Lymphadenectomy in minimally invasive esophagectomy versus open esophagectomy for esophageal cancer; Is there a difference?

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Abstract

Background*:* The presence of lymph node metastasis is an important prognostic factor for survival in patients with curable esophageal cancer. Lymphatic drainage system of the esophagus is unique due to submucosal lymphatic spread of esophageal tumors so it is unpredictable and highly variable. Minimally invasive esophagectomy (MIE) has lesser complications in resectable esophageal when compared to open esophagectomy (OE). So, we aim to evaluate lymphadenectomy in minimally invasive esophagectomy versus open esophagectomy for esophageal cancer and its impact on short- and long-term outcomes.

Methods*:* This prospective study was conducted in the surgical oncology department at South Egypt Cancer Institute (SECI) Assiut University (open esophagectomy cases) and Fujita Health University Japan (minimally invasive cases) and included sixty patients diagnosed with esophageal cancer, 20 patients operated by open technique and 40 patients operated by minimally invasive surgery (20 cases thoracoscopic and 20 cases robotic). All patients were divided into two groups (Open and Minimally invasive) then the minimally invasive group was furtherly subdivided into two groups (Thoracoscopic and Robotic). Each group was compared by demographic, clinical, pathological, and surgical factors (Operative time, blood loss, transfusion requirement, and duration of hospital stay), morbidity, mortality, and long term outcomes (Disease-free survival, Over-all free survival) were also assessed.

Results*:* patients with open esophagectomy had significantly high ICU stay and lower hospital stay in comparison to other groups. Thoracoscopy and robotic groups had insignificant differences regarding hospital stay and ICU stay. Excised lymph nodes were significantly higher among thoracoscopic and robotic groups in comparison to open group while the number of positive lymph nodes had insignificant differences between the three groups. As regards postoperative complications, the open group showed a significant increase in the number of patients with postoperative respiratory complications.

Conclusion*:* Lymph nodes harvest was significantly higher among thoracoscopic and robotic esophagectomy in comparison to open esophagectomy with significantly lower postoperative respiratory complications and ICU stay. So, MIE is considered a good and safe alternative to open esophagectomy

Keywords: Esophageal Neoplasms, Prospective Studies, Esophagectomy, Robotic Surgical Procedures, Thoracoscopy, Lymph Node Excision, Prognosis.

Introduction:

Esophageal cancer (EC) is considered as the sixth most common cause of cancer mortality and despite the squamous cell carcinoma type is more prevalent, the incidence of esophageal adenocarcinoma is increasing[1]. Surgery for EC has been associated with significant rates of morbidity and mortality especially respiratory complications and the prognosis is still poor, with a five-year survival rate of < 15% [2, 3]. Radical open esophagectomy with complete lymph node (LN) dissection, including total mediastinal nodal dissection, is the cornerstone of the multimodality therapy with a curative intention for EC [4, 5]. The National Comprehensive Cancer Network (NCCN) guidelines and the Union for International Cancer Control (UICC) staging manual recommend that at least 12–15 nodes should be removed[6, 7].

The presence of lymph node metastasis is an important prognostic factor for survival in patients with curable esophageal cancer. Lymphatic spread of esophageal tumors is unpredictable and highly variable due to unique anatomy of submucosal lymphatic drainage system of the esophagus [8]. To increase the prospect of radical excision of all positive lymph nodes and thereby improve regional tumor control and long-term survival, esophagectomy together with an extended 2-field (posterior mediastinum, upper abdomen) lymphadenectomy is generally recommended [9]. Transthoracic esophagectomy is the standard approach to achieve an extended lymph node clearance [10]. The value of an extended lymphadenectomy for esophageal cancer is debated. Some recent reports demonstrate no association between Lymph node yield (LNY) and survival. Other studies recommend an extended removal of 6–30 LNs for survival improvement; this association has not yet been evaluated in larger cohorts [11, 12]. In this study, we aim to evaluate lymphadenectomy in minimally invasive esophagectomy versus open esophagectomy for esophageal cancer and its impact on short- and long-term outcomes.

Patients and Methods:

This prospective study was conducted in the surgical oncology department at South Egypt Cancer Institute (SECI) Assiut University (open esophagectomy cases) and Fujita Health University Japan (minimally invasive cases) between March 2014 and September 2018.

Sixty patients diagnosed with esophageal cancer and enrolled in this study, 20 patients operated by open technique and 40 patients operated by minimally invasive surgery (20 cases thoracoscopic and 20 cases robotic). All patients were divided into two groups (Open and Minimally invasive) then the minimally invasive group was furtherly subdivided into two groups (Thoracoscopic and Robotic). Each group was compared by demographic, clinical, pathological, and surgical factors (Operative time, blood loss, transfusion requirement, and duration of hospital stay), morbidity, mortality, and long term outcomes (Disease-free survival, Overall free survival) were also assessed.

Neoadjuvant or induction chemotherapy (Cisplatin 80 mg/m2 on days 1 and 29 + 5- fluorouracil 800 mg/m2 on days 1–5 and 29–33) was administered to patients with T3, any N, M0 cancer or T<2, N >2, M0 cancers.

SECI ethical committee approved the study, and all patients were provided informed consent after explanation and discussion of the procedure.

Inclusion criteria:

All consented patients assigned to undergo elective resection of esophageal cancer with T1, T2, and T3 Tumors were included in the study.

Exclusion criteria:

-prior pneumonectomy

-severely comorbid patients

-stage IV esophageal cancer patients.

-Patients with extensive pleural adhesions were excluded from the minimally invasive technique.

Types of interventions:

Laparoscopic-assisted thoracoscopic, robotics, and conventional open esophageal resection. The anastomosis is either performed by esophageal stapler or handsewn. The patients were admitted to the intensive care unit immediately post-operation, until extubation and the stabilization of vital signs. All the patients were nil by mouth for at least the first 3-4 days post-operation. An examination of the vocal fold mobility was routinely performed in the second week post-operation for patients, especially the minimally invasive technique as they were more susceptible to recurrent laryngeal nerve injury due to upper mediastinal lymph node dissection.

Data Collection:

Data on the patients' demographics, medical comorbidities, locations of the tumors, operative details, histopathology of the removed specimen, postoperative short term outcomes, long term outcomes as recurrence and survival were also collected and entered into a database for esophageal malignancy.

End Points:

Primary short-term endpoints:

- Nodes collected (no.)
- Safety margin (cm)

Secondary short-term endpoints

- Operative time
- Blood loss and transfusion requirement
- Recovery of gastrointestinal function (time to resume a normal diet, time first passing flatus, time of first bowel motion)
- Duration of hospital stay
- Morbidity and mortality

Long term outcomes:

- Disease free survival
- Overall free survival.

Follow up:

Detailed history and examination every 3 months for any possible late complications. CT examination for chest, abdomen, and pelvis is performed routinely every 6 months for all patients. When LN or systemic metastasis was suspected, positron emission tomography scanning was performed for confirmation.

Statistical Analysis:

Data was collected and analyzed using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data were expressed in the form of mean ± SD or median (range) while nominal data were expressed in the form of frequency (percentage). Chi²-test was used to compare the nominal data of different groups in the study while the student t-test was used to compare mean of different two groups and ANOVA test for more than two groups followed by post-Hoc analysis. Kaplan –Meier analysis was used for survival analysis. Multivariate regression analysis was used to determine predictors of relapse and death in studied patients. The level of confidence was kept at 95% and the P-value was significant if < 0.05.

Results:

Patients' characteristics:

The mean age of patients with open intervention was 48.95 ± 9.36 years, 13 (65%) of them were males and 15 (75%) of them had normal spirometry. In the case of patients with thoracoscopic; mean age was 63.75 ± 7.25 years, 15 (75%) of them were males and 13 (65%) of them had normal spirometry (Table 1).

In those patients with robotic intervention, the mean age was 64.30 ± 5.12 years, 19 (95%) of them were males and 16 (80%) of them had normal spirometry. As regarding ASA (American Society of Anesthesiologists) Physical Status Classification System, it was noticed that the majority of all enrolled had ASA class II. There were only three patients with ASA class III; one of them had thoracolaparoscopic surgery while the other two patients had robotic intervention.

All intervention had insignificant differences regarding sex, spirometry, and ASA, but the age of patients was significantly higher among thoracoscopic and robotic groups in comparison to patients who had an open intervention. Also, the body mass index was significantly higher in the case of open intervention in comparison to other groups.

Table 1: Patients characteristics

	Intervention			*P*
	Open	Thoraco-laparos-copic	Robotic	
Age (years)	48.95 ± 9.36	63.75 ± 7.25	64.30 ± 5.12	< 0.001*
Sex				0.06
Male	13 (65%)	15 (75%)	19 (95%)	
Female	7 (35%)	5 (25%)	1 (5%)	
Spirometry				0.55
Normal	15 (75%)	13 (65%)	16 (80%)	
Obstructive	5 (25%)	7 (35%)	4 (20%)	
ASA				0.34
I	10 (50%)	6 (30%)	5 (25%)	
II	10 (50%)	13 (65%)	13 (65%)	
III	0	1 (5%)	2 (10%)	
BMI (kg/m^2)	25.25 ± 3.55	20.69 ± 3.47	22.59 ± 2.70	< 0.001*
Significance	*P*1	*P*2	*P*3	
Age	< 0.001	< 0.001	0.97	
Sex	0.64	0.41	0.22	
Spirometry	0.51	0.54	0.72	
ASA	0.43	0.26	0.49	
BMI	< 0.001	0.03	0.16	

Data expressed as frequency (percentage), mean (SD). ***P***-value was significant if < 0.05. **BMI**: body mass index. *P* indicates the difference between different interventions; ***P*1** compared between open and thoracoscopy technique; ***P*2** compared between open and robotic technique; ***P*3** compared between robotic and thoracoscopy technique

Tumor Characteristics:

It was noticed that the lower third of the esophagus is the most frequently affected third in the current study where 14 (70%), 12 (60%) and 8 (40%) patients of open, thoracoscopy, robotic group had lower esophageal cancer. Seven patients in the current study had received neoadjuvant chemotherapy; six of them had robotic intervention and the other patient had thoracoscopic intervention (Table 2).

Three-field (McKeown) esophagectomy was performed in all patients with thoracoscopy and robotic groups. Three-field (McKeown) and Ivor Lewis esophagectomy were performed in 14 (70%) and 6 (30%) patients of open intervention, respectively.

It was noticed the operative time was significantly lower in patients with open esophagectomy (397.01 ± 86.62 minute; *P*< 0.001) in comparison to other groups. Thoracoscopy and robotic group had insignificant differences as regarding operative time (711.85 ± 94.86 vs. 716.4 ± 75.24; *P*= 0.98).

Blood loss was significantly lower with thoracoscopic (163 ± 91.64 ml) and robotic group (279.25 ± 21.9 ml) in comparison to open esophagectomy (548.50 ± 136.7 ml; *P*< 0.001) but both thoracoscopic and robotic group had insignificant differences as regarding blood loss.

The posterior route of reconstruction was performed in all patients with exception of two patients; one in the thoracoscopic group and the other was in the robotic group where substernal reconstruction was performed. Also, the stomach was the organ of reconstruction with the exception of two patients from the robotic group where jejunum was used.

Hospital stay:

It was noticed that patients with open esophagectomy had significantly high ICU stay and lower hospital stay in comparison to other groups. Thoracoscopy and robotic groups had insignificant differences regarding hospital stay and ICU stay (Table 3).

Pathological evaluation:

It was noticed that three studied groups had insignificant differences regarding pathological evaluation with exception of;

- In open esophagectomy group 6 (30%) and 14 (70%) patients were T2 and T3 tumor stage, respectively, In Thoraco-laparoscopic group; 5 (25%), 7 (35%), 4 (20%) and 4 (20%) patients were T1, T2, T3 and T4, respectively, while in robotic group 9 (45%), 4 (20%), 5 (25%), and 2 (10%) patients were T1, T2, T3 and T4, respectively.
- None of those with open esophagectomy had residual tumors while two patients from the thoracoscopic group and five patients from the robotic group had microscopic residual tumors.
- Regarding histopathological evaluation; all patients with robotic esophagectomy, 19 (95%) of the

thoracoscopic group, and five patients with open esophagectomy had squamous cell carcinoma. Adenocarcinoma was presented in five patients with open esophagectomy and one patient with thoracoscopy (Table 4).

Table 2: Tumor characteristics and operative data

	Intervention			*P*
	Open	Thoraco-laparos-copic	Robotic	
Location				
Upper	0	2 (10%)	4 (20%)	0.19
Middle	6 (30%)	6 (30%)	8 (40%)	
Lower	14 (70%)	12 (60%)	8 (40%)	
Neoadjuvant chemotherapy	0	1 (5%)	6 (30%)	< 0.001*
Type				
Three-field (McKeown)	14 (70%)	20 (100%)	20 (100%)	< 0.001*
Ivor Lewis	6 (30%)	0	0	
Operative time (min.)	397.01 ± 86.62	711.85 ± 94.86	716.4 ± 75.24	< 0.001*
Blood loss (ml)	548.50 ± 136.7	163 ± 91.64	279.25 ± 21.9	< 0.001*
Route of reconstruction				
Posterior	20 (100%)	19 (95%)	19 (95%)	0.59
Substernal	0	1 (5%)	1 (5%)	
Organ of reconstruction				
Stomach	20 (100%)	20 (100%)	18 (90%)	0.12
Jejunum	0	0	2 (10%)	
Significance	***P*1**	***P*2**	***P*3**	
Location	0.10	0.09	0.11	
Neoadjuvant chemotherapy	0.65	< 0.001	< 0.001	
Type	< 0.001	< 0.001	---	
Operative time	< 0.001	< 0.001	0.98	
Blood loss	< 0.001	< 0.001	0.06	
Route of reconstruction	0.65	0.65		
Organ of reconstruction	---	0.60	0.60	

Data expressed as frequency (percentage). ***P***-value was significant if < 0.05. *P* indicates the difference between different interventions; ***P*1** compared between open and thoracoscopy technique; ***P*2** compared between open and robotic technique; ***P*3** compared between robotic and thoraco-laparoscopic technique

Table 3: Hospital stay in enrolled patients

	Intervention			*P*
	Open	Thoraco-laparos-copic	Robotic	
Hospital stay (day)	16.01 ± 4.56	28.45 ± 5.28	25.25 ± 11.05	< 0.001*
ICU stay (day)	4.30 ± 2.22	1.7 ± 0.75	1.55 ± 0.79	< 0.001*
Significance	*P*1	*P*2	*P*3	
Hospital stay	< 0.001	0.03	0.64	
ICU stay	< 0.001	< 0.001	0.93	

Data expressed as frequency (percentage), mean (SD). ***P***-value was significant if < 0.05. **ICU**: intensive care unit. ***P*** indicates the difference between different procedures; ***P*1** compared between open and thoracoscopy technique; ***P*2** compared between open and robotic technique; ***P*3** compared between robotic and thoraco-laparoscopic technique

Table 4: Pathological evaluation of patients

	Intervention			*P*
	Open	Thoraco-laparos-copic	Robotic	
pT stage				
T1	0	5 (25%)	9 (45%)	< 0.001*
T2	6 (30%)	7 (35%)	4 (20%)	
T3	14 (70%)	4 (20%)	5 (25%)	
T4	0	4 (20%)	2 (10%)	
pN stage				
N0	7 (35%)	14 (70%)	7 (35%)	0.18
N1	6 (30%)	4 (20%)	9 (45%)	
N2	4 (20%)	1 (5%)	3 (15%)	
N3	3 (15%)	1 (5%)	1 (5%)	
Pathological stage				
I	4 (20%)	11 (55%)	7 (35%)	0.13
II	10 (50%)	3 (15%)	7 (35%)	
III	6 (30%)	6 (30%)	6 (30%)	
Residual tumor(R1)	1(5%)	2 (10%)	4 (20%)	0.32
Pathological grade				
GI	6 (30%)	7 (35%)	5 (25%)	0.60
GII	10 (50%)	12 (60%)	13 (65%)	
GIII	4 (20%)	1 (5%)	2 (10%)	
Histopathology				
Adenocarcinoma	5 (25%)	1 (5%)	0	0.02*
SCC	15 (75%)	19 (95%)	20 (100%)	
Significance	*P*1	*P*2	*P*3	
T stage	0.01	0.04	0.54	
N stage	0.45	0.11	0.08	
Pathological stage	0.47	0.34	0.07	
Residual tumor	0.06	0.01	0.04	
Pathological grade	0.22	0.08	0.14	
Histopathology	0.04	0.03	0.21	

Data expressed as frequency (percentage), mean (SD). ***P***-value was significant if < 0.05. **SCC**: squamous cell carcinoma. *P* indicates the difference between different interventions; ***P*1** compared between open and thoracoscopy technique; ***P*2** compared between open and robotic technique; ***P*3** compared between robotic and thoracoscopy technique.

Dissected and positive lymph nodes:

Excised lymph nodes were significantly higher among thoracoscopic and robotic groups in comparison to the open group while the number of positive lymph nodes had insignificant differences between the three groups (Table 5).

Table 5: Dissected and positive lymph nodes

	Intervention			*P*
	Open	Thoraco-laparos-copic	Robotic	
Dissected LNs	22.35 ± 9.89	44.50 ± 13.14	40.55 ± 12.07	< 0.001*
Positive LNs	6.06 ± 3.39	2.48 ± 0.75	3.05 ± 1.09	0.06
Significance	*P*1	*P*2	*P*3	
Dissected LNs	< 0.001	< 0.001	0.69	
Positive LNs	0.09	0.11	0.14	

Data expressed as mean (SD). ***P***-value was significant if < 0.05. **LNs**: lymph nodes. *P* indicates the difference between different interventions; ***P*1** compared between open and thoracoscopy technique; ***P*2** compared between open and robotic technique; ***P*3** compared between robotic and thoracoscopy technique.

Dissected lymph nodes based on their location:

As regarding the location of LNs dissected or positive LNs (chest, abdomen, and neck), thoracoscopic and robotic groups had insignificant differences (Table 6).

Table 6: Dissected lymph nodes based its location

	Thoraco-laparoscopic group	Robotic group	*P*-value
At chest			
Dissected LNs	24.15 ± 7.02	23.55 ± 7.50	0.79
Positive LNs	0.73 ± 0.30	1.97 ± 1.01	0.14
At neck			
Dissected LNs	4.72 ± 2.35	5.53 ± 1.80	0.73
Positive LNs	0	0.78 ± 0.25	0.16
At abdomen			
Dissected LNs	18.85 ± 10.40	16.40 ± 7.38	0.39
Positive LNs	0.94 ± 0.45	0.88 ± 0.55	0.73

Data expressed as mean (SD). P-value was significant if < 0.05. LNs: lymph nodes

Post-operative complications in the current study:

As regards postoperative complications, the open group showed a significant increase in the number of patients with postoperative respiratory complications six patients (30%). Anastomotic leakage was the most frequent complication where it occurred in 10 patients; 5 (25%), 2 (10%), and 3 (15%) patients of open, thoracoscopic, and robotic groups, respectively. Injury of RLN occurred in one patient in the thoracoscopic group and another one in the robotic group (Table7).

Table 7: Postoperative complications

	Intervention			*P*
	Open	Thoraco-laparos-copic	Robotic	
Respiratory	6 (30%)	2 (10%)	1 (5%)	**0.03***
Leakage	5 (25%)	2 (10%)	3 (15%)	0.07
RLN injury	0	1 (5%)	1 (5%)	0.59
Abscess	2 (10%)	1 (5%)	0	0.34
Stenosis	3 (15%)	1 (5%)	0	0.15
30 days mortality	3 (15%)	0	1 (5%)	0.14
Conversion to other procedure	---	0	0	
Significance	*P*1	*P*2	*P*3	
Respiratory	.02	0.01	0.19	
Leakage	0.19	0.10	0.14	
RLN	0.65	0.65	---	
Abscess	0.35	0.08	0.65	
Stenosis	0.09	0.06	0.65	

Data expressed as mean (SD). ***P***-value was significant if < 0.05. **RLN**: recurrent laryngeal nerve injury. *P* indicates the difference between different interventions; ***P*1** compared between open and thoracoscopy technique; ***P*2** compared between open and robotic technique; ***P*3** compared between robotic and thoracoscopy technique.

Survival analysis:

Disease-free survival:

Relapse occurred in 9 (45%), 5 (25%), and 8 (40%) patients of open, thoracoscopic, and robotic groups, respectively. it was noticed that mean disease-free survival in all patients was 54.58 months while it was 31.29, 55.21, and 52.28 months in open, thoracoscopic, and robotic group, respectively with the tendency to have higher DFS in robotic and thoracoscopic groups in comparison to open group but did not reach statistical significance. The 3-year DFS was 40%, 60%, and 50% in open, thoracoscopic, and robotic groups, respectively (Table 8) (Figure 1).

Overall survival:

It was noticed that the median overall survival in all patients was 61 months while it was 32, 51, and 57 months in the open, thoracoscopic and robotic group, respectively with significantly higher overall survival in robotic and thoracoscopic groups in comparison to the open group. 3-year overall survival was 40%, 60%, and 65% in the open, thoracoscopic, and robotic group, respectively (Table 9) (Figure 2).

Table 8: Disease-free survival in all studied groups

	Disease-free survival	95% confidence interval	*P*-value
Intervention			
Open	31.29	23.78-38.80	
Thoracoscopy	55.21	41.82-68.59	0.55
Robotic	52.28	24.72-62.85	
Total	54.58	45.60-63.57	

Table 9: Overall survival in all studied groups

	Overall survival	95% confidence interval	*P*-value
Intervention			
Open	32	22-42	
Thoracoscopy	51	46-61	0.04*
Robotic	57	34-75	
Total	53	42-75	

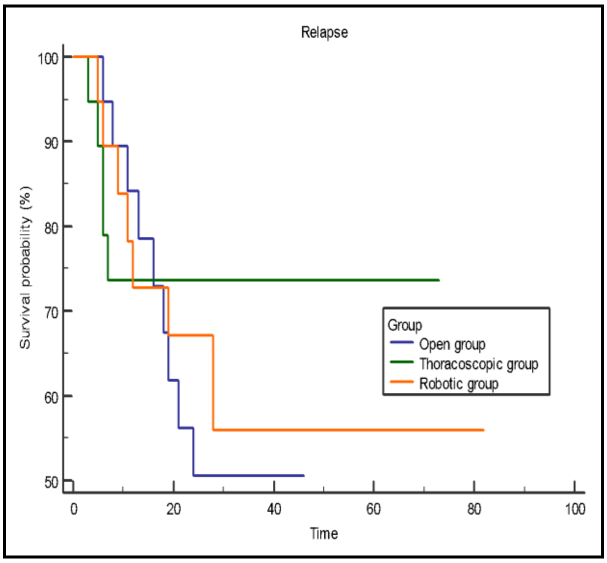

Figure 1: DFS in all studied groups

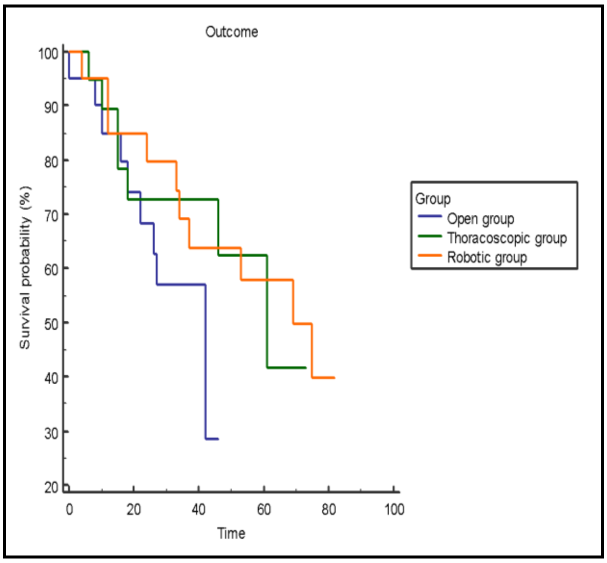

Figure 2: Overall survival in all studied groups

Multivariate regression analysis for prediction of relapse:

The following variables were predictors for relapse in studied patients; male sex, nodal stage≥2, pathological stage≥2, and total LNs> 20 with adjusted $R^2$was 0.51 (Table 10).

Table 10: Multivariate regression analysis for prediction of relapse

`	Odds ratio	95% confidence interval	*P* value
Age	0.99	0.66-1.45	0.40
Male sex	1.06	1.01-1.93	< 0.001*
BMI	1.1	0.86-2.11	0.22
Respiratory Complications	1.01	0.82-1.98	0.32
Anastomotic leakage	0.97	0.70-1.67	0.46
Nodal stage ≥2	1.07	1.05-1.19	< 0.001*
Pathological stage ≥2	1.72	1.05-1.99	< 0.001*
Total LNs > 20	2.22	1.78-5.67	< 0.001*

The following variables were predictors for death in studied patients; nodal stage≥2, and pathological stage≥2 with adjusted R^2 was 0.38 (Table 11).

Table 11: Multivariate regression analysis for prediction of death

`	Odds ratio	95% confidence interval	*P* value
Age	1.22	1.11-3.23	0.09
Nodal stage ≥2	1.37	1.22-3.11	< 0.001*
Pathological stage ≥2	1.58	1.13-3.27	< 0.001*
Relapse	0.4	0.33-1.55	0.33

Discussion:

Currently, there is no established scientific evidence supporting the practice of MIE as an alternative to open esophagectomy (OE). To date, several single-institution studies and a number of other meta-analyses have shown acceptable short-term outcomes of thoracoscopic esophagectomy for esophageal cancer, however, its effect on the long-term survival of patients with ESCC needs further investigation [13].

We tried in this study to detect the association between the number of lymph nodes examined (LNEs) and accurate staging and survival for esophageal cancer with MIE versus OE.

The mean age of patients in this study with open intervention was 48.95 ± 9.36 years, 13 (65%) of them were males. In the case of patients with thoracoscopy; the mean age was 63.75 ± 7.25 years, 15 (75%) of them were males. In those patients with robotic intervention, the mean age was 64.30 ± 5.12 years, 19 (95%) of them were males. Also, body mass index was significantly higher in the case of open intervention in comparison to the MIE group due to the nature of the Egyptian patient with higher BMI in comparison to Japanese people [14].

Surgical resection together with radical lymphadenectomy still a critical element in the treatment of esophageal cancer. So, most of studies considering the application of MIE have focused on the extent of lymphadenectomy, especially for mediastinal LN dissection. Regarding the number of retrieved mediastinal and/or total LNs, most studies have demonstrated that thoracoscopic esophagectomy is almost equivalent to OE. A previous meta-analysis emphasized that the number of retrieved LNs was significantly higher with thoracoscopic esophagectomy than with OE[15].

In this study, the dissected lymph nodes were significantly higher in the thoracoscopic (44.50 ± 13.14) and robotic group (40.55 ± 12.07) than the open group (22.35 ± 9.89) but when sub-analysis between thoracoscopic and robotic was done no significant difference between the two groups was found. Patients with esophageal cancer always have a high cancer metastatic rate on the recurrent laryngeal nerve (RLN) lymph node. Hence, having an accurate lymph node dissection during esophagectomy is significantly important [16].

The specific characteristics of thoracic ESCC, which is far more common than esophageal adenocarcinoma in Asia and South America, include the widespread and random patterns of LN metastasis along cervical and abdominal areas and therefore the relatively high risk of metastasis to the upper mediastinal LN along the bilateral RLNs. On the opposite side, esophageal adenocarcinoma is common in North America and Europe, so surgeons in these regions don't consider upper mediastinal LN dissection [17].

Ye et al. compared the lymph node dissection at specific anatomical sites and the results reflected some limitations of the MIE surgical technique. The LNS rate at the left -RLN region (the most difficult site for exposing lymph nodes) of the patients within the MIE group was only 43.9%, as compared to 80.2% within the open group, indicating a big difference between the 2 groups [18].

Suda et al ., tried to overcome this problem by their technique which include division of the upper esophagus at the level of the aortic arch by linear stapler then being mobilized circumferentially to facilitate LN dissection on the left side of the esophagus. The divided esophagus on the caudal part with infracarinal, periesophageal, and lower posterior mediastinal lymph nodes were dissected on the pericardium, left pleura, descending aorta, and diaphragm, then, dissection along the left RLN was done [19].

Lagergren et al. studied a cohort of patients who underwent esophagectomy for esophageal cancer between 2000–2012. With 83.5% adenocarcinomas and with 47% 5-year survival, they found that the extent of lymphadenectomy wasn't statistically related to all-cause or disease-specific mortality. Patients with excised LNs >20 LNS didn't demonstrate a statistically significant decrease in all-cause 5-year mortality when compared with excised lymph nodes <10 LNS. Therefore, they assumed that the extent of lymph node dissection might not affect 5-year all-cause or disease-specific survival [20]. Another meta-analysis study including 2,303 patients from 9 international centers concluded that the number of dissected LNs was an independent predictor factor of survival, and to optimize this benefit a minimum of 23 LNs should be dissected [21].

When we tried to detect the predictors for relapse and death, we found that the main predictors for relapse were: male gender, nodal stage >1, pathological stage >1, and total harvested lymph nodes >20. However, the main predictors for death were only nodal stage >1 and pathological stage >1.

The number of metastatic lymph nodes is usually associated with the increased potentiality of tumor relapse, but the relation between the total number of harvested LNs and relapse cannot be easily explained. However recently some authors referred to the prognostic significance of occult metastatic lymph nodes (MLNs).

Department of Surgical Oncology in Osaka City University Hospital tried to study occult metastatic LNs (MLNs), metastases not detected by hematoxylin-eosin staining were identified by immunohistochemistry (IHC). A total of 6558 LNs were examined by IHC staining; 362 overt MLNs and 143 occult MLNs were detected. When the number of occult MLNs was added to the number of pathological (p) N-status, the number of total MLNs was related to postoperative relapse. Consequently, 6 of 22 patients (27%) who were pathological node-negative converted to node-positive by considering total MLNs [22]. This may explain the correlation between the increase in relapse rate in this study when dissected Lymph nodes more than 20 lymph nodes.

In conclusion, Lymph nodes harvest was significantly higher among thoracoscopic and robotic groups in comparison to the open group. So, MIE is considered a good alternative to open esophagectomy with significantly lower postoperative respiratory complications and ICU stay. Also, patients with LNs harvest more than 20 were associated with increased relapse rate but this needs to be investigated by larger prospective randomized studies.

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Contributions of authors:

GA, HF, MM was the Egyptian surgeons' team responsible for performing open surgery done for included patients. NM, SS, KS, IK, UI, MM was the surgeons' team responsible for performing minimally invasive surgery done for included patients. MM, HF, NM, SS, KS, IK, UI were responsible for data collection and follow up of patients. MM, HF, NM, SS, KS, IK, UI was responsible for conception and design. NM, SS, KS, IK, UI were responsible for analysis, interpretation of data, and drafting of the manuscript. All authors participated in the final revision of the manuscript before submission.

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