Original Article

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Risk factors for postoperative recurrence of pT2-3N0M0 esophageal squamous cell carcinoma and patterns of its recurrence

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SUMMARY This study aimed to explore the patterns of postoperative recurrence in patients with pT2-3N0M0 esophageal squamous cell carcinoma (ESCC) and to identify the risk factors for the recurrence. Patients with pT2-3N0M0 ESCC who were treated at our hospital from January 2010 to August 2019 were divided into three categories: those with anastomotic recurrence, those with lymph node recurrence, and those with hematogenous metastasis. The sites of initial recurrence and metastasis were counted and potential risk factors were analyzed using univariate and multivariate Cox proportional hazard regression. Four hundred and eighty-five patients with pT2-3N0M0 ESCC were ultimately included, 176 (36.29%) of whom experienced tumor recurrence or metastasis. Cox multivariate analysis revealed that the postoperative T-stage, procedure, tumor location, and degree of differentiation were independent risk factors for postoperative recurrence ($P < 0.05$). The median time of recurrence was 38 months, and the most common site of recurrence was the lymph nodes in 126 patients (71.59%), followed by hematogenous metastasis in 73 patients (41.47%), and anastomotic recurrence in 21 patients (11.93%). 119 patients (67.61%) experienced recurrence within 36 months, with a probability of recurrence of 84.09% within 5 years, and recurrence remained relatively unchanged after 5 years. The proportion of postoperative lymph node recurrence and hematogenous metastasis in patients with pT3N0M0 ESCC was significantly higher than that in patients with pT2N0M0 ESCC ($P < 0.05$). At higher tumor locations in the body, the proportion of lymph node recurrence increased ($P < 0.05$). In conclusion, postoperative T-stage, procedure, tumor location, and degree of differentiation were independent risk factors for postoperative recurrence in pT2-3N0M0 ESCC, with regional lymph node recurrence being the most common pattern, emphasizing the importance of regional lymph nodes in this context.

Keywords pT2-3N0M0 esophageal squamous cell carcinoma (ESCC), postoperative recurrence, risk factor, regional lymph node

1. Introduction

Esophageal cancer (EC) is a common malignant tumor of the digestive system in China. Fifty percent of patients have confirmed EC each year, and more than 90% of EC is squamous cell carcinoma, which has been a major public health problem (*1*). Radical resection combined with systemic lymph node dissection was the standard treatment for ESCC, and regional recurrence and distant metastasis were largely responsible for postoperative treatment failure (*2*). A study has reported that positive lymph nodes were the key factor affecting postoperative recurrence and survival status in patients with ESCC, but patients with ESCC and negative lymph nodes also exhibited a high probability of postoperative recurrence (approximately 30%) (*3*). Therefore, the indicators that may affect postoperative recurrence and prognosis in patients with ESCC and negative lymph nodes, and pT2-3N0M0 in particular, need to be studied further.

Currently, studies on risk factors for recurrence in patients with ESCC and negative lymph nodes after radical esophagectomy are conflicting. Several studies have found that the prognosis for patients with ESCC with negative lymph nodes was influenced by the T-stage and the degree of tumor histological differentiation (*4,5*). A crucial task has been to determine the risk factors for postoperative recurrence of EC. Patients with high-risk factors need to be screened for recurrence, postoperative adjuvant treatment needs to be actively provided, and regular monitoring needs to be enhanced.

To investigate the risk factors affecting postoperative recurrence of pT2-3N0M0 ESCC, we conducted a

study at the First Affiliated Hospital of Anhui Medical University. We analyzed demographic and pathological data from patients with pT2-3N0M0 ESCC who underwent radical surgery. This study also analyzed the patterns of postoperative recurrence in order to provide a reference for postoperative monitoring and treatment of patients with ESCC.

2. Patients and Methods

2.1. Patient selection

Information on patients who underwent radical surgery at this Hospital from January 2010 to December 2020 was screened. To allow for a sufficient frequency of follow-up, we ultimately included 485 patients with pT2-3N0M0 ESCC and summarized all patient data. All patients provided informed consent at the time of surgery, including consent to publish and report their data.

The inclusion criteria were as follows: 1) Received radical surgery (R0 resection); 2) The postoperative pathological diagnosis was squamous cell carcinoma; 3) The postoperative pathological staging was pT2-3N0M0 (according to the 8th edition of the AJCC TNM staging system); 4) Having complete postoperative pathological data; 5) Did not undergo any anti-tumor treatment before surgery, including chemotherapy, radiotherapy, immunotherapy, tumor intervention therapy, or laser therapy; and 6) Information on recurrence is available.

The exclusion criteria were as follows: 1) Age under 18 and over 85; 2) Lack of complete postoperative clinical and pathological data; 3) Lack of specific information on postoperative recurrence; 4) Have a history of malignant tumors in the past, or have been found to have primary malignant tumors in other locations during follow-up; 5) Cervical esophageal cancer or gastroesophageal junction tumor; and 6) Progression-free survival (PFS) of less than 3 months.

2.2. Diagnosis of recurrence

The diagnostic criteria for lymph node recurrence included: 1) Enhanced computed tomography (CT) or magnetic resonance (MR) imaging indicating a short axis of ≥ 10 mm or the presence of ≥ 3 affected lymph nodes in the same area, or necrosis or capsule invasion of lymph nodes; 2) Affected lymph nodes found in the tracheoesophageal sulcus, regardless of size, accompanied by hoarseness or vocal cord paralysis; 3) Dynamic imaging revealed changes in lymph nodes, such as a significant increase in lymph node volume, number, or the appearance of new lymph nodes; 4) There is a clear diagnosis of cancer metastasis based on puncture cytology or pathological biopsy; 5) Positron emission tomography (PET) revealed a standardized uptake value (SUV) of ≥ 2.4.

Diagnosis criteria for anastomotic recurrence: 1) Clear diagnosis based on gastroscopy and pathology; 2) Results of PET were positive and indicative of recurrence based on the patient's symptoms.

Hematological metastasis occurred in the lungs, liver, bone, and other areas, mainly due to new lesions discovered through imaging studies, such as CT, ultrasound, MR, or PET.

We only counted the sites that were first identified as recurrence or metastasis. If there were 2 or more sites with recurrence or metastasis and the interval was within 1 month, those were all recorded. If different sites of recurrence or metastasis were found in an interval longer than 1 month, only the first recurrence or metastasis was recorded.

2.3. Regional lymph nodes

Based on the Japan Esophagus Society (JES) standard lymph node anatomy and the range of lymph node drainage areas in the abdominal cavity of patients with gastric cancer, the sites where lymph node recurrence first occurred were statistically classified as cervical lymph node area recurrence, mediastinal lymph node area recurrence, or abdominal lymph node area recurrence (*6,7*).

The specific scope was as follows: 1) Neck lymph nodes: 100-104 groups of lymph nodes; 2) Mediastinal lymph nodes: Uniformly including the upper, middle, and lower mediastinal lymph nodes, this is a group of 105-112 lymph nodes; 3) Abdominal lymph nodes: 1-16 groups of lymph nodes.

2.4. Follow-up

All patients were followed up immediately after surgery, and the deadline was December 2021. The follow-up methodology mainly involved retrieving information from the outpatient or inpatient system. Several patients were contacted by telephone to obtain more detailed and accurate information on diagnosis, treatment, and recurrence. The frequency of follow-up was once every 2-4 months within 2 years after surgery, once every 6 months within 2-5 years after surgery, and once every 1 year after 5 years after surgery. The postoperative follow-up included an esophageal barium swallow or radioactive iodine uptake study, imaging studies of the neck, chest, and abdomen, and CT and MR. Ultrasound of the neck or abdomen could also be performed. If abnormalities were found, further examination was required. Based on the patient's specific circumstances and symptoms, a bone scan, PET, gastroscopy, endoscopic ultrasound, puncture cytology, or biopsy pathology examination could be performed as necessary to assist in diagnosis.

2.5. Statistical analysis

The software IBM SPSS Statistics (version 27.0;

IBM Crop, Armonk, NY, USA) and R Foundation for Statistical Computing, Vienna, Australia (version 4.2.2) were used for statistical analysis. Counts used a chi square test or Fisher's exact probability test. The relevant pathological factors that affect postoperative recurrence were first analyzed using univariate and multivariate Cox regression. Disease-free survival (DFS) was defined as the period from the date of esophageal cancer surgery to the date of tumor recurrence or death at any location, or until the last follow-up date. Overall survival (OS) was defined as the time from when radical surgery for esophageal cancer was undergone to the time of death or last follow-up for any reason. All time events were estimated using Kaplan-Meier analysis and were compared using the log-rank test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of patients

We ultimately enrolled 485 patients with pT2-3N0M0 ESCC, and measured 13 relevant variables, including patient age, sex, T-stage, procedure, the degree of differentiation, the location of the primary tumor, the diameter (long and short axes) of the tumor, the number of lymph nodes dissected, postoperative adjuvant treatment, vessel invasion, perineural invasion, and carcinoma nodules. Up to the last follow-up, 309 of 485 patients with ESCC (63.71%) did not experience tumor recurrence or metastasis, while 176 patients (36.29%) experienced tumor recurrence or metastasis. The median time of recurrence was 38 months (ranging from 3 to 141 months), and 119 patients (67.61%) experienced recurrence within 36 months.

Considering the patient's recurrence status, patients were divided into two groups and a statistical analysis of the included factors was performed. Except for the procedure, T-stage, location of the esophageal tumor, degree of differentiation, and postoperative adjuvant treatment plan, there were no significant differences in the research factors between the groups ($P < 0.05$). The baseline data of all patients are shown in Table 1.

Until the last follow-up, the median duration of follow-up was 56 months (range: 3-144 months). Of the 485 enrolled patients, 286 survived, 199 experienced tumor recurrence or death. The median OS of all patients was 57 months (range 5-141 months), and the median OS of patients in the recurrence group was 49 months (range 5-140 months). The survival curves of the two groups are shown in Figure 1.

3.2. Cox regression analysis

Cox univariate analysis indicated that the T-stage, procedure, the degree of differentiation, tumor diameter, and postoperative adjuvant treatment were risk factors for postoperative recurrence ($P < 0.05$), while other factors did not impact recurrence significantly.

Multivariate Cox analysis revealed that the T-stage, procedure, tumor location, and degree of differentiation were independent risk factors for postoperative recurrence ($P < 0.05$). As can be seen in Table 2, the risk of postoperative recurrence in patients with pT3N0M0 ESCC was significantly higher than in patients with pT2N0M0 ESCCs (HR = 5.21, 95% CI 2.70-7.33, $P < 0.01$). In terms of procedure selection, the risk of postoperative recurrence caused by open esophagectomy (OE) was 1.48 times higher than that of minimally invasive esophagectomy (MIE) (HR = 1.48, 95% CI 1.07-2.03, $P = 0.02$), and the combination of MIE and OE did not impact postoperative recurrence. Compared to ESCC in the upper thoracic region, the risk of recurrence in the middle and lower thoracic regions decreased by 42% ($P = 0.03$) and 54% ($P = 0.01$), respectively. Compared to poorly differentiated ESCC, the risk of recurrence decreased by 46% ($P = 0.04$).

3.3. Patterns of postoperative recurrence

The results of this study depict that the time of recurrence ranged from 3 months to 141 months (median time of recurrence: 24 months), and 176 patients with pT2-3N0M0 ESCC experienced recurrence or metastasis. The rate of recurrence was 36.29%. There were 126 patients with lymph node recurrence (71.59%), 73 with hematogenous metastasis (41.47%), and 21 with anastomotic recurrence (11.93%). Several patients also experienced concurrent recurrence and metastasis. The majority of patients experienced recurrence within 3 years (67.61%), with a probability of recurrence of 84.09% within 5 years. After that, recurrence was basically unchanged.

Among lymph node recurrence, mediastinal lymph nodes were most often affected (13.20%), followed by the cervical lymph nodes (10.31%) and abdominal lymph nodes (5.98%). In hematogenous metastases, lung metastasis was the most common (5.36%), followed by bone metastasis (4.54%), liver metastasis (3.51%), and other metastases such as brain metastasis, pleural metastasis, and malignant serous effusion (3.92%). Some patients also experienced multiple organ metastases at the same time. The specific distribution is detailed in Table 3 and Figure 2.

3.4. Analysis of recurrence patterns

Multivariate analysis shows that both the T-stage and tumor location were independent risk factors for PFS. The two indicators' impact on OS was further analyzed. Results indicated that the T-stage was a high-risk factor affecting OS ($P < 0.01$), while the location of tumor did not impact OS significantly (Figure 3).

As shown in Table 4, compared to patients with

Table 1. Baseline characteristics of included patients

Characteristics	Total (n = 485)	Group with recurrence (n = 176)	Group without recurrence (n = 309)	P value
Sex				0.23
Male	367 (75.67%)	139 (78.98%)	228 (73.79%)	
Female	118 (24.33%)	37 (21.02%)	81 (26.21%)	
Age				0.72
≤ 55 years	66 (13.61%)	21 (11.93%)	45 (14.56%)	
56-66 years	248 (51.13%)	92 (52.27%)	156 (50.49%)	
> 66 years	171 (35.26%)	63 (35.80%)	108 (34.95%)	
T-stage				< 0.01
T2N0	386 (75.59%)	98 (55.68%)	288 (93.20%)	
T3N0	99 (20.41%)	78 (44.32%)	21 (6.8%)	
Procedures				0.04
MIE	240 (49.48%)	76 (43.18%)	164 (53.07%)	
OE	198 (40.82%)	85 (48.30%)	113 (36.57%)	
MIE and OE	47 (9.69%)	15 (8.25%)	32 (10.36%)	
Location				0.01
Upper thoracic region	40 (8.25%)	20 (11.36%)	20 (6.47%)	
Middle thoracic region	326 (67.22%)	125 (71.02%)	201 (65.05%)	
Lower thoracic region	119 (24.54%)	31 (17.61%)	88 (28.48%)	
Differentiation				0.04
Poorly differentiated	106 (21.86%)	43 (24.43%)	63 (20.39%)	
Moderately differentiated	326 (67.22%)	122 (69.32%)	204 (66.02%)	
Well-differentiated	53 (10.93%)	11 (6.25%)	42 (13.59%)	
Tumor diameter (long axis)				0.05
≤ 3 cm	234 (48.25%)	74 (42.05%)	160 (51.78%)	
> 3 cm	251 (51.75%)	102 (57.95%)	149 (48.22%)	
Tumor diameter (short axis)				0.89
≤ 3 cm	417 (85.98%)	152 (86.36%)	265 (85.76%)	
> 3 cm	68 (14.02%)	24 (13.64%)	44 (14.24%)	
Vessel invasion				0.19
Yes	33 (6.80%)	8 (4.55%)	25 (8.09%)	
No	452 (93.20%)	168 (95.45%)	284 (91.19%)	
Perineural invasion				0.33
Yes	19 (3.92%)	9 (5.11%)	10 (3.24%)	
No	466 (96.08%)	167 (94.89%)	299 (96.76%)	
Carcinoma nodules				0.90
Yes	16 (3.30%)	6 (3.41%)	10 (3.24%)	
No	468 (96.49%)	169 (96.02%)	299 (96.76%)	
Resected lymph nodes				0.29
< 15	325 (67.01%)	112 (63.64%)	213 (68.93%)	
≥ 15	160 (32.99%)	64 (36.36%)	96 (31.07%)	
Postoperative treatment				< 0.01
Surgery only	268 (55.26%)	80 (45.45%)	188 (60.84%)	
Radiotherapy	49 (10.10%)	18 (10.23%)	31 (10.03%)	
Chemotherapy	137 (28.25%)	69 (39.20%)	68 (22.01%)	
Radiochemotherapy	31 (6.39%)	9 (5.11%)	22 (7.12%)	

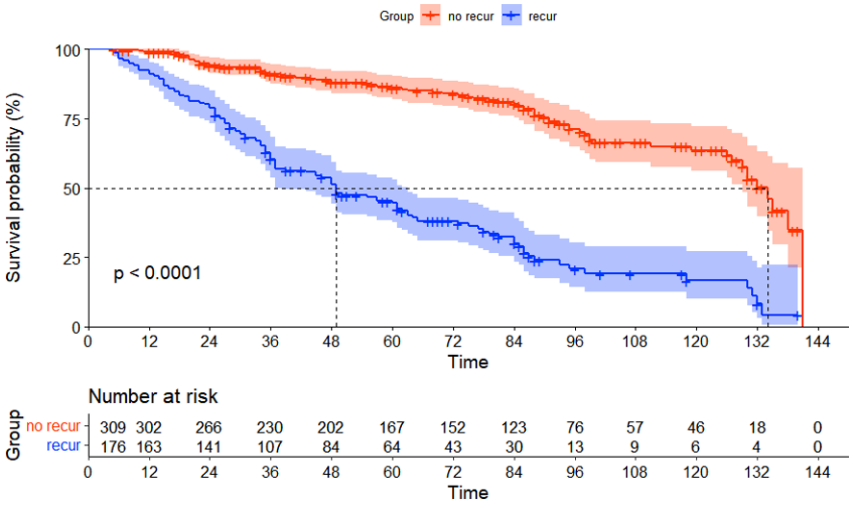

Figure 1. OS curves for patients in the group with recurrence and the group without recurrence.

Table 2. Univariate and multivariate Cox analysis of variables affecting the postoperative recurrence of pT2-3N0M0 ESCC

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Sex						
Male	1.00					
Female	0.79	0.55-1.13	0.20			
Age						
≤ 55 years	1.00					
56-66 years	1.13	0.70-1.82	0.61			
> 66 years	1.33	0.81-2.19	0.26			
T-stage						
T2N0	1.00			1.00		
T3N0	5.88	4.30-8.03	< 0.01	5.21	2.70-7.33	< 0.01
Procedures						
MIE	1.00			1.00		
OE	1.49	1.09-2.03	0.01	1.48	1.07-2.03	0.02
MIE and OE	0.96	0.55-1.67	0.88	1.15	0.66-2.07	0.63
Location						
Upper thoracic region	1.00			1.00		
Middle thoracic region	0.69	0.43-1.12	0.13	0.58	0.35-0.95	0.03
Lower thoracic region	0.45	0.26-0.79	< 0.01	0.46	0.25-0.83	0.01
Differentiation						
Poorly differentiated	1.00			1.00		
Moderately differentiated	0.94	0.66-1.33	0.71	0.86	0.61-1.24	0.43
Well-differentiated	0.44	0.22-0.86	0.02	0.54	0.27-1.07	0.04
Tumor diameter (long axis)						
≤ 3 cm	1.00			1.00		
> 3 cm	1.35	1.00-1.82	0.04	1.12	0.82-1.54	0.47
Tumor diameter (short axis)						
≤ 3 cm	1.00					
> 3 cm	1.07	0.69-1.64	0.78			
Vessel invasion						
Yes	1.00					
No	0.62	0.31-1.274	0.19			
Perineural invasion						
Yes	1.00					
No	0.83	0.68-1.61	0.40			
Carcinoma nodules						
Yes	1.00					
No	0.90	0.44-2.24	0.98			
Resected lymph nodes						
< 15	1.00					
≥ 15	0.98	0.68-1.41	0.91			
Postoperative treatment						
Surgery only	1.00			1.00		
Radiotherapy	1.96	1.42-2.71	0.01	1.31	0.93-1.84	0.12
Chemotherapy	1.31	0.78-2.18	0.30	1.03	0.60-1.76	0.91
Radiochemotherapy	1.09	0.54-2.16	0.82	0.85	0.42-1.72	0.65

T2 ESCC, the rate of recurrence in patients with T3 ESCC was significantly high ($P < 0.01$). In terms of hematogenous metastasis, the total probability of postoperative hematogenous metastasis in T3 ESCC was higher than that in T2 ESCC. Patients with ESCC in the T3 stage exhibited a higher proportion of bone metastasis and other metastasis, but there were no significant differences in the proportion of liver metastasis and lung metastasis. The probability of anastomotic recurrence in ESCC in the T3 stage was slightly higher than that in the T2 stage, but the difference was not statistically significant ($P = 0.05$).

Similarly, the patterns of recurrence were analyzed at different locations (Table 5). The results indicated that the proportion of mediastinal lymph node recurrence varied depending on the location of the tumor. As the location moved up, the proportion of lymph node recurrence increased ($P < 0.05$). However, there were no statistical differences in different regional lymph nodes. Pulmonary and bone metastases were the most common types of hematogenous metastasis, but statistical analysis revealed that there were no significant differences in the proportion of hematogenous metastasis and anastomotic recurrence after surgery in different locations ($P < 0.05$).

4. Discussion

The current study found that the postoperative T-stage, procedure, location, and degree of differentiation were

independent risk factors for postoperative recurrence in patients with pT2-3N0M0 ESCC. The T-stage was an important basis for defining pathological staging of EC, revealing the depth of longitudinal infiltration of the tumor. Multiple studies have shown that the T-stage was a risk factor for postoperative recurrence and poor prognosis of ESCC (*4,8*). The current study indicated that patients with pT3N0M0 ESCC had a significantly higher rate of recurrence than patients with pT2N0M0 ESCC, which was consistent with other studies. Considering the continued advancement of endoscopic surgery technology, MIE surgery had gradually become more accepted, but OE surgery was still the main procedure. There is continuous debate about the clinical safety and effectiveness of the two surgeries, as their pros and cons are still not entirely clear (*9*). Some studies have shown that MIE was able to clear a wider range of lymph nodes than OE and was safer. Postoperative pulmonary complications and perioperative mortality rates were also lower (*10,11*), which is supported by the current study.

Table 3. Number and proportion of patients with different forms of recurrence

Recurrence	Patients.	Proportion
Anastomotic recurrence	21	4.33%
Lymph node recurrence	126	25.98%
Cervical lymph nodes	50	10.31%
Mediastinal lymph nodes	64	13.20%
Abdominal lymph nodes	29	5.98%
Hematogenous metastases	73	15.05%
Liver metastasis	17	3.51%
Lung metastasis	26	5.36%
Bone metastasis	22	4.54%
Other metastases	19	3.92%
Lymph node recurrence and anastomotic recurrence	10	2.06%
Lymph node recurrence and hematogenous metastases	41	8.45%
Anastomotic recurrence and hematogenous metastases	5	1.03%
Anastomotic recurrence, hematogenous metastases, and lymph node recurrence	4	0.82%

A study has reported that the further down the legion is located, the greater the incidence of postoperative lymph node recurrence and hematogenous metastasis (*12*). The results of this study indicate that, compared to the upper thoracic region, the prognosis for a tumor in the upper thoracic region decreased by 42% and 54% ($P < 0.05$) in the middle and lower thoracic regions. Complete resection of a tumor located in the upper thoracic region is more difficult to achieve due to the limitations of the complex anatomical structure of the neck. Other studies have pointed out the difficulty of thoroughly clearing lymph nodes during surgery in patients with upper thoracic ESCC due to postoperative complications such as aspiration, chylothorax, and recurrent laryngeal nerve injury caused by neck lymph node dissection (*13,14*). The poorer the degree of differentiation, the higher the risk of postoperative recurrence or metastasis (*15,16*). In this study, postoperative pathology revealed a lower risk of recurrence in well-differentiated than poorly differentiated ESCC (HR = 0.54, $P < .05$), while there was no significant difference in moderately differentiated ESCC.

Vessel invasion was a histopathological feature associated with invasiveness and was closely associated with the increased risk of tumor metastasis. A study (*17*) found that in patients with negative lymph nodes, vessel invasion and the T-stage were independent predictors for survival and DFS ($P < 0.001$), but it was not the same for patients with positive lymph nodes. Carcinoma nodules are often reported in gastrointestinal cancer, and especially in colorectal cancer or gastric cancer, and they are believed to be closely related to prognosis (*18*). There are few studies on cancer nodules in EC. The current study indicated that the aforementioned factors did not impact recurrence in patients with pT2-3N0M0 ESCC ($P < 0.05$). Given the sample size of patients with pT3N0M0 ESCC was relatively small in this study, further confirmation in a larger sample is still required in the future.

The current results revealed that age, sex, the tumor diameter, and the number of lymph nodes dissected

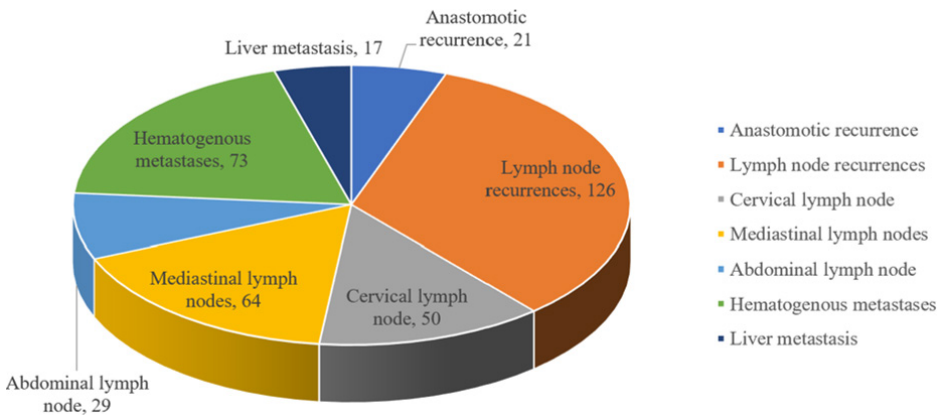

Figure 2. Pie chart of the distribution of different types of recurrence.

Table 4. Distribution of the postoperative recurrence of ESCC in different T-stages

Recurrence	Total (n = 485)	T2 stage (n = 386)	T3 stage (n = 99)	P value
Lymph node recurrence	126 (25.98%)	69 (17.88%)	57 (57.58%)	< 0.01
Cervical lymph nodes	50 (10.31%)	25 (6.48%)	25 (25.25%)	< 0.01
Mediastinal lymph nodes	64 (13.20%)	36 (9.33%)	28 (28.28%)	< 0.01
Abdominal lymph nodes	29 (5.98%)	18 (4.66%)	11 (11.11%)	0.03
Hematogenous metastases	73 (15.05%)	44 (11.40%)	29 (29.29%)	< 0.01
Liver metastasis	17 (3.51%)	12 (3.11%)	5 (5.05%)	0.36
Lung metastasis	26 (5.36%)	19 (4.92%)	7 (7.07%)	0.45
Bone metastasis	22 (4.54%)	11 (2.85%)	11 (11.11%)	< 0.01
Other metastases	19 (3.92%)	10 (2.59%)	9 (9.09%)	0.01
Anastomotic recurrence	21 (4.33%)	13 (3.37%)	8 (8.08%)	0.05

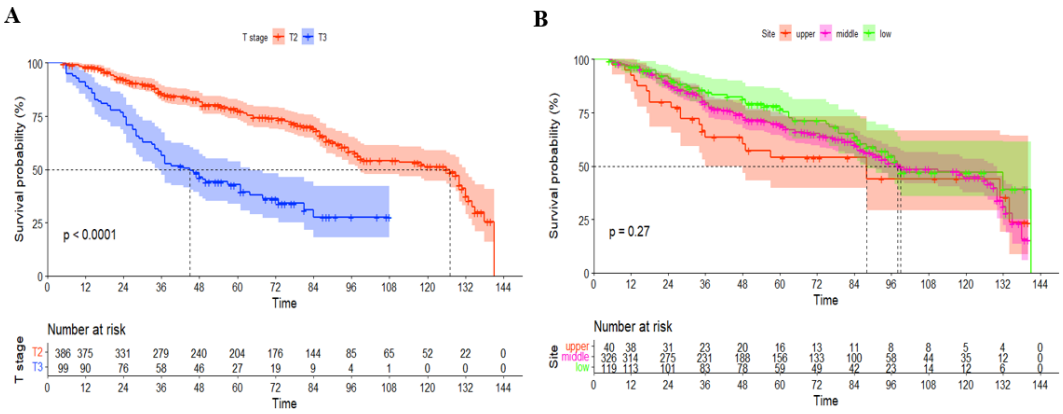

Figure 3. Kaplan-Meier curves for independent risk factors affecting OS. A, T-stage; **B**, Site.

Table 5. Distribution of the postoperative recurrence of ESCC in different locations

Recurrence	Upper thoracic region (n = 40)	Middle thoracic region (n = 326)	Lower thoracic region (n = 119)	P value
Lymph node recurrence	15 (37.50%)	89 (27.30%)	22 (18.49%)	0.04
Cervical lymph nodes	6 (15.00%)	33 (10.12%)	11 (9.24%)	0.57
Mediastinal lymph nodes	8 (20.00%)	46 (14.11%)	10 (8.40%)	0.12
Abdominal lymph nodes	3 (7.50%)	18 (5.52%)	8 (6.72%)	0.82
Hematogenous metastases	6 (15.00%)	52 (15.95%)	15 (12.61%)	0.68
Liver metastasis	1 (2.50%)	11 (3.37%)	5 (4.20%)	0.86
Lung metastasis	3 (7.50%)	17 (5.21%)	6 (5.04%)	0.82
Bone metastasis	2 (5.00%)	16 (4.91%)	4 (3.36%)	0.78
Other metastases	1 (2.50%)	15 (4.60%)	3 (2.52%)	0.54
Anastomotic recurrence	3 (7.50%)	15 (4.60%)	3 (2.52%)	0.34

were not risk factors for postoperative recurrence of pT2-3N0M0 ESCC. These findings differed with the results of previous studies (*19,20*). This may be due to the high heterogeneity of patients enrolled from different hospitals, thus resulting in inconsistent results. Previous studies have reported that EC postoperative adjuvant therapy, as a necessary treatment to prevent local recurrence and improve prognosis, was especially recommended for stage III-IV ESCC or patients with positive lymph nodes (*21*). According to the NCCN guidelines, providing postoperative adjuvant treatment is not recommended for patients with pT2-3N0M0 ESCC. However, clinicians may choose to provide postoperative adjuvant treatment based on the individual characteristics of patients. A study has shown that, compared to simple surgery during the same period, postoperative adjuvant radiotherapy reduced the rate of metastasis and local recurrence of pT3N0M0 ESCC (P = 0.001) and improved 5-year DFS and OS (*22*). In the current study, some patients received adjuvant treatment after surgery. Univariate analysis indicated that postoperative adjuvant chemotherapy reduced the risk of postoperative recurrence, but such impact did not reach statistical significance in multivariate analysis, which perhaps was due to the small sample size.

This study has several strengths. First, this study explored the pattern of postoperative recurrence in patients with pT2-3N0M0 ESCC and identified the risk factors for the recurrence as previous studies have reported mixed results in this field. Second, a prospective cohort study design was used as it is the strongest research design in observational studies. Finally, patients

enrolled in this study were relatively homogeneous because they were from the same hospital.

However, this study also has some limitations. First, this is a single center study, with limited generalizability. Second, comprehensive and systematic evaluation of factors that affect recurrence or metastasis in patients with pT2-3N0M0 ESCC was difficult as only a small set of risk factors were considered in this study. In a future study, imaging parameters and highly sensitive and specific biomarkers will be linked to further explore the risk factors for postoperative recurrence in EC, which may provide practical diagnostic and treatment strategies for patients with pT2-3N0M0 ESCC.

In conclusion, the current results indicated that the postoperative T-stage, procedure, tumor location, and degree of differentiation were independent risk factors affecting postoperative recurrence in patients with pT2-3N0M0 ESCC. Results also revealed that regional lymph node recurrence was the most common recurrence in EC patients, which often occurred within 3 years. These results indicate that the clinical monitoring of EC patients with the high-risk factors mentioned above, and especially those involving regional lymph nodes, should be enhanced.

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