

# Factors affecting long-term survival in elderly patients undergoing radiotherapy for esophageal carcinoma

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Received January 22, 2014; Accepted March 27, 2014

DOI: 10.3892/mco.2014.285

**Abstract.** This study was conducted with the aim to analyze the factors affecting the 1-, 3- and 5-year survival rate of elderly patients with esophageal carcinoma. Between 2004 and 2008, a total of 371 patients aged  $\geq 70$  years treated with radiotherapy alone were enrolled in this study. The clinical characteristics and radiotherapy dose were evaluated by survival rate and the 1-, 3- and 5-year overall survival (OS) rates were found to be 42, 13.2 and 9.16%, respectively. The univariate analysis revealed significant differences in T, N, M and clinical stage and radiotherapy dose (all P-values  $< 0.05$ ) and no significant differences in gender (all P-values  $> 0.05$ ). There was a difference in tumor location when only comparing the 3- and 5-year OS rates ( $P=0.031$  and  $P=0.025$ , respectively). The multivariate analysis identified clinical stage as an independent factor for the 1-year OS rate ( $P=0.003$ ), whereas radiotherapy dose and clinical stage were found to be independent factors for the 3- and 5-year OS rates (all P-values  $> 0.05$ ). In the analysis of radiotherapy dose, we observed no significant difference in the 1-year OS rate between the radiation dose (DT)  $> 60$  Gy and the  $50 \text{ Gy} \leq \text{DT} < 60$  Gy groups ( $P=0.363$ ); however, there were statistically significant differences in the 3-year OS rate between the  $50 \text{ Gy} \leq \text{DT} < 60$  Gy and the other groups ( $P=0.039$  and  $P=0.032$ ); there were no significant differences in the 5-year OS rate among the dose groups (all P-values  $> 0.05$ ). In conclusion, according to the findings of this retrospective study, radiotherapy alone for elderly patients with esophageal cancer does not appear to be acceptable and there is a need for a more effective treatment. T, N, M and clinical stage and radiotherapy dose were identified as factors significantly affecting the 1-, 3- and 5-year OS in elderly patients with esophageal carcinoma, although a higher radiotherapy dose with normal fractionation did not appear to improve the OS rate.

## Introduction

Radiotherapy has become increasingly important in the treatment of esophageal carcinoma, due to refinements in radiotherapy planning systems and technological improvements. However, the majority of randomized studies tend to exclude patients aged  $\geq 70$  years, resulting in the lack of decision-making information for the physicians regarding the management of elderly patients. Elderly patients represent a unique cohort with a higher risk of significant medical comorbidities and a presumably higher therapy risk compared to younger patients. Therefore, treatment decision making for such patients may be challenging (1,2). The aim of this retrospective study was to assess the long-term outcomes in a larger population of elderly patients with esophageal carcinoma treated with radiotherapy alone by evaluating the 1-, 3- and 5-year overall survival (OS) rates and analyzing the affecting factors.

## Patients and methods

**Patient characteristics.** Between July, 2004 and December, 2008, a total of 371 patients aged  $\geq 70$  years were treated by radiotherapy in our institution. The histological diagnosis was squamous cell carcinoma of the esophagus; 70 patients presented with underlying diseases, of whom 52 patients (14%) had 1 concurrent disease, 16 (4.3%) had 2 diseases and 2 (0.5%) had  $\geq 3$  diseases, including heart disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease and anaemia.

**Staging.** Staging was performed according to the TNM classification of the Union for International Cancer Control in 2009. Clinical staging was based on esophagography, esophagoscopy, color Doppler and computed tomography of the neck, chest and abdomen. Endoscopic ultrasonography, magnetic resonance imaging, bronchofiberscopy, ultrasonography or bone scintigraphy was additionally performed if indicated for individual staging.

**Radiotherapy.** A total of 275 patients underwent conventional two-dimensional radiotherapy and the remaining 96 patients received three-dimensional conformal radiotherapy. The treatment details were previously described (1). Radiotherapy was performed using 6 or 8 MV linear accelerators with normal fractionation (1.8-2.0 Gy/fraction, 5 days/week), with a

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**Key words:** elderly, esophageal carcinoma, long-term survival, radiotherapy

Table I. Patient characteristics and univariate analysis.

Characteristics	No.	1-year OS			3-year OS			5-year OS		
		%	$\chi^2$	P	%	$\chi^2$	P	%	$\chi^2$	P
Gender			0.821	0.365		0.845	0.358		0.850	0.356
Male	244	43.4			13.5			9.4		
Female	127	39.4			12.6			8.7		
Location			3.782	0.286		8.870	0.031		9.337	0.025
Cervical	14	42.9			0			0		
Upper	88	50			23.9			17		
Middle	230	39.1			10.9			7.8		
Lower	39	41			7.7			2.6		
cT			31.766	0.000		34.723	0.000		37.797	0.000
cT1	46	52.2			10.9			6.5		
cT2	173	50.9			17.3			12.7		
cT3	89	37.1			13.5			10.1		
cT4	63	17.5			3.2			0		
cN			18.784	0.000		14.697	0.000		13.078	0.001
cN0	184	50.5			15.8			10.9		
cN1	146	36.3			11			6.8		
cN2	41	24.4			9.8			9.8		
cM			38.091	0.000		26.446	0.000		22.838	0.000
cM0	340	44.7			13.8			9.4		
cM1	31	12.9			6.5			6.5		
cStage			102.072	0.000		82.811	0.000		77.889	0.000
I	98	63.3			20.4			13.3		
II	136	50			15.4			11.8		
III	98	22.4			6.1			3.1		
IV	39	10.3			5.1			5.1		
Dose (Gy)			46.551	0.000		66.187	0.000		66.325	0.000
>60	130	40			16.9			11.5		
60	148	52.7			16.2			11.5		
50-60	53	35.8			5.7			3.8		
<50	40	17.5			0			0		

OS, overall survival.

maximum prescribed dose of 72 Gy. No patients in this study underwent chemotherapy.

**Follow-up.** The patients were seen weekly during the radiotherapy course and every 3-6 months following treatment completion. The follow-up was conducted through outpatient records, ward records and telephone interviews.

**Statistical analysis.** Statistical analysis was performed with the Chi-squared test for two-proportion comparisons. The survival rates were calculated from the date of treatment initiation until death or the last follow-up for surviving patients with the Kaplan-Meier method. The differences between survival rates were assessed with the log-rank test. A multivariate analysis was performed using the Cox regression model. Only the factors that were proven to be

significant on univariate analysis were entered into the multivariate analysis.  $P < 0.05$  was considered to indicate a statistically significant difference. All the analyses were performed with SPSS software for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

## Results

**Outcomes.** At the end of the follow-up period, 32 patients had been lost to follow-up, with an overall follow-up rate of 91.4%. The median survival time was 17.85 months (range, 2-101 months). The median patient age was 75 years (range, 70-90 years). A total of 32 patients remained alive with no evidence of disease and 2 patients remained alive but presented with osseous metastasis. The 1-, 3- and 5-year OS rates were 42, 13.2 and 9.16%, respectively.

Table II. Cox regression model multivariate analyses.

Variables	1-year OS			3-year OS			5-year OS		
	$\beta$ -value	SE	P-value	$\beta$ -value	SE	P-value	$\beta$ -value	SE	P-value
Length	0.083	0.132	0.529	0.052	0.117	0.659	0.065	0.116	0.576
Node	0.004	0.167	0.982	-0.083	0.148	0.574	-0.087	0.146	0.554
Metastasis	0.070	0.348	0.840	0.027	0.320	0.932	0.015	0.318	0.963
cStage	0.571	0.192	0.003 <sup>a</sup>	0.446	0.166	0.007 <sup>a</sup>	0.421	0.163	0.010 <sup>a</sup>
Dose	0.088	0.077	0.250	0.231	0.066	0.000 <sup>a</sup>	0.233	0.066	0.000 <sup>a</sup>

<sup>a</sup>Statistically significant. OS, overall survival; SE, standard error.

Table III. Difference between dose groups.

Dose groups	1-year OS						3-year OS			5-year OS		
	1,2	1,3	1,4	2,3	2,4	3,4	1,2	2,3	1,3	1,2	2,3	1,3
$\chi^2$	4.486	0.273	6.833	4.439	15.753	3.811	0.025	3.739	4.049	0.000	2.694	2.712
P-value	0.023	0.363	0.006	0.025	0.000	0.041	0.500	0.038	0.032	0.568	0.081	0.078

OS, overall survival.

**Patient characteristics.** The baseline characteristics of the patients are summarized in Table I. There were no statistically differences in gender. However, there were significant differences in T, N, M and clinical stage and radiotherapy dose. There was also a difference in tumor location when only comparing the 3- with the 5-year OS rates. In case of cervical esophageal cancer, the 3- and 5-year OS rates were 0.

**Multivariate analysis.** The factors that were identified as significant on univariate analysis were included in the multivariate analysis and are summarized in Table II. The Cox regression model indicated that clinical stage was an independent factor affecting the 1-, 3- and 5-year OS rates, radiotherapy dose was an independent factor affecting the 3- and 5-year OS rates, whereas tumor length, number of lymph nodes and the presence of metastasis were not independent factors affecting long-term survival.

**Dose groups and survival.** The effect of different radiation dose (DT) on long-term survival is summarized in Table III. The patients were divided into four groups by dosage: DT>60 Gy (group 1, median DT 66 Gy); DT=60 Gy (group 2); 50 Gy≤DT<60 Gy (group 3, median DT 54 Gy) and DT<50 Gy (group 4, median DT 30 Gy). We observed no differences in the 1-year OS rate between groups 1 and 3; however, there were statistically significant differences in the 3-year OS rate between group 3 and the other groups. There were no differences in the 5-year OS rate among dose groups.

**Cause of death.** A total of 337 patients (90.8%) had succumbed to their disease at the end of the follow-up period: 273 patients

(73.6%) had succumbed to local recurrence and/or distant metastasis of the primary tumor; 35 patients (9.4%) had succumbed to radiotherapy-related complications, including 15 cases of esophageal fistula, 13 pulmonary infections and 7 cases of gastrointestinal bleeding; 15 patients (4%) had succumbed to underlying diseases, including heart disease in 5, diabetic complications in 8 and cerebral infarction in 2 patients; the cause of death in the remaining 14 patients (3.8%) was unknown.

## Discussion

This was a large-scale, single-institution, retrospective study on radiotherapy outcome in 371 elderly patients with esophageal cancer. Our results revealed that the 1-, 3- and 5-year OS rates were lower compared to those reported with chemoradiotherapy by Kong *et al* (3) (42, 13.2 and 9.16 vs. 70, 36.7 and 28%, respectively) and the 5-year OS was lower compared to that reported with surgical treatment by Liu *et al* (4) (9.16 vs. 21.2-43.5%). Age was found to be a significant factor affecting the OS rate. It was previously reported that age as a continuous variable is associated with an unfavorable outcome, demonstrating a bimodal pattern of risk on cause-specific survival, although the magnitude of the effect was modest (5). In addition, other retrospective studies often excluded distant metastasis or added chemotherapy and these are not in the scope of our research. Comorbid conditions may also be an important factor. In our study, 70 patients (18.9%) presented with 1-3 concomitant diseases and 8 deaths were attributed to diabetic complications. A higher mortality risk was reported for esophageal carcinoma patients with concurrent diabetes (6). However, these were not considered as significant factors in other studies (7). It appears that treatment with radiotherapy alone for

elderly patients with esophageal carcinoma is insufficient and there is a need for a more suitable and effective treatment, such as targeted therapy or low-risk chemotherapy.

It was confirmed by univariate and multivariate analysis that T, N, M and clinical stage and radiotherapy dose were important prognostic factors for long-term survival, which was consistent with currently available reports (8,9). Of note, we observed that different pathological changes were associated with different survival results. Cervical esophageal carcinoma exhibited significantly lower survival compared to that of thoracic esophageal carcinoma. The available published data regarding the prognostic value of esophageal carcinoma location are currently scarce. Early detection and diagnosis offers the best chance of survival.

It was previously demonstrated that higher radiotherapy doses may not be effective in reducing recurrence rates but are associated with significantly higher toxicity (10). We also observed no differences between the  $DT > 60$  Gy and  $50 \text{ Gy} \leq DT < 60$  Gy groups and our results were consistent with those of Li and Guo (11). Two patients with stage IV disease, with T stage 1-2, N stage 1-2 and M stage (osseous metastasis) remained alive at 5 years, suggesting that a proportion of esophageal carcinoma patients with osseous metastasis may exhibit longer cancer-related survival.

In conclusion, radiotherapy alone for the treatment of elderly patients with esophageal cancer is not acceptable and there is a need for a more suitable and effective treatment. T, N, M and clinical stage and radiotherapy dose were identified as factors significantly affecting the 1-, 3- and 5-year OS rate, whereas a higher radiotherapy dose with normal fractionation did not improve the OS rate.

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