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Original Article

Significance of intratreatment tumor volume change during chemoradiotherapy for potentially resectable thoracic esophageal squamous cell carcinoma

Duojie Li[1,3,4*], Qun Zhang[1,3,4*], Yan Yang[3,4*], Hongmei Yin[3,4], Chaomang Zhu[3,4], Xianming Li[1,2]

[1]Jinan University, Guangzhou, Guangdong, China; [2]Department of Radiation Oncology, The Second Clinical Medical College (Shenzhen People's Hospital) of Jinan University, Shenzhen, Guangdong, China; [3]Department of Radiotherapy, The First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui, China; [4]Anhui Province Key Laboratory of Translational Cancer Research, Bengbu Medical College, Bengbu, Anhui, China. [*]Equal contributors.

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Abstract: Objective: The purpose of this study was to investigate the clinical significance of tumor response assessment at a twentieth fraction of radiotherapy when predicting the survival of patients with potentially resectable esophageal squamous cell carcinoma (ESCC). Methods: A total of 123 ESCC patients with clinical stages II to IV_a were enrolled and analyzed. Gross tumor volume (GTV) of the esophagus (GTV_e) and GTV of the metastatic lymph node (GTV_{nd}) were manually contoured by at least 2 senior professional radiotherapists on the simulated computed tomography (CT) images in a process that followed the delineating rules for ESCC. Results: The GTV_e reduction ratio (RR) and GTV_{nd} RR were calculated based on the evaluation of the tumor volume at a twentieth fraction of radiotherapy. Univariate analysis showed that GTV_e and GTV_{nd} before treatment, and GTV_e RR and GTV_{nd} RR at the twentieth fraction of radiotherapy were all significantly associated with complete clinical response (cCR) and overall survival (OS). The Kaplan-Meier method was used to estimate OS and locoregional recurrence-free survival (LRRFS). Conclusions: The GTV_e RR ≥27.92% and GTV_{nd} RR ≥21.49% at a twentieth fraction of radiotherapy are positive predictive factors of LRRFS, and according to multivariate analysis, only GTV_e RR at the twentieth fraction of radiotherapy ≥27.92% is prognostic for a favorable OS.

Keywords: Esophageal neoplasms, definitive chemoradiotherapy, computed tomography, interim response, prognosis

Introduction

Esophageal squamous cell carcinoma (ESCC) is the main histological type of esophageal cancer (EC) in Asian countries, comprising about 90% of the total cases of EC in China reported in 2016 [1]. Since the early symptoms of ESCC are not obvious, ESCC is often diagnosed in the advanced clinical stage, which results in poor efficacy of simple surgical treatment. An increasing amount of evidence from studies such as the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) and an important Chinese clinical trial suggests that the survival of patients with locally advanced ESCC is prolonged by neoadjuvant chemoradiotherapy (CRT) followed by surgery [2, 3]. However, the effectiveness and safety of this approach still remains controversial in China and other Asian countries.

Various factors, such as tumor location and histological type, influence the treatment approach for esophageal cancer between Asian and European or North American countries, therefore the treatment strategies adopted in Asian countries, especially in China, are often different from those in European or North American countries [4]. In China, considering surgical complications and quality of life, many patients with potentially resectable ESCC often choose concurrent chemoradiotherapy (CCRT) instead of surgery, but the local recurrence rate is still high after CCRT [5]. For patients with potentially resectable ESCC, if we can predict which patients may have short-term recurrence after

CRT during definitive CCRT, physicians can make follow-up surgery plans for these patients as soon as possible after reaching the neoadjuvant CRT dose. Therefore, we can convert definitive CCRT to neoadjuvant CRT plus surgery in patients who are initially reluctant to undergo surgery first. With this, we can further improve the clinical outcome of potentially resectable ESCC.

Computed tomography (CT) is currently widely used globally and is the most commonly used imaging method for evaluating the treatment response of solid tumors, especially in developing countries such as China. There is growing evidence that primary tumor volume as measured by CT is an important prognostic factor to predict disease recurrence and survival in patients with ESCC [6-8]. Recently, Yeom et al. [9] reported the important value of interim response to predict the prognosis of locally advanced ESCC during definitive CCRT. In their study, the clinical significance of intermediate remission was assessed using spiral CT images, including the reduction in area and maximum diameter of the primary lesion and lymph nodes. Although the area and maximal diameter of the primary lesion and lymph node were compared at the same level of axial CT image, we found it difficult to determine whether the area measured at the time of image acquisition was representative of the overall tumor burden.

Therefore, the primary aim of our study was to evaluate whether tumor volume changes of the primary esophageal lesion and metastatic lymph node during treatment were associated with disease recurrence and overall survival (OS) in patients with locally advanced thoracic ESCC who received definitive CCRT. For potentially resectable ESCC patients who are initially reluctant to accept surgery, it is very important to evaluate their treatment response to neoadjuvant CRT to quickly identify patients who are unlikely to achieve a complete response and subsequently advocate for intensification of treatment, such as surgery.

Patients and methods

Patient characteristics

This retrospective study included 123 cases of potentially resectable thoracic ESCC who were inoperable for medical reasons or who declined surgery and received definitive CCRT in the First Affiliated Hospital of Bengbu Medical College between January 2014 and December 2018. Patients enrolled in the study had biopsy-confirmed ESCC with CT-measurable esophageal primary lesions and metastatic lymph nodes. Before treatment, all patients were assessed with color Doppler ultrasonography of the neck and abdomen, chest, and abdominal CT scans and 18F-fluorodeoxy glucose positron emission tomography (PET-CT) scans were selected if the physician deemed it necessary. All patients were staged according to the eighth edition of the American Joint Commission on Cancer (AJCC) staging system criteria, and the staging of patients prior to 2017 was based on retrospective data (**Table 1**).

Radiotherapy

The gross tumor volume (GTV) of esophageal carcinoma (GTV_e) was identified by diagnostic and radiotherapy planning CT images, esophagography, esophagoscopy, and/or endoscopy. The GTV of metastatic lymph nodes (GTV_{nd}) was identified by diagnostic and radiotherapy planning CT images, lymph node ultrasound, and/or PET-CT. The delineation of target volumes and organs at risk (OARs) was conducted based on the Radiotherapy and Oncology Group (RTOG) guidelines. The clinical target volume (CTV) of the esophageal primary lesion was defined as the upper and lower margin of the esophageal tumor plus 3 cm, without lateral margin expansion. The planning target volume (PTV) was generated by measuring 1 cm outside of the CTV. For lymph nodes, a 1 cm expansion was made from the GTV_{nd} to planning GTV_{nd} ($PGTV_{nd}$). All radiotherapy plans were generated in the Pinnacle system (Philips Medical Systems [Cleveland] Inc., Cleveland, OH, USA; version 9.8) and were administered using a 6 MV photon beam. Simultaneous integrated boost (SIB) intensity-modulated radiotherapy technology was used in all radiotherapy plans. The prescribed radiotherapy doses of GTV_e and GTV_{nd} were 54-66 Gy at 1.8-2.2 Gy per fraction, once daily, for 5 fractions per week. Plans were normalized to 95% of the PTV and received more than 98% of the prescribed dose.

Chemotherapy

The main concurrent or sequential CRT chemotherapy regimen was a platinum-based 2-drug regimen. One regimen was platinum plus fluo-

Table 1. Characteristics of patients and tumors

Characteristics	Total	cCR	Non-cCR	*P*-value
	n=123	n=47 (%)	n=76 (%)	
Age (years)	123	47	76	0.543
<60	7	3 (6.38%)	4 (5.26%)	
≥60	116	44 (93.62%)	72 (94.74%)	
Gender	123	47	76	0.289
Male	86	31 (65.96%)	55 (72.37%)	
Female	37	16 (34.04%)	21 (27.63%)	
TNM stage	123	47	76	0.116
II	46	21	25	
III	34	15	19	
IVA	43	11	32	
GTV_e (cm^3)	123	47	76	0.001
<26.62	56	30 (63.83%)	26 (34.22%)	
≥26.62	67	17 (36.17%)	50 (65.78%)	
GTV_e RR (%)		47	76	0.000
<27.92	70	16 (34.04%)	54 (71.05%)	
≥27.92	53	31 (65.96%)	22 (28.95%)	
GTV_{nd} (cm^3)	65	23	42	0.016
<2.34	24	13 (56.53%)	11 (26.19%)	
≥2.34	41	10 (43.47%)	31 (73.81%)	
GTV_{nd} RR (%)	65	23	42	0.000
<21.49	40	6 (26.09%)	34 (80.95%)	
≥21.49	25	17 (73.91%)	8 (19.05%)	

cCR, clinical complete response; GTV_e, GTV of esophageal carcinoma; RR, reduction ratio; GTV_{nd}, GTV of lymph node; TNM stage, clinical cancer stage according to the American Joint Committee of Cancer the eighth edition TNM classification and staging system.

rouracil, while the other was platinum combined with paclitaxel. The dose and schedule were 20-30 mg/m^2 of cisplatin on days 1-3, 100-150 mg/m^2 of paclitaxel on day 1, and 600 mg/m^2 of 5-fluorouracil on days 1-4, every 4 weeks in most locally advanced ESCC patients. Concurrent chemotherapy was administered in the first and fourth weeks of radiotherapy and adjuvant chemotherapy was performed 1 month after the end of radiotherapy. Of the 123 ESCC patients, 104 (84.55%) patients chose adjuvant chemotherapy. The median number of chemotherapy cycles was 4. Some elderly patients who could not tolerate intravenous chemotherapy chose S-1 or capecitabine oral chemotherapy.

Assessment of overall treatment response

All participants underwent spiral CT exams before undergoing CRT at the twentieth fraction of radiotherapy and 1 month after completion of radiotherapy. The thickness of the enhanced simulated CT scan which was transferred to the Pinnacle treatment planning system was 3-5 mm. The esophageal primary tumor was delineated on each relevant slice of the planning CT scan. Metastatic lymph nodes were delineated by enhanced simulated CT, neck, and abdominal ultrasound or PET-CT. The volume of GTV_e or GTV_{nd} was then calculated using the volume computation function integrated into the Pinnacle system. The GTV_e reduction ratio (RR) at the twentieth fraction of radiotherapy was calculated according to the following formula: GTV_e RR = 100% × (pretreatment GTV_e - GTV_e at the twentieth fraction of radiotherapy)/pretreatment GTV_e. The same method was used to calculate GTV_{nd} RR.

All participants were followed up 1 month after CRT, then every 3 months for 2 years after treatment, and every 6 months for 2 to 5 years, following the Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 [10]. At each follow-up visit, the participants underwent a physical examination, blood routine examination, ultrasound of the abdomen, neck, and supraclavicular regions, and a chest CT scan. A PET-CT or biopsy of the primary site or lymph node was performed at the discretion of the treating physician. Clinical complete response (cCR) was defined as the esophageal primary tumor or metastatic lymph node not being visible on the histological examination, endoscopy, chest CT, and/or PET-CT scan. Local treatment failure was defined as disease recurrence after achieving cCR or non-cCR after CRT.

Ethics approval statement

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College (No. 2021KY032), and written informed consent was provided by all participants.

Statistical analyses

The enrollment date was the start date of CRT of the potentially resectable thoracic ESCC. All

participants were followed up at the specified time, for which the deadline was their last visit, death, or 31 July 2021. Continuous variables, such as GTV_e, GTV_{nd}, GTV_e RR, and GTV_{nd} RR, were converted into binary variables by using the receiver operating characteristic (ROC) curve. Chi-square test was used to compare GTV_e, GTV_{nd}, GTV_e RR, GTV_{nd} RR, and other clinic characteristics in different cCR groups. Prognostic factors with P<0.1 in univariate analysis, such as data of GTV_e, GTV_{nd}, GTV_e RR, and GTV_{nd} RR, were included in further analysis with multivariate Cox proportional hazards models. We calculated OS from the date of diagnosis to the date of death or the last day of follow-up. Local regional recurrence-free survival (LRRFS) was calculated from the date of diagnosis until primary tumor progression or recurrence in a local regional lymph node. We analyzed OS and LRRFS using the Kaplan-Meier method. A *P*-value <0.05 was considered significant. All statistical analyses were conducted with IBM SPSS statistics 20.0 software (IBM Corp., Armonk, NY, USA).

Results

Patient and tumor characteristics

Of all the 123 ESCC patients, 86 were male, 37 were female, and the median age was 70 (range, 52 to 85) years. All patients completed radiation therapy as planned, and 99 (80.49%) patients completed 2 cycles of intravenous chemotherapy. The last day of follow-up was 31 July 2021, with a median follow-up time of 54 months (31 to 87 months). The clinical characteristics of all patients are listed in **Table 1**. The optimal cut-off values of GTV_e, GTV_{nd}, GTV_e RR, and GTV_{nd} RR were 26.62 cm^3 (range, 4.72 to 101.30 cm^3; sensitivity 65.79%; specificity 63.83%; 95% confidence interval [CI]: 0.540 to 0.762), 2.34 cm^3 (range, 0.65 to 38.29 cm^3; sensitivity 76.19%; specificity 66.67%; 95% CI: 0.606 to 0.880), 27.92% (range, 6.11 to 48.11%; sensitivity 71.5%; specificity 65.96%; 95% CI: 0.0.609 to 0.795), and 21.49% (range, 5.96 to 40.06%; sensitivity 73.91%; specificity 80.95%; 95% CI: 0.682 to 0.927), respectively. During the follow-up period, 86 (69.9%) participants reported treatment failure, including distant metastasis, incomplete remission, and recurrence after achieving cCR. Among these 86 failure cases, 42 (48.8%) were locoregionally uncontrolled, including esophageal recurrence or periesophageal regional lymph node metastasis, 10 (11.6%) were recurrence after achieving cCR, 22 (25.6%) were distant metastasis, and 11 (12.8%) were both locoregional failure and distant metastasis.

Interim analysis and clinical complete response

Efficacy was evaluated 1 month after CCRT. A total of 47 patients (38.2%) were assessable for cCR, and 76 patients (61.8%) were assessable for non-cCR. The proportion of pretreatment GTV_e ≥26.62 cm^3 and GTV_{nd} ≥2.34 cm^3 in the cCR group was significantly lower than that in the non-cCR group (36.2% vs. 65.8%, P=0.001 and 43.8% vs. 73.81%, P=0.016, respectively). The interim response evaluation indexes, such as GTV_e RR ≥27.92% and GTV_{nd} RR ≥21.49%, in the cCR group were significantly higher than those in the non-cCR group (65.9% vs. 28.9%, P=0.000; and 73.9% vs. 19.1%, P=0.000, respectively). However, there were no differences between the cCR and non-CCR groups in baseline clinical characteristics, such as gender, age, tumor location, and clinical stage.

Interim analysis and LRRFS

Next, we investigated the first site of disease progression in all enrolled ESCC patients after CCRT. Univariate analysis showed that GTV_e (P=0.036), GTV_e RR (P=0.000), GTV_{nd} (P=0.037), and GTV_{nd} RR (P=0.010) were significantly associated with 3 year- LRRFS (**Table 2**). Multivariate analysis showed that GTV_e RR ≥27.92% (P=0.000) and GTV_{nd} RR ≥21.49% (P=0.023) at the twentieth fraction of radiotherapy were positive predictive factors for LRRFS (**Table 3**). **Figure 1** presents the Kaplan-Meier curves for LRRFS. Participants with pretreatment GTV_e <26.62 cm^3 had favorable LRRFS, the median regional LRRFS was 32.0 (95% CI: 5.0 to 70.0) vs. 20.0 (95% CI: 4.0 to 74.0) months (P=0.043) in patients with GTV_e <26.62 cm^3 vs. GTV_e ≥26.62 cm^3, respectively (**Figure 1A**). The GTV_e RR ≥27.92% (P=0.002; **Figure 1C**) and GTV_{nd} RR ≥21.49% (P=0.024; **Figure 1D**) at the twentieth fraction of radiotherapy were positive predictive factors of LRRFS. In contrast, GTV_{nd} (P=0.650; **Figure 1B**) was not significantly associated with LRRFS.

Table 2. Univariable analysis of 3 years OS and LRRFS for all patients

Factors	Univariable analysis			
	3 years OS (%)	*P*-value	3 years LRRFS (%)	*P*-value
Age (years)		0.287		0.414
<60	14.29		14.29	
≥60	32.76		26.72	
Gender		0.057		0.100
Male	26.74		22.09	
Female	43.24		35.13	
TNM stage		0.143		0.182
II	32.61		23.91	
III	32.35		29.41	
IVA	30.23		25.58	
GTV_e (cm^3)		0.042		0.036
<26.62	35.71		30.36	
≥26.62	28.36		22.39	
GTV_e RR (%)		0.001		0.000
<27.92	20.00		5.71	
≥27.92	47.17		52.83	
GTV_{nd} (cm^3)		0.037		0.037
<2.34	37.50		29.17	
≥2.34	14.63		12.20	
GTV_{nd} RR (%)		0.02		0.01
<21.49	10.00		5.00	
≥21.49	44.00		40.00	

OS, overall survival; LRRFS, locoregional recurrence-free survival; GTV_e, GTV of esophageal carcinoma; RR, reduction ratio; GTV_{nd}, GTV of lymph node; TNM stage, clinical cancer stage according to the American Joint Committee of Cancer the eighth edition TNM classification and staging system.

Interim analysis and OS

Pretreatment GTV_e (P=0.042) and GTV_{nd} (P=0.037), and GTV_e RR (P=0.001) and GTV_{nd} RR (P=0.020) at the twentieth fraction of radiotherapy were significantly associated with 3 year-OS in univariate analysis (**Table 2**). Multivariate analysis showed that only GTV_e RR ≥27.92% (P=0.000) was a positive predictive factor of OS. In contrast, GTV_{nd} RR was not significantly associated with OS (P=0.063) (**Table 3**). **Figure 2** presents the Kaplan-Meier curves for OS; participants with GTV_e <26.62 cm^3 had better OS than those with GTV_e ≥26.62 cm^3 before treatment (P=0.043; **Figure 2A**), while GTV_{nd} (P=0.129; **Figure 2B**) and GTV_{nd} RR (P=0.051; **Figure 2D**) were not significantly associated with OS. Patients with GTV_e RR ≥27.92% also had favorable OS. The median OS was 34.0 (95% CI: 5.0 to 72.0) versus 22.0 (95% CI: 4.0 to 60.0) months in participants with GTV_e RR ≥27.92% versus GTV_e RR <27.92%, respectively (P=0.002; **Figure 2C**).

Discussion

In recent years, the emergence of neoadjuvant CRT for locally advanced EC has benefited a considerable number of patients in Western countries [11]. However, ESCC in China is fundamentally different from esophageal adenocarcinoma in Western countries in terms of its incidence site, sensitivity to CRT, and treatment failure pattern [12, 13]. For patients with potentially resectable locally advanced ESCC, the use of neoadjuvant CRT remains controversial in Asian countries, especially in China and Japan, where treatment strategies are often different from those in Western countries.

In China, considering surgical complications and quality of life, many patients with potentially resectable ESCC often choose radical CCRT instead of surgery. However, for patients with locally advanced ESCC who refuse surgery, the 5-year OS rate after radical CCRT is only about 30-40%. The challenge of radical chemoradiotherapy is subsequent development of locally uncontrolled cancer or recurrence, of which the incidence is as high as 40-60% [5, 14]. In our study, the initial site of disease progression for 46 patients (37.4%) was the esophagus, and 25 patients (20.3%) had the first recurrence of regional lymph nodes, which is similar to findings from existing research.

Although it is well known that local recurrence is the main mode of failure in ESCC after CRT, there is still a lack of specific and sensitive indicators to predict local recurrence after CRT in ESCC [15, 16]. Generally, a larger GTV indicates a larger tumor load and a higher local recurrence rate after CRT in patients with ESCC. Chen et al. [17] reported that the survival rate of patients with esophageal tumor volume (GTV_e) ≤20 cc before treatment was better than

Table 3. Multivariable analysis of 3 years OS and LRRFS for all patients

Factors	Multivariable analysis					
	3 years OS (%)	*P*-value	RR	3 years LRRFS (%)	*P*-value	RR
GTV_e (cm^3)		0.149	1.352		0.062	1.584
<26.62	35.71			30.36		
≥26.62	28.36			22.39		
GTV_e RR (%)		0.000	0.261		0.000	0.132
<27.92	20.00			5.71		
≥27.92	47.17			52.83		
GTV_{nd} (cm^3)		0.764	1.098		0.698	1.152
<2.34	37.50			29.17		
≥2.34	14.63			12.20		
GTV_{nd} RR (%)		0.063	0.867		0.023	0.298
<21.49	10.00			5.00		
≥21.49	44.00			40.00		

OS, overall survival; LRRFS, locoregional recurrence-free survival; GTV_e, GTV of esophageal carcinoma; RR, reduction ratio; GTV_{nd}, GTV of lymph node; TNM stage, clinical cancer stage according to the American Joint Committee of Cancer the eighth edition TNM classification and staging system.

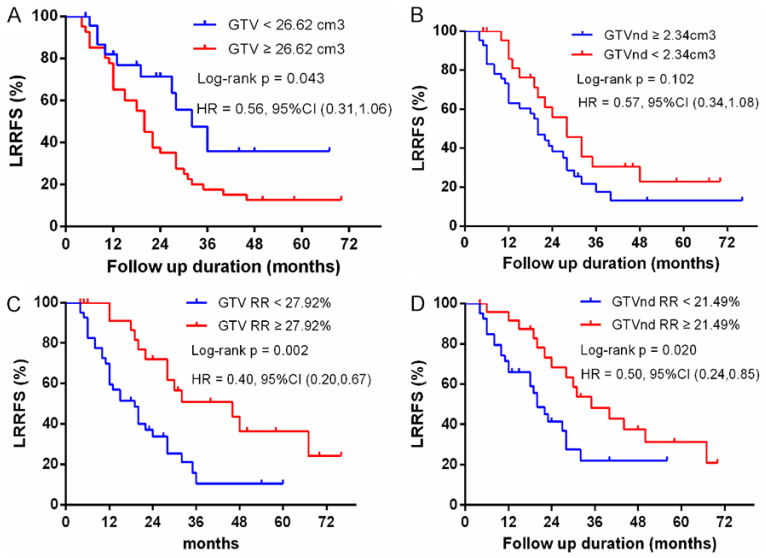

Figure 1. Kaplan-Meier analysis of LRRFS rates shows different GTV_e, GTV_{nd}, GTV_e RR, and GTV_{nd} RR with LRRFS. A. GTV_e and LRRFS rates. B. GTV_{nd} and LRRFS rates. C. GTV_e RR and LRRFS rates. D. GTV and RR and LRRFS rates. LRRFS, locoregional recurrence-free survival; GTV_e, GTV of esophageal carcinoma; RR, reduction ratio; GTV_{nd}, GTV of lymph node.

that of patients with GTV_e >20 cc. In our study, patients with GTV_e <26.62 cm^3 had significantly better median OS than those with GTV_e ≥26.62 cm^3 (P=0.043; **Figure 2A**). In contrast, GTV_{nd} <2.34 cm^3 (P=0.650; **Figure 2B**) had no significant correlation with OS. Our analysis showed that patients with lymph node metastasis may have a greater chance of distant metastasis, which offsets the survival benefit of smaller lymph node size.

Currently, the RECIST is the most widely used tool to evaluate the efficacy and prognosis of tumor treatment [18]. As a tool for evaluating the therapeutic response to tumor treatment, CT is a low cost and good quality technology, especially in developing countries such as China. Esophageal tumors will gradually shrink with the increase of radiotherapy dose and the rate of GTV_e and GTV_{nd} change which we defined as GTV_e RR and GTV_{nd} RR is more important than GTV_e and GTV_{nd} when predicting tumor prognosis. Univariate analysis showed that GTV_e <26.62 cm^3 (P=0.036) before treatment and GTV_e RR ≥27.92% (P=0.001) at the twentieth fraction of radiotherapy were both positive predictive factors of OS. However, in the multivariate analysis, GTV_e RR at the twentieth fraction of radiotherapy was the only predictor of OS. The prognostic value of GTV_e RR and GTV_{nd} RR varies greatly from study to study. Similar to our results, Yang et al. [19] found that the change rate of tumor volume during radiotherapy can be used as an independent factor affecting the survival rate of patients with head and neck tumors. Therefore, the change rate of esophageal tumor volume during radiotherapy can be a feasible predictor to find patients who will not reach cCR after radiotherapy, for which we can then carry out individualized remedial treatment plans as soon as possible. Voncken et al. [20] studied tumor volume change rates of 56 patients with EC before

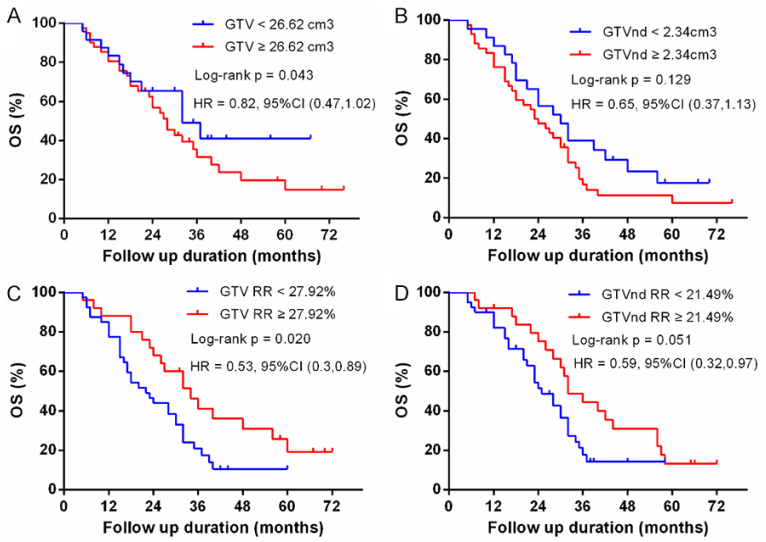

Figure 2. Kaplan-Meier analysis of overall survival (OS) rates shows different GTV_e, GTV_{nd}, GTV_e RR, and GTVnd RR with OS. A. GTV_e and OS rates. B. GTV_{nd} and OS rates. C. GTV_e RR and OS rates. D. GTV_{nd} RR and OS rates. OS, overall survival; GTV_e, GTV of esophageal carcinoma; RR, reduction ratio; GTV_{nd}, GTV of lymph node.

and after neoadjuvant chemoradiotherapy. Their results showed that the relative reduction of primary tumor volume ≥20% was significantly correlated with a higher pathologic complete response (pCR) ratio and longer local recurrence rate.

Recently, Huang et al. [21] reported the predictive value of intratreatment primary tumor volume change during definitive CRT for ESCC treatment outcomes. For potentially resectable EC, local regional lymph node metastasis is very common, but the article did not mention the clinical value of volume changes in lymph nodes in the analysis. Therefore, the other primary purpose of our research was to study the GTV_{nd} and GTV_{nd} RR during CRT for EC with CT. In our study, GTV_{nd} RR ≥21.49% (P=0.023) at the twentieth fraction of radiotherapy was powerful predictor for LRRFS but not for OS. The main reason may be that the patients with lymph node metastasis have a later clinical stage and a shorter OS time; conversely, the group with lymph node metastasis may have greater distant metastasis rates, which leads to the effect of GTV_{nd} RR on LRRFS but no effect on OS. So far, our study was the first to evaluate GTV_{nd} and GTV_{nd} RR for potentially resectable thoracic ESCC patients undergoing definitive CCRT.

According to the latest assessment of Concord-3 (2018), the survival rate of EC in China increased from 22.9% in 2000-2004 to 27.1% in 2005-2009 and to 29.7% in 2010-2014 [22]. The survival rate of EC has been improving, which is largely due to the change from a single-subject treatment mode to a multi-subject treatment mode based on surgery. However, in the NEOCRTEC5010 study [3], the postoperative pCR rate in the neoadjuvant CRT group reached 43.2%. So, is there any need for patients receiving pCR to undergo resection of esophageal cancer? A recently published meta-analysis by Wang et al. [23] showed that surgery did not improve the long-term survival of patients with EC who achieved cCR after neoadjuvant CRT, compared with non-operative treatment, but only increased disease-free survival (DFS) for 2 years (hazard ratio [HR] =3.186; 95% CI: 2.071 to 4.901). Therefore, for potentially resectable ESCC, a surgery exemption is acceptable if chemoradiotherapy can achieve cCR or pCR. In clinical practice, it is necessary to predict local recurrence after CRT in advanced ESCC patients, which can help us to find potential radiotherapy-sensitive patients and select personalized treatment strategies according to individual sensitivity. Doing so can improve the quality of life, improve the local control rate, and prolong survival time [24, 25]. In our study, pretreatment GTV_e <26.62 cm^3 (P=0.001), GTV_{nd} <2.34 cm^3 (P=0.016), GTV_e RR ≥27.92% (P=0.000), and GTV_{nd} RR ≥21.49% (P=0.000) at the twentieth fraction of radiotherapy were positive predictive factors of cCR in univariate analysis.

In the future, for patients with potentially resectable thoracic ESCC who are initially reluctant to first undergo surgery, if we can predict which patients may have short-term recurrence in the primary esophageal lesion after CRT during definitive CCRT, we can make follow-up surgery plans for these patients as soon as possible after reaching the neoadjuvant CRT dose.

Therefore, we can convert definitive CCRT to neoadjuvant CRT plus surgery.

This study had certain limitations which may limit the generalizability of its results. First, this was a retrospective analysis; some patients did not receive the same chemotherapy regimen or radiation dose. Second, certain diagnostic radiology methods, such as PET-CT and intra-esophageal ultrasound, were not mandatory in our study protocol and may have affected GTV_e size to some extent. Last, although GTV_{nd} and GTV_{nd} RR were involved in prognostic analysis in our study, only about 30% of participants had measurable lymph node metastasis, which led to a smaller study population.

Conclusion

For ESCC patients, as conducted by univariate analysis, pretreatment of GTV_e, GTV_{nd}, GTV_e RR, and GTV_{nd} RR at the twentieth fraction of radiotherapy are all significantly associated with cCR and OS. The GTV_{nd} RR ≥21.49% and GTV_e RR ≥27.92% at the twentieth fraction of radiotherapy are positive predictive factors of LRRFS. Only GTV_e RR at the twentieth fraction of radiotherapy ≥27.92% is a prognostic factor for a favorable OS according to multivariate analysis. For patients with potentially resectable thoracic ESCC who are initially reluctant to have surgery first, GTV_e RR is a reliable indicator to predict their survival after reaching the neoadjuvant CRT dose. Therefore, we can convert CCRT to neoadjuvant CRT plus surgery and create individualized treatment plans.

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Disclosure of conflict of interest

None.

Abbreviations

ESCC, esophageal squamous cell carcinoma; GTV, gross tumor volume; GTV_e, GTV of esophageal; GTV_{nd}, GTV of metastatic lymph node; OS, overall survival; AJCC, American Joint Committee on Cancer; GTV_e RR, GTV_e reduction ratio; GTV_{nd} RR, GTV_{nd} reduction ratio; cCR, complete clinical response; pCR, pathologic complete response; LRRFS, locoregional recurrence-free survival; WHO, World Health Organization; CROSS, chemoradiotherapy for oesophageal cancer followed by surgery study; CCRT, concurrent chemoradiotherapy.

Address correspondence to: Xianming Li, Department of Radiation Oncology, The Second Clinical Medical College (Shenzhen People's Hospital) of Jinan University, Shenzhen 518020, Guangdong, China. Tel: +86-75525533018; E-mail: li.xianming@szhospital.com

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