



Retrospective Study

Lymph node dissection in esophageal carcinoma: Minimally invasive esophagectomy vs open surgery

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Abstract

AIM: To compare lymph node dissection results of minimally invasive esophagectomy (MIE) and open surgery for esophageal squamous cell carcinoma.

METHODS: We retrospectively reviewed data from patients who underwent MIE or open surgery for esophageal squamous cell carcinoma from January 2011 to September 2014. Number of lymph nodes resected, positive lymph node (pN+) rate, lymph node sampling (LNS) rate and lymph node metastatic (LNM) rate were evaluated.

RESULTS: Among 447 patients included, 123 underwent MIE and 324 underwent open surgery. The number of lymph nodes resected did not significantly differ between the MIE and open surgery groups (21.1 ± 4.3 vs 20.4 ± 3.8 , respectively, $P = 0.0944$). The pN+ rate of stage T3 esophageal squamous cell carcinoma in the open surgery group was higher than that in the MIE group (16.3% vs 11.4%, $P = 0.031$), but no differences were observed for stages T1 and T2 esophageal squamous cell carcinoma. The LNS rate at left para-recurrent laryngeal nerve (RLN) site was significantly higher for open surgery than for MIE (80.2% vs 43.9%, $P < 0.001$), but no differences were noted at other sites. The LNM rate at left para-RLN site in the open surgery group was significantly higher than that in the MIE group, regardless of pathologic T stage.

CONCLUSION: For stages T1 and T2 esophageal squamous cell carcinoma, the lymph node dissection result after MIE was comparable to that achieved

by open surgery. However, the efficacy of MIE in lymphadenectomy for stage T3 esophageal squamous cell carcinoma, particularly at left para-RLN site, remains to be improved.

Key words: Esophageal cancer; Lymph node; Minimally invasive; Surgery

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Core tip: Previous studies have not reported in detail whether minimally invasive esophagectomy (MIE) can achieve the same lymph node dissection results as open surgery. In particular for esophageal squamous cell carcinoma, it remains unknown whether MIE can meet the technical requirements for each anatomical site in lymph node dissection from the mediastinum to the upper abdomen. Our study found that for stages T1 and T2 esophageal squamous cell carcinoma, the lymph node dissection result after MIE was comparable with that after open surgery. However, the efficacy of MIE in lymphadenectomy for stage T3 esophageal squamous cell carcinoma, particularly at left para-RLN site, remains to be improved.

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INTRODUCTION

Esophageal carcinomas are a group of malignant tumors with poor prognoses. Among esophageal carcinomas, squamous cell carcinoma has a particularly poor prognosis, primarily because of extensive lymph node metastasis in three anatomical regions: the neck, mediastinum, and upper abdomen^[1-8]. From 1980s, Japanese surgeons started to investigate three-field lymph node dissection to improve the prognosis of esophageal squamous cell carcinoma. In several studies, the 5-year survival was reported to be improved by approximately 10%. However, three-field lymph node dissection has not been widely accepted because of its complicated procedure and high risk of postoperative complications^[9-12].

Minimally invasive esophagectomy (MIE) has been into a rapid development period. Its safety and efficacy to improve patients' life quality have been demonstrated in previous reports^[13-18].

However, previous studies have not reported in detail whether MIE can achieve the same lymph node dissection results as open surgery. In particular for esophageal squamous cell carcinoma, it remains

unknown whether MIE can meet the technical requirements for each anatomical site in lymph node dissection from the mediastinum to the upper abdomen. This study attempts to retrospectively review the data from patients with esophageal squamous cell carcinoma who were treated at Shanghai Chest Hospital and compare the lymph node dissection results of MIE and open surgery.

MATERIALS AND METHODS

A total of 1343 patients who underwent surgeries to treat esophageal carcinoma at Shanghai Chest Hospital from January 2011 to September 2014 were retrospectively analyzed. The inclusion criteria were as follows: (1) diagnosed with squamous cell carcinoma; (2) underwent either open surgery or MIE; (3) received thoraco-abdominal two-field lymph node dissection; (4) *via* right-side thoracotomy; and (5) the esophageal-gastric anastomosis site was either at the thoracic apex or neck. All the surgeons involved in this study were experienced in both open and thoracoscopic esophagectomy and followed the same principle and technical requirement of lymph node dissection.

To better evaluate the efficacy of the surgeries for dissecting lymph nodes in different anatomical sites under thoracoscopy and laparoscopy, the mediastinal and abdominal lymph node metastasis regions were regrouped for this study (Table 1).

Preoperative evaluation

All patients received enhanced chest and abdominal computed tomography (CT) examinations, cervical CT scan examination or ultrasonic examination, and upper gastrointestinal endoscopic examination before operation. Any tumor involved middle and upper thoracic esophagus was examined by bronchoscopy. Positron emission tomography (PET) or PET-CT was used only in those patients who were willing to pay themselves and with possible distal metastasis. Primary tumor and mediastinal lymph node staging by the endoscopic ultrasound (EUS) examination was performed in all patients, except any patient who had such a narrow esophagus that a gastrointestinal endoscope could not pass through. Cranial magnetic resonance imaging (MRI) and bone emission CT scan were used selectively. The preoperative diagnosis of lymph node metastasis was based on radiology or EUS, endobronchial ultrasound or ultrasound-guided fine-needle aspiration biopsy. Patients who were diagnosed with cT₃ and cN₂ would receive inductive treatment after informed consent was obtained.

Surgical technique

The tri-incisional approach (McKeown) was adopted as the surgical approach for MIE. The esophageal-gastric anastomosis was performed at the neck.

Table 1 Group of lymph nodes

Region	Group
Upper mediastinal region	Right para-recurrent laryngeal nerve (RLN)
	Left para-RLN
Carinal and hilar region	Upper para-esophagus
	Subcarinal
Middle-low para-esophageal region	Left and right para-bronchi
	Middle and low para-esophagus
Intraperitoneal region	Supra-diaphragm
	Para-cardia
	Lesser gastric curvature Para-celiac artery and left gastric artery

Patients were in the left lateral recumbent position and leaned forward 30° while the esophagus in the thoracic cavity was freed, and the lymph nodes in the thoracic cavity were dissected under artificial pneumothorax. Afterward, patients were in the supine position while patients' stomachs were freed, and the lymph nodes in the upper abdomen were dissected under laparoscopy. A small midline abdominal incision (8 cm) was made below the xiphoid process to allow completion of the tailoring of the tubular stomach, which was uplifted to the neck to be anastomosed to the esophagus via the substernal or posterior mediastinal pathway. The McKeown or Ivor Lewis approach was used for the open surgery, and the thoraco-abdominal two-field lymph node dissection was required for both approaches.

Evaluation indices included the number of lymph nodes resected, lymph node metastatic (LNM) rate and positive lymph node (pN+) rate in different T stages, and the lymph node sampling (LNS) rate and LNM rate at different sites in the two groups.

Statistical analysis

All statistical analyses were performed with SPSS version 20 (IBM Corp., Armonk, NY). Continuous variables are expressed as mean ± SD. Comparisons of categorical variables were done using χ^2 or Fisher's exact test, and those of continuous variables were done using Student's *t*-test. *P*-values less than 0.05 were considered statistically significant.

RESULTS

A total of 447 patients who met the inclusion criteria were included in this study. Of all the included patients, 324 underwent open surgery (226 males and 98 females with a mean age of 60.3 years), and 123 underwent MIE (97 males and 26 females). There were no significant differences in baseline characteristics, including gender, height, weight, smoking history, the American Society of Anesthesiologists (ASA) score and the rate of complete resection (Table 2). The postoperative pathological diagnostic results revealed

Table 2 Characteristics of the open surgery and minimally invasive esophagectomy groups

	Open surgery (<i>n</i> = 324)	MIE (<i>n</i> = 123)	<i>P</i> value
Age (yr)	60.3 ± 7.8	60.1 ± 6.3	0.782 ¹
Gender			0.055 ²
Male	226	97	
Female	98	26	
ASA grade			0.820 ²
I	15	6	
II	248	97	
III	61	20	
Height (cm)	170.2 ± 4.8	171.1 ± 4.9	0.585 ¹
Weight (kg)	65.2 ± 9.8	66.8 ± 8.1	0.152 ¹
Smoker			0.912 ²
Never	123	46	
Current or former	201	77	
pT stage			
Tis	3	4	0.077
T1	20	36	< 0.001
T2	46	72	< 0.001
T3	225	11	< 0.001
T4	30	0	< 0.001
Resection rate			0.479 ²
R0	313	121	
R1	6	2	
R2	5	0	
Inductive chemo/radio therapy	40%	14%	0.788 ²
pTis/T1/T2	0	0	
pT3	15	6	0.912 ²
pT4	25	0	0.002
LNM rate			
pTis	0	0/4	
pT1	6 (30)	10/36, 27.8%	0.860 ²
pT2	20 (43.4)	29/72, 40.3%	0.731 ²
pT3	125 (55.6)	5/11, 45.5%	0.511 ²
pT4	22 (73.3)	0	
Surgical approach			< 0.001
Macheen	225	123	
Ivor-Lewis	99	0	

¹The *t* test; ²Fisher's exact test. LNM rate = number of patients with positive lymph nodes/number of total patients. LNM: Lymph node metastatic; MIE: Minimally invasive esophagectomy; ASA: American Society of Anesthesiologists.

that there were no significant differences in the LNM rates between the open surgery group and MIE group in different T stages. Only 6 patients received inductive chemo/radio-therapy in the MIE group, and those patients' postoperative pathological stages were all T3. Forty patients received inductive chemo/radio-therapy in the open surgery group, of whom 15 were in stage pT3 and 25 in stage pT4. The ratio of the number of patients who received inductive chemo/radio-therapy to the total number of patients in the open surgery group was higher than the ratio in the MIE group; however, there was no significant difference between the two groups.

Table 3 lists the lymph node dissection results for open surgery and MIE in different T stages. The number of lymph node resected did not significantly differ between the MIE and open surgery groups

Table 3 Comparison of the number of lymph node dissections and the rate of positive lymph nodes according to pathological T stage *n* (%)

	Number of lymph node dissections		<i>P</i> value ¹	Rate of positive lymph nodes		<i>P</i> value ²	χ^2
	Open	MIE		Open	MIE		
pTis	18.3 ± 1.5	19.8 ± 1.3	0.2150	0	0		
pT1	19.3 ± 4.1	21.4 ± 3.8	0.0593	21 (5.0)	50 (5.8)	0.579	0.308
pT2	20.2 ± 3.2	22.1 ± 6.6	0.0715	98 (10.1)	190 (11.0)	0.494	0.468
pT3	20.3 ± 5.8	23.2 ± 4.1	0.1030	733 (16.3)	32 (11.4)	0.031	4.626
pT4	21.5 ± 3.6	0		130 (17.8)	0		
Total	20.4 ± 3.8	21.1 ± 4.3	0.0944	982 (14.8)	272 (9.5)	< 0.001	49.222

¹The *t* test; ²The χ^2 test. The rate of positive lymph nodes (pN+) = number of metastatic lymph nodes/number of removed lymph nodes. MIE: Minimally invasive esophagectomy.

Table 4 Comparison of lymph node sampling rates according to pathological T stage (Including Tis, T1-T4)

		LNS rates		<i>P</i> value ¹	χ^2
		Open (<i>n</i> = 324)	MIE (<i>n</i> = 123)		
Upper mediastinum	R-RLN	262	100	0.916	0.011
	L-RLN	260	54	< 0.001	56.345
Subcarinal and parabrachial	Upper para-esophagus	272	102	0.794	0.068
	Subcarinal	307	112	0.150	2.074
	Left and right parabrachial	310	120	0.353	0.863
Mid and low para-esophagus and diaphragm	Mid and lower para-esophagus	299	110	0.334	0.933
	Diaphragm	128	46	0.683	0.167
Intraperitoneal	Para-cardial	310	116	0.541	0.374
	Lesser gastric curvature	275	105	0.897	0.017
	Left gastric artery	272	106	0.560	0.339

¹The χ^2 test. LNS rates = number of patients undergoing lymph node sampling/number of total patients. LNS: Lymph node sampling; RLN: Recurrent laryngeal nerve; MIE: Minimally invasive esophagectomy.

(20.4 ± 3.8 vs 21.1 ± 4.3, respectively, *P* = 0.0944). There were no significant differences in the pN+ rates between the pT1 stage patients in the two groups or between the pT2 stage patients in the two groups. However, the pN+ rate of the pT3 patients in the open surgery group was significantly higher than the pN+ rate of the patients in the MIE group (16.3% vs 11.4%, *P* = 0.031, χ^2 = 4.626). In addition, the overall pN+ rate of the patients in the open surgery group was higher than that in the MIE group (14.8% vs 9.5%, *P* < 0.001, χ^2 = 49.222).

Lymph node dissection results in different anatomical regions (the upper mediastinum, left and right para-RLNs, carina and hilus, lower mediastinum, peritoneum, etc.) are summarized in Table 4. Comparison of the LNS rates of the two groups revealed that the LNS rate at the left para-RLN site in the patients in the open surgery group was significantly higher than that in the patients of the MIE group (80.2% vs 43.9%, *P* < 0.001, χ^2 = 56.345); there were no significant differences in the LNS rates at other sites between the two groups. Table 5 lists the results of the LNM rates of the two groups. The LNM rates in the upper mediastinal region (including the left and right para-RLNs and upper para-esophagus), lesser gastric curvature and middle and lower para-esophagus of the patients in the open surgery group were significantly higher than those in

the MIE group. However, the results of stages pTis, T1 and T2 patients indicated that only the LNM rate at the left para-RLN site in patients in the open surgery group was significantly higher than the rate in the MIE group (10.1% vs 3.6%, *P* = 0.045); there were no significant differences in the LNM rates at other sites.

DISCUSSION

Esophageal carcinomas rank 7th on the list of fatal tumors and 4th on the list of fatal tumors among male patients. Esophageal squamous cell carcinoma, one type of esophageal carcinoma, is prevalent among Asian populations and has an incidence rate of more than 90%. Different from the conservative approaches that are often adopted in Western countries for treating esophageal carcinomas, radical surgical resection combined with systematic lymph node dissection has always been used as a significant approach for treating esophageal carcinomas in Asian countries, for example in Japan. Although neoadjuvant therapy has been increasingly accepted, surgeries remain the most valuable approach for treating esophageal carcinomas. Lymph node metastasis along the long axis of the esophagus can get to the neck in the upward direction and to the level of the celiac trunk in the downward direction. Given the previous studies, radical tumor

Table 5 Comparison of lymph node metastatic rates according to pathological T stage

		pTis, T1-4		P value	χ^2	pTis, T1-2		P value	χ^2
		Open (n = 324)	MIE (n = 123)			Open (n = 69)	MIE (n = 112)		
Upper	R-RLN	71	10	0.001	11.416	6	9	0.876	0.024
mediastinum	L-RLN	30	4	0.032	4.578	7	4	0.045 ²	
	Upper para-esophagus	40	2	0.001	12.034	1	2	0.999 ²	
Subcarinal and	Subcarinal	36	11	0.505	0.445	5	8	0.979	0.001
parabronchial	Left and right parabronchial	30	11	0.918	0.011	5	9	0.847	0.037
Mid and low	Mid and lower para- para-esophagus	59	10	0.008	6.939	6	9	0.876	0.024
and diaphragm	Diaphragm	3	1	0.910	0.013	1	1	0.999 ¹	
Intraperitoneal	Para-cardial	42	13	0.426	0.634	8	12	0.854	0.034
	Lesser gastric curvature	15	0			3	0	0.042 ¹	
	Left gastric artery	51	13	0.163	1.944	8	13	0.998	0.001

¹The Fisher's exact test; ²The χ^2 test. LNM rate = number of patients with positive lymph nodes/number of total patients. LNM: Lymph node metastatic; RLN: Recurrent laryngeal nerve; MIE: Minimally invasive esophagectomy.

resection and lymph node dissection (as extensive as possible) may be used to improve the prognosis of a patient with a low tumor load, particularly with a number of metastatic lymph nodes within N2.

The MIE technique has become increasingly popular, and this has been particularly remarkable in China^[14]. Currently, there are no universally accepted criteria that determine which patients can receive MIE treatment. Whether MIE can be performed often depends on the experience of the surgeon. Many studies have focused on investigating whether MIE has the same safety level and capabilities for controlling tumors and improving the long-term prognosis and quality of life of patients as open surgery^[13,14,16,17,19-23]. An important European randomized controlled trial demonstrated that MIE can better protect the pulmonary function of patients and can improve patients' long-term quality of life^[24]. However, the exact oncological surgical results of MIE were not described in detail; the results only showed that the LNS rate of the patients in the MIE group was higher than that of the patients in the open surgery group. However, thorough lymph node dissection is particularly important in treating esophageal squamous cell carcinoma. MIE is affected by such aspects as the position of the patient, the assistant exposing technique and the learning curve; however, many aspects merit more study. To address this issue, a detailed retrospective analysis was conducted in this study. Our research indicates that there were no significant differences in the number of lymph nodes resected and the pathologic LNM rates between the MIE group and the open surgery group in different T stages, demonstrating that MIE can achieve the comparable staging and prediction results with open surgery in terms of lymph node dissection. However, the pN+ rate of the stage T3 patients in the MIE group was significantly lower than that in the open surgery group (11.4% vs 16.3%, $P = 0.031$, $\chi^2 = 4.626$); there were no significant

differences in the pN+ rates for stages T1 and T2 esophageal squamous cell carcinoma between the two groups. Such a phenomenon has several causes. First, the preoperative patient screening was biased – stages T1 and T2 patients with even lower N stages were more likely to be selected to undergo MIE treatment; thus, MIE could achieve the comparable lymph node dissection results with open surgery for stages T1 and T2 esophageal squamous cell carcinoma. Second, MIE did not reach the same *en bloc* lymph node dissection level as open surgery, therefore, the obtained numbers of positive lymph nodes of patients with advanced stages were relatively low, and hence, it is necessary to provide such high-risk patients with more positive preoperative induction and postoperative adjuvant treatments. Third, the lymph node dissection results of the stage T3 patients in the MIE group were inferior to the results of the open surgery group; however, because only 11 patients were included in the MIE group in this study, it is necessary to increase the sample size to more thoroughly evaluate the difference between MIE and open surgery in terms of the lymph node dissection results of stage T3 patients.

A comparison of lymph node dissection results at specific anatomical sites was also done. The outcome reflected the limitation of the surgical technique used in the patients in the MIE group in this study. The LNS rate at the left para-RLN site (the most difficult site for exposing lymph nodes) of the patients in the MIE group was only 43.9%, whereas this value in the patients in the open surgery group was as high as 80.2%, indicating a significant difference between the two groups. This study further analyzed the LNM rates at different anatomical regions. In terms of the overall LNM rate (including Tis and T1-4), the LNM rates in the upper mediastinal region of the patients in the MIE group were lower than the rates of the patients in the open surgery group. The patients in the MIE group were primarily stages T1 and T2 patients. To

eliminate the effect generated by the biased inclusion process, we analyzed the stages T1 and T2 patients in separate groups. It has been proved that the LNM rate at the left para-RLN site in the MIE group was significantly lower than that in the open surgery group, but there were no significant differences in the other regions. Hence, lymph node dissection at the left para-RLN site remains a key technique of MIE that requires improvement. Currently, the following techniques were adopted to rectify the aforementioned shortcomings: (1) a single-lumen endotracheal tube-aided blocker is used to reduce the tracheal tension to allow easier exposure of the left space of the trachea during surgery; (2) the left RLN is moved upward through the assistant traction of the esophagus to allow easier lymph node dissection anterior to the nerves; and (3) the auxiliary artificial pneumothorax is used to enlarge the mediastinal space. After using these techniques, the LNS rate at the left para-RLN site recently increased to above 90%, which is similar to the results of the previously mentioned study.

Limitations of the study

This study was a single-center retrospective study; during the medical case accumulation process, the initial learning curve may have affected the results. In addition, the sample size is not sufficiently large; in particular, there are few stage T3 patients (only 11 patients) in the MIE group. However, considering the fact that the current MIE technique remains applicable to stages T1 and T2 patients, this study nevertheless reflects the basic surgical oncological results of the current MIE technique. Furthermore, this study did not statistically analyze the patients' survival rates, therefore, the best evidence for the lymph node dissection effect in MIE is lacking. In the future, a multicenter prospective randomized controlled study with a large sample size is expected to be conducted to verify the lymph node dissection effect of MIE.

In summary, we conducted a retrospective comparative study of MIE and conventional open surgery for treating esophageal squamous cell carcinoma. The initial results indicate that MIE could achieve the comparable lymph node dissection results with the open surgery, particularly for stages T1 and T2 esophageal squamous cell carcinoma. However, the lymph node dissection at the left para-RLN site remains a major technical challenge for MIE.

COMMENTS

Background

Previous studies have not reported in detail whether minimally invasive esophagectomy (MIE) can achieve the same lymph node dissection results as open surgery. In particular for esophageal squamous cell carcinoma, it remains unknown whether MIE can meet the technical requirements for each anatomical site in lymph node dissection from the mediastinum to the upper abdomen. This study attempts to retrospectively review the data from patients with esophageal squamous cell carcinoma who were treated at Shanghai Chest Hospital and compare the lymph node dissection results of MIE and open surgery.

Research frontiers

MIE has been into a rapid development period. Its safety and efficacy to improve patients' life quality have been demonstrated in previous reports. The main aim of this study was compare lymph node dissection results of minimally invasive esophagectomy and open surgery for esophageal squamous cell carcinoma.

Innovations and breakthroughs

The authors conducted a retrospective comparative study of MIE and conventional open surgery for treating esophageal squamous cell carcinoma. This study is a large cohort. The initial results indicate that MIE could achieve the comparable lymph node dissection results with the open surgery, particularly for stages T1 and T2 esophageal squamous cell carcinoma.

Applications

This study proved that MIE could achieve the comparable lymph node dissection results with the open surgery, particularly for stages T1 and T2 esophageal squamous cell carcinoma. This is very important for the development of MIE.

Terminology

MIE could achieve the comparable lymph node dissection results with the open surgery, particularly for stages T1 and T2 esophageal squamous cell carcinoma. However, the lymph node dissection at the left para-RLN site remains a major technical challenge for MIE.

Peer-review

Previous studies have not reported in detail whether MIE can achieve the same lymph node dissection results as open surgery. In particular for esophageal squamous cell carcinoma, it remains unknown whether MIE can meet the technical requirements for each anatomical site in lymph node dissection from the mediastinum to the upper abdomen. This study found that for stages T1 and T2 esophageal squamous cell carcinoma, the lymph node dissection result after MIE was comparable with that of open surgery. However, the efficacy of MIE in lymphadenectomy for stage T3 esophageal squamous cell carcinoma, particularly at left para-RLN site, remains to be improved.

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