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Unilateral versus bilateral nodal irradiation: current evidence in the treatment of squamous cell carcinoma of the head and neck

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Abstract

Cancers of the head and neck region often present with nodal involvement. There is a long-standing convention within the community of head and neck radiation oncology to irradiate both sides of the neck electively in almost all cases to include both macroscopic and microscopic disease extension (so called elective nodal volume). International guidelines for the selection and delineation of the elective lymph nodes were published in the early 2000s and were updated recently. However, diagnostic imaging techniques have improved the accuracy and reliability of nodal staging and as a result, small metastases that used to remain undetected and were thus in the past included in the elective nodal volume, will now be included in high-dose volumes. Furthermore, the elective nodal areas are situated close to the parotid glands, the submandibular glands and the swallowing muscles. Therefore, irradiation of a smaller, more selected volume of the elective nodes could reduce treatment-related toxicity. Several researchers consider the current bilateral elective neck irradiation strategies an overtreatment and show growing interest in a unilateral nodal irradiation in selected patients.

The aim of this article is to give an overview of the current evidence about the indications and benefits of unilateral nodal irradiation and the use of SPECT/CT-guided nodal irradiation in squamous cell carcinomas of the head and neck.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer and cause of cancer-related death worldwide with more than 500,000 new cases and 380,000 deaths yearly[1]. HNSCC is usually diagnosed in a locally advanced but curable stage and can be treated with either surgery or radiotherapy, with or without concomitant radiosensitizing chemotherapy. The well-considered use of these treatment modalities has led to a current 5-year overall survival rate for HNSCC patients of 50-90%, in function of the initial tumour stage[2–4]. The head and neck area has a rich regional lymphatic network and therefore HNSCC has a strong tendency to metastasize to the regional lymph nodes. As the presence of regional metastases is an important prognostic factor in HNSCC[5], determining lymph node metastases is critical for both prognosis and treatment choice. It is not uncommon that small nodal metastases remain undetected as they are below the detection threshold of physical examination and diagnostic imaging. Clinically undetectable metastases are also known as 'microscopic' or 'occult' disease. The patterns of lymphatic drainage in the head and neck area have been assessed by several large-scale studies evaluating the site of nodal metastases in neck dissection specimens[6–9]. Since then, a binary concept was introduced in the radiation treatment of HNSCC, distinguishing separate target volumes for macroscopic disease and for occult disease. The gross tumour volume (GTV) identifies the extent and location of demonstrable macroscopic disease and will encompass the tumour and the detectable lymph node metastases using information from clinical examination and diagnostic imaging. The clinical target volume (CTV) is created by expansion of the GTV in order to cover potential occult disease spread in the surrounding normal tissue. The target volume for occult lymph node metastases is the elective CTV and will cover the most relevant routes of potential lymphatic spread of disease. Elective nodal irradiation (ENI) has the potential to achieve high control rates in cervical lymph node levels with high risk of subclinical disease[10,11].

There is a long-standing convention within the head and neck radiation oncology community to irradiate both sides of the neck electively in almost all HNSCCs. International guidelines for the selection and delineation of the elective lymph nodes were published in the early 2000s and were updated recently[12,13]. However, some authors suggest that the current treatment paradigm needs to be reconsidered, as it does not take into account new diagnostic imaging techniques[14]. Recent diagnostic imaging techniques have

indeed significantly improved the accuracy and reliability of nodal staging[15–18]. As a result, small metastases that used to remain undetected and were thus included in the elective CTV, will now be included in high-dose volumes and the current elective CTV is likely to have a lower tumour load[14]. Furthermore, the elective nodal areas are situated close to the parotid glands, the submandibular glands and the swallowing muscles. Therefore, irradiation of a smaller, more selected volume of the elective CTV could reduce treatment-related toxicity. Several researchers consider the current bilateral elective neck irradiation (B-ENI) an overtreatment and show growing interest in unilateral nodal irradiation (UNI) in selected patients.

The aim of this article is to give an overview of the current evidence about the indications and benefits of unilateral nodal irradiation (UNI) and SPECT/CT-guided ENI in the definitive radiation treatment of squamous cell carcinomas of the oral cavity, oropharynx, hypopharynx and larynx.

Risk assessment for occult metastases in contralateral cN0 neck

In HNSCC primarily treated with radiotherapy, the main concern when considering UNI is the potential risk of missing contralateral metastatic lymph nodes. According to the current guidelines, predefined nodal levels should be included in the elective volume if the chance of occult disease exceeds 10-15%[13,19–21]. The decision whether to treat the contralateral neck electively is based on the probability of micrometastasis for the given subsite. However, HNSCC originate from multiple anatomic regions with differences in potential metastatic spread and we currently have no non-invasive diagnostic modality for identification of occult metastasis in patients with a clinically and radiographically negative neck (cN0). As shown in Table 1, several pathologic studies have investigated the predictors of contralateral metastases for oral cavity cancer (OCSCC)[6,22–28], oropharyngeal cancer (OPSCC)[6,19,29-45], hypopharyngeal cancer (HPC)[19,22,46–53] and laryngeal cancer (LC)[52,54–60] by performing a bilateral neck dissection. International guidelines are based on the results of these studies[13]. However, caution is required, as it concerns heterogeneous and historical data with low patient numbers and short follow-up time. Furthermore, some studies date back from a time that nodal staging was still performed by clinical palpation and the incidence of occult contralateral lymph node metastases (CLNM) will likely be overestimated. However, the studies mentioned in Table 1 stress the complexity of understanding and assessing the patient's individual risk for CLNM.

Radiotherapy studies omitting contralateral neck irradiation

Several studies have investigated the safety of UNI in OPSCC[33,61–78]. Table 2 provides an overview of all articles in which definitive radiation treatment was limited to the ipsilateral neck and the incidence of contralateral regional failure (cRF) and disease stage were clearly reported. Isolated cRF is generally very low with <2% in all 1206 patients. O'Sullivan et al. were the first to report a higher cRF rate in patients with soft palate involvement[61]. Based on their results, most later studies excluded patients with midline involvement. One of the largest series (185 patients) reporting UNI for OPSCC was published by Al-Mamgani et al.[72] 70% of patients had tonsillar cancer, whereas 25% had cancer of the soft palate (≥ 1 cm from the midline) and 5% of the lateral pharyngeal wall. With a median follow-up of 4.1 years, 1.1% of patients developed cRF. Several smaller retrospective series confirm the reported low rates of cRF in selected OPSCC patients with a primary tumour ≥1 cm away from the midline[73–76]. However, it is important to note that most studies exclusively included patients with tonsillar cancer. In the few studies that included other OPSCC subsites, tonsillar carcinomas were over-represented[62,77,78]. It is, therefore, generally accepted that patients with lateralized tonsillar OPSCC have a very low risk of cRF. Controversy exists about the risk for patients with cN2 disease, especially cN2b (metastasis in multiple ipsilateral lymph nodes ≤ 6cm)[36]. High cRF rates were published by Maskell et al. in 2019, who reported all cRF to occur in T1 tonsillar primaries with multiple nodes ≤6 cm[68]. This finding was confirmed by a study of Lynch et al., a series of 136 patients, in which of the six patients that developed true isolated cRF, all had N2b disease[33]. These findings were, however, not confirmed by several other studies that included a significant amount of patients with N2b disease[62,64–66]. The study of Hu et al. reported no cRF, although 62% of patients had multiple involved ipsilateral nodes ≤6 cm[62]. Cramer et al. reported no cRF in 23 patients treated with UNI for lateralized T1-2N1-2b tonsillar cancer, of which 18/23 patients were N2b[67]. In a propensity-score matched analysis of 241 patients with tonsillar cancer who underwent tonsillectomy and were treated with UNI, Kim et al. found no cRF in 61 patients with pathologic T1-2N2a[79]. Among 79 patients with N2b disease, cRF was 7.9% (3/38) in ipsilateral RT group vs 0% in bilateral RT group. However, two of the three patients with cRF also experienced local recurrence.

It is clear that the administration of UNI has been extensively investigated in tonsillar cancer and, to lesser extent, in other OPSCC subsites. However, less research is done in OCSCC, HPC and LC. Cerezo et al. were the only authors that, in addition to OPSCC patients, also included patients with primary OCSCC[77]. The study included eight patients with cT1-T2 lateralized tonsillar carcinoma and 12 patients with cT1-T2 lateralized primary tumour of the oral cavity. With a median follow-up time of 3 years, no cRF was found. Just recently, an abstract was published, examining dose and volume de-escalation for elective neck treatment of oropharyngeal and laryngeal cancer. For OPSCC, only involved and immediately adjacent stations were treated. At a median follow-up of 24.7 months for surviving patients, there were no solitary elective nodal recurrences[80]. Because of the higher incidence of contralateral metastasis in HPC and LC, there are no data available on the incidence of cRF in patients treated with UNI in this patient population. In the above-mentioned abstract, at least bilateral levels II and III were treated in all LC patients.

Based on the previously mentioned studies, we can conclude that there is a slowly growing evidence in literature supporting the concept of unilateral nodal irradiation (UNI) in well-lateralized OPSCC with very limited risk of cRF. However, caution is required translating the results to daily practice. First of all, almost all studies are single-centre retrospective analyses, with small sample sizes and rather short follow-up time. Secondly, cRF varied widely between all reported studies. One reason for this may be that the inclusion criteria for UNI among centres differed. Higher incidence of cRF might partly be explained by the fact that in some centres N3 or T3 patients were treated unilaterally, while some centres only included T1-2 patients. Nevertheless, in most studies, T3 tumours were under-represented in the group that was treated with UNI, as they are more likely to involve midline structures. Therefore, conclusions can only be safely drawn for T1-T2 tumours. Understandably, distinctly higher cRF rates were found in the few studies that included patients with tumours involving the midline. As the reported studies were published from 1999 up until now, we must take into account the evolution in imaging techniques. The introduction of MRI and PET/CT has significantly improved the nodal staging, facilitated the selection of subgroups and thereby reduced the likelihood of cRF. In addition, the use of chemotherapy differed greatly between studies. For example, in the study of Dan et al. 89% of patients received chemotherapy, compared to 28% in the study of Kennedy et al.[73,76] A significant amount of patients in the above mentioned studies was treated with older

radiotherapy techniques, in which the contralateral neck can be treated, not-intentionally, to dose levels which might be enough to sterilize occult disease. As some older studies used 2D-3D RT techniques[61,69,71,78], more recent studies made use of the newer intensity-modulated radiation therapy (IMRT) technique[33,72]. Some studies combined 3D and IMRT techniques[70,73–76]. However, as also noted by the group of Al-Mamgani, the incidence of cRF was not significantly increased by the use of conformal radiotherapy techniques[81]. The definition of well-lateralized tumour was not clear in all studies, although most studies defined it as the lateral one-third of the base of tongue/soft palate or at least 1 cm away from the midline. Finally, almost no studies stratified according to HPV status. As the incidence of HPV positive OPSCC has significantly increased over the last three decades, incidence of cRF and patient outcome of the older studies might not be translatable to the present.

According to the above-mentioned studies, cRF after UNI in OPSCC is rare, but still occurs in a significant part of patients treated with UNI, depending on the risk factors. The pioneer study of O'Sullivan demonstrated that extension of the primary tumour into midline structures was highly predictive of cRF. Later studies have added multiple node involvement as predictor for cRF. We need to keep in mind that even after bilateral ENI, cRF occurs in 2.8% of cases[82]. Nevertheless, proper case selection and adherence to guidelines for the use of a unilateral approach are essential. The American Society of Clinical Oncology advises to treat patients with T1-T2 and N0-N1 well-lateralized tonsillar cancer, without soft palate extension or base of tongue involvement, with UNI[83]. For patients with T1-2 lateralized N2a and N2b tonsillar cancer, guidelines are less clear-cut, as they state that UNI may be delivered, after careful weighing the relative benefits of unilateral treatment versus the potential risk for cRF. The ambiguity about the UNI of N2b disease is reflected in slight differences in guidelines. For example, the American Radium Society did not reach consensus this year about the UNI of N2b OPSCC patients, due to the lack of level 1 evidence supporting specific treatment decisions[84]. However, 2012 ACR Appropriateness Criteria recommend bilateral neck irradiation in case of ≥N2b[36]. Table 3 provides an overview of the existing evidence for the elective treatment of the neck, depending on subsite and tumor specifics. Since inclusion criteria were not uniform in all reviewed studies, prospective, preferably randomized, clinical trials addressing the suitability of UNI in HNSCC are needed.

The value of the sentinel lymph node biopsy

Over the last years, sentinel lymph node biopsy (SLNB) has emerged as an alternative or additional staging procedure for cervical lymph nodes[85]. The procedure is based on the concept that tumour cells spread from the primary site to a single node or group of nodes, before progressing to the remainder of the lymph nodes. The biology of HNSCC seems ideally suited for this technique, as we know that the dissemination of disease happens in a relatively orderly manner from one nodal basin to the next[7,44,86,87]. A radiotracer, possibly in conjunction with coloured dye, injected into the primary tumour allows for identifying the sentinel nodes. Visualization of the sentinel nodes can be performed with the help of a lymphoscintigraphy, either or not with SPECT/CT, or with the intraoperative use of a hand-held gamma probe and/or portable gamma-camera with excision and histopathological evaluation of the sentinel nodes. The first experience with SLNB in HNSCC was published by Alex and Krag in 1996[88]. Since then, many centres followed with validation and observational studies. For assessment of the SLNB procedure, negative predictive value (NPV) is commonly used, representing the probability of a negative neck dissection after a negative SLNB. To date, the predominant clinical experience with SLNB has been with oral cavity tumours. Multiple studies have assessed the reliability of SLNB in cT1-2N0 OCSCC[89–97]. Govers et al. performed a meta-analysis on these studies and found a NPV ranging from 92% to 100%[85]. In 2014, the results of a Dutch multi-institutional trial involving four institutions and 62 patients found SLNB to have a sensitivity of 80% and a NPV of 88%[98]. The prospective EORTC Sentinel European Node Trial (SENT) recruited 415 patients with T1-2 OCSCC[99]. Positive SNs were found in 23%. A false-negative result occurred in 14% of patients, sensitivity of SLNB was 86% and NPV was 95%. The latest and largest meta-analysis compromising 66 studies and 3566 patients indicated that SLNB has an excellent diagnostic accuracy for predicting occult cervical LN metastases in clinical T1-T2N0 OCSCC, with a NPV of 94%[100]. A significant amount of studies includes both oral cavity and oropharyngeal cancers, stage T1-T2N0 with NPV ranging between 88% and 100%[101–111]. In these studies, OCSCCs and OPSCCs are considered as one group. However, they have different characteristics, which can cause different results for SLNB. In the mentioned studies, OCSCC were significantly over-represented as compared to OPSCC. Furthermore, only a few subsites of OPSCC were investigated (mostly soft palate and

base of tongue). Broglie et al. were the first to investigate the reliability of SLNB in 111 patients with exclusively T1-2 oropharyngeal cancers[112]. They found a NPV of 96%.

It is clear that the SLNB concept has been investigated frequently for oral and, to a lesser extent, for oropharyngeal cancer. However, less research has been done in the area of laryngeal and hypopharyngeal cancer. Tomifuji et al. reported the results of SLNB procedure on 20 patients with cT2-4N0 laryngeal and hypopharyngeal cancer and found an accuracy of 95%[113]. Interestingly, 40% of patients expressed a bilateral lymphatic spread pattern and the incidence of occult metastasis was much lower in glottic cancer (14%) compared to hypopharyngeal cancer (67%), which confirms empirical evidence. Lawson et al. performed SLNB on 29 patients with T1-3N0 supraglottic cancer[114] and reported a NPV between 91 and 100%. An important finding in this study is that the only additional positive lymph node that was not found with the SLNB technique, was in the prelaryngeal region, an area where the activity at the injection site might hide the SLN (shine-through effect). Flach et al. reported sentinel lymph node identification in 92% of 13 included laryngeal cancer patients with a previously untreated neck[115]. Lopez et al. found a NPV of 78.6% in N0 laryngeal patients[116]. Some other studies, mainly investigating OC/OPSCC, included some LC and HPC patients[101,105,117–120] and concluded that SLNB technique for N0 patients appears to be safe. However, it is important to note that the number of LC and especially HPC patients in these studies was very limited.

For early stage OCSCC, multiple studies proved that SLNB procedure counts as a reliable staging method and may serve as an alternative for elective neck dissection in experienced centres[121]. Yoshimoto and Hoft reported a significant higher false negative rate for T3 OCSCC compared to early stages[105,120]. Of note is that T3 tumours in these studies were classified according the 7th TNM edition, meaning that these tumours were larger than 4 cm. It might be more difficult for a larger primary tumour site to be completely surrounded by injected radiocolloid. Until further research is done, T3 OC tumours, particularly if larger than 4 cm, do not qualify for SLNB procedure. This is confirmed by the 2020 National Comprehensive Cancer Network (NCCN) guidelines that advise SLNB only for T1-T2 oral cavity tumours. Several studies found SLNB to be less reliable for floor-of-mouth tumours, presumably due to the close proximity of the injection site to the primary draining nodes with a consequent shine-through effect[90–92,111,122]. Although this finding was not confirmed by the EORTC SENT study, a Dutch multicentre retrospective study showed a significant

different sensitivity for floor-of-mouth tumours (n=131) compared to tumours of other oral cavity sites (n=357): 63% vs. 86%. NPV was 90% and 95%, respectively[123]. NCCN guidelines therefore mention that caution must be exercised when replacing neck dissection by SLNB in floor-of-mouth tumours. Concerning OPSCC, only one study performed SNLB on a substantial amount of patients[112]. The low number of patients with oropharyngeal cancers in the other studies did not allow pooling the results for OPSCC. In addition, not all oropharyngeal subsites were represented. Therefore, we may not simply assume that the high sensitivity of SLNB for OCSCC applies for all OPSCC. The same is true for laryngeal and hypopharyngeal cancers, which were significantly underrepresented in the few studies including LC and HPC. The above mentioned studies report rather wide ranges of NPV and sensitivity, which can presumably be explained by various causes. First, slightly different inclusion criteria are applied. For example, in the multicenter study of Flach et al[98], 36% of patients had a floor-of-mouth tumor, which may negatively influence accuracy, whereas these patients were excluded in several other studies. Secondly, a statistically significant difference in NPV between experienced and novice surgeons has been observed[124]. The EORTC SENT study reported a 14% false negative rate partially due to the learning curve effect[99]. Another limitation, possibly influencing the reported results, is that the quality of histopathological analysis of SLNB and neck dissection specimens is different to evaluate and may vary across institutions. A recent meta-analysis reports a significant difference in sensitivity of SLNB between studies where immunohistochemistry and step serial sectioning was performed, compared to older studies in which these techniques were not applied[165]. Furthermore, accuracy of SLNB is influenced by the choice of reference standard, which differed between studies. Some studies performed neck dissection irrespective of the SLNB result, while others reserved neck dissection for SLNB positive patients only, in combination with long-term observation of SLNB negative patients[85,98-100]. Follow-up of the untreated neck seems to be a better reference standard, since histopathological examination may miss minimal disease, leading to overestimation of sensitivity and NPV. Lastly, the incidence of occult lymph node metastases and follow-up time need to be taken into account, as they affect NPV and sensitivity, respectively. Determination of N0-disease differed between studies, as visualized in Table 1A of the meta-analysis of Govers et al.[85]

SPECT/CT-guided Elective nodal irradiation

Several studies have proven that SPECT/CT has the potential to detect more SLNs than dynamic planar lymphoscintigraphy alone[122,125–132]. As a result, the interest for SPECT/CT-guided elective radiation treatment has been increasing. Daisne et al. were the first to examine the feasibility of SPECT/CT lymphoscintigraphy for selective prophylactic irradiation of the neck in cN0 head and neck cancer patients[133]. The group of Antoni Van Leeuwenhoek hospital recently published the results of their prospective SUSPECT trial investigating feasibility, safety and benefits of SPECT/CT-guided ENI of the node-negative contralateral neck[134]. Fifty patients with lateralized T1-3N0-2b tumours of the oropharynx, oral cavity, larynx and hypopharynx underwent SPECT/CT after peritumoural 99mTc-nanocolloid injection. Patients without contralateral lymph drainage received UNI (82%). If drainage to only one contralateral lymph node was visible, ENI to the contralateral neck was limited to only the level containing the SLN (18%). After a median follow-up of 33 months, cRF was observed in only one patient (2%). The patient had a T2N2b tonsillar fossa carcinoma that was treated unilaterally and developed a contralateral lymph node metastasis in level II. A similar prospective, non-randomized phase I-II study was conducted by Longton et al.[135] Forty-four patients with tumours of oropharynx, oral cavity, larynx (except glottis cT1) or hypopharynx and cN0 stage received ENI of all node levels containing up to the 4 hottest SLNs. Four patients developed a nodal relapse, of which only 1 (2.3%) occurred outside the elective volume. It was a cT4a left soft palate tumour not crossing the midline that presented purely contralateral lymphatic drainage according to SPECT/CT, although the patient developed an ipsilateral recurrence in level Ib. These findings suggest that one can maybe avoid contralateral ENI in absence of contralateral lymphatic drainage, but not ipsilateral ENI in advanced stage tumours.

Although the results of the prospective studies regarding SPECT/CT-guided ENI are promising, we must be careful to draw firm conclusions regarding the current clinical practice. An important advantage of SLNB is its ability to identify ‘skip’ metastases. Unpredictable lymphatic drainage patterns for lateralized tumours were reported in 9%-16% of cases[90,98,99,135,136]. For midline tumours, Mølstrøm et al. observed exclusive unilateral lymphatic drainage in 28.5% of patients, whereas the European SENT trial reported 40%[99,137].

However, limitations are the relatively small sample size and the heterogeneous distribution of tumoural subsites. In both studies, OPSCC and LC were much more prevalent, compared to the low number of patients with OCSCC and HPC. Furthermore, the role of concomitant chemotherapy was not evaluated. One of the most important limitations of the SLN technique is the risk of a false-negative result. This was well illustrated by the case of the patient, showing a lymphatic drainage exclusively contralateral to the tumour, that relapsed shortly after in the ipsilateral neck[135]. The authors hypothesized that the presence of a subclinical nodal metastasis obstructed the hilum of the node and therefore only contralateral drainage was visualized. Therefore, it is mandatory to exclude gross lymph node involvement using conventional imaging, e.g. CT, MRI and/or ultrasound. Another possibility could be that in large tumours deep drainage would not be mapped. Nevertheless, it seems that the inclusion criteria for both studies might be too broadly defined and that the existing evidence on patient selection for SLNB was not sufficiently considered. The same applies for the contralateral relapse in the T2N2b tonsillar cancer patient in the study of De Veij Mestdagh et al.[134] Given the uncertainties about N2b stage for UNI, the inclusion of N2b patients may have been unfortunate, especially since most studies assessing reliability of SLN have been performed on cN0 patients. We can conclude that SLNB has become a well investigated nodal staging tool, but there remain some uncertainties that require further research before implementing SPECT/CT-guided ENI. Before conducting new radiotherapy trials, it seems appropriate to firstly validate the reliability of the SLN procedure on ≥T3, N+ and floor-of-mouth OC tumours and OPSCC, LC and HPC. The higher resolution of PET/CT may solve the problem of 'shine through phenomenon' for lymphoscintigraphy of floor-of-mouth OC tumours[138].

Volume de-escalation in HPV positive oropharyngeal squamous cell carcinoma

Over the past few decades, the incidence of human papillomavirus (HPV)–associated cancers of the oropharynx has increased, while the incidence of HPV negative tobacco-driven OPSCC has declined. Patients with HPV positive OPSCC tend to be more frequently male, younger, and have a better performance status and prognosis[139]. It is therefore desirable to minimize long-term toxicity in this population. Over the last years, the interest in dose and volume de-escalation in the HPV positive population has increased. Although the general consensus exists that treatment de-escalation for HPV positive OPSCC is feasible, the optimal

approach has not yet been established. Concerning volume de-escalation, only few studies evaluating the safety of UNI made a distinction between HPV positive and HPV negative patients, as most studies predate the HPV era. Furthermore, TNM8 staging for HPV positive tumours was not taken into account yet and current guidelines are based on studies using the TNM7-classification. Interestingly, HPV positive patients tend to present more often with multiple lymph nodes, so the question if UNI is suitable in the presence of multiple ipsilateral lymph nodes is especially relevant in this population[140]. Ye et al. reported slightly higher cRF rates in HPV positive patients treated with UNI (3.5% for HPV positive patients versus 2.5% for HPV negative patients, p=0.63)[141]. This was not confirmed by Liu et al.[74], although HPV status was unknown for a significant part of the patient cohort. Huang et al. conducted a retrospective review of a cohort of T1-T2 tonsillar cancers treated with UNI and B-ENI between 1999 and 2014[142]. Only two patients developed a cRF, of which one patient was HPV positive and the other was HPV negative. In the OPTIMA trial, patients with HPV positive OPSCC stratified into low and high risk, received three cycles of induction chemotherapy and the radiation dose was determined based on response to chemotherapy[143]. Notably, the study also includes volume de-escalation, as the elective volume was limited to the first echelon of non-involved nodes at the time of diagnosis. The authors conclude that a risk-stratified dose and volume de-escalated radiotherapy after induction chemotherapy is associated with favourable oncologic outcomes. All findings support the American Radium Society's advice that HPV status is not a contraindication for UNI[84].

Effects on treatment-related toxicity

The most important advantage of UNI for well-selected patients is the decrease in dose deliverance to the contralateral neck and important organs at risk, such as the salivary glands and the swallowing muscles. B-ENI (compared to UNI) has been identified as a strong predictor for grade ≥2 dysphagia and xerostomia at 6 months after treatment[144–146] and worse HRQOL scores at the EORTC QLQ-HN35 dry mouth and swallowing subscales[147]. A significant reduction of toxicity in patients treated with UNI, compared to B-ENI, was found in a prospective study by Jensen et al., with 20% vs. 61% for grade ≥ 2 xerostomia and 10% vs. 22% for grade ≥ 2 dysphagia[78]. Similar results were reported by Liu et al. (toxicity rate of 22% vs 7%, p = 0.013) with the caveat that these series had an imbalance in disease stages between the UNI and B-ENI group[74]. In addition, bilateral treatment in their series was delivered by non-conformal techniques. A lower

acute and late toxicity profile using UNI was also reported by Al-Mamgani et al.[72], as they compared toxicity results with a large series on IMRT for OPSCC[148]. Cramer et al. reported a smaller rate of hospitalisation (17% vs 61%, p<0.01) and less weight loss (6.3% vs 8.4%) in patients treated with UNI[67]. Chronowski et al. reported a significantly lower acute dysphagia-related toxicity[70]. In the OPTIMA trial, acute grade 3+ mucositis, grade 3+ dermatitis and the need for PEG-tube were significantly lower with de-escalated treatment[143]. Bilateral neck irradiation was one of the most important predictors for PEG-tube dependency in 450 HNSCC patients treated by chemoradiation[153]. It is therefore clear that a strictly UNI will generally lead to less toxicity and better quality of life. However, we need to keep in mind that the mentioned studies included patients that met the current conditions for UNI. These patients represent only part of HNSCC patients. Therefore, we need to take into account a tumour site effect on the toxicity profiles for the group that was treated with B-ENI. For example, a base of tongue tumour in close proximity to the midline will lead to higher dose on swallowing structures compared to a lateralized tonsil tumour, regardless of the elective neck treatment.

With regard to the SPECT/CT guided ENI studies, evaluating toxicity benefits is somewhat more complex because not all patients were irradiated purely unilaterally. In the study of De Veij Mestdagh et al., compared to the matched B-ENI group, patients treated with SPECT/CT-guided ENI had significantly lower incidences of grade ≥2 dysphagia (54% vs. 82%; $p < 0.001$), tube feeding (10% vs. 50%; $p < 0.001$) and late grade ≥2 xerostomia (9% vs. 54%; $p < 0.001$)[134]. For dysphagia, hypothyroidism and laryngeal oedema, significantly larger NTCP reductions were found in the group that received UNI. Inclusion criteria for both SPECT/CT-guided ENI studies are rather broad, as they include tumours originating from all subsites. Dysphagia is known to be mainly dependent on the mean dose to the pharyngeal constrictor muscles and the supraglottic larynx[149]. As these are midline structures, dysphagia might be reduced less in primary tumours crossing the midline. However, Longton et al.[135] observed a significant decrease of mean dose on several swallowing structures in SPECT/CT-guided ENI group, particularly in the case of unilateral lymphatic drainage. It is assumed that severe xerostomia could be avoided if at least 1 parotid gland were spared to a mean dose ≤ 20 Gy or if the mean dose to both parotid glands were ≤ 25 Gy[150]. In the study of Longton et al., more than 50% of the patients presented with bilateral lymphatic drainage. Therefore, the impact of a

SPECT/CT-guided ENI on toxicity could be reduced, as an important part of OCSCC and OPSCC will drainage to contralateral level II, which is close to the parotid gland. Still, a significant reduction of the mean dose to the parotid glands was observed in HPC/LC tumours with a bilateral lymphatic drainage, probably due to the preferential drainage to level III[135].

Future perspectives

The EORTC Head and Neck Cancer Group recently presented a future trial, EORTC2047, which will be a phase III randomized controlled trial to investigate SPECT/CT-guided elective contralateral neck treatment in lateralized OPSCC. Inclusion will be limited to patients with T1-T3 tonsillar or base of tongue cancer not involving the midline, with no contralateral nodes or involved ipsilateral nodes not larger than 6cm on imaging. In the experimental arm, patients will receive UNI and SPECT/CT-guided contralateral ENI. The control arm will receive B-ENI according to international guidelines[13]. The INFIELD trial (NCT03067610) is a prospective phase II dose and volume de-escalation study for stage I-IV OPSCC and LC (with exclusion of stage I-II glottic cancer). The EVADER trial (NCT03822897) is a Canadian Cancer Trials Group phase II study to evaluate the efficacy of primary definitive (chemo)radiotherapy utilizing volume reduced ENI in patients with low-risk HPV positive OPSCC. The SAVER trial (NCT04609280) will also investigate volume de-escalation in the HPV positive population, however combined with dose de-escalation. The SUSPECT2 study aims to expand the inclusion criteria of the original SUSPECT study, with inclusion of stage T1-4N0-2b HNSCC not crossing the midline[134]. If no contralateral drainage is visualized, the patient will be treated with UNI. In case of contralateral lymph drainage, a contralateral SLNB will be performed. If pathologic evaluation finds no metastasis, the patient is treated with UNI. In Belgium, the SEMIRAHN trial was recently presented. This is a prospective randomized multi-centre phase II study of dose and volume de-escalation. Patients with OC/OPSCC, LC and HPC with ipsilateral lymph node metastases will be included. Patients with contralateral drainage according to 99mTc-nanocolloïd drainage will be randomized between two different arms: whole level versus SLN only irradiation. Patients with the primary tumour not crossing the midline, expressing ipsilateral drainage only, will receive UNI. Patients with the primary tumour crossing the midline, expressing ipsilateral drainage only, will be excluded.

Other approaches with higher resolution lymphography using nonradioactive tracers currently under investigation include MRI and CT lymphography. These techniques use peritumoural injections of gadolinium- and iodine-based contrast agents, respectively, and may be used to guide unilateral or bilateral ENI in HNSCC patients and even neck treatment of selected lymph node levels[151,152].

Reducing the elective nodal volume in the radiotherapy of HNSCC thus holds a great promise to reduce both acute and long-term side effects for the patient. However, accurate selection criteria and close follow-up of the untreated neck are primordial not to compromise tumour control rates. Results of ongoing clinical trials will hopefully deliver good criteria allowing a more restrictive approach regarding nodal dose-volumes.

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Appendix

OCSCC	OPSCC
T-stage[26–28] Ipsilateral N+[26,28] High histopathological grade[28] Midline extension[26,27] FOM involvement[8,22–25,27] Tumour site: *risk ↑ for FOM and OT*[22–25] *risk ↓ for lateralized OCSCC*[6,22]	T-stage[29,39,43–45] N-stage[30,31,33,42,45] ECE[32,33] Tumour site: *risk ↑ for BOT, soft palate and posterior pharyngeal wal*[19,22,39,41,42] *risk ↓ for tonsillar carcinoma*[34–37,39,42,45]
HPC	**LC**
Ipsilateral N+[46,52,53] Midline extension[46,48–51] Involvement medial wall of PS[50]	T-stage[59] Ipsilateral N+[56] Subglottic extension[57] ECE[56,57,60] Tumour site: *risk↑ for supraglottic cancer*[52,56–59] *risk↓ for glottic cancer (especially T1)*[54,55]

Table 1. Predictors of occult contralateral metastases based on pathological examination after bilateral neck dissection. OCSCC: oral cavity squamous cell carcinoma; OPSCC: oropharyngeal squamous cell carcinoma; HPC: hypopharyngeal carcinoma; LC: laryngeal carcinoma; ECE: extracapsular extension; FOM: floor-of-mouth; BOT: base of tongue; OT: oral tongue; PS: pyriform sinus. General probability of CLNM in lateralized OCSCC is typically <10%, however higher incidences are reported for FOM and OT tumours. Midline structures in OPSCC show increased risk for CLNM, as opposed to tonsillar cancers. HPC have a high overall incidence for CLNM of +/- 30%. For T1 glottic tumours, the risk of CLNM is very low. Supraglottic carcinomas are associated with a higher rate of CLNM.

	Sample size	Inclusion criteria	cRF (N)	Isolated cRF (N)	Median FU in months
O'Sullivan et al.[61]	228	cT1-4N0-3 tonsillar cancer	8	3	68
Jackson et al.[71]	136	cT1-4N0-3 tonsillar cancer	4	4	60
Al-Mamgani et al.[72]	185	cT1-3N0-2b well-lateralized OPSCC	2	2	185
Lynch et al.[33]	136	cT1-3N0-3 lateralized tonsillar cancer	8	6	136
Chronowski et al.[70]	102	cT1-2N0-2b lateralized tonsillar cancer	2	1	102
Kennedy et al.[73]	76	cT1-2N0-2b lateralized tonsillar cancer	1	1	76
Dan et al.[76]	61	cT1-3N1-2b lateralized tonsillar cancer	1	1	37
Liu et al.[74]	58	cT1-3N0-3 tonsillar cancer	0	0	102
Jensen et al.[78]	40	cT1-3N0-3 OPSCC	1	1	40
Kagei et al.[69]	32	cT1-4N0-3 lateralized tonsillar and soft palate cancer	0	0	32
Koo et al.[75]	20	cT1-3N0-2b lateralized tonsillar cancer	0	0	20
Cerezo et al.[77]	20	cT1-2N0-2b lateralized OPSCC and OCSCC	0	0	58
Maskell et al.[63]	53	cT1-2N0-2b lateralized tonsillar cancer	NR	4	68
Hu et al.[62]	36	cT1-3N0-2b lateralized OPSCC	0	0	32
Cramer et al.[67]	23	cT1-2N1-2b lateralized tonsillar cancer	0	0	30

Table 2. Overview of 15 studies in which UNI was administered and the incidence of cRF and disease stage were reported. cRF (N): number of patients with contralateral regional failure; isolated cRF (N): number of patients with contralateral regional failure with controlled disease at the primary tumour site; NR not reported. Median FU: follow-up in months. Isolated cRF is <2% (23/1206 patients).

<table>
<tr><th>SUBSITE</th><th colspan="2"></th><th colspan="3">RECOMMENDATION</th><th>LEVEL OF EVIDENCE (GRADE)</th></tr>
<tr><td>ORAL CAVITY</td><td colspan="2"></td><td colspan="3">Definitive unilateral RT: patients unfit for surgery who would normally receive unilateral neck dissection[83,155]</td><td>Moderate</td></tr>
<tr><td rowspan="6">OROPHARYNX</td><td rowspan="4">Isolated tonsillar cancer cT1-2</td><td></td><td>ASTRO[154]</td><td>NCCN[155]</td><td>ASCO[83]</td><td></td></tr>
<tr><td>cN0 or single node ≤ 3 cm</td><td>Unilateral RT</td><td>Unilateral RT</td><td>Unilateral RT</td><td>Moderate</td></tr>
<tr><td>Multiple ipsilateral nodes (cN2b) ≤ 6 cm</td><td>Bilateral RT</td><td>N.R.</td><td>Uni/bilateral RT*</td><td>Low</td></tr>
<tr><td>Tongue base extension</td><td>Bilateral RT</td><td>Bilateral RT</td><td>Uni/bilateral RT**</td><td>Low</td></tr>
<tr><td>Soft palate extension</td><td>Uni/bilateral RT***</td><td>Bilateral RT</td><td>Uni/bilateral RT**</td><td>Low</td></tr>
<tr><td>Tonsillar cancer cT3-4</td><td></td><td colspan="3">Bilateral RT[83,154,155]</td><td>Moderate</td></tr>
<tr><td rowspan="3">Tongue base cancer</td><td rowspan="2"></td><td>ASTRO[154]</td><td>NCCN[155]</td><td>ASCO[83]</td><td></td></tr>
<tr><td>Lateralized</td><td>Bilateral RT</td><td>Bilateral RT</td><td>Unilateral RT</td><td>Low</td></tr>
<tr><td>Approaching midline</td><td>Bilateral RT</td><td>Bilateral RT</td><td>Bilateral RT</td><td>Moderate</td></tr>
<tr><td>Other subsites OPC</td><td></td><td colspan="3">Bilateral RT[83,154,155]</td><td>Moderate</td></tr>
<tr><td>HYPOPHARYNX</td><td colspan="2"></td><td colspan="3">Bilateral RT[155-157]</td><td rowspan="3">Strong evidence for current guidelines, no reported trials for UNI</td></tr>
<tr><td rowspan="2">LARYNX</td><td>Supraglottic/subglottic carcinoma</td><td rowspan="2"></td><td colspan="3">Bilateral RT[155,157]</td></tr>
<tr><td>Glottic carcinoma</td><td colspan="3">Bilateral RT (no ENI for cT1****)[156,158-161]</td></tr>
<tr><td>NASOPHARYNX</td><td colspan="2"></td><td colspan="3">Bilateral RT[155,157,162-164]</td><td></td></tr>
</table>

Table 3. Overview of recommendations, depending on subsite and tumor specifics. Level of evidence is scored according to the GRADE system.

N.R: No Recommendation; ASTRO: American Society for Radiation Oncology; NCCN: National Comprehensive Cancer Network; ASCO: American Society of Clinical Oncology; * Unilateral RT may be delivered after careful weighing the benefits of unilateral RT versus the potential risk; ** Bilateral RT if within 1 cm of midline; *** unilateral RT if < 1 cm soft palate extension; **** For T1 glottic carcinomas, observation of the neck is generally recommended[156, 158-160] . Some institutions report their results of T2 glottic tumors treated with the same approach[161], however this is not generally recommended. As early stage oral cavity carcinomas are mostly treated surgically, elective neck dissection is the preferred approach. However, if surgery is not feasible, unilateral RT can be performed if patients would qualify for a unilateral neck dissection according to existing surgery guidelines[83,155]. Regarding the treatment of tonsillar carcinoma and tongue base carcinoma, ASTRO, NCCN and ASCO have inconsistent recommendations. Moderate evidence for unilateral RT in oropharyngeal carcinoma currently only exists for cT1-2 tonsillar carcinoma with single node ≤ 3 cm.