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Relative tumor volume is a better independent prognostic factor in esophageal squamous cell carcinoma

Results of a retrospective study

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Abstract

The present study is to evaluate the significance in prognosis of relative tumor volume (RTV) in patients with non-resectable esophageal squamous cell carcinoma (ESCC) treated by definitive radiotherapy alone or in combination with chemotherapy.

Fifty-eight consecutive patients with ESCC in UICC stage I to IV were retrospectively analyzed. Relative primary gross volume (RGTVp) was defined as primary gross volume (GTVp) divided by body volume. Relative primary gross volume for lymph nodes (RGTVnd) was defined as primary gross volume for lymph nodes (GTVnd) divided by body volume. The relationships were analyzed between overall survival (OS), disease free survival (DFS), local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and RGTVp (RGTVnd) in univariate and multivariate analyses.

The cut-off values of 0.947 and 0.007 were determined for RGTVp and RGTVnd, respectively. The 3-year OS, DFS, and LRFS for patients with RGTVp $\leq$ 0.947 vs RGTVp $>$ 0.947 was 65.4% vs 25.0% ($P = .001$), 46.2% vs 12.5% ($P = .002$), and 90.1% vs 42.0% ($P < .001$). RGTVp was an independent risk factor for OS ($P = .046$), DFS ($P = .015$) and LRFS ($P = .032$), but showed no association with DMFS in univariate and multivariate analyses. The 3-year DFS and DMFS for patients with RGTVnd $\leq$ 0.007 vs RGTVnd $>$ 0.007 was 44.4% vs 20.0% ($P = .023$), and 62.9% vs 24.6% ($P < .004$). RGTVnd was associated with DMFS ($P = .012$) in multivariate, but showed no associated with DFS.

The present study demonstrates that RTV was an independent factor relevant to prognosis for ESCC. It provides new clinical basis for personalized therapeutic regimens and might be included in the staging system.

Abbreviations: 18F-FDG-PET = 18F-fluoro deoxyglucose positron emission tomography, CT = computed tomography, CTV = clinical target volume, DFS = disease free survival, DMFS = distant metastasis-free survival, EC = esophageal cancer, ESCC = esophageal squamous cell carcinoma, EUS = endoscopic ultrasound, GTV = gross tumor volume, GTVnd = primary gross volume for lymph nodes, GTVp = primary gross volume, IMRT = intensity-modified radiotherapy, LRFS = local recurrence-free survival, MRI = magnetic resonance imaging, OS = overall survival, PTV = planning target volume, RGTVnd = relative primary gross volume for lymph nodes, RGTVp = relative primary gross volume, ROC = receiver operating characteristic, RTV = relative tumor volume.

Keywords: esophageal squamous cell carcinoma, intensity-modulated radiotherapy, prognosis, relative tumor volume, tumor burden

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This project fully considered and protected the rights and interests of the study objects. It meets the criteria of Ethical Review Committee. The Medical Ethics Committee of First Affiliated Hospital of Guangxi Medical University has approved the protocol (Approval Number: 2018KY-E-042), and all methods were performed in accordance with the relevant guidelines and regulations.

All participants provided written informed consent.

The authors declare that they have no competing interests.

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1. Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer death and the seventh most common cancer worldwide.[1] The current preoperative TNM classification system for EC, based on EUS (Endoscopic ultrasound) and Computed Tomography (CT), is used worldwide, and considered as the most significant indicator relevant to prognosis. However, in clinical practice, EUS examination was limited in some patients due to esophageal obstruction, making it difficult to differentiate T2 lesions from T3 lesions.[2] Moreover, TNM classification system was based on a database of esophagectomy patients who had not undergone induction or adjuvant therapy.[3] This indicated that the TNM classification system remains coarse and inaccurate, particularly under the current treatment mode of patients with non-resectable disease. However, more than 50% of patients with EC are diagnosed in the late stages, making it difficult for surgical treatment.[4]

Tumor volume can be considered as a potential prognostic factor, since intensity-modified radiotherapy (IMRT) is based on CT simulation planning system and target contouring system, and hence it is widely used. In the past few years, some works have reported a significant correlation between the survival rate and tumor volume.[5,6] However, different cut-off values of tumor volume were postulated by different studies, for instance, Créhange et al first reported that 100 cm^3 was the optimal cut-off value to distinguish OS.[7] Chen et al suggested that the cut-off value of tumor volume was 20 cm^3,[8] and Chen et al demonstrated that 39.41 cm^3 could be an adequate cut-off value as an independent risk factor.[9] Whereas, Boggs et al reported that the cut-off value for local failure and 5-year distant failure were 85 cc and 46 cc,[10] respectively. Consequently, tumor volume has not been widely used as a prognostic factor. One of the most important reasons for this is the lack of a uniform standard to decide the optimal cutoff point.

Therefore, in the current study, we proposed a staging system by relativizing the tumor volume, based on the tumor burden differences in individuals, and elucidated that the relative tumor volume (RTV) had a predictive value in patients with esophageal squamous cell carcinoma (ESCC). This new theory aimed to establish an effective and available standard widely.

2. Materials and methods

2.1. Patients

Fifty-eight patients with ESCC diagnosed based on the histopathology, from January 1, 2012 to December 31, 2014, were included in our retrospective analysis. The inclusion criteria were: patients with

(1) the initial diagnosis of ESCC,
(2) EC staging under UICC stage I to IV (according to the 7th Union for International Cancer Control),
(3) body weight $\geq$50 kg and $\leq$100 kg,
(4) Karnofsky performance status (KPS) score >80 values patients who underwent IMRT,
(5) hematological and biochemical profiling before undergoing any treatment,
(6) regular follow-up.

The exclusion criteria were:

(1) any prior treatment for NPC,
(2) history of any previous or synchronous malignancy and complications,
(3) contraindications of radiotherapy.

2.2. Pretreatment assessment

The fundamental pretreatment evaluations included complete medical history, physical examination, hematologic and biochemical profile, barium meal X-ray examination, EUS, CT scan of the neck, chest and abdomen, and bone emission CT scans. Some patients underwent 18F-fluoro deoxyglucose positron emission tomography (18F-FDG-PET) or magnetic resonance imaging (MRI). All the patients provided written informed consents before study initiation.

2.3. Radio (chemo)therapy

Twenty-nine patients underwent IMRT with a linear accelerator (clinac iX, Varian, Palo alto, California in the United States) using 6 MV photons at the first affiliated hospital of guangxi medical university and other 29 patients with a 6 MV photon beam from a linear accelerator (Siemens Primus, Germany) at the second affiliated hospital of guangxi medical university. Patients underwent definitive radiotherapy alone or in combination with platinum-based chemotherapy (total radiation dose $\geq$50 Gy). All treatments were planned based on CT simulation planning system, with 5 mm slice thickness throughout the entire neck and thorax. The delineation of the target volumes was referred to barium meal X-ray examination, endoscopic ultrasonography, MRI, and 18F-FDG-PET. The planning system can automatically reconstruct to a three-dimensional image and calculate the tumor volume. Two radiation oncologists reviewed these new tumor volumes for accuracy and consistency. The target volumes were defined as follows: primary gross tumor volume (GTVp) and metastases lymphnodes (GTVnd) were recontoured separately. Gross tumor volume (GTV) involves primary esophageal tumor and metastatic lymph nodes. High-risk clinical target volume (CTV) was defined as GTV+3 cm margins in the esophageal long axis both inferiorly and superiorly, and GTV+0.5 cm margins in the esophageal short axis to encompass potential submucosal invasions. Planning target volume (PTV) was generated by adding 1 cm margins.

2.4. Definition and calculation of relative tumor volume

Relative primary gross volume (RGTVp) was defined as GTVp divided by body volume. Relative primary gross volume for lymph nodes (RGTVnd) was defined as GTVnd divided by body volume. Body volume = $1.015W - 4.937$ (where W is the patient's weight before treatment).[11]

2.5. Follow-up

Patients were asked to visit the clinic every 3 months during the first 2 years and then every 6 months thereafter, until death or the final follow-up. Each follow-up included hematological, biochemical profile, CT scan, endoscopy, and bone emission CT scans.

2.6. Statistical analyses

All the statistical analyses were performed by SPSS22.0 statistical software. Receiver operating characteristic (ROC) curve analysis was performed to obtain the cut-off values for GTVp, RGTVp, GTVnd, and RGTVnd. The patients were separated into 2 different groups by the cut-off values, and overall survival (OS), disease-free survival (DFS), local relapse-free survival (LRFS), and distant metastasis-free survival (DMFS) between the 2

groups were evaluated. A univariate analysis was performed via Kaplan–Meier method and the 2-sided log-rank test. Multivariate analysis was performed through Cox regression. Two-sided P values $<.05$ were considered statistically significant.

3. Results

3.1. Patient demographics

The median follow-up period was 26 (range:1–68) months. A total of 53 (91.4%) patients were male. Thirty-nine (67.2%) patients presented stage T4. Forty-three (74.1%) patients presented stage III, and 6 (10.3%) presented stage IV. Table 1 shows the clinical characteristics of the 58 patients with ESCC.

3.2. Optimal threshold for tumor volume

ROC optimal cut-off values were calculated and compared GTVp to T classification in OS, which was 54.150 cm^3. AUC of initial GTVp was 0.857 ($P<.001$). The optimal cut-off point for the comparison of RGTVp to T classification in OS was 0.947. AUC of initial RGTVp was 0.860 ($P<.001$). The optimal cut-off values for the correlation between GTVnd, RGTVnd and N classification in OS were 0.365 cm^3 and 0.007, respectively ($P<.001$; Table 2).

3.3. Survival rates

All patients showed that the 1, 2, 3, and 5-year OS was 63.8%, 51.7%, 43.1%, and 30.5%, respectively; the 1, 2, 3, and 5-year DFS was 44.8%, 29.3%, 27.6%, and 20.4%, respectively; the 1, 2, 3, and 5-year LRFS was 74.5%, 67.7%, 64.7%, and 64.7%, respectively; and the 1, 2, 3, and 5-year DMFS was 51.7%, 37.7%, 35.6%, and 26.4%, respectively. Thirty-eight patients died from different causes: 23 patients of distant metastasis, 6 patients of locoregional recurrence, 8 patients of both distant metastasis and locoregional recurrence, and 1 patient of coronary heart disease. Twenty-six patients presented with distant metastasis (7 multiple site metastasis, 6 cases of lung, 5 distant lymph nodes, 4 bone, 1 liver,1 pericardium,1 stomach, and 1 pleura), 7 patients presented with locoregional recurrence, and 11 presented with both distant metastasis and recurrence.

The optimal cut-off values for GTVp and GTVnd were 54.150 cm^3 and 0.365cm^3, respectively. The results of univariate analysis showed that patients with GTVp $>54.150\,cm^3$ vs GTVp $\leq$ 54.150 cm^3 showed 3-year OS, DFS, LRFS, DMFS of 17.9 vs 66.7% ($P<.001$), 7.1 vs 46.7% ($P<.001$), 36.1vs 88.2% ($P<.001$), 22.1 vs 46.7% ($P=.020$), respectively. Patients with GTVnd $>0.365\,cm^3$ vs GTVnd $\leq 0.365\,cm^3$ showed 3-year OS, DFS, LRFS, DMFS of 37.5 vs 55.6% ($P=.151$), 20.0 vs 44.4% ($P=.023$), 60.9 vs 70.7% ($P=.327$), 24.6 vs 62.9% ($P=.004$), respectively.

We proposed a new theory of RTV taking into account the individual tumor burden. The optimal cut-off values of RGTVp and RGTVnd were 0.947 and 0.007, respectively. The patients with RGTVp >0.947 vs RGTVp ≤ 0.947 showed 3-year OS, DFS, LRFS, DMFS of 25.0 vs 65.4% ($P=.001$, Fig. 1), 12.5 vs

Table 1

Patient characteristics.

Characteristics	N (%)	Range	Mean
Sex			
Male/Female	53 (91.4)/5 (8.6)		
Age (years)		38–78	59
Age ≥ 60y/ age < 60y	23 (39.7)/35 (60.3)		
UICC stage			
T1/T2/T3/T4	0 (0)/7 (12.1)/12 (20.7)/39 (67.2)		
N0/N1/N2/N3	18 (31.0)/23 (39.7)/13 (22.4)/4 (6.9)		
M0/M1	6 (10.3)/52 (89.7)		
I/II/III/IV	2 (3.5)/7 (12.1)/43 (74.1)/6 (10.3)		
Tumor length (cm)		3–18	9.7
≥9.7 cm/<9.7 cm	28 (48.3)/30 (51.7)		
Tumor location			
Cervical	4 (6.9)		
Upper thoracic	17 (29.3)		
Mid-thoracic	30 (51.7)		
Lower thoracic	7 (12.1)		
chemotherapy			
Yes/No	47 (81.0)/11 (19.0)		
necrosis			
Yes/No	25 (43.1)/33 (56.9)		
posttreatment perforation			
Yes/No	4 (6.9)/54 (93.1)		
Histology			
G1/G2/G3	17 (29.3)/26 (44.8)/15 (25.9)		
Follow-up time (months)		1–68	26

Table 2

ROC optimal cut-off values of prognostic factors.

Variable	Cutoff point	AUC	95% CI		P
GTVp (cm^3)	54.150	0.857	0.758	0.956	.000
GTVnd (cm^3)	0.365	0.898	0.808	0.988	.000
RGTVp	0.947	0.860	0.764	0.956	.000
RGTVnd	0.007	0.901	0.814	0.987	.000

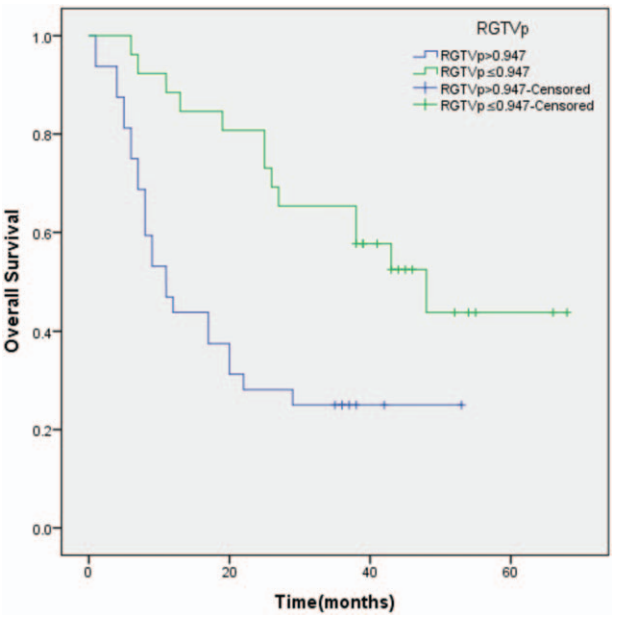

Figure 1. Effect of Relative primary gross volume for ESCC (RGTVp) on overall survival. ESCC = esophageal squamous cell carcinoma, RGTVp = relative primary gross volume.

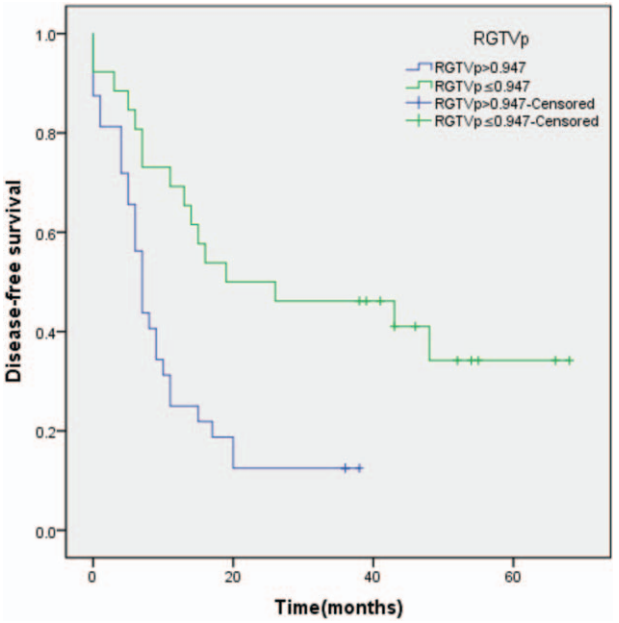

Figure 2. Effect of Relative primary gross volume for ESCC (RGTVp) on disease-free survival. ESCC = esophageal squamous cell carcinoma, RGTVp = relative primary gross volume.

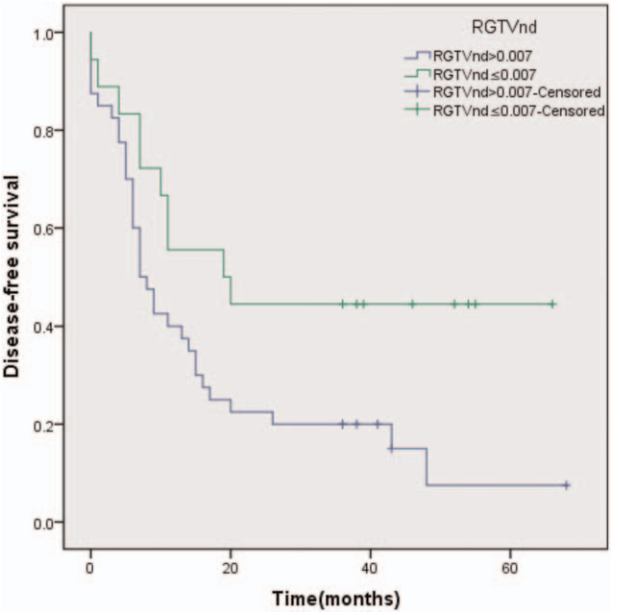

Figure 4. Effect of Relative gross tumor volume of metastases lymph nodes for ESCC (RGTVnd) on disease-free survival. ESCC = esophageal squamous cell carcinoma, RGTVnd = relative primary gross volume for lymph nodes.

46.2% ($P=.002$, Fig. 2), 42.0 vs 90.1% ($P<.001$, Fig. 3), 26.7 vs 46.2% ($P=.056$), respectively. Patients with RGTVnd > 0.0.007 vs RGTVnd ≤ 0.007 showed 3-year OS, DFS, LRFS, DMFS of 37.5 vs 55.6% ($P=.151$), 20.0 vs 44.4% ($P=.023$, Fig. 4), 60.9 vs 70.7% ($P=.327$), 24.6 vs 62.9% ($P=.004$, Fig. 5), respectively.

Furthermore, the results of univariate analysis showed that the differences of the 3-year OS for UICC stage grouping ($P=.011$), T classification ($P=.039$), tumor length ($P=.019$) were statistically significant; the differences of the 3-year DFS for UICC stage ($P=.042$), N classification ($P=.023$), and posttreatment perforation ($P=.044$) were statistically significant; the differences of the 3-year LRFS for T classification ($P=.013$), and necrosis ($P=.002$) were statistically significant; the differences of the 3-year DMFS for N classification ($P=.004$), tumor length ($P=.048$) and posttreatment perforation ($P=.021$) were statistically significant. (Table 3).

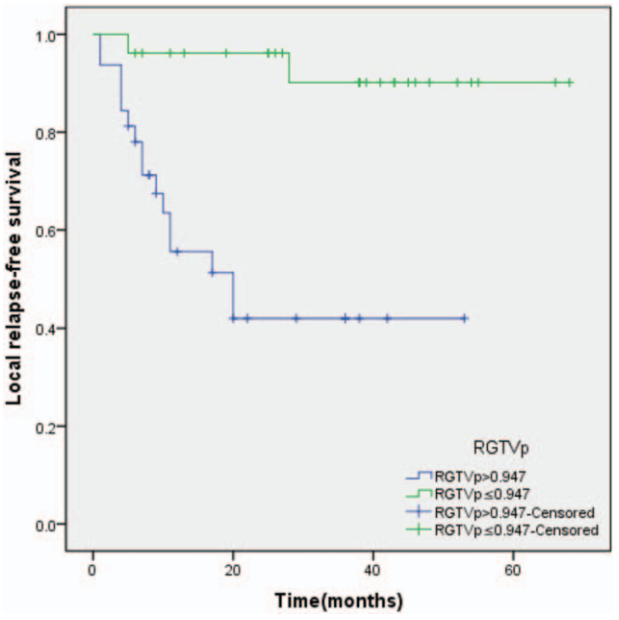

Figure 3. Effect of Relative primary gross volume for ESCC (RGTVp) on local relapse-free survival. ESCC = esophageal squamous cell carcinoma, RGTVp = relative primary gross volume.

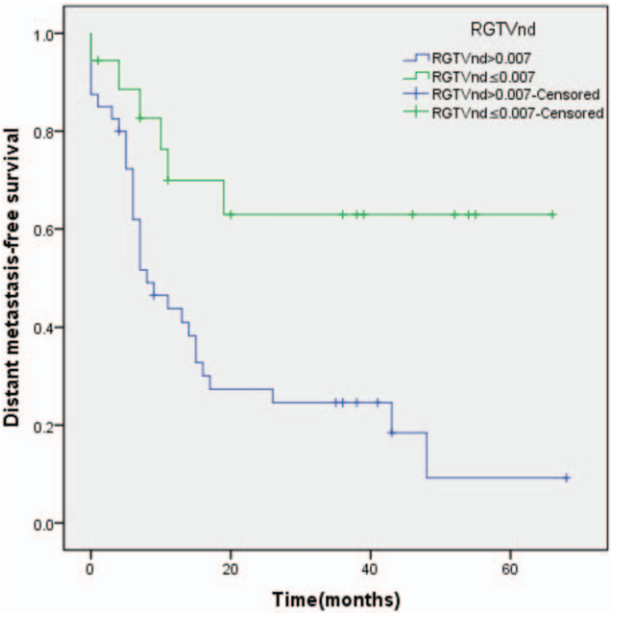

Figure 5. Effect of Relative gross tumor volume of metastases lymph nodes for ESCC (RGTVnd) on distant metastasis-free survival. ESCC = esophageal squamous cell carcinoma, RGTVnd = relative primary gross volume for lymph nodes.

Table 3

Impact of prognostic factors on treatment according to univariate analysis (log-rank test).

Characteristics	N	OS (%)	Log-Rank test	P	DFS (%)	Log-Rank test	P	LRFS (%)	Log-Rank test	P	DMFS (%)	Log-Rank test	P
Sex													
Male	53	39.6	1.673	.196	22.6	3.777	.052	62.9	0.569	.451	31.0	2.538	.111
Female	5	80.0			80.0			80.0			80.0		
Age (years)													
Age ≥ 60 yr	23	47.8	0.676	.411	39.1	3.695	.055	71.8	0.428	.513	41.1	1.549	.213
Age < 60 yr	35	40.0			20.0			59.6			32.7		
UICC stage													
III-IV	49	36.7	6.456	**.011**	22.4	4.141	**.042**	59.3	2.118	.146	31.6	2.505	.114
I-II	9	77.8			55.6			88.9			55.6		
T classification													
T4	39	63.2	4.262	**.039**	23.1	1.394	.238	53.3	6.207	**.013**	35.6	0.134	.715
T1–3	19	33.3			36.8			86.8			36.8		
N classification													
N0	18	55.6	2.058	.151	44.4	5.167	**.023**	70.7	0.327	.568	62.9	8.300	**.004**
N1–3	40	37.5			20.0			60.9			24.6		
Tumor length													
≥ 9.7 cm	28	32.1	5.540	**.019**	21.4	3.528	.060	61.0	1.309	.253	27.7	3.922	**.048**
<9.7 cm	30	53.3			33.3			68.3			43.7		
Tumor location													
Cervical	4	25.0	1.594	.661	25.0	3.015	.389	37.5	3.770	.287	25.0	2.384	.497
Upper thoracic	17	35.3			23.5			76.0			31.7		
Mid-thoracic	30	46.7			33.3			70.0			41.5		
Lower thoracic	7	57.1			14.3			34.3			28.6		
chemotherapy													
Yes	47	42.6	0.219	.640	25.5	1.576	.209	60.9	0.764	.382	35.0	1.190	.275
No	11	45.5			36.4			81.8			40.0		
necrosis													
Yes	25	32.0	2.494	.114	20.0	0.821	0.365	43.2	9.991	**.002**	36.8	0.012	.912
No	33	51.5			33.3			81.5			35.1		
posttreatment perforation													
Yes	4	25.0	0.278	.598	0.0	4.071	**.044**	66.7	0.019	.889	0.0	5.341	**.021**
No	54	44.4			29.6			64.3			38.4		
GTVp													
≤54.150 cm^3	30	66.7	19.162	**.000**	46.7	13.98	**.000**	88.2	17.6	**.000**	46.7	5.378	**.020**
>54.150 cm^3	28	17.9			7.1			36.1			22.1		
RGTVp													
≤0.947	26	65.4	10.348	**.001**	46.2	9.644	**.002**	90.1	13.82	**.000**	46.2	3.663	.056
>0.947	32	25.0			12.5			42.0			26.7		
GTVnd													
≤0.365 cm^3	18	55.6	2.058	.151	44.4	5.167	**.023**	70.7	0.327	.568	62.9	8.300	**.004**
>0.365 cm^3	40	37.5			20.0			60.9			24.6		
RGTVnd													
≤0.007	18	55.6	2.058	.151	44.4	5.167	**.023**	70.7	0.327	.568	62.9	8.300	**.004**
>0.007	40	37.5			20.0			60.9			24.6		

Multivariate analysis revealed that GTVp was independent factor relevant to prognosis for OS (hazard ratio (HR) 4.100; $P=.001$), DFS (HR2.795; $P=.004$), and LRFS (HR5.953; $P=.017$). RGTVp was independent significant prognostic factor for OS (HR2.275; $P=.046$), DFS (HR2.349; $P=.015$), LRFS (HR5.990; $P=.032$). Furthermore, GTVnd (HR 0.342; $P=.019$), RGTVnd (HR0.321; $P=.012$) and N classification were correlated with the DMFS. While the differences of the survival rates for UICC stage grouping, and T classification were not statistically significant ($P>.05$, Tables 4 and 5).

Table 4

Multivariate analysis of prognostic factors.

	OS				DFS				LRFS				DMFS			
Variable	HR	95% CI		P	HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
UICC stage	3.070	0.638	14.778	.162	1.124	0.335	3.772	.850								
T classification	1.374	0.580	3.259	.470					0.673	0.122	3.721	.650				
N classification													0.342	0.140	0.837	.019
Tumor length	2.028	1.033	3.980	.040									1.457	0.733	2.897	.283
necrosis									0.558	0.174	1.787	.326				
perforation					0.445	0.154	1.342	.153					0.430	0.139	1.327	.142
GTVnd					1.929	0.883	4.214	.099					0.342	0.140	0.837	.019
GTVp	4.100	1.777	9.460	.001	2.795	1.392	5.612	.004	5.953	1.373	25.812	.017	1.855	0.915	3.763	.087

Table 5

Multivariate analysis of prognostic factors.

	OS				DFS				LRFS				DMFS			
Variable	**HR**	**95% CI**		***P***	**HR**	**95% CI**		***P***	**HR**	**95% CI**		***P***	**HR**	**95% CI**		***P***
UICC stage	3.751	0.785	17.93	.098	1.324	0.406	4.319	.642	0.693	0.127	3.791	.673				
T classification	1.153	0.483	2.751	.749												
N classification													0.321	0.132	0.782	.012
Tumor length	1.602	0.809	3.173	.177									1.486	0.754	2.931	.252
Necrosis									0.468	0.149	1.467	.193				
Perforation					0.483	0.163	1.427	.188					0.326	0.119	1.102	.071
RGTVnd					1.978	0.900	4.343	.089					0.321	0.132	0.782	.012
RGTVp	2.275	1.016	5.095	.046	2.349	1.178	4.683	.015	5.990	1.165	30.797	.032				

4. Discussion

Combined chemotherapy and radiotherapy regimens are currently the standard therapeutic regimens for ESCC patients who were inoperable or locally advanced.[12] During IMRT era, tumor volume delineation was considered as critical prognostic factors. Some evidences explained how large-sized tumors were correlated with increased risk of outcomes in carcinomas at cellular or molecular level. First, the bigger the tumor is, the more T-cell needs to be reinvigorated by PD-1 antibody. Clinical failures in patients were not only the result of inability to induce immune reanimation, but rather due to an imbalance between T-cell reanimation and tumor burden.[13] Second, due to the lack of blood supply in the large tumor center, it provides a favorable micro-environment for the rapid proliferation of hypoxic cells, which is resistant to radiotherapy.[14] Third, large-sized tumors gradually increase unfavorable radiobiological factors.[15] Therefore, it is necessary to increase radiotherapy dosage to achieve satisfactory therapeutic effect for large-sized tumors.[16] Additionally, there are several clinical data confirming that tumor volume was a powerful independent factor relevant to prognosis in carcinomas, such as lung carcinoma, Hodgkin lymphoma, nasopharyngeal carcinoma, head and neck cancer, and other malignant tumors.[17–20] But the tumor volume has not yet been applied to the UICC staging system in EC.

Previous studies have shown the prognostic value of tumor volume with EC patients. Créhange et al first reported that patients with tumor volume $<100\,cm^3$ had a higher OS than those with tumor volume $\geq 100\,cm^3$. Chen et al showed that group of tumor volume $<20\,cm^3$ could have a better survival rate and they were treated with three-dimensional conformal radiotherapy. Boggs et al reported that the cut-off values for local failure and 5-year distant failure were 85 cc and 46 cc, respectively. Chen et al reported that tumor volume $>39.41\,cm^3$ was correlated with an increased risk of OS and PFS.[7–10] These evidences highlighted the prognostic significance of tumor volume, exhibiting it as a powerful predictor than traditional TNM staging. Our data from 58 ESCC patients further proved this conclusion.

This study indicated that tumor volume as a powerful indicator relevant to prognosis for ESCC. The patients were divided into 2 groups: $GTVp > 54.150\,cm^3$ and $GTVp \leq 54.150\,cm^3$. The univariate analysis demonstrated that the 3-year OS of patients with $GTVp \leq 54.150\,cm^3$ was significantly higher than those with $GTVp > 54.150\,cm^3$; also, DFS, LRFS, and DMFS were better. We classified the patients into 2 groups according to GTVnd: $GTVnd > 0.365\,cm^3$ and $GTVnd \leq 0.365\,cm^3$. The 3-year DFS and DMFS for patients with $GTVnd \leq 0.365 cm^3$ demonstrated a better outcome than those with $GTVnd > 0.365\,cm^3$.

In our study, both univariate and multivariate analyses demonstrated that GTVp was as independent factor relevant to prognosis for OS, DFS, and LRFS, but was not an independent factor relevant to prognosis for DMFS. GTVnd was the independent factor relevant to prognosis for DMFS. The possible reason was that distant metastasis in ESCC patients, with the application of IMRT, was closely related to lymph node metastasis instead of GTVp. Furthermore, UICC stage grouping, and T classifications were not independent factors relevant to prognosis for ESCC, in this study. This result indicated the deficiency of the current UICC classification system.

Several studies have proposed novel theories to consummate the existing UICC staging system, such as MTV,[21] tumor-to-blood standard uptake ratio (SUR),[22] and postneoadjuvant pathologic evaluation.[23] We suggested that tumor volume was a powerful factor relevant to prognosis for ESCC. However, the difference of cut-off values for tumor volume in different studies limited its clinical application widely. Therefore, it is still unclear how to classify tumor volume reasonably and find the standard method.

Since the proportion of tumor burden expressed in different patients with the same tumor volume was different, we proposed RTV to individualize the tumor volume by body volume. RGTVp defined as GTVp divided by body volume and RGTVnd defined as GTVnd divided by body volume can minimize the impact of individual tumor burden. There was a similar theory applied in nasopharyngeal carcinoma in a previously published article of our team.[15] Moreover, the cut-off values of 0.947 and 0.007 were determined for RGTVp and RGTVnd, respectively. The univariate and multivariate analyses indicated that patients with $RGTVp \leq 0.947$ had a better prognosis than those with $RGTVp > 0.947$ for OS, DFS, and LRFS, but not for DMFS.

Similarly, in RGTVnd, the univariate and multivariate analyses also showed that patients with $RGTVnd \leq 0.007$ had higher DMFS than those with $RGTVnd > 0.007$. Thus, RGTVnd was considered as the independent factor relevant to prognosis for DMFS. This might be the same reason presented by GTVp.

Goals for future clinical staging include the use of available clinical staging tools more uniformly, improved modalities to achieve more accurate data, and information about all clinical cancer categories and the modalities used to formulate specific therapies. This in turn will potentially improve the prognostication and may facilitate a precise cancer care. Thus, we proposed the theory of RTV and confirmed its prediction for the prognosis of patients with ESCC. Nevertheless, there are some limitations in this study. Our findings are retrospective and require prospective studies in a larger patient population to confirm.

In conclusion, RTV is an independent factor relevant to prognosis for ESCC. It provides a new way to rational

application of the tumor volume and helps to establish common standards and facilitate multi-center communication.

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