ROBOTIC TRANSTHORACIC ESOPHAGECTOMY VERSUS THORACOSCOPIC ESOPHAGECTOMY IN COMBINED WITH LAPAROSCOPY FOR ESOPHAGEAL CANCER

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ABSTRACT

***Background**: Extended mediastinal with bilateral recurrent laryngeal nerves (RLNs) lymph node dissection (LND) is critical to curative surgery in the treatment of esophageal squamous cell carcinoma (ESCC). Some reports in Robotic transthoracic esophagectomy (RTE) have some advantages over Thoracoscopic esophagectomy (TE) in increasing the exposure and accuracy of mediastinal LND. However, published data was still limited.* ***Objectives**: To evaluate early results of RTE combined with laparoscopy to treat ESCC.* ***Methods**: This was a prospective non-randomized comparative study. All patients who underwent RTE or TE for esophageal squamous cell carcinoma were included in the study. The primary endpoints were operation results, morbidity, and mortality. The secondary endpoint was early oncological results, including lymph node harvested, lymph node metastasis, short-term local recurrence, and survival time.* ***Results**: From 8/2018 - 8/2020, at Cho Ray Hospital, we performed 109 cases of esophagectomy for esophageal SCC, of which 19 cases (17.4%) were RTE (group 1), and the other 90 cases (82.6%) were TE (group 2). There was no statistical difference in the staging of group 1 compared to group 2, with predominant cases at stages IB, IIA, and IIB (68.5% vs. 54.4%). Group 1 had a longer operation time than group 2 at the thoracic phase (480 (420-540) vs. 410 (380-450), p=0.001, Mann-Whitney test). Left LRN exposure was better in the RTE group than the TE group; however, LRN injuries seemed to be increased with the RTE group (p=0.028 Fisher's exact test), probably due to the short learning curve. There was also no difference in the number of mediastinal lymph nodes harvested, including lymph nodes along bilateral LRN.* ***Conclusion**: RTE combined with laparoscopy is feasible, safe, and effective in treating esophageal SCC. RTE could be a good option in transthoracic esophagectomy for ESCC.*

***Keywords**: robotic transthoracic esophagectomy, thoracoscopic esophagectomy.*

I. INTRODUCTION

Esophageal squamous cell carcinoma (ESCC) has a high degree of malignancy with a high rate of lymph node metastasis [1]. Therefore, surgical resection with extensive lymph node dissection combined with neoadjuvant chemoradiation therapy has become an essential therapeutic strategy for esophageal cancer of stages II and III [6]. Thoracoscopic and laparoscopic esophagectomy has become the most popular minimally invasive techniques as they can lower pulmonary complication rates and comparable long-term outcomes with open techniques [7-8]. Extended mediastinal lymph node dissection (LND) with bilateral recurrent laryngeal nerves (RLNs) is the key to curative surgery in the treatment of esophageal cancer [2, 10]. However, this seems to be the most challenging part of mediastinal lymph node dissection with the thoracoscopic approach as of its limitation in the exposure of anatomic landmarks, 2D vision, and instrumentation. Robotic esophagectomy was first reported in 2006 by van Hillegersberg et al. [4] and showed a promising future for minimally invasive surgery to treat esophageal cancer. We have

performed thoraco-laparoscopic esophagectomy for esophageal cancer since 2003, with about 50 – 60 cases per year [14]. In August 2018, we started RTE combined with laparoscopy to treat esophageal cancer at Cho Ray Hospital. The study aimed to evaluate this new operative approach's feasibility and preliminary results.

II. MATERIALS AND METHODS

This was a prospective non-randomized comparative study. All patients who underwent RTE or TE for esophageal squamous cell carcinoma were included in the study. In both groups, abdominal phases were performed by laparoscopic approach. The gastric conduit and esophagogastric conduit anastomosis were performed on the left cervical level. The primary endpoints were operation results, morbidity, and mortality. The secondary endpoints were early oncological results, including lymph node harvested, lymph node metastasis, short-term local recurrence, and survival time. Inclusion criteria included squamous cell esophageal cancer with clinical T stage ≤ cT4a based on CT scan and endoscopic ultrasound with no distant metastasis and patient's agreement with RTE or TE. For patients with > cT3 or cN+, 3 to 6 cycles of neoadjuvant chemotherapy (DCX or DCF) were performed. The esophagectomy was performed after 4-6 weeks after the chemotherapy. Exclusion criteria included those patients with significant right pleural adhesions that prevent thoracoscopic or robotic transthoracic approach, previous thoracotomy, or recurrent cancer.

2.1. Techniques of operation

2.1.1. Robotic Transthoracic phase

The patient was in the left lateral decubitus position. General anesthesia with one-lung ventilation (right lung deflation). CO_2 inflation of right pleural with 8mmHg pressured with seven trocar positions. The assistant surgeon was standing in front of the patient.

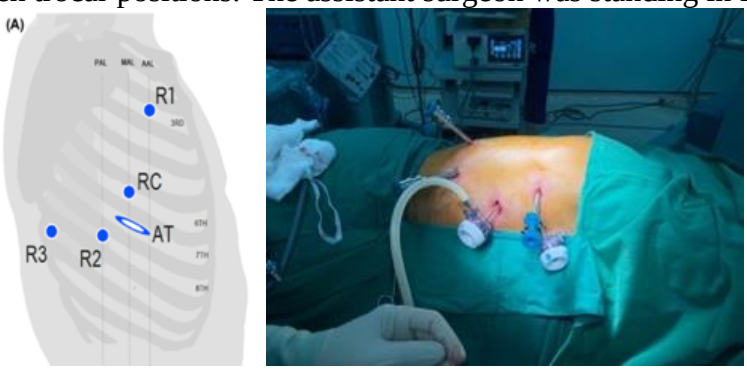

Figure 1. Right thoracic trocar positions: Robotic camera (RC), Robotic arm 1 (R1), Robotic arm 2 (R2) and Robotic arm 3 (R3), Assistant trocar (AT)

Exploratory thoracoscopy was performed first to assess the respectability of the lesion. Esophagus was mobilized in one block with fat tissue and lymph nodes. The dissection started from the right diaphragmatic cruz upward on the anatomic space in front of the pericardiac membrane, preserving the meso-esophagus, including the lower mediastinal, peri-carina, and bilateral main bronchial lymph nodes. The semiazygot vein was clipped by hem-o-lock and transected. The right bronchial artery was also clipped and transected in most cases. Esophageal dissection was performed in the upper mediastinum

with bilateral peri LRN lymph node dissection. A counter-clockwise technique was also used for LND along the RLNs. Attention was paid not to injuring the thoracic duct at this level. Esophagus was transected above the carina with an endoscopic linear stapler to facilitate lymph node dissection. Lung inflation was requested, and a 20F chest tube was inserted into the right pleural space.

2.1.2. Thoracoscopic phase

The patient was in the same position as in robotic transthoracic surgery. The monitor was set to the back side, upward to the head of the patient. Surgeons and assistants were standing on the ventral side of the patients.

2.1.3. Abdominal phase

In both groups, the abdominal phase was performed with laparoscopy. Starting to liberate the greater curvature, preserving the right and left gastroepiploic vessels. On the lesser curvature, the right gastric artery was clipped and transected at the level about 5cm from the pylorus, preserving 3 - 4 branches of vessels to the antrum. Lymph node dissection was performed with pericardial lymph nodes (groups 1, 2, 3a) and 7, 8a, 9, and 11p. The left gastric artery and vein were transected at the origins. A kockerization was made to maximize the approaching of gastric conduit for cervical anastomosis. Esophagus was separated from diaphragmatic cruzs and pulled into the abdominal cavity. Hiatal cruzs were closed with continuous 3.0 barbed suture (V-Loc or Stratafix) if a substernal route was expected. A 4 cm mini-laparotomy was made in the midline umbilicus. Linear staplers removed part of the lesser curvature and cardia, and a gastric conduit was made. We prefer a significant gastric conduit with a wide about 4-5 cm length and about 35- 40cm length.

2.1.4. Cervical phase

A skin incision was made in the low anterior cervical region. Esophagus was exposed from the left side. Cervical lymph node dissection was performed bilaterally along the recurrent laryngeal nerves, para-carotid veins, and arteries lymph node below the cricoid cartilage and the supraclavicular lymph nodes. The gastric conduit was brought up to the left neck through the posterior mediastinum or substernal route. An end-to-side esophageal–gastric conduit anastomosis was performed with circular stapler 25 (CDH25 or EEA25). Closed suction was put bilaterally on the neck. Skin and fascia were closed. Feeding jejunostomy was made in all cases.

2.1.5. Statistical methods

The Chi-square, Fisher's, or Mann-Whitney tests were used to compare categorical variables. Survival was estimated using the Kaplan-Meier method, and the significance of differences was determined using the log-rank test. All statistical tests were done by SPSS software v.26. Statistical significance was accepted for *P* values <0.05.

III. RESULTS

Table 1: Patients' characteristics

Patients' characteristics	Total (n = 109)	RTE (n = 19)	TE (n = 90)	p value
Gender (male/female)	106/3	19/0	87/3	1.000
Age (median, min-max)	58 (41-77)	60 (47-75)	58 (41-77)	0.211
Performance status				1.000
0	97	17 (89.5%)	80 (88.9%)	
1	12	2 (10.5%)	10 (11.1%)	

Patients' characteristics	Total (n = 109)	RTE (n = 19)	TE (n = 90)	p value
Smoking		11 (57.9%)	50 (55.6%)	0.852
Respiratory function				0.671
No limitation	87	17 (89.5%)	70 (77.8%)	
Mild limitation	18	2 (10.5%)	16 (17.8%)	
Medium limitation	4	0	4 (4.4%)	
Co-morbidities	32	7 (36.8%)	25 (27.8%)	
Tumor locations				0.195
Upper thoracic	4	2 (10.5%)	2 (2.2%)	
Middle thoracic	50	9 (47.4%)	41 (45.6%)	
Lower thoracic	55	8 (42.1%)	47 (52.2%)	
Differentiation				0.593
Poorly	13	3 (15.8%)	10 (11.1%)	
Medium	90	16 (84.2%)	74 (82.2%)	
Well	6	0	6 (6.7%)	
Neoadjuvant CX (DCX**)	85	13 (68.4)	72 (80%)	0.359
Neoadjuvant CRX	5	1 (5.3%)	4 (4.4%)	0.624

* TB: Tuberculosis, ** DCX: docetaxel, cisplatin and capecitabine

From August 2018 to August 2020, at Cho Ray Hospital, 109 patients with esophageal SCC underwent minimally invasive esophagectomy with extended lymph node dissection. There were 19 cases with RTE (group 1) and 90 patients with TE (group 2). In both groups, the abdominal phase was performed by laparoscopic approach, and a cervical esophagogastric conduit anastomosis was done on the left cervical level. Tumors were located in both groups' middle and lower thoracic parts. Most of the tumors had medium differentiation SCC of the esophagus. In group 1, neoadjuvant chemotherapy and chemoradiation therapy were 68.4% and 5.3%, respectively. In group 2, these numbers were 80% and 4.4%, respectively.

Table 2: Operative outcomes

Operation characteristics	Total (n = 109)	RTE (n = 19)	TE (n = 90)	p value
Operation time	420 (260-600)	480 (300-600)	410 (260-540)	0.001
Blood loss	Minimal	Minimal	Minimal	
Gastric conduit location				0.450
Posterior mediastinum	43	9 (47.4%)	34 (37.8%)	
Retrosternum	66	10 (52.6%)	56 (62.2%)	

In the RTE group, the median total operation time was 480 minutes (300-600 mins) which is longer than those in the TE group 410 (260-540 mins) (p = 0.001). The blood loss was minimal. Retrosternum was the preferred location for bringing up the gastric conduit in both groups.

Table 3: Postoperative morbidities

Postoperative morbidities	total (n = 109)	RTE (n = 19)	TE (n = 90)	p value
Intraoperative accident	5	1 (5.2%)	4 (4.4%)	1.000
Injury of left pleural/ cardiac membrane (sutured)	2	1	1	
Injury of left bronchial membrane (sutured)	2	0	2	
Pulmonary injury (sutured)	1	0	1	
Pneumonia	9	1 (5.2%)	8 (8.9%)	0.329
Subcutaneous emphysema (degree 1)	6	1 (5.2%)	5 (5.5%)	1.000
Pneumothorax	5	0 (0%)	5 (5.5%)	1.000
Pleural effusion (II degree)	1	0	1	1.000
Cervical anastomotic leak	8	1 (5.2%)	7 (7.8%)	0.362
RLN palsy	28	9 (47.4%)	19 (21.1%)	0.028
Chyle leak	2	0 (0%)	2 (2.2%)	1.000
30-day mortality	2	0 (0%)	2 (2.2%)	1.000

There was 1 case of an intraoperative accident in the RTE group compared with 4 cases of tearing injury of the left pleural and cardiac membrane in the TE group.

Only 1 case (5.2%) with an anastomotic leak was recorded in the RTE group, while 7 cases (7.7%) in the TE group. All these cases were treated conservatively. We noticed only 1 case (5.2%) with pneumonia in the RTE group versus 8 cases (8.9%) in the TE group. However, the RTE group had more RLN palsy than those of the TE group (9 cases [47.4%] vs. 19 cases [20.1%], respectively). There was no mortality in the RTE group, and the TE group's mortality rate was 2.2% (2 cases). In the first case, the patient got an anastomotic leak on postoperative day 5 and had severe pneumonia. The patient got an anastomotic leak in the second case and had severe postoperative pancreatitis. The patient was reoperated for abdominal cavity lavage and drainage. Multiorgan failure was the cause of his death.

Table 4. Pathological results

Pathological results		Total (n = 109)	RTE (n = 19)	TE (n = 90)	P value
Harvested mediastinal LN	Total	16 (4-36)	20 (8-36)	16 (4-33)	0.091
	Para Right RLN	4 (0-10)	4 (0-9)	4 (0-10)	0.239
	Para Left RLN	2 (0-11)	4 (0-11)	2 (0-9)	0.063
	Middle mediastinum	5 (1-12)	6 (2-8)	4.5 (1-12)	0.162
	Lower mediastinum	5 (0-14)	5 (1-9)	5 (0-14)	0.191
pT stages	pTis	10	3	7	0.464
	pT1a	6	2	4	
	pT1b	16	3	13	
	pT2	35	7	28	
	pT3	28	3	25	
	pT4a	14	1	13	
pN stages	0	64	13	51	0.893
	1	27	4	23	

Pathological results		Total (n = 109)	RTE (n = 19)	TE (n = 90)	P value
	2	13	2	11	
	3	5	0	5	
Staging (AJCC 7th) (pTNM)	0	10	3 (15.8%)	7 (7.8%)	0.297
	IB	17	4 (21.1%)	13 (14.4%)	
	IIA	15	1 (5.3%)	14 (15.6%)	
	IIB	30	8 (42.1%)	22 (24.4%)	
	IIIA	18	1 (5.3%)	17 (18.9%)	
	IIIB	6	1 (5.3%)	5 (5.6%)	
	IIIC	13	1 (5.3%)	12 (13.3%)	

The median number of mediastinal lymph nodes harvested was slightly increased in the RTE group than the TE group (20 vs. 16), but the difference was insignificant for both total lymph nodes, lymph nodes at right RLN and left RLN. The number of metastatic lymph nodes was also not significantly different between the two groups (Table 4). Regarding postoperative pathological staging, most patients were at early stages in both groups. For stage IIIA, the RTE group had fewer patients than the TE group (5.3% vs. 18.9%, p = 0.297).

With the mean follow-up time of 15.3 ± 7.3 months (6 – 32 months), we noticed 3 cases of cervical lymph node recurrence in the TE group compared with no RTE group. There was 1 patient with lower thoracic ESCC in the TE group who got liver metastasis 18 months after surgery and died at 21 months. Overall survival in group 1 and group 2 were 100% and 93.7%, respectively (**Figure 2**).

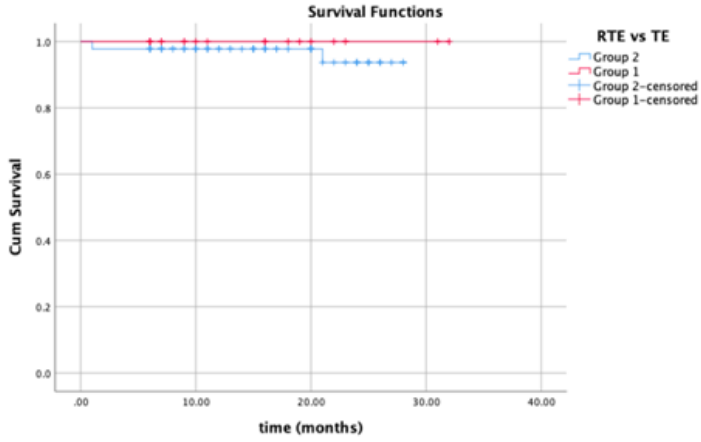

Figure 2. Overall survival with the Kaplan-Meier method

IV. DISCUSSION

The most common location of mediastinal nodal metastasis in ESCC is along the bilateral RLNs [1]. Many authors emphasized that the complete mediastinal lymphadenectomy in ESCC should include lymph nodes along the bilateral RLNs [3,5]. Furthermore, bilateral RLN dissection requires precise exposure and meticulous technique to remove lymphatic nodes while preserving the integrity of nerves completely. Since introducing the Da Vinci Robot, we have had another option for minimally invasive surgery for esophageal cancer.

In this study, we used the robot Da Vinci Si with four arms for only the thoracic phase. Some authors used robots in the thoracic and abdominal phases [13,15]. Our approach (RTE) was reasonable as we could have the advantages of robotic dissection in the mediastinal and para RLN lymph nodes – the most challenging part of ESCC surgery. Furthermore, we preferred a laparoscopic approach in the abdominal phase to deploy two surgical teams simultaneously (one for cervical dissection and one for laparoscopic dissection). It would save time and compensate for longer operation time with the robotic transthoracic dissection. We noticed that more surgeons are now using this hybrid approach [10,12].

In this study, we have seen that RTE had provided more mediastinal lymph node harvested, especially in the left RLN lymph nodes, compared to the TE group, though this difference was insignificant (20 LN vs. 16 LN, p = 0.091). Our results were similar to other authors in that RTE might have a better capability in harvesting more lymph nodes along RLN areas [4,11]. A retrospective, propensity-matched study by Chao et al. [2], comparing 37 cases with RTE with 104 patients with TE, has found that RTE allowed for achieving a higher mean number of dissected nodes along the RLN area (especially in the left side) compared with TE, without increasing RLN palsy and pulmonary complications rates.

A robotic system had better benefits in dissecting lymph nodes along the RLNs. First, the 3D self-controlled magnified operation viewed by automatic camera allowed better visualization of the deep view in the upper mediastinal area compared to the traditional 2D monitor, which the assistant controlled. Second, a third robotic arm allowed a steady, clear, and excellent counter-traction during lymph node dissection. This would help the surgeon to gain more control of the operation. Third, the combination of articulated fine robotic instruments with sharpness (scissors) or energy devices (bipolar, monopolar, harmonic) allowed surgeons to have a meticulous, fully controlled dissection in this area. That might explain why all of these features may decrease the rates of RLN injury.

However, to gain control of the robotic system, surgeons need to have a specific learning curve achievement with strictly academic training and case experiences. That might explain why in our study, the RLNs palsy was significantly higher in RTE compared with the TE group (47.4% vs. 21.1%, p = 0.028) even though the number of lymph nodes harvested was higher in the RTE group. Some authors suggested that the learning curve for robotic esophagectomy with an experienced laparoscopic surgeon should be at least 20 cases [9,15].

We also noticed a decrease in postoperative complications of the RTE vs. the TE groups. Moreover, there were no statistically significant differences between the groups. This might suggest a better improvement in the operative results of RTE in our next series when we have a better learning curve and experiences. Furthermore, a randomized controlled trial would be appropriate to evaluate better the short-term and long-term results of these two approaches.

Nevertheless, we also noticed the disadvantages of robotic surgery in esophagectomy for esophageal cancer. First, longer operation time was the backward of RTE, especially when we did not get through the learning curve and the trend for more meticulous dissection with the robot system. Second, the 3D camera view was only for chief surgeons rather than for the assistant. So there might be a certain gap in getting the same information from the operation field, which might prevent the optimal teamwork for robotic surgery. This could be improved in the next generations of robotic systems. Third, robotic surgery was not insured by medical insurance in our country,

so patients had to pay more compared to other minimally invasive surgeries. Hopefully, robotic systems will be more competitive in the future.

Finally, this study still had some limitations. Firstly, this was a non-randomized study with a small number of patients in the RTE group, and our follow-up time needs to be longer for evaluation of oncologic purposes. Additional follow-up on this group including new patients to the study will follow.

V. CONCLUSION

RTE combined with laparoscopy was feasible, safe, and effective in treating ESCC. RTE helped to expose better and harvest more lymph nodes along RLNs and in the mediastinum. RLNs palsy was the common complication in the first series of RTE. Other post-operative results were comparable to TE regarding postoperative complications, short-term local recurrence, and distal metastasis. RTE could be a good option in transthoracic esophagectomy for ESCC.

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