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Delayed postoperative radiotherapy might improve the long-term prognosis of locally advanced esophageal squamous cell carcinoma

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ABSTRACT

Objective: There is no consensus on the optimal timing of postoperative radiotherapy (PORT) for locally advanced esophageal squamous cell carcinoma (ESCC). We aimed to determine whether the timing of PORT affects the long-term prognosis of ESCC, and plotted nomograms to predict survival.

Methods: We retrospectively analyzed 351 ESCC patients who underwent radical surgery and PORT. Receiver operating characteristic curves were used to estimate the optimal cutoff point of the time interval between surgery and PORT. Cox proportional hazards regression was used to identify prognostic predictors. Overall survival (OS) and progression-free survival (PFS) were predicted using nomograms.

Results: The median follow-up was 53 months (range: 3–179 months). Compared to early PORT, PORT at >48 days after surgery was associated with better OS (adjusted hazard ratio [HR]: 1.406, $p = 0.037$) and PFS (adjusted HR: 1.475, $p = 0.018$). In the chemotherapy subgroup, incorporation of chemotherapy timing into the analysis suggested that 2–4 chemotherapy cycles followed by PORT was the optimal treatment schedule as compared to 0–1 chemotherapy cycle followed by PORT and concurrent chemoradiotherapy (5-year PFS: 65.9% vs. 51.0% vs. 50.1%; $p = 0.049$). The nomograms for OS and PFS were superior to the TNM classification (concordance indices: 0.721 vs. 0.626 and 0.716 vs. 0.610, respectively).

Conclusions: Delayed PORT (>48 days) provides better survival benefit than early PORT among ESCC patients. PORT following 2–4 chemotherapy cycles might lead to the best survival rate. The nomogram plotted in this study effectively predicted survival and may help guide treatment.

Introduction

According to GLOBOCAN 2018, esophageal cancer is the seventh most common cancer worldwide and the sixth leading cause of death; every year, there are more than 572,000 new cases of esophageal cancer worldwide, with more than 508,000 deaths [1]. Approximately half of all new cases are diagnosed in China [2]. Fortunately, however, advances in the detection and treatment of esophageal cancer have led to an increase in the likelihood of survival between 2000 and 2018 [3].

Surgery is the mainstay of treatment for resectable esophageal cancer. However, almost 40% of patients who undergo surgery alone develop locoregional recurrence, and almost 30% of them develop distant metastases, with no significant difference between the timing of locoregional recurrence and the timing of systemic recurrence [4]. Many studies have shown that compared with surgery alone, surgery followed by radiotherapy or chemoradiotherapy is associated with better locoregional control and longer survival [5–7]. However, the prognostic implications of the time interval between surgery and postoperative radiotherapy (PORT) are not well established, and the optimal time for

Abbreviations: PORT, postoperative radiotherapy; ESCC, esophageal squamous cell carcinoma; OS, overall survival; PFS, progression-free survival; AJCC, American Joint Committee on Cancer; pT classification, pathological T classification; pN classification, pathological N classification; LNR, lymph node ratio; HR, hazard ratio; ROC, receiver operating characteristic; AUC, area under the curve; C-index, concordance index; SEER, Surveillance, Epidemiology, and End Results; SD, standard deviation; 2D, two dimensional; 3D, three dimensional; CI, confidence interval.

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initiating radiation after surgery so as to maximize patient survival remains an open question.

Studies on the effects of the time interval between radiotherapy and surgery for esophageal cancer have mainly focused on the interval between neoadjuvant radiotherapy and surgery [8–10]. Few studies have explored the effects of the interval between surgery and PORT [11,12], and important confounding factors such as the number of lymph nodes removed and the sequence of postoperative adjuvant treatments, which may account for prognostic differences, have been ignored. Although the interval between surgery and PORT has been more thoroughly studied for other malignancies, the results obtained have been mixed [13–15]. The optimal timing of PORT after surgery for locally advanced esophageal squamous cell carcinoma (ESCC) is important for clinicians to establish a treatment strategy, but remains to be reliably determined. Therefore, the present study aimed to determine the survival impact of the timing of PORT after surgery for ESCC and to develop a new prognostic model to predict the 5-year overall survival (OS) and progression-free survival (PFS).

Materials and methods

Patients

The study subjects consisted of 351 patients with locally advanced ESCC who underwent complete resection (R0 resection) and PORT at Fujian Cancer Hospital between June 2006 and June 2016. The time interval between the surgery and PORT as well as other clinical data were retrospectively collected. The inclusion criteria were pathologically proven squamous cell carcinoma, R0 resection with negative margins, and surgery followed by PORT. The exclusion criteria were neoadjuvant radiotherapy, PORT performed after tumor recurrence or metastasis, unknown interval between surgery and PORT, incomplete outcome data, and a second malignant primary cancer.

Data collection

The following patient- and tumor-related factors were collected: age, sex, comorbidities, tumor location, tumor differentiation, pathological T (pT) classification, pathological N (pN) classification, tumor length, the number of positive lymph nodes, vascular tumor emboli, and nerve invasion. The treatment-related characteristics included neoadjuvant chemotherapy, surgical approach, number of lymph nodes removed, postoperative complications, adjuvant chemotherapy, time interval between surgery and PORT, radiation technology, and radiation dose. We also calculated the lymph node ratio (LNR), which was defined as the ratio of positive to removed lymph nodes. We used the 8th edition of the American Joint Committee on Cancer (AJCC) staging system to reclassify all patients in our study.

Statistical analysis

The primary outcome measure was OS, and the secondary outcome measure was PFS. OS was measured from the date of the surgery to the date of death from any cause or the date of the last follow-up. PFS was measured from the date of the surgery to the date on which evidence of tumor progression was found, the date of death from any cause, or the date of the last follow-up. Continuous data were compared using the Wilcoxon-Mann-Whitney nonparametric test. Categorical data were compared using the Pearson chi-square test or the Fisher exact test. Since the clinical interpretation and application of hazard ratios (HRs) is easier, the time interval was analyzed as a categorical variable rather than a continuous variable. Receiver operating characteristic (ROC) curve analysis was conducted to estimate the optimal cutoff points for the time interval between surgery and PORT, and the LNR. Differences in OS and PFS between groups were assessed using log-rank tests and demonstrated using Kaplan-Meier curves. The clinicopathological and treatment-related factors collected were subjected to univariate Cox analysis. Those factors with $p < 0.10$ in the univariate Cox analysis were then incorporated into the multivariate Cox analysis to identify independent predictors of survival. All tests were two-sided, and $p < 0.05$ was considered significant. All statistical analyses were performed using SPSS *v*25.0 (IBM Inc., Armonk, NY, USA).

Nomogram construction and validation

Using the results of the multivariate Cox analysis, we constructed nomograms integrating all the independent prognostic factors. The 5-year OS and PFS rates were predicted using the rms packages of the R software (version 4.0.1). The Harrell concordance index (C-index) and the area under the ROC curve (AUC) were used to test the prognostic accuracy of the model among patients with locally advanced ESCC after radical resection and PORT. The consistency between the actual observed survival rates and the predicted survival rates was evaluated using calibration curves. Bootstrapping with 1000 re-samples was used to evaluate both the discrimination and calibration of the model.

Results

Patient characteristics

A total of 351 patients were included in this study. On the basis of the ROC curves for both OS and PFS, we divided the time interval between surgery and PORT as a dichotomous variable at a cutoff point of 48 days. Thus, patients were divided into an early PORT group (≤48 days) and a delayed PORT group (>48 days). The baseline demographic, tumor, and treatment characteristics of the patients in the two groups are listed in Table 1. The median interval between surgery and PORT was 57 days (range: 19–160 days). The median follow-up period from the date of the surgery to the date of death or the last follow-up was 53 months (range: 3–179 months). At the first diagnosis, 69.23% of patients were aged less than 60 years. In all, 78.63% of the patients were male, and 60.40% of the tumors were located in the middle third of the esophagus. The most common pT and pN classifications were pT3 (56.98%) and pN1 (48.72%). The optimal cut-off value for LNR calculated using ROC curves was 0.075, patients with LNR < 0.075 account for 56.70%. The patients in the delayed PORT (>48 days) group had a higher proportion of postoperative complications (27.16% vs. 5.56%, $p < 0.001$), greater number of lymph nodes removed (median, 33 vs. 29, $p = 0.002$), and a higher probability of pN+ disease (72.02% vs. 60.19%, $p < 0.004$) than those in the early PORT (≤48 days) group.

Progression-free survival

The 5-year PFS was 52.5% (95% confidence interval [CI]: 0.472–0.578), and the median PFS was 48 months (range: 2–173 months). The interval between surgery and PORT significantly influenced the PFS (Fig. 1A). The 5-year PFS rates in the early and delayed PORT groups were 41.0% (95% CI: 0.316–0.504) and 58.0% (95% CI: 0.517–0.643; $p < 0.001$), respectively.

The results of the univariate and multivariate Cox regression analyses of factors influencing PFS are shown in Table 2. On univariate Cox regression analysis, initiation of PORT at ≤48 days after surgery was associated with a 1.7-fold increase in the probability of tumor progression (HR: 1.703, 95% CI: 1.256–2.309; $p = 0.001$) in comparison with initiation of PORT after 48 days. Multivariate Cox regression analysis showed that in comparison with a time to PORT of >48 days, a time to PORT of ≤48 days was associated with a 1.5-fold increase in the probability of tumor progression (adjusted HR: 1.475, 95% CI: 1.068–2.037; $p = 0.018$). Additional factors associated with a poorer PFS were male sex as compared to female sex (adjusted HR:

Table 1
Demographic, clinicopathological, and treatment characteristics of patients.

Variable		≤48 days $n=108$ (%)	>48 days $n=243$ (%)	p
Age (years)	≤60	78 (72.22)	165 (67.90)	0.418
	>60	30 (27.78)	78 (32.10)	
Sex	Male	90 (83.33)	186 (76.54)	0.152
	Female	18 (16.67)	57 (23.46)	
Comorbidities	No	86 (79.63)	192 (79.01)	0.895
	Yes	22 (20.37)	51 (20.99)	
Tumor location	Upper	30 (27.78)	58 (23.87)	0.686
	Middle	64 (59.26)	148 (60.90)	
	Lower	14 (12.96)	37 (15.23)	
Tumor differentiation	Poor	12 (11.11)	32 (13.17)	0.750
	Moderate	85 (78.70)	191 (78.60)	
	Well	11 (10.19)	20 (8.23)	
pT classification	1	3 (2.78)	10 (4.12)	0.588
	2	17 (15.74)	42 (17.28)	
	3	59 (54.63)	141 (58.02)	
	4	29 (26.85)	50 (20.58)	
pN classification	0	43 (39.81)	68 (27.98)	0.004
	1	54 (50.00)	117 (48.15)	
	2	5 (4.63)	44 (18.11)	
	3	6 (5.56)	14 (5.76)	
Number of positive lymph nodes	Mean ± SD	2.70 ± 3.89	2.99 ± 3.97	0.136
	Median	1.50	2.00	
Number of lymph nodes removed	Mean ± SD	29.54 ± 11.77	34.47 ± 13.62	0.002
	Median	29.00	33.00	
LNR	<0.075	63 (58.33)	136 (55.97)	0.715
	≥0.075	45 (41.67)	107 (44.03)	
Tumor length (cm)	Mean ± SD	4.50 ± 1.65	4.30 ± 1.58	0.301
	Median	4.00	4.00	
Vascular tumor emboli	No	78 (72.22)	168 (69.14)	0.560
	Yes	30 (27.78)	75 (30.86)	
Nerve invasion	No	98 (90.74)	206 (84.77)	0.130
	Yes	10 (9.26)	37 (15.23)	
Neoadjuvant chemotherapy	No	99 (91.67)	225 (92.59)	0.764
	Yes	9 (8.33)	18 (7.41)	
Surgical approach	Open	76 (70.37)	133 (54.73)	0.006
	Endoscopic	32 (29.63)	110 (45.27)	
Postoperative complications	No	102 (94.44)	177 (72.84)	<0.001
	Yes	6 (5.56)	66 (27.16)	
Adjuvant chemotherapy	No	32 (29.63)	36 (14.81)	0.001
	Yes	76 (70.37)	207 (85.19)	
Radiation technology	2D	76 (70.37)	112 (46.09)	<0.001
	3D	32 (29.63)	131 (53.91)	
Radiation dose (cGy)	Mean ± SD	5125.09 ± 322.64	5110.40 ± 312.23	0.308
	Median	5000	5000	

SD, standard deviation; pT classification, pathological T classification; pN classification, pathological N classification; LNR, lymph node ratio; 2D, two dimensional; 3D, three dimensional.

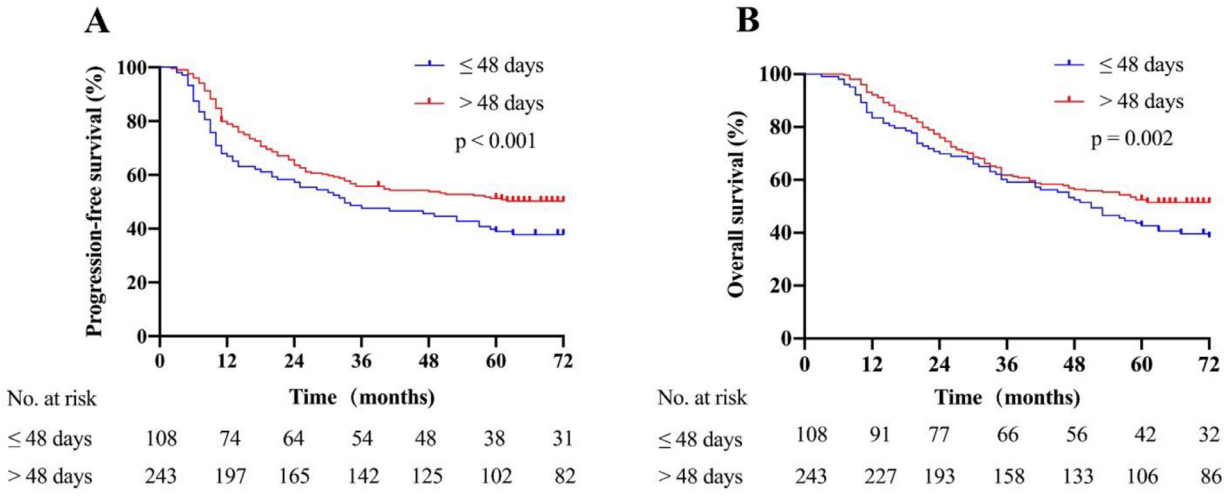

Fig. 1. Kaplan-Meier curves according to time interval categories for the whole study population (univariate analysis) showing (A) progression-free survival ($p < 0.001$) and (B) overall survival ($p = 0.002$).

Table 2
Factors associated with progression-free survival: univariate and multivariate Cox proportional hazards models.

Variable	n	Univariate Analysis			Multivariate Analysis		
		HR	95% CI	p	HR	95% CI	p
Age (years)		0.703	0.516–	0.026	0.764	0.549–	0.111
≤60/ >60	243/108		0.959			1.064	
Sex		1.770	1.174–	0.006	1.611	1.050–	0.029
Male/female	276/75		2.671			2.473	
Comorbidities		0.754	0.532–	0.112	–		
No/yes	278/73		1.068				
Tumor location		0.898	0.634–	0.543	–		
Upper/middle and lower	88/263		1.271				
Tumor differentiation		0.971	0.609–	0.902	–		
Poor/well and moderate	44/307		1.548				
pT classification		0.602	0.396–	0.017	0.769	0.496–	0.241
T1 and T2/T3 and T4	72/279		0.914			1.192	
pN classification		0.518	0.363–	<0.001	0.683	0.427–	0.110
N0/N1 and N2 and N3	111/240		0.739			1.090	
Number of positive lymph nodes	351	1.083	1.057–1.110	<0.001	1.057	1.018–1.097	0.004
Number of lymph nodes removed	351	0.984	0.972–0.996	0.008	0.984	0.969–0.999	0.036
LNR		0.358	0.263–	<0.001	0.532	0.345–	0.004
<0.075/ ≥0.075	199/152		0.486			0.820	
Tumor length (cm)	351	1.175	1.072–1.288	0.001	1.143	1.037–1.259	0.007
Vascular tumor emboli		0.692	0.505–	0.021	0.991	0.699–	0.961
No/yes	246/105		0.947			1.406	
Nerve invasion		1.008	0.644–	0.973	–		
No/yes	304/47		1.577				
Neoadjuvant chemotherapy		1.184	0.643–	0.588	–		
No/yes	324/27		2.181				
Surgical approach		1.603	1.159–	0.004	1.439	1.023–	0.037
Open/endoscopic	209/142		2.217			2.024	
Postoperative complications		1.081	0.739–	0.688	–		
No/yes	279/72		1.581				
Adjuvant chemotherapy		1.391	0.976–	0.068	1.814	1.219–	0.003
No/yes	68/283		1.982			2.698	
Radiation technology		1.116	0.822–	0.483	–		
2D/3D	188/163		1.515				
Radiation dose (cGy)	351	1.001	1.000–1.001	0.001	1.001	1.000–1.001	0.007
Time interval (days)		1.703	1.256–	0.001	1.475	1.068–	0.018
≤48/ >48	108/243		2.309			2.037	

HR, hazard ratio; 95% CI, 95% confidence interval; pT classification, pathological T classification; pN classification, pathological N classification; LNR, lymph node ratio; 2D, two dimensional; 3D, three dimensional.

1.611, 95% CI: 1.050–2.473; $p = 0.029$), each increment in the number of positive lymph nodes (adjusted HR: 1.057, 95% CI: 1.018–1.097; $p = 0.004$), each increment in tumor length (adjusted HR: 1.143, 95% CI: 1.037–1.259; $p = 0.007$), open approach as compared to endoscopic approach (adjusted HR: 1.439, 95% CI: 1.023–2.024; $p = 0.037$), no adjuvant chemotherapy as compared to adjuvant chemotherapy (adjusted HR: 1.814, 95% CI: 1.219–2.698; $p = 0.003$), and each increment in radiation dose (adjusted HR: 1.001, 95% CI: 1.000–1.001; $p = 0.007$). Factors associated with improved PFS were each increment in the number of lymph nodes removed (adjusted HR: 0.984, 95% CI: 0.969–0.999; $p = 0.036$) and LNR < 0.075 as compared to LNR ≥ 0.075 (adjusted HR: 0.532, 95% CI: 0.345–0.820; $p = 0.004$).

Overall survival

The 5-year OS was 54.1% (95% CI: 0.488–0.594), and the median OS was 53 months (range: 3–179 months). The time interval between surgery and PORT significantly affected OS (Fig. 1B). The 5-year OS rates in the early and delayed PORT groups were 44.6% (95% CI: 0.352–0.540) and 58.6% (95% CI: 0.521–0.651; $p = 0.002$), respectively.

The results of the univariate and multivariate Cox regression analyses of factors influencing OS are shown in Table 3. On univariate Cox regression analysis, early PORT was associated with a 1.6-fold increase in mortality (HR: 1.615, 95% CI: 1.192–2.189; $p = 0.002$) in comparison with delayed PORT. Multivariate Cox regression showed that in comparison with a time to PORT of >48 days, a time to PORT of ≤48 days was associated with a 1.4-fold increase in mortality (adjusted HR: 1.406; 95% CI: 1.020–1.938; $p = 0.037$). Additional factors associated with poorer OS were male sex as compared with female sex (adjusted HR: 1.539, 95% CI: 1.003–2.362; $p = 0.048$), each increment in the number of positive lymph nodes (adjusted HR: 1.048, 95% CI: 1.011–1.087; $p = 0.012$), each increment in tumor length (adjusted HR: 1.156, 95% CI: 1.048–1.275; $p = 0.004$), open approach as compared to endoscopic approach (adjusted HR: 1.466, 95% CI: 1.042–2.063; $p = 0.028$), no adjuvant chemotherapy as compared to adjuvant chemotherapy (adjusted HR: 2.025, 95% CI: 1.350–3.038; $p = 0.001$), and each increment in radiation dose (adjusted HR: 1.001, 95% CI: 1.000–1.001; $p = 0.002$). Additional factors associated with improved OS were classification N0 as compared to classifications N1–N3 (adjusted HR: 0.597, 95% CI: 0.371–0.960; $p = 0.033$), each increment in the number of lymph nodes removed (adjusted HR: 0.982, 95% CI: 0.967–0.997; $p = 0.020$), and LNR < 0.075 as compared to LNR ≥ 0.075 (adjusted HR: 0.539, 95% CI: 0.350–0.830; $p = 0.005$).

Prediction nomogram for conditional survival

We plotted prognostic nomograms integrating all the independent predictors of PFS (Fig. 2) and OS (Fig. 3). Each factor was assigned points according to its coefficient. The 5-year PFS and OS rates were predicted by the sum of these points. The discriminative ability of the nomograms was compared with that of the 8th AJCC TNM classification. Our prediction model had an optimism-adjusted C-statistic for OS of 0.721 (95% CI: 68.346–75.981), which was superior to that of the 8th AJCC TNM classification (0.626, 95% CI: 58.994–66.249). The C-index for PFS (0.716, 95% CI: 67.856–75.385) was also superior to that

Table 3
Factors associated with overall survival: univariate and multivariate Cox proportional hazards models.

Variable	n	Univariate Analysis			Multivariate Analysis		
		HR	95% CI	p	HR	95% CI	p
Age (years)		0.660	0.484–	0.009	0.796	0.569–	0.185
≤60/ >60	243/108		0.900			1.115	
Sex		1.739	1.153–	0.008	1.539	1.003–	0.048
Male/female	276/75		2.623			2.362	
Comorbidities		0.743	0.524–	0.096	0.748	0.514–	0.131
No/yes	278/73		1.054			1.090	
Tumor location		0.908	0.641–	0.585	–		
Upper/middle and lower	88/263		1.285				
Tumor differentiation		0.957	0.600–	0.852	–		
Poor/well and moderate	44/307		1.525				
pT classification		0.584	0.384–	0.011	0.697	0.447–	0.112
T1 and T2/T3 and T4	72/279		0.886			1.088	
pN classification		0.489	0.343–	<0.001	0.597	0.371–	0.033
N0/N1 and N2 and N3	111/240		0.696			0.960	
Number of positive lymph nodes	351	1.076	1.051–1.102	<0.001	1.048	1.011–1.087	0.012
Number of lymph nodes removed	351	0.985	0.973–0.996	0.011	0.982	0.967–0.997	0.020
LNR		0.364	0.268–	<0.001	0.539	0.350–	0.005
<0.075/ ≥0.075	199/152		0.494			0.830	
Tumor length (cm)	351	1.188	1.084–1.301	<0.001	1.156	1.048–1.275	0.004
Vascular tumor emboli		0.652	0.477–	0.008	0.930	0.658–	0.682
No/yes	246/105		0.893			1.315	
Nerve invasion		0.952	0.608–	0.830	–		
No/yes	304/47		1.490				
Neoadjuvant chemotherapy		1.127	0.612–	0.701	–		
No/yes	324/27		2.077				
Surgical approach		1.546	1.118–	0.009	1.466	1.042–	0.028
Open/endoscopic	209/142		2.138			2.063	
Postoperative complications		1.000	0.683–	0.999	–		
No/yes	279/72		1.463				
Adjuvant chemotherapy		1.432	1.004–	0.047	2.025	1.350–	0.001
No/yes	68/283		2.042			3.038	
Radiation technology		1.085	0.799–	0.602	–		
2D/3D	188/163		1.474				
Radiation dose (cGy)	351	1.001	1.000–1.001	0.001	1.001	1.000–1.001	0.002
Time interval (days)		1.615	1.192–	0.002	1.406	1.020–	0.037
≤48/ >48	108/243		2.189			1.938	

HR, hazard ratio; 95% CI, 95% confidence interval; pT classification, pathological T classification; pN classification, pathological N classification; LNR, lymph node ratio; 2D, two dimensional; 3D, three dimensional.

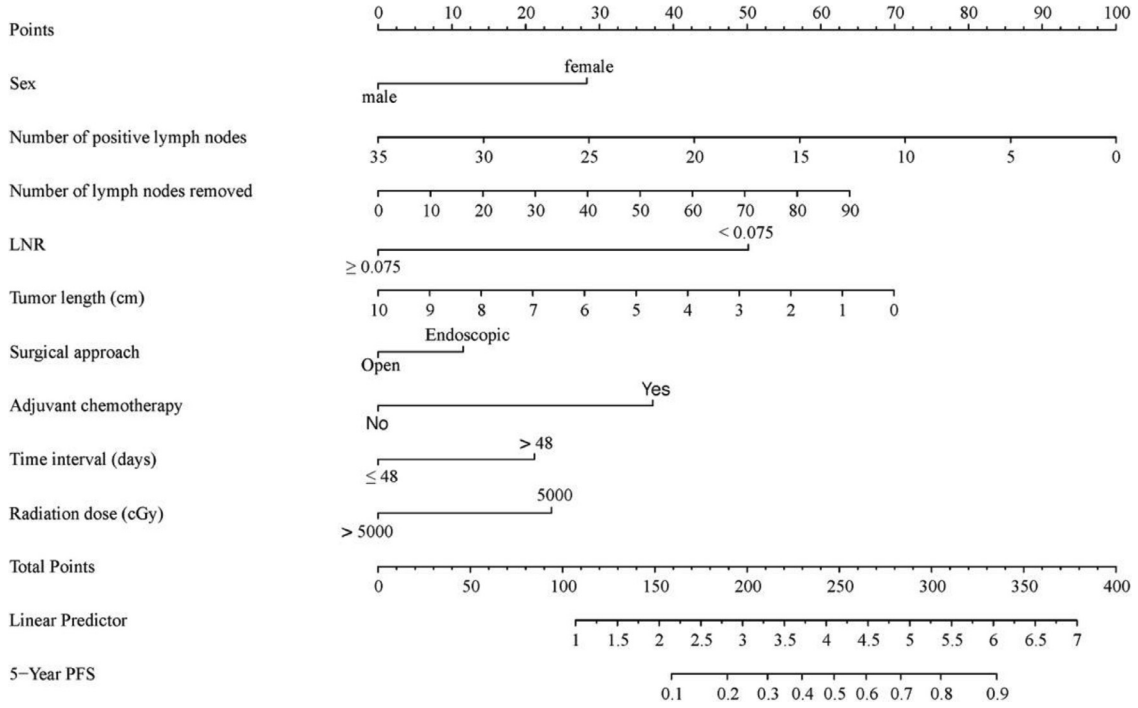

Fig. 2. Nomogram predicting the 5-year PFS rate of patients with ESCC after radical surgery. The nomogram added up the points identified on the scale for each independent variable. The total points projected on the bottom scale indicate the probabilities of 5-year PFS rates.
PFS, progression-free survival; ESCC, esophageal squamous cell carcinoma; LNR, lymph node ratio.

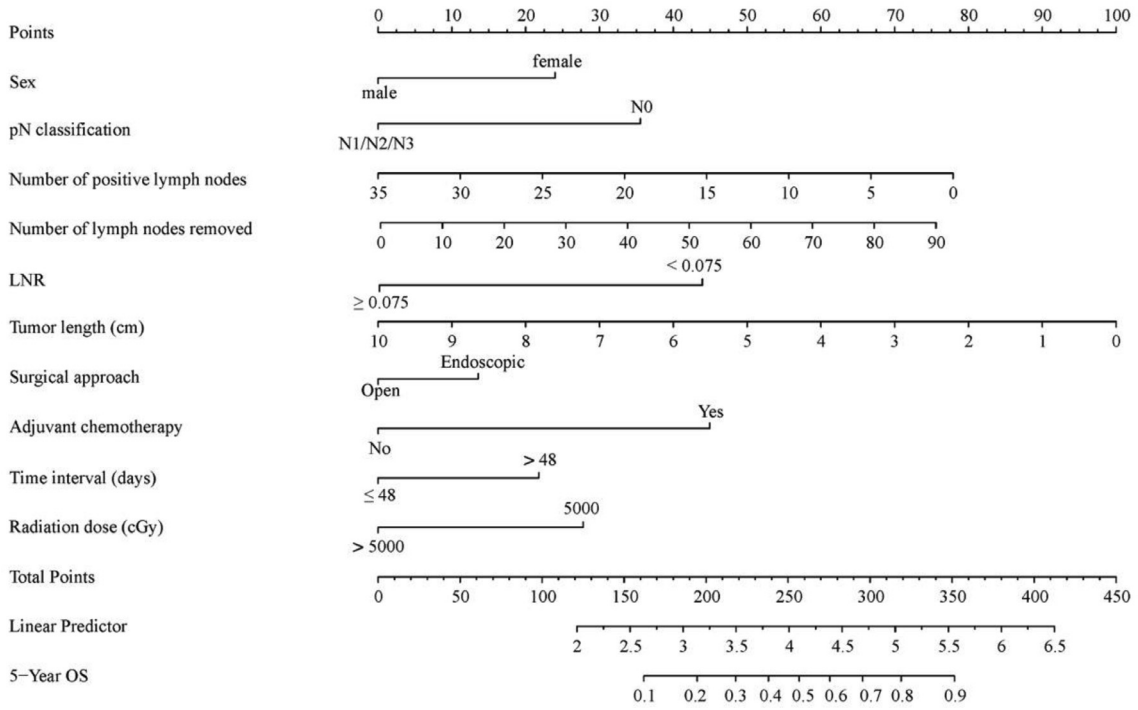

Fig. 3. Nomogram predicting the 5-year OS rate of patients with ESCC after radical surgery. The nomogram added up the points identified on the scale for each independent variable. The total points projected on the bottom scale indicate the probabilities of 5-year OS rates.
OS, overall survival; ESCC, esophageal squamous cell carcinoma; pN classification, pathological N classification; LNR, lymph node ratio.

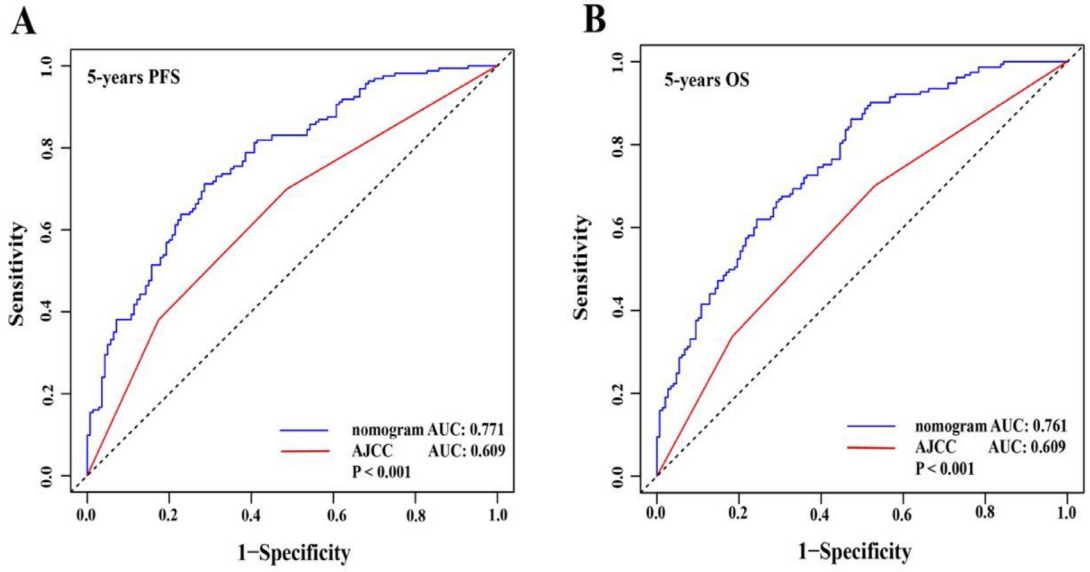

Fig. 4. ROC curves with AUC values to compare the prognostic accuracy of the nomogram and the 8th AJCC TNM staging system. The blue lines represent the survival rates predicted by the nomogram, whereas the red lines represent the survival rates predicted by the AJCC TNM staging system. The AUCs of the two models predict the 5-year PFS rates (A) and the 5-year OS rates (B).
ROC, receiver operating characteristic; AUC, area under the curve; AJCC, American Joint Committee on Cancer; PFS, progression-free survival; OS, overall survival.

of the 8th AJCC TNM staging (0.610, 95% CI: 57.199–64.892). Furthermore, AUC models were used to evaluate the prognostic accuracy of the nomograms (Fig. 4). For predicting the 5-year PFS rate, the AUC of our nomogram was significantly greater than that of the AJCC staging system (0.771 vs. 0.609, $p < 0.001$). For predicting the 5-year OS rate, the AUC of our nomogram was also significantly greater than that of the AJCC staging (0.761 vs. 0.609, $p < 0.001$).

Calibration curves were generated to validate the consistency between the actual observed survival rates and the survival probability predicted using the nomograms (Fig. 5). The results indicated that the nomograms were well calibrated.

Survival stratified by chemotherapy

We found that adjuvant chemotherapy was an independent prognostic factor. Among the patients who received adjuvant chemotherapy, both PFS ($p = 0.008$) and OS ($p = 0.014$) significantly differed between the early and delayed PORT groups (Fig. 6A and 6B). In our study,

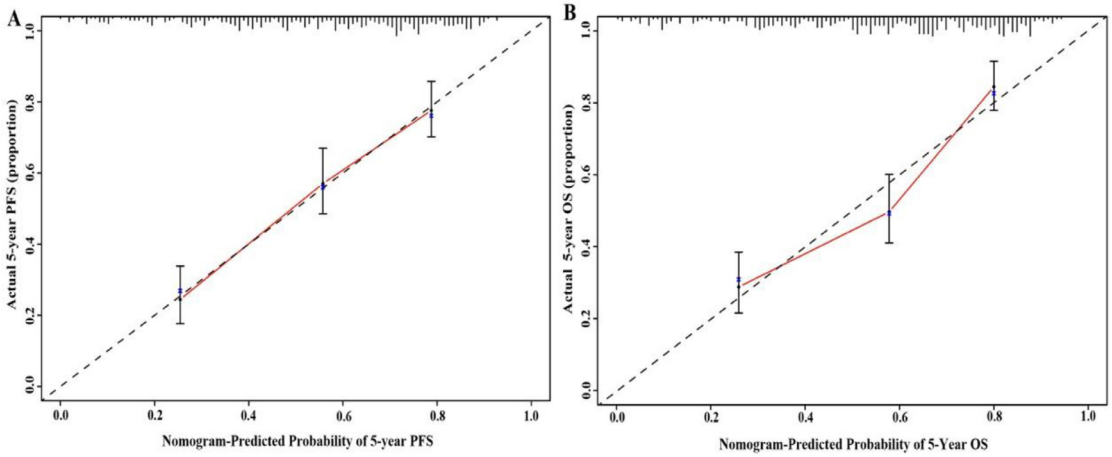

Fig. 5. Calibration plots of the nomograms for 5-year PFS prediction (A) and 5-year OS prediction (B). The x axis displays the nomogram-predicted probability, while the y axis displays the actual survival rates estimated by the Kaplan-Meier method. The dotted line indicates an excellent calibration model, with complete concordance between the predicted survival probabilities and the actual survival rates. The vertical bars indicate 95% CIs.
PFS, progression-free survival; OS, overall survival; CI, confidence interval.

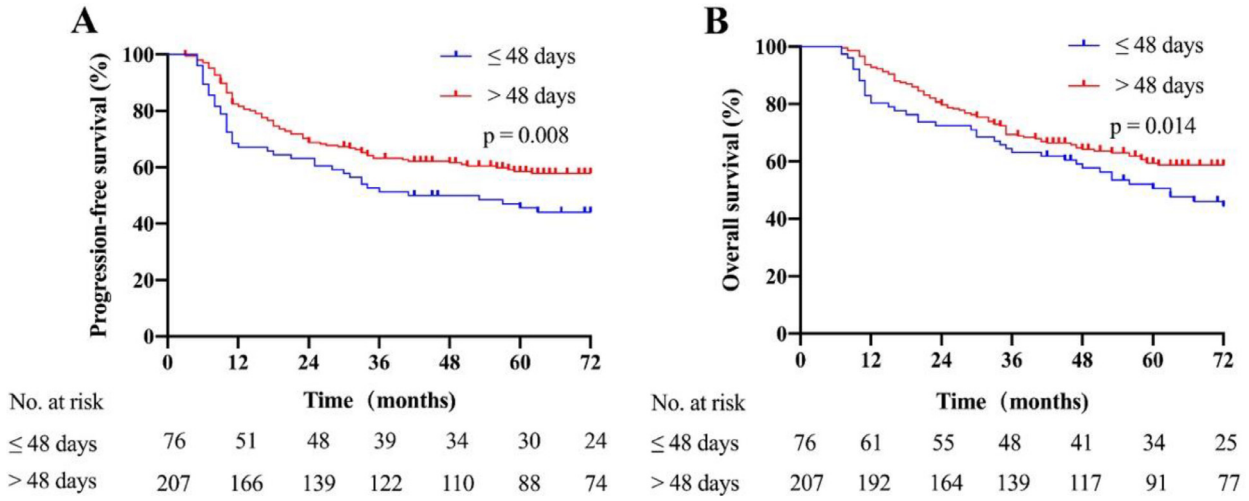

Fig. 6. Kaplan-Meier curves according to time interval categories among patients who received adjuvant chemotherapy (univariate analysis) showing (A) progression-free survival ($p = 0.008$) and (B) overall survival ($p = 0.014$).

99 patients received concurrent chemoradiotherapy, and 184 patients received sequential chemoradiotherapy. In the sequential chemoradiotherapy group, the number of patients who did not undergo chemotherapy before PORT and those who underwent 1, 2, 3, or 4 cycles of chemotherapy before PORT were 10, 93, 51,16, and 14, respectively. After incorporating chemotherapy timing into our analysis, we found that treatment with 2–4 cycles of chemotherapy followed by PORT was associated with the best PFS (median PFS: 58 months, 5-year PFS: 65.9%; $p = 0.049$), followed by 0–1 cycles of chemotherapy before PORT (median PFS: 46.5 months, 5-year PFS: 51.0%) and concurrent chemoradiotherapy (median PFS: 42 months, 5-year PFS: 50.1%). However, these subgroups did not show significant differences in OS ($p = 0.09$).

Discussion

Adjuvant therapy for locally advanced esophageal cancer is very important, though the optimal timing of PORT in patients who have undergone radical resection of esophageal cancer remains to be determined. In the present study, after adjustments for numerous confounding factors, we found that initiating PORT ≥48 days after the surgery was associated with a better OS (adjusted HR: 1.406, $p = 0.037$) and PFS (adjusted HR: 1.475, $p = 0.018$). To the best of our knowledge, this is the first study to include the time interval between surgery and PORT for locally advanced ESCC in nomograms.

Two studies have previously attempted to explore the influence of the time interval between surgery and PORT on the survival of patients with esophageal cancer [11,12]. A retrospective study by Yamada et al. showed a higher mortality rate among patients who received PORT after 40 days after surgery than among those who started PORT within 40 days, though the difference in mortality was not significant [12]. In another retrospective study, Wang et al. reported that a delay in initiating PORT of longer than 26 days did not appear to have a survival cost, but a delay of longer than 42 days had a detrimental impact on OS [11]. The inconsistencies in the above results and those of our study may be attributable to differences in both patient composition and confounding factors. All patients enrolled in our study had squamous cell carcinoma. Furthermore, we found that some confounding factors, such as LNR and surgical approach, were also independent prognostic factors for survival. Although the majority of the patients in our present study and the two studies cited above received adjuvant chemoradiotherapy, the above two studies did not consider the effects of the sequence of adjuvant radiotherapy and chemotherapy, so they did not have sufficient evidence to draw reliable conclusions. Furthermore, the discriminative

ability of the nomogram constructed in this study showed a clear prognostic superiority over the 8th AJCC staging (C-index for OS: 0.721 vs. 0.626, C-index for PFS: 0.716 vs. 0.610).

Studies on the time interval between surgery and PORT for some other tumors have shown no survival benefit to starting PORT too early [14,16]. A retrospective study of head and neck cancer by Graboyes et al. found that early radiation was not associated with improved survival, as compared to initiating PORT 5–6 weeks after surgery [14]. Sura et al. retrospectively evaluated patients with pN2 non-small-cell lung cancer who underwent adjuvant chemoradiotherapy after surgery, and demonstrated that a time to radiation of ≥8 weeks with sequential chemotherapy was associated with improved survival [16]. Consistent with the above results, our data showed a superior OS of 58.6% and a superior PFS of 58% for delayed PORT (≥48 days) as compared to 44.6% and 41.0%, respectively, for early PORT (<48 days). The potential mechanisms underlying the association between early radiotherapy and poor prognosis may include the following: (1) early radiotherapy impedes wound healing; (2) poor shrinkage in the surgical area leads to a larger target volume for radiation therapy; (3) hypoxia in the tissue surrounding the surgical bed induces tumor resistance [17]; and (4) it may be more beneficial to perform another adjuvant therapy before PORT.

With a single predictor, such as the AJCC staging system, it is difficult to accurately predict the prognosis of ESCC after surgical resection. As other important prognostic factors are not considered, patients with the same tumor stage may have different clinical outcomes. In our nomogram, specific predicted 5-year OS and PFS rates were assigned for each total score, which may help clinical decision-making. A survival nomogram of esophageal cancer patients undergoing radical surgery has been developed before [18]. However, currently available nomograms do not take into account the interval between surgery and PORT. The nomogram developed in our study had a high C-index and large AUC, was well-calibrated, and could provide better predictive performance for individual patients.

Sex was found to be an independent predictor affecting long-term prognosis in our study. A large analysis based on the Surveillance, Epidemiology, and End Results (SEER) database also showed that female patients have significantly better outcomes than male patients, especially in ESCC [19]. We found that for every 1 cm increase in tumor length, the risk of death and disease progression relatively increased by 15.6% and 14.3%, respectively. Yendamuri et al. recommended that tumor length be incorporated into the current staging system for esophageal cancer to better evaluate long-term survival and determine postoperative treatment options [20]. In recent years, endoscopic surgery has been increasingly used instead of open surgery. Our research showed that endoscopic surgery has a survival advantage over open surgery. A meta-regression analysis identified 55 relevant studies that drew the conclusion that endoscopic surgery, due to its minimally invasive nature, can be recommended as a standard surgical approach for esophageal cancer [21]. The landmark RTOG 94–05 randomized controlled trial and the interim analysis founded that increasing radiation dose from 50.4 to 64.8 Gy has no benefit in increasing locoregional control or OS [22]. In our research, the minimum radiation dose was 5000 cGy, and for each additional 1 cGy, the risk of death or disease progression was relatively increased by 1%.

A study on esophageal cancer found that pN+, increased number of positive nodes, and an increase in the pN classification were associated with a poor prognosis [23]. During esophagectomy, more extensive lymph node dissection provides benefit in terms of locoregional control and may also improve OS [24]. An analysis of esophageal cancer in the SEER database showed that the mortality rate of patients with 30 or more lymph nodes removed was significantly lower than that of patients with less than 30 lymph nodes removed [25]. Our multivariate analysis also showed that as the number of lymph nodes removed increased, both OS ($p = 0.020$) and PFS ($p = 0.036$) improved. Consistent with our results, a study has reported that LNR is an independent predictor of survival in esophageal cancer [26]. In our study, ROC curve analysis showed that the best cutoff value of LNR was 0.075, and patients with LNR < 0.075 were found to have better survival than patients with LNR ≥ 0.075.

Wong et al. discovered that adjuvant chemoradiotherapy can improve prognosis as compared to adjuvant radiotherapy alone [27]. We found that in patients who received adjuvant chemotherapy, the initiation of PORT tended to be delayed. A subgroup analysis of patients who received chemotherapy, stratified by time interval, showed that delayed PORT (≥48 days) significantly improved OS ($p = 0.014$) and PFS ($p = 0.008$). After incorporating the chemotherapy timing, the results suggested that provided R0 resection has been achieved, receiving 2–4 cycles of adjuvant chemotherapy between surgery and radiation therapy was beneficial. The potential benefits of this treatment schedule may include adequate wound healing, a smaller target volume for radiation therapy, sufficient time for tissue re-oxygenation, a vascular network that facilitates the passage of chemotherapy drugs, and earlier treatment of occult, disseminated micrometastatic disease. The above treatment schedule may lead to good local control and also reduce the occurrence of distant metastasis, though further research is needed to ensure that it has deterministic benefits.

Some limitations of our study should be noted. First, this study is a single-institution analysis, which may be subject to selection bias. Second, the study did not allow for the correction of all potential confounding factors, such as patients' nutritional status and adverse effects of radiation therapy. Third, currently, there is wide variation in the sequence of adjuvant treatments for ESCC, including concurrent therapy, sequential therapy, and sandwich therapy. More prospective studies and clinical trials are needed to identify the treatment options with the maximum benefits.

Conclusions

In conclusion, the present study identified that delayed PORT (>48 days) was associated with better survival in patients with ESCC who had undergone R0 resection. Treatment with chemotherapy followed by PORT may achieve the best survival benefit. The nomograms we established provided a clear prognostic superiority, in terms of OS and PFS, over the 8th AJCC TNM staging.

Ethics approval and consent to participate

The current study was approved by the ethics committee of Fujian Medical University Cancer Hospital, Fuzhou, China (YKT2020-010-01) and conducted in accordance with the principles of the Declaration of Helsinki and its amendment. All patients provided written informed consent prior to treatment, and all the information was anonymized prior to analysis.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions statement

All authors helped to perform the research. MQL and JLL: Conceptualization, Methodology, Software, Writing - original draft preparation. ZKZ and XHC: Visualization, Investigation, Writing - review & editing,

Formal analysis. YQD and JYM: Project administration. SYH and YBH: Data curation, Investigation, Writing - review & editing. JCL: Funding acquisition, Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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