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Clinical Investigation

Individualized Prophylactic Neck Irradiation in Patients with cN0 Head and Neck Cancer Based on Sentinel Lymph Node(s) Identification: Definitive Results of a Prospective Phase 1-2 Study

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Purpose: This prospective, nonrandomized, interventional phase 1-2 study investigated the individualization of elective node irradiation in clinically N0 head and neck squamous cell carcinoma by sentinel lymph node (SLN) mapping with single-photon emission computed tomography/computed tomography (SPECT/CT) and its impact on tumor control and radiation-related toxicity.

Methods and Materials: Forty-four patients with clinically N0 head and neck squamous cell carcinoma treated with definitive (chemo-)radiation therapy were imaged with SPECT/CT after ^{99m}Tc nanocolloid injection around the tumor. The neck levels containing up to the 4 hottest SLNs were selected for prophylactic irradiation. A comparative virtual planning was performed with the selection of neck levels based on the current international guidelines. Regional control was monitored as a function of the selected volume. Dosimetric data for the organs at risk were compared between the plans. Normal tissue complication probability (NTCP) rates were derived for xerostomia, dysphagia, and hypothyroidism to predict the clinical benefit and correlated to quality-of-life (QoL) assessments at 6 months.

Results: Sixteen percent of patients presented unpredicted lymphatic drainage, and 48% drained unilaterally. The nodal clinical target volume based on lymphoscintigraphy was smaller than the nodal clinical target volume based on international guidelines by a factor of 2 ($P < .0001$). After a median follow-up of 46 months, only 1 patient experienced a regional relapse in a nonirradiated area. Significant median dose reductions to organs at risk were observed, particularly to contralateral salivary glands in patients with unilateral drainage (14.6-28.1 Gy) and to the thyroid gland in all patients (22.4-48.9 Gy). Median NTCP reductions were observed for xerostomia (0.3% to 13.7%), dysphagia (1.7% to 10.8%), and hypothyroidism (14.0% to 36.1%). QoL at 6 months was improved, particularly in patients irradiated unilaterally.

Conclusions: Neck SLN mapping with SPECT/CT individualizes and reduces the elective nodal target volumes without compromising the regional control. The NTCP rates were reduced and favorable QoL were observed in all patients, particularly in the case of unilateral irradiation.

Introduction

Owing to the dense (and often bilateral) regional lymphatic network, the incidence of lymph node metastases is high in head and neck squamous cell carcinoma (HNSCC). Despite the use of modern imaging, the risk of occult metastases in clinically node-negative (cN0) oral cavity cancer (OCC), oropharynx cancer (OPC), larynx cancer (LAC), or hypopharynx cancer (HPC) lies between 20% and 40%.[1-8] Because nodal involvement is a major prognostic factor,[9] bilateral elective node irradiation (ENI), after International Guidelines (IG) for selection and delineation,[10-12] is the rule in most cN0 HNSCC, at the cost of substantial morbidity.

In the case of surgery for cT1-2N0 OCC/OPC, a sentinel lymph node (SLN) biopsy may be proposed as an alternative to elective neck dissection in experienced centers.[13-16] The radioactive tracer injected submucosally around the primary tumor migrates to the first echelon node(s) that show the highest probability of harboring occult metastases.[17] This highly sensitive, specific, and negative predictive valued diagnostic technique decreases surgery-induced morbidity and individually identifies the drainage mapping. Moreover, 30% to 50% cases of HNSCC have a true bilateral drainage, and up to 15% to 30% present an unexpected nodal drainage.[1,4,5,7] Using IG for ENI volumes selection thus bears an intrinsic risk of useless irradiation in at least 50% and/or geographic miss in up to 30% of HNSCC cases.

The SLN was historically identified with planar lymphoscintigraphy (LS) imaging and handheld gamma probe. Currently, hybrid single photon emission computed tomography/computed tomography cameras (SPECT/CT) provide the 3-dimensional LS details, which are particularly important given the complex anatomy of head and neck.[18,19] In cN0 patients treated with radiation therapy, identifying the SLN with SPECT/CT is an attractive concept because it may help to individualize the ENI volume and hence reduce the dose to critical organs at risk (OARs) involved in radiation-induced toxicity (eg, xerostomia and swallowing dysfunction[20]), that can negatively affect quality of life (QoL).

In a seminal phase 1 study, we demonstrated the feasibility of SLN mapping with SPECT/CT-LS to guide the selection of the ENI clinical target volume (CTVn) in 10 patients with cN0 HNSCC. In comparison to ENI CTVn selected according to IG (CTVn-IG), the absolute CTVn-LS were divided by 2.[21] As initially planned, we extended to a phase 2 study, recruiting 34 additional patients with cN0 HNSCC. The primary endpoint was oncologic safety as reflected by the 2-year regional recurrence rate outside of the CTVn-LS. Secondary endpoints were the overall survival (OS), the impact on dose distribution to OARs, and the subsequent impact on normal tissue complication probability (NTCP) rates (for xerostomia, dysphagia, and hypothyroidism) and QoL at 6 months.

Methods and Materials

Patients and study design

Patients selected for this study presented with pathologically proven invasive primary HNSCC of OCC, OPC, LAC (except glottic cT1), or HPC; cN0 and without distant

metastases as assessed by imaging (fluorodeoxyglucose combined positron emission tomography and iodine-contrasted CT [FDG-PET/CT], complemented by a magnetic resonance imaging scan of the neck in the case of contraindication to iodine injection); age $\geq$18 years; a performance status of 0 to 1; and referral by the multidisciplinary tumor board for definitive radiation therapy (with or without chemotherapy or targeted therapy) with a mandatory ENI. Nodes were deemed cN0 if the shortest diameter was $\leq$5 mm at retropharyngeal level and $\leq$10 mm at any other level and/or exhibited no central necrosis. In dubious cases (high FDG uptake or size in level 2 between 11 and 15 mm), ultrasonography with fine needle aspiration cytology had to be performed. Exclusion criteria were pregnancy or no active contraception for nonmenopausal women; HNSCC originating from nose, sinuses, esophagus, salivary glands, or nasopharynx; non-HNSCC histologies; recurrence or second malignancy; history of cancer in the last 5 years (excluding basal cell carcinoma of the skin and in situ squamous cell carcinoma of the cervix); known hypersensitivity to iodine or nanocolloid injection; "violated neck" (ie, previous surgery or radiation therapy to the neck); and any psychological, familial, sociologic, or geographic condition potentially hampering compliance with the study protocol and follow-up schedule.

Close follow-up was performed, including evaluation of tumor response by FDG-PET/CT 12 weeks after the end of treatment (EOT) and neck imaging with iodine-contrast CT at 6, 12, 18, and 24 months post-EOT. Toxicities were scored/graded with the Radiation Therapy Oncology Group (RTOG) scale. QoL data were collected using the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire, core module (QLQ-C30) and head and neck module (QLQ-H&N35) and were scored using the recommended EORTC Quality-of-Life Group procedures. Toxicities and QoL were evaluated at baseline and at the imaging time points.

The study was approved by the independent ethics committees of CHU-UCL-Namur (national reference number: B039201215085). All patients gave preliminary written informed consent.

Radiotracer injection, SPECT/CT acquisition, and radiation therapy planning

The methodology is extensively described in the phase 1 study paper[21]: after simulation with a thermoplastic mask, patients were referred to the surgeon within the 7 days for peritumoral injection with ^{99m}Tc-labeled human serum albumin colloid (18.5-37.0 MBq in 1 mL).[21] Because surgical expertise increases the sensitivity of the method, only head and neck surgeons who had extensive experience with the SLN dissection performed the injections, which consisted of 4 submucosal aliquots at 1 to 5 mm from macroscopic tumor edges, with a fifth injection in the center of the larger tumors, according to standard surgical protocol. Patients with oral cavity and/or accessible oropharyngeal tumors were injected without sedation in the nuclear medicine department, and the others were injected during endoscopy under short sedation in the operating room. SPECT/CT images were acquired on 2 hybrid cameras, either a Siemens SYMBIA T (Siemens, Erlangen, Germany) or GE Discovery NM/CT 670 (GE Healthcare, Waukesha, WI), using well-defined acquisition parameters.[21] Except for the first 7 patients, patients were positioned with the mask in radiation therapy conditions on a flat carbon tabletop between 1 and 4 hours after the injection of the radioactive tracer.[21]

Images were reviewed by a head and neck radiation oncologist and a nuclear medicine specialist with OsiriX MD v2.0.1 software (Pixmeo, Bernex, Switzerland). All SLNs were recorded according to their relative maximal activity and anatomic location according to the standardized RT nomenclature.[11] Only the 4 hottest nodes were considered for radiation therapy planning.

Two different CTVn volumes were delineated: first, the CTVn-IG with node levels selected according to primary tumor location and extension[10] (for dosimetric comparisons only, done before the SPECT/CT acquisition to avoid any bias from the SLN migration knowledge); then the CTVn-LS, selecting all node levels containing up to the 4 hottest SLN. The whole level containing at least 1 of the 4 hottest SLN rather than the SLN alone had to be selected to cover the risk of secondary invasion of non-SLNs.[7] An illustrative case of target volume changes is shown in the phase 1 study paper.[21] Patients were treated according to CTVn-LS. The primary gross tumor volume was delineated identically in both plans. The planning target volume (PTV) margin was 4 mm. OARs were delineated according to current guidelines.[22]

In cases of radiation therapy alone, altered fractionation was prescribed with 69 and 55.5 Gy in 30 fractions to the primary PTV and nodal PTV (PTVn), respectively. In cases of radiosensitization, conventional fractionation was prescribed with 70 and 59.5 Gy in 35 fractions to primary PTV and PTVn, respectively. All patients were treated with a simultaneous integrated boost technique using volumetric arc modulated radiation therapy (RapidArc, Varian, Palo Alto, CA), and dose calculations were done with the analytical anisotropic algorithm (Varian). To avoid bias, the same dosimetrist optimized both plans at the same time, mandatorily starting with the LS one. The mean dose difference (ΔDmean) between both plans for each OAR was defined as Dmean in the IG plan minus Dmean in the LS plan.

NTCP models

Three validated NTCP models were used to calculate the difference between IG and LS plans in predicted radiation-induced moderate-to-severe xerostomia at 6 months after

EOT,[23] dysphagia grade ≥2 at 6 months after EOT,[24] and hypothyroidism.[25]

NTCP rate difference (ΔNTCP) was defined as NTCP value in IG plan minus NTCP value in LS plan.

Statistics

Based on surgical series,[1,2,6-8,26] the risk of regional relapse outside CTVn-LS should lie between 3% to 10% and could be considered acceptable because close follow-up of the neck is performed, with potential salvage treatment in the event of regional recurrence. Assuming a 2-year regional relapse rate outside the CTVn-LS of 5% and an unacceptable rate of 15%, the power calculation ($\alpha = 0.05$, $P = .8$) of the study based on the 1-stage Fleming procedure method resulted in 44 eligible patients.

OS was estimated using Kaplan−Meier methodology. Local and regional failures were estimated using cumulative incidence functions, in which death was considered a competing risk because dead patients cannot develop a recurrence.

R (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. Because normality could not be assumed, median and interquartile ranges were computed. The differences in Dmean and NTCP values between IG and LS plans were analyzed with the Wilcoxon-signed rank test with continuity corrections. Because NTCP models for xerostomia and dysphagia give predictive values at 6 months after EOT, we reported the physician-reported RTOG toxicity grades and patient-reported EORTC QLQ-H&N35 scores for xerostomia and dysphagia at 6 months post-EOT. Data compared between patients with unilateral and bilateral lymphatic drainage depending on their primary tumor location were analyzed with Mann−Whitney U test. P values ≤.05 were considered statistically significant.

Results

Patients

Between January 2013 and August 2018, 49 patients were assessed for eligibility. Three were excluded because they declined to participate or did not meet inclusion criteria. Among the 46 patients undergoing the pre−radiation therapy per-protocol procedure, 2 were excluded from further analyses because of early treatment termination due to complications unrelated to the study protocol and received salvage surgery (Fig. E1; available online at https://doi.org/10.1016/j.ijrobp.2020.03.021). This left 44 patients for analysis, including the first 10 patients from the phase 1 study.[21] Most OPCs were p16-negative. Nine patients received concomitant radiochemotherapy (5 three-weekly cisplatin, 2 three-weekly carboplatin/5-fluorouracil, and 2 weekly cetuximab) (Table 1). The majority of the tumors were T2-3 LAC or OPC (Table 2). Nearly two-thirds were treated with an altered fractionation regimen, and all ended their radiation therapy course within the prescribed overall treatment time.

SLN identification and patterns of drainage

All 44 patients underwent radioactive tracer injection and SPECT/CT acquisition without any procedure-related side effects. The nanocolloid was injected in 16 conscious patients because the tumor was directly accessible to injection. This was performed during an endoscopy under short general anesthesia in all the 28 other patients. Tracer migration was observed in all patients. In 1 patient with a LAC, the SLN activity was hidden by the tumor burden on the SPECT/CT, but it was subsequently detected in homolateral level III by the surgeon with a collimated, handheld gamma probe. On average, 3.3 nodes were detected per patient.

Twenty-one patients (48%) had a unilateral lymphatic drainage, with all but 1 being ipsilateral to the primary tumor (1 patient with OPC not crossing the midline drained toward the contralateral levels IB and II). Six OPCs (40%) crossed the midline and presented bilateral lymphatic drainage. Lymphatic drainage was mainly observed in level II in OCC/OPC and in levels II and III in HPC/LAC. In comparison to the selection of nodal levels according to IG, 7 unpredicted lymphatic drainages were observed: 2 in level VIIb and 2 in level VIIa in T2 tonsil carcinomas and 1 in level Ib in a T4a soft palate carcinoma; 2 patients with

Table 1 Patient and treatment characteristics (N = 44)

Characteristics	N	%
Sex		
Male	37	84
Female	7	16
Age: range (median), y	43-92 (63)	
<70 y	37	84
>70 y	7	16
Tumor site		
Oral cavity	1	2
Larynx	22	50
Hypopharynx	6	14
Oropharynx	15	34
HPV−	13	
HPV+	0	
Unknown	2	
T-stage		
T1	3	7
T2	25	57
T3	13	29
T4	3	7
Concurrent systemic treatment		
Platin-based	7	16
Cetuximab	2	4

Abbreviation: HPV = human papillomavirus.

Table 2 Disease characteristics (N = 44)

	Oral cavity	Oropharynx			Larynx		Hypopharynx
Tumor site	Hard palate	Tonsil	Soft palate	Base of tongue	Supraglottic	Glottic	Pririform sinus
T stage							
T1	0	0	1	0	0	0	2
T2	0	6	5	1	2	9	2
T3	0	1	0	0	5	5	2
T4	1	0	1	0	1	0	0

HPC/LAC had an unexpected drainage in level VIb, 1 in a T3 HPC and 1 in a T3 supraglottic carcinoma (Table 3).

Outcome

Median follow-up was 46 months (range, 7-72 months). 2-years OS was 79.2% (95% confidence interval [CI], 62.6%-89%). The 2-year cumulative incidence rates for local and regional recurrences were 12.1% (95% CI, 1.9%-22.3%) and 9.5% (95% CI, 0.5%-18.5%), respectively.

Eight patients developed a recurrence during follow-up. Four presented a local primary tumor recurrence, 1 had only a nodal relapse, and 3 had simultaneous locoregional recurrences. Three patients had a regional recurrence within the prophylactic PTVn-LS, whereas only 1 (2.3%) occurred outside of the CTVn-LS. It was that left soft palate tumor not crossing the midline, staged cT4a, that presented purely contralateral lymphatic drainage according to SPECT/CT. It was treated according to this finding but showed a level Ib left recurrence on the 3-month PET/CT. After salvage neck dissection, 3 nodal metastases, including 1 in rupture capsular, were diagnosed in levels Ib, II, and III left. The patient underwent postoperative chemoradiation therapy on the left neck, but the tumor recurred locally 3 months after; it was reoperated and fully controlled until the patient's death of a nononcological etiology 6 months after reoperation.

Radiation therapy planning data

The CTVn-LS (median = 92 cm^3) and related PTV (median = 219 cm^3) were systematically smaller than the respective CTVn-IG (median = 188 cm^3) and PTVn-IG (median = 405 cm^3) ($P < .0001$) (Fig. 1).

The median Dmean to salivary glands, swallowing structures, and thyroid gland extracted from the IG and LS plans revealed a higher benefit in patients showing a unilateral lymphatic drainage in comparison to those with a bilateral one, particularly for the contralateral salivary glands. Considering the pharyngeal constrictor muscles (PCM), the benefit was to a great extent modulated by the relative location of the primary tumor, the inferior PCM being better spared in OCC/OPC and the superior PCM being better spared in LAC/HPC. For the thyroid gland, the median ΔDmean values were significant in all subgroups, ranging from 22.4 to 48.9 Gy (Table 4).

NTCP, toxicity, and QoL

The median NTCP values for the IG and LS plans, as well as the median ΔNTCP values, were calculated according to the validated models previously described. According to the NTCP model for xerostomia,[23] 4 patients presenting moderate-to-severe xerostomia at baseline were excluded from this analysis. Statistically significant ΔNTCP values were observed for xerostomia, dysphagia, and hypothyroidism in favor of LS plans, except for xerostomia in patients with OCC/OPC with bilateral lymphatic drainage (Table 5). For the QoL analysis, 3 patients were excluded due to the absence of follow-up at 6 months after EOT. Higher scores indicate more serious symptoms. Although not significant, we observed relevant (>10-points) differences between the mean results of patient-reported xerostomia and dysphagia as well as a trend toward fewer physician-reported grade 2 events in patients with OCC/OPC with unilateral lymphatic drainage compared with those with bilateral drainage. The QoL and RTOG scores for xerostomia and dysphagia in LAC/HPC patients are particularly good, whatever the drainage pattern (Table 6).

Discussion

SLN mapping is intended to identify the first echelon node(s) preferentially draining the lymph flow coming from the tumor and its direct surroundings. When no SLN biopsy is performed, SPECT/CT imaging helps to identify and locate the nodes with the highest probability of harboring malignant cells. In this prospective phase 2 study, we assessed the potential benefit of using SPECT/CT-based SLN mapping to individually tailor the ENI volume in patients with nonoperated cN0 HNSCC eligible for definitive (chemo-)radiation therapy.

The 2-year cumulative incidence of regional recurrences was 9.5%. Only 1 patient experienced a nodal relapse outside of the PTVn-LS, representing a 2-year rate of regional relapse outside of the PTVn-LS of 2.3%, far below the ≤15% prespecified rate.

In all LS plans, we observed a highly statistically significant reduction of the ENI volumes compared with IG

Table 3 Number of drained neck levels based on SLN identification by SPECT/CT

Unilateral lymph drainage on SPECT/CT (n = 21)		Bilateral lymph drainage on SPECT/CT (n = 23)		
Oral cavity and oropharyngeal carcinoma (n = 6)	n	*Oral cavity and oropharyngeal carcinoma (n = 10)*	Ipsilateral, n	Contralateral, n
Level Ib	1	Level Ib	0	0
Level II	6	Level II	10	9
Level III	3	Level III	1	1
Level IV	1	Level IV	0	0
Level V	0	Level V	0	0
Level VI	0	Level VI	0	0
Level VIIa	0	Level VIIa	2	0
Level VIIb	0	Level VIIb	0	2
Hypopharyngeal and laryngeal carcinoma (n = 15)		*Hypopharyngeal and laryngeal carcinoma (n = 13)*		
Level Ib	0	Level Ib	0	0
Level II	12	Level II	7	7
Level III	13	Level III	11	9
Level IV	5	Level IV	3	0
Level V	0	Level V	0	0
Level VI	0	Level VI	3	0
Level VIIa	0	Level VIIa	0	0
Level VIIb	0	Level VIIb	0	0

Abbreviations: SLN = sentinel lymph node; SPECT/CT = single-photon emission computed tomography/computed tomography.

plans. We also observed that almost half of the patients presented only unilateral lymphatic drainage. This volume de-escalation based on SLN mapping presented several dosimetric benefits that, in turn, favorably affected the NTCP values for xerostomia, dysphagia, and hypothyroidism and, most importantly for the patient, severe late toxicity and QoL. Xerostomia and dysphagia remain the most frequently reported side effects after radiation therapy in HNSCC, even with the implementation of intensity modulated radiation therapy.[27-29] A meta-analysis suggested that severe xerostomia could be avoided if at least 1 parotid gland were spared to a Dmean $\leq$20 Gy or if the Dmean to both parotid glands were $\leq$25 Gy.[30] Dysphagia is mainly dependent on the Dmean to the PCM and the supraglottic larynx.[31] Moreover, a multivariate analysis identified bilateral lymph node irradiation as an important independent risk factor for swallowing dysfunction 6 months post-EOT.[32] In our study, in the case of unilateral irradiation, significant median ΔDmean around 15 Gy and 27 Gy was observed to the contralateral parotid and submandibular glands, respectively. A significant reduction of the Dmean to parotid glands was also observed in HPC/LAC with a bilateral lymphatic drainage, probably due to the preferential drainage in level III. We also observed a significant Dmean decrease in several swallowing structures, particularly in the case of unilateral lymphatic drainage, as already described in the literature.[32] These dosimetric advantages translated to QoL improvements given the observed NTCP gains and patient-reported outcomes in the EORTC H&N35 questions for xerostomia and dysphagia 6 months post-EOT.

Our results are in line with the study from Amsterdam that also demonstrated significant dose reductions to the same OARs and corresponding NTCP values in patients with lateralized T1-3 N0-2b HNSCC with limited or no contralateral lymphatic drainage on SPECT/CT.[33] However, their population had a greater proportion of patients with unilateral lymphatic drainage (80%) compared with the present one (48%).

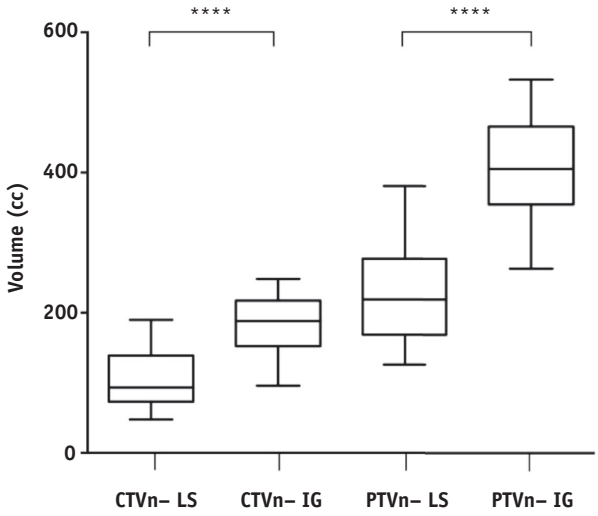

Fig. 1. Box plots of elective clinical (CTVn) and planning target volumes (PTVn) in cubic centimeters, delineated according to international guidelines (IG) or single-photon emission computerized tomography/computed tomography lymphoscintigraphy (LS). $****P \leq .05$.

Table 4 Comparative dosimetry of clinically significant OARs

OAR	IG plan Median D_{mean} (Gy)	LS plan Median D_{mean} (Gy)	Median ΔD_{mean} (Gy)	*P* value*
Unilateral lymphatic drainage on SPECT/CT (n = 21)				
Oral cavity and oropharyngeal carcinoma				
Parotid gland (ipsilateral)	28.5	29.8	−0.4	.69
Parotid gland (contralateral)	26.5	14.3	14.6	.03†
Submandibular gland (ipsilateral)	55.5	53.1	0.7	.56
Submandibular gland (contralateral)	47.1	20.3	26.2	.03†
Superior PCM	59.3	52.7	5.9	.03†
Middle PCM	44.0	32.9	7.1	.03†
Inferior PCM	41.8	18.8	23.1	.03†
Supraglottic larynx	31.1	20.3	14.1	.06
Thyroid gland	53.0	4.0	46.3	.03†
Hypopharyngeal and laryngeal carcinoma				
Parotid gland (ipsilateral)	18.9	16.0	1.9	.002†
Parotid gland (contralateral)	19.5	4.0	15.2	<.001†
Submandibular gland (ipsilateral)	39.2	36.5	3.4	.006†
Submandibular gland (contralateral)	41.6	11.9	28.1	<.001†
Superior PCM	36.0	20.9	17.5	<.001†
Middle PCM	49.1	42.5	3.4	.002†
Inferior PCM	58.6	57.3	0.9	.03†
Supraglottic larynx	66.2	65.3	0.5	.17
Thyroid gland	56.1	20.1	23.6	<.001†
Bilateral lymphatic drainage on SPECT/CT (n = 23)				
Oral cavity and oropharyngeal carcinoma				
Parotid gland (ipsilateral)	26.0	24.0	1.45	.04†
Parotid gland (contralateral)	23.0	22.8	0.55	.29
Submandibular gland (ipsilateral)	50.15	46.3	0.6	.02†
Submandibular gland (contralateral)	42.0	39.0	0.2	.25
Superior PCM	63.4	62.3	0.15	.08
Middle PCM	47.6	44.2	0.8	.42
Inferior PCM	43.9	19.0	24.4	.002†
Supraglottic larynx	36.7	27.7	4.2	.03†
Thyroid gland	53.3	2.1	48.9	.004†
Hypopharyngeal and laryngeal carcinoma				
Parotid gland (ipsilateral)	20.9	18.8	0.6	.03†
Parotid gland (contralateral)	20.1	18.3	0.7	.02†
Submandibular gland (ipsilateral)	38.8	35.6	1.6	.005†
Submandibular gland (contralateral)	38.5	32.0	1.7	.001†
Superior PCM	35.7	29.6	8.3	.003†
Middle PCM	55.0	54.2	0.6	.11
Inferior PCM	60.6	59.4	0.4	.18
Supraglottic larynx	66.7	65.9	0.05	.27
Thyroid gland	56.6	34.3	22.4	<.001†

Abbreviations: IG = International guidelines; LS = SPECT/CT lymphoscintigraphy; OAR = organ at risk; PCM = pharyngeal constrictor muscle; SPECT/CT = single-photon emission computed tomography/computed tomography.

* Wilcoxon signed rank test, 2-sided.

† $P \leq .05$.

Another potential benefit of using the SLN procedure is the identification of unexpected drainage patterns on an individual basis, outside of standard guidelines. In the current study, 7 patients (16%) showed unpredicted lymphatic drainages in the CTVn-LS compared with CTVn-IG, reducing the risk of nodal geographic miss, even if this is really low—around 1% of all patients with HNSCC treated in the intensity modulated radiation therapy era.[34] The reasons why nodal relapses are mostly never observed outside of treatment volumes are varied and mostly hypothetical. First, statistically, a roughly 20% to 40% risk of occult metastases multiplied by a 16% risk of unpredicted drainage returns a 3% to 6% risk of not covering these eventual metastases. Second, geographically, these nodes often lie in the vicinity of the primary tumor (eg, retropharyngeal nodes at a short distance of the

Table 5 Comparison of NTCP values

	IG plan	LS plan		
	Median NTCP, %	Median NTCP, %	Median ΔNTCP	*P* value*
Unilateral lymphatic drainage on SPECT/CT (n = 21)				
Oral cavity and oropharyngeal carcinoma				
Xerostomia	45.1	31.7	11.7	.03†
Dysphagia	20.0	6.3	10.8	.03†
Hypothyroidism	39.6	5.4	36.1	.03†
Hypopharyngeal and laryngeal carcinoma				
Xerostomia	36.5	22.3	13.7	<.001†
Dysphagia	15.9	7.2	8.9	<.001†
Hypothyroidism	20.6	3.3	14.0	<.001†
Bilateral lymphatic drainage on SPECT/CT (n = 23)				
Oral cavity and oropharyngeal carcinoma				
Xerostomia	40.7	40.8	0.6	.5
Dysphagia	20.1	16.0	1.9	.02†
Hypothyroidism	17.9	1.0	17.1	.004†
Hypopharyngeal and laryngeal carcinoma				
Xerostomia	37.7	36.6	0.3	.04†
Dysphagia	17.7	10.9	5.7	.007†
Hypothyroidism	53.1	23.8	27.1	<.001†

Abbreviations: IG = international guidelines; LS = SPECT/CT lymphoscintigraphy; NTCP = normal tissue complication probability; SPECT/CT = single-photon emission computed tomography/computed tomography.
* Wilcoxon signed rank test, 2-sided.
† $P \leq .05$.

soft palate tumor or level VI nodes next to a hypopharyngeal tumor) and may receive an incidental dose that would be sufficient to sterilize small tumor foci. Last, it is worth mentioning that concepts and recommendations do not always evolve as fast as knowledge (eg, selecting the retropharyngeal nodes for soft palate tumors is not recommended in the ENI selection guidelines,[10,12] though this drainage pattern is recognized[11] and may be integrated in local guidelines of experienced centers).

The present study also has limitations such as a relatively small sample size and a majority of early-stage diseases with a majority that did not require

Table 6 Scores of QLQ-H&N35 and RTOG for xerostomia and dysphagia

	Oral cavity/oropharyngeal cancers			Hypopharyngeal/laryngeal cancers		
	ULD (n = 6)	BLD (n = 8)	*P* value*	ULD (n = 13)	BLD (n = 14)	*P* value*
QLQ-H&N35 (mean [SD])						
Xerostomia	44.3 (45.6)	66.4 (31.0)	.3	21.3 (30.8)	22.9 (31.5)	.9
Dysphagia	13.7 (22.1)	31.0 (34.7)	.4	12.4 (19.4)	8.3 (21.2)	.2
Late toxicity (RTOG score) (%)						
Xerostomia			.1			.9
G0	33.3	0		71.4	69.3	
G1	50.0	50.0		28.6	30.7	
G2	16.7	50.0		0	0	
G3	0	0		0	0	
Dysphagia			.2			.9
G0	83.4	37.5		78.6	84.6	
G1	16.6	37.5		21.4	7.7	
G2	0	20.0		0	7.7	
G3	0	0		0	0	

Abbreviations: BLD = bilateral lymphatic drainage; G0 = grade 0; G1 = grade 1; G2 = grade 2; G3 = grade 3; QLQ-H&N35 = Quality-Of-Life Questionnaire Head and Neck module; RTOG = Radiation Therapy Oncology Group; SD = standard deviation; ULD = unilateral lymphatic drainage.
* Mann–Whitney U test.

concurrent chemotherapy. In addition, it was conducted at a single center with the help of surgeons having prior recognized expertise in SLN dissection in patients with HNSCC.

One of the most important limitations of the SLN technique is the risk of a false-negative result. This is well illustrated by the case of the patient showing a lymphatic drainage exclusively contralateral to the tumor. He relapsed shortly after the EOT in an anatomically logical level in the ipsilateral hemi-neck. In a multivariate analysis on patients with operated cT1-2 OCC with false-negative SLNs at pathologic analysis, 3 factors could predict positive non-SLNs: lymphovascular invasion, positive margins, and non-SLN extracapsular spread.[3] In the present case, it is hypothesized that the presence of a subclinical nodal metastasis obstructed the hilum of the node and that only the contralateral drainage was visualized. Another possibility could be that in large tumors (ie, cT3-4), deep drainage would not be mapped.[1,35] The small number of cT4 tumors (7%) precludes us from drawing any conclusion. The value of SLN in this subpopulation will require further investigations in surgically treated patients. In doubtful cases of SLNs detected only in the contralateral neck, we cautiously recommend considering the risk of aberrant lymphatic drainage and basing the selection of the CTVn on the IG.

It may also be possible to observe a false-positive issue due to a false-positive flow. This could happen in tumors close to midline for which a small difference in the technique or site of injection could induce a bilateral flow pattern instead of a unilateral one. Once again, this potential limitation strengthens the importance of using a standardized protocol performed by surgeons with expertise in the field of SLN biopsy.

Another potential limitation resides in the radioactive tracer used. Owing to its prolonged retention within the primary tumor, ^{99m}Tc-labeled human serum albumin colloid might induce a phenomenon of "shine-through phenomenon," referring to the primary tumor radioactivity that could obscure potential adjacent radioactive SLNs, as described with floor-of-mouth tumors.[1] This was also observed in the patient with LAC for whom no SLN was imaged on SPECT/CT but was subsequently detected with the collimated handheld gamma probe in the ipsilateral level III. This tracer also drains rapidly to second or third echelon nodes, increasing the risk of including more nodes than necessary.

A novel radiopharmaceutical agent, ^{99m}Tc-tilmanocept (TcTM), has recently been approved for SLN detection in OCC surgery.[36] TcTM presents several advantages such as a more rapid injection site clearance and a more prolonged retention within the SLN compared with nanocolloid.[37] Therefore, TcTM deserves further investigations in the frame of future studies.

The nodal volume de-escalation based on SLN identification represents a new field of research to de-intensify the current neck treatment with the goal of decreasing morbidity without compromising oncologic safety. ENI dose reduction is another way to de-escalate the treatment intensity. Currently, thanks to modern imaging, nodes to be treated electively are smaller than when the elective dose of 50 Gy (equivalent dose in 2-Gy fractions [EQD2Gy]) was empirically established. As a consequence, the required dose may be lower.[38] A recent multicenter randomized controlled trial assessed an elective dose of 40 Gy (EQD2Gy) compared with 50 Gy (EQD2Gy) and showed a significant reduction of salivary toxicity and a trend toward less dysphagia at 6 months post-EOT in the 40-Gy arm without statistically significant differences in survival and estimated nodal recurrence rates between the arms.[39,40] In a multicenter, phase 2 study about to open, we are going to explore both volume and dose de-escalation strategies to the contralateral ENI volume in HNSCC with ipsilateral positive neck. Because the sensitivity and specificity of the SLN technique are highly dependent on the surgeon's experience, only head and neck surgeons with extensive expertise will be allowed to participate in this multicenter study.

Conclusions

This phase 2 study on 44 patients with nonoperated cN0 demonstrates that individualized SPECT/CT-guided selection of prophylactic nodal radiation therapy volume is feasible and safe, with only 1 relapse outside of the PTV after a median follow-up of 46 months. It leads to ENI volume de-escalation and hence to a significantly reduced dose to the different OAR, which translates to a significant reduction in xerostomia, dysphagia, and hypothyroidism. However, extensive surgical expertise with the SLN technique remains of utmost importance, and caution is required in the case of illogical drainage. Although this SLN-mapping study is based on a relatively small sample size with a majority of early-stage tumors, it provides promising data for individual ENI volume selection that deserve further investigation in larger, multicenter trials.

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