

Clinical features, outcomes and treatment-related pneumonitis in elderly patients with esophageal carcinoma

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Abstract

AIM: To investigate the clinical features and prognoses of elderly patients with esophageal carcinoma and to compare the effects of radiotherapy and rates of treatment-related pneumonitis (TRP) between elderly and non-elderly patients.

METHODS: A total of 236 patients with esophageal carcinoma who received radiotherapy between 2002 and 2012 were enrolled. The patients were divided into two groups: an elderly group (age ≥ 65 years) and a non-elderly group (age < 65 years). The tumor position and stage, lymph node and distant metastases, and incidence and severity of TRP were compared. Multivariate analysis was applied to identify independent prognostic factors.

RESULTS: The median overall survival times after radiotherapy in the elderly and non-elderly groups were 18.5 and 20.5 mo, respectively. Cox regression analysis showed that TRP grade and tumor-node-metastasis

(TNM) stage were independent prognostic factors in the elderly group. High-dose radiotherapy (> 60 Gy) was associated with a high incidence of TRP. Tumor TNM staging was significantly different between the two groups in which TRP occurred. Multivariate analysis showed that TNM stage was an independent prognostic factor. Esophageal carcinoma in elderly patients was relatively less malignant compared with that in non-elderly patients.

CONCLUSION: An appropriate dose should be used to decrease the incidence of TRP in radiotherapy, and intensity modulated radiation therapy should be selected if possible.

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Key words: Esophageal carcinoma; Radiation therapy; Elderly patients; Treatment-related pneumonitis; Survival rate

Core tip: We found that the tumor characteristics of esophageal cancer in elderly patients were relatively less malignant compared with those in non-elderly patients. The incidence of lymph node and distant metastases, and recurrence or metastasis after radiotherapy were lower. The incidence of treatment-related pneumonitis was much higher in the elderly patients. A proper radiation dose could improve the curative effect and decrease the incidence of treatment-related pneumonitis in elderly patients.

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INTRODUCTION

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of death from cancer. Esophageal cancer often occurs in patients older than 30 years. It is difficult for patients who are diagnosed late or have upper esophageal cancer to receive radical surgical treatment. The incidence of esophageal cancer in the elderly is relatively higher, and strict indications for surgery restrict their surgical opportunities; thus, radiation therapy is an effective therapy for these patients^[1-9].

A relatively poorly differentiated tumor and a low metabolic rate reduce the distant metastasis rate in elderly patients^[10]. The effects of radiation therapy are often better in elderly compared with non-elderly patients with esophageal cancer, and the survival time is relatively longer. However, elderly patients often suffer from chronic underlying diseases, resulting in poor tolerance of radiotherapy. In addition, lung dysfunction in elderly patients is one of the main causes of TRP, which influences the effects of radiation and reduces the survival rate. Therefore, it is worthwhile to study how to achieve the best curative effects and fewest complications of radiation therapy in elderly patients.

In this study, we investigated the relevant problems associated with radiation therapy in elderly patients with esophageal carcinoma by comparing tumor biological characteristics, survival rate, TRP incidence, and other factors between elderly and non-elderly patients with esophageal carcinoma.

MATERIALS AND METHODS

Patients

A total of 236 patients with esophageal carcinoma who received radiotherapy in the Radiotherapy Department of Zhongshan Hospital between January 2002 and December 2012 were enrolled and divided into two groups: (1) an elderly group (age ≥ 65 years; mean age: 80 years, range: 65-91 years), consisting of 129 patients (93 men and 36 women); and (2) a control group (age < 65 years; mean age: 56 years, range: 40-64 years), consisting of 107 patients (87 men and 20 women). All of the patients were diagnosed with esophageal carcinoma by pathology and were able to complete the entire radiation therapy plan. The mean survival duration among all of the patients after radiotherapy was 19 mo (stage I, 22 mo; stage II, 20 mo; stage III, 11 mo; stage IV, 10 mo).

Treatment

All of the patients received 6 or 15 MV of radiotherapy with a linear accelerator (Oncor Adant-gard, Siemens, Munich, Germany), a simulator (Evolution, Nucletron Veenendaal, Netherlands), and a three-dimensional treatment planning system (Pinnacle 7.6c, Philips, Madison, United States). The median dose was 60 Gy (range: 40-74 Gy), and each individual dose was 2 Gy. Radiotherapy was indicated for patients with stage I or II

esophageal carcinoma who could not tolerate surgery due to poor cardiopulmonary function or other diseases, patients who refused surgery and patients with stage III esophageal carcinoma.

Three-dimensional conformal radiation therapy

Immobilization of body position: The vacuum body film fixed position was used.

Computed tomography scan: Metal tags were placed on the body surface in relative positions after immobilization. Computed tomography (CT) scans were performed to obtain 3-mm-thick slices from the upper orifice of the esophagus to the hepatic hilar region.

Delineation of normal tissue: Important tissues and organs, such as the lungs, trachea and spinal cord, were delineated.

Delineation of irradiated target area: The gross tumor volume (GTV) covered the primary esophageal tumor and mediastinal lymph node metastasis, and the clinical target volume (CTV), based on the GTV, comprised the subclinical focus. The planning target volume, based on the CTV, considered the influence of uncertain factors, such as positioning errors.

The radiation area for patients with cervical esophageal carcinoma ranged from the throat area to the level of the trachea carina. The radiation area for patients with lower cervical and upper thoracic esophageal carcinoma ranged from the entrance to the esophagus to the level of the pulmonary vein. The radiation area for patients with mid-thoracic esophageal carcinoma ranged from the thoracic entrance to the cardiac region. The radiation area for patients with lower thoracic esophageal carcinoma covered a 0.5-cm margin around the tumor, including lymph node metastases of the upper abdomen.

Follow-up

All of the patients with esophageal carcinoma were followed until December 31, 2012. The mean follow-up period for the surviving patients was 39.4 mo (range: 13-84 mo), and the follow-up rate was 100%. Survival status, disease development, reasons for death and occurrence and time of TRP were recorded. The chest CT films or X-rays of the patients were compared before and after radiotherapy to assess whether radiation lung injury occurred. The severity of TRP was evaluated according to the Radiation Therapy Oncology Group (RTOG) criteria.

Statistical analysis

The χ^2 test was applied to compare the following differences between the two groups: the biological characteristics of tumors; the incidence of treatment-related pneumonitis; and the incidence and severity of TRP. The Kaplan-Meier method was used to assess the one-, three- and five-year survival rates. Univariate analysis was performed to assess the survival rate and the incidence

Table 1 Biological characteristics of tumors in elderly and non-elderly patients with esophageal carcinoma *n* (%)

Clinicopathological parameter	<i>n</i>	Non-elderly	Elderly	<i>P</i>
Gender				0.098
Male	180	93 (51.7)	87 (48.3)	
Female	56	36 (64.3)	20 (35.7)	
Tumor location				0.066
Cervical esophagus and upper thoracic portion	64	29 (43.3)	38 (56.7)	
Mid-thoracic portion	49	61 (57.0)	46 (43.0)	
Lower thoracic portion		39 (62.9)	23 (37.1)	
Tumor type				0.000
Adenocarcinoma	31	27 (87.1)	4 (12.9)	
Squamous cell carcinoma	205	102 (49.8)	103 (50.2)	
Distant metastasis				0.021
M0	216	123 (56.9)	93 (43.1)	
M1	20	6 (30.0)	14 (70.0)	
Recurrence and metastasis after radiotherapy				0.008
Yes	143	88 (61.5)	55 (38.5)	
No	93	41 (44.1)	52 (55.9)	
Lymph node metastasis				0.000
N0	111	74 (66.7)	37 (33.3)	
N1	125	55 (44.0)	70 (56.0)	
TNM stage				0.002
I	101	68 (67.3)	33 (32.7)	
II	83	37 (44.6)	46 (55.4)	
III	32	18 (56.3)	14 (43.8)	
IV	20	6 (30.0)	14 (70.0)	

Tumor position was judged according to the esophageal tumor site segmentation criteria of the International Union for Cancer Control (1997 edition). Tumor stage was judged according to esophageal tumor tumor-node-metastasis staging criteria. TNM: Tumor, node, metastasis.

of TRP. Cox-regression analysis was used in the multivariate analysis of survival and TRP incidence. $P \leq 0.05$ was considered significant. All the data were analyzed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Comparison of biological characteristics of tumors

There were no significant differences in gender or tumor location between the two groups. In the elderly group, the incidence of lymph node and distant metastases was lower ($P < 0.001$, $P = 0.021$), and the tumor TNM stage was earlier ($P = 0.002$). In addition, the number of squamous cell carcinomas was lower ($P < 0.001$), and the incidence of recurrence or metastasis after radiotherapy was lower ($P = 0.008$).

Treatment-related pneumonitis

Based on the RTOG criteria, the major complication was radiation pneumonia. The overall incidence of TRP was 22.9% (54/236) in all patients, and the median time to occurrence of TRP after radiotherapy was 2.7 mo. In the elderly group, 25.6% of the patients developed TRP after radiotherapy (33/129), and the incidences of grades II, III and IV TRP were 15.5% (20/129), 10.1% (13/129) and 0% (0/129), respectively. In the non-elderly group,

19.6% of the patients developed TRP after radiotherapy (21/107), and the incidences of grades II, III and IV TRP were 13.1% (14/107), 6.5% (7/107) and 0% (0/107), respectively. There was no significant difference in the incidence of TRP between the two groups. In addition, there was no correlation between TRP grade or tumor type and distant (lymphatic) metastasis.

Survival analysis

In the elderly group, two patients survived. One hundred and twenty seven patients died, of whom 115 died of esophageal carcinoma and the other 12 died of other diseases. Among these 12 patients, three died of myocardial infarction, one of renal failure, four of respiratory function failure caused by chronic bronchitis and four of cerebrovascular accidents. The 1-, 3- and 5-year survival rates after radiotherapy were 69.7%, 10.3% and 1.6%, respectively. The median survival time was 18.5 mo (SE = 1.083, 95%CI: 16.377-20.623). In the non-elderly group, two patients survived. One hundred and five patients died, of whom 103 died of esophageal carcinoma and the other 2 died of TRP and severe pneumonia caused by chemotherapy, respectively. The 1-, 3- and 5-year survival rates after radiotherapy were 72.9%, 11.2% and 1.2%, respectively. The median survival time was 20.5 mo (SE = 1.112, 95%CI: 18.321-22.679). The proportion of patients who died of other diseases in the elderly group was significantly higher than that in the control group (Table 1). Kaplan-Meier analysis and the log-rank test showed that the tumor TNM stage was significantly different between the patients with or without TRP ($P = 0.000$).

Prognosis analysis

Significant differences in survival time were observed according to the presence of TRP, TRP grade, distant metastasis and tumor TNM stage in the elderly group. Pathological type, distant metastasis, tumor TNM stage, presence of TRP and TRP grade showed significant differences in the non-elderly group (Table 2).

Cox regression analysis was used in the multivariate analysis of the above factors. We identified the independent prognostic factors in the elderly group, which included tumor TNM stage and the presence of TRP. The independent prognostic factors in the non-elderly group were distant metastasis and tumor TNM stage (Table 3). Multivariate Cox regression analysis showed that TNM stage was an independent prognostic factor (Table 4).

DISCUSSION

Although elderly patients with esophageal carcinoma are physically weaker than young patients, studies have shown that elderly patients with esophageal carcinoma have advantages with respect to biological characteristics. Some elderly patients prefer conservative nonsurgical treatment because of concern regarding complications post-surgery.

Table 2 Univariate analysis of prognostic factors

	<i>n</i>	Survival rate (elderly)			<i>P</i>	<i>n</i>	Survival rate (non-elderly)			<i>P</i>
		1 yr	3 yr	5 yr			1 yr	3 yr	5 yr	
Gender					0.837					0.800
Male	93	66.5%	10.8%	2.2%		87	71.3%	12.7%	0.5%	
Female	36	77.8%	8.3%	-		20	77.5%	5.3%	1.6%	
Tumor type					0.878					0.039
Squamous	102	67.5%	11.2%	1.5%		103	74.8%	11.7%	0.3%	
Non-squamous	27	75.9%	5.6%	0%		4	25.0%	-	-	
Tumor location					0.360					0.212
Upper thoracic	29	72.4%	8.6%	4.3%		38	71.1%	17.5%	4.8%	
Mid-thoracic	61	71.9%	12.1%	0%		46	67.4%	4.3%	-	
Lower thoracic	39	62.8%	10.3%	-		23	87.0%	10.8%	-	
Lymphatic metastasis					0.053					0.063
N0	74	77.0%	9.5%	1.0%		37	81.1%	18.5%	2.0%	
N1	55	59.6%	9.3%	0.5%		70	68.6%	6.6%	0%	
Distant metastasis					0.000					0.000
M0	123	71.4%	10.9%	1.7%		93	81.7%	12.9%	2.0%	
M1	6	20.8%	-	-		14	14.3%	-	-	
TNM stage					0.000					0.000
I	68	80.9%	11.8%	0.8%		33	84.8%	23.9%	5.1%	
II	37	67.1%	11.2%	0.5%		46	91.3%	0.79%	-	
III	18	44.0%	2.5%	0%		14	42.9%	-	-	
IV	6	25.0%	-	-		14	14.3%	-	-	
TRP					0.000					0.026
Yes	33	59.1%	0%	-		21	57.1%	-	-	
No	96	72.8%	13.5%	2.2%		86	76.7%	13.1%	1.8%	
TRP grade					0.000					0.047
II	20	81.0%	0%	-		14	64.0%	-	-	
III	13	22.1%	-	-		7	42.9%	-	-	
IV	0	-	-	-		0	-	-	-	
Radiation dose					0.620					0.969
≤ 60 Gy	58	72.4%	10.3%	0%		54	70.4%	13.9%	0.5%	
> 60 Gy	71	67.4%	10.4%	2.3%		53	75.5%	7.0%	1.5%	

TNM: Tumor, node, metastasis; TRP: Treatment-related pneumonitis.

Table 3 Multivariate analysis of prognostic factors in the elderly and non-elderly esophageal carcinoma groups

Variable	Elderly		Non-elderly	
	<i>P</i>	HR (95%CI)	<i>P</i>	HR (95%CI)
Pathological type	0.433	1.201 (0.759-1.901)	0.451	0.661 (0.224-1.944)
TRP	0.268	0.359 (0.059-2.199)	0.862	1.223 (0.126-11.838)
TRP grade	0.057	2.044 (0.980-4.261)	0.640	1.254 (0.486-3.235)
Distant metastasis	0.223	1.969 (0.662-5.861)	0.025	3.166 (1.155-8.679)
TNM stage	0.024	1.348 (1.040-1.748)	0.001	1.789 (1.271-2.517)

TNM: Tumor, node, metastasis; TRP: Treatment-related pneumonitis.

In the present study, the incidence of lymph nodes metastasis at the time of initial diagnosis in the elderly group was lower than that in the control group. In addition, the grade of tumor was relatively lower and tumor growth was relatively slower in elderly compared with non-elderly patients with esophageal carcinoma. However, the elderly patients did not show a significantly higher survival rate. This result might just be explained by the age. The elderly patients were physically weaker and suffered from more chronic diseases, which affected the prognoses of elderly patients with esophageal carcinoma. Our results demonstrated that more patients died of other diseases in the elderly group compared to the non-elderly group. Therefore, in the elderly group, favor-

able and unfavorable factors offset each other, and make no benefit for long-term survival.

Tumor stage is closely related to lymph node and distant metastases, which are important factors that affect the prognoses of patients with esophageal carcinoma^[11]. The results of our data analysis also suggested that tumor stage had a significant influence on prognosis. In addition, our research also showed that tumor position was not an independent factor affecting survival. The analysis of tumor type showed a significant difference between these two groups. Although the number of adenocarcinomas in the non-elderly group is more than that in the elderly group, squamous cell carcinoma was still the major type in the two groups.

Table 4 Multivariate Cox regression analysis of prognostic factors in patients in whom treatment-related pneumonitis occurred

	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>df</i>	<i>P</i>	<i>Exp(B)</i>	95%CI for <i>Exp(B)</i>	
							Lower	Upper
TRP grade	0.465	0.315	2.182	1	0.140	1.592	0.859	2.949
Lymph node metastasis	-0.459	0.461	0.989	1	0.320	0.632	0.256	1.561
Distant metastasis	-0.113	0.923	0.015	1	0.902	0.893	0.146	5.454
Tumor TNM stage	0.592	0.296	3.983	1	0.046	1.807	1.011	3.231
Radiation dose	-0.425	0.316	1.811	1	0.178	0.654	0.352	1.214

B: Regression coefficient; *SE*: Standard error; *df*: Degree of freedom; *TNM*: Tumor, node, metastasis; *TRP*: Treatment-related pneumonitis.

TRP is a major adverse reaction to radiotherapy, which can even lead to patient death. In this study, we found that TRP was characterized by pulmonary cord-like shadows, relatively stiff lesions confined to the radiation area and lesions with shapes similar to that of the radiation field. Subsequently, the univariate analysis showed that the development of TRP after radiotherapy had a significant effect on survival, indicating that greater attention should be paid to TRP prevention and administration of active treatment if TRP occurs. The multivariate analysis showed that the occurrence of TRP is an independent prognostic factor for patients with esophageal carcinoma.

Most of the literature has reported that the incidence of radiation pneumonitis and pulmonary fibrosis after radiotherapy is approximately 10%^[12-14]. In this study, the overall incidence of TRP was 22.9%, and most of these cases were grade II TRP, consistent with most previous reports. It has been proved that intensity-modulated radiation therapy can improve the tumor target dose, reduce the dose to normal tissue around the target and improve the local control rate and prognosis^[15]. In the present study, most patients, however, were enrolled earlier, without intensity-modulated radiation therapy. Hence, the incidence of TRP was increased compared to that in other studies. This suggested that the application of intensity-modulated radiation therapy (IMRT) was important for reducing the incidence of TRP.

Currently, most studies have suggested that the total dose, single dose and volume or area of the irradiated lung are correlated with the incidence and severity of TRP, and 60 or 70 Gy has often been a cut-off dose when comparing these factors^[13,16]. In the present study, the difference in TRP grade between the two groups (< 60 Gy and > 60 Gy) was statistically significant, indicating that the main factor associated with the development of TRP was the radiation dose. This conclusion is consistent with the opinions of the several scholars mentioned above.

Some researchers have suggested that TRP has different effects in different locations of the lung^[17-25]. In general, TRP occurrence at the bottom of the lung is more frequent than that at the top of the lung. The incidence of TRP occurring in the hilar and mediastinal areas was relatively greater than in other areas^[18]. This investigation concluded that tumor position was not an independent prognostic factor for TRP.

Notably, the incidence of TRP in the elderly pa-

tients was higher than that in the non-elderly patients, suggested that it might need a limitation of radiation exposure time and a control of total dose. However, the two choices are a double-edge sword. A lower dose or less time is adverse for tumor control. Therefore, for the elderly patients, personalized radiotherapy is of importance, and IMRT should be selected if possible.

Esophageal carcinoma in elderly patients was relatively less malignant compared with that in non-elderly patients. The incidence of TRP in the elderly patients was higher than that in the non-elderly patients. Therefore, an appropriate dose should be used to decrease the incidence of TRP in radiotherapy, and IMRT should be selected if possible.

COMMENTS

Background

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of death from cancer. A relatively poorly differentiated tumor and a low metabolic rate reduce the distant metastasis rate in elderly patients. However, elderly patients often suffer from chronic underlying diseases, resulting in poor tolerance of radiotherapy.

Research frontiers

In this study, authors investigated the relevant problems associated with radiation therapy in elderly patients with esophageal carcinoma by comparing tumor biological characteristics, survival rate, treatment-related pneumonitis (TRP) incidence, and other factors between elderly and non-elderly patients with esophageal carcinoma.

Innovations and breakthroughs

Authors found the tumor characteristics of esophageal cancer in elderly patients were relatively less malignant compared with those in non-elderly patients. The incidence of lymph node and distant metastases, and recurrence or metastasis after radiotherapy were lower. The incidence of treatment-related pneumonitis was much higher in the elderly patients.

Applications

A appropriate dose should be used to decrease the incidence of TRP in radiotherapy, and intensity modulated radiation therapy should be selected if possible.

Terminology

The patients were divided into two groups: an elderly group (age ≥ 65 years) and a non-elderly group (age < 65 years).

Peer review

Their results suggest that esophageal carcinoma in elderly patients was relatively less aggressive compared with that in non-elderly patients. Therefore a proper radiation dose could improve therapeutic effects of radiotherapy and decrease the incidence of TRP in elderly patients.

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