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Original Research

Definition and risk factors of early recurrence based on affecting prognosis of esophageal squamous cell carcinoma patients after radical resection

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ABSTRACT

Early recurrence after surgery could affect cancerous patients' prognosis, but the definition of early recurrence and its risk factors for esophageal squamous cell carcinoma (ESCC) patients are still unclear. This study analyzed the clinical data of 468 post-surgery recurrent ESCC patients retrospectively. A minimum *p*-value approach was used to evaluate the optimal cut-off value of recurrence free survival (RFS) to define early recurrence. Risk factors of early recurrence were developed based on a Cox model. The optimal cut-off value of RFS to distinguish early recurrence was 21 months (p <0.001). Independent risk factors for early recurrence included tumor locations (HR=0.562, p <0.001), pathological T stage (HR=1.829, p <0.001), tumor diameter (HR=1.344, p = 0.039), positive lymph nodes (HR=1.361, p <0.001), and total resected lymph nodes (HR=1.271, p = 044). For the late recurrent patients, there was a much more significant survival advantage for recurrence after concurrent chemoradiotherapy than that after sequential chemoradiotherapy and radiotherapy alone (p = 0.0066). In conclusion, this study defined 21 months of RFS as early recurrence and also identified its risk factors. Concurrent chemoradiotherapy was suggested as preferred post-relapse treatment for late recurrent ESCC patients.

Introduction

Esophageal cancer (EC) is the seventh highest incident malignancy in humans and is the sixth leading cause of tumor-related mortality worldwide [1]. Despite the advances in the diagnosis and treatment of EC, the long-term survival rates are still not satisfactory. In 2010–2014, 5-year age-standardized net survival was about 10–30% in most countries [2]. Some previous studies have reported that early recurrence predicted a shorter overall survival time after the radical resection for various cancers, including pancreatic cancer [3], gastric cancer [4], lung cancer [5], hepatocellular carcinoma [6], and intrahepatic cholangiocarcinoma [7]. Esophageal squamous cell carcinoma (ESCC) is the predominant histologic subtype, accounting for about 90% of all EC cases [8]. Approximately 27.1–52.6% of patients who undergo esophagectomy may experience recurrence [9]. Early tumor recurrence is the leading cause of death for ESCC patients who have undergone esophageal cancer resection. In a clinical setting, distinguishing patients with high early recurrence risk after resection helps clinicians make decisions regarding surveillance and therapeutic strategies. Thus, it is important to investigate the clinical features and patterns of patients with a high risk of early recurrence.

However, the definition of early recurrence in both an academic and a clinical setting is unclear as arbitrary cutoff values vary between 6 and 24 months, as reported in previous studies [10-12]. Takahashi et al., Yoshida et al., and Hamai et al. defined early recurrence as relapse within 6 months after surgery or the neoadjuvant chemoradiotherapy (NCRT) followed by surgery [10,13,14], while Davies AR's study thought tumor recurrence and death of EC patients within 1 year as early recurrence and found that poor differentiation and ≥3 positive lymph nodes were risk factors of early recurrence [11]. Yukiharu H's study considered 2 years as the threshold value of early recurrence for EC patients and identified pathological lymph node metastasis as the risk factor for early recurrence [12]. To the best of our knowledge, no previous study has been conducted with the primary goal of dividing ESCC patients into early and late recurrence groups based on the statistical evaluation of the optimal cut-off value to be distinguished in prognosis.

In the present study, 468 post-surgery recurrent ESCC patients were included retrospectively. We calculated the optimal cut-off value of recurrence-free survival (RFS) to define the early and non-early recur-

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rence of ESCC patients by employing the "minimum *P*-value" method, according to its influence on overall survival of ESCC patients, which is expected to become an outcome indicator prior to overall survival (OS). Additionally, we identified clinicopathologic factors associated with early ESCC recurrence based on a Cox model. We further explored the prognostic ability of post-relapse treatments between the patients with early and non-early recurrence, which may guide clinicians in making decisions regarding therapeutic strategies.

Methods

Study population

A total of 468 patients with local recurrence after radical resection for ESCC between June 2008 and August 2012 at the Anyang Cancer Hospital were included. All patients were from high-incidence areas in the Taihang Mountains of China. The inclusion criteria for participants in this study were (1) ESCC confirmed by postoperative histology, (2) receiving two-field dissection, and (3) negative resection margin. Exclusion criteria were (1) not first diagnosis of ESCC, (2) use of preoperative neoadjuvant therapy, and (3) use of postoperative adjuvant therapy. Tumor stages were determined according to the Tumor-Node-Metastasis system of the American Joint Committee on Cancer and the International Union Against Cancer (2002) [15]. All the clinical data of participants were collected from electronic medical record system of Anyang Cancer Hospital.

Definition

Recurrence

Lymph node (LN) recurrence was diagnosed comprehensively with ultrasonography, computed tomography (CT), positron emission tomography (PET)-CT, and physical findings. The diagnostic criteria for LN recurrence were (1) short-axis diameter≥1 cm; (2) incomplete capsule; (3) lymph node fusion; (4) lymph node central necrosis; and (5) standard uptake value (SUV)>2.5. The recurrence at anastomotic site was detected by CT, PET-CT, or esophagoscopy with pathological validation.

Overall survival (OS): OS was defined as the time from esophagectomy to either death or final follow-up.

Recurrence-free survival (RFS): RFS was calculated from the date of esophagectomy to the date of recurrence or last follow-up if recurrence did not occur.

Post-recurrence survival (PRS): PRS referred to the time from first relapse to either death or last follow-up.

Treatments

The recurrent ESCC patients received treatment according to the NCCN guidelines of Esophageal and Esophagogastric Junction Cancers in the corresponding year, combined with patients' physical conditions, basic diseases, and economic conditions.

Radiotherapy

The daily fractional dose of RT was 1.8~2.0 Gy administered 5 days per week, and the total dose was 40–70 Gy, with a median dose of 59.4 Gy. Electron-beam radiation therapy (EBRT) was performed on lymph nodes in the supraclavicular region when necessary.

Combined chemotherapy

A total of 166 patients (35.5%) received combined chemotherapy. Among them, 109 patients received a concurrent chemoradiotherapy (CCRT) with the median number of cycles being 2 (range 1–4), while 57 patients received a sequential chemoradiotherapy (SCRT), consisting of a 5-fluorouracil (5-FU) plus cisplatin (FP) regimen or a docetaxel (DOC) plus cisplatin (TP) regimen.

Follow-up

The patients were followed up from their surgery to May 30, 2019. The median follow-up time was 35 months (range: 6–262 months). After hospital discharge, the patients were followed-up regularly every 3 months during the first 2 years, every 6 months from years 3 to 5, and once a year afterward. Most routine follow-up observations included a physical examination, laboratory tests, neck and upper-abdominal ultrasonography or CT, and an endoscopic examination and PET-CT to confirm or exclude potential recurrence. Bone emission computed tomography (ECT) scan and magnetic resonance imaging (MRI) was performed for those with highly suspicious bone metastases.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22 (IBM, NY, USA), Python 3.6 (https://www.python.org/), and third-party tools packages such as pandas (https://pandas.pydata.org/), scipy (https://www.scipy.org/), numpy (https://numpy.org/), matplotlib (https://matplotlib.org/), lifelines (https://lifelines.readthedocs.io/en/latest/), and other implementations. Difference of categorical variables in the distribution between groups were assessed with Chi-square or the Fisher's exact test, as appropriate. *P* values less than 0.05 were considered statistically significant. The survival curve was plotted according to the Kaplan-Meier method, and the differences of survival distributions between subgroups were compared by the log-rank test. A minimum *p*-value approach [16,17] was performed to evaluate the optimal cut-off value of RFS to divide the patients into early recurrence and late/non-recurrence based on duration of OS. The log-rank test was applicated for different durations of RFS to identify the best cut-off time point with the lowest *p*-value in this approach. Kaplan-Meier analysis was conducted to assess the impact of the variables on RFS, PRS, or OS by lifelines of Python and survminer package (depending on ggplot2 package) of R software. Variables with a *p*-value of <0.05 were included in the following multivariate Cox proportional hazards model to identify the independent risk factors associated with RFS by survival package in R 3.5. The variables were selected based on AIC value.

Results

Clinicopathological characteristics of the patients

A total of 468 ESCC patients with radical esophagectomy were included in the final analysis. Demographic, perioperative clinicopathological, and treatment characteristics of the entire study population are summarized in Table 1. The median follow-up for the entire cohort was 35 months (range: 6–262 months). During the follow-up period, 225 (46.3%) of 486 patients had recurred after a median RFS of 12 months (95% CI 11–13). Patients most often experienced mediastinal recurrence ($n = 291$, 62.2%), followed by multiple-site recurrence ($n = 258$, 55.1%), supraclavicular region ($n = 45$, 9.6%), anastomotic site ($n = 15$, 3.2%), or abdominal ($n = 4$, 0.9%) recurrence. The median OS for all patients in this study was 35 months (95% CI 33–38) with 13 patients (2.8%) currently alive. The median PRS for the entire cohort was 17 months (95% CI 16–19). The probability density plot of survivals showed that relapse cases centered in less than 10 months after ablation, and PRS peaked at around 13 months after relapse (Fig. 1A). The OS peaked around 25 months after surgery. Further, the coefficient of determination (R^2) indicated the strength of associations between RFS and PRS or OS, where values near 1 suggested surrogacy and values close to 0 implied no association. Apparently, there was no direct relation between RFS and PRS (R^2=0) (Fig. 1B), but there was a connection between RFS and OS (R^2=0.488) (Fig. 1C).

Table 1
Clinicopathological characteristics of all patients.

Variable	Number	Percentage (%)
Median age (range)	61 (39–82)	
Gender		
Male	295	63.0
Female	173	37.0
Tumor diameter (cm)		
<5	387	82.7
≥5	81	17.3
Tumor Location		
Upper thorax	81	17.3
Middle thorax	338	72.2
Lower thorax	49	10.5
Tumor differentiation		
Well	22	4.7
Moderate	293	62.6
Poor	153	32.7
Clinicopathological type		
Medullary type	246	52.6
Ulcerative type	166	35.5
Narrow type	9	1.9
Fungating type	8	1.7
Other types	39	8.3
Pathological T		
T1	43	9.2
T2	120	25.6
T3	284	60.7
T4	21	4.5
Pathological stage		
I or II	291	62.2
III	177	37.8
Positive LN		
Yes	212	45.3
No	256	54.7
TLNs		
Median (range)	10 (1–32)	
<10	200	42.7
≥10	268	57.3
LNR		
Median (range)	0 (0–1)	
=0	256	54.7
>0	212	45.3
LN Recurrence site		
Supraclavicular region	45	9.6
Mediastinal	291	62.2
Abdominal	4	0.9
Anastomotic site	15	3.2
Multiple	258	55.1
LN size (cm)		
<2.5	265	56.6
≥2.5	203	43.4
Treatment response		
CR	193	41.2
PR	189	40.4
SD or PD	86	18.4
Radiotherapy dose (Gy)		
<59.4	68	14.5
≥59.4	400	85.5
Radiotherapy	302	64.5
Chemoradiotherapy		
Concurrent	109	23.3
Sequential	57	12.2
Median of Survival (months, 95% CI)		
Recurrence-free survival	12 (11–13)	
Post-recurrence survival	17 (16–19)	
Overall survival	35 (33–38)	
Death		
Yes	455	97.2
No	13	2.8

LN, lymph node; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; TLNs, total number of resected LNs; LNR, ratio of positive LNs.
Tumor diameter definition: the maximum value of three-dimensional measurements in pathology report.

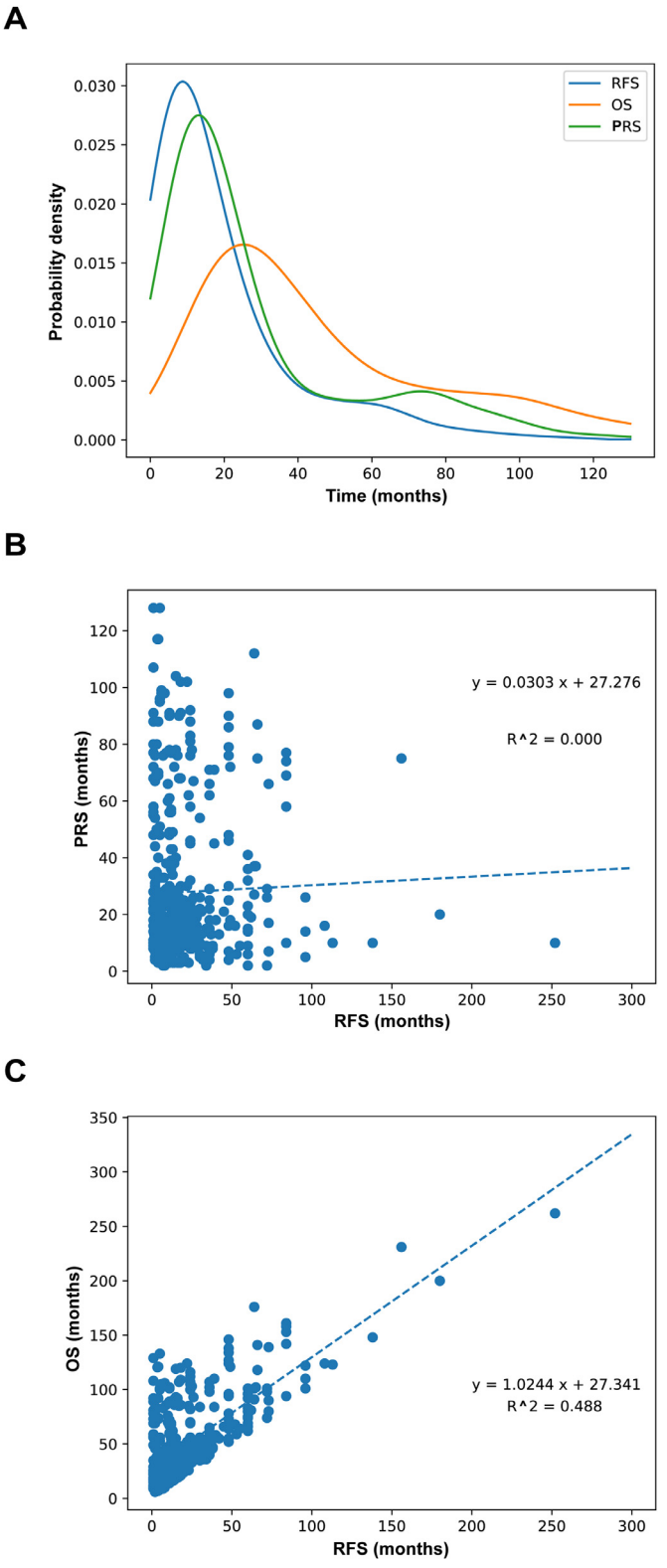

Fig. 1. The probability density distribution and correlations of survivals in all patients.
(**A**) Probability density plot of overall survival (OS) (orange line), recurrence-free survival (RFS) (blue line), and post-recurrence survival (PRS) (green line) distribution in all patients. (**B, C**) Correlations between RFS and PRS (**B**) and RFS and OS (**C**) in all patients.

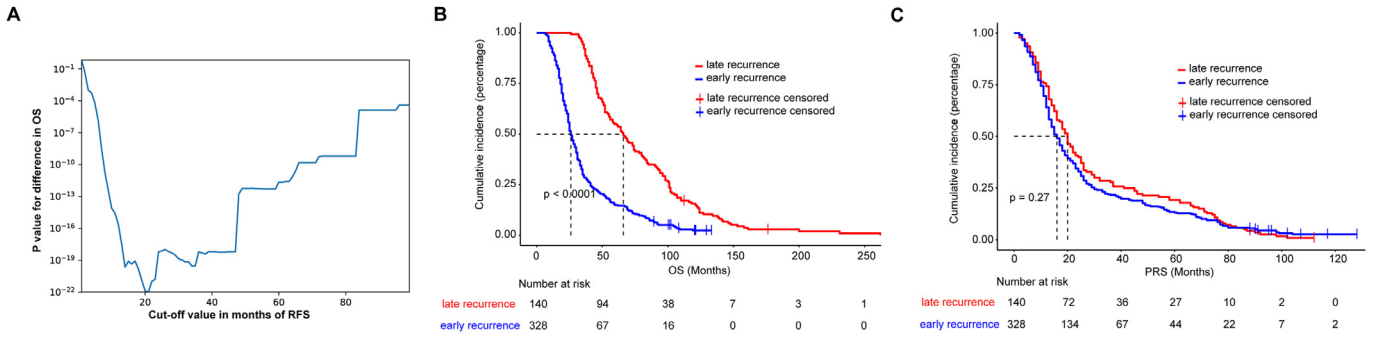

Fig. 2. Defining early and late recurrence.
(**A**) Different cutoff thresholds (x-axis), with the corresponding *p* values (y-axis), show that the optimal threshold for defining early and late recurrence based on the difference in overall survival is 21 months. (**B, C**) Kaplan-Meier Curves showing the difference of OS (**B**) and PRS (**C**) between early and late recurrence.

Defining early and late recurrence

We classified casually 468 ESCC patients into early recurrent and late recurrent groups by successively assigning a value as cut-off of RFS within its range, then every *p* value was calculated by Kaplan-Meier analysis to assess the impact of early recurrence on OS. Fig. 2A presents all *p* values corresponding to every cut-off of RFS, and we got the minimum *p* value (p = 1.05E-22) when the cut-off of RFS was 21 months. Thus, we defined patients whose RFS was <21 months as early recurrence patients. Table 2 shows and compares the clinicopathological features of patients according to early recurrence and late recurrence divisions. Patients with early recurrence more frequently had a larger tumor, an advanced pathological stage, positive lymph nodes, and a larger total number of resected lymph nodes (TLNs). Additionally, early recurrent patients had upper and lower thorax tumors with a higher ratio, whereas patients with middle thorax tumors were more frequently found in the late recurrence group. Furthermore, patients with late recurrence had more often received CCRT, whereas early recurrent patients had received radiotherapy or SCRT with higher frequency. Patients in the late recurrence group usually had better responses to the therapies—namely, a much higher ratio of complete response (CR) and a slightly higher ratio of partial response (PR). On the other hand, the ratio of patients with stable disease (SD) or progression of disease (PD) was notably higher in the early recurrence cohort.

Patients with early recurrence less than 21 months (n = 328, 70.1%) had a median RFS of 8 months (95% CI 7–9), with a median PRS of 16 months (95% CI 15–18), whereas the median RFS in the late (≥21 months) recurrence cohort (n = 140, 29.9%) was 36 months (95% CI 34–48) followed by a median PRS of 20 months (95% CI 16–23). The median OS was significantly longer for patients with late recurrence (66 months, 95% CI 56–75) when compared with patients with early recurrence (26 months, 95% CI 25–29; P <0.001) (Fig. 2B). Likewise, the median PRS of patients with late recurrence was longer than that of patients with early recurrence with no significance (p = 0.27) (Fig. 2C).

Independent risk factors associated with RFS of early recurrence

Subsequently, we examined potential risk factors of early recurrence in patients who developed local recurrence after operation, and corresponding Kaplan-Meier curves of RFS were generated based on different variables with a primary endpoint of early recurrence (RFS <21 months) (Fig. 3 **and supplementary Fig. 1**). The Kaplan-Meier curves revealed that tumor diameter, locations, pathological stage, pathological T stage, positive lymph nodes, clinicopathological types, and TLNs were each significantly associated with RFS recurrence within 21 months after operation (p <0.05). Further multivariate Cox regression analysis demonstrated 5 variables as the independent predictive indicators for early recurrence of ESCC patients developing local recurrence after surgery, including tumor locations (HR=0.562, p <0.001), pT stage (HR=1.829, p <0.001), positive lymph nodes (HR=1.361, p <0.001), tumor diameter (HR=1.344, p = 0.039), and TLNs (HR= 1.271, p = 0.044) (Fig. 4).

Prognostic differences of post-relapse therapeutic strategies between early and late recurrence

Despite the wide acceptance of RT or CRT as a standard treatment for postoperative recurrence, the optimal choice of the combined modalities of CT and RT remains controversial. Several studies have reported a poor survival of patients with early recurrence, though no studies have clearly compared the prognostic differences of different therapeutic strategies between patients with early and late recurrence in ESCC. To elucidate whether people with early or late recurrence could benefit from the similar therapeutic strategies or not, Kaplan-Meier curves were constructed based on therapeutic strategies between early and late recurrent groups (Fig. 5). To our surprise, there was no significant difference in PRS among early recurrent patients undergoing different treatments including RT alone, concurrent, and sequential CRT (p >0.05) (Fig. 5A), whereas the clinical outcomes differed dramatically in the late recurrent group of patients with different treatments (p <0.01) (Fig. 5B). The post-recurrent five-year survival rate of early recurrent patients is the highest in CCRT treated group (19.4%), followed by RT-alone (12.5%) and SCRT (8.9%), respectively, which is different from that of the late recurrence group. Obviously, the late recurrent patients have the best post-recurrent five-year survival under CCRT (33.3%), which conferred a significant survival benefit compared with SCRT (25%) or RT alone (11.6%).

Discussion

Early recurrence has been known as a risk event for worse survival outcome in various cancers, suggesting the possible connection between RFS duration and OS. However, the definition of early recurrence in both academic and clinical setting is still unclear. Additionally, progression-free survival (PFS) has been reported to be an alternative surrogate for OS in patients with advanced breast cancer [18], metastatic colorectal cancer [19], stage II–III melanoma [20], or advanced HCC [21]. To the extent of our knowledge, there have been no studies evaluating PFS or RFS as a surrogate endpoint in resectable esophageal cancer except one literature-based meta-analysis, which assessed the trial level correlations between PFS and OS in resectable esophageal cancer with preoperative therapy [22].

Our study indicated that the best cut-off time point to differentiate between early and late recurrence in ESCC, based on subsequent prognosis, is a recurrence-free interval of 21 months. This probably would be the first research to discuss the clinical significance about the optimal cut-off time point determined by minimum P approach in ESCC. However, we found that there was no significant difference in PRS between

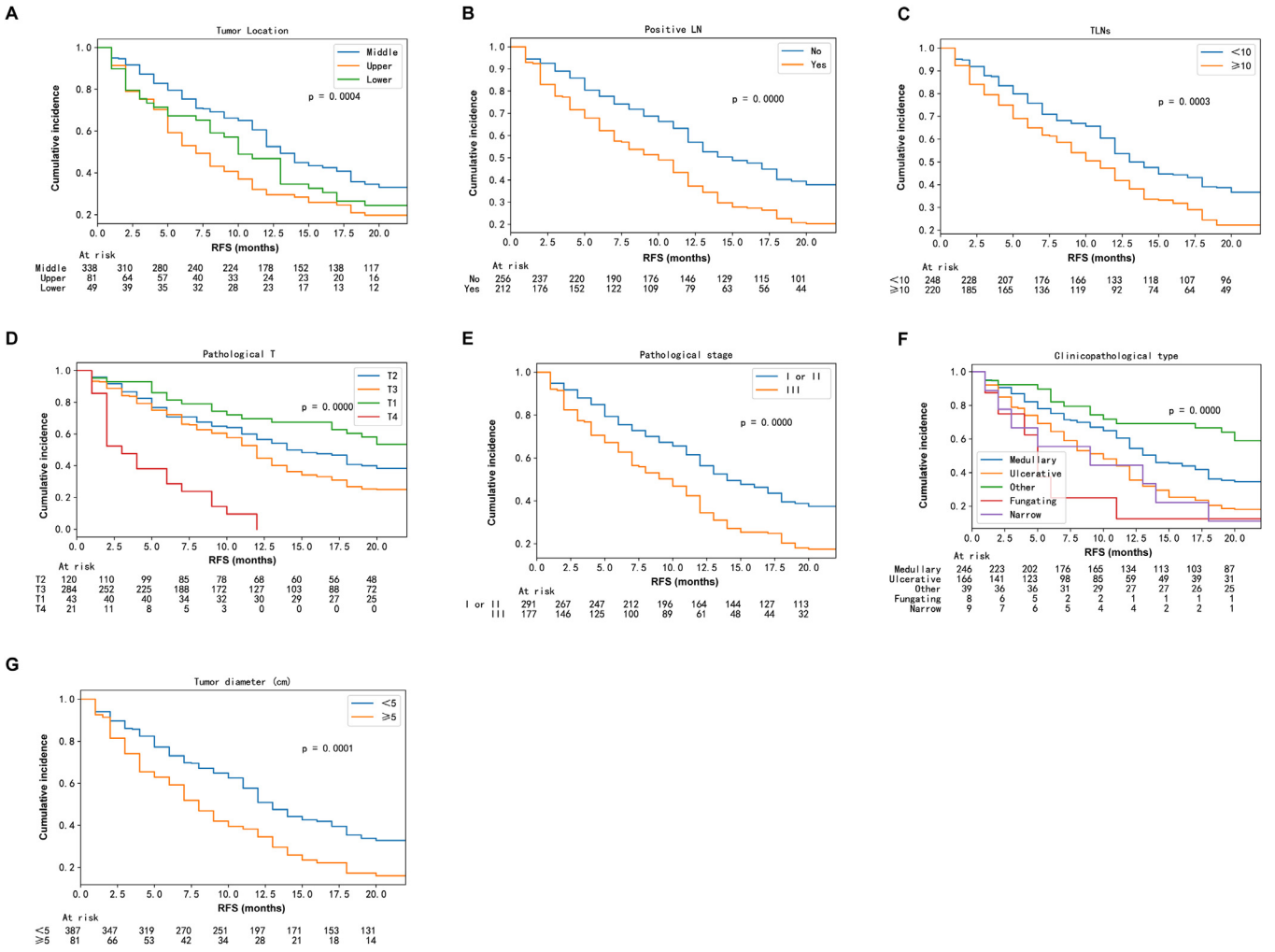

Fig. 3. Kaplan-Meier Curves of important perioperative variables.
Kaplan-Meier Curves of important perioperative variables significantly associated with RFS (p <0.05) with a primary endpoint of early recurrence (RFS <21 months), including (**A**) tumor location, (**B**) positive lymph node (LN), (**C**) TLNs, (**D**) pathological T stage, (**E**) pathological stage, (**F**) clinicopathological type, and (**G**) tumor diameter.

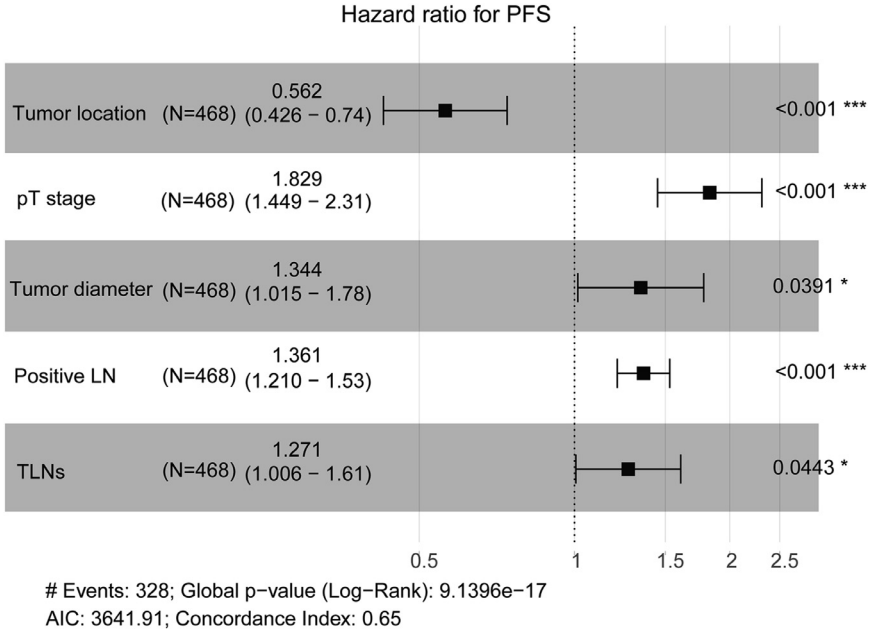

Fig. 4. Forest plot of hazard ratio based on multivariate Cox proportional hazards model.

Table 2
Clinicopathological characteristics of the patients with recurrence.

Variable	Early Recurrence (n = 328), n (%)	Late Recurrence (n = 140), n (%)	p value
Age (years)			0.051
<70	285 (86.9%)	111 (79.3%)	
≥70	43 (13.1%)	29 (20.7%)	
Gender			0.876
Male	208 (63.4%)	87 (62.1%)	
Female	120 (36.6%)	53 (37.9%)	
Tumor diameter (cm)			0.009
<5	193 (58.8%)	101 (72.1%)	
≥5	135 (41.2%)	39 (27.9%)	
Tumor Location			0.042
Upper thorax	65 (19.8%)	16 (11.4%)	
Middle thorax	226 (68.9%)	112 (80.0%)	
Lower thorax	37 (11.3%)	12 (8.6%)	
Tumor differentiation			0.413
Well	16 (4.9%)	6 (4.3%)	
Moderate	199 (60.7%)	94 (67.1%)	
Poor	113 (34.5%)	40 (28.6%)	
Clinicopathological type			<0.001
Medullary type	161 (49.1%)	85 (60.7%)	
Ulcerative type	136 (41.5%)	30 (21.4%)	
Narrow type	8 (2.4%)	1 (0.7%)	
Fungating type	7 (2.1%)	1 (0.7%)	
Other types	16 (4.9%)	23 (16.4%)	
Pathological T			<0.001
T1	20 (6.1%)	23 (16.4%)	
T2	74 (22.6%)	46 (32.9%)	
T3	213 (64.9%)	71 (50.7%)	
T4	21 (6.4%)	0 (0.0%)	
Pathological stage			<0.001
I or II	182 (55.5%)	109 (77.9%)	
III	146 (44.5%)	31 (22.1%)	
Positive LN			<0.001
Yes	169 (51.5%)	43 (30.7%)	
No	159 (48.5%)	97 (69.3%)	
TLNs			0.001
<10	124 (37.8%)	76 (54.3%)	
≥10	204 (62.6%)	64 (45.7%)	
LN size (cm)			0.331
<2.5	191 (58.2%)	74 (52.9%)	
≥2.5	137 (41.8%)	66 (47.1%)	
Treatment response			0.025
CR	126 (38.4%)	67 (47.9%)	
PR	132 (40.2%)	57 (40.7%)	
SD or PD	70 (21.3%)	16 (11.4%)	
Radiotherapy dose (Gy)			0.964
<59.4	48 (14.6%)	20 (14.3%)	
≥59.4	280 (85.4%)	120 (85.7%)	
Post-relapse treatments			0.043
Radiotherapy	216 (65.9%)	86 (61.4%)	
Concurrent-CRT	67 (20.4%)	42 (30.0%)	
Sequential-CRT	45 (13.7%)	12 (8.6%)	

CRT, chemoradiotherapy.

early and late recurrent patients (Fig. 2C), which indicated that overall prognosis of patients after radical resection was mainly impacted by RFS. This result provided evidence that RFS had the potential to be an alternative surrogate for OS in ESCC patients receiving radical resection. Therefore, it is crucial to explore clinical risk factors of early recurrence, which helps clinicians to distinguish poor-prognosis patients in advance. Additionally, independent risk factors associated with early ESCC recurrence after resection were identified, including primary tumor locations, pathological T stage, positive lymph nodes, tumor diameter, and TLNs. Although predictive factors associated with early recurrence after esophagectomy have been previously reported, early recurrence in these studies is commonly defined as occurring during the first postoperative year without statistical assessment of the cut-off value [11,23,24]. The grade of differentiation, depth of invasion, lymph node metastasis, number of lymph node metastases, and marginal status were identified as valid prognostic factors in predicting early death by Zhu et al. [23]. Subsequently, Davies et al. confirmed the predictor of the tumor differentiation grade and demonstrated other three factors including pathological tumor stage, completeness of resection, and poor response to chemotherapy as independent indicators in their study about factors associated with early recurrence and death after esophageal cancer surgery [11]. A more recent study by Mantziari et al. not only assessed perioperative parameters like pathological T stage and an increased positive-to-resected lymph node ratio but also included a demographic variable—namely, preoperative smoking into their multivariable model [24]. Consistently, the present study also showed that pathological T stage, positive lymph nodes, and TLNs were independent predictors for early recurrence. Further, we also found primary tumor location to be a valuable risk factor. This could be due to the different definition of early recurrence (<21 months) in our study.

More importantly, we evaluated the prognostic differences of two modalities of CRT compared with RT alone in patients with early or late recurrence. For the late recurrent patients, there was a significant PRS advantage for CCRT over SCRT or RT alone. In comparison, al-

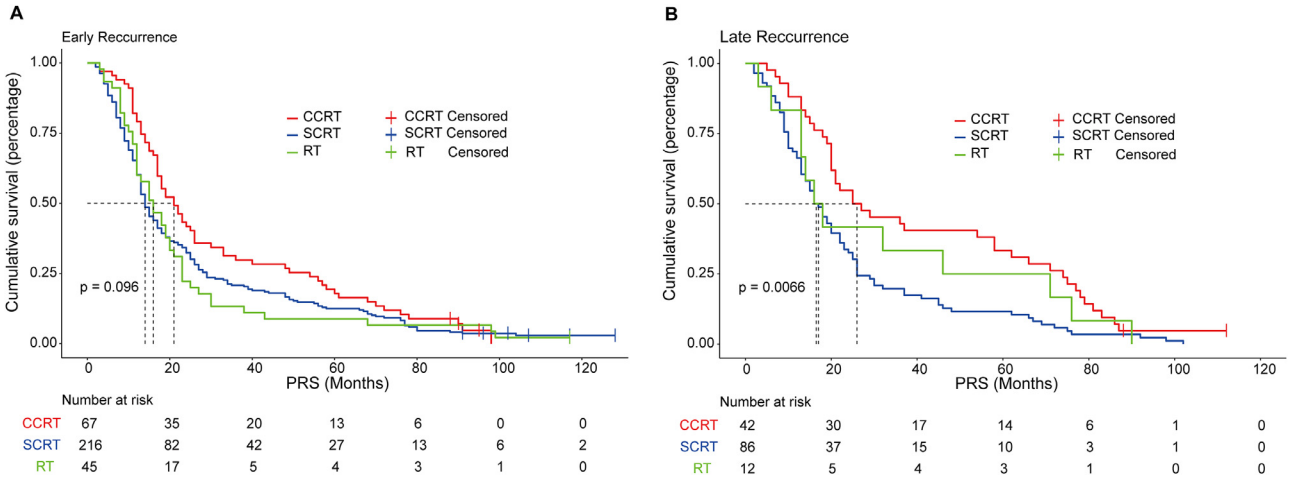

Fig. 5. Kaplan-Meier Curves demonstrating prognostic differences of post-relapse therapeutic strategies between early (A) and late recurrence (B). Blue line indicates radiotherapy (RT) alone; orange line indicates concurrent chemoradiotherapy (CCRT); and green line indicates sequential chemoradiotherapy (SCRT).

though CCRT was associated with the best post-recurrent five-year survival compared with RT alone or SCRT in the early recurrent patients, no statistically significant difference was observed among these three types of treatments in the long run. Thus, proper distinction of early or late recurrence may facilitate clinicians in making therapeutic decisions to improve patients' survival and quality of life.

Despite the novelties in this study, there are some limitations worthy of statement. First, numerous patients were excluded such as patients with different therapy strategies or loss to follow-up, which may limit the generalizability of our findings to the overall population of ESCC patients. The results of this study are specifically instructive with regard to ESCC patients who are undergoing surgery but have not received preoperative neoadjuvant therapy and postoperative adjuvant therapy. Second, this was a retrospective study involving a single center with a small sample size. Finally, this study lacked specific information with regard to clinical factors like serum biomarkers [25] or demographic indicators [24] besides perioperative parameters.

Conclusions

This study recruited 468 ESCC patients who developed tumor recurrence after their surgery and defined 21 months as the optimal threshold of RFS for dividing patients into early and late recurrence according to the influence on OS. Primary tumor location, pathological T stage, positive lymph nodes, and TLNs were shown to be independently associated with early recurrence. More importantly, we suggested concurrent chemoradiotherapy as the primary treatment strategy for late recurrent patients considering clinical guidelines.

Ethics approval and consent to participate

This research was approved by the Ethical Review Committee of Anyang Cancer Hospital and written informed consent was obtained from all participants. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration.

Abbreviations

EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; RFS, recurrence-free survival; OS, overall survival; PRS, post-recurrence survival; LN, lymph node; HR, hazard ratio; NCRT, neoadjuvant chemoradiotherapy; CCTR, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy

Authors contributions

YZ, JG, PM, and FZ conceived of and designed the study. AZ, HY, and JL collected and organized the data. YZ, JG, JZ, and PM analyzed and interpreted the data. YZ, JG, SW, and FZ reviewed and edited the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

CRediT authorship contribution statement

Yaowen Zhang: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Junhui Gao:** Conceptualization, Methodology, Formal analysis, Writing – original draft. **Anping Zheng:** Data curtion. **Haijun Yang:** Data curtion. **Jian Li:** Data curtion. **Shouxin Wu:** Writing – original draft. **Jiangman Zhao:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Peng Meng:** Methodology, Formal analysis, Writing – original draft. **Fuyou Zhou:** Conceptualization, Writing – review & editing.

Ethics approval and consent to participate

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2021.101066.

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