



Risk Factors of Tumor Relapse in Patients with Clinical Stages 1–3 Esophageal Squamous Cell Carcinoma after Curative Surgery

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Background: The aim of this study was to determine the risk factors for disease progression in patients with clinical stages 1–3 squamous cell carcinoma (SCC) of the esophagus after curative surgery. **Methods:** This is a retrospective study of postoperative risk factors for patients with SCC after esophagectomy. The factors related to disease progression, including stage, clinical tumor response, operation types, number of resected lymph node number, standard uptake value (SUV), tumor differentiation, lymphovascular space invasion, perineural invasion, extracapsular invasion, and tumor regression grade, were analyzed. **Results:** A total of 73 patients treated between 2011 and 2015 were included in the study. Twenty-six patients developed disease recurrence, including 10 locoregional and 16 distant metastases. Clinical tumor response, procedure types, tumor differentiation, extracapsular invasion, and average standard uptake value (SUVmax) were significantly associated with overall survival. On multivariate analysis, clinical tumor response ($P = 0.044$), minimally invasive esophagectomy (MIE) ($P = 0.006$), and tumor differentiation ($P = 0.042$) remained independent predictors for the disease progression. **Conclusions:** Clinical tumor response, MIE, tumor differentiation, extracapsular invasion, and average SUVmax of tumor (postconcurrent chemoradiotherapy) were independent predictors for the disease progression. Our findings put forward the postoperative predictors of disease progression in esophageal SCC to identify high-risk patients and deliver proper treatment.

Key words: Squamous cell carcinoma, esophageal cancer, local recurrence, distant metastasis

INTRODUCTION

Outcomes of esophageal cancer are related to the extent of the disease and other medical conditions, but generally, tend to be fairly poor (5-year survival rate around 13%–18%) because of the diagnosis is often late.¹ Patients with locally advanced and potentially curable esophageal cancer should be cared for in a trimodality treatment, which involves induction concurrent chemoradiotherapy (CCRT) followed by esophagectomy.² However, a significant fraction of disease recurrence after trimodality treatments still reported in the previous works of literature.^{3–5} The CROSS trial demonstrated a 49.4-month median overall survival in the chemoradiotherapy surgery

group compared to 24 months in the surgery alone cohort. In addition, 34.7% of patients experienced disease recurrence after preoperative chemoradiotherapy and surgery.⁶ Although patients with pathologic major response are reported to have a better prognosis after surgery than those without, approximately 40% of the formers develop local or systemic recurrence and die from the disease progression.⁷ In another multi-center study, there were still 29.3% of patients with disease recurrences in pathologically complete response after receiving treatment for esophageal cancer.⁵ Irrespective of the pathological response to preoperative CCRT, the majority

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How to cite this article: Kuo YS, Lee CL, Yun PJ, Sung YC, Wu TH, Huang HK, et al. Risk factors of tumor relapse in patients with clinical stages 1–3 esophageal squamous cell carcinoma after curative surgery. J Med Sci 2020;40:59-67.

Received: April 24, 2019; Revised: June 26, 2019;
Accepted: August 20, 2019; Published: October 04, 2019
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of patients experienced recurrence at distant sites.⁶⁻⁸ Several risk factors associated with disease progression followed esophagectomy have been defined in the literature, such as poor pathological response to preoperative CCRT, positive lymph nodes after CCRT, and the presence of lymphovascular space invasion (LVSI).⁵⁻¹⁰ In addition, the 8th tumor, node, and metastasis (TNM) edition for esophageal cancer was released in 2016 and included major revisions, especially in stage IV esophageal cancer. Understanding the patterns of disease recurrence after esophagectomy will provide insight into the effectiveness of multimodality treatment planning. In this study, we focus the recurrence patterns in patients with esophageal squamous cell carcinoma (SCC) after curative surgery and to identify postoperative predictors for disease progression. In selected patients with high-risk factors, to provide more intensive follow-up and adjuvant treatments is believed to reduce tumor recurrences and prolong patients' survival.

METHODS

We conducted a single-institution retrospective cohort study, in which we reviewed patients who had undergone esophagectomy for pathologic stage I to III esophageal SCC at Tri-Service General Hospital (TSGH) between 2011 and 2015. Of the 271 patients who underwent esophagectomy at our hospital, 73 were enrolled in the study [Figure 1]. The staging was performed using the 8th edition of the American Joint Committee on Cancer Staging Manual. This study was approved by the Institutional Review Board of our hospital (1-106-05-088) on June 07, 2017. We extracted baseline information from a prospectively maintained database, including demographic variables, pathologic details, preoperative staging and treatment details, and postoperative disease status. Exclusion criteria included loss of follow-up or no curative treatment, histology type other than SCC, salvage esophagectomy, clinical stage I and IV SCC of the esophagus, R1 or R2 resection, upper-third esophageal cancer, and synchronous double cancer. A total of 73 patients who underwent esophagectomy with R0 resection was eligible for this study. Details on recurrences were obtained from medical records from TSGH and outside hospitals, when available, as well as from documented patient communications. Recurrence status was censored on the date of the final TSGH clinic visit or outside communication.

Preoperative assessment for staging

Pretreatment staging included history taking, physical examination, pulmonary functional tests, panendoscopy, endoscopic ultrasonography (EUS), computed tomography (CT) of the chest, and whole-body positron emission

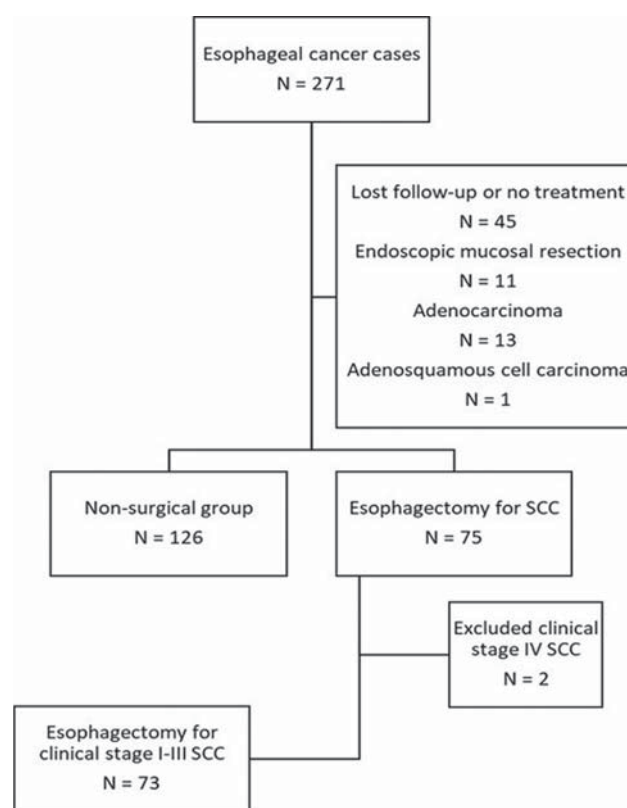


Figure 1: Our study enrolled a total of 271 patients with esophageal cancer and excluded 72 patients. One hundred and six patients received chemotherapy and radiation therapy. Only 75 patients with squamous cell carcinoma of esophagus had esophagectomy. We only evaluated 73 patients with clinical stages 1–3 esophageal squamous cell carcinoma

tomography (PET) scan. The enlarged mediastinal lymph node (short axis >1 cm) or positive nodes at PET scan were proved by the EUS with a needle biopsy. Flexible bronchoscopy was routinely done in patients with middle-third esophageal cancer to rule out the direct invasion to trachea-bronchial trees.

Induction chemoradiation therapy

Induction chemotherapy consisting of the 5-fluorouracil and cisplatin regimen was performed for patients with above clinical stage T1b esophageal cancer and performance status of 0-1 (Eastern Cooperative Oncology Group) and normal hepatorenal function. Chemotherapy consisted of five cycles of concurrent paclitaxel 50 mg/m² and carboplatin, starting on days 1, 8, 15, 22, and 29. A total radiation dose of 41.4 Grey was administered in 23 fractions of 1.8 Grey, five fractions per week, starting on the 1st day of chemotherapy.

Surgical interventions

All patients underwent McKeown procedure as an operative approach. Thoracotomy with subtotal esophagectomy and

mediastinal lymphadenectomy were performed through a right thoracotomy in the left lateral decubitus position. Minimally invasive esophagectomy (MIE) included video-assisted thoracoscopic surgery (VATS) with the mobilization of the esophagus and systemic lymphadenectomy. In the abdominal procedure, preparation of a gastric conduit and upper abdominal lymphadenectomy were performed through an upper midline laparotomy (hybrid MIE) or using a 4-port laparoscopic approach (total MIE). The gastric tube was pulled up through the posterior mediastinal route and then was connected with cervical esophagus with primary anastomosis.

Postoperative surveillance

Screening for complications was performed routinely based on clinical symptoms. Blood tests, including serum C-reactive protein and X-ray imaging, were performed on postoperative days 1–5, 7, and as necessary thereafter. Complications from the day of surgery until hospital discharge were reviewed by attending physicians at the time of discharge. The average period of follow-up was 84 months.

Definition of disease progression

Disease progression was identified as locoregional recurrences or distant metastases. Locoregional recurrences were defined as recurrences at the anastomotic site or mediastinal lymph nodes. Lymph node recurrences at the celiac trunk or in the supraclavicular region were considered as distant metastases. Distant metastases were defined as nonregional lymph node recurrences, systemic metastases, malignant pleural effusions, or peritoneal metastases. Details on recurrences were obtained from medical records of TSGH and outside hospitals, when available, as well as from documented patient communications. Recurrence status was censored on the date of the final TSGH clinic visit or outside communication.

Parameters

The factors related to the disease progression, including TNM stage (8th edition), clinical tumor response, types of procedure, resected lymph node number, standard uptake value (SUV_{max}) of fluoro-2-deoxy-D-glucose (FDG), LVSI, perineural invasion, extracapsular invasion, and tumor regression grade (TRG), were analyzed. Clinical tumor response was used Response Evaluation Criteria in Solid Tumors (RECIST) and decreased SUV after the induction of CCRT. The RECIST specification establishes a minimum size for measurable lesions, limits the number of lesions to follow, and standardizes unidimensional measures.^{11,12} Types of the procedure included (1) thoracotomy with esophagectomy and exploratory laparotomy with gastric tube reconstruction,

(2) VATS esophagectomy and exploratory laparotomy with gastric tube reconstruction, and (3) MIE. The calculation method of TRG systems is to categorize the amount of regressive changes after treatment mostly refer onto the amount of therapy-induced fibrosis in relation to residual tumor or the estimated percentage of residual tumor in the same tumor site.¹³ TRG was determined by pathologist and classified based on the proportion of residual tumor cells in the area where tumor was thought to have existed before neoadjuvant chemotherapy as follows: Grade 0 (no therapeutic effect), Grade 1 (residual tumor cells $\geq 2/3$), Grade 2 ($1/3 \leq$ residual tumor cells $< 2/3$), Grade 3 (residual tumor cells $< 1/3$), and Grade 4 (no residual tumor). Definition of smoking habit: a physical addiction to tobacco products for at least 1 year. According to the Dietary Guidelines for Americans,¹⁴ moderate alcohol consumption is defined as having up to 1 drink/day for females and up to 2 drinks/day for males. All our patients received cease smoking and alcoholic consumption after the treatment of esophageal cancer.

Statistical analysis

Pearson's Chi-square test was used to compare categorical variables. The Student's *t*-test was used for the comparison of continuous variables. The Cox regression model was utilized for univariable and multivariable survival analysis. The backward method was used to optimize the multivariable model. Survival curves were plotted using the Kaplan–Meier method and compared by the log-rank test. All calculations were performed using statistical product and service solutions (version 18, SPSS Inc., Chicago, IL, USA), and a two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 showed significant differences between patients with or without disease progression (recurrences or metastases) in smoking habits ($P = 0.032$), upstage of clinical stage after adjusting by the AJCC 8th edition ($P = 0.007$), average SUV_{max} of tumor (post-CCRT) ($P = 0.040$), and MIE ($P = 0.015$). The tumor histology showed 7 (9.58%) patients with well-differentiated carcinoma, 36 (49.31%) patients with moderately differentiated carcinoma, and 30 (41.1%) patients with poorly differentiated carcinoma. Thirty-nine (53.42%) patients had lower-third esophageal cancer. Sixty (82.2%) patients had a smoking habit. Sixty-six (90.4%) patients had received induction chemoradiation therapy. Twenty (27.39%) patients had significant clinical tumor response. Using the criteria of the AJCC/UICC 8th edition, ten (13.7%) patients were pathological stage 0, four (5.47%) patients were pathological stage IA,

Table 1: Demographics of patients with squamous cell carcinoma of esophagus

	Relapse (<i>n</i> =26), <i>n</i> (%)	No relapse (<i>n</i> =47), <i>n</i> (%)	<i>P</i>
Gender			
Male	25 (96.15)	45 (95.74)	0.554
Female	1 (3.85)	2 (4.26)	
Differentiation			
Well	0	7 (14.89)	0.147
Moderate	12 (46.15)	24 (51.06)	
Poor	14 (29.79)	16 (34.04)	
Location			
Middle	16 (61.54)	18 (38.3)	0.058
Lower	10 (38.46)	29 (61.7)	
Induction CCRT			
Yes	24 (92.31)	42 (89.36)	0.687
No	2 (7.69)	5 (10.64)	
Smoking			
Yes	18 (69.23)	42 (89.36)	0.032 ^a
No	8 (30.77)	5 (10.64)	
LVSI			
Yes	4 (15.38)	3 (6.38)	0.216
No	22 (84.62)	44 (93.62)	
Perineural invasion			
Yes	4 (15.38)	3 (6.38)	0.216
No	22 (84.62)	44 (93.62)	
Extracapsular invasion			
Yes	4 (15.38)	5 (10.64)	0.561
No	22 (84.62)	42 (89.36)	
Drinking			
Yes	16 (61.54)	32 (68.09)	0.579
No	10 (38.46)	15 (31.91)	
Clinical tumor response			
Yes	18	2	0.070
No	0	32	
Tumor regression grade			
1	7 (26.92)	6 (12.77)	0.455
2	0	3 (6.38)	
3	9 (34.62)	21 (44.68)	
4	10 (38.46)	17 (36.17)	
Upstage (clinical)			
Yes	0	11 (23.4)	0.007 ^a
No	26 (100)	36 (76.6)	

Table 1: Contd...

	Relapse (<i>n</i> =26), <i>n</i> (%)	No relapse (<i>n</i> =47), <i>n</i> (%)	<i>P</i>
Upstage (pathologic)			
Yes	4 (15.38)	8 (17.02)	0.859
No	22 (84.62)	39 (82.98)	
Clinical stage (8 th)			
I	1 (3.85)	5 (10.64)	
II	9 (34.62)	14 (29.79)	
III	16 (61.54)	21 (44.68)	
IVA	0	7 (14.89)	
Pathologic stage (8 th)			
No residual tumor	9 (34.62)	11 (23.4)	
0	1 (3.85)	9 (19.15)	
1A	1 (3.85)	3 (6.38)	
1B	5 (19.23)	8 (17.02)	
2A	4 (15.38)	6 (12.77)	
2B	2 (7.69)	2 (4.26)	
3A	0	6 (12.77)	
3B	4 (15.38)	2 (4.26)	
Age (years)	55.38±4.74	57.85±8.6	0.181
BMI	22±12.85	22.17±3.53	0.395
Margin distance	3.24±1.86	3.7±1.82	0.307
Avg SUVmax of tumor (pre-CCRT)	12.06±6.71	12.58±6.46	0.748
Avg SUVmax of tumor (post-CCRT)	4.73±2.68	3.41±1.86	0.040 ^b
Delta Avg SUVmax of tumor	8.83±6.67	10.82±6.58	0.297
Anti-SCC (ng/mL)	1.98±1.40	1.69±1.29	0.404
Operations			
Thoracotomy + laparotomy	5 (19.23)	5 (10.64)	0.313
VATS + laparotomy	9 (34.62)	7 (14.89)	0.052
MIE	12 (46.15)	35 (74.47)	0.015 ^a
Dissected lymph nodes, <i>n</i> (%)			
Thoracotomy + laparotomy, 10 (13.7)	7.40±4.28	8.20±5.85	0.811
VATS + laparotomy, 16 (21.9)	8.44±5.92	6.86±2.80	0.525
MIE, 47 (64.4)	11.33±5.77	13.54±7.44	0.355

^aSignificance was assessed using Chi-square tests, ^bSignificance was assessed using Student's *t*-tests. SCC=Squamous cell carcinoma; CCRT=Concurrent chemoradiotherapy; LVSI=Lymphovascular space invasion; BMI=Body mass index; VPI=Visceral pleural invasion; FDG=Fluro-2-deoxy-D-glucose; Avg SUVmax=Average maximum standard uptake value of FDG; Anti-SCC=Anti-squamous cell carcinoma antigen; VATS=Video-assisted thoracoscopic surgery; MIE=Minimally invasive esophagectomy

13 (17.8%) patients were pathological stage IB, ten (13.69%) patients were pathological stage IIA, four (5.47%) patients were pathological stage IIB, six (8.21%) patients were

Contd...

pathological stage IIIA, and six (8.21%) patients were pathological stage IIIB. Forty-seven (64.38%) patients received MIE, 21.91% (16/73) patients received VATS and laparotomy, and 13.69% (10/73) of patients underwent an open thoracotomy and laparotomy for esophageal resection. The mean $\pm$ standard deviation and a median number of the total resected lymph node were 9.29 ± 5.34 , respectively.

Table 2 revealed the failure patterns in 73 patients who had a disease progression. With respect to the locoregional recurrences, the anastomosis is the major recurrent site (40%, 5/16). For distant metastasis, the lung is the major recurrent site (56.25%, 9/16). Overall tumor relapse arose in 26 (35.6%) patients, including 15 locoregional recurrences and 16 distant recurrences. Thirteen patients had both locoregional and distant recurrences.

In the univariable analysis [Table 3], smoking habit (heart rate [HR]: 0.268, $P = 0.038$), MIE (HR: 0.294, $P = 0.018$), and average SUVmax of a tumor (post-CCRT) (HR: 1.314, $P = 0.05$) were prognostic factors for disease relapse. In the multivariable analysis, the independent factors significantly associated with disease progression were clinical tumor response (HR: 67.54, $P = 0.044$), MIE (HR: 0.26, $P = 0.006$), tumor differentiation (HR: 11.16, $P = 0.042$), extracapsular invasion (HR: 35.93, $P = 0.049$), and average SUVmax of tumor (post-CCRT) (HR: 1.89, $P = 0.03$).

There are no statistical significances in clinical tumor response [$P = 0.069$, Figure 2], operation types [$P = 0.811$, Figure 3], and tumor differentiation [$P = 0.877$, Figure 4]. Overall survival was only significantly related to extracapsular invasion [$P = 0.043$, Figure 5].

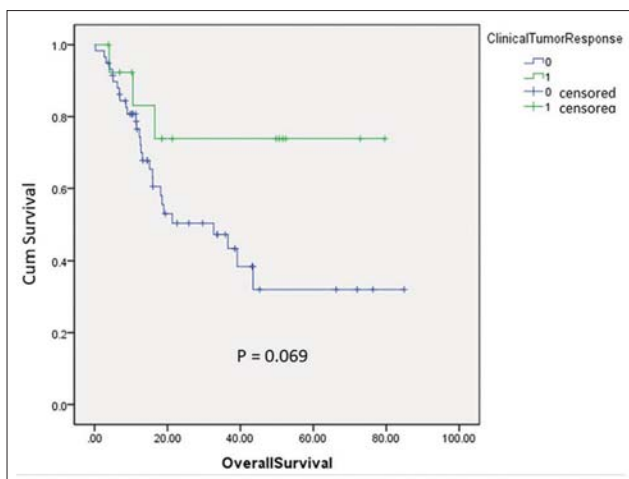


Figure 2: The correlation between clinical tumor response and overall survival. It was not statistically significant in clinical tumor response among overall survival ($P = 0.069$). However, there was a trend that patients with positive clinical tumor response had a better survival

DISCUSSIONS

Despite medical advances in the recent decades for the treatment of esophageal carcinoma, low survival rates, and high tumor relapse are still impressed. It is important to identify failure patterns and prognostic factors for esophageal cancer. In our study, upstage of the clinical stage, smoking, high average SUVmax of a tumor (post-CCRT), and procedure type (non-MIE) were the risk factors of disease relapse. However, the independent prognostic factors followed esophagectomy were positive clinical tumor response, MIE, well differentiation, extracapsular invasion, and low average SUVmax of a tumor (post-CCRT). Few articles addressed the 8th edition of the AJCC system for esophageal cancer.

Table 2: Failure patterns in 26 patients who had disease progression

	<i>n</i> (%)
Locoregional recurrence (10 patients)	
Anastomosis	6 (40)
Cervical lymph node	2 (13.33)
Mediastinal lymph node	9 (60)
Celiac lymph node	2 (13.33)
Distant metastasis (16 patients)	
Lung	9 (56.25)
Liver	2 (12.5)
Bone	4 (25)
Malignant pleural effusion	2 (12.5)
Distant lymph node	3 (18.75)
Brain	3 (18.75)
Kidney	1 (6.25)

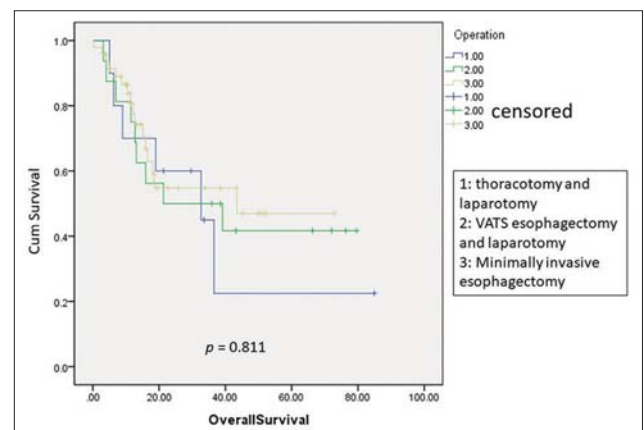


Figure 3: The correlation between operation types and overall survival. It was not statistically significant in operation types among overall survival ($P = 0.811$). There was a trend that patients with minimally invasive esophagectomy had a better overall survival

Table 3: Univariable and multivariable analysis to identify significant factors for disease progression of squamous cell carcinoma

	Univariable			Multivariable		
	HR	(95% CI)	P	HR	(95% CI)	P
Age	0.955	0.892-1.022	0.181			
cT	0.997	0.55-1.809	0.993			
cN	1.241	0.709-2.171	0.45			
pT	1.166	0.774-1.757	0.461			
pN	0.986	0.365-2.663	0.978	0.326	0.006-18.445	0.586
Upstage (pathologic)	0.886	0.239-3.282	0.857	0.129	0.002-8.909	0.343
Clinical tumor response	0.427	0.107-1.696	0.227	67.54	1.111-4104.3	0.044 ^b
Procedure types						
Thoracotomy + laparotomy	2	0.521-7.682	0.313			
VATS + laparotomy	3.025	0.968-9.451	0.057			
MIE	0.294	0.107-0.809	0.018 ^a	0.26	0.002-0.341	0.006 ^b
Resected lymph node number (≥ 15 vs. < 15)	0.508	0.16-1.608	0.249			
Tumor differentiation (well/moderate vs. poor)	2.059	0.777-5.452	0.146	11.16	1.086-113.77	0.042
Tumor location (middle vs. lower)	0.388	0.145-1.039	0.06	0.34	0.052-2.221	0.26
TRG (+ vs. -)	1.103	0.41-2.966	0.846	1.001	0.397-2.522	0.999
Smoking (+ vs. -)	0.268	0.077-0.931	0.038 ^a	0.292	0.019-4.411	0.374
Alcohol drinking (+ vs. -)	1.333	0.49-3.625	0.573			
LVSI (+ vs. -)	2.667	0.548-12.97	0.224			
Perineural invasion (+ vs. -)	2.667	0.548-12.97	0.224	3.536	0.213-58.601	0.378
Extracapsular invasion (+ vs. -)	1.527	0.372-6.27	0.557	35.93	1.016-1270.2	0.049 ^b
Avg SUVmax of tumor (pre-CCRT)	0.987	0.916-1.065	0.744			
Avg SUVmax of tumor (post-CCRT)	1.314	0.991-1.742	0.05 ^a	1.89	1.063-3.36	0.03 ^b
Delta avg SUVmax of tumor	0.952	0.869-1.044	0.295			
Anti-SCC (ng/mL)	1.177	0.804-1.725	0.402			

^aSignificance was assessed using Chi-square tests, ^bSignificance was assessed using Student's *t*-tests. VATS=Video-assisted thoracoscopic surgery; MIE=Minimally invasive esophagectomy; TRG=Tumor regression grade; LVSI=Lymphovascular space invasion; CCRT=Concurrent chemoradiotherapy; Avg SUVmax=Average maximum standard uptake value of FDG; Anti-SCC=Anti-squamous cell carcinoma antigen; FDG=Fluoro-2-deoxy-D-glucose; CI=Confidence interval; HR=Hazard ratio

In the 8th edition for esophageal SCC, there is significant rearrangement, renaming, and no net change in the number of stage subgroups.¹⁵ Clinical stage 4 is restricted to M1 disease while applying the AJCC 7th edition. However, clinical stage 4 is restricted to T4N0-2 disease in the AJCC 8th edition. Upstage after applying clinical AJCC 8th edition is the risk factor for disease relapse, which can explain more correctly the poor prognosis and high recurrence in this group.

Kataki *et al.*¹⁶ performed a retrospective study of electronically recorded data of the Hospital Cancer Registry for the period of May 2014 to December 2014 for the upper aerodigestive tract (UADT) cancers. Tobacco habits were more prevalent in males (67.3%–94.3%) compared to females (5.7%–32.7%). There was a higher risk in males in most of UADT cancers associated with tobacco use ($P < 0.05$),

which is consistent with the high prevalence of tobacco use among males, and smoking is also a risk factor for disease relapse in our study cohort.

Esophagectomy with extended lymph node dissection is the foremost treatment for locally advanced esophageal cancer^{17,18} and is one of the most invasive gastrointestinal surgeries.¹⁹⁻²¹ Postoperative complications and an excessive inflammatory response are known unfavorable prognostic factors in patients with esophageal cancer.^{5,8,9} Therefore, less invasive surgical procedures are highly desirable, both to attenuate surgical stress and to improve long-term outcomes. Recently, MIE, which consists of thoracoscopic and laparoscopic approaches, is increasingly performed for esophageal cancer as a less invasive procedure.^{22,23} Yamashita *et al.* conducted a retrospectively study from 551 patients who underwent

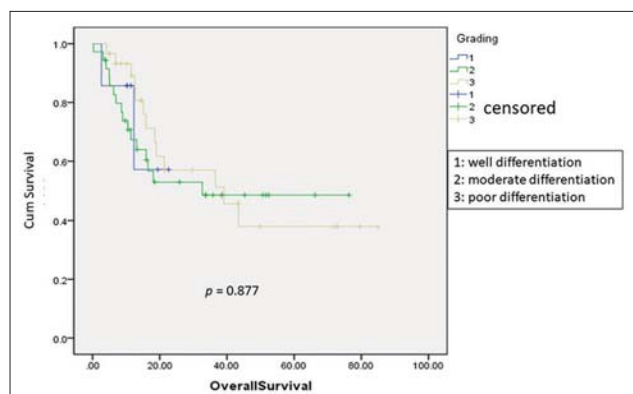


Figure 4: The correlation between tumor differentiation and overall survival. It was not statistically significant in tumor-differentiated grading among overall survival ($P = 0.877$). There was a trend that patients with good differentiation had a better overall survival

curative esophagectomy for esophageal cancer from 2005 to 2014. The patterns of recurrence were compared between MIE and open esophagectomy (OE). Although the rates of distant lymph node, distant organ, disseminated, and local recurrences were similar between the two groups, the MIE group had a lower rate of regional lymph node recurrence than the OE group (5.0 vs. 14.0%).²³ In our study, MIE is a preferable prognosis factor for disease relapse. Although whether MIE confers a prognostic advantage in patients with esophageal SCC remains unclear, the artificial pneumothorax and magnified view could improve the quality of mediastinal lymph node dissection.

PET-CT provides additional information on the pathophysiological and biological characteristics of tumor.^{24,25} In the systematic review and meta-analysis by Goense *et al.*, the sensitivity of PET-CT ranged between 89% and 100%, and the specificity ranged between 55% and 94% for the detection of recurrent esophageal carcinoma.²⁶ Tamand *et al.* identified 71 patients with unresectable or metastatic esophageal carcinoma who had PET/CT prior to palliative treatment. SCC patients had higher SUVmax and SUVmean compared to patients with adenocarcinoma of the esophagus.²⁷ Goense *et al.*²⁶ reported that local failure in SCC patients most commonly occurred in high FDG uptake regions after CCRT. Our study also showed high FDG uptake regions, postinduction CCRT was the independently poor prognostic factor for disease relapse. Knight *et al.* mentioned poor or no response to chemotherapy was also an independent risk factor for isolated systemic recurrence.²⁸ In our study, multivariable analysis showed clinical tumor response is a prognostic factor for disease progression. The present study has several limitations. This is a single-center study which lacks the external validity, and the sample size

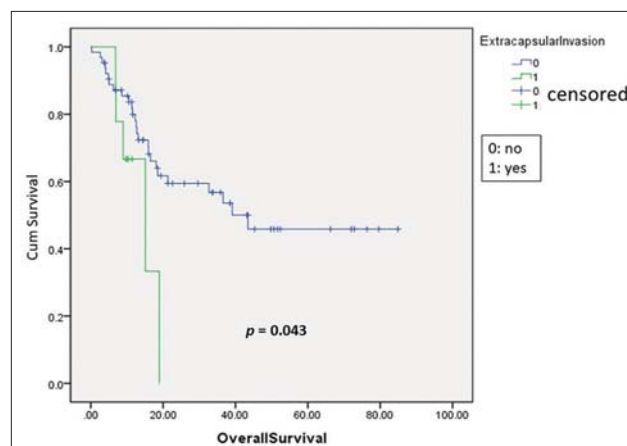


Figure 5: The correlation between extracapsular invasion and overall survival. It was statistically significant in extracapsular invasion among overall survival ($P = 0.043$). Patients without extracapsular invasion had a better overall survival

was relatively small which may lead to a large variation in the univariable and multivariable analysis compared to previous studies.

CONCLUSIONS

Based on our study, we revealed that anastomosis was the most common site for local recurrence, and the lung was the most common distal recurrent organ. High average SUVmax of a tumor (post-CCRT), no clinical tumor response, poor differentiation of tumor, and extracapsular invasion were independent risk factors for disease relapse. Our findings put forward the patterns of metastasis in esophageal cancer, which could help clinicians to identify patients with metastasis in close surveillance and deliver proper treatment.

Acknowledgments

This research was supported by the Cancer Registry Group, Tri-Service General Hospital.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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