JBUON 2015; 20(6): 1585-1591
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Very long-term outcomes of minimally invasive esophagectomy for esophageal squamous cell carcinoma

Yingwei Zhu[1], Weichang Chen[2]

[1]Wuxi Second People's Hospital, Wuxi, Jiangsu, 214002, People's Republic of China; [2]The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, People's Republic of China

Summary

Purpose: *The most critical parameter in the evaluation of the effectiveness of minimally invasive esophagectomy for esophageal squamous cell carcinoma (SCC) is long-term outcome. In this study, patients in whom more than 5 years had elapsed since they had undergone minimally invasive esophagectomy for esophageal SCC were identified, and the 5-year overall survival (OS) rate and 5-year disease-free survival (DFS) rate were evaluated as the long-term outcomes.*

Methods: *The stage, histology, perioperative complications, recurrence, and survival data were carefully reviewed in 49 patients who underwent minimally invasive esophagectomy for esophageal SCC between January 2008 and January 2010.*

Results: *Postoperative 30-day complications were observed in 12 (24.5%) patients. There was no postoperative 30-day mortality. Recurrence was observed in 26 patients (53.1%): of these, 9 (18.4%) developed local recurrence and 14 (28.6%) distant metastasis. Three patients (6.1%) had both local and distant metastases. During the study period, there were 22 (44.9%) deaths, of which 20 were due to cancer and 2 were due to other causes. The patient 5-year OS and DFS rates were 58 and 45%, respectively.*

Conclusion: *Minimally invasive esophagectomy for the treatment of esophageal SCC is as feasible and safe as open esophagectomy in terms of both very long- and short-term outcomes.*

Key words: *esophagectomy, esophageal squamous cell carcinoma, minimally invasive surgery, prognosis*

Introduction

Minimally invasive esophagectomy was introduced more than a decade ago and minimally invasive esophagectomy has been applied for radical resection of esophageal carcinoma [1-3]. Several investigators have reported that the long- and short-term outcomes of minimally invasive esophagectomy for esophageal carcinoma are comparable to those of open esophagectomy [4-6]. However, median follow-up period in these studies was no longer than 40 months on average [7-15] and certainly longer follow-up periods would be needed for more accurate estimation of the long-term outcomes. In this study, patients in whom more than 5 years had elapsed after minimally invasive esophagectomy for esophageal SCC were identified, and the long-term OS and DFS were evaluated as the very long-term outcomes; in addition, the nature and frequency of postoperative 30-day complications were also evaluated as the short-term outcomes after minimally invasive esophagectomy with radical intent.

Methods

This retrospective study complied with the Declaration of Helsinki rules and was approved by the Ethics Committee of The First Affiliated Hospital of Soochow University. The need for informed consent from all patients was waived because of its retrospective nature.

Correspondence to: Weichang Chen, MD. The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, People's Republic of China. Tel and Fax: +86 512 65223637, E-mail: weichangchenwx@163.com
Received: 04/07/2015; Accepted: 22/07/2015

There were 53 patients who had undergone minimally invasive esophagectomy with radical intent for esophageal SCC from January 2008 to January 2010. During the study period, the surgical approach was converted to open resection in 4 (7.5%) cases. These 4 cases were excluded from the study. Data about the patients in regard to age, sex, medical comorbidities, clinical stage, pathological stage, postoperative 30-day complications, postoperative 30-day mortality, long-term OS and DFS rates were carefully reviewed. The indications for minimally invasive esophagectomy were patients who underwent radical surgery for clinical T1-3N0M0 stage esophageal SCC, tumors in the middle and lower thoracic esophagus, without neoadjuvant therapy, with no evidence of metastasis or extended resection. The resection was performed with curative intent. The procedures of the minimally invasive esophagectomy were as follows: thoracoscopic esophageal mobilization and mediastinal lymphadenectomy, laparoscopic gastric mobilization, gastric tube insertion, abdominal lymphadenectomy and hand-sewn esophagogastric anastomosis. A detailed procedure of minimally invasive esophagectomy has been described in a previous study [16].

The routine preoperative evaluation included upper gastrointestinal endoscopy, upper gastrointestinal endoscopic ultrasound, computed tomographic scans of the brain, chest, and upper abdomen and ultrasonography of the neck. Positron emission tomography-computerized tomography (PET-CT), mediastinoscopy and bone scanning were performed in selected cases. The clinical stage of esophageal SCC was based on the 7th edition of the TNM classification of esophageal carcinoma which was proposed by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) [17-21]. For those of the patients operated before 2010, their staging was recalculated to match the 7th TNM classification by UICC and AJCC.

Postoperative 30-day complications were classified using the Clavien-Dindo classification [22], which simplified the definition of postoperative complications and graded the severity of these events. Major complications were defined as grades 3, 4 and 5. Minor complications were classified as 1 and 2. The definition of Clavien–Dindo classification was as follows: Grade 1: oral medication or bedside medical care required; Grade 2: intravenous medical therapy required; Grade 3: radiologic, endoscopic, or operative intervention required; Grade 4: chronic deficit or disability associated with the event; and Grade 5: death related to surgical complication.

All the patients were followed with a standard oncologic protocol of surveillance that included abdominal and chest computed tomography scan and ultrasonography of neck every 6 months after minimally invasive esophagectomy. Upper gastrointestinal endoscopy was suggested once a year after minimally invasive esophagectomy. The last follow up was May 2015. Tumor recurrence was diagnosed by history, physical examination, endoscopic evaluation, radiologic investigations, or pathology when available. Recurrence was classified as locoregional recurrence, distant metastasis and mixed. Locoregional disease was defined as recurrence within the esophageal bed, the regional lymph nodes, or the anastomosis. Distant disease included metastasis at distant organ sites (brain, lung, liver, bone, ovary, adrenals, distant lymph nodes or other organs) [23-25]. OS was assessed from the date of minimally invasive esophagectomy until the last follow up or death due to any cause. DFS was calculated from the date of surgery until the date of cancer recurrence or death of any cause.

Table 1. Patient characteristics

Characteristics	*N (%)*
Age, years (range)	58 (42-74)
Sex	
Male	32 (65.3)
Female	17 (34.7)
ASA score	
I	31 (63.3)
II	16 (32.7)
III	2 (4.0)
Comorbidity	
None	31 (63.3)
Present	18 (36.7)
Liver cirrhosis	2 (4.1)
Hypertension	8 (16.3)
Diabetes mellitus	4 (8.2)
COPD	2 (4.1)
Arrhythmia	3 (6.1)
Stable angina	2 (4.1)
Clinical TNM stage (7th AJCC-UICC)	
IB	7 (14.3)
IIA	29 (59.2)
IIB	13 (26.5)

COPD: chronic obstructive pulmonary disease

Statistics

Data were presented as mean ± standard deviation for variables following normal distribution. For data following non-normal distribution, results were expressed as median and range. The 5-year OS and DFS rates were calculated using the Kaplan–Meier method with log rank test. Univariate analyses were performed to identify prognostic data related to OS and DFS. Univariate variables with probability values <0.05 were selected for inclusion in the multivariate Cox regression model. SPSS (Statistical Package for Social Sciences) 13.0 for Microsoft Windows version (SPSS Inc., Chicago, ILL, USA) was used for statistical analyses.

Results

The characteristics of the 49 patients are shown in Table 1. Of these, 18 (36.7%) patients had either a single or more medical comorbidities

Table 2. Surgical data, postoperative course and pathology

Data	*N (%)*
Operative time (min)	250 (range 210-400)
Blood loss (ml)	210 (range 190-420)
Postoperative stay (days)	8 (range 7-35)
Retrieved lymph nodes	20 (range 16-28)
Pathological TNM stage (7th AJCC-UICC)	
IB	5 (10.2)
IIA	14 (28.6)
IIB	21 (42.9)
IIIA	5 (10.2)
IIIB	2 (4.1)
IIIC	2 (4.1)
Surgical margin (R0/R1/R2)	49/0/0
Complications	
Anastomosis leakage	5 (10.2)
Recurrent laryngeal nerve injury	3 (6.1)
Arrhythmia	2 (4.1)
Atelectasis	1 (2.0)
Pneumonia	1 (2.0)
Major complications	10 (20.4)
Minor complications	2 (4.1)

Table 3. Long-term oncological outcomes

Outcomes	*N (%)*
Recurrence	
No	23 (46.9)
Yes	26 (53.1)
Locoregional	9 (18.4)
Cervical lymph node	2 (4.1)
Anastomosis	4 (8.2)
Mediastinal lymph nodes	3 (6.1)
Distant	14 (28.6)
Brain	4 (8.2)
Liver	5 (10.2)
Lung	3 (6.1)
Bone	2 (4.1)
Mixed	3 (6.1)
Status of last follow-up	
Alive	27 (55.1)
Dead	22 (44.9)
Due to cancer	20 (40.8)
Not related to cancer	2 (4.1)

and 42 (85.7%) were diagnosed preoperatively as having locally advanced disease.

The surgical data, postoperative cancer stage, surgical margin and postoperative 30-day complications are shown in Table 2. Postoperative 30-day complications were observed in 12 (24.5%) patients. Anastomotic leakage, recurrent laryngeal nerve injury, and arrhythmia were the major postoperative 30-day complications, and were observed in 5, 3, and 2 patients, respectively, followed by pneumonia and atelectasis. According to the Clavien-Dindo classification, most complications were classified as minor. No postoperative 30-day death was observed in our series.

The long-term outcomes of the patients after minimally invasive esophagectomy are shown in Table 3. The median postoperative follow-up period was 68 months (range 5-75). Recurrences were observed in 26 (53.1%) patients. The recurrence location was local in 9 patients (18.4%), and distant in 14 (28.6%). Three patients had both local and distant metastases. During the study period, there were 22 (44.9%) deaths, of which 20 (40.8%) were due to cancer and (4.1%) were due to other causes.

Pathologically, locoregional recurrence rates of stage I, II and III disease were 0, 14.3 and 44.4%, respectively. Similarly, the distant metastasis rates of stage I, II and III disease were 0, 22.9 and 66.7%, respectively (Table 4).

The 5-year OS of the 49 patients was 58% (Figure 1). The 5-year OS of stage I, II and III disease was 95, 64 and 38%, respectively. The 5-year DFS of the 49 patients was 45% (Figure 2). The 5-year DFS of stage I, II and III disease were 95, 51 and 29%, respectively (Table 5).

In regard to prognostic factors for OS, age, tumor size, pathological T stage and pathological N stage were prognostic factors in univariate analysis. In multivariate analysis, pathological T stage and pathological N stage were independent prognostic factors for OS survival (Table 6).

In regard to prognostic factors for DFS, tumor size, pathological T stage and pathological N stage were prognostic factors in univariate analysis. In multivariate analysis, pathological T stage and pathological N stage were independent prognostic factors (Table 7).

Discussion

Radical esophagectomy is generally accepted as a standard surgical procedure for operable esophageal SCC, and minimally invasive esophagectomy is also applied for this condition. Several studies have documented better short-term outcomes after minimally invasive esophagectomy than after open esophagectomy [26-30]. The immune functions in the early postoperative course also appear to be better preserved in cases undergoing minimally invasive esophagectomy [26-

Table 4. Pattern of recurrence according to pathologic stage

Pathologic stage	*Locoregional*	*Distant*	*Mixed*
I	0 (0)	0 (0)	0 (0)
II	5 (10.2)	8 (16.3)	1 (2.0)
III	4 (8.4)	6 (12.2)	2 (4.1)

Table 5. Five-year overall and disease-free survival rates

Pathologic stage	*Overall survival (%)*	*Disease-free survival (%)*
I	95	95
II	64	51
III	38	29

Table 6. Prognostic factors for overall survival after esophagectomy

Factors	*Univariate p value*	*Multivariate p value*
Age	0.041	
Sex	0.158	
Comorbidity	0.541	
Operation time	0.032	
Tumor size	0.025	
Tumor location	0.025	
Pathological T state	0.011	0.004
Pathological N stage	0.025	0.010
Adjuvant therapy	0.351	

Table 7. Prognostic factors for disease-free survival after esophagectomy

Factors	*Univariate p value*	*Multivariate p value*
Age	0.458	
Sex	0.355	
Comorbidity	0.421	
Operation time	0.240	
Tumor size	0.018	
Tumor location	0.654	
Pathological T state	0.021	0.010
Pathological N stage	0.025	0.018
Adjuvant therapy	0.541	

30]. However, the most critical parameters in the evaluation of the feasibility and efficacy of minimally invasive esophagectomy for esophageal SCC would be the long-term outcomes. The 5-year time point is generally accepted as a landmark for evaluation of the outcomes after resection of a neoplasm. In this study, the long-term outcomes were evaluated in patients in whom more than 5 years had elapsed after minimally invasive esophagectomy for esophageal SCC.

In our study, recurrence was observed in 26 (53.1%) patients. The sites of recurrence and the prevalence determined in our study were consistent with previously reported results for open resection [31-33]. It is also generally accepted that the 5-year OS rate after open esophagectomy of stage I, II and III disease is about 70-98%, 40-60% and 10-40%, respectively [31-33]. Previous studies have reported that the outcomes after minimally invasive esophagectomy were equal to those after open esophagectomy and that the surgical

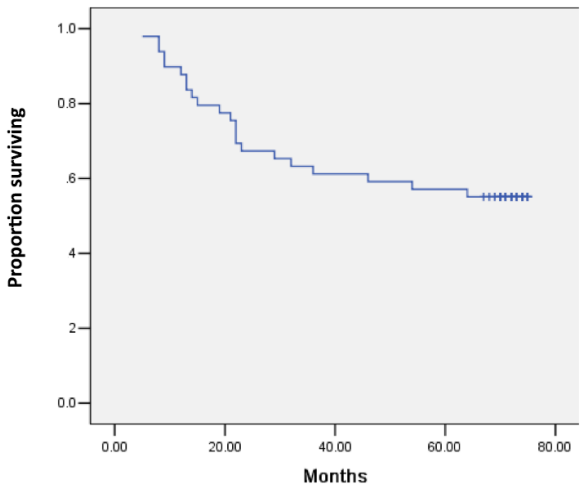

Figure 1. Overall survival of patients who underwent minimally invasive esophagectomy for esophageal squamous cell carcinoma.

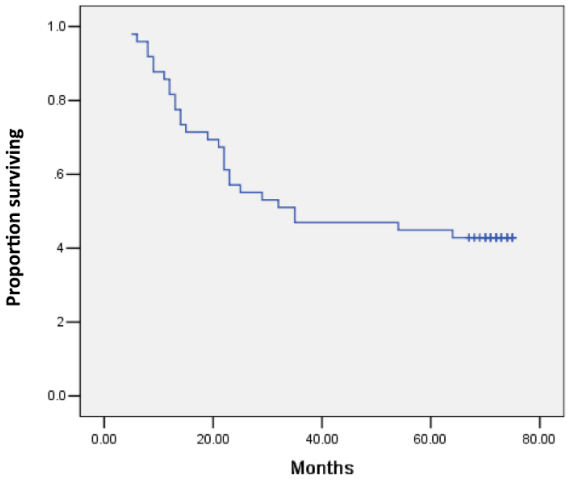

Figure 2. Disease-free survival of patients who underwent minimally invasive esophagectomy for esophageal squamous cell carcinoma.

approach itself did not influence the outcomes [7-15]. In our series, 5-year OS and DFS rates were comparable to results after conventional open resection.

Regarding technical aspects, mediastinal lymph node dissection and abdominal lymphadenectomy using combined thoracoscopic-laparoscopic approach is controversial, although several authors have documented its feasibility and safety in experienced hands [7-11]. With the combined thoracoscopic-laparoscopic technology, visualization is sometimes better than for conventional open resection because the minimally invasive instruments can enter a narrow space [7-10].

It is generally accepted that postoperative 30-day morbidity and mortality occur approximately 20–40% and 0–5%, respectively, after open esophagectomy for esophageal SCC [31-33]. Several investigators have reported the corresponding figures for minimally invasive esophagectomy to be approximately 10– 30% and 0– 3%, respectively [26-30]. In our series, postoperative 30-day morbidity was observed in 12 patients without postoperative 30-day mortality. Our results are consistent with previous reports on minimally invasive esophagectomy and suggest that minimally invasive esophagectomy for esophageal SCC is as safe as open resection.

There are several limitations in this descriptive study. First, all cases were performed by a single surgeon with advanced thoracoscopic and laparoscopic training and expertise. Thus, the reproducibility of the results of this study may initially vary when the procedure is performed by less experienced surgeons, until proficiency is reached. Second, this is a retrospective review of a prospectively maintained database and suffers the drawbacks inherent in this arrangement.

In conclusion, in terms of very long-term outcomes, minimally invasive esophagectomy for the treatment of esophageal SCC is similar to open resection with radical intent. In addition, in view of the short-term outcomes determined in this study, minimally invasive esophagectomy also appears to be a highly safe operation.

Acknowledgements

We sincerely thank the patients, their families and our hospital colleagues who participated in this research.

References

1. Tirumani H, Rosenthal MH, Tirumani SH et al. Esophageal Carcinoma: Current Concepts in the Role of Imaging in Staging and Management. Can Assoc Radiol J 2015;66:130-139.
2. Rice TW, Blackstone EH. Esophageal cancer staging: past, present, and future. Thorac Surg Clin 2013;23:461-469.
3. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol 2014;6:112-120.
4. Peyre CG, Peters JH. Minimally invasive surgery for esophageal cancer. Surg Oncol Clin N Am 2013;22:15-25.
5. Levy RM, Trivedi D, Luketich JD. Minimally invasive esophagectomy. Surg Clin North Am 2012;92:1265-1285.
6. Sun F, Li X, Lei D et al. Surgical management of cervical esophageal carcinoma with larynx preservation and reconstruction. Int J Clin Exp Med 2014;7:2771-2778.
7. Schoppmann SF, Prager G, Langer FB et al. Open versus minimally invasive esophagectomy: a single-center case controlled study. Surg Endosc 2010;24:3044-3053.
8. Kinjo Y, Kurita N, Nakamura F et al. Effectiveness of combined thoracoscopic-laparoscopic esophagectomy: comparison of postoperative complications and midterm oncological outcomes in patients with esophageal cancer. Surg Endosc 2012;26:381-390.
9. Singh RK, Pham TH, Diggs BS, Diggs BS, Perkins S, Hunter JG. Minimally invasive esophagectomy provides equivalent oncologic outcomes to open esophagectomy for locally advanced (stage II or III) esophageal carcinoma. Arch Surg 2011;146:711-714.
10. Sundaram A, Geronimo JC, Willer BL et al. Survival and quality of life after minimally invasive esophagectomy: a single-surgeon experience. Surg Endosc 2012;26:168-176.
11. Lee JM, Cheng JW, Lin MT, Huang PM, Chen JS, Lee YC. Is there any benefit to incorporating a laparoscopic procedure into minimally invasive esophagectomy? The impact on perioperative results in patients with esophageal cancer. World J Surg 2011;35:790-797.
12. Zingg U, McQuinn A, DiValentino D et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer. Ann Thorac Surg 2009;87:911-919.
13. Dolan JP, Kaur T, Diggs BS et al. Impact of comorbidity on outcomes and overall survival after open and minimally invasive esophagectomy for locally advanced esophageal cancer. Surg Endosc 2013;27:4094-4103.
14. Parameswaran R, Veeramootoo D, Krishnadas R, Cooper M, Berrisford R, Wajed S. Comparative experience of open and minimally invasive esophagogastric resection. World J Surg 2009;33:1868-1875.
15. Noble F, Kelly JJ, Bailey IS et al. A prospective comparison of totally minimally invasive versus open Ivor Lewis esophagectomy. Dis Esophagus 2013;26: 263-271.
16. Xie MR, Liu CQ, Guo MF, Mei XY, Sun XH, Xu MQ. Short-term outcomes of minimally invasive Ivor-Lewis esophagectomy for esophageal cancer. Ann Thorac Surg 2014;97:1721-1737.
17. Hong SJ, Kim TJ, Nam KB et al. New TNM staging system for esophageal cancer: what chest radiologists need to know. Radiographics 2014;34:1722-1740.
18. Li Y, Lin Q, Wang L et al. Application of sequential (18) F-FDG PET/CT scans for concurrent chemoradiotherapy of non-surgical squamous cell esophageal carcinoma. J BUON 2014;19:517-523.
19. Djuric-Stefanovic A, Saranovic D, Micev M et al. Does the computed tomography perfusion imaging improve the diagnostic accuracy in the response evaluation of esophageal carcinoma to the neoadjuvant chemoradiotherapy? Preliminary study. J BUON 2014;19:237-244.
20. Li JC, Liu D, Chen MQ et al. Different radiation treatment in esophageal carcinoma: a clinical comparative study. J BUON 2012;17:512-516.
21. Yegin EG, Duman DG. Staging of esophageal and gastric cancer in 2014. Minerva Med 2014;105:391-411.
22. Clavien PA, Barkun J, de Oliveira ML et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187-196.
23. Chikawa H, Kosugi S, Kanda T et al. Prognostic significance of initial recurrence site in hematogenous recurrence of esophageal squamous cell carcinoma. Hepatogastroenterology 2014;61:2241-2246.
24. Yamashita M, Takenaka HY, Nakagawa K. Semi-radical chemoradiotherapy for 53 esophageal squamous cell carcinomas with supraclavicular lymph node metastasis in a single institutional retrospective study. Hepatogastroenterology 2014;61:1971-1978.
25. Yang X, Huang Y, Feng JF. Is there an association between ABO blood group and overall survival in patients with esophageal squamous cell carcinoma? Int J Clin Exp Med 2014;7:2214-2218.
26. Guo W, Ma L, Zhang Y et al. Totally minimally invasive Ivor-Lewis esophagectomy with single-utility incision video-assisted thoracoscopic surgery for treatment of mid-lower esophageal cancer. Dis Esophagus 2014. [Epub ahead of print]
27. Braghetto M, Cardemil HG, Mandiolla BC, Masia LG, Gattini SF. Impact of minimally invasive surgery in the treatment of esophageal cancer. Arq Bras Cir Dig 2014;27:237-242.
28. Dhamija A, Dhamija A, Hancock J et al. Minimally invasive oesophagectomy is more expensive than open despite shorter length of stay. Eur J Cardiothorac Surg 2014;45:904-909.
29. Kubo N, Ohira M, Yamashita Y et al. The impact of combined thoracoscopic and laparoscopic surgery on pulmonary complications after radical esophagectomy in patients with resectable esophageal cancer. Anticancer Res 2014;34:2399-2404.
30. Luketich JD, Alvelo-Rivera M, Buenaventura PO et al. Minimally invasive esophagectomy: outcomes in

222 patients. Ann Surg 2003; 238:486-494; discussion 494-495.

31. Morita M, Yoshida R, Ikeda K et al. Advances in esophageal cancer surgery in Japan: an analysis of 1000 consecutive patients treated at a single institute. Surgery 2008;143:499-508.
32. Wang J, Wu N, Zheng QF et al. Evaluation of the 7th edition of the TNM classification in patients with resected esophageal squamous cell carcinoma. World J Gastroenterol 2014;20:18397-18403.
33. Ren X, Zhao Z, Huang W et al. Analysis of the characteristics and factors influencing lymph node metastasis in thoracic esophageal carcinoma and cancer of the gastric cardia. Hepatogastroenterology 2015;62:73-76.