Gross tumor volume is an independent prognostic factor in patients with postoperative locoregional recurrence of esophageal squamous cell carcinoma

YU SHI[1,2*], XIAOLIN GE[1*], ZHENZHEN GAO[1,3], SHENXIANG LIU[1,4], XINCHEN SUN[1] and JINHUA LUO[5]

[1]Department of Radiotherapy, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029; [2]Department of Radiotherapy, Affiliated Hospital of Nantong University, Nantong, Jiangsu 226001; [3]Department of Oncology, The Second Affiliated Hospital of Jiaxing University, Jiaxing, Zhejiang 314000; [4]Department of Oncology, Affiliated Hospital of Yangzhou University, Yangzhou, Jiangsu 225100; [5]Department of Thoracic Surgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, P.R. China

Received April 15, 2019; Accepted June 10, 2019

DOI: 10.3892/ol.2019.10529

Abstract. Many cases of esophageal squamous cell carcinoma (ESCC) involve lymph node and distant metastases after esophagectomy, and most patients relapse within 2 years. Intensity-modulated radiotherapy (IMRT) is an important treatment for these cases of recurrence in ESCC and is widely used in clinical practice. A retrospective study of 137 postoperative patients with locoregional recurrences of ESCC who received IMRT was carried out. Kaplan-Meier survival curves and log-rank tests of univariate analysis was performed to assess whether there was a significant association between demographic and clinical features and death after recurrence. For multivariate analysis, the statistically significant results from the Kaplan-Meier method were subjected to Cox regression analysis. A total of 109 male and 28 female patients were included. There were 21 (15.3%), 58 (42.3%), 36 (26.3%), 3 (2.2%), 17 (12.4%), and 2 (1.5%) recurrences in the anastomotic, supraclavicular, mediastinal, tumor bed, polyregional, and abdominal regions, respectively. Univariate analysis showed that the gross tumor volume (GTV) of radiation (<27 vs. ≥27 cm^3) and the number of lymph nodes were significantly associated with survival. The survival rates of patients at 1, 2, 3 and 5 years with GTV<27 cm^3 were 72.7, 51.5, 37.1 and 25.9%, respectively, and with GTV≥27 cm^3 were 63.7, 26.9, 17.9 and 0%, respectively. The significant independent prognostic factor was GTV [<27 vs. ≥27 cm^3; hazard ratio (HR), 1.746; 95% confidence interval (CI), 1.112-2.741]. In conclusion, GTV of radiation (<27 vs. ≥27 cm^3) is an independent factor in predicting locoregional recurrence after ESCC. Patients with GTV<27 cm^3 are likely to have a better prognosis.

Correspondence to: Dr Xinchen Sun, Department of Radiotherapy, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing, Jiangsu 210029, P.R. China
E-mail: rvw64v@163.com; sunxinchen2012@163.com

Dr Jinhua Luo, Department of Thoracic Surgery, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing, Jiangsu 210029, P.R. China
E-mail: ljhua1966@126.com

*Contributed equally

Key words: esophageal squamous cell carcinoma, prognostic factors, radiation therapy

Introduction

Esophageal carcinoma (EC) is one of the most fatal and prevalent human malignancies worldwide, that due to its rapidly increasing incidence, it has gained worldwide attention (1). Esophageal squamous cell carcinoma (ESCC) is the most lethal pathological type, accounting for ~90% of total EC cases, and China alone contributes to more than half of the global ESCC cases (2). At present, surgery is the main treatment for EC, but the 5-year survival rate after simple surgery is 31-55% (3). Most patients have lymph node involvement and distant metastases after esophagectomy and the 5-year survival rate of ESCC patients with metastasis is only 5-47% (4-6). Moreover, locoregional recurrence and distant metastasis are the most common cause of treatment failure (7). The most common recurrence sites include the anastomosis and regional lymph nodes, which lead to a relatively poorer prognosis (8,9). The overall 2-year post-recurrence survival rate is 12.6%, and the median postoperative survival is 6 months for patients with postoperative recurrence of ESCC (10). Significant difficulty is often encountered in identifying the appropriate treatment method from the limited available treatment options for recurrence following resection.

Recent advances in radiation techniques and chemotherapy may lead to the improvement of the treatment outcomes of postoperatively recurrent ESCC. Three-dimensional conformal radiotherapy (3D-CRT)-based concurrent chemoradiotherapy (CCRT) has been reportedly effective against the recurrence of ESCC after radical surgery (9). 3D-CRT for

lymph node stations near ESCC with involved-field irradiation may deliver considerable doses of incidental nodal irradiation and promote the elimination of subclinical lesions (11). Intensity-modulated radiotherapy (IMRT), a more advanced form of 3D-CRT, is a high-precision conformal technique that allows physicians to modulate the intensity of the radiation and apply high-radiation doses to the tumor (12). Postoperative precautionary IMRT has high local control rate and acceptable side-effects on thoracic ESCC (13). In this study, we evaluated the survival of ESCC patients that received IMRT for the treatment of postoperative recurrence and evaluated the prognostic factors affecting survival.

Patients and methods

Acquisition of clinical data. A total of 137 ESCC patients, who received IMRT for postoperative locoregional recurrence at The First Affiliated Hospital of Nanjing Medical University (Nanjing, China) from August 2003 to January 2018, were retrospectively studied. Locoregional recurrence was defined as anastomotic or lymph node recurrence and was confirmed by enhanced computed tomography (CT) and biopsy under endoscopy, respectively. All patients were diagnosed with ESCC by postoperative pathology and distant metastasis was ruled out by imaging. The study was approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University. Patients who participated in this research had complete clinical data. Signed informed consents were obtained from the patients or their guardians.

Clinical data of postoperative tumor recurrence were collected including sex and age, previous treatment (neoadjuvant therapy, postoperative radiotherapy (PORT), and/or chemotherapy), grades of differentiation, primary esophageal tumor location, TNM staging, number and diameter of metastatic lymph nodes, recurrence sites, CCRT, death from recurrence, gross tumor volume (GTV), and survival time after recurrence.

Treatment and follow-up assessment. IMRT was performed according to the standard program in our Department. Briefly, patients were fixed in position with a thermoplastic immobilizer. For treatment simulation and planning purposes, CT scanning images were obtained to determine the radiation treatment plan and target volume. The CT scan range included the full mediastinum, lower neck, and upper abdomen, with a layer spacing of 5 mm. The images were transmitted to the IMRT treatment planning system and the attending physician's outline of the GTV was reviewed by the chief physician. The GTV included positive lymph nodes based on CT and positron emission tomography (PET), including swollen lymph nodes identified by physical examination and positive lymph nodes shown by PET-CT. The clinical target volume (CTV) was defined as the GTV plus a 1-1.5 cm radial margin, including high-risk regional lymph nodes. The planning target volume (PTV) contained a 0.5-cm extension on the basis of the CTV. The reference dose point was located at the central part of the GTV and was optimized using a dose volume histogram with a 95% isodose curve covering the PTV. The treatment plan was reviewed and confirmed by the chief physician. In this study, the median dose of radiation therapy was 62.2 Gy (range, 40-80 Gy). The X-ray irradiation energy was 6 MV administered 5 times/week with a test dose of 2 Gy each time. The maximum doses to the endangered organs, the lungs, and spine were $V_{20} \leq 25\%$, $V_{30} \leq 20\%$, and ≤45 Gy, respectively.

Intravenous or oral chemotherapy, CCRT, continuous chemoradiotherapy, radiotherapy alone or chemotherapy dose were taken into account according to the patient's age, general condition, Karnofsky Performance Status (KPS) score, treatment tolerance and compliance. Follow-up data included physical examinations, such as clinical evaluations and CT scans every 3 months. Tumor-related deaths were documented.

Statistical analysis. Statistical analysis was performed using IBM SPSS 19.0 software (IBM Corp.). Quantitative data were expressed as the mean ± standard deviation (SD) or median (interquartile range), while qualitative data were expressed as numbers and percentages. The mean/median survival times with 95% CIs at different levels were assessed by the Kaplan-Meier method (14). Univariate analyses using Kaplan-Meier survival curves and log-rank tests were performed to assess whether there was a significant association between demographic and clinical features, such as sex, age, postoperative treatment, and degree of differentiation, and death after recurrence. Statistical significance was determined using the conventional $P<0.05$ criterion. For multivariate analysis, the statistically significant results from the Kaplan-Meier method were subjected to Cox regression analysis (15), which was used to analyze the effect of multiple variables on survival time.

Results

Patient characteristics. The clinical and pathological characteristics of the patients are presented in Tables I and II. Between 2003 and 2018, a total of 109 male and 28 female patients were included, with an average age of 62.22±6.56 years (range, 44-82 years). Ninety-seven patients (70.8%) were ≥60 years of age. A total of 43.8% of patients received PORT and/or chemotherapy or neoadjuvant therapy. Based on TNM staging, 38 (27.7%), 53 (38.7%), and 46 (33.6%) patients had stage I, II, and III ESCC, respectively. The locations of the primary ESCCs removed by radical resection included the upper, middle, and lower thoracic esophagus in 14 (10.2%), 67 (48.9%), and 56 (40.9%) patients, respectively. There were 21 (15.3%), 58 (42.3%), 36 (26.3%), 3 (2.2%), 17 (12.4%), and 2 (1.5%) recurrences in the anastomotic, supraclavicular, mediastinal, tumor bed, polyregional, and abdominal regions, respectively. Ninety-four patients underwent CCRT. The median GTV of radiation was 27.06 cm^3 with interquartile range (14.03, 70.48) cm^3. The analysis showed that the average survival time after recurrence was 18.83±14.71 months. Of the 137 patients who underwent IMRT, 84 (61.3%) died. As shown in Table III, the 2-year survival rates of patients with anastomotic, supraclavicular, and mediastinal lymph node recurrence were 36.4, 41.4, and 37.5%, respectively. The 2-year survival rates of patients with 0, 1, and 2-6 lymph node recurrences were 38.9, 50.8, and 19.7%, respectively, and the 2-year survival rates for patients with and without CCRT were 41.2 and 34.9%, respectively.

Univariate analysis showed that the GTV of radiation (<27 vs. ≥27 cm^3) and the number of lymph nodes were

Table I. Patient characteristics (qualitative variables).

Characteristics	No. of patients	Constituent ratio (%)
Sex		
Males	109	79.6
Females	28	20.4
Age (years)		
<60	40	29.2
≥60	97	70.8
Postoperative therapy		
No	77	56.2
Radiotherapy	11	8.0
Chemotherapy	34	24.8
Radiotherapy and chemotherapy	13	9.5
Neoadjuvant therapy	2	1.5
Differentiation grades		
Poor	56	40.9
Moderate	76	55.5
Well	3	2.2
Unknown	2	1.5
Primary tumor location		
Upper	14	10.2
Middle	67	48.9
Lower	56	40.9
TNM staging		
I	38	27.7
II	53	38.7
III	46	33.6
No. of lymph nodes		
None	24	17.5
1	63	46.0
2-6	15	10.9
Fusion	35	25.5
Recurrence sites		
Anastomotic	21	15.3
Supraclavicular lymph nodes	58	42.3
Mediastinal lymph nodes	36	26.3
Tumor bed	3	2.2
Polyregional lymph nodes	17	12.4
Abdominal lymph nodes	2	1.5
CCRT		
Yes	94	68.6
No	43	31.4
Death		
Yes	84	61.3
No	53	38.7

CCRT, concurrent chemoradiotherapy.

Table II. Patient characteristics (quantitative variables).

Characteristics	Values	Range
Age (years)	62.22±6.56	44-82
Lymph node diameter (cm)	2.73±1.88	0-7.9
GTV (cm^3)	27.06 (14.03, 70.48)	1.73-385.6
Survival time after recurrence (months)	18.83±14.71	2-81

Age, lymph node diameter and survival time after recurrence are expressed as the mean ± SD, and GTV as the median (interquartile range). GTV, gross tumor volume.

significantly related to survival. Other factors, such as differentiation grade and recurrence site, were not related to survival (Table III, Fig. 1). The 1-, 2-, 3-, and 5-year survival rates of patients with GTV<27 cm^3 were 72.7, 51.5, 37.1, and 25.9%, respectively, and with GTV≥27 cm^3 were 63.7, 26.9, 17.9, and 0%, respectively. Multivariate regression analysis with a Cox model showed that the GTV of radiation was a significant independent prognostic factor and was significantly related to the risk of death after recurrence [HR (95% CI), 1.746 (1.112-2.741); P=0.016] (Table IV). According to the results, the risk of death for patients with GTV≥27 cm^3 was 1.746 times that for patients with GTV<27 cm^3, with a statistically significant difference.

Discussion

Currently, surgery is the primary treatment for ESCC. However, the overall recurrence rate of ESCC patients after radical resection ranges from 34 to 79%, while the rate of locoregional recurrence is 21-68% (16,17). Evidence has indicated that the number of lymph nodes involved and the depth of primary tumor invasion may help in evaluating the recurrence risk in ESCC patients following curative surgery (17). EC guidelines for the national comprehensive cancer network (NCCN) suggest that some patients with local recurrence after surgery can tolerate CCRT (18,19). Approximately 28% of patients with ESCC achieved long-term survival with the use of CRT for lymph node recurrence after curative resection (20). Current radiation techniques using 3D-CRT with enhanced accuracy using daily image guidance have improved the accuracy of irradiation (21). The incidental irradiation doses with involved-field irradiation have significantly impacted the control of micro-metastasis and may contribute to the elimination of subclinical ESCC lesions (11). It has been reported that the tolerance to 3D-CRT combined with chemotherapy is better than that of the simple 3D-CRT , which is a feasible technology and can improve the overall survival (OS) rate of patients with recurrent ESCC mediastinal lymph node metastasis after surgery (22). In the present study, ESCC patients with anastomotic or lymph node recurrence received IMRT or IMRT-based CCRT and the factors affecting their survival were investigated.

Previous studies have indicated that the number and regions of lymph node recurrences after ESCC are also important factors influencing the efficacy of salvage chemoradiotherapy (23). Jingu *et al* reported that the median OS

Table III. Kaplan-Meier analysis of risk factors related to death after tumor recurrence.

Characteristics	Median (95% CI)	P-value (log-rank)	1-year survival rate (%)	2-year survival rate (%)	3-year survival rate (%)	5-year survival rate (%)
Sex		0.160				
Male	28.48 (22.13, 34.82)		65.1	34.9	25.3	13.5
Female	36.85 (23.58, 50.12)		68.0	57.7	43.2	-
Age (years)		0.169				
<60	27.90 (17.33, 38.48)		50.2	30.4	-	15.2
≥60	30.46 (24.24, 36.68)		75.5	42.6	28.2	-
Diameter of nodes (cm)		0.184				
<2.6 (n=66)	29.76 (22.52, 37.00)		73.7	43.3	29.5	11.1
≥2.6 (n=71)	29.00 (20.96, 37.03)		62.9	35.0	-	18.2
GTV (cm^3)		**0.013**				
<27 (n=68)	35.76 (27.44, 44.09)		72.7	51.5	37.1	25.9
≥27 (n=69)	22.48 (16.98, 27.98)		63.7	26.9	17.9	0.0
Postoperative therapy		0.286				
No	32.40 (25.24, 39.55)		71.0	47.1	37.7	16.2
Radiotherapy	21.69 (16.36, 27.02)		-	35.1	-	-
Chemotherapy	25.41 (15.51, 35.31)		56.8	27.1	17.0	-
Radiotherapy and chemotherapy	16.00 (10.08, 21.92)		38.5	-	-	-
Grades of differentiation		0.689				
Poorly	30.48 (21.75, 39.20)		65.3	44.0	30.0	20.0
Moderately	29.90 (21.93, 37.87)		69.6	39.7	31.2	12.5
Well	18.67 (15.82, 21.51)		66.7	-	-	-
Primary tumor location		0.162				
Upper	29.82 (17.60, 42.04)		71.4	53.6	-	-
Middle	30.85 (23.18, 38.52)		75.2	43.7	28.1	14.1
Lower	26.70 (18.86, 34.55)		58.9	29.1	-	-
TNM staging		0.222				
I	24.64 (18.24, 31.04)		71.1	37.8	21.6	-
II	32.70 (24.67, 40.74)		74.4	49.2	-	13.1
III	27.60 (17.78, 37.43)		57.7	27.4	-	-
Location of lymph nodes		0.073				
No	23.86 (16.12, 31.59)		62.5	38.9	15.6	-
Supraclavicular lymph nodes	31.55 (23.61, 39.48)		69.4	40.9	-	18.2
Mediastinal lymph nodes	37.85 (24.05, 51.66)		74.0	53.2	39.9	-
Polyregional lymph nodes	13.40 (8.42, 18.39)		53.3	-	-	-
No. of lymph nodes		**0.025**				
None	23.86 (16.12, 31.59)		62.5	38.9	15.6	-
1	38.74 (29.28, 31.59)		77.3	50.8	38.1	-
2-6	25.56 (10.70, 40.42)		63.2	19.7	-	-
Fusion	21.66 (13.72, 29.60)		54.0	-	-	0.0
Recurrence sites		0.838				
Anastomotic	23.25 (15.39, 31.12)		61.9	36.4	14.5	-
Supraclavicular lymph nodes	32.03 (23.82, 40.24)		71.1	41.4	-	18.4
Mediastinal lymph nodes	29.44 (18.19, 40.70)		58.5	37.5	28.2	-
Polyregional lymph nodes	18.45 (13.33, 23.57)		70.1	-	-	-
CCRT		0.513				
No	30.63 (20.81, 40.45)		55.3	34.9	-	-
Yes	28.78 (22.46, 35.10)		74.5	41.2	28.5	7.9

Bold indicates statistical significance. CI, confidence interval; GTV, gross tumor volume; CCRT, concurrent chemoradiotherapy.

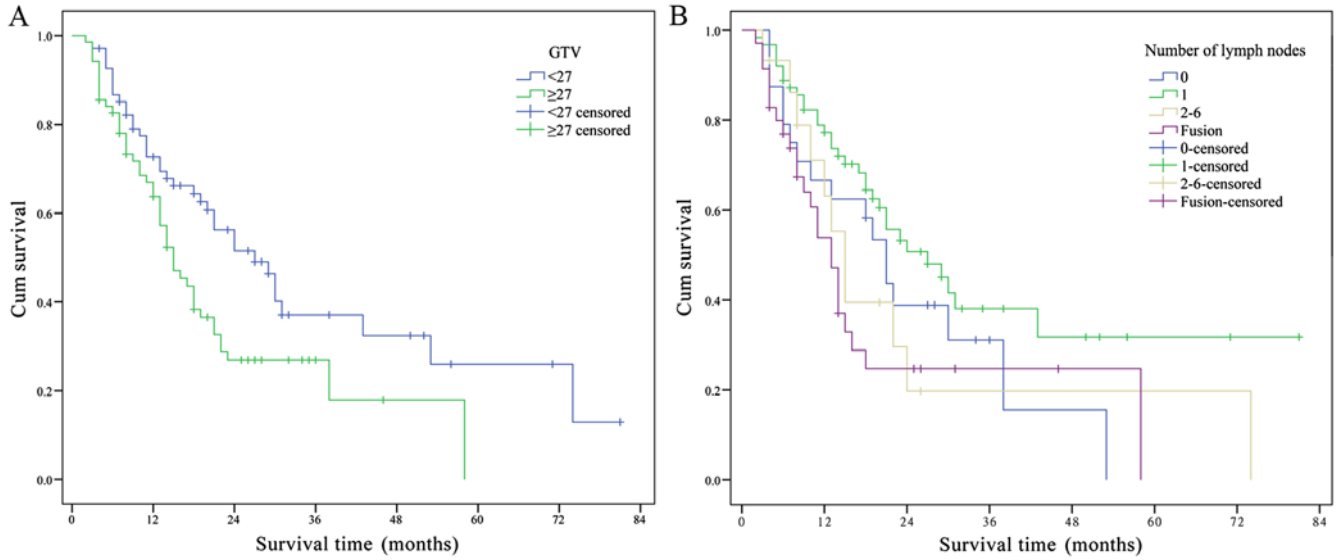

Figure 1. Kaplan-Meier curves estimating the OS of 137 patients with postoperative locoregional recurrence according to (A) the GTV and (B) the number of lymph nodes. OS, overall survival; GTV, gross tumor volume.

Table IV. Multivariate regression model analysis of risk factors related to death after tumor recurrence.

			95.0% CI for HR	
Factors	P-value	HR	Lower	Upper
GTV	0.016	1.746	1.112	2.741
No. of lymph nodes	0.813	1.068	0.616	1.853

CI, confidence interval; HR, hazard ratio; GTV, gross tumor volume.

rates of single and multiple recurrent regions after EC surgery were 39.0 and 6.5 months, respectively, after radiotherapy and chemotherapy, and the number of recurrent lesions was a significant prognostic factor (23). Miyata *et al* reported that the OS rate of patients with ≥4 recurrent lymph nodes after ESCC surgery was significantly lower than that in patients with <4 recurrent lymph nodes (24). Chen *et al* reported 5-year OS rates for 1-2, 3-6, and ≥7 recurrent lymph nodes after ESCC resection of 33, 17, and 12%, respectively, and patients with more recurrent lymph nodes had worse prognoses (25). In the current study, although Kaplan-Meier analysis showed that the number of lymph nodes was a risk factor related to death after tumor recurrence, multivariate regression model analyses showed that the number of lymph nodes was not an independent prognostic factor.

The risk factor GTV of radiation was a significant independent prognostic factor for survival after recurrence in patients receiving IMRT treatment. The GTVs were contoured as visible tumors on CT scans (26). Most of the lymphatic recurrences after surgery among patients diagnosed with ESCC would have been covered by the proposed PORT CTV (21). The GTV has been demonstrated to be an independent prognostic factor for survival in multiple cancers treated with radiation therapy (27,28). Ma *et al* reported that the GTV of radiation (≥5 vs. <5 cm^3) was an important independent prognostic factor in patients with recurrent ESCC (22). However, this study confirmed that GTV of radiation (<27 vs. ≥27 cm^3) is an important independent prognostic factor for the risk of death after recurrence treated by IMRT.

This study has several limitations. Its retrospective design may have a potential bias. In addition, because of the different doses and schedule used in this study, the optimal treatment for locoregional recurrence has not been determined.

In conclusion, our retrospective study showed that the GTV of radiation is an independent prognostic factor in ESCC patients with postoperative locoregional recurrence. Patients with a GTV≥27 cm^3 have a higher risk of death.

Acknowledgements

Not applicable.

Funding

This study was supported by grants from the National Natural Science Foundation of China (nos. 81703028, 81472809, 81502653 and 81672983). We would like to thank everyone involved for their support, and the patients who participated in this study.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YS and XG performed the retrospective analyses and wrote the manuscript. ZG and SL performed the statistical analysis and revised the manuscript. XS and JL designed the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (Nanjing, China). Patients who participated in this research had complete clinical data. Signed informed consents were obtained from the patients or their guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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