

Original Article

Survival benefit of (neo-)adjuvant radiotherapy to patients with T₂₋₃N₀M₀ stage squamous cell esophagus carcinoma

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Received January 6, 2016; Accepted July 10, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: Background and Aims: This study is designed to analyze survival benefit of (neo-)adjuvant radiotherapy to patients with T₂₋₃N₀M₀ stage squamous cell esophagus carcinoma (SCEC). Methods: T₂₋₃N₀M₀ stage SCEC patients were selected from the Surveillance Epidemiology and End Results data. Survival effect of (neo-)adjuvant radiotherapy to T₂₋₃N₀M₀ stage SCEC was explored. Results: Univariate and multivariate analysis showed age, sex, and neoadjuvant radiotherapy were the prognostic factors of survival (P<0.05). Further analysis showed that neoadjuvant radiotherapy significantly reduces risk of death in T3 stage (HR 0.445, P<0.05), but not significantly in T2N0M0 stage (HR 1.159, P>0.05). Adjuvant radiotherapy showed no significant survival benefit in either T2N0M0 or T3N0M0 stage. Conclusions: sex, age, and neoadjuvant radiotherapy are independent prognostic factors of T₂₋₃N₀M₀ SCEC. Significant survival benefit of neoadjuvant radiotherapy is only observed in patients in T3N0M0 stage SCEC, but not in T2N0M0 stage. Adjuvant radiotherapy does not show survival benefit in either T2N0M0 or T3N0M0 stage SCEC.

Keywords: Esophageal cancer, squamous cell carcinoma, surgery, adjuvant radiotherapy, prognostic factor

Introduction

Squamous cell esophageal carcinoma (SCEC) is one of the most common malignancy of esophageal tumors. Treatment of SCEC varies by disease stages [1-3]. Chemotherapy with or without radiotherapy is the standard treatment of metastatic SCEC [2]. Multimodality therapy with chemotherapy and radiotherapy is the most rational treatment strategy of locally advanced SCEC [1, 4]. As for early stage of SCEC, surgery is the main treatment method, but whether (neo-)adjuvant radiotherapy should be given before or after surgery to the SCEC patients with T₂₋₃N₀M₀ stage is not clear.

The Surveillance, Epidemiology, and End Results (SEER) Program is a cancer related database founded by the National Cancer Institute (NCI) in the United States. It collects and reports cancer incidence and survival data from population-based cancer registries and covers

approximately 28% of the US population. With large information of cancer, it is an important tool to analyze carcinoma.

In view of above, we used SEER data for the analysis of SCEC. Aim to explore the efficacy of adjuvant radiotherapy to the early stage (T₂₋₃N₀M₀) SCEC.

Patients and methods

Patients and clinical data

SEER data between 1973 and 2012 ["Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2014 Sub (1973-2012 varying)"] were chosen for this study. The National Cancer Institute's SEER*Stat software (Version 8.2.1) was used for the identity of patients. We included: (1) cases of primary esophageal cancer (C15.0-C15.9) with a confirmed diagnosis of

(neo-)adjuvant radiotherapy to T₂₋₃N₀M₀ SCEC

Table 1. Summary of characteristics and characteristics stratified by treatment

Variable		All patients (%)	Surg	RT + Surg	Surg + RT	χ^2	P-value ψ
Sex	Female	152 (41.2)	78	58	16	4.646	0.098
	Male	217 (58.8)	89	107	21		
Race	Black	60 (16.3)	26	25	9	6.755	0.149
	White	277 (75.1)	123	131	23		
	Other	32 (8.6)	18	9	5		
T Stage	T2	136 (36.9)	63	63	10	1.715	0.424
	T3	233 (63.1)	104	102	27		
Age	65-	179 (52.3)	70	106	17	17.25	0.000***
	65+	160 (47.7)	97	59	20		
Radiotherapy	Surg	167 (45.3)	167	-	-	-	-
	RT + Surg	165 (47.7)	-	165	-	-	-
	Surg + RT	37 (10.0)	-	-	37	-	-

Abbreviations: RT + Surg = neoadjuvant radiotherapy + surgery; Surg + RT = surgery + adjuvant radiotherapy. ψ chi-square test. ***P<0.001, chi-square test.

microscopically, (2) entire squamous cell histology (Histologic/Behavior codes: 8070/3) based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3), (3) year of diagnosis between 2004 and 2012, (4) stage 2a of ajcc6 (T₂₋₃N₀M₀) cancer, and (5) received surgery combined with or without radiation. We excluded patients with (1) unknown age, sex, race, T, N, M stage, (2) "radiation both before and after surgery", "intraoperative radiation therapy", "intraoperative radiation with other radiation given before or after surgery", "surgery both before and after radiation (for cases diagnosed 1/1/2012 and later)", or "sequence unknown, but both surgery and radiation were given", (3) cases diagnosed solely on autopsy or death certificate. Survival data were extracted at 1-month intervals for a maximal follow-up of 60 months.

This study was based on public data from the SEER database. The reference number we obtained for the permission to access research data files was 10612-Nov2014. No human subjects or personal identifying information were used in this study. No informed consent was required in this study. This study was approved by the Review Board of Huai'an First People's Hospital, Huai'an, China.

Statistical analysis

The enrolled population was divided into three groups based on different treatments: patients who were treated with surgery alone (Surg group), surgery following with radiotherapy (RT

+ Surg group), and surgery followed by radiotherapy (Surg + RT group). Chi-square test was used to analyze the difference of these three groups. Univariate analysis with log-rank test and multivariate analysis with Cox proportional hazards regression model were performed to examine the clinical factors' association with cause-specific survival (CSS) and overall survival (OS) respectively, with a statistically significant difference at P<0.05. Finally, stratified Cox regression survival analysis was performed based on different T stages. All analysis was performed in the population with a clear record of analytical variable. All analysis was performed with survival package [5, 6] of R [7] (version 3.2.1).

Results

A total of 369 cases were selected from the SEER database. Of which, 167 patients (45.3%) received surgery alone (Surg), 165 patients (47.7%) received surgery with neoadjuvant radiotherapy (RT + Surg), 37 (10.0%) patients received adjuvant radiotherapy with surgery (Surg + RT). Most of the patients were white race (75.1%) and T3 stage (63.1%). Percentage of male was 58.8%, and the median age of all patients was 64 years. Independence test of the patients' treatment assignment and clinical characteristics indicated an obvious association between adjuvant treatment assignment and age. Patients with age younger than 65 years were more likely to receive neoadjuvant radiotherapy combined with surgery, those older than 65 years were more likely to receive

(neo-)adjuvant radiotherapy to T₂₋₃N₀M₀ SCEC

Table 2. Multivariate Cox proportional hazards regression analysis of SCEC patients

Variable	Univariate analysis		Multivariate analysis	
	χ^2	P-value†	HR (95% CI)	P-value‡
Sex	4.3	0.039*		
Female Vs Male			0.643 (0.477-0.867)	0.004**
T Stage	1.3	0.258		
T2 Vs T3			0.835 (0.620-1.125)	0.236
Age	11.8	<0.001***		
65- Vs 65+			0.618 (0.457-0.835)	0.002***
Race	1.0	0.593		
White Vs Black			0.747 (0.511-1.093)	0.134
Other Vs Black			0.642 (0.353-1.168)	0.147
Radiation	9.7	0.008**		
RT + Surg Vs Surg			0.633 (0.459-0.874)	0.005**
Surg + RT Vs Surg			0.858 (0.551-1.337)	0.499

Abbreviations: HR = hazard ratio; CI = confidence interval. †Log-rank test. ‡Cox regression model test. **P<0.05, ***P<0.01, **** P<0.001.

Table 3. Multivariate Cox proportional hazards regression analysis of radiotherapy based on different stages of SCEC

Stage	OS	
	HR (95% CI)	P-value‡
T2		
RT + Surg Vs Surg	1.159 (0.686-1.958)	0.581
Surg + RT Vs Surg	0.892 (0.365-2.181)	0.803
T3		
RT + Surg Vs Surg	0.445 (0.293-0.676)	0.000***
Surg + RT Vs Surg	0.804 (0.482-1.339)	0.402

Abbreviations: HR = hazard ratio; CI = confidence interval. ‡Cox regression model test. ***P<0.001, Cox regression model test.

surgery alone. A detailed listing of the patient characteristics and pathological features was presented in **Table 1**.

For the survival analysis of SCEC, Survival effect of clinical characteristics was evaluated with the univariate log-rank test (**Table 2**). Sex, age, and radiotherapy combined with surgery were significantly associate with survival time (P<0.05). T stage and race showed no significant association with survival (P>0.1).

Multivariate analysis performed by the Cox regression model also indicated sex and age being independent prognostic factors of survival time (P<0.05). Female patients with age younger than 65 years were believed to have a longer survival time (**Table 2**).

Finally, we performed further multivariate Cox regression analysis to assess the efficacy of (neo-)adjuvant radiotherapy to survival time based on different T stages, by adjusting sex, race, age (**Table 3**). The results displayed that only neoadjuvant radiation therapy in T3N0M0 stage can significantly improve survival time (HR 0.445, 95% CI 0.293-0.676).

Discussion

Squamous cell esophageal cancer is one of the two major histological subtypes of esophageal cancer in the world, with a highly incidence in so-called Asian belt, including Turkey, north-eastern Iran, Kazakhstan, and northern and central China [1, 8-10]. It's risk factors mainly contains tobacco use, Alcohol consumption, injury, low socioeconomic status, and so on [11, 12]. Treatment of SCEC varies depends on different stages [1]. As for local tumors, surgery is the standard procedure for patients with locally limited (cT1/T2, N0) and some resectable advanced carcinoma (cT3, T4, Nx). Adjuvant or neoadjuvant treatment with chemoradiotherapy for patients with locally advanced tumors is well established [13-15]. While for some early stage esophageal cancer, chemotherapy is believed not to be a suitable adjuvant treatment of surgery [16], but the efficacy of radiation therapy before or after surgery to early stage esophagus cancer is not clear. Some studies proved radiotherapy before or after surgery benefits long-time survival [17, 18], but others indicated no significant survival benefit of neoadjuvant [16,19, 20] or adjuvant radiotherapy [16, 20, 21].

In this study, we summarized the clinical characteristics of T₂₋₃N₀M₀ stage operated SCEC with information provided by the population-based SEER database from 1973 to 2012. The characteristics used for analysis in our study contained sex, race, T stage, age, and radiation therapy. We found that SCEC is more likely to present at T3 stage, young, male, and white

patients. More than half of SCEC patients received adjuvant or neoadjuvant radiation therapy (57.7%), of which, neoadjuvant radiotherapy contained 47.7%. Independence chi-square test between radiation therapy and other factors showed that radiation therapy was associated with age. Younger patients are more likely to receive neoadjuvant radiotherapy combined with surgery, while the older were more likely to receive surgery alone. Univariate survival analysis of clinical characteristics showed that survival time was associated with sex, age, and radiotherapy ($P < 0.05$), but of no association with T stage and race ($P > 0.1$). Multivariate Cox proportional hazards regression analysis displayed that sex, age, and neoadjuvant radiation therapy were all significantly associated with survival ($P < 0.05$). Death risk of female was lower than male (HR 0.643, 95% CI 0.477-0.867). Patients younger than 65 years had a lower risk of death (HR 0.618, 95% CI 0.457-0.835). Neoadjuvant radiotherapy could reduce nearly 40% of death hazards (HR 0.633, 95% CI 0.459-0.874). Further multivariate analysis of neoadjuvant or adjuvant radiotherapy based on different T stages showed that neoadjuvant radiotherapy can reduce more than 50% risk of death in T3 stage (HR 0.445, 95% CI 0.293-0.676), but not significantly reduce death risk in T2 stage (HR 1.159, 95% CI 0.686-1.958). Adjuvant radiotherapy could not significantly decrease death risk in either T2 stage or T3 stage.

In conclusion, our study demonstrates that age, sex, and neoadjuvant radiotherapy are prognostic associated factors in T₂₋₃N₀M₀ stage SCEC. Survival benefit of neoadjuvant radiotherapy is only significant in T3N0M0 stage SCEC, but not significant in T2N0M0 stage. Adjuvant radiotherapy shows no survival benefit to either T2N0M0 or T3N0M0 stage SCEC.

Acknowledgements

Thanks are due to Tao Li, Weiguo Zhu, Changhua Yu, Quan Zhang, Honglei Luo, Peng Pan, Jin Peng, Dongcheng He, and Fuzhi Ji for their assistance with literature research of this paper.

Disclosure of conflict of interest

None.

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