Original Article

Selective Curative Approaches for Thoracic Esophageal Cancer

Prakob   Luechakiettisak, MD

Department of Surgery, Suratthani Hospital, Suratthani, Thailand

Abstract   *Objective:*   To determine the survival probability of patients with carcinoma of the esophagus who underwent en bloc esophagectomy and to compare two en-bloc surgical approaches.

Materials and Methods: Between October 2005 and September 2008, 81 patients with the diagnosis of esophageal carcinoma were treated at Suratthani Hospital. Esophagectomy was performed on 64 (79%) of these patients, 18 of whom had upper or mid esophageal carcinoma and underwent three-phase esophagectomy, while 46 had low esophageal carcinoma and underwent the Ivor Lewis operation. We analyzed the location and histology of the tumor, the number and level of lymph nodes, operative morbidity and mortality, and their influence on survival probabilities.

Result: The overall survival probability at 5 years was 19 %. The 5-year survival probabilities for the three-phase esophagectomy (upper and mid esophageal cancer) and the Ivor Lewis operation (low esophageal cancer) were 4 % and 25%, respectively, which were significantly different. There was no left cervical lymph node metastasis in patients who underwent the Ivor Lewis operation. The most common complication was wound infection. Most patients died from sepsis or myocardial infarction. The overall operative (hospital) mortality rate was 8 %.

Conclusion: Location of the tumor should strongly influence the type of surgery performed for esophageal carcinoma, and seemed to significantly affect the survival probabilities in the present study.

Keywords: Esophageal carcinoma, three-phase esophagectomy, Ivor Lewis operation

INTRODUCTION

Patients with thoracic esophageal carcinoma usually present late in the course of their disease. By the time symptoms develop, such as dysphagia, the tumor has spread beyond the esophagus in most cases. Many patients have major adjacent organ involvement, mainly the aorta, trachea and bronchus, precluding surgical resection. The result of treatment for thoracic esophageal cancer is therefore poor.

For patients with resectable disease and those with cancer confined within the chest, surgery remains the basic method of management for this malignancy. The en-bloc operation, which includes not only a complete removal of the tumor but also an extended dissection of the lymph nodes in the mediastinum and abdomen, is one mainstay of treatment for this malignancy for the past 20 years. The location of the malignancy usually determines the approach of en-

Correspondence address: Prakob Luechakiettisak, MD, Department of Surgery, Suratthani Hospital, Amphur Maung, Suratthani 84000, Thailand; Telephone: +668 1691 9199; Fax: +66 7728 3259; Email: prakob.luechakiettisak@gmail.com

bloc surgery.

The aim of this prospective non-randomized study was to evaluate the outcomes of a series of patients with intrathoracic esophageal cancer, who underwent either three-phase esophagectomy with lymph node dissection or Ivor Lewis esophagectomy with extended lymph node dissection by using tumor location to select the type of surgery.

PATIENTS AND METHODS

Between October 2005 and September 2008, patients at Suratthani Hospital with histologically proven thoracic esophageal cancer were recruited into the study. Patients with multiple distant metastasis or in advanced, inoperable, stages by clinical and endoscopic evidence or radiologic investigations were excluded from the study. Thus patients in the study underwent potentially curative esophagectomy. Data extracted for analysis included the location and histology of the tumor, the number and level of lymph nodes removed, operative time, hospital stay, operative morbidity, hospital mortality and survival time.

Before surgery all patients underwent barium swallowing, esophagogastroscopy with biopsy, plain chest radiography, computed tomography of the chest and abdomen and echocardiography. Bronchoscopy was performed in patients with tumors at the level of 20 to 25 cm from upper incisor teeth. Patients included in the study were divided into two groups. The first group consisted of patients with malignancy located between 20 and 25 cm from the incisor teeth. Three-phase esophagectomy was performed in these patients. The first phase or step of the operation was via right thoracotomy using the posterolateral incision at the fourth intercostal space. An en-bloc resection of the tumor was done along with additional mediastinal, paraesophageal, paratracheal, para-aortic and subcarinal lymph node dissection. The second step was the intraabdominal part via a midline incision. The stomach was mobilized by dividing the left gastric and left gastroepiploic arteries. The celiac nodes were dissected, and a feeding jejunostomy tube was placed. The last step was via a left cervical incision. The stomach was pulled up to the neck and anastomosed to the cervical esophagus by hand after left cervical lymph node dissection.

The second group consisted of patients with tumors below 25 cm from the incisor. The procedure used was the Ivor Lewis operation, performed as follows: Through an abdominal incision, a stomach tube was created, and a feeding jejunostomy tube placed. The thoracic esophagus was resected via a right thoracotomy incision. Lymphatic dissection was the same as for the three-phase esophagectomy, including a left cervical lymph node dissection (done as a part of the present study). The stomach tube was anastomosed to the proximal esophagus by hand using synthetic absorbable sutures via the thoracotomy incision. However, if the estimated free proximal margin was less than 5 cm, the procedure was converted to the three phase operation to maintain at least 5-cm margins. We did not perform a pyloroplasty or any drainage procedures after gastric pull up.

All patients underwent contrast-enhanced radiologic study for the assessment of the integrity of the esophagogastric anastomosis, 7 days after the operation. Operative mortality was defined as hospital death within the first 30 days after operation. All tumors were staged by the TNM classification system (7th ed). Survival time was defined as the duration between the year of the index operation till the year of death before September 2011, otherwise survival was censored at that time.

Continuous variables were summarized as mean and standard deviation or median and range as appropriate. Categorical variables were summarized as counts and percentages. Survival probabilities were calculated using a spline-based smoothed estimation method for interval-censored data. Statistical analysis was performed using Stata 9 software (Stata Corp, College Station, TX, USA).

RESULTS

There were 81 patients with histologically proven esophageal cancer during the recruitment period. Seventeen patients were excluded because of metastasis and advanced disease, leaving a total of 64 patients in the study. There were 44 men and 20 women. The median age was 61 years, with a range between 38 and 74 years. There were 18 patients in the three-phase esophagectomy group, and 46 patients in the Ivor Lewis group. Clinical characteristics of patients in the

Table 1 Clinical Characteristics

	Three-phase esophagectomy N =18	Ivor Lewis esophagectomy N =46
Age (years): median (range)	60 (40 to 73)	61 (38 to 74)
Sex: M/F (%)	11/7 (61/39)	33/13 (72/28)
Grade of dysphagia: number (%)		
Grade 1	0	0
Grade 2	0	0
Grade 3	4 (22)	3 (7)
Grade 4	10 (56)	31 (67)
Grade 5	4 (22)	12 (26)
Grade 6	0	0

No statistically significant differences between groups for all characteristics (at 5% level)

two groups are presented in Table 1. Pathological findings are presented in Table 2. The outcomes of the operations are presented in Table 3.

The median ages of patients in the three-phase esophagectomy and Ivor lewis groups were 60 years (range, 40 to73 years) and 61 years (range, 38 to 74 years) respectively. Most patients were presented with grade 4 to 5 dysphagia. There were higher proportions of men in both the three-phase esophagectomy (61%) and Ivor Lewis groups (72%). All these characteristics were not significantly different between the two groups at the 5% level (Table 1).

All patients in the three-phase esophagectomy group had squamous cell carcinoma of the esophagus, while 72% (33/46) of patients in the Ivor Lewis group had squamous cell carcinoma (p = 0.013 by Fisher's exact test) (the remaining had adenocarcinoma). The majority of patients in both groups had poorly differentiated cancer. The majority had TNM stage III disease. Regional node metastasis was almost the same for both groups, but patients in the Ivor Lewis group had no left cervical lymph node metastasis, which was the only statistically significant finding (p < 0.001 by Fisher's exact test; Table 2).

The operative time was similar for both groups of patients, as was the length of hospital stay. Similar types of complications occurred in both groups of patients. There was a tendency for more pneumonia to occur in patients undergoing the Ivor Lewis operation.

Table 2 Pathological findings

Pathological findings	Three-phase esophagectomy N = 18	Ivor Lewis esophagectomy N =46
Squamous cell carcinoma: number (%)		
Well-differentiated	6 (33)	7 (15)
Moderated -differentiated	3 (17)	3 (7)
Poorly - differentiated	9 (50)	23 (50)
Adenocarcinoma: number (%)		
Well-differentiated	0	3 (7)
Moderated -differentiated	0	0
Poorly - differentiated	0	10 (22)
Lymph node involvement: number (%)		
Celiac node	4 (22)	16 (35)
Subcarinal node	15 (83)	36 (78)
Paratracheal node	14 (78)	37 (80)
Mediastinal node	10 (56)	28 (61)
Para esophageal node	12 (67)	30 (65)
Left cervical lymph node	6 (34)	0
Staging: number (%)		
I	0	0
IIa	0	2 (4)
IIb	3 (17)	2 (4)
III	15 (83)	42 (92)
IV	0	0

No statistically significant differences between groups for almost all findings (at 5% level), except the presence of adenocarcinoma (Fisher's exact test p = 0.013), and left cervical node metastasis (Fisher's exact test p <0.001)

Table 3 Outcomes of esophagectomy

Operative outcomes	Three-phase esophagectomy N = 18	Ivor Lewis esophagectomy N = 46
Complications and death: number (%)		
Pneumonia	1 (6)	6 (13)
Anastomosis leakage	1 (6)	2 (4)
Wound infection	2 (11)	4 (9)
Myocardial contusion	1 (6)	1 (2)
Death	1 (6)	4 (9)
Duration of operation (hours): median (range)	4.3 (3.5 to 5.1)	4.2 (3.5 to 4.6)
Hospital stay (days): median (range)	20 (11 to 30)	21 (13 to 45)
Follow-up time (years): median (range)	2.5 (1 to 5)	4 (1 to 7)

No statistically significant differences between groups for almost all findings (at 5% level), except follow-up time (rank test p = 0.022)
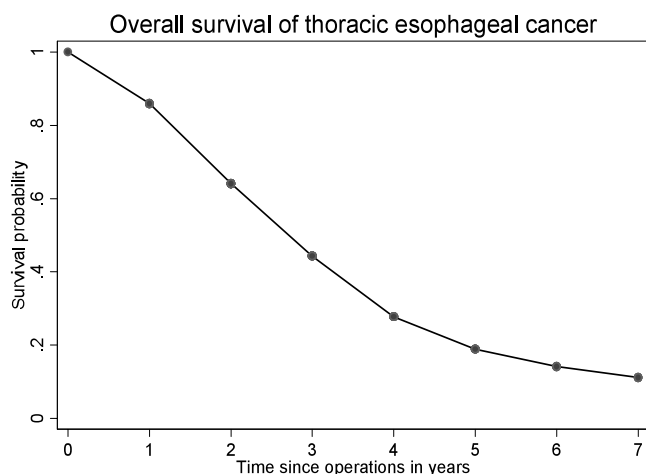
Figure 1 Smoothed overall survival probability of thoracic esophageal cancer patients who underwent en-bloc esophagectomy
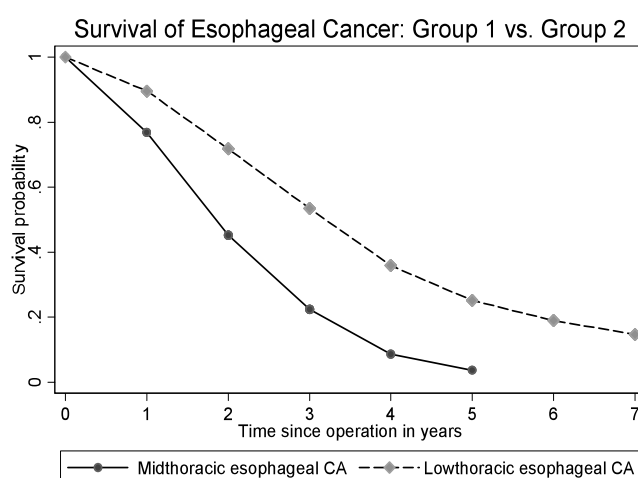
Figure 2 Comparing the smoothed survival probability of groups 1 (three-phase esophagectomy) and 2 (Ivor lewis esophagectomy) patients

The hospital mortality rate was 8 % (5 in 64 patients). All hospital mortality was due to either sepsis or myocardial infarction. Patients in the Ivor Lewis group were followed for a significantly longer time (p = 0.022 by rank test; Table 3).

The overall survival probabilities at 1 year, 3 years and 5 years after operation were 82% (95% CI: 75% to 92%), 44% (95% CI: 32% to 56%) and 19% (95% CI: 11% to 29%), respectively. The smoothed overall survival curve is presented in Figure 1. The survival probabilities for the three-field esophagectomy group at 1 year, 3 years and 5 years were 77% (95% CI: 58% to 88%), 22% (95% CI: 9% to 40%) and 4% (95% CI: 0 to 14%), respectively. The survival probabilities for

the Ivor Lewis esophagectomy group at 1 year, 3 years and 5 years were 90% (95% CI: 80% to 95%), 53% (95% CI: 39% to 66%) and 25% (95% CI: 14% to 38%), respectively. The survival probabilities of the two groups, shown in Figure 2, were statistically different by the log-rank test (p = 0.006).

DISCUSSION

Although esophagectomy remain the standard surgical treatment for patients with operable esophageal cancer, the result of treatment remains poor. The 5-year survival rates in most series (Table 4) rarely exceed 30% even for those in whom potentially

Table 4 Results of esophagectomy for esophageal cancer from previous reports

Author	Year	N	Operation	Death Rate (%)	Complications (%)	Adeno/ Squamous	5-yr survival (%)
Karl[8]	2000	143	TT	2.1	29	82/18	29 (3-yr)
Orringer[2]	1999	800	TH	4.5	NS	69/28	23
Vigneswarren[6]	1997	132	TH	2.3	72	77/23	21
Ellis[1]	1997	454	TH/TT	3.7	30	67/33	30
Lieberman[4]	1995	258	TT	5	NS	52/48	27
Putnam[3]	1994	221	TT/TH	6.8	75	66/33	19
Gertsch[5]	1993	100	TH	3	68	57/43	23
Golminc[9]	1993	67	TH/TT	7.4	51	all squamous	NS
Gelfand[7]	1992	160	TH	2.5	NS	75/25	23

NS, not stated; TH: transhiatal, TT: transthoracic

curative resection is performed (R0 resection). Many centers believe that en bloc esophagectomy is a reasonable treatment for esophageal cancer because of the poor prognosis[1-9]. The long term survival of patients with esophageal cancer is poor due to extensive tumor invasion through the muscular layer and lymphatics, as well as late presentation. Therefore, esophagectomy with complete removal of metastatic regional lymph nodes is considered by some as essential for a curative resection of esophageal carcinoma.

This en-bloc resection, however, has not been clearly shown to improve long term survival over other types of resection. Additionally, the en bloc surgical approach of choice, i.e. either the three phase or the Ivor Lewis approach, remains controversial[10-13]. In the present study, we reviewed the long term outcomes of our series of operable esophageal cancer patients who underwent potentially curative en-bloc esophagectomy, and compared the three-phase and Ivor Lewis approaches. Although the present study cannot directly answer the question of long term benefits or the superiority of either operation, we hope our data can contribute something to the discussion.

We chose the three-phase esophagectomy and the Ivor Lewis operation for patients with esophageal cancer over other non-en bloc operations, such as transhiatal esophagectomy, for several reasons. En-bloc approaches enabled the complete visualization and resection of all abdominal and thoracic esophagus along with the mediastinal lymph tissue. The gastroesophageal anastomosis either at the apex of right chest in the Ivor Lewis operation, and at the left neck in the three-phase esophagectomy, can be done with minimal tension. The proximal margin of resection

can be examined and made grossly tumor-free with ease. Left cervical lymph node dissection can be performed routinely.

Patients in the present series were assigned to each operative approach based on tumor location. We can tailor the lymph node dissection based on tumor location. For example, in a nationwide Japanese study[14], correlations between regional node involvement and tumor location were found. In patients with upper thoracic cancer, the rate of cervical node metastasis was 42.3%, that for mediastinal nodes was 63.1%, and for abdominal nodes 19%. Metastatic rates for middle thoracic esophageal cancer were 27.5% for cervical nodes, 55.8% for mediastinal nodes and 41% for abdominal nodes. For lower thoracic esophagus, metastasis was seen in 10.9% of cervical nodes, 43.5% of mediastinal nodes, and 67.4% of abdominal nodes[14]. We chose to perform three-phase esophagectomy for thoracic esophageal cancer, and Ivor Lewis operation for lower esophageal cancer because of these lymph node metastasis-tumor location correlations.

In the present study patients in group 1 with mid thoracic esophageal cancer who underwent three-phase esophagectomy had 34% cervical node metastasis rate, 56 to 83% mediastinal group node metastasis rate mainly in subcarinal nodes and 22 % abdominal node metastasis rate (Table 2). Patients in group 2 with low esophageal cancer who underwent Ivor Lewis operation had no cervical lymph node metastasis, but had metastasis to the mediastinal nodes in 61 to 80 % of patients mainly in the paratracheal nodes, and 35 % metastasis to the abdominal lymph nodes. These findings are in accord with the Japanese study[14], and show a biological behavior consistent with the fact that

the esophageal submucosa is rich in lymphatics that extend longitudinally as well as laterally. The longitudinal network of lymphatics implies frequent cancer spread to nodes in neck, the thorax, and the abdomen despite tumor location. Once a tumor has breached the muscular layers, the incidence of positive regional nodes exceeds 75%[15].

The overall survival of resectable, nonmetastatic thoracic esophageal cancer in the present study was 19% at 5 years. Few patients with mid-thoracic esophageal cancer who underwent three-phase esophagectomy survived up to 5 years, with an estimated 4% 5-year survival based on a statistical model. However, patients with low thoracic esophageal cancer had a 25% 5-year survival rate after Ivor Lewis esophagectomy. These survivals were significantly different. Our operative mortality was 6 to 9%, with very few anastomotic leakages (4 to 6%). There was a 6 to 13% rate of postoperative pneumonia. These outcomes were similar to other studies[16].

Results of the present study compared favorably with those previously published. Skinner et al have shown that both the number of metastatic lymph node and depth of tumor invasion had adverse effects on survival[10]. Therefore, en-bloc esophagectomy with complete removal of metastatic lymph nodes and resection of the digestive tract for at least 10 cm on either side of the tumor and complete excision of adjacent involved tissues should be expected to improve long term survival[11-13]. The number of positive nodes was another important determinant of survival as reported by Akiyama et al[17], which predicted worse prognosis in patients with seven or more positive nodes. Baba et al[18] reported that injection of technetium labeled rhenium colloid into the esophageal wall can help identify lymphatic structures that may contain metastatic cancer.

In the present study, location of the tumor was significantly related to the survival probabilities. Higher thoracic esophageal cancers were probably more aggressive biologically even after adjustment for tumor stage, with the presence of cervical node metastasis a marker of aggressiveness. The different en-bloc operative approaches probably had no significant effect on survival. Nonetheless, different en-bloc operations are still recommended for tumors at different locations, because rates of cervical lymph node metastasis differ, such that these nodes may not need to be removed in

low esophageal cancer, and the esophagogastric anastomosis site can differ as well.

Finally, squamous cell carcinoma was the most common type of esophageal cancer in the present study. Despite a rising incidence of adenocarcinoma of the esophagus, especially in Western clinics[19,20], squamous cell carcinoma of esophagus remains the dominant type in Thailand.

CONCLUSION

The author believes that en bloc esophagectomy should be the standard of care for esophageal carcinoma, and the result of the present study may encourage other medical centers to improve on the technique and to select cases for this operative approach based on the location of the cancer. However, the procedures are technically demanding and time consuming. Postoperative care requires careful attention, especially for pulmonary complications and detection of anastomosis leakage and wound infection. From the above evidence, it can be concluded that this aggressive surgical approach is at least competitive with other standards of treatment for thoracic esophageal cancer.

REFERENCES

1. Ellis FH Jr, Heatly GJ, Krasna MJ, et al. Esophagogastrectomy for carcinoma of the esophagus and cardia: a comparison and results after standard resection in three consecutive eight-year intervals with staging criteria. J Thorac Cardiovasc Surg 1997;113:836-46.

2. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg 1999;230:392-403.

3. Putnam JB, Suell DM, McMurtrey MJ, et al. Comparison of three techniques of esophagectomy within a residency training program. Ann Thoracic Surg 1994;57:319-25.

4. Lieberman MD, Shriver CD, Bleckner S, et al. Carcinoma of the esophagus. Prognostic significance of histologic type. J Thorac Cardiovasc Surg 1995;109:130-8.

5. Gertsch P, Vauthey JN , Lustenberger AA, et al. Long-term results of transhiatal esophagectomy for esophageal carcinoma. A multivariate analysis of prognostic factors. Cancer 1993;72:2312-9.

6. Vigneswarren WT, Trastek VF, Pairolero PC, et al. Transhiatal and transthoracic resection for lower-third esophageal carcinoma. Am J Surg 1997;174:320-4.

7. Gelfand GA, Finley RJ, Nelems B, et al. Transhiatal esophagectomy for carcinoma of the esophagus and cardia. Arch Surg 1992;127:164-7.

8.   Karl RC, Schreiber R, Boulware D, et al. Factors affecting morbidity, mortality, and survival in patients undergoing Ivor-Lewis esophagogastrectomy. Ann Surg 2000;231:635-643.

9.   Golminc M, Maddern G, Le Prise E, et al. Oesophagectomy by a transhiatal approach or thoracotomy : a prospective randomized trial. Br J Surg 1993;80-367-70.

10. Skinner DB, Ferguson MK, Soriano A, et al. Selection of operation for esophageal cancer based on staging. Ann Surg 1986;204:391-401.

11. Orringer MB, Sloan H. Esophagectomy without thoracotomy. J Thorac Cardiovasc Surg 1987;76:643-654.

12. Skinner DB. En bloc resection for neoplasms of the esophagus and cardia. J Thorac Cardiovasc Surg 1983;85:59-71.

13. Orringer MB, Forastiere AA, Perez -Tamayo C, et al. Chemotherapy and radiation therapy before transhiatal esophagectomy for esophageal carcinoma. Ann Thorac Surg 1990;49:348-355.

14. Isono K, Sato H, Nakayama K. Results of a nationwide study on the three fields o lymph node dissection in esophageal cancer. Oncology 1991;48:411.

15. American Joint Committee on Cancer. AJCC Cancer Staging Handbook. Philadelphia: Lippincott-Raven;1998:67.

16. Kato H , Watanabe H, Tachimori Y, et al. Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. Ann Thorac Surg 1991;51:931-5.

17. Akiyama H, Tasurumaru M, Udagawa Y, et al. Systematic Lymph node dissection for cancer: effective or not? Dis Esoph 1994;7:1-12.

18. Baba M, Aikou T, Yoshinaka H, et al. Long-trem result of subtotal esophagectomy with three-field lymphadenec-tomy for carcinoma of the thoracic esophagus. Ann Surg 1994;219:310-6.

19. Pera M, Cameron AJ, Trastek VF, et al. Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. Gastroenterology 1993;104:510-3.

20. Visbal AL, Allen MS, Miller DL, et al. Ivor Lewis esophagogastrectomy for esophageal cancer. Ann Thorac Surg 2001;71:1803-8.