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Neoadjuvant radiation target volume definition in esophageal squamous cell cancer: a multicenter recommendations from Chinese experts

Dan Han[1†], Jinling Dong[2†], Qifeng Wang[3], Baosheng Li[1], Jun Liu[4], Hui Liu[5], Bo Qiu[5], Wencheng Zhang[6], Hong Yang[7], Wenbin Shen[8], Yaowen Zhang[9], Xiangzhi Zhu[10], Yi Wang[3], Lei Wu[3], Hongfu Sun[1] and Wei Huang[1*]

Abstract

Background This study aimed to establish a consensus on the delineation of target volumes for neoadjuvant radiation therapy (nRT) in esophageal squamous cell carcinoma (ESCC) within China.

Methods From February 2020 to June 2021, nine ESCC patients who received nRT were retrospectively selected from Sun Yat-sen University Cancer Center and Shandong Cancer Hospital. A panel from eight cancer radiotherapy centers performed two rounds of nRT target volume delineation for these patients: the first round for cases 1–6 and the second for cases 7–9. Online meetings were held after each delineation round to discuss findings. The consistency of delineations across centers was compared using mean undirected Hausdorff distances (Hmean), dice similarity coefficients (DSC), and total volumes, analyzed with the Mann-Whitney U test.

Results The second round of delineations showed improved consistency across centers (total clinical target volume (CTVtotal): mean DSC = 0.76–0.81; mean Hmean = 2.11–3.14 cm) compared to the first round (CTVtotal: mean DSC = 0.63–0.64; mean Hmean = 5.66–7.34 cm; DSC and Hmean: $P < 0.050$ between rounds), leading to the formation of a consensus and an atlas for ESCC nRT target volume delineation. A proposal was reached through evaluating target volume delineations, analyzing questionnaire survey outcomes, and reviewing pertinent literature.

Conclusions We have developed guidelines and an atlas for target volume delineation in nRT therapy for ESCC in China. These resources are designed to facilitate more consistent delineation of target volumes in both clinical practice and clinical trials.

Keywords Esophageal squamous cell cancer, Neoadjuvant radiation, Target volume

†Dan Han and Jinling Dong contributed equally to this work.

*Correspondence:
Wei Huang
alvinbird@163.com
Full list of author information is available at the end of the article

Introduction

In the 2020 worldwide cancer statistics, esophageal cancer (EC) is identified as the seventh most prevalent cancer, registering 604,000 new cases, and emerges as the sixth leading cause of cancer mortality globally, with China accounting for nearly half of these cases and fatalities [1, 2]. EC displays notable geographical variations, with esophageal squamous cell carcinoma (ESCC) being the predominant histological subtype in China, comprising 85.79% of the cases [3]. Over 50% of EC patients are diagnosed at advanced stages, leading to a mere 25–36% five-year survival rate when treated with surgery alone [4].

The Dutch CROSS study and the Chinese NEOCRTEC5010 study have established the foundation for neoadjuvant chemoradiotherapy (nCRT) as the standard treatment for operable locally advanced ESCC [5, 6]. As nCRT is deployed, it introduces a series of challenges, particularly the debated topic of defining the radiation target area within nCRT. Radiation oncologists from five European centers firstly put forward a proposal for defining the radiation target volume in the neoadjuvant radiotherapy (nRT) for EC [7]. However, regional disparities in the pathology of EC are evident, with esophageal adenocarcinoma (EAC) is more prevalent in Western countries, including Europe and North America, while ESCC predominantly affecting Eastern Asia, Eastern and Southern Africa [8, 9]. It raises the question of whether this European consensus applies to the ESCC characteristic of China. Firstly, the lymphatic drainage patterns of ESCC and EAC are distinct and critically influence the delineation of radiation fields in the nRT; despite this, there is a paucity of research on the lymph node metastasis distribution specific to EAC, and the data concerning both tumor types are markedly heterogeneous; this variability presents challenges in formulating evidence-based protocols for both neoadjuvant treatments, specifically in radiation field optimization [10]. Secondly, ESCC and EAC exhibit differences in tumor location, predisposing factors, metastasis, and prognosis [11]. Thirdly, with the onset of the immunotherapy era, there has been a surge in clinical trials exploring the combination of radiotherapy and immunotherapy [12–16]; this integration of radioimmunotherapy introduces novel challenges in target volume delineation; moreover, to enable a fair comparison of treatment outcomes across various radiotherapy techniques and different centers, there is a pressing need for standardized guidelines on the delineation of radiation target volumes.

Through a comparative and analytical review of target volume delineation across eight cancer radiotherapy centers over two rounds, our goal was to achieve a consensus proposal and develop an atlas for the definition of target volumes in nRT for ESCC within China.

Materials and methods

Participating centers and cases selection

The study was conducted by eight premier cancer radiotherapy institutions across China, including Shandong Cancer Hospital, Anyang Cancer Hospital, the Fourth Hospital of Hebei Medical University, Sichuan Cancer Hospital, Shanghai Chest Hospital, Tianjin Cancer Hospital, Jiangsu Cancer Hospital, and Sun Yat-sen University Cancer Center. This team, comprising eight radiation oncologists and eight radiologists, selected nine ESCC cases that had received nRT from Shandong Cancer Hospital (cases 1–3, 7–9) and Sun Yat-sen University Cancer Center (cases 4–6). The delineation of nRT target volumes was carried out in two rounds, focusing on cases 1–6 in the first round and cases 7–9 in the second round. These cases were strategically chosen to cover a wide range of primary tumor locations and metastatic lymph node involvements within the thoracic esophagus—upper (cases 1, 4, 7), middle (cases 2, 5, 8), and lower (cases 3, 6, 9) segments. Patient demographics and tumor characteristics are detailed in Table 1, with computed tomography (CT) or positron emission tomography/CT (PET/CT) images provided when available, to depict the primary tumor and involved lymph nodes. Additionally, in this study, 18 radiation therapy centers in China participated in a survey questionnaire on the delineation of nRT target volumes.

Consensus process

Step 1: The first delineation round involved outlining target volumes for six cases, adhering to institutional guidelines.

Step 2: A questionnaire was conducted to gather information on nRT practices across 18 radiotherapy centers.

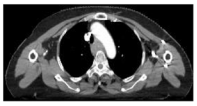
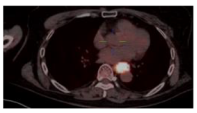
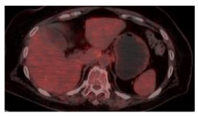
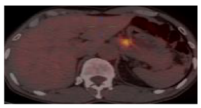
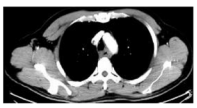
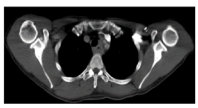
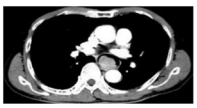
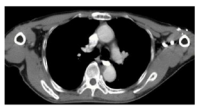
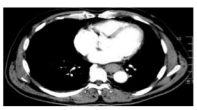
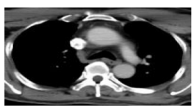
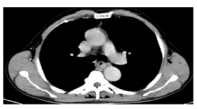
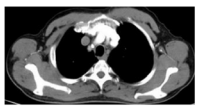
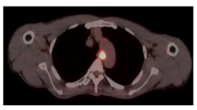
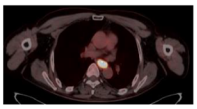
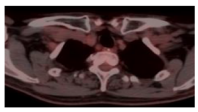
Step 3: A consensus meeting was held to review and discuss the findings from the initial questionnaire and the first delineation round, leading to the proposal of a preliminary target volume guideline.

Step 4: The proposed consensus, along with detailed delineation instructions and an atlas, was then distributed for feedback.

Step 5: In the second delineation phase, target volumes for three additional ESCC cases were outlined, incorporating feedback from the previous step.

Step 6: The final step culminated in the establishment of a consensus on the delineation guidelines, which was comprehensively documented in an atlas.

Table 1 Characteristics of cases for delineation

case	location	Clinical stage	primary tumor	metastatic lymph node(s)	yp stage
1	UTE	T3N0M0			T0N0M0
2	MTE	T3N1M0			T0N0M0
3	LTE	T3N2M0			T2N2M0
4	UTE	T3N1M0			T2N0M0
5	MTE	T3N1M0			T0N0M0
6	LTE	T3N2M0			T0N1M0
7	UTE	T3N1M0			T0N0M0
8	MTE	T3N0M0			T3N0M0
9	LTE	T3N1M0			T0N1M0

Abbreviations: *UTE* upper thoracic esophagus, *MTE* middle thoracic esophagus, *LTE* lower thoracic esophagus.

Statistical analysis

The delineated target volumes were centrally gathered in digital imaging and communications in medicine format and uploaded into Eclipse software (Version 15.3) for each case. The volumes, including the gross tumor volume of the primary tumor (GTVp), gross tumor volume of the lymph nodes (GTVn), and the total clinical target volume (CTVtotal), were compared and consolidated into a unified scan per case. Subsequently, these unified volumes were transferred to 3D Slicer software (Version 4.11.20200930) for quantitative analysis [17]. This analysis included measuring the mean undirected Hausdorff distances (Hmean), the dice similarity coefficient (DSC), and the total volume difference between the first and second delineation rounds. The Hmax/Hmean and DSC metrics quantitatively assessed the consistency across the contouring centers in defining the target volumes [18, 19]. The collected data underwent statistical analysis utilizing the Mann-Whitney U test for continuous variables, employing SPSS software (version 26.0). We evaluated differences in the DSC and Hmean across the eight centers that participated in both delineation rounds. Discrepancies were deemed statistically significant if the *P*-value was less than 0.05.

Results

First delineation round of cases 1–6

During our analysis, we found variability in delineation practices among eight centers. The DSC indicated moderate consistency, with values ranging from 0.67 to 0.90

for the GTVp and 0.44 to 0.78 for the CTVtotal. The Hmean further reflected this inconsistency, with ranges from 0.77 to 6.22 cm for GTVp and 2.84 to 13.12 cm for CTVtotal. The primary issues contributing to the variations were centered around three main areas: the first issue was the differing assessments of positive lymph nodes; the second issue concerned the cranio-caudal expansion from the GTVp to the clinical target volume of the primary tumor (CTVp), with some centers adopting a 2 cm expansion, while others opted for 3 cm; another significant area of dispute involved selective irradiation of specific lymphatic drainage areas, such as the supraclavicular region, with variations between centers in expanding the GTVn by 0.5–0.6 cm to form the clinical target volume of the lymph nodes (CTVn) versus including the entire lymph node drainage area.

Questionnaires

We collected feedback through questionnaires from 18 cancer radiotherapy centers across China, as summarized in Table 2. A majority of the centers, 83.33% (15 out of 18), opted for an involvement-based approach for radiation field selection. In terms of defining the CTVp from GTVp, 14 (77.78%) centers chose a radial expansion of 0.5 cm; uniformly, all centers concurred on a cranio-caudal expansion of 2–3 cm, with half (9 centers) specifically favoring a 3 cm expansion. For the expansion from the GTVn to the CTVn, 61.11% (11 out of 18) of centers applied a uniform expansion of 0.5 cm in all directions. Similarly, 61.11% (11 out of 18) of the centers expanded the CTV to form the planning target volume (PTV) by 0.5 cm. Additionally, 77.78% (14 out of 18), were amenable to including the surgical anastomosis within the radiation therapy field.

Meeting for preliminary consensus

In addition to radiologists and radiation oncologists who participated in the panel, a physicist and a thoracic surgeon specializing in esophageal therapy in each center also attended the meeting and gave constructive comments. A preliminary consensus on nRT target

Table 2 Summary of questionnaire survey of 18 cancer centers†

Question	Answers	*N*/18	(%)
The selection of radiation field	IFI	15	83.33
	ENI	0	0.00
	Others	3	16.67
How many centimeters does GTVp expand to form CTVp radially and cranio-caudally?	0.5 cm, 3.0 cm	6	33.33
	0.6 cm, 3.0 cm	1	5.56
	0.8 cm, 3.0 cm	2	11.11
	0.5–0.7 cm, 2.0 cm	1	5.56
	0.5 cm, 2.0–3.0 cm	1	5.56
	0.5 cm, 2.0 cm	7	38.89
	Others	0	0
How many centimeters does GTVn expand to form CTVn in all directions?	0.3 cm	1	5.56
	0.3–0.5 cm	1	5.56
	0.5 cm	11	61.11
	0.6 cm	4	22.22
	Others	1	5.56
How many centimeters does CTV expand to form PTV?	0.3–0.5 cm	1	5.56
	0.5 cm	11	61.11
	0.6 cm	3	16.67
	0.8 cm	1	5.56
Is neoadjuvant therapy feasible for supraclavicular lymph node metastasis?	Yes	10	55.56
	No	8	44.44
Whether to accept surgical anastomosis in the radiation field?	Yes	14	77.78
	No	4	22.22

18 cancer centers†: Shanghai Chest Hospital, Shandong Cancer Hospital, The Fourth Hospital of Hebei Medical University, Anyang Cancer Hospital, Tianjin Medical University Cancer Institute and Hospital, Jiangsu Cancer Hospital, Sun Yat-sen University Cancer Center, Sichuan Cancer Hospital, Henan Cancer Hospital, Henan Province People's Hospital, West China Hospital of Sichuan University, The First Affiliated Hospital of Soochow University, Xinjiang Cancer Hospital, Xijing Hospital, Fujian Medical University Union Hospital, Cancer Hospital of the Chinese Academy of Medical Sciences, Shanxi Cancer Hospital, Beijing Cancer Hospital

Abbreviations: *IFI* involved field irradiation, *ENI* elective nodal irradiation, *GTVp* gross tumor volume of the primary tumor, *GTVn* gross tumor volume of the lymph nodes, *CTV* clinical target volume, *CTVp* clinical target volume of the primary tumor, *CTVn* clinical target volume of the lymph nodes, *PTV* planning target volume

delineation has reached through discussion and analysis of the first round of target delineation.

All centers that participated in the working panel agreed to apply margins of an expansion of 0.5–0.6 cm radially and 2.0–3.0 cm cranio-caudally along the esophageal wall, including the paraoesophageal lymph nodes drainage area, from the GTVp to the CTVp. The importance of accurately distinguishing between benign and malignant lymph nodes was emphasized, highlighting the necessity for close collaboration with radiologists and the comprehensive use of multimodal imaging techniques, such as PET-CT and magnetic resonance imaging (MRI), to aid diagnosis [20].

Second delineation round of cases 7–9

Due to inconsistencies in lymph node assessments between centers in the first round, we conducted preliminary discussions before the second round of delineation to pinpoint the locations of metastatic lymph nodes. We matched cases from the second delineation round with those from the first to assess consistency across rounds.

Table 3 GTVp delineation agreement between centers

		UTE	MTE	LTE
DSC, mean ± SD	Round 1	0.81 ± 0.07	0.77 ± 0.06	0.80 ± 0.06
	Round 2	0.87 ± 0.31	0.81 ± 0.07	0.80 ± 0.09
	P	0.016	0.237	0.735
Hmean, mean ± SD (mm)	Round 1	1.73 ± 0.83	3.63 ± 1.44	2.68 ± 1.56
	Round 2	1.23 ± 0.50	2.12 ± 1.08	2.38 ± 1.99
	P	0.258	0.035	0.735
Volume, mean ± SD (cm^3)	Round 1	38.65 ± 7.20	36.79 ± 11.49	33.88 ± 6.84
	Round 2	24.69 ± 2.92	27.59 ± 6.32	22.53 ± 5.87
	P	0.000	0.053	0.007

Abbreviations: *GTVp* gross tumor volume of the primary tumor, *DSC* dice similarity coefficient, *SD* standard deviation, *Hmean* mean undirected Hausdorff distances, *UTE* upper thoracic esophagus, *MTE* middle thoracic esophagus, *LTE* lower thoracic esophagus

The DSC, Hmean, and volumes for the GTVp and the CTVtotal in the second round from the eight centers participating in both rounds are detailed in Tables 3 and 4. In the second round of GTVp delineation, the DSC values were higher, and the Hmean values were lower, indicating greater overlap and higher consistency between the delineations. Similarly, the second round demonstrated enhanced consistency across centers for the CTVtotal, with mean DSC values between 0.76 and 0.81 and Hmean between 2.11 and 3.14 cm, an improvement from the first round (mean DSC: 0.63–0.64; Hmean: 5.66–7.34 cm; DSC and Hmean: $P < 0.05$). This increased uniformity was consistent for target volumes of upper, middle, and lower thoracic ESCC, across rounds (DSC and Hmean: $P < 0.05$). Additionally, the overall target volumes in the second delineation were smaller than those in the first for upper ($P = 0.001$), middle ($P = 0.000$), and lower ($P = 0.002$) thoracic ESCC.

Meeting for final consensus and atlas

The meeting after the second round of delineation focused on the delineation of CTVp and CTVn. A consensus was obtained for the delineation of the GTVp, GTVn, CTVp, CTVn, and CTVtotal in patients with ESCC undergoing nRT. This consensus was achieved through the analysis of target volume delineations, results from questionnaire surveys, and a review of relevant literature. After the meeting the atlas (Figs. 1, 2 and 3) for target volume delineation was generated.

The CROSS trial highlighted that in 213 EC patients undergoing involved field irradiation (IFI), 11 instances (5.2%) encountered in-field recurrences, with merely 2 cases presenting isolated in-field recurrence without distant metastasis [21]. Concurrently, a retrospective analysis of 118 patients revealed no significant survival or local control benefits at the primary site for the 73 patients subjected to elective nodal irradiation (ENI) targeting

Table 4 CTVtotal delineation agreement between centers

		UTE	MTE	LTE
DSC, mean ± SD	Round 1	0.63 ± 0.13	0.64 ± 0.08	0.63 ± 0.12
	Round 2	0.81 ± 0.03	0.76 ± 0.05	0.80 ± 0.09
	P	0.001	0.008	0.019
Hmean, mean ± SD (mm)	Round 1	5.66 ± 2.86	5.81 ± 1.67	7.34 ± 3.55
	Round 2	2.11 ± 0.53	2.90 ± 0.61	3.14 ± 1.62
	P	0.000	0.001	0.005
Volume, mean ± SD (cm^3)	Round 1	148.89 ± 44.47	139.53 ± 31.76	165.31 ± 54.27
	Round 2	83.91 ± 18.25	81.33 ± 16.27	95.71 ± 25.59
	P	0.001	0.000	0.002

Abbreviations: *CTVtotal* the clinical target volume of the total volume, *DSC* dice similarity coefficient, *SD* standard deviation, *Hmean* mean undirected Hausdorff distances, *UTE* upper thoracic esophagus, *MTE* middle thoracic esophagus, *LTE* lower thoracic esophagus

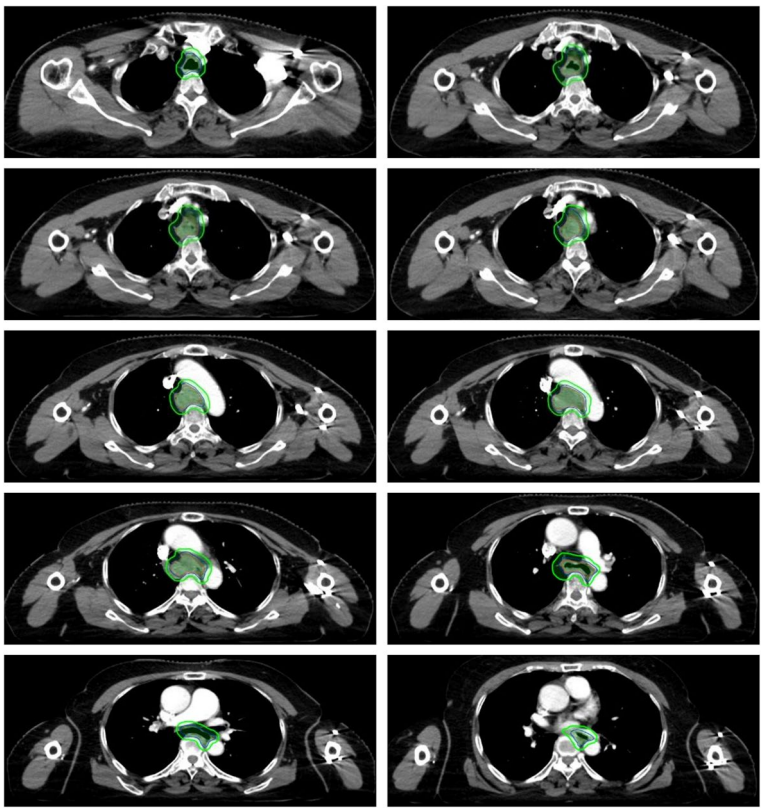


Fig. 1 Consensus atlas for cT3N0M0 upper thoracic esophagus cancer. Gross tumor volume (GTV) of the primary tumor is depicted in red, representing the actual tumor size. The clinical target volume (CTV) of the primary tumor, illustrated in blue, is achieved by expanding the GTV 2.0 cm in the cranio-caudal direction and 0.5 cm radially along the esophageal wall. The planning target volume (PTV), shown in green, is created by a uniform expansion of 0.5 cm around the entirety of the CTV

either supraclavicular ($n=54$) or abdominal ($n=19$) lymph nodes [22]. Moreover, a comprehensive meta-analysis spanning 29 studies and encompassing 5,212 patients indicated no notable differences between IFI and ENI regarding loco-regional recurrence-free survival, overall survival (OS), R0 resection rates [23]. Additional research found comparable disease-free survival and OS rates between IFI and ENI groups, though ENI was associated with a heightened risk of radiation-induced adverse events [24]. In a retrospective study comparing clinicopathologic outcomes and lymphatic spread patterns among neoadjuvant chemotherapy, nCRT, and neoadjuvant immunochemotherapy in locally advanced ESCC, the nCRT group using the IFI model achieved a promising pCR rate and demonstrated superior therapeutic response in the primary lesion [25]. Hence, efforts to improve loco-regional control, such as expanding the irradiation field, may have a limited effect on enhancing OS rates in nCRT for EC. We acknowledge the follow-up results of a randomized phase 3 trial indicating that concurrent chemoradiotherapy with ENI improves long-term survival in locally advanced ESCC in the setting of definitive chemoradiotherapy [26]. However, we believe there are fundamental differences between definitive chemoradiotherapy and nCRT. NCRT is followed by surgery, which helps to clear high-risk lymph nodes in the cervical, thoracic, and abdominal regions, including the esophagus 5 cm above and below the primary lesion. Table 5 shows the comparison between the CROSS and NEOCRTEC5010 studies.While the CROSS [5] study included prophylactic irradiation for some high-risk lymph node regions, it did not show improved local control rates or survival compared to the NEOCRTEC5010 study [6], which did not use ENI. A meta-analysis by Kumagai et al. [27] showed that nCRT increases the incidence of postoperative adverse events in patients with ESCC with postoperative complications primarily involving cardiac and pulmonary-related adverse reactions. Prospective studies by the Radiation Therapy Oncology Group (RTOG) [28] have shown a significant association between V20 and the severity of radiation pneumonitis, and research by Wei et al. [29]. identified pericardial V30 as a major risk factor for pericardial effusion. IFI can reduce target volume, providing more reliable protection

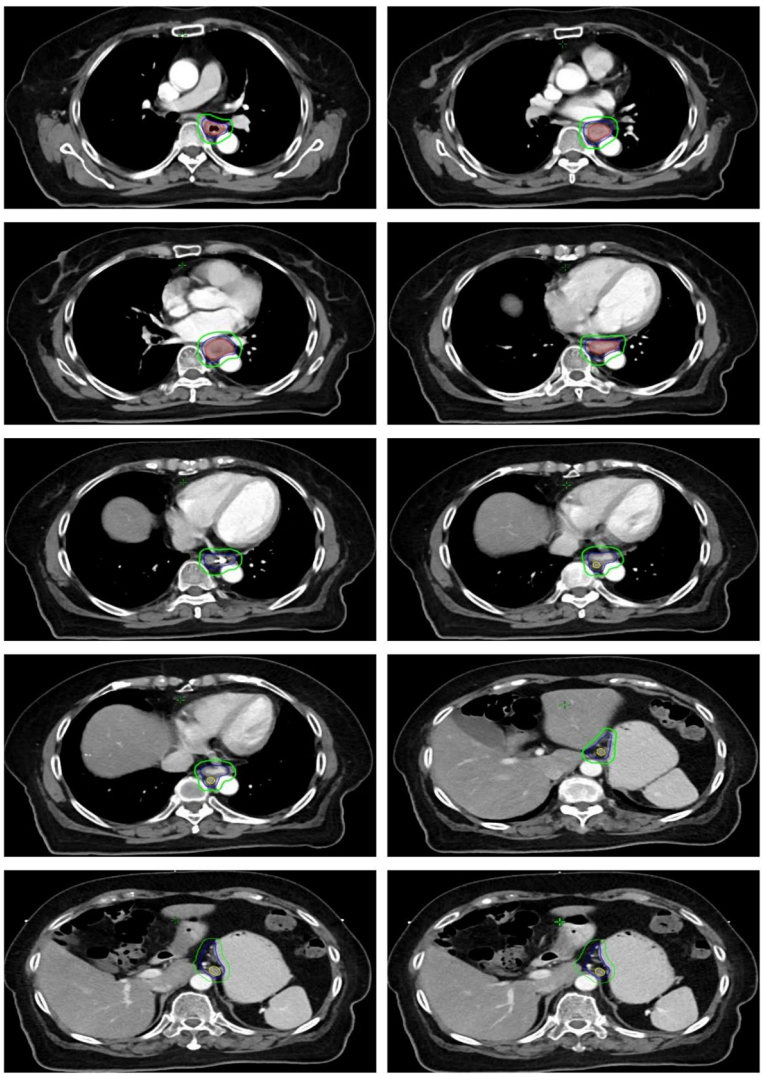


Fig. 2 Consensus atlas for cT3N1M0 middle thoracic esophagus cancer. Gross tumor volume of the primary tumor or pathological lymph nodes (GTVp/n) is illustrated: GTVp is shown in red, representing the primary tumor mass, while GTVn, indicating pathological lymph nodes, is depicted in yellow. The clinical target volume for the primary tumor or lymph nodes (CTVp/n) involves strategic expansions from GTVp/n: CTVp is derived from GTVp with a 2.0 cm expansion cranio-caudally and a 0.5 cm expansion radially along the esophageal wall. CTVn is formulated by expanding GTVn by 0.5 cm in areas with paraoesophageal lymph node drainage. Additionally, for lymph nodes affected in the celiac area, CTVn incorporates a 1.0 cm margin cranio-caudally. The planning target volume (PTV), shown in green, is a uniform 0.5 cm expansion surrounding the total clinical target volume (CTVtotal), which is presented in blue and constitutes the combined volumes of CTVp and CTVn

for the heart and lungs. Given the lower in-field recurrence rate and enhanced safety with neoadjuvant IFI, we suggest the use of IFI in neoadjuvant radiotherapy for ESCC.

- **GTVp** includes the primary tumor, and should be determined by combining the results of multimodal image fusion (gastroenterography, enhanced CT, MRI, PET/CT, upper gastrointestinal endoscopy and endoscopic ultrasonography (EUS). GTVp includes the entire esophagus wall but not the fat surrounding the esophagus. If markers such as titanium clips are placed at tumor margins, they should be included in the GTVp [30].
- **GTVn** includes metastatic lymph nodes. Similarly, multimodal image fusion (enhanced CT, MRI, PET/CT and EUS) are required. Lymph nodes with the following imaging characteristics should be considered suspicious for malignancy: short-axis diameter $\geq$ 10 mm on CT/MRI ($\geq$ 5 mm for paratracheal and paraesophageal lymph nodes), eccentric calcification, ring enhancement similar

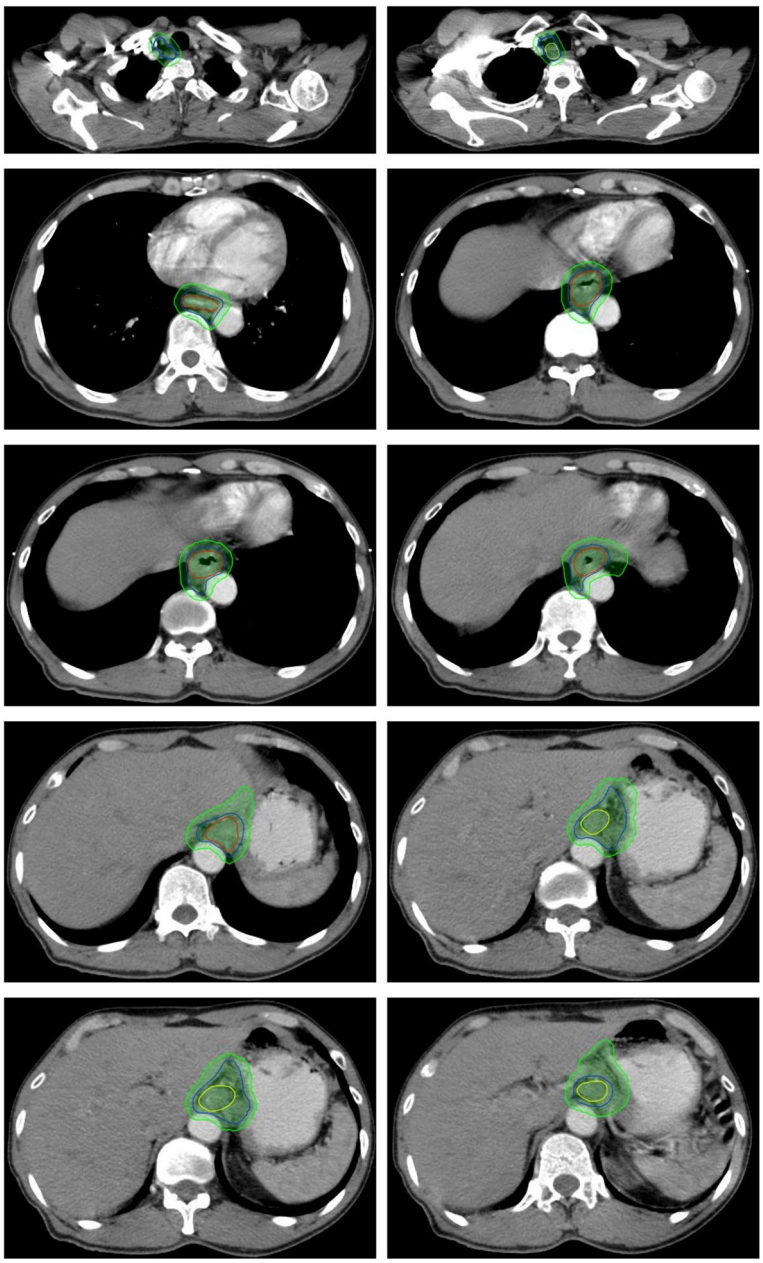


Fig. 3 Consensus atlas for cT3N1M0 lower thoracic esophagus cancer. GTVp/n represents the gross tumor volume of the primary tumor or pathological lymph nodes, with GTVp (shown in red) encompassing the primary tumor and expanded by 2.0 cm cranio-caudally and 0.5 cm radially along the esophageal wall to form the clinical target volume for the primary tumor (CTVp). GTVn (depicted in yellow) identifies pathological lymph nodes, expanded by 0.5 cm in paraoesophageal lymph node drainage areas to create CTVn. For the 106recR and celiac lymph nodes, CTVn includes a 1.0 cm cranio-caudal margin around the lymph node drainage area. The total clinical target volume (CTVtotal), illustrated in blue, aggregates CTVp and CTVn. Surrounding CTVtotal, the planning target volume (PTV) is visualized in green, marked by a uniform 0.5 cm expansion to ensure comprehensive coverage for radiation treatment planning

to that of the primary tumor, and high standardized uptake values (SUV) on PET-CT (excluding inflammatory lymph nodes).We emphasize the importance of collaboration with radiologists. However, when in doubt that the lymph nodes can affect the patient's treatment, it is recommended to use fine-needle aspiration cytology [31–34]. Considering that the position of abdominal lymph nodes is significantly influenced by the state of gastric filling, measures such as stabilizing

Table 5 The comparison between the CROSS and NEOCRTEC5010 studies

Parameter	CRSOSS	NEOCRTE 5010
number of patients	368	451
patient inclusion	esophageal adenocarcinoma (75%) and squamous cell carcinoma (25%)	esophageal squamous cell carcinoma (100%)
chemotherapy regimen	Carboplatin + Paclitaxel	vinorelbine + Cisplatin
radiation dose	41.4 Gy/23F	40 Gy/20F
radiation technique	three-dimensional conformal	three-dimensional conformal
photon energies	equal to or greater than 6 MV	6-8MV
GTV	the primary tumor and any enlarged regional lymph nodes	primary tumor and any enlarged regional lymph nodes
CTV	a 1.5 cm radial margin around the GTV	a proximal and distal margin of 3 cm and a 0.5- to 1.0-cm radial margin around the GTV
PTV	a proximal and distal margin of 4 cm, in case of tumor extension into the stomach, a distal margin of 3 cm will be chosen	an 8-mm margin of the clinical target volume
primary endpoint	OS	OS
pCR rate	29%	43.2%
median DFS	23 months	100.1 months
OS results	47% at 5 years	59.9% at 5 years

Abbreviations: *GTV* gross tumor volume, *CTV* clinical target volume, *PTV* planning target volume, *OS* overall survival, *DFS* disease-free survival, *pCR* pathological complete response

the degree of gastric filling and enhancing image-guided interventions should be implemented during radiotherapy to ensure quality control.

- **CTVp** expands from GTVp by 0.5 cm radially and 2.0–3.0 cm cranio-caudally, covering the esophageal wall and paraesophageal lymph nodes [35]. The feasibility for smaller expansions requires further research. Adjustments to CTVp should be made for surrounding anatomy like muscles, bones, and vessels, excluding areas without invasion.
- **CTVn** includes the GTVn with an expansion of 0.5–1 cm in all directions [36]. CTVn should be corrected for anatomy (muscles, bones, large vessels, and organs at risk) if there is no invasion.
- **CTVtotal** includes CTVp and CTVn. When skip metastasis is present (the distance between CTVn and CTVp exceeds 3 cm), it is permissible to delineate CTVn separately without connecting it to CTVp.
- Internal target volume (**ITV**) is determined based on tumor motion assessed by 4D CT.
- **PTV** is expanded by 5 mm in all directions from the ITV (CTV), with a longitudinal extension up to 8 mm (actual expansion can be decided based on quality control data from each center).
- The consensus recommends a nRT dose of 40.0–50.4 Gy over 20–28 fractions, and for trials combining with immunotherapy, the advised dose is 40.0–41.4 Gy across 20–23 fractions [14, 15].

Discussion

Precise delineation of the tumor volume is crucial for the effective execution of nRT for ESCC patients. Despite this, there's a lack of a universally accepted standard for defining irradiation volumes, leading to significant variability in tumor delineation. A prospective study investigating the precision of volume delineation in EC for nCRT found that in 35% of cases, the macroscopic tumor extended beyond the GTV, and in 14% of cases, beyond the CTV, among patients with macroscopic residual tumors [37]. The discrepancy between the delineated tumor volumes and the actual tumor location is associated with a marked decrease in OS, highlighting the urgent need for enhanced precision in mapping tumor volumes to improve therapeutic outcomes.

In the European target delineation guidelines [7], CTVn is defined by a 1.0 cm expansion around GTVn and a 3.0 cm superior-inferior extension from GTVp, covering lymphatic drainage zones such as the azygos vein, main pulmonary artery window, gastric coronary vein, subcarinal, paratracheal/pretracheal, pericardial, and supraclavicular regions. The consensus among most experts is that the European target delineation guidelines might be overly extensive, potentially elevating the risk of complications and diminishing the population of normal lymphatic cells, which could negatively impact the prognosis [38–40]. A study [41] on lung cancer also revealed that the effective radiation dose to immune cells is a critical independent risk factor for diminished OS and local progression-free

survival in patients enrolled in the RTOG 0617 trial, underscoring radiation-induced immune suppression as a key determinant in tumor control efficacy.

In the era of immunotherapy, the merging of nRT and/or chemotherapy with immunotherapy for EC has emerged as a significant research focus, with increasing attention on the associated toxicities of such combinations. The PALACE-1 study [15], involving patients with ESCC undergoing surgery after preoperative pembrolizumab and concurrent chemoradiotherapy, affirmed the feasibility of this regimen for resectable ESCC. Notably, postoperative pulmonary complications such as pneumonia and atelectasis were reported in 22% of cases each. Meanwhile, in the PERFECT study [14], which examined 40 patients with resectable EC treated with nCRT combined with atezolizumab, 83% (33 patients) proceeded to surgery, experiencing predominantly pulmonary (30%, 10/33) and cardiac (21%, 7/33) perioperative complications. Additionally, a retrospective study [42] analyzed the impact of concurrent chemoradiotherapy combined with pembrolizumab on subsequent surgery, finding that although the pembrolizumab group did not experience an increase in surgical risks, the incidence of acute respiratory distress syndrome was higher than in the concurrent chemoradiotherapy alone group. This highlights the necessity of carefully balancing therapeutic efficacy against potential side effects in the context of combined treatments. Given the compounded toxicity observed with combined immunotherapy, particularly radiation or immune-related pulmonary toxicity, optimizing the target area of nRT is crucial. We recommend IFI and, for clinical trials combining radiotherapy with immunotherapy, suggest a dose of 40.0–41.4 Gy delivered over 20–23 fractions.

Through collaborative discussions and case-by-case analyses of the target volumes delineated by each center, we have achieved a consensus and subsequently developed an atlas for the delineation of target volumes for nRT in ESCC in China. Nevertheless, it's important to recognize the limitations of these guidelines. A notable limitation is the lack of clinical validation or direct correlation with patient outcomes for our consensus, underlining the necessity for its effectiveness and safety to be assessed through future clinical trials. Furthermore, we acknowledge that these recommendations and the atlas may not be universally applicable to all individual patients. Consistent with contemporary radiation treatment planning techniques, the process of contouring and treatment planning should be personalized, with each plan meticulously tailored to the specific clinical circumstances of the patient.

Conclusions

This is the first report to define a consensus on the delineation of target volumes of nRT in ESCC in China. The establishment of this consensus significantly enhances the implementation of nRT for ESCC, ensuring precise target volume delineation. Moreover, it lays a solid groundwork for the design and execution of future clinical trials focusing on nRT in ESCC.

Abbreviations

EC	Esophageal cancer
ESCC	Esophageal squamous cell carcinoma
nCRT	Neoadjuvant radiotherapy
EAC	Esophageal adenocarcinoma
CT	Computed tomography
PET/CT	Positron emission tomography/computed tomography
GTVp	Gross tumor volume of the primary tumor
GTVn	Gross tumor volume of the lymph nodes
CTVtotal	Clinical target volume of the total volume
Hmean	mean undirected Hausdorff distances
DSC	Dice similarity coefficient
CTVp	Clinical target volume of the primary tumor
CTVn	Clinical target volume of the lymph nodes
PTV	Planning target volume
MRI	Magnetic resonance imaging
IFI	Involved field irradiation
ENI	Elective nodal irradiation
OS	Overall survival
EUS	Endoscopic ultrasonography
ITV	Internal target volume

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Han Dan and Jinling Dong contributed equally to this work. JLD, DH, QFW, BSL and WH conceived, designed, and supervised the project. JLD, LJ, HL, BQ, WCZ, YH, WBS, YWZ and XZZ contributed to the design of the study, writing the protocol, and data preparation, analysis, and interpretation. JLD, DH, FHS, YW and LW drafted the manuscript. BSL, WH, JLD and DH performed the quality assessment and revised the manuscript. All authors have read and approved the submitted version.

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Availability of data and materials

The data underlying this article are available in the article and in its online supplementary material.

Declarations

Ethics approval and consent to participate

The conduct of this study was retrospectively reviewed and granted ethical approval by the Institutional Review Board (IRB) of the Shandong First Medical

University Affiliated Cancer Hospital Ethics Committee (approval number: SDTHEC2022001005). Given the retrospective nature of the research, the requirement for patient consent was formally waived by the aforementioned IRB. All research procedures were executed in strict accordance with the ethical principles set forth in the Declaration of Helsinki, ensuring the protection of human subjects in biomedical research. To maintain patient confidentiality, all patient records were anonymized and de-identified prior to the data analysis phase.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences, No. 440, Jiyan Road, Huaiyin distract, Jinan 250117, Shandong Province, China. [2]Department of Oncology, Yankuang New Journey General Hospital, Zoucheng 273500, China. [3]Department of Radiation Oncology, Radiation Oncology Key Laboratory of Sichuan Province, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu 610041, China. [4]Department of Radiation Oncology, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200050, China. [5]Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou 510060, China. [6]Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer, Tianjin 300060, China. [7]Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Esophageal Cancer Institute, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, China. [8]Department of Radiation Oncology, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050017, China. [9]Department sixth of Radiotherapy, Anyang Cancer Hospital, The Fourth Affiliated Hospital of Henan University of Science and Technology, Anyang 455001, China. [10]Department of Radiation Oncology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Nanjing Medical University Affiliated Cancer Hospital, Nanjing 210009, China.

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