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REVIEW

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Delineation of clinical target volume in nasopharyngeal carcinoma

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Abstract

Radiotherapy is the mainstay treatment modality for nasopharyngeal carcinoma (NPC). Intensity-modulated radiation therapy (IMRT), as the standard technique, achieves the purpose of improving target coverage and better sparing of normal tissue. Increased attention has been given to explore various strategies for deescalating treatment intensity. The optimization of clinical target volume (CTV) is one of the most active research areas being widely discussed. Although the International Guidelines for the delineating of CTV in NPC had provided important references for clinicians, there are marked variations in practice among different institutions. This article reviews the development of CTV delineation in non-metastatic NPC patients among centers, and compares the similarities and differences in CTV delineation of various current guidelines in the hope of providing insights for future investigation. This review aims to provide a comprehensive summary of the development and evolution of CTV delineation on primary tumor and lymph nodes for definitive radiotherapy in non-metastatic NPC through historical lens. We also compare the differences of CTV delineation ways. In addition, we look into the clinical and practical challenges of CTV delineation, hoping to provide direction for future research.

Keywords Nasopharyngeal carcinoma, Intensity-modulated radiation therapy, Clinical volume target, Prognosis

Owing to its ability to deliver a higher radiation dose to the target volume while sparing adjacent organs at risk (OARs), intensity-modulated radiotherapy (IMRT) has become standard of care since mid 2000's. Target delineation is one of the most important step for high quality IMRT. While GTV is based on the tumor suggested by imaging. CTV aiming to cover microscopic disease is largely based on empirical data and clinical experience. IMRT has a dose distribution advantage in that only small volumes of OARs adjacent to the Gross Tumor volume (GTV) are irradiated with a high dose, with most OARs receiving the safe tolerance dose of radiation [1]. The pattern of local recurrence reported by different literatures is mainly in-field failure, with the recurrence in the GTV is the most common, out-field recurrence is rarely observed [2]. Although the incidence and severity of dry mouth are significantly reduced by using IMRT, there are still some radiotherapy-related sequelae, such as hearing loss, vision loss, temporal lobe damage, endocrine dysfunction, and skin fibrosis [3]. Therefore, on the basis of the existing target delineation criteria, in order to reduce adverse reactions and improve the quality of life. GTV delineation is based on the findings of imaging examination, physical examination and nasopharyngoscopy, and there is little difference in the delineation concept and practice among the centers, while the delineation of clinical target volume (CTV) is mainly based on the experience of conventional radiotherapy, and is defined to include specific margin and anatomical structures. Clinical practice of CTV delineation varies among

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different centers. Thus, exploring strategies to further improvement of CTV delineation is needed [4].

Since the first utilization of IMRT in NPC in early 2000, CTV delineation has undergone several iterations reflecting accumulated knowledge on disease behaviour and clinical experience. Several version of guidelines have been developed which provided important references for clinicians, there are marked variations in practice among different institutions. It has been suggested that current CTV might still be too generous and there are rooms for further improvement. Optimizing CTV delineation has become one of the most active research areas in IMRT.

1 Evolution of primary CTV delineation

In 2000, the University of California, San Francisco (UCSF) group reported their experience of IMRT in NPC for the first time [5]. Primary CTV (CTVp) was defined as primary GTV (GTVp) and the margin of potential microscopic invasion of the tumor, including the entire nasopharynx, retropharyngeal lymph nodes, clivus, skull base, pterygopalatine fossa, parapharyngeal space, sphenoid sinus, nasal cavity, and posterior 1/3 of maxillary sinus. The prescribed doses of GTVp and CTVp were 65–70 Gy and 59.4 Gy, respectively. Subsequently, Radiation Therapy Oncology Group (RTOG) conducted a Phase II multi-center clinical trial (RTOG0225) to further explore the efficacy of IMRT in NPC [6]. The definition of CTV was further profiled: $CTV_{70\ Gy}$ was defined as GTV with a 5 mm expansion, and $CTV_{59.4\ Gy}$ was defined as $CTV_{70\ Gy}$ with a 5 mm expansion. They adopted the same CTV structural coverage as that of UCSF (Table 1). The 2-year loco-regional progression-free rates (LRPF) were 89.3%. Subsequently, the provisions outlined in the guidelines for NPC CTV became the reference standard, and were adopted by various institutions, which showed ideal efficacy and acceptable toxic profiles [7]. However, the delineation of RTOG0225 was directly inferred from the experience of conventional radiotherapy, with respectively large coverage volume, and the personalized differentiation is not made according to the different stages of patients and sites of invasion, resulting the unnecessary irradiation of OARs, which would ultimately directly affect the life quality of patients.

In view of these problems, RTOG 0615 carried out in 2006 slightly modified the coverage volume of CTV. The anterior boundary was reduced from 1/3 to 1/4–1/3 of the posterior of nasal cavity and maxillary sinus; the posterior boundary to 1/2–2/3 of the anterior clivus (including the entire clivus if involved), the upper boundary to

Table 1 Delineation and comparison of CTV in nasopharyngeal carcinoma

	RTOG 0225	RTOG 0615	International Guidelines	China Guidelines	Reduced-volume IMRT in Fujian Province
High-risk primary lesions					
CTV1	GTVp + 5 mm	GTVp + 5 mm	GTVp + 5 mm (90%); GTVp + 5 mm ± whole NP (55%)	GTVp + 5-10 mm + Whole NP + nasopharyngeal mucosa and 5 mm submucosa	GTVp + 5–10 mm + whole NP
CTV2	GTVp + 10 mm	GTVp + 10 mm	GTVp + 10 mm + whole NP (76%)	GTVp + 5-10 mm	CTV1 + 5–10 mm
Posterior nasal cavity	1/3	1/4–1/3	At least 5 mm in front of the posterior nostril (71%)	5 mm in front of the posterior nostril	5 mm in front of the posterior nostril
Posterior maxillary sinus	1/3	1/4–1/3	At least 5 mm in front of posterior wall	5 mm in front of posterior wall	5 mm in front of posterior wall
Ethmoidal cells	-	-	Covering the plough bone (90%)	Portion	Posterior part
Clivus	Total	1/2–2/3	1/3; full coverage of infiltrated patients (86%)	1/3 (+ anterior 1/3 of the vertebral body)	1/3 (covering the entire clivus if infiltrated)
Cavernous sinus	T3-4 stage	T3-4 stage only covered the infiltrated lateral cavernous sinus	T3-4 stage only covered the infiltrated lateral cavernous sinus (86%)	-	T3-4 stage only covered the infiltrated lateral cavernous sinus
Sphenoid sinus	1/2 inferior	T1-2 stage covering the inferior part; T3-4 stage covering entire sphenoid sinus	T1-2 stage covering the 1/2 inferior; T3-4 stage covering entire sphenoid sinus (90%)	Basal part of sphenoid bone	1/2 inferior (entire sphenoid sinus if involved)
Cervical metastatic lymph node					
CTV1-N	GTVnd + 5 mm	GTVnd + 5 mm	GTVnd + 5 mm	-	-
CTV2-N	CTV1-N + 5 mm	CTV1-N + 5 mm	CTV1-N + 5 mm	-	GTVnd + 3-5 mm

cover the inferior sphenoid sinus (including the entire sphenoid sinus and cavernous sinus in patients T3 and T4), and the inferior and bilateral boundaries were not adjusted (Table 1).

In 2010, China Nasopharyngeal Carcinoma Clinical Staging Committee formulated "Expert Consensus on Target Volume and Dose Guidelines for Nasopharyngeal Carcinoma IMRT" based on radiotherapy experience of various Chinese centers. GTV (receiving 70 Gy) delineation is based on the findings of imaging examination, physical examination and nasopharyngoscopy, without a 5 mm expansion. CTV-high dose (receiving 60–62 Gy) was defined as primary tumor volume which included GTVp with a 5 mm expansion and also covered the entire nasopharyngeal mucosa. CTV-low dose (receiving 54–56 Gy) was 5–10 mm expansion form CTV-high dose which covered the high-risk area and the following structures were properly considered according to the location and extension of tumor invasion: nasal cavity and posterior maxillary sinus, pterygopalatine fossa, part of posterior ethmoid sinus, parapharyngeal space, skull base, part of cervical spine and clivus. However, this consensus was established in the early adoption of IMRT, and covers large volume.

In 2018, the International Guidelines for the delineation of CTV for NPC were established, based on published guidelines and existing findings, it was thoroughly discussed by a number of experienced NPC specialists [8], aim to provide practical reference for oncologists to delineate radiotherapy target volume (Table 1). CTV-high dose (receiving 66 Gy) refers to high-risk CTV which included GTV with a 5 mm expansion. CTV-low dose refers to intermediate-risk which included 5 mm expansion from CTV-high dose.

Although international guidelines provide reference for CTV delineation, however, wider margins may be needed in cases with suboptimal imaging or in case of doubt about possible tumor involvement. The final target volumes did not consider individual patients' factors. Since majority NPC tumor invasion pattern and a low-risk of simultaneous bilateral tumor invasion at anatomic sites around the nasopharynx [9]. Therefore, researchers from Harvard University conducted a study individualized delineation of CTV based on the orderly patterns of tumor invasion. They designed individual CTV according to the tumor invasion region. Regardless of anatomical bony landmarks, unilateral tumors only included ipsilateral parapharyngeal space, pterygopalatine fossa, foramina ovale, Meckel's space and cavernous sinus. Irradiation of nasal cavity, maxillary sinus, ethmoid sinus and sphenoid sinus was prevented only when involved and high-risk involved. And the 5-year local control rate were 94% without out-field recurrence.

To optimize CTV delineation, Fujian Cancer Hospital explored the possibility of "reduced-volume" IMRT for NPC. CTV-low dose (receiving 54–56 Gy) was defined as GTV with a 10 mm expansion. However, the structure coverage was reduced. Most specifically is only covered the anterior 1/3 of the clivus in contrast to the RTOG 0225 which covered the entire clivus and RTOG 0615 which covered the anterior 1/2–2/3 of the clivus. At the same time, They only covered 5 mm posterior maxillary sinus in contrast to the RTOG 0225 which covered the posterior 1/3 of the maxillary sinus and RTOG 0615 which covered posterior 1/4–1/3 of the maxillary sinus. In addition, the prescribed dose of CTV-low dose in reduced-volume IMRT radiotherapy plan (54–56 Gy) was lower than that of RTOG 0225/0615 (56–59.4 Gy). Their reported the 3-year and 5-year regional relapse-free survival (RRFS) rates were 98% and 97%, respectively [10, 11]. Although the outcome of "reduced-volume" IMRT was excellent, two issues regarding the necessity of CTV-high dose delineation and the optimal margin of CTV-low dose remained undetermined. A prospective series from Fujian Cancer Hospital utilized de-intensification technique that omitted the contouring of CTV-high dose and narrowed the margin of CTV-low dose from 10 to 8 mm, namely "modified reduced-volume IMRT" was initiated to evaluate the efficacy and feasibility of this renew technique. Preliminary dosimetric evaluation of "modified reduced-volume IMRT" showed that the 60 Gy isodose curve generated naturally by this technique could well wrap the target area of CTV-high dose. The 4-year estimated locoregional recurrence free survival (LRFS), RRFS, distance metastasis free survival (DMFS) and overall survival (OS) were 96.6%, 97.7%, 87.7% and 92.4%, respectively [12]. The "modified reduced-volume IMRT" simplified the CTV delineation and IMRT optimization without compromise survival outcome.

In 2010, FRANK et al. [13] reported their IMRT results of 175 NPC patients in Hong Kong. CTV_{70Gy} was comparable to GTV, covering all primary lesions. CTV_{60Gy} includes the entire nasopharynx, retropharyngeal lymph nodes, clivus, skull base, pterygopalatine fossa, parapharyngeal space, inferior sphenoid sinus, 1/3 of nasal cavity and posterior maxillary sinus, and high-risk lymph node region. The CTV_{60Gy} contains the CTV_{70Gy} at least 5 mm expansion (unless the GTV is adjacent to critical normal tissue). CTV_{54Gy} covers the low-risk lymph node region. Their 3-year LRFS, RRFS and OS were 93.6%, 93.3% and 87.2%, respectively [13]. In 2011, Yi et al. from the Cancer Hospital of the Chinese Academy of Medical Sciences reported their results of IMRT, in which CTVp included skull base, parapharyngeal space, pterygopalatine fossa, foramina fracture, foramina ovale and other skull base pathways as well as the posterior 1/3 of

nasopharynx and maxillary sinus, with a security boundary of 1–1.5 cm [14]. As a result, the 3-year OS and local control rates were 92.9% and 91.6%, respectively. In 2014, Lu TX et al. from Sun Yat-sen University Cancer Hospital reported the results of 868 patients with non-metastatic NPC. CTV-high dose defined as the GTV with a 5–10 mm expansion for potential microscopic spread, including the entire nasopharynx mucosa plus a 5 mm submucosal volume [15]. CTVp2 was defined as the margin of CTVp1 by 5-10 mm (reduced to 3–5 mm when adjacent to the important organs such as the brainstem and spinal cord), while considering the location and extent of tumor invasion including the posterior pharyngeal lymph node region, clivus, skull base, pterygopalatine fossa, parapharyngeal space, inferior sphenoid sinus, nasal cavity and posterior maxillary sinus. The prescribed doses of GTVnx, CTVp1, CTVp2 and CTVnd were 68 Gy, 60 Gy, 54 Gy and 60–66 Gy, respectively, and the 5-year LRFS and RRFS results were 91.8% and 96.4%, respectively. Hu et al. from the Affiliated Cancer Hospital of Fudan University published their results of IMRT from 370 NPC patients. CTV-high dose was defined as GTV plus the high-risk region of 5–10 mm margin. CTV-low dose includes the anterior half of the clivus and the inferior part of the sphenoid sinus, which is similar to RTOG 0225 [16]. The prescription dose of GTV in T1-2 patients was 66 Gy / 30 F, and that in T3-T4 patients was 70.4 Gy / 32 F. The doses of CTV-high dose and CTV-low dose were 60 Gy and 54 Gy, respectively. After a median follow-up time of 26 months, the 2-year LRFS was 95.5%, and only 3 of 22 patients with local recurrence recurred in the field.

Since the application of IMRT in several centers has reported excellent local free survival and acceptable toxicity while smaller CTV than RTOG 0225/0615, and these results further optimization of the CTV definition.

1.1 Evolution of cervical lymph node CTV delineation

Recommendations for the delineation of cervical lymph node CTV have evolved several versions. Extensive involvement of neck lymph node (LN) is a prominent and well-recognized clinical characteristic of NPC owing to the extensive submucosal lymphatic capillary network that lacks valves. Therefore, elective neck irradiation was a standard recommendation for all patients in the conventional radiation therapy era, and continued in the IMRT era. In 2003, major cooperative groups in Europe and North America put forward CT-based international consensus guidelines for the delineation of the neck CTV in node-negative neck patients, building upon the Robbins classification [17]. The guidelines were expanded in 2006 to encompass node-positive cases and postoperative neck scenarios [18], and subsequently updated in 2013 to incorporate a broader range of neck LN levels, along with more precise delineations of anatomical boundaries [19]. The guidelines serve as a valuable tool for radiation oncologists, promoting consistent delineation of the neck CTV and facilitating data sharing among institutions. However, it remains uncertain whether these guidelines, which were primarily developed based on patients with head and neck squamous cell cancer, are optimal for NPC. A clinical investigation by Lin et al [20] proposed a new level VIIc to include a medial group of retropharyngeal LNs, recommended moderate extended boundaries for levels Vb and VIIa, and suggested that the boundaries for levels Ib, II, IV, and Vc might be reduced. The international guidelines, published in 2018, presented a refined and clarified scope for the delineation of the neck CTV of NPC. The high-risk nodal CTV for full therapeutic dose is derived from expansion of involved nodes. The prophylactic intermediate-risk nodal region CTV, is defined by the neck CTV as set out in expert consensus guidelines [8]. However, certain aspects still require further investigation and confirmation. We conducted a comprehensive review on the key considerations of the neck CTV delineation, with a particular focus on the prophylactic irradiation of level Ib, lower neck and retropharyngeal lymph nodes.

According to the rule of sequential lymph node metastasis in the neck of NPC, lymph nodes in level Ib are not in the way of lymphatic drainage in the nasopharynx, and the probability of metastasis is 2–4% [21]. It is controversial whether routine prophylactic irradiation is needed in this area. The recommended indications for selective irradiation in level Ib were lymph node metastasis in level Ib, invasion of the submandibular gland, invasion of the anatomical structure that drain to level Ib as the first echelon site (oral cavity, anterior 1/2 of nasal cavity), extracapsule extension (ECE) of level II lymph nodes (91% agreed), and maximum diameter of lymph node in level II > 2 cm (68% agreed), but a part of the terms were found to have a low consensus level and no prospective clinical evidence [8]. A study by Fujian Cancer Hospital selected level Ib sparing IMRT in NPC patients based on the International Guideline. Other eligibility criteria for analysis were designed according to the recommendation of International Guideline for selective coverage of level Ib [22]. A total of 450 patients were enrolled, 60 of them received level Ib-covering IMRT due to the International Guideline according to our protocol. For the remaining 390 patients who only fulfilled the last two criteria and/or level Ib involvement with negative pathological results, level Ib-sparing IMRT was delivered, with a median follow-up time of 112 months (range 6 to 194 months), reported 5- and 10-year RRFS were 95.4% and 92.9%, respectively. Twenty-two patients occurred regional

recurrence at censorship (median 44.5 months), only 4 (4/390, 1.03%) were recorded as level Ib recurrence. It shows that level Ib-sparing IMRT should be safe and feasible for patients who only had level II involvement with ECE, and/or had a e maximal axial diameter (MAD) of greater than 2 cm in level II, and/or level Ib involvement with negative pathological results. A propensity score-matched cohort study from China also revealed that the sparing of neck level Ib appears to be a safe and feasible strategy in patients who present with radiologic extranodal extension (rENE) or level II MAD ≥ 20 mm, and negative lymph nodes in level Ib [23].

Most clinical protocols, such as RTOG 0225, recommend the routine elective irradiation of node groups II to V and the supraclavicular nodal areas, regardless of the nodal status [6]. However, this recommendation is based on retrospective data where the evaluation of node status was largely based on clinical palpation alone. With the routine use of modern imaging, the exact volumes that need to be irradiated to obtain the optimal outcomes became controversial, especially for patients with node-negative disease. In 2013, Li et al. reported that prophylactic upper neck irradiation is sufficient for patients with node-negative NPC [24]. A total of 301 patients with node-negative NPC were randomly assigned to receive primary plus prophylactic upper neck irradiation (UNI, 153 patients) or primary plus whole-neck irradiation (WNI, 148 patients). Patients in both groups received irradiation to the primary tumor and the upper neck nodal regions, and patients in the WNI group also received irradiation to the lower neck. The 3-year OS was 89.5% in the UNI group and 87.4% in the WNI group. The 3-year RRFS was 89.8% and 89.3%, and the 3-year DMFS was 91.7% and 90.9% for the UNI and WNI groups, respectively. The results showed that prophylactic upper neck irradiation is sufficient for patients with node-negative NPC. In 2022, the phase III trial study by Tang et al. [25] proposed a personalized neck irradiation technique for NPC, which involves including only the bilateral upper neck (above the caudal border of cricoid cartilage) in the UNI for patients without node-metastasis, thus avoiding irradiation of the lower neck. For patients with unilateral node-metastasis, prophylactic irradiation is only required on the ipsilateral upper neck. This irradiation technique reduces the irradiation volume of important organs such as the lower neck skin, organs, esophagus, and thyroid, significantly reducing the radiation-induced sequelae such as hypothyroidism, dysphagia, and neck tissue injury, improving patients' quality of life. Elective UNI of the uninvolved neck provides similar regional control and results in less radiation toxicity compared with standard WNI in patients with N0-N1 NPC. Regional control and survival outcomes were comparable in UNI at the contralateral uninvolved neck and standard WNI in nasopharyngeal carcinoma patients with unilateral N3 disease. A retrospective study initiated by Tang et al. [26] analyzed 291 patients with unilateral N3 NPC and found that regional control and survival outcomes were comparable in UNI at the contralateral uninvolved neck and standard WNI.

As retropharyngeal lymph nodes are the primary draining nodes for nasopharyngeal carcinoma and have a high rate of involvement at initial diagnosis, complete coverage of both medial and lateral retropharyngeal lymph nodes (MRLN and LRLN) has been the standard approach for radiotherapy treatment of NPC for several decades. The MRLN is situated between the pharyngeal constrictors and the prevertebral fascia near the midline, and prophylactic irradiation of the MRLN may lead to relatively high radiation exposure of the pharyngeal constrictors. Despite the use of intensity-modulated radiation therapy, reports suggest that a significant proportion of patients with NPC experience late dysphagia, silent aspiration in patients with dysphagia, and aspiration pneumonia related to swallowing, which results in poor quality of life. An open-label, non-inferiority, multicenter, randomized, phase III trial demonstrated that medial retropharyngeal lymph node (MRLN) sparing radiotherapy is non-inferior to standard radiotherapy in terms of local relapse risk, while resulting in reduced radiation-related toxicity and improved patient-reported outcomes in patients with non-metastatic NPC [27].

1.2 Summarization and prospect

As the NPC IMRT has achieved excellent local regional control, current studies show that the definition of CTV developed from 2DRT is too extensive. It is feasible to further narrowed the definition of CTV equivalent to GTV expand 5 mm and 5 mm and reduced the preventive radiation dose to 54-56 Gy. It is also practicable alternative of CTV only include ipsilateral parapharyngeal structure in NPC patients with unilateral nasopharyngeal invasion, which protected a part of the contralateral nasopharyngeal mucosa and parapharyngeal structure from irradiation.

There are still some issues in the delineation of CTV in NPC should be explored, for example, how to define the delineation range of CTV when the tumor is adjacent to OARs; Whether the extrapsular invasion of cervical metastatic lymph nodes needs to expand the boundary expansion range, application of AI technology in clinical work, etc. These problems and disputes need to be further studied in clinical and scientific research in the future.

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