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Guidelines

Selection of lymph node target volumes for definitive head and neck radiation therapy: a 2019 Update

Julian Biau [a,b,*], Michel Lapeyre [b], Idriss Troussier [a], Wilfried Budach [c], Jordi Giralt [d], Cai Grau [e], Joanna Kazmierska [f], Johannes A. Langendijk [g], Mahmut Ozsahin [a], Brian O'Sullivan [h], Jean Bourhis [a,1], Vincent Grégoire [i,*,1]

[a] Department of Radiation Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [b] Department of Radiation Oncology, Jean Perrin Cancer Center, Clermont-Ferrand, France; [c] Department of Radiation Oncology, University Hospital Düsseldorf, Germany; [d] Department of Radiation Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; [e] Department of Oncology, Aarhus University Hospital, Denmark; [f] Department of Radiation Oncology, Greater Poland Cancer Centre, University of Medical Sciences, Poznan, Poland; [g] Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, the Netherlands; [h] Department of Radiation Oncology, University of Toronto, The Princess Margaret Hospital, Canada; [i] Radiation Oncology Department, Léon Bérard Cancer Center, Lyon, France

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ABSTRACT

Background and purpose: In 2000, a panel of experts published a proposal for the selection of lymph node target volumes for definitive head and neck radiation therapy (Radiother Oncol, 2000; 56: 135–150). Hereunder, this selection is updated and extended to also cover primary sites not previously covered.
Patients and methods: The lymphatic spread of head and neck cancers into neck lymph nodes was comprehensively reviewed based on radiological, surgical and pathological literature regarding both initial involvement and patterns of failure. Then a panel of worldwide head and neck radiotherapy experts agreed on a consensus for the selection of both high- and low-risk lymph node target volumes for the node negative and the node positive neck.
Results: An updated selection of lymph node target volumes is reported for oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, paranasal sinuses, nasal cavity and carcinoma of unknown primary as a function of the nodal staging (UICC 8th edition).
Conclusions: The selection of lymph node target volumes for head and neck cancers treated with IMRT/VMAT or other highly conformal techniques (e.g. proton therapy) requires a rigorous approach. This updated proposal of selection should help clinicians for the selection of lymph nodes target volumes and contribute to increase consistency.
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Intensity Modulated Radiation Therapy (IMRT), Volumetric Modulated Arctherapy (VMAT) or other highly conformal techniques (e.g. proton therapy) are techniques that allow precise targeting of the volumes to be irradiated while protecting healthy tissue. In 2018, it is the standard method of irradiation of head and neck cancers [1–5]. Because of their precision, these techniques require that each target volume be strictly and rigorously defined. The delineation and selection of these volumes is complex and requires a solid learning curve.

The lymphatic spread of head and neck cancers into neck lymph nodes is relatively consistent and follows predictable pathways [6–11]. As an example, oral cavity tumors mainly drain into the levels I to III in contrast to oropharyngeal tumors, which mainly drain into levels II and III, and to a lesser extent IV and V [12]. Furthermore, the incidence of occult metastases in lymph nodes is not negligible, according to tumor location [12]. For these reasons, the need for adequate nodal target volume delineation is crucial in head and neck cancer IMRT/VMAT [12–18].

In 2000 and 2006, Grégoire et al. published recommendations for the selection of lymph node target volumes in definitive [12,17] head and neck cancer radiotherapy (RT). In these recommendations, only tumors arising from oral cavity, oropharynx, hypopharynx and larynx were considered. In 2014, Grégoire et al. updated the international consensus guidelines for the delineation of the neck node levels of head and neck cancers [18]. The purpose of this article is to present an updated proposal for the selection of lymph node target volumes in definitive IMRT/VMAT for head and neck cancers.

* Corresponding authors at: Centre Jean Perrin, Department of Radio-oncology, 58 rue Montalembert, 63011 Clermont-Ferrand, France, (J. Biau). Centre Léon Bérard, Department of Radiation Oncology, 28 rue Laennec 69008 Lyon, France, (V. Grégoire).
E-mail addresses: Julian.biau@clermont.unicancer.fr (J. Biau), Vincent.gregoire@lyon.unicancer.fr (V. Grégoire).
[1] Contributed equally as senior authors.

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This update will provide:

- recommendations for both negative and positive neck according to the latest nodal classification (8th edition UICC/AJCC TNM) [19,20]
- recommendations only based on studies including at least imaging for nodal evaluation
- recommendations regarding the use of ipsilateral only neck irradiation
- recommendations with subsites specificities for each primary tumor localization
- recommendations for new locations such as paranasal sinuses, nasal cavity and cervical lymph nodes from unknown primary
- recommendations according to the latest neck node levels terminology [18].

Selection of lymph node target volumes for definitive IMRT

Nodal gross tumor Volume: GTV-N

For the selection of the GTV-N, the first step is the collection and interpretation of all necessary diagnostic elements:

- clinical examination: the cervical palpation will look for hard masses evocative of neck lymph nodes. Signs of extra-nodal extension (ENE) will be searched for: skin infiltration, soft tissue invasion with a deep attachment to underlying muscle tissue or adjacent structures or clinical signs of nerve damage.
- analysis of initial diagnostic imaging: CT-scan +/− Magnetic Resonance Imaging (MRI) +/− [18F]-fluoro-2-deoxy-D-glucose Positron Emission Tomography (18FDG-PET). Reading only the individual reports is insufficient and complete analysis of images is required.

The second step is the analysis of planning CT-scan as the loco-regional situation may have evolved since initial diagnostic imaging. Planning CT-scan should extend at least from a few cm above the base of the skull to a few cm below the lower border of the clavicle with slice thickness of 2–3 mm (preferably 2 mm). To enhance vascular and soft tissue contrast and to facilitate the delineation, the use of intravenous contrast enhancement is required (unless contra-indications).

Unlike primary tumors that can have mucosal extensions visible only at clinical examination, lymph node metastases are better identified by imaging examinations (except for certain skin infiltrations). Unlike the primary tumor, co-registration of planning CT-scan with MRI and/or PET-scan to delineate the GTV-N usually does not provide any additional information [21–23].

A lymph node is considered suspicious based on several criteria: a smallest transverse diameter of more than 10 mm (5–8 mm for retropharyngeal lymph nodes [level VIIa] and 12–15 mm for upper jugular lymph nodes [level II]), central necrosis irrespective of the size, rounded rather than oval shape, loss of fatty hilum, visible peripheral extensions showing evidence of extracapsular spread and the presence of more than three lymph nodes of size between 6 and 8 mm grouped [24–30]. Van den Bosch et al. [31] investigated the patterns of recurrence in electively irradiated lymph nodes of 264 patients with cT2-T4 N0 M0 SCC of the oropharynx, larynx or hypopharynx. One thousand one hundred and sixty-six nodes, considered as non-pathological and thus treated with elective dose, were analyzed. Volumetric analysis showed an increased risk of recurrence with increasing nodal volume. The summed long- and short-axis diameter of $\geq$17 mm was a predictive factor for recurrence. The authors suggested that not overtly pathologic nodes with a summed diameter $\geq$17 mm may require a higher than elective radiation therapy dose.

Another point is the use of 18FDG-PET in neck staging. 18FDG-PET should be interpreted with caution for the delineation of lymph node metastases, as the risk of false positives and false negatives (especially for necrotic lymph node metastases) is not negligible [32,33].

Low-risk nodal clinical target volume: CTV-N-LR

The intergroup consensus of 2014 for the delineation of lymph node levels summarizes the various lymph node levels in the neck; it complements the first consensus published in 2003 [13,18]. It describes the different levels: level Ia (submental), Ib (submandibular), II (upper jugular), III (middle jugular), IVa (lower jugular) and IVb (medial supraclavicular), Va and Vb (upper and lower posterior triangle), Vc (lateral supraclavicular), VIa (anterior jugular) and VIb (prelaryngeal, pretracheal and paratracheal), VIIa (retropharyngeal) and VIIb (retro-styloid), VIII (parotid), IX (buccofacial) and Xa (retroauricular and subauricular) and Xb (occipital).

Proposals for the selection of lymph node volumes to be treated for the main tumor localizations are discussed below and summarized in Tables 1–6.

CTV-N-LR selection follows the general principles described hereunder:

- The selection of these volumes depends on the risk of occult metastases. The CTV-N-LR should encompass all regions that have a probability to contain occult metastases of 10–15% or more [13,14,16,17].
- The risk of occult metastases is related to location, tumor extension, lymph node involvement, natural history of cancer and staging of disease [6–10,12,34].
- For some well lateralized tumors (see section on *Oral cavity* and *Oropharynx-Tonsil*), ipsilateral neck IMRT can be proposed; however, if the tumor approaches or crosses the midline, treatment of the contralateral neck is also necessary [13,15,17,35,36]. A particular attention has to be paid in case of important ipsilateral nodal tumor burden that can modify physiological lymph node drainage and thus increase the risk of contralateral recurrences [35,37].
- Some anatomic regions can have crossing lymph node drainage, like the soft palate, the base of tongue, the tongue, the larynx, the hypopharynx and the nasopharynx [6,7,34], and therefore bilateral neck irradiation is usually recommended.
- If the tumor infiltrates adjacent structures, lymph nodes volumes at risk associated with these structures have to be included in the CTV-N-LR, e.g. a node-negative tonsil fossa tumor infiltrating the retromolar trigone requiring treatment of the ipsilateral level Ib [15,17,36].
- For clinical lymph node positive (cN+) patients, it is recommended to extend the CTV-N-LR to include the adjacent levels [15,17,36]. For example, in the case of a large single lymph node in level II abutting to the sub-mandibular gland, it is recommended to also include level Ib. In the case of a bulky involvement of the upper part of level II, it is recommended to also include level VIIb.
- When an involved lymph node is closely abuts a muscle, the skin, the parotid gland and/or show clear clinical and/or radiological extra-capsular infiltration, it is recommended to include these structures in the vicinity of the node in the CTV-N-LR, at least for the entire invaded level and at least with a 1 cm margin in all directions [17].
- Some authors proposed to select an intermediate risk nodal CTV (CTV-N-IR) in the CTV-N-LR for cN+ patients. The concept of intermediate risk nodal CTV is based on the notion that there would be a differentially higher risk of infra-clinical disease in some clinically uninvolved neck levels or in the entire level(s)

Table 1
Selection of low risk nodal target volumes for oral cavity cancers.

Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in CTV-N-LR	
	Ipsilateral Neck	Contralateral Neck[1]
N0-1 (in level I, II, or III)	I, II[2], III, +IVa[3], +IX[4]	I, II[2], III, +IVa[3]
N2a-b	I, II, III, IVa[5], Va,b[6,7], +IX[4]	I, II[2], III, +IVa[3]
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	I, II, III, IVa[5], Va,b, +VIIb[7], +IX[4]	I, II, III, +IVa[3]

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; CTV-N-LR, low risk nodal clinical target volume.
[1] Unilateral treatment is recommended for N0-N2a lateralized tumors of upper and lower alveolar ridge, lateral floor of mouth and buccal mucosa; and discussed for N2b patients. It could be considered for N0-N1 lateral border of oral tongue not approaching the midline by less than 1 cm.
[2] Level IIb could be omitted if no cervical lymph nodes involvement on the same side.
[3] For anterior tongue tumor and any oral cavity tumor with extension to the oropharynx (e.g., anterior tonsillar pillar, tonsillar fossae, base of tongue); for N1 tumor with involvement of level III.
[4] For tumor of the buccal mucosa.
[5] Level IVb should be included in case of involvement of level Iva.
[6] Level V could be omitted if only levels I to II are involved.
[7] Level VIIb should be included in case of bulky involvement of the upper part of level II.

Table 2
Selection of low risk nodal target volumes for p16− oropharyngeal cancers*.

Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in CTV-N-LR	
	Ipsilateral Neck	Contralateral Neck[1]
N0-1 (in level II, III, or IV)	(Ib)[2], II, III, IVa[3], +VIIa for posterior pharyngeal wall tumor	II, III, IVa, +VIIa for posterior pharyngeal wall tumor
N2a-b	Ib, II, III, IVa[3], Va,b, +VIIa, +VIIb[4]	II, III, IVa, +VIIa for posterior pharyngeal wall tumor
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	Ib, II, III, IVa, Va,b, +VIIa, +VIIb[4]	II, III, IVa, +VIIa for posterior pharyngeal wall tumor

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; CTV-N-LR, low risk nodal clinical target volume.
[1] Unilateral treatment is recommended for N0-N2a tonsil fossa tumor not infiltrating the soft palate nor the base of tongue; and discussed for N2b patients.
[2] Any tumor with extension to the oral cavity (e.g., retromolar trigone, mobile tongue, inferior gum, oral side of anterior tonsillar pillar), and/or in case of anterior involvement of level II.
[3] Level IVb should be included in case of involvement of level IVa.
[4] Level VIIb should be included in case of bulky involvement of the upper part of level II.
* For p16+ oropharyngeal cancers, the total number of positive lymph nodes, their size and their sites (homolateral, contralateral, bilateral) have to be taken into account for defining the low risk nodal target volume selection and not only the new AJCC/UICC 8th edition classification; there is no data to suggest a different selection compared to p16- tumors.

invaded by pathologic node(s); furthermore it would take into account delineation uncertainty that may be responsible for "underdosage" [38]. This volume is optional and, up-to-date, there are no published data suggesting that this volume might influence the efficacy of head and neck cancers IMRT. Some authors also proposed to include small lymph nodes with borderline signs of involvement in the CTV-N-IR [39].

Oral cavity (Table 1)

Squamous cell carcinomas of the oral cavity have the lowest absolute incidence of lymph node metastases of all head and neck localizations [7,13]. In short, the oral cavity has lymphatic drainage

Table 3
Selection of low risk nodal target volumes for hypopharyngeal cancers.

Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in the CTV-N-LR	
	Ipsilateral Neck	Contralateral Neck[1]
N0	II, III, IVa, +VIIa for posterior pharyngeal wall tumor + VI for apex of piriform sinus, postcricoïd and/or esophageal extension	II[2], III, IVa, +VIIa for posterior pharyngeal wall tumor + VI for esophageal extension
N1, N2a-b	Ib, II, III, IVa[3], Va,b, +VIIa + VIIb[4] + VI for apex of piriform sinus, postcricoïd, esophageal extension, and/or possibly N2b	II[2], III, IVa, +VIIa for posterior pharyngeal wall tumor + VI for esophageal extension
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	Ib, II, III, IVa[3], Va,b, +VIIa + VIIb[4], +VI	II[2], III, IVa, +VIIa for posterior pharyngeal wall tumor + VI for esophageal extension

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; CTV-N-LR, low risk nodal clinical target volume.
[1] Unilateral neck treatment for small tumor of the lateral wall of the piriform sinus.
[2] Level IIb could be omitted if no cervical lymph nodes involvement on the same side.
[3] Level IVb should be included in case of involvement of level IVa.
[4] Level VIIb should be included in case of bulky involvement of the upper part of level II.

Table 4
Selection of low risk nodal target volumes for laryngeal cancers (glottic T1 excluded).

Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in the CTV-N-LR	
	Ipsilateral Neck	Contralateral Neck
N0-1 (in level II, III, or IV)	II[1,2], III, IVa[3], +VI for transglottic or subglottic extension	II[1], III, IVa, +VI for transglottic or subglottic extension
N2a-b	II[2,3,4], III, IVa[3], Va,b, +VI for transglottic or subglottic extension	II[1], III, IVa, +VI for transglottic or subglottic extension
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	Ib, II, III, IVa[3], Va,b, +VIIb[4] + VI	II[1], III, IVa, +VI for transglottic or subglottic extension

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; CTV-N-LR, low risk nodal clinical target volume.
[1] Level IIb could be omitted if no cervical lymph nodes involvement on the same side.
[2] Level Ib should be included in case of anterior involvement of level II.
[3] Level IVb should be included in case of involvement of level IVa.
[4] Level VIIb should be included in case of bulky involvement of the upper part of level II.

to levels Ia, Ib, II and III. The inner cheek (buccal mucosa) can have additional lymph drain to the level IX [15,16]. Robbins et al. [40] has suggested that for N0 patients no elective lymph node dissection of level IIb was necessary [41]. Analogically the level IIb may not be included in the CTV-N-LR for patients with homolateral N0.

For well lateralized oral cavity tumors (other than oral tongue), the general probability for contralateral lymph node metastases is typically low below 10% [6,7], illustrating the possibility of ipsilateral neck treatment in appropriate cases. Vergeer et al. [37] reported the outcomes of 123 patients with well-lateralized squamous cell carcinomas treated with unilateral surgery and unilateral postoperative RT. Most patients (85%) had oral cavity cancers, with 41% tumors of the gingiva and 21% of the buccal mucosa. Contralateral metastases developed in only 7 patients (6%). On univariate and multivariate analyses, the number of lymph node metastases in the ipsilateral neck was the sole signif-

Table 5
Selection of low risk nodal target volumes for nasopharyngeal cancers (according to recent international guidelines [68]).

Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in the CTV-N-LR	
	Ipsilateral Neck	Contralateral Neck
N0	II-V, VIIa, VIIb[1]	II-V, VIIa, VIIb[1]
N1, N2	II-V, VIIa, VIIb[1,2,3,4]	II-V, VIIa, VIIb[1,2,3,4]
N3	Ib-IVb, Va,b,c, VIIa, VIIb	Ib-IVb, Va,b,c, VIIa, VIIb

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; CTV-N-LR, low risk nodal clinical target volume.
[1] Levels IV and Vb could be omitted for patients with no cervical lymph nodes involvement on the same side.
[2] + level Ib in case of disease involvement of the submandibular gland, and/or involvement of structures that drain to level Ib as the first echelon site, and/or level II involvement (adenopathy >2 cm and/or with extra-nodal extension suspicion).
[3] Level IVb in case of level III–IVa involvement.
[4] Level Vc in case of level Va,b involvement.

Table 6
Selection of low risk nodal target volumes for nasal and paranasal sinuses cancers.

Localization	Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in the CTV-N-LR	
		Ipsilateral Neck	Contralateral Neck[1]
Maxillary sinus	N0[2]	Ib-III, VIIa, IX	Ib-III, VIIa
	N1-N3	Ib-V[3,4], VIIa, IX	Ib-V[3,4], VIIa
Ethmoid sinus	N0	– [5]	– [5]
	N1-N3	Ib-V[3,4], VIIa	Ib-V[3,4], VIIa
Nasal cavity	N0[2]	Ib-III, VIIa, +IX for anterior third nasal cavity involvement	Ib-III, VIIa
	N1-N3	Ib-V[3,4], VIIa, +IX for anterior third nasal cavity involvement	Ib-V[3,4], VIIa

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; CTV-N-LR, low risk nodal clinical target volume.
[1] Unilateral irradiation for maxillary sinuses and nasal cavity cancers not crossing the mid-line without contralateral neck involvement.
[2] Prophylactic neck irradiation for T3-T4 squamous cell carcinoma and sinonasal undifferentiated carcinoma (SNUC).
[3] Level IVb should be included in case of involvement of level IVa.
[4] Level VIIb should be included in case of bulky involvement of the upper part of level II.
[5] Prophylactic neck irradiation for Kadish stage ≥C and/or Hyams grade III/IV esthesioneuroblastoma (levels II–III, VIIa).

icant prognostic factor with regard to contralateral neck recurrences. The 5-year contralateral neck control 99% in N0 cases, 88% in N1 or N2a cases, and 73% in N2b cases ($p = 0.008$). One should be careful with ipsilateral neck irradiation only in case of N2b disease, especially in case of important nodal tumor burden that could modify the physiological lymph node drainage.

Concerning oral tongue tumors, Byers et al. [8] evaluated the frequency of 'skip metastases' in 270 patients with tumors of the oral tongue. Twelve patients (4.5%) had metastasis in level III only, and nine patients (3.3%) in level IV only. Furthermore, in 90 of these patients which were pN0 and did not receive postoperative RT, 9 (10%) subsequently developed recurrence in level IV. Therefore, level IVa should probably be included in the CTV-N-LR for anterior tongue tumors, even for N0 patients [41]. Furthermore, the lymph drainage of the oral tongue, and to a lower extent, the lymph drainage the floor of mouth, can have direct significant cross-over with a higher risk of contralateral lymph node metastases [7,41–43], especially for tumors arising at or crossing the midline and/or with important depth of invasion. Ganly et al. [43] reported the outcomes of 164 patients with early stage oral tongue squamous cell cancer who underwent partial glossectomy and ipsilateral elective neck dissection without receiving postoperative RT. The regional recurrence rate was 5.7% for tumors with a thickness of less than 4 mm and 24% for tumors with a thickness equal or more than 4 mm. Multivariate analysis indicated that tumor thickness was the only independent predictor of neck failure. Regional recurrence was ipsilateral in 61% of patients and contralateral in 39% of patients. Koo et al. [44] reported the outcomes of 66 patients with N0-N2b oral cavity cancer patients (mainly oral tongue tumors [62%] and of floor of mouth tumors [27%]) with cN0 contralateral neck (evaluated by physical examination and imaging, using either CT scan or MRI) undergoing bilateral neck dissection. Clinically negative, but pathologically positive contralateral lymph nodes, were detected in 11%. The rate of contralateral occult neck metastasis was significantly higher when ipsilateral neck metastasis was present than when it was not ($p = 0.002$). The authors noted that the risk of contralateral occult neck involvement in the oral cavity squamous cell carcinomas was significantly higher for T3 or greater tumors and/or for tumors crossing the midline and with unilateral metastases.

Oropharynx (Table 2)

The overall incidence of lymph node metastases is over 60% for squamous cell carcinomas of the oropharynx [6,12,13]. Tumors of the soft palate, the posterior pharyngeal wall and the base of tongue show lymph node metastases on both sides via crossing lymph vessels [7,12,13,45]. For this reason, even for lateralized tumors of these localizations, bilateral neck treatment is usually still recommended. However, the lymphatic drainage of the tonsil is mainly unilateral [7,10,12,13,35]. Although no randomized controlled trials have compared the outcomes of ipsilateral vs. bilateral neck irradiation for well lateralized tonsil cancers, there is growing evidence in the literature [35,46–50] supporting the concept of ipsilateral only IMRT to the neck with very limited risk of contralateral failures. In a recent meta-analysis, Al-Mamgani et al. discussed the results of 11 retrospective studies including 1116 patients [47]. The incidence of contralateral failures correlated with involvement of midline and T-category. Kim et al. [46] recently reported the results of a propensity score matching analysis of patients with squamous cell carcinoma of the tonsil receiving postoperative ipsilateral versus bilateral neck radiotherapy. There were no contralateral neck recurrences in the 61 patients with T1-2/N0-2a regardless of the treatment. For the 79 patients with N2b disease, contralateral neck recurrence was more common in the ipsilateral treated group than in the bilateral treated group (7.9% vs. 0.0%), but the difference was not significant ($p = 0.107$), maybe due to the lack of power of this study. We however recommend to be cautious with ipsilateral neck irradiation only in case of N2b disease, especially in case of bulky nodes that could modify the physiological lymph node drainage. In 2001 and 2017, the Princess Margaret Hospital published their experience in ipsilateral radiation for tonsillar carcinoma [49,51]. In their experience, ipsilateral radiation was considered in N0-N2b patients with very lateralized tonsillar primaries limited to the lateral one-third of the "hemi-structure" of the base of tongue or soft palate, defined as ≤1 cm of superficial mucosa extension, without muscle involvement or any suspicion of deeper penetration [49]. From the cohort treated between 1970 and 1991, of the 228 patients treated with ipsilateral radiation, only 8 (3.5%) experienced contralateral neck failures, with a median follow up of 7 years [51]. From the cohort treated between 1999 and 2014, of the 96 patients treated with ipsilateral radiation, only 2 (2%) experienced contralateral neck failures, with a median follow-up of 5 years, regardless of HPV status. Both experienced salvage treatments and were disease free respectively at 8 and 12 years [49]. The authors concluded that their data supported the continued use of ipsilateral radiation in the current HPV era for selected T1-

T2N0-N2a, and possibly T1-T2N2b, tonsillar cancer, regardless of the HPV status.

Hypopharynx (Table 3)

The overall incidence for lymph node metastases in patients with tumors of the hypopharynx is high, ranging from 65 to 80% on initial diagnosis [12,13]. The most commonly involved lymph nodes are level II (67–75%), level III (33–75%) and to a lesser extent level IV [7,10,52,53]. The number of reported detected contralateral lymph node metastases is lower, but should not be neglected because of the anatomic cross-lymphatic drainage of the hypopharyngeal region [6,7]. Koo et al. [54] reported the outcomes of 43 patients with N0-3 piriform SCC with cN0 contralateral neck who underwent bilateral neck dissection. Contralateral occult lymph node metastases were detected in 16% patients. The risk of contralateral occult metastases was significantly higher for patients with cN+ ipsilateral neck ($p = 0.035$) and for tumors with extension across the midline ($p = 0.010$).

The risk of level VI lymph node metastases is particularly important in the case of piriform sinus tumors with apex and/or upper esophagus invasion [53,55]. Chung et al. [55] reported the outcomes of 68 patients with hypopharyngeal SCC who underwent level VI node dissection. The occult nodal metastasis rate detected in level VI following surgery with neck dissection was 14.3%. Invasion of the apex of the piriform sinus was associated with level VI nodal metastasis on multivariate analysis ($p = 0.005$), and ipsilateral multilevel metastasis ($p = 0.046$) on univariate analysis. Joo et al. [56] reported the outcomes of 64 previously untreated patients with squamous cell carcinoma (SCC) of the hypopharynx who underwent surgery with curative intent. They found that there was a significant correlation between para-tracheal lymph node metastasis (level VIb) and cervical metastasis ($p = 0.005$), and between the primary tumor site (postcricoid, 57.1%; piriform sinus, 20.0%; posterior pharyngeal wall, 8.3%) ($p = 0.039$) and level VI involvement. Wu et al. [57] analyzed the risk factors for level VIIa (retropharyngeal) metastasis in 218 patients with carcinoma of the hypopharynx based on pretreatment CT-scan and/or MRI. The respective level VIIa disease detection rates were as follows: 11.2% for piriform sinus carcinoma, 36.4% for pharyngeal wall carcinoma, and 23.1% for postcricoid extension. On multivariate analysis, the primary tumor sub-site ($p = 0.024$), bilateral cervical lymph node metastasis ($p = 0.007$), the number ($p = 0.026$) and size of cervical lymph nodes ($p = 0.028$), and level V metastasis ($p = 0.045$) were associated with the presence of level VIIa metastasis.

Larynx (Table 4)

For T1 glottic tumors, with no lymphatic drainage, the risk of occult lymph node metastases is very low and thus, observation of the neck is generally recommended [58–60]. Some institutions report their results of T2 glottic tumors, with generally minimal supraglottic invasion, treated with the same approach (observation of the neck) [58,61]. However, this strategy is less consensual. For other stages, the reported overall incidence of lymph node metastases varies between 26% and 55% [7,62]. Especially the supraglottic larynx has a rich lymphatic drainage, resulting in high incidence of occult neck metastases [53]. The lymphatic drainage of the larynx is mainly to levels IIa, III, VI and to a lesser extent IVa [7,15]. Ma et al. [63] reported the outcomes of 212 T2-T4 cN0 glottic cancer patients. The overall lymph node metastatic rate was 14.6%. Metastatic rates in levels II, III, and IV were 10.2%, 14.6%, and 2.5%, respectively. T-category and pathological differentiation were the significant risk factors for lymph node metastases. The risk of level VIb lymph node metastases is relatively high, especially for tumors with subglottic extension [7,15,53]. Weber et al. [64] found level VIb metastases in 18% of laryngeal carcinomas, and 27% in case of subglottic extension. Level VIb metastases carry a high risk for subsequent metastasis to the superior mediastinum [65].

Nasopharynx (Table 5)

Tumors of the nasopharynx show a very high rate of lymph node metastases in about 80% of the patients with anatomic cross-lymphatic drainage [66]. The lymphatic vessels drain mainly to the retropharyngeal lymph nodes (VIIa), retrostyloid (VIIb), levels II, III and Va [66–68], and should be included in the CTV-N-LR, even for N0 patients as the risk of occult metastases is high. Recent consensus guidelines have been published discussing the selection of the CTV-N-LR [68,69]. They suggest that for patients with no cervical lymph nodes involvement on the ipsilateral side, levels IV and Vb could be omitted.

Paranasal sinuses (Table 6)

Paranasal sinuses include maxillary, ethmoid, sphenoid and frontal sinuses. Squamous cell carcinoma of the maxillary sinus and adenocarcinoma of the ethmoid sinus are the most common of these tumors. The incidence of cervical lymph node metastases is relatively low and prophylactic irradiation of the cN0 neck is still controversial [70–73].

Ahn et al. [74] analyzed the risk of lymph node metastasis in SCC of the maxillary sinus based on a SEER (*Surveillance, Epidemiology and End Results*) analysis. Five hundred fifty patients with maxillary sinus SCC were identified from 2004 to 2010. T-category was significant for nodal involvement. T1 patients had a rate of 8.2% of nodal involvement, T2 a rate of 18.6 and T3-T4 a rate of 22.3%. The most commonly involved sites were levels Ib and II. Dubal et al. [75] updated this SEER analysis with 854 patients with maxillary sinus SCC treated from 2004 to 2012. Neck involvement was seen in 7.6% of T1 tumors, 22.2% of T2 tumors, 18.5% of T3 tumors, and 12.2% of T4 tumors. Guan et al. [72] analyzed the patterns of lymph nodes recurrences in 59 patients with paranasal sinuses and nasal cavity SCC treated with modern RT techniques. All patients had pre-treatment and follow-up MRI. Thirty percent of patients had nodal involvement at diagnosis, with levels VIIa, Ib and IIa being the most common sites involved. During follow-up, neck recurrence was seen in 12% of patients. Level Ib and II were the most common sites of recurrence. None of the 19% of patients who received elective nodal irradiation developed a neck recurrence. Most of the nodal recurrences were observed in patients with T4 disease, while only one was seen with T3 disease, and none with T1/T2 disease. Wiegner et al. [76] reported similar outcomes. Homma et al. [77] reported the outcomes of 128 patients with T4 maxillary sinus SCC treated between 2006 and 2007. Of the 128 patients, 21.9% had lymph node metastasis at diagnosis. Ten percent of patients who did not receive elective neck treatment (either surgery or radiotherapy) developed lymph node metastasis. When all these data are combined, it seems reasonable to recommend prophylactic lymph nodes irradiation for T3-T4 maxillary sinuses SCC. For sinonasal undifferentiated carcinoma (SNUC), which usually have a more aggressive behavior, prophylactic lymph node irradiation should be more systematic [78,79].

For ethmoid adenocarcinomas, prophylactic lymph nodes' irradiation is usually not recommended. Inclusion of the level VIIa can be discussed [80]. Bhayani et al. [81] reported their experience of 66 patients with sinonasal adenocarcinoma. Nodal disease was seen at initial presentation in 1 patient. Recurrent disease occurred regionally in 3 patients, of whom 2 also had concomitant local recurrence.

Nasal cavity (Table 6)

The issues for CTV-N-LR selection for SCC of the nasal cavity are similar to those of SCC of the paranasal sinuses. The SEER analysis by Ahn et al. [74] analyzed 733 patients with nasal cavity SCC. Initial nodal involvement rate was 9.3%. T1-T3 patients had lower rates of initial nodal involvement (4–10%), whereas T4a–T4b patients had higher rates (22.2%, $p < 0.001$). The most commonly involved sites were levels Ib and II. Tumors invading the anterior subsites of the nasal cavity can have additional lymph node drainage to level IX [82,83]. Unsal et al. [84] update this SEER analysis with 1180 patients with nasal cavity SCC and reported similar findings. Thus, as for maxillary sinuses SCC, it seems reasonable to recommend prophylactic lymph nodes irradiation for T3-T4 nasal cavity SCC. For SNUC prophylactic lymph node irradiation should be more systematic [78,79].

For esthesioneuroblastoma (olfactory neuroblastoma), the management of the neck is more controversial [85-88]. Peacock et al. [87] reported the outcomes of 52 cN0 patients treated from 1965 to 2010 with surgery +/− adjuvant RT without elective neck treatment. The 10-year delayed cervical lymph node metastasis estimate was 41% (n = 17). The delayed cervical lymph node metastases were unilateral in 11 patients, and bilateral in 5 patients. The median time to delayed cervical lymph node metastasis was 58 months, with the longest development at 146 months. Jiang et al. [88] reported the outcomes of 71 cN0 patients treated between 1970 and 2013. Thirteen patients (18.3%) developed neck nodal relapses, with a median time to progression of 62.5 months. None of these 13 patients received prophylactic neck irradiation. Elective nodal irradiation was associated with significantly improved regional nodal control at 5 years (regional control rate of 100% for elective nodal irradiation vs 82%; $p = 0.001$) but not overall survival. All but one of the nodal recurrences occurred in Kadish C patients, who did not have elective nodal irradiation. Studies by the University of Michigan and the University of Florida also demonstrated that Kadish C patients without elective neck treatment had nodal recurrence rate of 20–44% [86,89]. Hyams pathological grades III and IV have also demonstrated a more aggressive behavior with poorer outcomes [85,90]. Regarding the data reported here, it seems reasonable to recommend prophylactic lymph node irradiation for Kadish $\geq$ C and/or Hyams grade III/IV esthesioneuroblastoma patients only.

Cervical nodes from carcinoma of unknown primary

Elective neck and mucosal volumes to be irradiated in cervical nodes from carcinoma of unknown primary tumor has been a perennial matter of controversy. Mucosal volumes are beyond the scope of this article and, therefore, will not be discussed further. The neck levels included in the CTV-N-LR will depend on the site of the positive cervical nodes and on the suspicion of the primary site. The recent 8th edition UICC/AJCC TNM classification requires specific evaluation to determine the likelihood of viral etiology in staging and evaluating patients presenting with unknown primary cancer cervical lymph node presentations [19,20]. The primary site will be suspected to be in the oropharynx for p16 positive squamous cell carcinoma lymph nodes, and in the nasopharynx for EBV positive nodes [91]. In the case of a suspected nasopharyngeal T0 tumor, bilateral neck irradiation is recommended regardless of the extent of the positive cervical nodes.

In other cases, when no specific tumor site has been found, oropharynx, larynx and hypopharynx can be suspected for squamous cell carcinomas. In such cases, ipsilateral versus bilateral neck irradiation is still controversial. In most retrospective series involving cervical nodes with unknown primary only a minority of patients received unilateral radiotherapy. Several retrospective studies, reporting on selected patients treated with unilateral cervical radiotherapy, have shown that contralateral cervical node recurrence was rare, estimated between 2 and 10%. Studies with bilateral cervical irradiation have estimated rates of contralateral cervical recurrence between 2 and 5%. No randomized prospective study was able to compare the two therapeutic strategies, except one that was terminated early due to lack of accrual [92–98]. In the absence of direct comparative studies, it seems difficult to favor one strategy over another. However, for selected patients, in particular with low tumor burden (N1 or N2a), a unilateral approach can be considered as appropriate. When a unilateral approach is considered, levels II to IVa are usually included in the CTV-N-LR for N1 patients and levels Ib to Va,b for $\geq$N2a patients (with inclusion of level IVb if level IVa is involved; inclusion of level Vc if levels Va and or Vb are invaded; and VIIb if upper level IIa is invaded). When a bilateral approach is considered, contralateral levels II–IVa are usually considered for inclusion in the CTV-N-LR of the contralateral node-negative neck.

High-risk definitive nodal clinical target volume: CTV-N-HR

CTV-N-HR includes the GTV-N with a surrounding margin due to the risk of rupture or ENE. Concerning the incidence of the ENE, Ghadjar et al. [99] analyzed 231 nodes with ENE and 200 nodes without ENE in 98 patients. The incidence of ENE was correlated with lymph node size: lymph node with a diameter of more than 10 mm had a risk of 48% of ENE whereas lymph node with a diameter of less than 5 mm only had a risk of 29%; $p < 0.001$. This correlation between the size of the lymph node metastasis and the incidence of ENE remains controversial. In the SEER series (*Surveillance, Epidemiology, and End Results Registry*) including 1648 patients, the incidence of ENE ranged from 11 to 28% and was independent of lymph node metastasis size [100]. Concerning the extent of the ENE, Apisarnthanarax et al. [101], in a series of 96 pN1 lymph nodes in 48 patients, found that infiltration beyond the capsule did not exceed 5 mm for 96% of the lymph nodes. Size was not a prognostic factor regarding the extent of the extracapsular infiltration. In the study by Ghadjar et al. [99], infiltration beyond the capsule did not exceed 5 mm in 97% of cases. Thus, in order to define the CTV-N-HR, a margin of 5 mm around the lymph node metastasis appears to be reasonable. In the case of lymph node metastasis shrinking after induction chemotherapy, the CTV-N-HR to be delineated corresponds to the initial region of the GTV-N before chemotherapy plus 5 mm [102]. Co-registration with pre-chemotherapy imaging can be useful to guide the delineation.

Words of caution

One must bear in mind that the data from which the concept of selection of lymph node target volumes is based are associated with possible biases that might limit its validity:

- the vast majority of reported series are retrospective studies, which included selected patients
- we favored series in which neck staging and patterns of failure were based on modern imaging techniques and not only on palpation. However, there is a lack of homogeneity in the imaging techniques used (CT-scan, and/or MRI, and/or 18FDG-PET) that might modify the incidence and distribution of the metastatic neck nodes, reflecting differences in sensitivity and specificity of these imaging modalities
- exact extent of neck dissection procedures, as well as radiation volumes are not always fully described, which might influence the interpretation of neck failures inside or outside the treated levels

- the incidence of level VI and VII node infiltration cannot be adequately estimated from the literature data due to the lack of appropriate diagnostic imaging and pathological/imaging correlation
- the concept of lymph node target volume selection is mainly drawn from data collected in large institutions with extensive experience in the multidisciplinary management of head and neck cancer patients. Therefore, implementation of recommendations for the selection of lymph node target volumes in less experienced institutions needs to be undertaken with great caution in the best interest of the patients.

In reading this proposal of selection, the following limitations must be understood:

- this proposal does not intend to give recommendations on the optimal strategy for neck management of patients. Such a decision remains at the discretion of the multidisciplinary head and neck tumor board and the medical team responsible for the care of the patient concerned. This proposal intends to give recommendations on the selection of lymph node target volumes when definitive RT has been decided
- this proposal does not apply to the treatment of recurrent neck after primary radiotherapy or surgery where lymph node drainage has been modified by the previous treatment. In this situation, the pattern of neck node spread may manifest in unpredictable pathways
- this proposal is not immutable and should be adapted according to results of forthcoming studies.

Conclusion

The selection of lymph node target volumes for head and neck cancers treated with IMRT/VMAT requires a rigorous approach. This updated proposal should help clinicians with the selection of lymph nodes target volumes and increase consistency.

Conflicts of interest

None for all authors.

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