Original Article

Surgical Outcome of Three-Field Lymph Node Dissection for Esophageal Cancer: First Report in Thailand

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Background: Esophageal squamous cell carcinoma is one of worst prognosis cancer due to extensive lymph node metastasis and local invasiveness. This is an initial experience in Thailand to perform esophagectomy with 3-field lymphadenectomy based on the Japanese standard. Our objective in this study is to evaluate surgical outcome of three-field lymph node dissection in terms of morbidity, mortality, survival and recurrent rate.

Materials and Methods: Between January 2013 and December 2019, a total of 31 patients had undergone esophagectomy with three-field lymph node dissection at the department of surgery, Siriraj hospital Mahidol University. All of the patients had primary squamous cell carcinoma of thoracic esophagus.

Results: None of the patients has 30-day postoperative mortality. Severe postoperative complication (Clavien-Dindo grade lllb-V) was 12.9%. Recurrent laryngeal nerve paresis was seen in eight patients (14.8%) and this injury occurred mainly on the left side. Metastasis lymph node rate was 54.9% which cervical node metastasis of middle and lower thoracic esophagus were 33.3% and 23.5%. Overall 3-year and 4-year survival rates were 40.0% and 24.0%, respectively. Recurrent rate was 35.4%.

Conclusion: Transthoracic esophagectomy with three-field lymph node dissection was performed in our study with no mortality and acceptable morbidity. High metastatic rate to cervical node indicates the necessity of three-field lymph node dissection (3FL) for thoracic esophageal carcinoma. Esophagectomy with three-field lymph node dissection should be standard procedure for esophageal cancer in Thailand.

Keywords: Esophageal cancer, Transthoracic esophagectomy, Three-Field lymph node dissection

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Esophageal cancer is the eighth common cancer worldwide, and because of its poor prognosis it is the sixth most common cause of cancer-related death[(1)]. Esophageal cancer was the eleventh common cancer in Thailand with 2,000 to 2,500 new cases diagnosed every year. At Siriraj Hospital, 80 to 100 new cases are encountered every year.

Appropriate therapeutic modality for esophageal squamous cell carcinoma such as endoscopic resection, surgery alone, perioperative adjuvant and palliative treatment depend on accurate staging evaluation. The treatment outcomes are related to the extent of the disease and concomitant medical conditions. Regarding the advanced stage of esophageal cancer of most cases, the prognosis is still poor. In general, surgical treatment is restricted with localized disease, without distant metastasis. Standard surgical resection with radical lymphadenectomy is carried out even if there is no definite evidence of lymphatic spread[(2)]. Multidisciplinary approach including pre-operative chemoradiation is often needed for increased resectability.

Transthoracic esophagectomy with three-field lymph node dissection (3FL) for esophageal carcinoma has been established by Japanese surgeons since the early 1980s.[3] This effort was prompted by reports that as many as 40% of patients with squamous cell cancer of the esophagus developed isolated cervical nodal metastases following a presumed curative resection[(4)]. Three field lymph node dissection was reported to have low recurrence rates, improved 5-year survival and the benefits of accurate staging but it also had high rate of recurrent nerve injury (2 to 20%)[(5)]. However, three-field lymph node dissection in esophageal cancer is still controversial in Thailand. Some surgeons agree with three-field lymph node dissection while others believe that two-field lymphadenectomy was enough because it had fewer complications.

Our objective in this study is to evaluate surgical outcome of three-field lymph node dissection in terms of morbidity, mortality, survival and recurrence. This study is report result of our initial practice of three-field lymph node dissection for esophageal squamous cell carcinoma and would be the first report in Thailand.

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Materials and Methods

Patient population

Between January 2013 and December 2019, a total of 31 patients with squamous cell carcinoma of the thoracic esophagus underwent transthoracic esophagectomy with three-field lymph node dissection at department of surgery, Siriraj hospital. Second primary cancers were excluded from this study.

Preoperative evaluation

Esophagogastroduodenoscopy with biopsy was done for initial evaluation of the tumor and computerized tomography (CT) of the neck, chest and upper abdomen was done in all cases. Clinical staging, T1-T3, any N and M0 cases would be considered for operative treatment. All patients were evaluated for pulmonary and cardiac function to determine their ability to endure the procedure. Generally, patients with an FEV1 more than 1.5 liters were feasible to precede to thoracotomy.

Operative technique

The operative steps were divided into to three phase, the first step is right thoracotomy, secondly is exploratory laparotomy for gastric tube reconstruction and the final step is bilateral neck node dissection and completion of the anastomosis. After general anesthesia via endotracheal tube was administered, a bronchial blocker was inserted for one lung ventilation. The patient position was adjusted in the left lateral decubitus and right thoracotomy was done via 4^{th} or 5^{th} intercostal space. The thoracic phase is entire esophageal mobilization from upper thoracic until crus of diaphragm include upper, mid and lower paraesophageal lymph node (lymph node group 105, 108, 110 respectively). Mediastinal lymph node was dissected along right and left recurrent laryngeal nerve (106rec R and 106rec L), supra right and left main bronchus (106tb R and 106tb L), subcarinal and infra bilateral main bronchus (107, 109 R, 109 L, respectively). Esophagus was divided above the lesion. The right chest drain was placed. Abdominal and neck phase concurrently underwent via supine position. The esophageal specimen was taken down via hiatus and en-bloc removal with gastric remnant including lymph node along lessor curvature site such as lymph node group 3, 5, 7, 8a, 9. Gastric tube was created and blunt pyloromyotomy was performed. Neck phase was done via bilateral collar incision and infra omohyoid lymph node dissection medial and lateral to carotid sheath (lymph node group 101 and 104). Bilateral recurrent laryngeal nerve was preserved. After proximal esophageal margin was transected at neck level, gastric tube was taking up to neck level through substernal route and esophago-gastric anastomosis was done by EEA 25. Feeding jejunostomy was done with feeding tube 12 fr. in diameter and enteral feeding will start on post operative day 1 to 2. The patient was transfer to ICU after operation and bed side endoscopic evaluation of vocal cord and gastric tube viability on 1^{st} post operative day for every case. Contrast study to demonstrate anastomosis was requested on post operative day 7.

Statistical analysis

Statistical analysis was done using paired Student's t-test by SPSS 17.0 software. Survival estimates were done by Kaplan-Meier method and the significance of differences in survival was evaluated by the log rank test. Values less than 0.05 were accepted as statistically significant. All data were analyzed using the Statistical Package for the Social Science (SPSS) version 21.0. The descriptive analysis was performed. Mean and standard deviation were used for quantitative data. Number and percentage were used for qualitative data. Survival outcome were analyzed by Kaplan-Meier analysis. Ethics consideration:151/2562 (EC1).

Results

Among the 31 esophageal squamous cell carcinoma patients, 27 were male and 4 were female, with a median age of 60 years (range 46 to 71 years). The demographics of patients were shown in Table 1. Middle thoracic esophageal cancer was most frequently in 48.4%, lower thoracic in 45.1% and upper thoracic in 6.5% of the patients. Mean size of the tumor in the pathologic specimen was 4.6 cm (range 0 to 10.0 cm). The incidence of moderately differentiated (G2) and well differentiated tumor (G1) was 92.9% and 0.7%, respectively. Nine patients received preoperative chemo-radiotherapy using cisplatin-fluorouracil (5FU) or paclitaxel-carboplatin with radiation 45 to 50.4 Gy. One patient received definite chemoradiotherapy of radiation 60 Gy and cisplatin-fluorouracil (5FU). Pathologic complete response was achieved after chemoradiotherapy in 4 patients (40%). According to TNM classification, T3 tumor had the highest incidence in our institution (61.3%). Lymph node metastasis was detected in 54.9% which cervical node metastasis rate of upper, middle and lower thoracic esophagus were 50%, 33.3% and 23.5% for each subgroup respectively. The distribution of lymph node metastasis was showed in Figure 1. The station lymph node metastasis of esophageal cancer in our institute was demonstrated in Figure 2. The incidence of metastasis (M1) was 6.5%. Most patients were in locally advanced stage, mainly in stage IIIB was 25.8%. The mean operative time was 8.1 hour. The mean estimated blood loss was 513 ml and no patients were re-operated. The operative data was shown in Table 2. The mean ICU stay and hospital stay were 5.0 days and 18.9 days, respectively. Four patients (12.9%) had lung parenchymal injury which resolved by suture repair. Trachea injury after tumor dissection occurred in one patient, receiving pre-operative concurrent chemoradiotherapy (CCRT) and it was primary repaired intra-operatively. Intra-operative, splenic injury was found in one patient (Table 3). None of the patient has 30-day postoperative mortality. Severe postoperative complication (Clavien-Dindo grade lllb-V) was occurred in 4 patients (12.9%). The incidence of postoperative pulmonary complications was 31.6%. The most common pulmonary complication was atelectasis occurring in 6 patients (11.1%). The bacterial pneumonia was found in 5 patients (9.3%). The cardiovascular

Table 1. Patient demographic data

Gender (male: female)	27: 4 (87.1%)
Age (years), mean ± SD	60±7.3 (range 46 to 71 years)
BMI (kg/m^2), mean ± SD	20.6±3.8
ASA, n (%)	
1 to 2	18 (58.1%)
3	13 (41.9%)
Smoking (pack-year), mean ± SD	27.7±18.4
Preoperative chemoradiotherapy	9 (29.0%)
Definitve chemoradiotherapy	1 (3.2%)
Tumor size (cm), mean ± SD	4.6±2.6
Tumour location, n (%)	
Upper thoracic esophagus	2 (6.5%)
Middle thoracic esophagus	15 (48.4%)
Lower thoracic esophagus	14 (45.1%)
Resection category	
R0	20 (64.5%)
R1	9 (29.0%)
R2	2 (6.5%)
T stage, n (%)	
pT 0	4 (12.9%)
pT 1	2 (6.5%)
pT 2	3 (9.7%)
pT 3	19 (61.3%)
pT 4	3 (9.7%)
N stage, n (%)	
pN 0	14 (45.2%)
pN 1	6 (19.4%)
pN 2	6 (19.4%)
pN 3	5 (16.1%)
M stage, n (%)	
M 0	29 (93.5%)
M 1	2 (6.5%)
TMN stage, n (%)	
0 (ypT0N0)	4 (12.9%)
I	1 (3.2%)
IIA	5 (16.1%)
IIB	4 (12.9%)
IIIA	3 (9.7%)
IIIB	8 (25.8%)
IIIC	4 (12.9%)
IV	2 (6.5%)

Table 2. Operative data

Operative approach, n (%)	
Open	28 (90.3%)
Video assisted thoracoscopic (VATS)	2 (6.5%)
Robotic	1 (3.2%)
Route, n (%)	
Substernal route	25 (80.6%)
Posterior mediastinal route	6 (19.4%)
Operative time (hour), mean ± SD	8.1±1.5
Blood loss (ml), mean ± SD	513.7±253.9

complication in 7.5% of the patients which congestive heart failure was 1.9% and arrhythmia was 5.6%. The incidence of early postoperative surgical complication was 31.5%. The

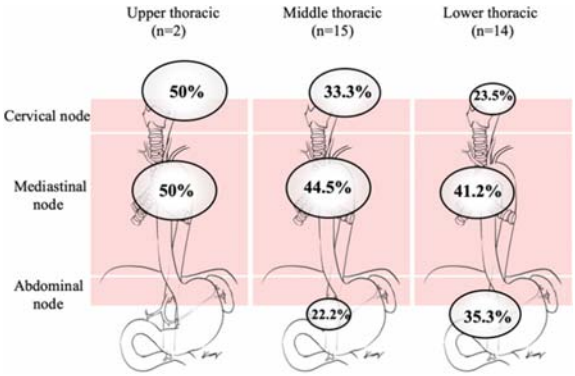

Figure 1. The distribution of lymph node metastasis in esophageal carcinoma according to location of tumor.

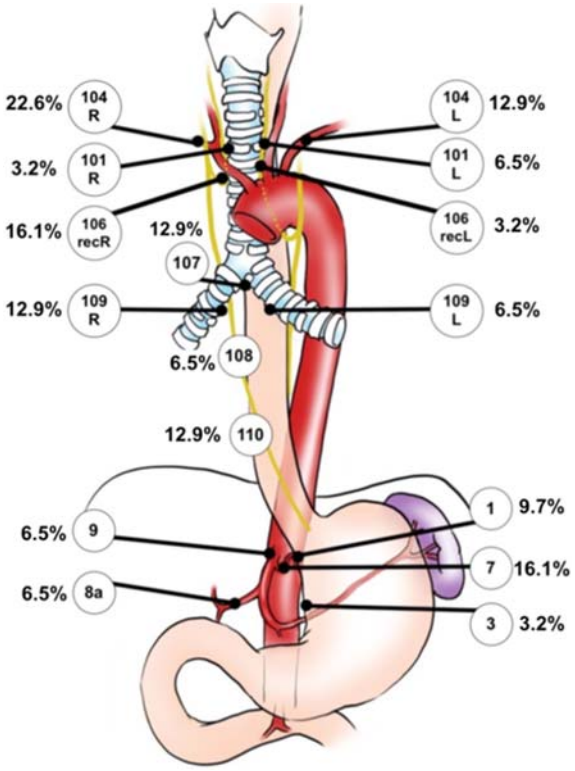

Figure 2. Station lymph node metastasis in esophageal cancer (31 patients).

anastomosis leakage occurred in two patients (3.7%) which were resolved by conservative treatment. One patient required esophageal stent placement to cover at the leakage site. The chylothorax occurred in five patients (9.3%) and all of them treated successfully with conservative treatment. Wound complication was found in 3.8%. The recurrent laryngeal nerve paresis was seen in eight patients (14.8%) that it

Table 3. Postoperative data and complications

Hospital stay (days), mean ± SD	18.9±7.1
ICU stay (days), mean ± SD	5.0±2.7
Clavien-Dindo grade of complication	
No complication	8 (25.8%)
Grade I	7 (22.6%)
Grade II	4 (12.9%)
Grade IIIa	8 (25.8%)
Grade IIIb	3 (9.7%)
Grade IVa	1 (3.2%)
Grade IVb-V (mortality)	0 (0%)
Intraoperative complications	
Lung parenchymal injury	4 (12.9%)
Tracheal injury	1 (3.2%)
Splenic injury	1 (3.2%)
Early postoperative surgical complications	
Anastomotic leakage	2 (3.7%)
Surgical site infection	1 (1.9%)
Wound dehiscence	1 (1.9%)
Chylothorax	5 (9.3%)
Recurrent nerve injury	8 (14.8%)
Left: right	7: 1
Early postoperative non-surgical complications	
Pulmonary	
Pneumonia	5 (9.3%)
Pneumothorax	1 (1.9%)
Atelectasis	6 (11.1%)
Pleural effusion	5 (9.3%)
Cardiovascular	
Congestive heart failure	1 (1.9%)
Arrhythmia	3 (5.6%)
Renal	
AKI	1 (1.9%)
Volume overload	1 (1.9%)
Neurology	
Stroke	1 (1.9%)
Delirium	3 (5.6%)
Infectious	
UTI infection	1 (1.9%)
Late postoperative complications	
Anastomotic stricture	7 (22.6%)

occurred mainly on the left side without upper airway obstruction. The median overall survival (OS) was 25.9 months (95% CI 19.5 to 32.2) and the maximum follow-up time was 42 months. The overall 3-year and 4-year survival rate were 40.0% and 24.0%, respectively (Figure 3). The recurrent rate was 35.4%. Ten patients (32.3%) had recurrence at cervical node and distant metastasis (liver, lung and bone metastasis). One patient (3.2%) had locoregional recurrence at surgical bed. The median disease-free survival (DFS) was 31.7 months (95% CI 23.8 to 39.7) and 3 years disease-free survival was 53%. Late postoperative anastomotic stricture was developed in 7 patients (22.6%) which resolved by esophageal dilatation.

Discussion

Esophageal cancer has high metastatic potential and a poor prognosis. Due to its abundant lymphatic flow,

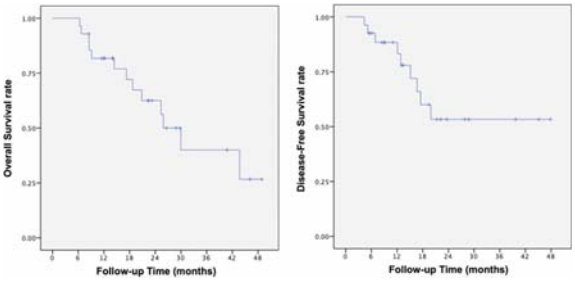

Figure 3. Survival curve after transthoracic esophagectomy with three-field lymph node dissection (3FL) for esophageal carcinoma (left; overall survival, right; disease-free survival).

lymph node metastasis can occur in early stage of cancer with 8 to 12% lymph node metastasis rate when tumor invades beyond muscularis mucosae. Lymph node metastasis is associated with depth of the tumor and it can be as high as 41% once the tumor invades into submucosa, 72% when it involves muscularis propria. This proves the necessity for lymph node dissection when tumors involved are beyond submucosa[2,3,6,7]. Radical lymph node dissection can accurately provide staging, minimizes regional recurrence and improves survival[5,8]. Achieving R0 resection, is one of the most important factors to predict the prognosis for esophageal cancer patients. Although aggressive lymph node dissection is associated with high morbidity, 41.9%[9], compared with 12.9% in our study. In experienced centers[2], low postoperative mortality (2 to 7%) was reported such as 3.8% by Altorki[8], 5.2% by Akiyama[2] and 6.4% by Tachibana[10]. In our study, we had 0% of early postoperative mortality rate. In a series of 1,791 patients from 35 institutions, Isono et al[5] reported an incidence of 30% for cervical lymph node involvement in thoracic esophageal cancer that the incidence of cervical nodal metastases was 42%, 28% and 11% for upper, middle thoracic and abdominal esophagus, respectively. Considering the high rate of lymphatic spread, they concluded that two-field lymphatic dissection (2FLD) was not enough for thoracic esophageal cancer but three-field lymph node dissection (3FL) significantly increased survival[5]. The 5-year survival rate of patients with curative surgery is 53.8% (T1: 77.4%, T2: 49.0%, T3: 44.0%, T4: 28.0%)[2]. The majority of the recurrence (97%) was detected within 3 years after surgery[11]. The 5-year survival rate for node-negative patients was 88% compared to 33% for patients with nodal metastases (p = 0.0007). Patients with cervicothoracic nodal metastases had 3-year and 5-year survival rates of 33% and 25%, respectively (median 17 months)[8]. Skinner has shown that both the number of metastatic lymph nodes and the depth of tumor invasion are important prognostic factors in multivariate analysis[12]. The rate of regional recurrence in standard three-field lymph node dissection (3FL) is 30%.

In our study, lymph nodal metastases were detected

in 54.9% which abdominal node nodal metastases in middle and lower thoracic esophageal cancer were found to be 22.2% and 35.3%, respectively. The most frequently metastases node was mediastinal lymph node which found 44.5% and 41.2% in middle and lower thoracic, respectively. Rate of cervical lymph node involvement is 33.3% and 23.5% for middle thoracic and lower thoracic cancer respectively. These are important data to support necessary cervical lymph node dissection to be standard procedure for squamous cell carcinoma surgery. Number of positive lymph nodes to the number of total nodes is also important in prognosis. Five-year survival rate for 1 to 7 positive nodes is 51.68% while it is 9.86% for eight or more positive nodes ($p = 0.0001$). More effective lymphatic node clearance is performed in three-field lymph node dissection (3FL)[2]. In our study, most patients were in locally advanced stages, mainly in stage IIIB. The recurrent rate was 35.4%. The 3-year overall survival rate was 40.0%. Compared to former study[13] the overall survival rate was rather low. This may be from a limited number of patients, short term follow-up period and advanced disease of the patients.

Conclusion

This study confirmed that three-field lymph node dissection (3FL) can be performed with no mortality and acceptable morbidity. High metastatic rate to cervical node indicates the need for three-field lymph node dissection (3FL) and we recommend that it should be standard procedure for esophageal cancer in Thailand.

What is already known on this topic?

Esophagectomy with three-field lymph node dissection (3FL) for esophageal carcinoma was reported to safe procedure without 30-day mortality and the patient have chance to gain 5-year survival and the benefits of accurate staging but it also had high rate of recurrent nerve injury.

What this study adds?

In our study, the middle and lower thoracic esophageal cancer had evidence of cervical lymph node metastasis indicating the need to do three-field lymph node dissection (3FL) for thoracic esophagus carcinoma.

Secondly, our study showed 40% complete pathologic response after pre-operative or definite chemoradiation. We need to find the solution for this patient to minimize morbidity whilst still keeping long-term survival.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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ผลการรักษาผู้ป่วยมะเร็งหลอดอาหารที่ได้รับการรักษาด้วยการผ่าตัดหลอดอาหารทางช่องอกและเลาะต่อมน้ำเหลืองบริเวณช่องอก ช่องท้อง และลำคอ ครั้งแรกในประเทศไทย

จิรวัฒน์ สว่างศรี, ฑิฆัมพร ถวัลย์ธนากร, ธรรมวัฒน์ ปรคนธรรพ์, อัษฎา เมธเศรษฐ

ภูมิหลัง: ในประเทศญี่ปุ่นมีการศึกษาพบว่า การกระจายตัวของต่อมน้ำเหลืองในผู้ป่วยมะเร็งหลอดอาหารในระยะที่ 2 ถึง 3 สามารถกระจายขึ้นบนและลงล่างไปสู่ระดับคอและช่องท้องส่วนบนตามลำดับการผ่าตัดหลอดอาหารทางช่องอกและเลาะต่อมน้ำเหลืองบริเวณช่องอก ช่องท้อง และลำคอ ช่วยเพิ่มอัตราการรอดชีพ (survival rate) อย่างมีนัยสำคัญและเป็นการรักษาที่เป็นมาตรฐาน สำหรับประเทศไทยการรักษามะเร็งในระยะดังกล่าวมีความสำคัญเนื่องจากเป็นผู้ป่วยในกลุ่มที่ยังหวังผลการรักษาได้เป็นส่วนใหญ่ แต่ยังไม่มีการศึกษาผลของการผ่าตัดหลอดอาหารทางช่องอกและเลาะต่อมน้ำเหลืองบริเวณช่องอก ช่องท้อง และลำคอ ในประเทศไทยมาก่อน

วัตถุประสงค์: เพื่อศึกษาผลการดูแลผู้ป่วยมะเร็งหลอดอาหารที่รับการรักษาด้วยวิธีการผ่าตัดหลอดอาหารทางช่องอกและเลาะต่อมน้ำเหลืองบริเวณช่องอก ช่องท้อง และลำคอ ทั้งในระยะสั้นและระยะยาว

วัสดุและวิธีการ: การศึกษาข้อมูลย้อนหลังในผู้ป่วยโรคมะเร็งหลอดอาหารทั้งหมดที่เข้ารับการรักษาด้วยวิธีการผ่าตัดหลอดอาหารทางช่องอกและเลาะต่อมน้ำเหลืองบริเวณช่องอก ช่องท้องและลำคอที่โรงพยาบาลศิริราช ตั้งแต่เดือนมกราคม พ.ศ. 2556 ถึง เดือนธันวาคม พ.ศ. 2562 และวิเคราะห์อัตราการรอดชีวิตในผู้ป่วยมะเร็งหลอดอาหารที่รับการรักษาด้วยวิธีการผ่าตัดหลอดอาหารทางช่องอกและเลาะต่อมน้ำเหลืองบริเวณช่องอก ช่องท้อง และลำคอ, อัตรากลับมาเป็นซ้ำของโรค, ศึกษาการกระจายไปต่อมน้ำเหลืองบริเวณคอ และอัตราการเกิดภาวะแทรกซ้อนภายหลังการผ่าตัด

ผลการศึกษา: ผู้ป่วยโรคมะเร็งหลอดอาหารทั้ง 31 คน ที่ได้รับการผ่าตัดหลอดอาหารทางช่องอกและเลาะต่อมน้ำเหลืองบริเวณช่องอก ช่องท้อง และลำคอ พบภาวะแทรกซ้อนหนัก ร้อยละ 12.9 แต่ไม่พบอัตราการเสียชีวิตใน 30 วันแรกหลังผ่าตัด พบการบาดเจ็บต่อเส้นประสาทที่เลี้ยงกล่องเสียงร้อยละ 14.8 การกระจายไปต่อมน้ำเหลืองทั้งหมด ร้อยละ 54.9 มะเร็งหลอดอาหารบริเวณช่องอกส่วนกลางและส่วนล่างมีการกระจายไปต่อมน้ำเหลืองบริเวณคอ ร้อยละ 33.3 และร้อยละ 23.5 มีอัตราการรอดชีพที่ 3 ปี และ 4 ปี เท่ากับ ร้อยละ 40.0 และร้อยละ 24.0 ตามลำดับ พบอัตรากลับมาเป็นซ้ำของโรคร้อยละ 35.4

สรุป: การรักษาผู้ป่วยมะเร็งหลอดอาหารที่ได้รับการรักษาด้วยการผ่าตัดหลอดอาหารทางช่องอกและเลาะต่อมน้ำเหลืองบริเวณช่องอก ช่องท้อง และลำคอ ไม่พบอัตราการเสียชีวิตจากการผ่าตัด พบภาวะแทรกซ้อนที่อาจเกิดขึ้นได้แต่ไม่รุนแรง พบการกระจายไปต่อมน้ำเหลืองบริเวณคอสูง ซึ่งเป็นข้อบ่งชี้ในการผ่าตัดเลาะต่อมน้ำเหลืองบริเวณช่องอก ช่องท้อง และลำคอ