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Clinical Research

The Prognostic Value of Oligo-Recurrence Following Esophagectomy for Esophageal Cancer

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Background: The concept of oligo-recurrence has not been generally applied in esophageal cancer. This study aimed to determine the prognostic significance of the number of recurrences in esophageal cancer.
Methods: Patients with squamous cell carcinoma who underwent curative esophagectomy with R0 or R1 resection and who experienced a confirmed recurrence were included. The study included 321 eligible participants from March 2001 to December 2019. The relationship between the number of recurrences and post-recurrence survival was investigated.
Results: The mean age was 63.8±8.1 years, and the majority of the participants (97.5%) were men. The median time to recurrence was 10.7 months, and the median survival time after recurrence was 8.8 months. Multiple recurrences with simultaneous local, regional, and distant locations were common (38%). In terms of the number of recurrences, single recurrences were the most common (38.3%) and had the best post-recurrence survival rate (median, 17.1 months; p<0.001). Patients with 2 or 3 recurrences showed equivalent survival to each other and longer survival than those with 4 or more (median, 9.4 months; p<0.001). In the multivariable analysis, the significant predictors of post-recurrence survival were body mass index, minimally invasive esophagectomy, N stage, R0 resection, post-recurrence treatment, and the number of recurrences (p<0.05).
Conclusion: After esophagectomy, the number of recurrences was the most significant risk factor influencing post-recurrence survival in patients with esophageal cancer. In esophageal cancer, oligo-recurrence can be defined as a recurrence with three or fewer metastases. More intensive treatment might be recommended if oligo-recurrence occurs.

Keywords: Esophageal neoplasms, Recurrence, Metastases, Survival

Introduction

Esophageal cancer is the sixth leading cause of cancer death worldwide, and its incidence is growing [1,2]. The prognosis has improved with multimodal treatment, such as preoperative chemotherapy and radiation therapy followed by surgical resection [3,4]. However, many individuals experience tumor recurrence within a few years after completing curative treatment [5-12]. Recurrent esophageal cancer has a poor prognosis, with a median survival duration of only 1 year after recurrence [7-13]. Therefore, identifying the factors that influence post-recurrence survival is critical for improving the prognosis.

Pathological tumor stage, local or distant recurrence, early recurrence, pre- or post-recurrence treatment, and the number of recurrent tumors have all been demonstrated to affect post-recurrence survival in esophageal cancer patients [12-22]. The concept of oligo-recurrence plays a meaningful role in treatment planning in sectors such as lung cancer, resulting in a better prognosis [23-25]. Although some findings have suggested that the number of recurrent tumors may affect the prognosis of esophageal cancer, the idea of oligo-recurrence has not been generally applied in this domain [20,22]. In recurrent malignancies, however, oligo-recurrence represents a smaller tumor burden and a lower degree of invasiveness. As a result, it may

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have predictive significance in esophageal cancer, much as it does in other malignancies.

The primary aim of this study was to determine the predictive importance in esophageal cancer of the number of recurrent tumors after esophagectomy. The secondary aim was to define the term "oligo-recurrence" in the context of esophageal cancer.

Methods

Ethics statement

This study was reviewed and approved by the institutional review board of Seoul National University Hospital (2022-08-09, H-2207-190-1345), and it followed the tenets of the Declaration of Helsinki. The requirement for informed consent of participants was waived due to the retrospective nature of the study.

Patients and inclusion criteria

Patients who underwent esophagectomy for esophageal cancer at our institution between March 2001 and December 2019 were included, and their medical data were reviewed retrospectively. The following were the criteria for inclusion: (1) squamous cell carcinoma; (2) esophagectomy with curative purpose; (3) R0 or R1 resection; and (4) recurrence verified by imaging or pathologic studies, specifically for the current study. In total, 321 patients were recruited.

Definition of terms

The staging of esophageal squamous cell carcinoma was conducted using the criteria outlined in the eighth edition of the American Joint Committee on Cancer staging manual. Instead of anatomic landmarks, the distance from the individual's incisors was used to establish the location of the tumor (upper, middle, or lower thoracic). Diagnostic imaging or histopathological biopsy was used to confirm recurrence. The recurrence pattern was classified as follows: Recurrence at the site of anastomosis or residual esophagus was defined as local recurrence, recurrence at mediastinal or upper abdominal lymph nodes was defined as regional recurrence, and recurrence in distant organs such as the lung, liver, bone, pleura, or peritoneum was defined as distant recurrence. The number of recurrent tumors was determined by adding the number of recurrent nodules in each site, in collaboration with a radiologist.

Post-recurrence treatment

The treatment strategy following recurrence was determined through comprehensive multidisciplinary care, involving the expertise of an oncologist. A substantial proportion of patients received concurrent multiple treatments, whereas those presenting with severe disease and poor performance did not undergo treatment. Surgical indications encompassed the control or manageability of primary tumors, complete resectability of lesions, sufficient physiological endurance for the procedure, and the absence of alternative medical treatments offering superior efficacy with lower toxicity than surgery.

Statistical analysis

The overall survival rate was estimated starting from the day of surgery. Post-recurrence survival was defined as the time after the recurrence was diagnosed. The Kaplan-Meier method was used to determine survival, and the log-rank test was used to determine statistical significance. In both univariable and multivariable studies, the Cox proportional hazards regression model was employed to assess the prognostic relevance of each component. A p-value less than 0.05 was considered to indicate statistical significance. IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA) was used to conduct the statistical analysis.

Results

Patient demographic data

The majority of the patients (n=313, 97.5%) were men, and most of them had smoked at some point (n=269, 83.8%). Their mean body mass index (BMI) was 22.2±3.0 kg/m^2. Patients with good performance status were operated on, and 98.7% of the patients (n=317) had a grade 0 or 1 performance status.

Patient operative and histopathological data

Table 1 summarizes the patients' surgical and histological information. Thoracotomy was used in 213 patients (66.3%), whereas robot-assisted surgery was performed in 76 patients (23.6%), thoracoscopic surgery was conducted in 21 patients (6.5%), and transhiatal resection was performed in 13 patients (4%). In 305 patients (95%), the stomach was employed as an esophageal substitute, while in 16 patients, the colon was used. Thoracic and cervical anasto-

Table 1. Clinical and histopathological data of 321 patients with recurrence after esophagectomy (N=321)

Variable	No. (%)
Surgical approach	
Thoracotomy	213 (66.3)
Robot-assisted surgery	76 (23.6)
Thoracoscopic surgery	21 (6.5)
Transhiatal resection	13 (4.0)
Tumor location	
Upper	51 (15.9)
Middle	106 (33.0)
Lower	164 (51.1)
Tumor infiltration	
pT0–1	88 (27.4)
ypT0–1	25 (7.7)
pT2	35 (10.9)
ypT2	14 (4.3)
pT3	111 (34.5)
ypT3	42 (13.0)
pT4	6 (1.9)
Lymph node involvement	
pN0	100 (31.1)
ypN0	27 (8.4)
pN1	67 (20.8)
ypN1	26 (8.0)
pN2	46 (14.3)
ypN2	15 (4.6)
pN3	27 (8.4)
ypN3	13 (4.0)
Tumor stage	
0–I	77 (23.9)
II	62 (19.3)
III	126 (39.2)
IV	56 (17.4)
Differentiation	
Well	50 (15.6)
Moderate	232 (72.3)
Poor	39 (12.1)
Lymph node dissection	
2-Field	207 (64.4)
3-Field	76 (23.6)
Completeness of resection	
R0	294 (91.5)
R1	27 (8.4)
Neoadjuvant treatment	81 (25.2)
Adjuvant treatment	105 (32.7)
Complications	
Vocal cord palsy	66 (20.5)
Leakage	16 (4.9)
Pneumonia	56 (17.4)

moses were performed in 167 (52%) and 154 (48%) patients, respectively.

The patients were distributed across different stages as follows: stage 0–I, 77 patients; stage II, 62 patients; stage III, 126 patients; and stage IV, 56 patients. Within the stage IV group, 41 patients were classified as stage IVA, with 1 patient exhibiting T4aN2M0, while the remaining 40 patients had N3. Furthermore, there were 15 patients in stage IVB who presented with a solitary distant organ metastasis amenable to surgical resection.

In 76 patients (23.6%), 3-field lymph node dissection was conducted. The median number of dissected lymph nodes was 36 (interquartile range, 21.5 to 50.5), and the most common tumor location was distal thoracic (51.1%, 164 patients). In 294 cases (91.5%), R0 resection was performed, while in 27 patients, R1 resection was performed (8.4%). Vocal cord palsy was the most common postoperative complication, probably related to cervical and recurrent laryngeal nerve lymph node dissection, and it occurred in 66 individuals (20.5%).

Table 2. Locations and patterns of recurrence in 321 patients with recurrence after esophagectomy (N=321)

Variable	No. (%)
Type of recurrence	
Local	14 (4.4)
Regional	96 (29.9)
Distant	89 (27.7)
Combined	122 (38.0)
Location distant recurrence	
Liver	23 (7.1)
Lung	65 (20.2)
Abdominal lymph nodes	23 (7.1)
Retroperitoneal	7 (2.1)
Bone	22 (6.8)
Other	34 (10.5)
No. of recurrent tumors	
1	123 (38.3)
2–3	82 (25.5)
>3	116 (36.1)
Recurrence within 1 year	129 (40.1)
Treatment used for recurrence	
None	71 (22.1)
Any treatment	250 (77.8)
Chemotherapy	168 (52.3)
Radiation therapy	199 (62.0)
Concurrent chemoradiotherapy	45 (14.0)
Surgery	56 (17.4)

Patterns of recurrence

Table 2 shows patients' locations and patterns of recurrence. The median time to recurrence was 10.7 months (range, 0.8 to 89.9 months), with 129 patients (40.1%) expe-

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riencing recurrence within 1 year after surgery. Only 14 patients (4.4%) had local recurrence, 96 patients (29.9%) had regional recurrence, 89 patients (27.7%) had distant recurrence, and 122 patients (38%) had combined recurrence. The lung was the site most commonly affected by distant recurrences (n=65, 20.2%). Chemotherapy (n=168, 52.3%), radiation therapy (n=199, 62%), concurrent chemoradiotherapy (n=45, 14.0%), and surgery (n=56, 17.4%) were used to treat the recurrences.

The most common type of case was patients with a single recurrent tumor (n=123, 38.3%). These single recurrences were observed in various locations: 82 cases in lymph nodes, 12 cases in the lungs, 9 cases at the anastomosis site, 4 cases in bone, 3 cases in the remnant esophagus, and 2 cases each in the liver, chest wall, and pleura. Additionally, there was 1 case each in the kidney, trachea, psoas muscle, stomach, arm, colon, and brain. Regarding the treatment approach for patients with single recurrence, 36 underwent surgery, 94 received radiation therapy, 63 received chemotherapy, 24 underwent concurrent chemoradiotherapy, and 13 did not receive any treatment.

Factors affecting survival after a recurrence

A Cox proportional hazards regression model was used to assess prognostic factors that affect post-recurrence survival (Table 3). The factors affecting survival after a recurrence were identified as BMI (p=0.014), minimally invasive esophagectomy (p=0.017), T stage (p=0.003), N stage (p=0.005), M stage (p=0.036), R0 resection (p=0.041), recurrence site (p<0.001), post-recurrence treatment (local, systemic, combined; p<0.001), recurrence within 1 year (p<0.001), and the number of recurrent tumors (p<0.001).

In the multivariable analysis, the independent factors affecting survival after recurrence were found to be BMI (p=0.028), minimally invasive esophagectomy (p=0.016), N

Table 3. Results of univariable and multivariable analyses of potential prognostic factors for post-recurrence survival

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Body mass index	**0.946 (0.905–0.989)**	**0.014**	**0.951 (0.910–0.995)**	**0.028**
Smoking history	0.954 (0.684–1.332)	0.784		
Minimally invasive esophagectomy	**0.698 (0.517–0.942)**	**0.017**	**0.678 (0.495–0.929)**	**0.016**
Location (thoracic)		0.885[a]		
Upper	1 (Ref)			
Middle	1.091 (0.732–1.624)	0.669		
Lower	1.027 (0.710–1.485)	0.888		
Tumor infiltration (pT)	1.206 (1.064–1.368)	0.003		
Lymph node involvement (pN)	**1.191 (1.055–1.343)**	**0.005**	**1.160 (1.024–1.315)**	**0.020**
Distant metastasis (M)	1.870 (1.042–3.357)	0.036		
3-Field lymph node dissection	0.979 (0.709–1.352)	0.897		
No. of harvested lymph nodes	0.943 (0.860–1.034)	0.211		
R0 resection	**0.643 (0.421–0.981)**	**0.041**	**0.639 (0.416–0.982)**	**0.041**
Recurrence site		<0.001[a]		
Local	0.649 (0.355–1.186)	0.160		
Regional	0.435 (0.319–0.593)	<0.001		
Distant	0.558 (0.406–0.766)	<0.001		
Combined	1 (Ref)			
Neoadjuvant treatment	1.134 (0.843–1.527)	0.406		
Adjuvant treatment	1.270 (0.972–1.660)	0.080		
Post-recurrence treatment		<0.001[a]		
No treatment	1 (Ref)			
Local	**0.165 (0.113–0.242)**	**<0.001**	**0.257 (0.171–0.388)**	**<0.001**
Systemic	**0.242 (0.151–0.387)**	**<0.001**	**0.227 (0.140–0.369)**	**<0.001**
Combined	**0.171 (0.121–0.242)**	**<0.001**	**0.226 (0.158–0.324)**	**<0.001**
Recurrence within 1 year	1.653 (1.280–2.134)	<0.001	1.299 (0.992–1.701)	0.057
No. of recurrent tumors	**1.789 (1.528–2.095)**	**<0.001**	**1.706 (1.424–2.044)**	**<0.001**

In the absence of specified references, values other than variables serve as references. Statistically significant results are marked in bold.
HR, hazard ratio; CI, confidence interval; Ref, reference.
[a]Overall p-value.

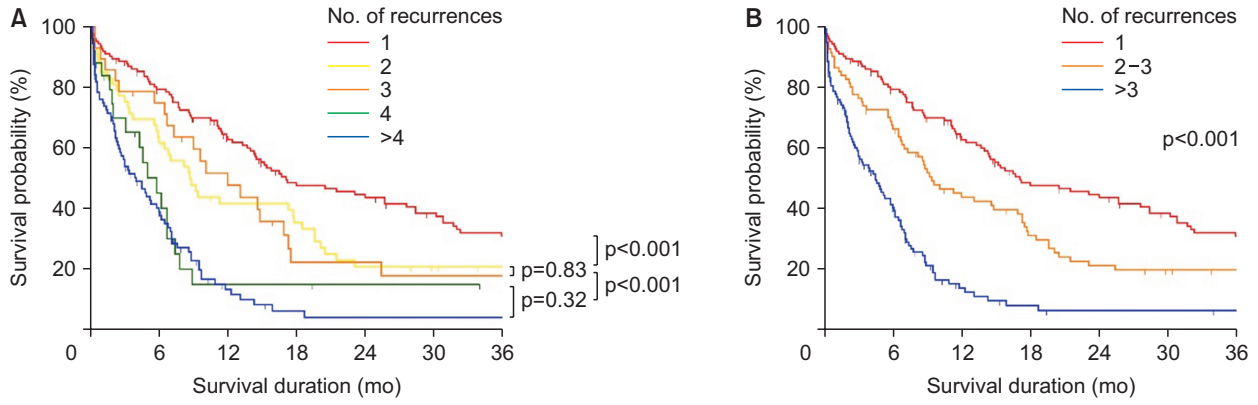

Fig. 1. Post-recurrence survival rate in 321 patients with recurrence after esophagectomy, according to the number of recurrent tumors. Survival curves were plotted by the Kaplan-Meier method. (A) Ungrouped. (B) Grouped.

stage (p=0.020), R0 resection (p=0.041), post-recurrence treatment (local, systemic, combined; p<0.001), and the number of recurrent tumors (p<0.001). Fig. 1A shows post-recurrence survival based on the number of recurrent tumors. When there was only 1 recurrent lesion, the survival rate was significantly higher than in the other cases (p<0.001). There was no significant difference in survival rate between patients with 2 and 3 recurrent lesions (p=0.83). The survival rate did not differ between patients with 4 recurrent lesions and those with more than 4 (p=0.32). Fig. 1B shows the survival curve subdivided by the number of recurrent lesions (1, 2 or 3, and >3). Overall, these groups' 1-year post-recurrence survival rates were 62.7%, 43.8%, and 12.5%, respectively, showing a significant difference in survival (p<0.001).

Discussion

We investigated 321 patients who experienced recurrent disease after undergoing curative surgery for esophageal squamous cell carcinoma. The N stage and the number of recurrent tumors were found to be independent predictive factors for poor post-recurrence survival. Furthermore, higher BMI, minimally invasive esophagectomy, R0 resection, and post-recurrence treatment improved the survival rate of the patients. There was a significant difference in post-recurrence survival across groups when categorized by one, 2 or 3, and more than 3 recurrent tumors. As a result, oligo-recurrence can be defined as the presence of 3 or fewer recurrent tumors.

Despite the widespread use of multimodal treatment, such as chemotherapy or radiation therapy, the high recurrence rate remains an obstacle to improving the prognosis of esophageal cancer. According to several studies, the recurrence rate after curative esophagectomy is between 36% and 52%, with a median time to recurrence of roughly 12 months [5-12]. Recurrent esophageal cancer has a poor prognosis, with a median survival time of 3 to 10 months after recurrence [7-13]. Similar to prior research, the median time to recurrence in our study was 10.7 months, and the median survival after recurrence was 8.8 months.

Understanding the prognostic factors that influence survival is crucial for identifying patients who, if given the proper treatment, may have a greater post-recurrence survival rate. Long-term survival following recurrence has been related to several factors. The number of recurrent tumors, N stage, R0 resection, interval before recurrences, and treatment after recurrence have all been found as prognostic factors. Our analysis showed several factors to be significant, whereas others were only marginally significant.

In our study, multivariable analysis revealed that the N stage and R0 resection were significant prognostic factors. The number of lymph node metastases is well known to be one of the most important prognostic factors in patients who have had esophagectomy [14]. The N stage was also observed to have a negative effect on post-recurrence survival in our study. Furthermore, several studies have demonstrated that esophageal cancer presents a higher recurrence rate and a lower overall survival rate among patients who undergo R1 resection compared to R0 resection [15,16]. Similarly, the findings of this study indicate that patients who undergo R0 resection experience a more favorable prognosis even in the presence of recurrence, in contrast to those who undergo R1 resection. R1 resection is associated with a higher local recurrence rate compared to R0 resection, and although the difference was not statistically significant in this study, our previous data indicate a notice-

able decrease in survival after recurrence in such cases [17]. This disparity may arise due to the common occurrence of poor oral intake among patients with local recurrence.

Minimally invasive esophagectomy was first introduced in the 1990s and was found by several studies to be a safe technique with good oncologic outcomes [26-28]. These studies also demonstrated that minimally invasive esophagectomy has advantages related to early postoperative outcomes, including reduced postoperative complications, early recovery, and improved quality of life. In terms of long-term outcomes, a recent meta-analysis by Gottlieb-Vedi et al. [29] including 14,592 patients from 55 relevant studies reported that minimally invasive esophagectomy was associated with lower 5-year and 3-year all-cause mortality and disease-specific mortality rates than open esophagectomy. Based on these results, it is not surprising that minimally invasive esophagectomy was identified in our study as a strong prognostic factor following recurrence.

Several studies have found a correlation between time to recurrence and survival after recurrence [12,18,19]. The shorter the period between recurrences, the greater the likelihood of aggressive malignant potential. As a result, a short time to recurrence indicates a poor prognosis after recurrence. In our study, patients who experienced recurrence within a year had a median survival time of 6.8 months, compared to 13.1 months for those whose recurrence took place later. Consistent with prior research, our study's univariable analysis demonstrated that the early recurrence group had diminished post-recurrence survival, albeit with only marginal significance in the multivariable analysis.

Any type of tumor-reductive treatment for a recurring lesion has also been documented as a predictive factor for post-recurrence survival [13,18-20]. In our study, the median post-recurrence survival was 10.5 months in the treated group and 1.2 months in the untreated group. Specifically, the survival durations for local, systemic, and combined treatments were observed to be 12.7 months, 8.8 months, and 9.5 months, respectively. In the multivariable analysis of our study, local, systemic, and combined treatments as post-recurrence interventions were all identified as significant factors influencing the survival rate after recurrence. It is unclear whether all patients experiencing recurrence had a performance status sufficient to receive treatment. Some patients were unable to undergo treatment due to poor performance status, which was due partly to the disease's rapid progression and partly to poor nutritional status, which is typical in patients with recurring esophageal cancer. A lower BMI was a poor prognostic factor following recurrence in this study. Although it is unclear to what extent the treatment may improve the chance of survival, patients who were able to undergo treatment had a better probability of survival following recurrence.

According to previous studies, the recurrence pattern is one of several factors that influence post-recurrence survival in esophageal cancer. Regional or distant recurrence is the most typical pattern of esophageal cancer recurrence [6-8]. Other studies have indicated that distant recurrence is a poor prognostic factor, since it is assumed to reflect more aggressive tumor biology and hematogenous metastases [18-21]. However, the most common pattern in our study was a combination of regional and distant recurrence. Furthermore, combined recurrence was found to be a poor prognostic factor in the univariable analysis, but not in the multivariable analysis. The pattern of recurrence location was not a predictor of survival following recurrence. Instead, in both univariable and multivariable analyses, the number of recurrences was a significant prognostic predictor.

Patients with a larger number of recurrent tumors had a lower post-recurrence survival rate, according to our study. The difference was more noticeable when participants were separated into groups of 1, 2 or 3, and more than 3 recurrent lesions. Patients with more than 3 recurrent lesions had a median post-recurrence survival of 4.5 months, compared to 17.1 months for patients with a single recurrence and 9.4 months for patients with 2 or 3 recurrent lesions. Patients with more than 3 recurrent tumor locations had a lower post-recurrence survival than those with fewer involved foci, according to Parry et al. [20]. They attributed the findings to the more aggressive behavior of cases with many recurrences, and most patients with multiple recurrences had a poor clinical condition when recurrence was diagnosed, making them ineligible for curative treatment. Patients with many recurrent tumors, especially those with more than 3 tumors, had considerably shorter post-recurrence survival, according to Miyata et al. [22]. Those researchers reasoned that patients with many recurrent cancers might be considered to have systemic recurrence at the time of diagnosis. Furthermore, compared to patients with a single recurrence, the proportion of patients who received radiation therapy or surgical resection as locoregional therapy was much lower among those with multiple recurrent tumors.

Hellman et al. [23] proposed the concept of oligometastases in 1995, and Niibe et al. [24] refined it as oligo-recurrence in 2006. Oligo-recurrence indicates having 1–5 met-

astatic or recurrent lesions that can be treated with local therapy under the conditions of a controlled primary lesion. The idea of oligo-recurrence was used to determine the treatment for recurring lesions in various cancers, including lung cancer, uterine cervical cancer, colorectal cancer, renal cell carcinoma, and breast cancer, and a positive prognostic effect has been observed in many studies [25]. Several studies have found that the number of recurrent tumors is an important prognostic factor in esophageal cancer [20,22]. However, as with distant recurrence, this was simply regarded as a finding reflecting cancer's aggressiveness, and it was assumed that the difference in post-recurrence survival arose mostly from differences in treatment. Although studies exist on local surgical control of the recurrence of esophageal cancer, the criteria for oligo-recurrence have not been explicitly presented, the sample size was small, or the effect was not statistically significant; thus, it is not yet accepted as a universal treatment guideline [30-32].

Even after considering patterns of recurrence or post-recurrence treatment, the number of recurrent lesions was revealed as the most important independent predictive factor in our study's multivariable analysis. Furthermore, when the number of recurrent lesions was separated into 1, 2 or 3, and more than 3, the results were more pronounced. Thus, we classified oligo-recurrence in esophageal cancer as three or fewer recurrent lesions, based on the number of recurrent lesions associated with a favorable prognosis in prior research and our own. We also suggest that locoregional treatments, such as surgical resection, should be employed aggressively in the case of oligo-recurrence of esophageal cancer if the patient's condition allows.

This study has several limitations. The first is that it was neither prospective nor randomized. Despite a concerted effort to account for all possible variables, unmeasured confounders could have skewed the analysis. In particular, minimally invasive esophagectomy, especially with robotic assistance, has been performed since the 2010s, which may have contributed a bias related to the participants' surgery dates. Second, the majority of recurrences were assessed using imaging techniques, with only a few cases confirmed by biopsy. Third, because this study only included patients with esophageal squamous cell carcinoma, it may be difficult to interpret in locations where adenocarcinoma is more prevalent.

In this study, we investigated prognostic factors for post-recurrence survival in patients with esophageal squamous cell carcinoma after curative esophagectomy. BMI, minimally invasive esophagectomy, the N stage, R0 resection, post-recurrence treatment, and the number of recurrent tumors were identified as risk factors, with the last being the most important. We defined oligo-recurrence in esophageal cancer as a recurrence with 3 or fewer metastases, and we suggest that oligo-recurrence should be treated more aggressively.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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