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Survival Impact of Delaying Postoperative Radiotherapy in Patients with Esophageal Cancer

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Abstract

The purpose of the current study was to retrospectively assess the effect of postoperative radiotherapy (RT) delay on survival for patients with esophageal cancer. From 2008 to 2011, patients with esophageal cancer who had undergone postoperative RT in five different hospitals in China were reviewed. Clinical data, including time interval between surgery to RT, were prospectively collected. Kaplan-Meier method was conducted to estimate the effect of each variable on progression-free survival (PFS) and overall survival (OS), with differences assessed by log-rank test. Univariate Cox proportional-hazards models were performed for both PFS and OS for all assumed predictor variables. Statistically significant predictor variables ($P < .05$) on univariate analysis were then included in multivariate Cox proportional-hazards models, which were performed to compare the effects of RT delay on PFS and OS. A total of 316 patients were finally enrolled in this prospectively multicentric study. Time to RT after surgery varied from 12 days to over 60 days (median, 26 days). Multivariate analysis showed that delay to RT longer than the median does not appear to be a survival cost. There was also no statistically difference in PFS ($P = .513$) or OS ($P = .236$) between patients stratified by quartiles (≤21 days vs ≧35 days). However, patients with particularly long delays (≧42 days) demonstrated a detrimental impact on OS ($P = .021$) but not PFS ($P = .580$). Delaying postoperative RT of esophageal cancer does not impact PFS, but results in a significant reduction on OS if delaying longer than 6 weeks.

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Introduction

Esophageal cancer has become the fourth lethal malignancy in China according to the study of 2017 National Cancer Statistics. It is estimated that 17, 290 new esophageal cancer cases and 15, 850 death cases will occur in 2018 nationwide [1]. Radiotherapy (RT) is an important means of postoperative adjuvant therapy for esophageal cancer, which can improve the local regional control rate and long-term survival rate. Chen et al. [2] retrospectively analyzed 1715 patients with thoracic esophageal squamous cell carcinoma who underwent radical esophagectomy and found that the 5-year overall

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survival (OS) rates were 21.3% versus 34.2% (median survival, 21.9 months vs 35.4 months) for surgery only versus surgery + postoperative RT, respectively ($P < .01$ for both). Macdonald et al. [3] investigated the effect of surgery plus postoperative chemoradiotherapy (CRT) on the survival of patients with resectable adenocarcinoma of the gastroesophageal junction and found that the median OS in the surgery-only group was 27 months as compared with 36 months in the CRT group, thus suggesting that postoperative CRT should be considered for all patients at high risk for recurrence of adenocarcinoma of the gastroesophageal junction who have undergone curative resection. In conclusion, postoperative RT can benefit certain patients with esophageal cancer.

Commonly, RT starts 2-4 weeks following surgery [4], allowing sufficient time for postoperative recovery without excessively delaying therapy. The effects of delayed initiation of postoperative RT on the survival of patients with esophageal cancer had not been extensively studied. Radiobiology principles infer that delay of RT may affect the outcome by permitting proliferation of clonogenic cells within the field and the spread of cancer beyond the treatment volume, leading to a decrease in the probability of local and distant control [5]. In other tumors, such as head and neck [6–9], breast [10,11], and lung cancer [12], delay in the initiation of postoperative RT appears to be recognized as a detrimental factor for survival. However, there is little definitive evidence about the appropriate interval between surgery and RT in esophageal cancer.

To help clarify this issue, we performed a retrospective multicenter study to investigate the effect of time interval to postoperative RT on survival in esophageal cancer.

Patients and Methods

Patient Population

Between January 2008 to December 2011, patients with esophageal cancer who had undergone postoperative RT in Qilu Hospital of Shandong University, Linyi People's Hospital, the Second People's Hospital of Dezhou, The 107th Hospital of the People's Liberation Army, and Yantai Affiliated Hospital of Binzhou Medical University constituted the study group for this article. Clinical data, including time interval between surgery to RT, were prospectively collected. Inclusion criteria included 1) patients older than 18 at diagnosis, 2) confirmed esophageal malignant carcinoma pathologically, and 3) surgical resection followed by RT or CRT. Exclusion criteria were 1) unknown available time interval between surgery and RT, 2) did not complete the whole RT, 3) received RT just until the tumor recurred, and 4) incomplete outcome data. The corresponding hospital ethics committee of each enrolled patient approved the study protocol.

Data Collection

The endpoint of the current study was the impact of RT delay on survival, including progression-free survival (PFS) and OS. Time interval for RT was defined as the time from the date of surgery to the first day of RT. The variables collected for each patient included demographic characteristics (age, sex), preoperative Karnofsky performance scale (KPS), characteristics of the disease (primary site, stage of tumor, histology, grade, nodal status), type of surgery and status of surgical margins, time interval for RT, field reduction, radiation technique, total RT dose, concurrent chemotherapy, chemotherapy agent, chemotherapy cycle, date of recurrence or progression, and date of death. All the relevant data were obtained from hospital records, and all the enrolled patients died relating to esophageal cancer.

Statistical Analyses

Kaplan-Meier method was conducted to estimate differences by log-rank test. Univariate Cox proportional-hazards models were performed for both PFS and OS for all assumed predictor variables. Statistically significant predictor variables ($P < .05$) on univariate analysis were then included in multivariate Cox proportional hazards models, which were performed to compare the effects of RT delay on PFS and OS when controlling for potential confounding variables. Statistical analyses were performed using software package SPSS (version 19, IBM Inc.).

Results

Patient Characteristics

Patient characteristics for this study are detailed in Table 1. A total of 316 patients (186 men, 130 women) were included, with a mean age of 56.8 ± 7.6 years. The median KPS score was 80 (range 60-100). Postoperative RT was delivered to all patients at a median dose of 58.6 ± 4.5 Gy. The median time from surgery to RT was 26 days (range 12-60 days). Moreover, patients were grouped into four quartiles by analyzing data of delay to therapy, with the first quartile including all patients with delays up to 21 days, the second quartile including 22-27 days, the third quartile including 28-34 days, and the fourth quartile including 35 days or longer. Patient demographics were compared between the stratification groups. The mean follow-up duration was 36 months.

Progression-free Survival

Median PFS for all patients was 18.6 months. Comparing to those with delay shorter or equal to the median delay (≤26 days), patients with a delay longer than the median delay (>26 days) resulted in no difference in PFS (18.4 vs 18.9 months, $P = .570$, Figure 1*A*). When evaluating the extremes of delayed therapy, no significant difference

Table 1. Patient Characteristics

Parameters		*N*	%	Median Time to Initiation of RT (Days)	*P* Value
Total number of patients		316			
Age	<65	178	56.3	28	.615
	≥65	138	43.7	29	
Gender	Female	130	41.1	29	.169
	Male	186	58.9	28	
Preoperative KPS	<70	103	32.6	33	.052
	≥70	213	67.4	26	
Surgical resection	Radical	156	49.4	31	.274
	Palliative	160	50.6	27	
Time to RT					
Continuous variable					
Median, days	≤26	152	48.1	22	.062
	>26	164	51.9	28	
Quartiles, days	≤21	76	24.1	17	.071
	22-26	84	26.6	24	
	27-34	86	27.2	30	
	≥35	70	22.2	42	
RT technology	3D-CRT	149	47.2	25	.469
	IMRT	167	52.9	28	
Concurrent CRT	No	54	17.1	34	.058
	Yes	262	82.9	28	

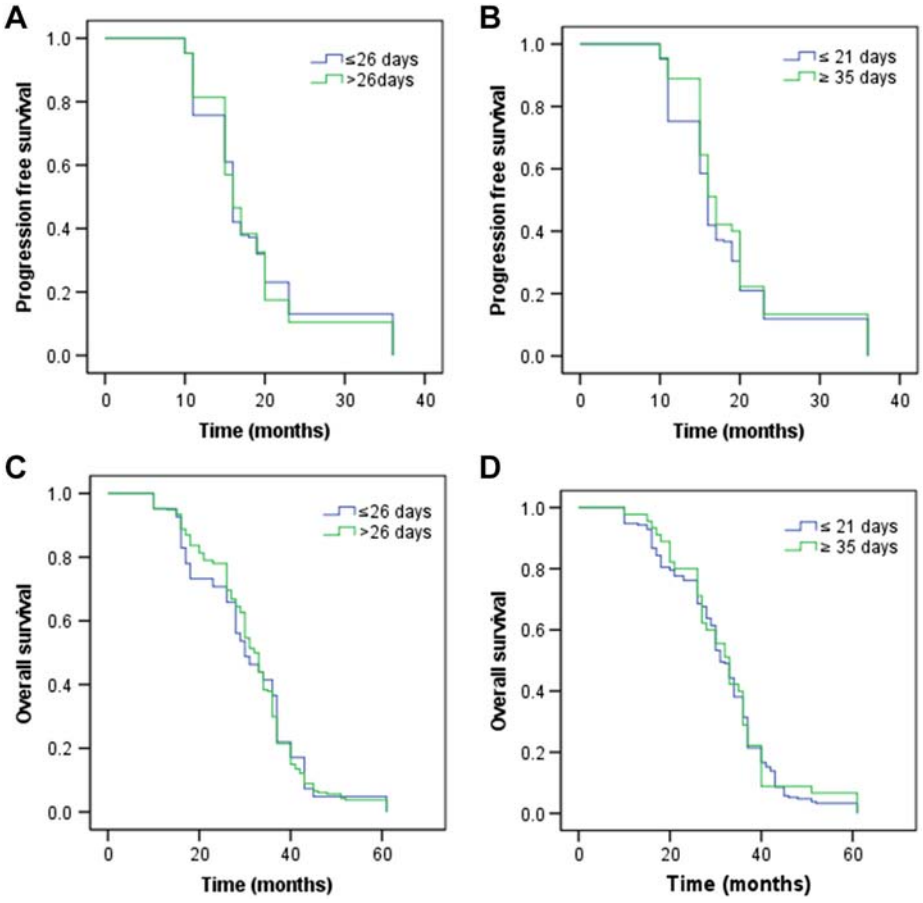

Figure 1. Graphs showing that delay of RT is not associated with worse PFS and OS. (A and C) Kaplan-Meier analysis of PFS and OS between those with shorter than median delay (≤26 days) and those with longer than median delay (>26 days). (B and D) Kaplan-Meier analysis of PFS and OS between those in the shortest quartile (≤21 days) and longest quartile (≥35 days) of delay.

(P = .513, Figure 1*B*) was found in PFS between patients in the shortest (≤21 days) and longest quartile (≥35 days).

To adjust the potential predictors of PFS, we conducted complimentary subgroup analyses. After multiple adjustments, only KPS score was found to be an independent predictor of PFS, with an adjusted HR of 1.54 (95% CI 1.31-1.97, P = .041) for preoperative KPS score ≥70 compared with <70. The time to initiation of postoperative RT was not found to be predictive of PFS, regardless of the threshold used in Cox models [continuous variable, HR 0.97 (95% CI, 0.92-1.07), P = .923; median, HR 1.13 (95% CI, 0.94-1.48), P = .570; second quartile as compared to first quartile, HR 1.23 (95% CI, 0.79-1.65), P = .317; third quartile as compared to first quartile, HR 1.13 (95% CI, 0.85-1.38), P = .472; fourth quartile as compared to first quartile, HR 1.06 (95% CI, 0.75-1.30), P = .513] (Tables 2 and 3).

As for other carcinoma, previous studies have suggested that significant delays of longer than 42 days (6 weeks) were associated with decreased survival [13]. We compared analysis of PFS between patients with ≥42 days delay to therapy and patients with <42 days delay; there were no significant difference in PFS between these two groups (P = .580, Figure 2*A*).

Overall Survival

Median OS for all patients was 35.6 months. A delay of longer than the median delay (>26 days) to start of RT did not affect OS compared with patients with shorter delay (34.2 vs 35.1 months, P =

Table 2. Univariate Analysis of PFS and OS.

Parameters		PFS Unadjusted Hazard Ratio		OS Unadjusted hazard ratio	
		HR	*P* Value	HR	*P* Value
Age	<65	1 (ref)		1 (ref)	
	≥65	1.12	.374	1.26	.217
Gender	Female	1 (ref)		1 (ref)	
	Male	1.20	.194	1.31	.187
Preoperative KPS	≥70	1 (ref)		1 (ref)	
	<70	1.26	**.045** *	1.49	**.039** *
Surgical resection	Radical	1 (ref)		1 (ref)	
	Palliative	0.95	.538	0.87	.683
Time to RT					
Continuous variable		0.97	.923	0.98	.862
Median, days	≤24	1 (ref)		1 (ref)	
	>24	1.13	.570	1.12	.429
Quartiles, days	≤21	1 (ref)		1 (ref)	
	22-27	1.23	.317	1.24	.306
	28-34	1.13	.472	1.15	.351
	≥35	1.06	.513	1.03	.236
RT technology	3D-CRT	1 (ref)		1 (ref)	
	IMRT	0.84	.132	0.92	.593
Concurrent CRT	No	1 (ref)		1 (ref)	
	Yes	0.93	.059	0.83	**.046** *

* $P < 0.05$.

Table 3. Multivariate Predictors of PFS and OS

Parameters		PFS Adjusted Hazard Ratio			OS Adjusted Hazard Ratio		
		HR	95% CI	*P* Value	HR	95% CI	*P* Value
Preoperative KPS	≥70	1 (ref)	-	-	1 (ref)		
	<70	**1.54**	1.31-1.97	**.041**	1.76	1.56-1.91	**.030**
Long delay, days	≤42	-	-	-	1 (ref)	-	-
	>42	-	-	-	1.766	1.10-3.16	**.021**
Concurrent CRT	No	-	-	-	1 (ref)	-	-
	Yes	-	-	-	1.23	1.03-1.45	**.048**

.429, Figure 1*C*). To evaluate the extremes of delayed therapy, no significant difference ($P = .236$, Figure 1*D*) was found in OS between patients in the shortest (≤21 days) and longest quartile (≥35 days).

Unadjusted and adjusted predictors of OS are summarized in Tables 2 and 3. After multiple adjustments, KPS score (adjusted HR 1.76, 95% CI 1.56-1.91, $P = .030$) and concurrent CRT (adjusted HR 1.23, 95% CI 1.03-1.45, $P = .048$) were found to be predictive factors of OS. The time to initiation of postoperative RT was not a predictor of OS, regardless of the threshold used in Cox models [continuous variable, HR 0.98 (95% CI, 0.94-1.06), $P = .862$; median, HR 1.12 (95% CI, 0.91-1.35), $P = .429$; second quartile as compared to first quartile, HR 1.24 (95% CI, 0.81-1.68), $P = .306$; third quartile as compared to first quartile, HR 1.15 (95% CI, 0.91-1.42), $P = .351$; fourth quartile as compared to first quartile, HR 1.03 (95% CI, 0.79-1.23), $P = .236$].

OS was also evaluated in the small subset of patients with ≧42 days delay to therapy and compared with patients with <42 days delay. Univariate Kaplan-Meier analysis of OS showed a significant difference of 30.2 versus 36.8 months ($P = .036$, Figure 2*B*). Multivariate Cox regression showed that longer delay had an HR of death of 1.766 (95% CI 1.102-3.158, $P = .021$).

Discussion

For adjuvant therapy of esophageal cancer, concerning about proliferation of carcinogenic cells, it has theoretically led to consider delaying the initiation of postoperative RT is detrimental to the prognosis of patients. However, the literature concerning the effect of timing of postoperative RT on the survival of patients with esophageal cancer is scarce.

Regarding the study about RT delaying, glioblastoma, lung cancer, and breast cancer had been thoroughly studied; however, the results were different. Most of the studies [14–18] found no statistically significant relationship between survival and the time from surgery to the initiation of RT. Do et al. [18] used multivariate analysis to assess the effect of radiotherapy delay on survival in a retrospective study of 182 patients with high-grade glioma and found no significant effect of delaying postoperative RT on OS. However, some other retrospective analyses found a significant unfavorable effect of shorter delays on OS [19–21]. Wurschmidt et al. [22] assessed the importance of time interval between surgery and postoperative RT in non–small-cell lung carcinoma; controlling the status of resection margins and performance status, they found that the 175 patients who were irradiated at <36 days after surgery had a significantly detrimental survival compared with the 165 patients irradiated at ≥36 days after surgery. On the other hand, the largest study [23] based on a pooled cohort of 2855 patients with glioblastoma demonstrated that the influence of long delay in initiation of RT did affect clinical outcome of patients, coming to an appropriate criterion with the delay limited within 6 weeks; this result was similar to three other studies which reported a significant negative effect of longer delays (more than 6 weeks) on OS [9,23,24].

In the present study, we attempted to retrospectively analyze the impact of postoperative RT delay on survival for patients with esophageal cancer. We found no significant difference in any carcinoma recurrence or progression between patients treated with postoperative RT within 42 days after surgery and those treated more than 42 days after surgery. However, there was definitely a significant decrease of OS for patients who waited for more than 42 days after

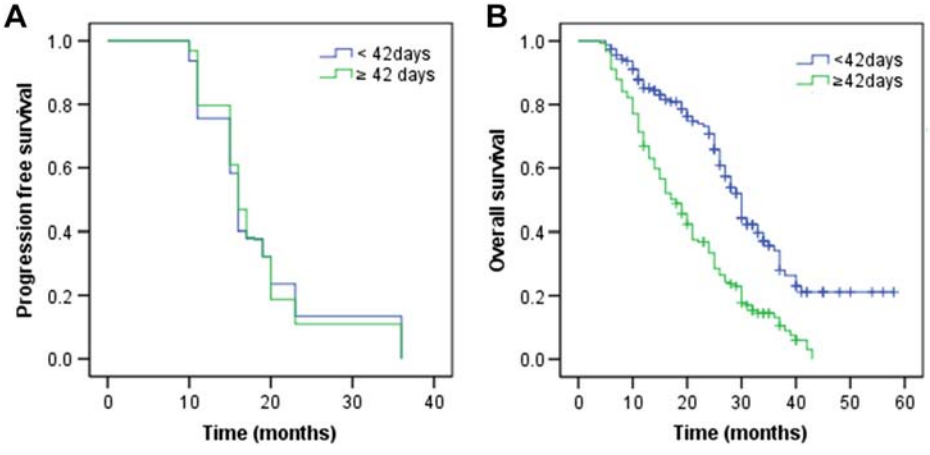

Figure 2. Graphs showing that significant delay (≧42 days) of RT is associated with worse OS but not PFS. (A) Kaplan-Meier analysis of PFS between those with treatment delay of longer and shorter than 42 days. (B) Kaplan-Meier analysis of OS between those with treatment delay of longer and shorter than 42 days.

surgery. As postoperative complications should be the reasons leading to the RT delay, which possibly worsen OS, we then compared the incidence rate of postoperative complications between patients with ≧42 days delay to therapy and patients with <42 days delay, finding no significant difference between these two groups (P = .067). Because specific reasons for delay to RT were not available during data collection, we cannot evaluate whether the small subset of patients, who initiate RT more than 42 days delay, suffered from impaired performance status or other diseases that could confound their unfavorable survival.

Our study is the first to evaluate the impact of delay in initiation of postoperative RT on survival of patients with esophageal cancer, finding that delay is associated with reduced OS but not PFS. This result emphases the importance of minimizing delays within 42 days during the treatment process, including reliable early communication between the surgical and oncology team. Despite considerable efforts being made to improve survival by developing new treatments strategies, the fact that RT remains vitally important for esophageal cancer should not be ignored. For a large percentage of patients with esophageal cancer, timely access to RT after surgical resection is of fundamental importance. For R0 resection patients, postoperative RT plus or minus fluorouracil-based chemotherapy was recommended for patients with stage III or above. For patients with stage T1-2N1M0 and wide range of vascular cancer, adjuvant chemoradiotherapy (CRT) should be considered as appropriate even in the early stage. For R1 and R2 resection patients, postoperative RT combined with fluorouracil-based chemotherapy should be performed. However, during our data collection, we found that lots of patients who needed postoperative RT received the treatment only until the carcinoma recurrence, months or years after the surgery; these large numbers of patients were ruled out. We speculated that these patients who were supposed to receive postoperative RT did not receive radiotherapy, possibly because of postoperative physical decline. Neoadjuvant CRT has become the standard treatment in Western countries. Results of two randomized clinical trials [25,26] and two meta-analyses [27,28] indicated that the OS could be improved by neoadjuvant CRT followed by surgery. Preoperative CRT can reduce tumor volume, eliminate subclinical lesions, promote occlusion of capillary lymphatic, and reduce distant metastasis. It can significantly improve the surgical resection rate and reduce surgical trauma. It is possible to improve long-term survival of ESCC patients, which need us to explore in future.

There are inescapable deficiencies to our study, largely due to the retrospective selection biases and limitations which are inherent to the use of multicentric data collection that was not originally created for the purposes of this study. Although we controlled potential confounding factors as much as possible, maybe the magnitude of association between delay and the outcomes was still underestimated because patients with more advanced disease might have experienced other active treatments. Moreover, different with most of Western countries, in China, squamous cell carcinoma accounts for more than 95% of esophageal cancers, so all patients enrolled in this study had squamous cell carcinoma. In addition, the combination of platinum and nonplatinum in chemotherapy regimen, and the toxicity of chemoradiotherapy, may affect the survival of patients, leading to the deviation of the results of this study.

In conclusion, given the result of this prospective multicentric study, delaying postoperative RT of esophageal cancer does not impact PFS, while leading to a significant reduction on OS if delaying longer than 42 days. We therefore recommend modest delay (less than 42 days) of postoperative RT, long enough to repair surgery wounds and optimize functional status, without a concern about negative impact on survival.

Acknowledgement

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Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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