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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	