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 ≤ 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 ≤ 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
1. Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer death and the seventh most common cancer worldwide. 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. Moreover, TNM classification system was based on a database of esophagectomy patients who had not undergone induction or adjuvant therapy. 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.

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. However, different cut-off values of tumor volume were postulated by different studies, for instance, Créhange et al first reported that 100cm³ was the optimal cut-off value to distinguish OS. Chen et al suggested that the cut-off value of tumor volume was 20cm³ and Chen et al demonstrated that 39.41cm³ could be an adequate cut-off value as an independent risk factor. Whereas, Boggs et al reported that the cut-off value for local failure and 3-year distant failure were 85cc and 46cc, 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 ≥50kg and ≤100kg,
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 ≥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 (GTIVnd) 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 GTIVnd divided by body volume. Body volume=1.015W−4.937 (where W is the patient’s weight before treatment).

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, GTIVnd, and RGTIVnd. 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 cm³. 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 cm³ 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 pleural), 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 cm³ and 0.365 cm³, respectively. The results of univariate analysis showed that patients with GTVp > 54.150 cm³ vs GTVp ≤ 54.150 cm³ showed 3-year OS, DFS, LRFS, DMFS of 17.9 vs 66.7% (P < .001), 7.1 vs 46.7% (P < .001), 36.1 vs 88.2% (P < .001), 22.1 vs 46.7% (P = .020), respectively. Patients with GTVnd > 0.365 cm³ vs GTVnd ≤ 0.365 cm³ showed 3-year OS, DFS, LRFS, DMFS of 25.0 vs 65.4% (P = .001, Fig. 1), 12.5 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) | 38–78 | 59 |
| Age (years) | 38 | 60.3 |
| 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) |
| MV/M1 | 6 (10.3)/52 (89.7) |
| Tumor length (cm) | 9.7 |
| ≥0.7 cm<9.7 cm | 28 (48.3)/30 (51.7) |
| Tumor location | 4 (6.9) |
| Upper thoracic | 17 (29.3) |
| Mid-thoracic | 30 (51.7) |
| Lower thoracic | 7 (12.1) |
| chemotherapy | 47 (81.9)/11 (19.0) |
| Yes/No | 25 (43.1)/53 (56.9) |
| necrosis | 4 (6.9)/54 (93.1) |
| posttreatment perforation | 17 (29.3)/26 (44.8)/15 (25.9) |
| Follow-up time (months) | 1–68 | 26 |

Figure 1. Effect of Relative primary gross volume for ESCC (RGTVp) on overall survival. ESCC = esophageal squamous cell carcinoma, RGTVp = relative primary gross volume.
46.2% \( (P = .002, \text{Fig. 2}) \), 42.0 vs 90.1% \( (P < .001, \text{Fig. 3}) \), 26.7 vs 46.2% \( (P = .056) \), respectively. Patients with \( \text{RGTV}_{\text{nd}} > 0.007 \) vs \( \text{RGTV}_{\text{nd}} \leq 0.007 \) showed 3-year OS, DFS, LRFS, DMFS of 37.5 vs 55.6% \( (P = .151) \), 20.0 vs 44.4% \( (P = .023, \text{Fig. 4}) \), 60.9 vs 70.7% \( (P = .327) \), 24.6 vs 62.9% \( (P = .004, \text{Fig. 5}) \), 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).
Multivariate analysis revealed that GTVp was independent factor relevant to prognosis for OS (hazard ratio (HR) 4.100; \(P = 0.001\)), DFS (HR 2.795; \(P = 0.004\)), and LRFS (HR 5.953; \(P = 0.017\)). RGTVp was independent significant prognostic factor for OS (HR 2.275; \(P = 0.046\)), DFS (HR 2.349; \(P = 0.015\)), LRFS (HR 5.990; \(P = 0.32\)). Furthermore, GTVnd (HR 0.342; \(P = 0.19\)), RGTVnd (HR 0.321; \(P = 0.012\)) 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 \((P > 0.05\), Tables 4 and 5).
Table 5

Multivariate analysis of prognostic factors.

| Variable    | OS HR 95% CI | DFS HR 95% CI | LFS HR 95% CI | DMFS HR 95% CI |
|-------------|--------------|---------------|---------------|---------------|
| UICC stage  | 3.751 0.785 17.93 | 1.324 0.406 4.319 | 0.693 0.127 3.791 | 0.673 0.127 3.791 |
| T classification | 1.153 0.483 2.751 | 0.483 0.163 1.427 | 1.978 0.900 4.343 | 2.275 1.016 5.095 |
| N classification |              |               |               |               |
| Tumor length | 1.602 0.809 3.173 | 1.648 0.419 4.167 | 1.486 0.754 2.931 | 2.130 0.843 5.237 |
| Necrosis     |              |               |               |               |
| Perforation  |              |               |               |               |
| GTVnd        | 1.978 0.900 4.343 | 1.978 0.900 4.343 | 1.978 0.900 4.343 | 1.978 0.900 4.343 |
| GTVp         | 2.275 1.016 5.095 | 2.349 1.178 4.883 | 2.349 1.178 4.883 | 2.349 1.178 4.883 |

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 <100cm³ had a higher OS than those with tumor volume ≥100cm³. Chen et al showed that group of tumor volume <20cm³ 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 85cc and 46cc, respectively. Chen et al reported that tumor volume >39.41cm³ was correlated with an increased risk of OS and DFS.[7–10] These evidences highlighted the prognostic significance of tumor volume, exhibiting it as a powerful predictor than traditional TNM staging. Our data from 38 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 cm³ and GTVp ≤ 54.150 cm³. The univariate analysis demonstrated that the 3-year OS of patients with GTVp ≤ 54.150 cm³ was significantly higher than those with GTVp > 54.150 cm³; also, DFS, LFS, and DMFS were better. We classified the patients into 2 groups according to GTVnd: GTVnd > 0.365 cm³ and GTVnd ≤ 0.365 cm³. The 3-year DFS and DMFS for patients with GTVnd ≥ 0.365 cm³ demonstrated a better outcome than those with GTVnd > 0.365 cm³.

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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