, we observed a gradual increase in the number of intrathoracic anastomoses and a decrease in the incidence of anastomotic leakage. This finding was evident in the stable phase, where despite a rise in the proportion of Ivor-Lewis RAMIE (67%), there was a decrease in the overall occurrence of anastomotic leakage. We have mentioned this information in the Discussion section.

Changes in the text: In this study, as the rate of the Ivor Lewis operation increased, conduit related complications decreased. Intra-thoracic anastomosis has a benefit in terms of the length of the conduit, which can reduce the incidence of stricture. In contrast to general expectations, our study revealed a higher rate of intrathoracic AL compared to cervical anastomosis (7.8% vs 4.0%). Performing intrathoracic anastomosis in the context of RAMIE can be a challenging procedure. During the learning phase, the implementation rate of RAMIE Ivor-Lewis was low due to a lack of proficiency, resulting in a higher incidence of AL. However, the cervical procedure of RAMIE McKeown, which was similar to open McKeown, was performed with proficiency, leading to a lower incidence of AL. As the proficiency in RAMIE increased, we observed a gradual increase in the number of intrathoracic anastomoses and a decrease in the incidence of intrathoracic AL. This finding was evident in the stable phase, where despite a rise in the proportion of Ivor-Lewis RAMIE (67%), there was a decrease in the overall occurrence of AL. Nevertheless, we consider the

7.8% rate of intrathoracic AL to be an acceptable outcome (Table S6). (line 283-294)

Table S6 Anastomotic leakage rates for intrathoracic and cervical anastomosis according to the learning period

Intrathoracic anastomosis	Anastomotic leakage Event/Total
Learning phase	3/6 (50.0%)
Developing phase	2/25 (8.0%)
Stable phase	17/251 (6.8%)
Total	22/282 (7.8%)
Cervical anastomosis	
Learning phase	2/44 (4.5%)
Developing phase	0/73 (0.0%)
Stable phase	6/85 (7.1%)
Total	8/202 (4.0%)

Values were presented as numbers (%).

Reviewer F

Comment 1: I believe that a more accurate description of the surgical technique for anastomosis is necessary, as well as a more detailed presentation of the surgical results. For instance, I would suggest adding a summary table of the anatomopathological characteristics.

Reply 1: We have provided additional details to enhance the surgical technique description for anastomosis. Furthermore, we added a summary table presenting the anatomopathological characteristics of the anastomotic site.

Changes in the text:

The sequential thoracic procedure was performed in the left semi-prone position. Three 8-mm ports were utilized for the robotic arms, while one 12-mm port was designated for the first assistant. Carbon dioxide (CO2) gas insufflation into the thoracic cavity was carried out as a standard procedure, maintaining a CO2 pressure of 6 mmHg. For intra-thoracic anastomosis, the camera port at the 5th intercostal space was extended by approximately 4 cm to allow for the insertion of a circular stapler into the thoracic cavity. The specimen was subsequently extracted through this port. Following partial transection of the esophagus at the highest level of the thoracic esophagus, a purse-string suture was performed using a robotic arm equipped with Maryland forceps and a needle holder. The anvil of the stapler was inserted into the proximal esophagus, and the purse-string suture was secured. The conduit in the abdomen was then pulled up into the thoracic cavity, and an esophago-gastric anastomosis was performed. Routinely, anastomosis of the conduit and proximal thoracic esophagus was performed at the level of the brachiocephalic artery. (line 125-137)

Table S1 The description of the anastomosis site.

Anastomosis site	
Oropharynx	The oropharynx is behind the oral cavity, below the soft palate and above the epiglottis. Anastomosis in the oropharynx is performed at the tongue base level, resulting in the removal of the tracheal inlet, which necessitates the need for a permanent tracheostomy.
Pharynx	It refers to the hypopharynx or laryngopharynx. The hypopharynx is located behind the larynx and extends to the esophagus. Anastomosis in the hypopharynx is performed at the commencement site of the esophagus, beyond the epiglottis and tracheal inlet. This surgical procedure does not require a permanent tracheostomy; however, it necessitates a more extensive dissection for adequate exposure of the target area.
Cervical esophagus	Anastomosis in the cervical esophagus involves pulling out the esophagus through a standard cervical incision and performing an anastomosis without the need for deep dissection towards the proximal portion of the esophagus.
Thoracic esophagus	It refers to the esophagus located within the thoracic cavity.

Comment 2: Furthermore, the surgical outcomes need to be more explicitly specified with regard to complications directly related to surgery, such as chylothorax, thoracic empyema, and cardiac arrhythmias. Anastomotic leak should be classified into types 1, 2, and 3. Therefore, in the Methods section, it would be appropriate to provide a better description of the inclusion and exclusion criteria.

Reply 2: We have included surgical complications in Table 3 and classified anastomotic leakage into Type 1, 2, and 3, which have been added to Table 3. We also provided a description of the definition in the Methods section.

Changes in the text:

Postoperative complications and outcome assessment

Most complications were evaluated based on the joint definitions of the Society of Thoracic Surgeons and the European Society of Thoracic Surgeons (11). The complications of AL were evaluated according to the Esophageal Complication Consensus Group guidelines (ECCG) (12). Minor leak of anastomotic leakage that does not require surgical therapy corresponds to anastomotic leak type I and type II of ECCG, and major leak that requires surgical therapy corresponds to type III of ECCG (12). (line 175-177)

Table 3 Postoperative morbidity and mortality

Variables	
Intraoperative transfusion	9 (1.8%)
Vocal cord palsy	148 (29.6%)
Unilateral / Bilateral	135 (91.2%) / 13 (8.8%)
Transient / Permanent	132 (89.1%) / 16 (10.9%)
Hyaluronic acid injection	98 (66.2%)
Overall morbidity	208 (41.6%)
Atrial fibrillation	22 (4.4%)
Chylothorax	19 (3.8%)
Empyema	5 (1.0%)
Respiratory complication	43 (8.6%)
Anastomotic leakage	33 (6.6%)
Minor leaks (Type I / II)	3 (0.6%) / 21 (4.2%)

Major leaks (Type III)	10 (2.0%)
Conduit necrosis	5 (1.0%)
Anastomotic stricture	88 (17.6%)
Re-operation within 90days	38 (7.6%)
30-day mortality	1 (0.2%)
90-day mortality	5 (1.0%)

Values were presented as numbers (%).

Comment 3: Lastly, the Conclusion section could be expanded with a mention of robotic-sewn anastomosis and its results. The authors can refer to the following work: doi: 10.1007/s11605-023-05616-w

Reply 3: Thank you for your valuable comment. We have added relevant information to the limitation section.

Changes in the text: This study had notable limitations. First, selection bias is inherent in a retrospective study conducted at a single institution. Second, RAMIE was conducted by a single surgeon, and the operative outcomes might have been influenced by 'surgeon bias'. Third, the clinical outcomes in this study were obtained through a well-established collaborative system involving highly experienced surgeons in their respective fields. Therefore, we believe that the impact of collaboration on the learning curve in our study is likely to be minimal. However, it may be challenging to generalize our learning curves to surgeons who do not have access to a similar collaborative system. Forth, the patient population in our study has different characteristics compared to esophageal cancer patients in the Western world. Therefore, it may be challenging to generalize our research findings. Fifth, we do not have data on the learning curve or surgical outcomes specifically related to robotic-sewn anastomosis. However, a recent study by Huscher et al. demonstrated excellent results with an anastomotic leakage (AL) rate of 10% in 40 patients who underwent intrathoracic robotic-sewn anastomosis (28). This indicates that as proficiency with RAMIE increases, complete robotic Ivor Lewis esophagectomy becomes feasible. (line 351-356)

Reviewer G

Comment 1: The largest limitation to this study, is that it reports the learning curve for only a

single surgeon. Learning curves can be high variable and are dependent on a number of factors. The inclusion of only 1 surgeon severely limits the generalizability of these results. The authors acknowledge this limitation, however I do think this point needs to be emphasized further.

Reply 1: Thank you for mentioning this important point. We have added a limitation to emphasize the difficulty of generalizing the results due to the procedure being performed by a single surgeon.

Changes in the text: This study had notable limitations. First, selection bias is inherent in a retrospective study conducted at a single institution. Second, RAMIE was performed by a single thoracic surgeon. Therefore, it may be challenging to generalize the learning curve and surgical outcomes of this study to other settings. (line 343-345)

Comment 2: It is unclear how the abdominal phase of the operation was performed. The description in the methods (lines 94-98) is quite confusing. Were these done open, laparoscopic or robotic? And if a combination of these methods were used, how many were performed each way? Was this performed by a different surgeon?

Reply 2: The number of procedures performed using open, laparoscopic, and robotic approaches is provided in Table 2. We have made modifications to the description in the Methods section to enhance its clarity and improve its meaning.

A stomach surgeon with experience in over 500 cases of laparoscopic, robotic, and open stomach surgeries participated in the first RAMIE procedure. He performed conduit formation robotically or laparoscopically, following the guidance and requests of the thoracic surgeon, in a manner consistent with the thoracic surgeon's procedure. Therefore, it is believed that there are minimal aspects influencing the learning curve for stomach conduit formation in the RAMIE procedure. However, in the early stages, there were often cases where problems occurred with the conduit itself, such as conduit fistula and necrosis, rather than anastomotic leakage. Consequently, it was deemed necessary to improve the gastric conduit formation strategy. The collaborative approach using a minimally invasive technique was discontinued, and the thoracic surgeon performed conduit formation through an open laparotomy while making changes to the conduit formation strategy. The current strategy was finalized in 2014. According to this strategy, 2cm of omentum is preserved from the right gastroepiploic artery (RGEA), efforts are made to prevent serosa injury to the conduit, and the width of the conduit is requested to be set at 5cm by the stomach surgeon. From the 82nd

case onwards, the stomach surgeon has been performing the procedure using a minimally invasive technique with the same strategy, resulting in a decrease in severe conduit problems.

Changes in the text: The RAMIE procedure consists of thoracic esophagectomy by robotic system, abdominal, and with or without cervical procedure. During the abdominal procedure, conduit was formed using the stomach, jejunum, or colon. Gastric conduit formation using a minimally invasive technique was performed by an experienced gastric surgeon. However, during the learning phase, there were instances of conduit-related issues, leading to the temporary use of an open laparotomy approach by the thoracic surgeon for conduit formation. In the developing phase, a change in the conduit formation strategy was introduced. The thoracic surgeon provided instructions to the gastric surgeon to create a gastric conduit using the same strategy and perform laparoscopic or robotic surgery entirely starting from the 82nd case. (line 118-124)

Comment 3: On line 103, please clarify what ICS stands for.

Reply 3: In line 103, I explicitly clarified that ICS stands for intercostal space.

Changes in the text: For intra-thoracic anastomosis, the camera port at the 5th intercostal space was extended by approximately 4 cm to allow for the insertion of a circular stapler into the thoracic cavity. (line 129)

Comment 4: While agree that esophagogram has a rate of false negative results, the lack of routine esophagography on all patients is a major limitations in terms of assessing for postoperative anastomotic leak. This must be acknowledged clearly.

Reply 4: As the experience in RAMIE accumulated, if there were no specific events during surgery and the resection margin of the anastomosis showed a complete donut shape, dietary training was initiated with sips of water on postoperative day 3 without the use of esophagography. Esophagogram was discontinued due to its low sensitivity rate in detecting leakages. Furthermore, there were instances where esophagography could not be performed promptly due to scheduling conflicts, resulting in delayed initiation of oral intake or aspiration pneumonia caused by the contrast medium. However, we acknowledge the limitation of not performing Esophagogram for evaluating anastomotic leakage. We have included this information in the Methods section.

Changes in the text:

Postoperative management

Sips of water were commenced from postoperative day 3, and if there were no significant events during the surgery, the resection margin of the anastomosis exhibited a complete donut shape, there are no signs of aspiration or leakage, and there is no sudden high fever, then the diet was advanced on the next day. Esophagography is a crucial examination for detecting postoperative anastomotic leakage. However, there have been instances where esophagography could not be conducted on time due to scheduling constraints, leading to delayed initiation of oral intake or potential complications such as aspiration pneumonia caused by the contrast medium. Esophagography to evaluate anastomosis site leakage and conduit was only performed on patients with suspected leakage because in patients with no intraoperative event, the sensitivity to detect AL may be low (5). (line 153-160)

Comment 5: The rate of VCP paralysis was quite high in this study. A VCP rate of 23.4% with in intrathoracic anastamosis is very high and not consistent with the prior literature. Even after the learning curve was completed at 50 days, the VCP rate seems quite high. Can the authors comment on why their VCP rate may be higher then most other studies? According to table S3, it appears to be related to the central neck dissection. Were patients with intrathoracic anastamosis still having a central neck dissection? If so, please elaborate as to why. There should be greater discussion of this entire point.

Reply 5: During the learning phase, the rate of vocal cord palsy (VCP) was remarkably high at 42%. Subsequently, in the developing phase, it improved to 20%, but in the stable phase, it reached 30.6%. The overall VCP rate of 29.6% in our study was higher compared to other studies. Factors associated with VCP occurrence in our study were the level of anastomosis and the performance of cervical lymph node dissection (CND). In the stable phase, a higher number of anastomoses were performed at the oropharynx level (n=2) and pharynx level (n=11). Additionally, the increased occurrence of VCP in the stable phase can be attributed to the higher number of CND procedures (n=77) performed during that period. This phenomenon is attributed by the extensive en bloc lymph node dissection in the superior mediastinum. The improved accessibility when using RAMIE allows the surgeon to operate more on the deeper side of the thoracic cavity, which could not have been replicated by conventional surgery. Instead, we underwent nearly 35 lymph node harvesting procedures during RAMIE, which are markedly higher, compared to other studies (18 to 30 lymph

nodes, on average) [1,2]. This consequence is also described in other studies, in which 26% and 29% of vocal cord palsy occurred after 44 and 38 of lymph node harvesting procedures [3,4].

1. Cerfolio RJ, Wei B, Hawn MT, Minnich DJ. Robotic Esophagectomy for Cancer: Early Results and Lessons Learned. Semin Thorac Cardiovasc Surg. 2016;28(1):160-9.
2. Sarkaria IS, Rizk NP, Finley DJ, Bains MS, Adusumilli PS, Huang J, et al. Combined thoracoscopic and laparoscopic robotic-assisted minimally invasive esophagectomy using a four-arm platform: experience, technique and cautions during early procedure development. Eur J Cardiothorac Surg. 2013;43(5):e107-15.
3. Park SY, Kim DJ, Yu WS, Jung HS. Robot-assisted thoracoscopic esophagectomy with extensive mediastinal lymphadenectomy: experience with 114 consecutive patients with intrathoracic esophageal cancer. Dis Esophagus. 2016;29(4):326-32.
4. Kim DJ, Hyung WJ, Lee CY, Lee JG, Haam SJ, Park IK, et al. Thoracoscopic esophagectomy for esophageal cancer: feasibility and safety of robotic assistance in the prone position. J Thorac Cardiovasc Surg. 2010;139(1):53-9 e1.

Although the rate of vocal cord palsy (VCP) in our study was relatively high at 29.6%, the majority of cases (89.1%) exhibited transient VCP, which is likely to improve with more meticulous surgical procedures.

In some cases, cervical lymph node dissection (CND) was performed even when intrathoracic anastomosis was carried out. If preoperatively there is no suspicion of lymph node metastasis above the upper mediastinum, thoracic anastomosis is performed. However, if intraoperatively frozen section analysis reveals positive recurrent laryngeal nerve (RLN) lymph node metastasis, additional CND is performed. Additionally, in patients who received neoadjuvant chemoradiotherapy (nCRT) and showed suspicion of lymph node metastasis above the upper mediastinum, additional CND is performed.

Changes in the text:

The VCP rate was 23.4% for intra-thoracic anastomosis and 37.8% for anastomosis at cervical level or above, with the intra-thoracic anastomosis rate being significantly lower (p=0.001). Compared to previous studies, the rate of vocal cord palsy in this study is higher at 29.6%. This elevated rate can be attributed to the extensive en bloc lymph node dissection in the superior mediastinum. The improved accessibility afforded by RAMIE enables

surgeons to reach deeper regions of the thoracic cavity, which would not have been possible with conventional surgery. As a result, we performed nearly 35 lymph node harvesting procedures during RAMIE, a significantly higher number compared to other studies where the average ranged from 18 to 30 lymph nodes (18,19). Similar findings have been reported in other studies, where vocal cord palsy occurred in 26% and 29% of cases after 44 and 38 lymph node harvesting procedures, respectively (20,21). (line 271-279)

Comment 6: The limitations should acknowledge that the majority of cases were performed on early stage patients who did not received neoadjuvant therapy. Operations after neoadjuvant therapy may be more difficult. So in practices with a higher proportion of cases with surgery after nCRT, the learning curve may be longer.

Reply 6: We have added a limitation acknowledging that the procedures were performed on patients in the early stages who did not receive neoadjuvant chemoradiotherapy (nCRT). In our study, there was an increased proportion of patients who received nCRT in the stable phase. This indicates that as the proficiency in RAMIE increased, the proportion of RAMIE surgeries in patients who received nCRT also increased. We agree that a higher proportion of patients receiving nCRT may lead to a longer learning curve.

Changes in the text:

This study had notable limitations. First, selection bias is inherent in a retrospective study conducted at a single institution. Second, RAMIE was performed by a single thoracic surgeon. Therefore, it may be challenging to generalize the learning curve and surgical outcomes of this study to other settings. Third, the clinical outcomes in this study were obtained through a well-established collaborative system involving highly experienced surgeons in their respective fields. Therefore, we believe that the impact of collaboration on the learning curve in our study is likely to be minimal. However, it may be challenging to generalize our learning curves to surgeons who do not have access to a similar collaborative system. Forth, the patient population in our study has different characteristics compared to esophageal cancer patients in the Western world. Therefore, it may be challenging to generalize our research findings. Fifth, we do not have data on the learning curve or surgical outcomes specifically related to robotic-sewn anastomosis. However, a recent study by Huscher et al. demonstrated excellent results with an anastomotic leakage (AL) rate of 10% in 40 patients who underwent intrathoracic robotic-sewn anastomosis (28). This indicates that as proficiency with RAMIE increases, complete robotic Ivor Lewis esophagectomy becomes

feasible. Lastly, it should be noted that the patient population in our study consisted predominantly of early-stage patients who did not receive nCRT. It is important to recognize that as the proportion of patients receiving nCRT increases, the learning curve may be longer, and the surgical outcomes may not be as favorable. (line 356-359)