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Comparison of radiation esophagitis associated with daytime versus evening radiotherapy in patients with esophageal carcinoma

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Abstract

Purpose Based on the demonstration of a circadian rhythm in the human oral mucosa cell cycle, with most cells in the G2/M phase in the afternoon and at night, the present study evaluated the severity of acute radiation esophagitis and treatment outcomes in esophageal squamous cell carcinoma patients receiving radiotherapy (RT) in the daytime versus in the evening.

Methods From the 488 eligible patients of esophageal squamous cell carcinoma receiving concurrent chemoradiotherapy (CCRT), 369 patients received RT in the daytime (before 19:00) and 119 patients received RT in the evening (after 19:00). The grades of radiation esophagitis (Common Terminology Criteria for Adverse Events version 5.0) and survival outcomes were compared in the two groups. Analyses were performed by using ordinal logistic regression and Cox proportional hazard regression.

Results The median follow-up was 27 months. In multivariate logistic regression models, evening treatment (after 19:00) (odds ratio, 1.660 [95% CI 1.094–2.518]), tumor length ≥ 5 cm (odds ratio, 1.632 [95% CI 1.102–2.416]), PGTV dose ≥ 59.34 Gy (odds ratio, 1.702 [95% CI 1.099–2.635]), female sex (odds ratio, 2.241 [95% CI 1.475–3.405]), and tumor location in cervical segment and upper thoracic (odds ratio, 1.665 [95% CI 1.043–2.658]) were associated with higher odds of radiation esophagitis. There was no difference in the overall survival (OS), locoregional relapse-free survival (LRFS), distant metastasis-free survival (DMFS), and progression-free survival (PFS) (all $p > 0.05$) between the daytime treatment group and evening treatment group. The results of the subgroup analysis showed that no significant difference was found in radiation esophagitis between the two groups with PGTV dose < 59.34 Gy, while there was a higher odds for the Grade 2 or higher radiation esophagitis in the evening treatment group than the daytime treatment group (odds ratio, 1.675 [95% CI 1.062–2.643]) with PGTV dose ≥ 59.34 Gy.

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Conclusion RT in the evening (after 19:00) was associated with higher odds to present esophagitis for esophageal squamous cell carcinoma patients, especially with higher radiation doses, but treatment outcomes did not differ according to the time of RT.

Keywords Radiotherapy, Esophageal squamous cell carcinoma, Radiation esophagitis, Circadian rhythm, Survival outcomes, Ordinal logistic regression

Introduction

Esophageal carcinoma (EC) ranks seventh most common malignancy and sixth leading cause of cancer-related death [1]. For patients who cannot be treated with surgery, definitive concurrent chemoradiotherapy (CCRT) is one of the optimal options for the treatment of EC [1–3]. The development of radiotherapy technology can increase the dose of the lesion and reduce the radiation dose of the normal tissue, thereby improving the local control rate and improving survival [2, 4]. However, acute radiation esophagitis (RE) remains an important and unsolved problem. Radiation-induced esophagitis is the most common local acute toxicity of radiotherapy (RT) peaked by week 3 or 4 in a course of radiotherapy and is sometimes a dose-limiting toxicity, which usually presents with self-limiting dysphagia [5]. Severe RE can necessitate hospitalization, initiation of percutaneous or parenteral feeding, and treatment interruption. These complications significantly affect the quality of life and can negatively impact long-term survival [6–8]. Therefore, it is important to reduce the acute toxicity of radiotherapy-related esophagitis.

Previous studies indicated that digestive tract mucosal protective agents, anti-inflammatory agents, analgesics, and traditional Chinese medicine could improve the symptoms of RE [9]. However, these approaches were mainly palliative and of limited effectiveness. Once acute RE occurs, management is mainly supportive. More and more studies have confirmed that circadian rhythm plays an important role in the side effects and prognosis caused by radiotherapy [10, 11]. It is well known that cancer cells often have different biorhythms than cells in surrounding healthy tissue [10]. Diurnal variation of cell cycle phase is an important determinant of radiation sensitivity [12]. As a result, the effects of the daytime and evening radiotherapy on esophagitis may be different. This pattern suggests that it may be possible to reduce the toxicity of acute RE by adjusting the radiation duration without increasing the cost.

Previous studies have investigated the relationship between the time of radiotherapy and the incidence of oral mucositis or acute skin reaction [11, 13]. Noh et al. demonstrated that RT in the late afternoon was associated with increased Grade 2 or more skin reactions after RT for breast cancer patients [11]. Bjarnason et al. conducted a prospective randomized trial for the effect of circadian rhythm on oral mucositis, and they identified that morning RT was associated with an apparent reduction in oral mucositis in a subset of patients receiving ≥ 66 Gy [13]. To the best of our knowledge, there were rare studies investigating the relationship of radiotherapy time for esophageal carcinoma in relation to acute RE, with a small sample size [14].

In this retrospective study, we evaluated the toxicity of acute RE associated with daytime radiotherapy and evening radiotherapy in patients with esophageal carcinoma treated with chemoradiotherapy.

Methods

Patients

In this study, we retrospectively evaluated 488 patients with EC who received concurrent chemoradiotherapy at Xijing Hospital between 2012 and 2022. These patients met the following conditions: (1) cannot undergo surgery or refuses surgery; (2) histopathological proof of esophageal cell squamous carcinoma (ESCC) without distant metastasis; (3) intensity modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) radiotherapy was used in all patients; (4) radiotherapy dose was ≥ 50 Gy; (5) PS score was less than or equal to 2; (6) No previous esophagitis. Among them, 369 patients received RT in the daytime (before 19:00) and 119 patients received RT in the evening (after 19:00).

Clinical or pathological stage was done according to the 8th edition of the American Joint Committee on Cancer TNM staging system,

Treatment

All patients received radiotherapy with IMRT/VMAT from day one, along with chemotherapy. The gross tumor volume (GTV) is defined as an area of tumor lesion of a certain size as determined by means of gastroscopy, computed tomography (CT), or positron emission tomography/computed tomography (PET/CT). The clinical target volume (CTV) is defined as the tumor target area, subclinical lesion, and the area that the tumor may invade, and is 3 cm above and below the GTV, and 0.5 cm at the lateral margin. Taking into account the movement of the irradiated organs and the error of the positioning

position, the planning target volume (PTV) and the planning gross tumor volume (PGTV) are to add a 0.5 cm edge to the CTV and GTV, respectively. All patients had a total radiation dose greater than 50 Gy with each exposure of 1.8–2.2 Gy five times a week. The specific chemotherapy regimens consisted of TPF (docetaxel 60 mg/m2/day on day 1, cisplatin 50 mg/m2/day on days 1 to 2, and 5-fluorouracil 500 mg/m2/day on days 1 to 3), TP (docetaxel 60 mg/m2/day on day 1 or paclitaxel 150 mg/m2/day on day 1 and day 8, cisplatin 50 mg/m2/day on days 1 to 2), PF (cisplatin 50 mg/m2/day on days 1 to 2 and 5-fluorouracil 500 mg/m2/day on days 1 to 3). The cycles were administered every 3 weeks.

Follow-up

Patients were reassessed for complications such as disease control, and survival every 3 months in the first two years, every 6 months in the second to fifth years, and annually thereafter. The primary endpoint of this study was the incidence and grade of acute RE (Table S1), which was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). The second endpoints of the study were overall survival (OS), locoregional relapse-free survival (LRFS), distant metastasis-free survival (DMFS), and progression-free survival (PFS). OS was defined as the overall time from the first day of diagnosis to death or last follow-up. LRFS was described as the time from the date of first treatment to local recurrence or death. DMFS was calculated from the first day of treatment to the first diagnosis of distant metastases. PFS was interpreted as the time from the first day of treatment to the first diagnosis of distant metastasis.

Statistical analysis

All statistical analyses were conducted using SPSS (version 26.0). The optimal cutoff values of age, RT time, RT dose, and tumor length were calculated individually according to the receiver operating characteristics (ROC) curve or average value to select the most relevant threshold to predict acute RE. Ordinal logistic regression was used for univariate and multivariable analysis of the association between radiotherapy time and acute RE (CTCAE Grade 2 or more). Those factors with $p < 0.1$ in the univariate analysis were then incorporated into the multivariate analysis to identify independent predictors of acute RE. The effect of radiotherapy time on different grade of RE were evaluated through Chi-square test. OS, LRFS, DMFS, and PFS were evaluated using Cox proportional hazard regression. Kaplan–Meier curves in the survival analysis were used to present the percent survival of 3-, and 5-year OS, LRFS, DMFS, and PFS. $P < 0.05$ was considered statistically significant.

Results

Patients and treatment

The clinicopathological and treatment details of this patient population are summarized in Table 1. The median age of patients was 66 years (IQR 60–72 years). There were 290 patients younger than 69 years old, accounting for 59.4%. There were 367 males (75.2%). The median radiotherapy time was fourteen o'clock (IQR nine to eighteen o'clock). At first diagnosis, the median length of the tumor at the patient's lesion site was 5 cm (IQR 4–6 cm). The median dose of PGTV was 59.4 Gy (IQR 59.4–61.6 Gy), of which 113 patients were less than 59.4 Gy, accounting for 23.2%. 192 patients (39.3%) recieved single-fraction dose of 1.8 and 2.0 Gy, and 296 patients (60.7%) recieved single-fraction dose of 2.12 and 2.2 Gy. 367 people (75.2%) scored 0–1 and 121 people (24.8%) scored 2. 385 patients (78.9%) had T3 and T4 disease, and 102 patients (78.9%) had N2 and N3 lesions. At the time of visit, 364 patients (74.6%) had dysphagia. There were 101 patients (20.7%) in stage I-II, 326 patients (66.8%) in stage III, and 61 patients (12.5%) in stage IV. The main tumor locations were in the lower thoracic of 181 patients (37.1%), the middle thoracic of 179 patients (36.7%), and the cervical segment and upper thoracic of 128 patients (26.2%).

Toxicity of radiation esophagitis

The univariable and multivariable analysis results of influencing factors of acute RE are shown in Table 2. Factors that significantly affected the outcome of acute RE included radiotherapy time, tumor length at the initial visit, PGTV dose, PGTV single-fraction dose, gender, dysphagia at the visit, and main tumor location. Briefly, acute RE was more likely to occur when radiotherapy was performed at 19:00 or later ($p = 0.017$, OR = 1.660, 95% CI = 1.094–2.518). Besides, tumor length ≥ 5 cm ($p = 0.014$, OR = 1.632, 95% CI = 1.102–2.416), PGTV dose ≥ 59.34 Gy ($p = 0.017$, OR = 1.702, 95% CI = 1.099–2.635), PGTV single-fraction dose = 2.12 and 2.20 ($p = 0.020$, OR = 1.543, 95% CI = 1.072–2.221), female patients ($p < 0.001$, OR = 2.241, 95% CI = 1.475–3.405), and patients without dysphagia at visit ($p = 0.017$, OR = 1.660, 95% CI = 1.094–2.518) were associated with higher odds of acute RE. For tumor location analysis, patients in the cervical segment and upper thoracic were more likely to develop acute RE than those in the lower thoracic segment ($p = 0.032$, OR = 1.665, 95% CI = 1.043–2.658), while there was no significant result in the middle thoracic segment.

Table 1 The characteristics of patients and tumors [M (Q_L, Q_U)/n (%)]†

Variables	Total
Age (years)	66 (60, 72)
Radiotherapy time (o'clock)	14(9,18)
Tumor length in gastroscope (cm)	5(4, 6)
PGTV dose (Gy)	59.4(59.4, 61.6)
PGTV fractionation (times)	28(28, 30)
PTV dose (Gy)	50.4(50.4, 50.4)
PTV fractionation (times)	28(28, 28)
Age (years)	
< 69	290(59.4)
≥ 69	198(40.6)
Radiotherapy time	
Before 19:00	369(75.6)
After 19:00	119(24.4)
Tumor length in gastroscope (cm)	
< 5	160(32.8)
≥ 5	328(67.2)
PGTV dose (Gy)	
< 59.4	113(23.2)
≥ 59.4	375(76.8)
PGTV fractionation (times)	
< 33	448(91.8)
≥ 33	40(8.2)
PTV dose (Gy)	
< 54.19	116(23.8)
≥ 54.20	372(76.2)
PTV fractionation (times)	
< 28	119(24.4)
≥ 28	369(75.6)
Single-fraction dose (Gy)	
1.8 and 2.0	192(39.3)
2.12 and 2.2	296(60.7)
Gender	
Male	367(75.2)
Female	121(24.8)
PS	
0–1	367(75.2)
2	121(24.8)
Dysphagia	
Yes	364(74.6)
No	124(25.4)
T stage	
1–2	103(21.1)
3–4	385(78.9)
N stage	
0–1	386(79.1)
2–3	102(20.9)
Clinical stage	
I-II	101(20.7)
III	326(66.8)
IV	61(12.5)
Main tumor location	
Lower thoracic	181(37.1)
Middle thoracic	179(36.7)
Cervical segment + Upper thoracic	128(26.2)

†The data was shown as Median ((Q_L, Q_U)) or number (percent)

In addition, we also compared the incidence of different grades of esophagitis before and after 19:00 (Table S2). The overall rates of grade 2 and 3 esophageal toxicities were 90.0% and 92.4, respectively. Among them, the incidence of grade 3 esophagitis after 19:00 (27.1%) was significantly higher than that before 19:00 (37.8%) ($p = 0.026$). However, no similar results were observed between the two groups for grade 2 esophagitis.

Subgroup analysis

To further distinguish the acute RE difference in patients on different risk stratification, a subgroup analysis was performed according to the PGTV dose (Table 3). In the subgroup of patients with ESCC disease receiving PGTV dose ≥ 59.34 Gy, RT in the daytime group achieved a lower odds of acute RE compared with RT in the evening group ($p = 0.027$, OR = 1.675, 95% CI = 1.082–2.643). However, there was no significant difference between the two groups in the PGTV dose < 59.34 Gy subgroup ($p = 0.657$, OR = 1.229, 95% CI = 0.494–3.060).

Survival outcomes

We included demographic, clinicopathologic, and radiotherapy time variables in the univariable analysis of OS, LRFS, DMFS, and PFS (Table 4). The radiotherapy time was not a prognosis factor for OS, LRFS, DMFS, and PFS by univariable analysis (Fig. 1). At last, multivariate analysis of OS showed the following factors to be statistically significant: PS score 2 ($p = 0.012$), dysphagia ($p = 0.009$), T3-4 stage ($p = 0.001$), clinical stage ($p = 0.043$ for stage IV), and patients in the lower thoracic segment ($p = 0.035$ for middle thoracic and $p = 0.001$ for cervical segment + upper thoracic). For LRFS, PS score 2–3 ($p = 0.006$), dysphagia ($p = 0.010$), T3-4 stage ($p = 0.001$), clinical stage ($p = 0.034$ for stage IV), and patients in the lower thoracic segment ($p = 0.002$ for cervical segment + upper thoracic) were statistically significant in multivariate analyses (Table 5). Besides, PS score 2 ($p = 0.011$), dysphagia ($p = 0.011$), T3-4 stage ($p = 0.002$), clinical stage ($p = 0.035$ for stage IV), and patients in the lower thoracic segment ($p = 0.025$ for middle thoracic and $p = 0.002$ for cervical segment + upper thoracic) were independently associated with worse DMFS. PS score 2

Table 2 Univariable and multivariate ordinal logistic regression analysis of factors affecting radiation esophagitis levels

Variables	Univariate				Multivariate			
	Coefficient	*P*	OR	95% CI	Coefficient	*P*	OR	95% CI
Age (years)	−0.016	0.109	0.984	0.965–1.004				
Radiotherapy time	0.011	0.557	1.011	0.975–1.048				
Tumor length in gastroscope (cm)	0.027	0.474	1.027	0.955–1.105				
PGTV dose (Gy)	0.044	0.106	1.045	0.991–1.102				
PGTV fractionation (times)	−0.023	0.627	0.977	0.892–1.072				
PTV dose (Gy)	0.020	0.418	1.020	0.972–1.071				
PTV fractionation (times)	0.054	0.199	1.056	0.972–1.147				
Age (years)								
< 69	0							
≥ 69	−0.246	0.180	0.782	0.546–1.120				
Radiotherapy time								
Before 19:00	0				0			
After 19:00	0.479	**0.021**	1.615	1.076–2.425	0.507	0.017	1.660	1.094–2.518
Tumor length in gastroscope (cm)								
< 5	0				0			
≥ 5	0.401	0.038	1.494	1.022–2.183	0.490	0.014	1.632	1.102–2.416
PGTV dose (Gy)								
< 59.34	0				0			
≥ 59.34	0.625	0.004	1.869	1.216–2.871	0.532	0.017	1.702	1.099–2.635
PGTV fractionation (times)								
< 28	0							
≥ 28	0.575	0.139	1.778	0.829–3.813				
PTV dose (Gy)								
< 52.0	0							
≥ 52.0	0.455	0.038	1.576	1.026–2.422				
PTV fractionation (times)								
< 29	0							
≥ 29	0.483	0.028	1.620	1.053–2.493				
Single-fraction dose (Gy)								
1.8 and 2.0	0							
2.12 and 2.2	0.434	0.020	1.543	1.072–2.221				
Gender								
Male	0				0			
Female	0.826	< 0.001	2.283	1.521–3.428	0.807	< 0.001	2.241	1.475–3.405
PS								
0–1	0							
2	−0.125	0.547	0.882	0.587–1.327				
Dysphagia								
Yes	0				0			
No	0.487	0.017	1.627	1.090–2.429	0.581	0.006	1.789	1.181–2.709
T stage								
1–2	0							
3–4	0.277	0.213	1.319	0.854–2.037				
N stage								
0–1	0							
2–3	0.411	0.060	1.509	0.983–2.315				
Clinical stage								
I-II	0							

Table 2 (continued)

Variables	Univariate				Multivariate			
	Coefficient	*P*	OR	95% CI	Coefficient	*P*	OR	95% CI
III	0.147	0.517	1.158	0.742–1.808				
IV	0.442	0.167	1.556	0.832–2.910				
Main tumor location								
Lower thoracic	0				0			
Middle thoracic	0.206	0.330	1.228	0.812–1.858	0.097	0.651	1.102	0.723–1.680
Cervical segment + Upper thoracic	0.642	0.005	1.900	1.212–2.980	0.510	0.032	1.665	1.043–2.658

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; OR: Odds ratio; CI: Confidence interval; *P* values less than 0.05 are highlighted in bold

Table 3 Ordinal logistic regression analysis of factors affecting radiation esophagitis levels

Variables	Coefficient	*P*	Odds ratio (OR)	Lower 95% CI for OR	*Upper* 95% CI for OR
PGTV < 59.34 Gy					
Radiotherapy time					
Before 19:00	0				
After 19:00	0.206	0.657	1.229	0.494	3.060
PGTV ≥ 59.34 Gy					
Radiotherapy time					
Before 19:00	0				
After 19:00	0.516	0.027	1.675	1.082	2.643

($p=0.007$), dysphagia ($p=0.011$), T3-4 stage ($p=0.003$), clinical stage ($p=0.029$ for stage IV), and patients in the lower thoracic segment ($p=0.003$ for cervical segment + upper thoracic) were statistically significant in multivariate analyses for PFS.

Discussions

Acute RE often occurs in patients with esophageal squamous cell carcinoma with radiotherapy, and it occurs during RT and often lasts several weeks after the completion of RT [5]. Reducing the incidence or the grade of esophagitis will greatly improve the living standards of patients, and at the same time prevent the interruption of treatment so as to obtain better treatment effects [7]. RT inhibits cell mitosis through high doses of radiation, and cells that are dividing are more sensitive to radiation [15]. Previous studies have revealed the greatest radiosensitivity for cells in the G2 and M phases in the late afternoon and relative radioresistance for cells in the late G1 phase in the morning [15]. Therefore, we speculate that daytime RT would be associated with less acute RE than evening RT. In this study, we found that patients treated with radiation therapy in the evening (19:00 and later) had a higher odds of developing acute RE and higher levels of esophagitis compared with daytime radiation therapy (before 19:00). However, no difference was found in survival between the two groups.

Several previous studies have reported the factors influencing acute RE such as radiation dose. Ren et al. reported increased toxicity of grade 2–3 acute esophagitis in locally advanced esophageal squamous cell carcinoma (ESCC) patients receiving high-dose radiotherapy [16], which is consistent with the results of our subgroup analysis. Yu et al. also found that high-dose exposure increased the incidence of grade 2 and above esophagitis [17]. In the present study, our results indicated that patients receiving RT dose ≥ 59.34 Gy were more likely to develop acute RE than those receiving RT dose < 59.34 Gy. Furthermore, patients received greater than 2 Gy in a single fraction were asscciated with higher odds of RE. Different from the results of other studies, we found that tumor length ≥ 5 cm, female, and absence of dysphagia affected the higher odds of esophagitis. We also demonstrated that tumor location in the upper chest and neck was an independent prognostic factor affecting the level of esophagitis, which may be related to the higher radiation dose received by the cervical esophagus.

In recent years, some studies have reported the impact of circadian rhythms on side effects and treatment outcomes in patients with cancer. Several research investigated the potential impact of the morning RT and

Table 4 Univariable Cox analysis of OS, LRFS, DMFS and PFS

Variables	OS		LRFS		DMFS		PFS	
	HR(95%CI)	*P*	HR(95%CI)	*P*	HR(95%CI)	*P*	HR(95%CI)	*P*
Age (years)	1.007(0.993–1.021)	0.335	1.004(0.991–1.018)	0.540	1.003(0.990–1.016)	0.671	1.001(0.988–1.014)	0.902
Radiotherapy time	0.994(0.970–1.019)	0.629	0.996(0.971–1.020)	0.722	1.001(0.977–1.025)	0.964	1.001(0.978–1.026)	0.910
Tumor length in gastroscope (cm)	1.064(1.018–1.112)	0.006	1.070(1.025–1.118)	0.002	1.062(1.016–1.109)	0.007	1.067(1.023–1.114)	0.003
PGTV dose (Gy)	1.007(0.974–1.041)	0.779	1.002(0.966–1.039)	0.923	0.994(0.959–1.030)	0.727	1.000(0.965–1.036)	0.994
PGTV fractionation (times)	0.997(0.939–1.060)	0.933	1.005(0.946–1.066)	0.882	1.003(0.944–1.065)	0.925	1.009(0.951–1.071)	0.761
PTV dose (Gy)	0.979(0.947–1.013)	0.222	0.985(0.954–1.018)	0.372	0.981(0.949–1.014)	0.252	0.986(0.954–1.018)	0.387
PTV fractionation (times)	0.963(0.909–1.019)	0.190	0.970(0.917–1.026)	0.288	0.963(0.910–1.018)	0.185	0.969(0.917–1.024)	0.259
Age (years)								
< 69	1.000		1.000		1.000		1.000	
≥ 69	1.285(1.009–1.636)	0.042	1.227(0.967–1.558)	0.092	1.168(0.922–1.480)	0.199	0.876(0.700–1.097)	0.249
Radiotherapy time								
Before 19:00	1.000		1.000		1.000		1.000	
After 19:00	1.083(0.823–1.426)	0.568	1.105(0.843–1.449)	0.468	1.116(0.853–1.460)	0.425	1.129(0.893–1.426)	0.311
Tumor length in gastroscope (cm)								
< 5	1.000		1.000		1.000		1.000	
≥ 5	1.317(1.015–1.708)	0.038	1.365(1.056–1.764)	0.017	1.299(1.008–1.676)	0.044	1.334(1.038–1.715)	0.024
PGTV dose (Gy)								
< 59.34	1.000		1.000		1.000		1.000	
≥ 59.34	0.766(0.580–1.011)	0.060	0.794(0.603–1.045)	0.100	0.769(0.586–1.010)	0.059	0.794(0.607–1.039)	0.093
PGTVfractionation (times)								
< 28	1.000		1.000		1.000		1.000	
≥ 28	1.056(0.646–1.727)	0.827	1.046(0.648–1.686)	0.855	1.055(0.646–1.724)	0.830	1.047(0.649–1.687)	0.851
PTV dose (Gy)								
< 52.0	1.000		1.000		1.000		1.000	
≥ 52.0	0.796(0.587–1.080)	0.142	0.868(0.647–1.163)	0.343	0.791(0.585–1.069)	0.127	0.855(0.640–1.142)	0.289
PTV fractionation (times)								
< 29	1.000		1.000		1.000		1.000	
≥ 29	0.819(0.604–1.111)	0.199	0.892(0.665–1.195)	0.444	0.809(0.598–1.093)	0.166	0.875(0.655–1.168)	0.364
Gender								
Male	1.000		1.000		1.000		1.000	
Female	0.902(0.682–1.192)	0.467	0.932(0.710–1.223)	0.610	0.883(0.672–1.162)	0.376	0.913(0.699–1.193)	0.506
PS								
0–1	1.000		1.000		1.000		1.000	
2	1.407(1.074–1.844)	0.013	1.435(1.100–1.874)	0.008	1.385(1.063–1.804)	0.016	1.406(1.083–1.825)	0.011
Dysphagia								
Yes	1.000		1.000		1.000		1.000	
No	0.604(0.443–0.824)	0.001	0.620(0.458–0.839)	0.002	0.613(0.453–0.829)	0.001	0.628(0.468–0.843)	0.002
T stage								
1–2	1.000		1.000		1.000		1.000	
3–4	2.170(1.533–3.070)	< 0.001	2.049(1.466–2.864)	< 0.001	2.064(1.476–2.885)	< 0.001	1.966(1.422–2.719)	< 0.001
N stage								
0–1	1.000		1.000		1.000		1.000	
2–3	1.317(0.991–1.750)	0.057	1.319(0.998–1.744)	0.052	1.355(1.028–1.787)	0.031	1.359(1.035–1.784)	0.027
Clinical stage								
I-II	1.000		1.000		1.000		1.000	
III	1.267(0.911–1.761)	0.159	1.216(0.883–1.674)	0.231	1.308(0.948–1.806)	0.102	1.251(0.915–1.712)	0.161
IV	2.382(1.569–3.617)	< 0.001	2.362(1.569–3.554)	< 0.001	2.321(1.539–3.500)	< 0.001	2.296(1.535–3.433)	< 0.001

Table 4 (continued)

Variables	OS		LRFS		DMFS		PFS	
	HR(95%CI)	*P*	HR(95%CI)	*P*	HR(95%CI)	*P*	HR(95%CI)	*P*
Main tumor location								
Lower thoracic	1.000		1.000		1.000		1.000	
Middle thoracic	0.787(0.602–1.028)	0.079	0.808(0.621–1.053)	0.114	0.784(0.603–1.020)	0.070	0.810(0.624–1.050)	0.112
Cervical segment + Upper thoracic	0.598(0.434–0.823)	0.002	0.629(0.461–0.860)	0.004	0.628(0.460–0.857)	0.003	0.658(0.486–0.891)	0.007

Odds ratio s and 95% confidence intervals were calculated by a stratified Cox proportional hazards model. Abbreviations: OS, overall survival; LRFS, local recurrence-free survival; DMFS, Distant Metastasis-free Survival; PFS, Progression-free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; *P* values less than 0.05 are highlighted in bold

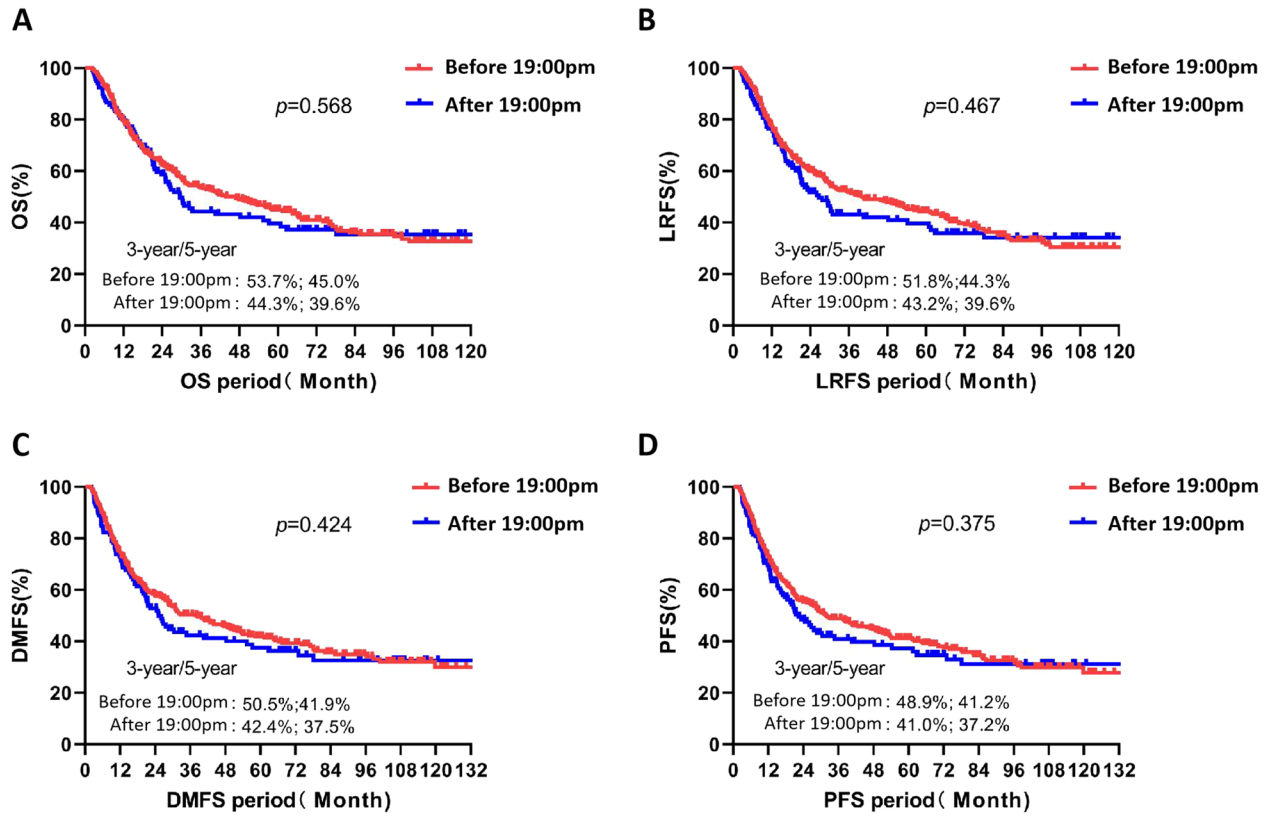

Fig. 1 Kaplan–Meier estimates of the OS (**A**), LRFS (**B**), DMFS (**C**), and PFS (**D**) for esophageal squamous cell carcinoma patients treated with definitive chemoradiotherapy in different radiotherapy time. OS, overall survival; LRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival; PFS, progression-free survival

afternoon RT on the severity and prevalence of radiation-induced oral mucositis in patients treated for head and neck squamous cell carcinoma. However, they did not demonstrate a significant difference in toxicity of daytime RT and evening RT [12, 13]. A recent prospective trial found that patients treated with RT before 15:00 developed severe mucositis (72% v.s. 57.1%) compared to those treated with RT in the evening [18]. Pragya et al. reported that morning radiotherapy induced higher levels of intestinal mucositis in patients with cervical cancer [19]. Jae et al. found that in breast cancer patients, the evening radiotherapy group was more likely to have acute skin reactions than the morning radiotherapy group [11]. In this study, we found that evening radiotherapy (after 19:00) was an independent prognostic factor affecting the level of esophagitis, suggesting that radiation time is a simple, cost-free way to limit the severity of acute RE. Interestingly, Hsu et al. found that high dose RT (median,

Table 5 Multivariate Cox analysis of OS, LRFS, DMFS and PFS

Variables	OS		LRFS		DMFS		PFS	
	HR(95%CI)	*P*	HR(95%CI)	*P*	HR(95%CI)	*P*	HR(95%CI)	*P*
PS								
0–1	1.000		1.000		1.000		1.000	
2	1.433(1.084–1.894)	0.012	1.464(1.113–1.926)	0.006	1.425(1.084–1.874)	0.011	1.443(1.103–1.888)	0.007
Dysphagia								
Yes	1.000		1.000		1.000		1.000	
No	0.651(0.471–0.900)	0.009	0.661(0.482–0.906)	0.010	0.666(0.486–0.912)	0.011	0.672(0.494–0.914)	0.011
T stage								
1–2	1.000		1.000		1.000		1.000	
3–4	1.923(1.325–2.790)	0.001	1.811(1.261–2.602)	0.001	1.787(1.247–2.560)	0.002	1.710(1.205–2.426)	0.003
Clinical stage								
I-II	1.000		1.000		1.000		1.000	
III	0.921(0.647–1.310)	0.645	0.909(0.644–1.281)	0.585	0.989(0.700–1.396)	0.950	0.964(0.688–1.349)	0.830
IV	1.573(1.014–2.442)	0.043	1.593(1.035–2.451)	0.034	1.593(1.034–2.455)	0.035	1.604(1.050–2.452)	0.029
Main tumor location								
Lower thoracic	1.000		1.000		1.000		1.000	
Middle thoracic	0.749(0.572–0.980)	0.035	0.773(0.593–1.009)	0.059	0.738(0.565–0.962)	0.025	0.769(0.592–1.000)	0.050
Cervical segment + Upper thoracic	0.569(0.413–0.786)	0.001	0.603(0.440–0.825)	0.002	0.603(0.441–0.824)	0.002	0.634(0.467–0.860)	0.003

Odds ratio s and 95% confidence intervals were calculated by a stratified Cox proportional hazards model. Abbreviations: OS, overall survival; LRFS, local recurrence-free survival; DMFS, Distant Metastasis-free Survival; PFS, Progression-free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; *P* values less than 0.05 are highlighted in bold

78 Gy) in the evening was significantly associated with a higher incidence of both acute gastrointestinal toxicities and acute genitourinary toxicities of any grade [20]. We also found that RT in the daytime group achieved a lower frequency of acute RE compared with RT in the evening group in patients with ESCC disease receiving PGTV dose ≥ 59.34 Gy.

Not only did RT timing modify the tolerability of healthy tissues, but also the survival outcomes. However, the effect of circadian rhythms on the survival of different cancer patients undergoing radiation therapy is currently controversial. It is worth mentioning that a retrospective analysis of the relevance of timing for gamma knife radiosurgery (GKRS) for brain metastasis of non-small cell lung cancer revealed that patients irradiated in the morning had better local control at 3 months (97% vs. 67%), lower rate of central nervous system (CNS)-related cause of death, and nearly double median survival time (9.5 months vs. 5 months) compared to those who underwent afternoon GKRS [21]. Guo et al. explored the impact of circadian rhythm on prognosis in different types of tumors and detected a greater tumor control probability with evening RT for cervical and esophageal cancer, but no benefit in the treatment of either lung cancer or nasopharyngeal carcinoma. The contradictory results may be due to a small sample size [14]. A more recent study showed that the daytime of RT did not yield any prognostic impact on PFS or OS in high-grade glioma patients [22]. Therefore, we suspect that radiotherapy timing may have an effect on survival, but the optimal timing for RT varies between organs. Among other factors affecting survival besides time, we found that PS score, presence or absence of dysphagia at presentation, T stage, clinical stage, and tumor location were associated with patient prognosis in the present study, which is consistent with previously reported results [23, 24].

This study had several limitations. Firstly, it was a retrospective study with the potential selection bias. Secondly, our study is limited to patients with ESCC and has no guiding significance for patients with esophageal adenocarcinoma. Thirdly, there may be some confounding factors that are not included in our study. Fourthly, we studied before 19:00 and after 19:00, and did not specifically analyze the treatment effect in a certain time period. Finally, the study was designed for patients receiving treatment in a single institution. It is necessary to conduct large-scale prospective studies to develop individualized treatment regimens, such as a certain time period, to demonstrate the impact of circadian rhythms on side effects such as esophagitis and the prognosis of patients with esophageal cancer.

Conclusion

RT in the evening (after 19:00) was associated with higher odds to present esophagitis for esophageal squamous cell carcinoma patients, especially with higher radiation doses, but treatment outcomes did not differ according to the time of RT. Individualized treatment time should be considered in the future.

Abbreviations

EC	Esophageal cancer
CCRT	Concurrent chemoradiotherapy
RE	Radiation esophagitis
RT	Radiotherapy
ESCC	Esophageal squamous cell carcinoma
IMRT	Intensity modulated radiation therapy
VMAT	Volumetric modulated arc therapy
GTV	Gross tumor volume
CT	Computed tomography
PET/CT	Positron emission tomography/computed tomography
CTV	Clinical target volume
PTV	Planning target volume
PGTV	Planning gross tumor volume
TPF	Docetaxel, cisplatin and fluorouracil
PF	Cisplatin and fluorouracil
TP	Paclitaxel and cisplatin
CTCAE	National cancer institute common terminology criteria for adverse events
OS	Overall survival
LRFS	Locoregional relapse-free survival
DMFS	Distant metastasis-free survival
PFS	Progression-free survival
GKRS	Gamma knife radiosurgery
CNS	Central nervous system

Supplementary Information

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Supplementary material

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Not applicable.

Author contributions

XG designed the whole project. ZC and CGJ were responsible for the literature search. LB and WB was responsible for data acquisition. XY and YYT analyzed the data. XY and YL wrote the manuscript. XG and ZLN was responsible for manuscript editing and revision. XG and ZLN provided scientific research funding support. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this article.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Air Force Medical University (ethical approval number: KY20172035-2).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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