SPECT/CT-guided elective nodal irradiation for head and neck cancer: Estimation of clinical benefits using NTCP models

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Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

SPECT/CT-guided elective nodal irradiation for head and neck cancer: Estimation of clinical benefits using NTCP models

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ARTICLE INFO

Article history:
Received 26 June 2018
Received in revised form 17 July 2018
Accepted 23 July 2018
Available online xxxx

Keywords:
Head and neck cancer
Radiotherapy
Elective nodal irradiation
Lymph drainage mapping
SPECT/CT
NTCP models

ABSTRACT

Background and purpose: The great majority of patients with lateralized head and neck squamous cell carcinoma (HNSCC) treated with radiotherapy routinely undergo bilateral elective nodal irradiation (ENI), even though the incidence of contralateral regional failure after unilateral ENI is low. Excluding the contralateral neck from elective irradiation could reduce radiation-related toxicity and improve quality-of-life. The current study investigated the dosimetric benefits of a novel approach using lymph drainage mapping by SPECT/CT to select patients for unilateral ENI.

Patients and methods: Forty patients with lateralized cT1-3N0-2bM0 HNSCC underwent lymph drainage mapping. Two radiation plans were made; the real plan with which patients were actually treated (selective SPECT/CT-guided plan irradiating the ipsilateral neck ± any contralateral draining level); and the virtual plan (standard plan according to institutional guidelines, as if the same patient would have been treated bilaterally). Radiation doses to clinically important organs-at-risk were compared between the two plans. We used five normal tissue complication probability (NTCP) models to predict the clinical benefits of this approach.

Results: Median dose reductions to the contralateral parotid gland, contralateral submandibular gland, glottic larynx, supraglottic larynx, constrictor muscle and thyroid gland were 19.2, 27.3, 11.4, 9.7, 12.1 and 18.4 Gy, respectively. Median NTCP reductions for xerostomia, contralateral parotid function, dysphagia, hypothyroidism and laryngeal edema were 20%, 14%, 10%, 20% and 5% respectively.

Conclusions: Selective SPECT/CT-guided ENI results in significant dose reductions to various organs-at-risk and corresponding NTCP values, and will subsequently reduce the incidence and severity of different troublesome radiation-related toxicities and improve quality-of-life.

Because of the rich lymphatic network in the head and neck region, there is a long-standing convention to electively irradiate the great majority of patients with head and neck squamous cell carcinoma (HNSCC) to both sides of the neck in order to reduce the risk of contralateral regional failure (cRF). For example, of 620 patients with HNSCC treated at our institution with (chemo) radiotherapy between 2009 and 2016 who had an indication for elective nodal irradiation (ENI), only 43 patients (7%) were treated to one side of the neck (data not published). However, there is increasing evidence that the incidence of cRF in lateralized HNSCC is <10%, both in studies where unilateral ENI was applied [1] and in those where a neck dissection was preceded by sentinel node procedure [2–5].

Bilateral ENI, as compared to unilateral ENI, is associated with higher incidence of acute and late radiation-induced toxicity with subsequent deterioration of quality-of-life (QoL) [6–11]. One way to reduce the incidence, duration and severity of these toxicities is by implementation of unilateral ENI, in patients where this can be justified. To this end, we initiated the SUSPECT study in our institution (ClinicalTrials.gov Identifier NCT02572661). The goal was to evaluate the safety and feasibility of unilateral ENI in patients with lateralized T1-3N0-2b HNSCC, as well as the impact of this approach on the incidence of cRF, toxicity, and QoL. All

Abbreviations: cRF, contralateral regional failure; ENI, elective nodal irradiation; HNSCC, head and neck squamous cell carcinoma; HPC, hypopharyngeal cancer; LC, laryngeal cancer; OCC, oral cavity cancer; OPC, oropharyngeal cancer; QoL, quality of life; SSG, selective SPECT/CT-guided.

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https://doi.org/10.1016/j.radonc.2018.07.023
0167-8140/

patients underwent lymph drainage mapping using SPECT/CT scans [12].

An explorative end point of the study is to investigate the impact of unilateral ENI on the radiation dose delivered to different organs-at-risk (OARs) in the neighborhood of the irradiated tumor. According to the study protocol, two radiation plans were made for the first 40 patients of the study; the real plan, with which patients are treated and which was guided by the findings of the SPECT/CT; and the standard bilateral plan, which was done according to institutional guidelines as if the same patient would have been treated to both sides of the neck outside the framework of the study. The purpose of the current study is to compare dose-volume parameters of both plans, and subsequently predict the difference in radiation-induced toxicities by using five normal tissue complication probability (NTCP) models.

Materials & methods

The study protocol obtained approval by the local Ethics Committee (NL15706.031.14) and patients were included after they had given written informed consent. Patients with primary HNSCC (T1-3N0-2bM0) located in the oral cavity, oropharynx, larynx (except T1 glottic), and hypopharynx, not crossing the midline and planned for treatment with (chemo)radiotherapy in curative setting were eligible. Patients with extra-capsular extension and those with N2b disease with more than 3 involved lymph nodes were excluded.

Between July 2015 and October 2017, 61 patients were included. The first 40 patients are the subjects of the current study. All patients underwent lymph drainage mapping and for all patients, a real plan and a virtual plan were generated for the dosimetric comparisons. The real plan is a selective SPECT/CT-guided (SSG) irradiation plan which was used to treat the neck. Patients with unilateral drainage were selected for unilateral ENI, while patients demonstrating contralateral drainage (to one draining area at most) were additionally irradiated to the involved level. This plan will further be denoted as 'SSG plan'. The virtual plan is the 'standard' bilateral irradiation plan which was made according to institutional guidelines, as if the same patient would have been treated outside the framework of the current study to both sides of the neck. This plan will further be denoted as 'bilateral plan'.

Selective SPECT/CT-guided and bilateral treatment plans

In both plans the primary tumor and, if present, the ipsilateral nodal metastases, were delineated identically according to clinical protocol. Two different Clinical Target Volumes (CTVs) were delineated for the elective nodal irradiation fields.

The CTV of the SSG plan consisted of the ipsilateral level II–IV in case of node-negative disease and level I–V in case of node-positive disease. In patients with only ipsilateral lymph drainage on SPECT/CT, the contralateral neck levels were not included in the CTV. In case of contralateral lymph drainage (to one draining area at most), the CTV included only the contralateral neck level containing tracer accumulation.

The CTV of the bilateral plan was based on internationally accepted guidelines [13] and represents the conventional ENI treatment as used in our institution. It consisted of the ipsilateral level II–IV in case of node-negative disease and level I-V in case of node-positive disease. Contralateral levels II–IV were always included in the CTV for the bilateral plan.

For both plans, a 3 mm isotropic margin was added to each CTV to generate the Planning Target Volume (PTV) for the ENI.

The OARs were delineated according to institutional guidelines and included the spinal cord, brainstem, cochlea, parotid glands, submandibular glands, thyroid gland, swallowing muscles, oral cavity, and the larynx [14]. Planning was performed with Pinnacle 9.10 (Philips Radiation Oncology Systems, Fitchburg, WI, USA). Treatment plan consisted of a dual volumetric modulated arc radiotherapy technique with a simultaneous integrated boost, according to the standard institutional protocol. The primary tumor received 70 Gy in 35 fractions of 2.0 Gy, 6 fractions per week in case of radiotherapy alone and 5 fractions per week in case of chemoradiation. The elective radiation dose consists of 54.25 Gy in 35 fractions of 1.55 Gy.

Mean irradiation dose (D_{mean}) to both parotid glands, both submandibular glands, constrictor muscles, the glottic and supraglottic larynx and the thyroid gland were recorded for both plans (physical dose).

Normal tissue complication probability models

The following NTCP models were chosen to predict the difference in toxicity:

- Beetz et al. [15] for *xerostomia*, predicting patient-reported moderate-to-severe xerostomia (EORTC QLQ-H&N35 questionnaire) at 6 months after treatment.
- Dijkema et al. [16] for *parotid function*, predicting stimulated individual parotid gland flow at 1 year after treatment of <25% compared to pretreatment flow.

Table 1
Patient demographics ($n = 40$).

	N	%
Age: range (median) in years	39–81 (62)	
Gender		
Male	34	85
Female	6	15
Tumor site		
Oropharynx	28	70
Oral cavity	2	5
Larynx	7	18
Hypopharynx	3	7
T-stage		
T1	7	18
T2	25	62
T3	8	20
N-stage		
N0	14	35
N1	10	25
N2a	1	3
N2b	15	38
AJCC-stage (7th edition)		
I	2	5
II	10	25
III	12	30
IVA	16	40
HPV status in oropharyngeal cancer ($n = 28$)		
HPV-positive	14	50
HPV-negative	14	50
Results of lymph drainage mapping		
Contralateral draining areas on SPECT/CT	8	20
Level I	0	0
Level II	4	10
Level III	2	5
Level IV	2	5
Level V	0	0
Follow-up: range (median) in months	3–32 (21)	

Abbreviations: AJCC-stage: American Joint Committee on Cancer; HPV: human papilloma virus; SPECT/CT: single photon emission computed tomography/computed tomography.

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- Christianen et al. [17] for *dysphagia*, predicting physician-rated swallowing dysfunction (≥grade 2) at 6 months after treatment.
- Boomsma et al. [18] for *hypothyroidism*, predicting elevated TSH values (>4 mIU/L) either in combination with a reduced [<11 pmol/L] or normal free T4, within 2 years after treatment.
- Rancati et al. [19] for *laryngeal edema*, predicting physician-rated laryngeal edema (≥grade 2) within 15 months from treatment.

The models of Beetz, Dijkema and Christianen were chosen because these models are used in a model-based selection tool for proton therapy [20,21], as part of a national indication protocol for proton therapy in the Netherlands. For this protocol, studies were appraised using TRIPOD criteria [22] and ranked by level of evidence in order to choose those most appropriate.

Per patient, NTCP-values were calculated for both plans, and ΔNTCP was defined as NTCP[SSG] minus NTCP[bilateral].

Statistical analysis

Data were analyzed using SPSS (SPSS Statistics for Windows, version 22; IBM Corporation, Armonk, NY, USA). Wilcoxon signed rank test was used to analyze the differences in radiation doses and NTCP values between the plans. Mann–Whitney–U test was used to analyze the differences in ΔD_{mean} and ΔNTCP between subgroups of patients. All reported p-values are from two-sided tests, at a significance level of $\alpha = 0.05$.

Results

Patient demographics are shown in Table 1. Thirty-two patients had only ipsilateral lymph drainage and were electively treated to the ipsilateral neck only. Eight patients had contralateral drainage on SPECT/CT in one level, and thus were electively treated to the ipsilateral neck and the contralateral neck level containing the tracer accumulation. Supplementary Fig. 1 shows the dose distribution of two plans: the SSG plan and the classic bilateral plan.

Radiotherapy doses to organs at risk

Table 2 shows the median D_{mean} to OAR for the bilateral and SSG plans. The differences between the two plans in terms of D_{mean} to OAR were statistically significant for all structures. For the large majority of patients and organs a considerable dose reduction could be achieved. Fig. 1 visualizes, for individual patients, the irradiation doses to OAR for both plans. For several OARs, significantly larger dose reductions were found in patients that had only ipsilateral lymph drainage ($n = 32$) than in the group that also had contralateral drainage in one level, and thus also received irradiation to the relevant contralateral neck level (contralateral submandibular gland [$p < 0.001$]; glottic larynx [$p < 0.001$] and supraglottic larynx [$p < 0.001$], constrictor muscles [$p < 0.001$] and thyroid gland [$p = 0.043$]). Similarly, in patients with oral cavity cancer (OCC) or oropharyngeal cancer (OPC), the dose reductions to the glottic larynx, supraglottic larynx and thyroid gland were significantly larger ($p < 0.001$, $p < 0.001$ and $p = 0.012$, respectively) than those found in patients with laryngeal cancer (LC) or hypopharyngeal cancer (HPC).

Normal tissue complication probability – plan comparison

Five patients had moderate-to-severe xerostomia at baseline and were excluded from analysis with the Beetz et al. NTCP model (but included in all other NTCP analyses). A summary of the median NTCP values for the bilateral and SSG plan, and the difference between the plans, is shown in Table 3. Fig. 2 visualizes, for individual patients, the NTCP values per toxicity category. Fig. 3 visualizes the spread of the ΔNTCP values. For dysphagia, hypothyroidism and laryngeal edema, significantly larger NTCP reductions were found in the group than had only ipsilateral lymph drainage,

Table 2
Comparison of dose distribution parameters.

	Bilateral plan		Selective SPECT/CT-guided plan		*p*-Value*	Median ΔD_{mean} (Gy)
Structure	Median D_{mean} (Gy)	Range	Median D_{mean} (Gy)	Range		
All patients (n = 40)						
Parotid glands	26.8	13.6–37.6	17.9	6.3–30.3	*<0.001*	−7.7
Parotid gland (contralateral)	23.3	11.1–37.0	3.3	1.2–21.7	*<0.001*	−19.2
Submandibular glands	53.2	37.1–60.2	39.8	29.5–59.2	*<0.001*	−13.4
Submandibular gland (contralateral)	43.7	35.5–55.4	18.4	4.0–49.7	*<0.001*	−27.3
Larynx (glottic)	45.2	33.3–69.7	32.2	18.7–69.5	*<0.001*	−11.4
Larynx (supraglottic)	46.7	33.9–70.0	36.4	18.6–69.7	*<0.001*	−9.7
Constrictor muscle	50.9	40.4–61.0	37.7	24.0–60.7	*<0.001*	−12.1
Thyroid gland	48.3	19.9–61.6	29.5	8.2–61.9	*<0.001*	−18.4
Only ipsilateral lymph drainage on SPECT/CT (n = 32)						
Parotid glands	27.0	13.6–37.6	17.7	6.3–26.8	*<0.001*	−8.2
Parotid gland (contralateral)	24.3	11.1–37.0	3.1	1.2–9.0	*<0.001*	−20.0
Submandibular glands	52.8	37.1–60.2	38.8	29.5–48.1	*<0.001*	−14.4
Submandibular gland (contralateral)	43.1	35.5–51.1	15.3	4.0–34.1	*<0.001*	−29.0
Larynx (glottic)	45.2	33.3–69.7	29.7	18.7–69.5	*<0.001*	−13.0
Larynx (supraglottic)	46.3	35.1–70.0	35.0	18.6–69.7	*<0.001*	−10.8
Constrictor muscle	50.8	40.4–60.9	36.4	24.0–54.1	*<0.001*	−13.7
Thyroid gland	48.7	43.2–54.5	28.8	20.7–52.4	*<0.001*	−18.9
Oral cavity and oropharyngeal carcinoma (n = 30)						
Parotid glands	27.8	14.6–37.6	20.6	8.3–30.3	*<0.001*	−7.7
Parotid gland (contralateral)	24.1	11.1–34.5	3.8	1.7–21.7	*<0.001*	−19.8
Submandibular glands	55.0	47.6–60.2	40.4	32.2–59.2	*<0.001*	−14.4
Submandibular gland (contralateral)	44.6	35.9–55.4	16.9	4.0–49.7	*<0.001*	−28.7
Larynx (glottic)	41.5	33.3–62.7	28.4	18.7–56.3	*<0.001*	−13.5
Larynx (supraglottic)	44.4	33.9–65.4	33.9	18.6–66.6	*<0.001*	−11.5
Constrictor muscle	49.7	40.4–61.0	35.9	24.0–60.4	*<0.001*	−13.5
Thyroid gland	47.7	19.9–53.2	27.3	8.2–42.3	*<0.001*	−19.0

Abbreviations: SPECT/CT: single photon emission computed tomography/computed tomography.
* Wilcoxon signed rank test, two-sided.

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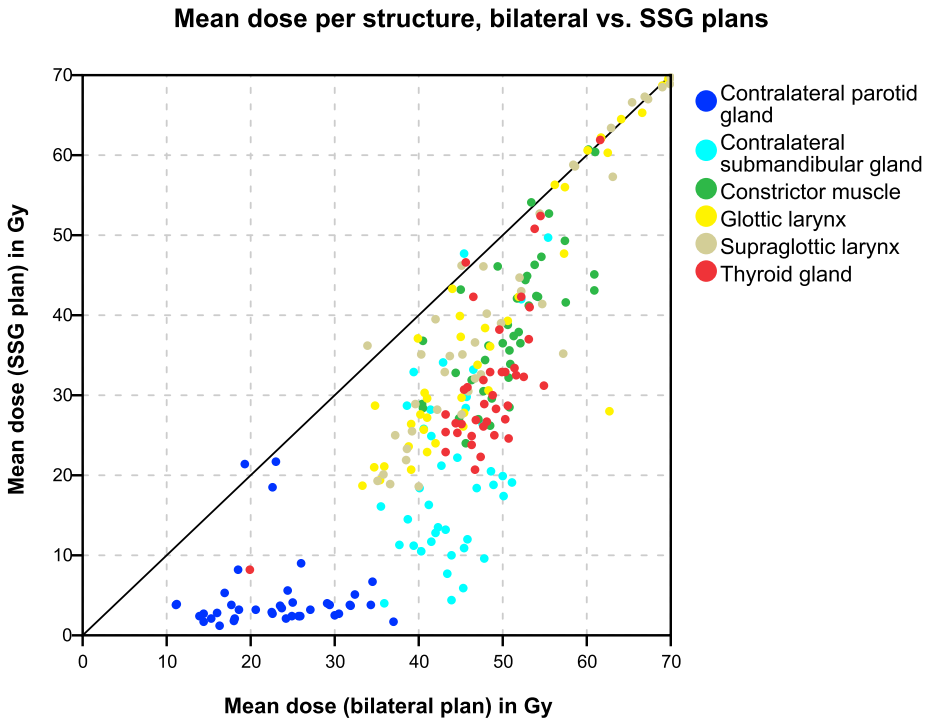

Fig. 1. D_{mean} in Gy to organs at risk (OARs), for individual patients. Per OAR, every colored dot represents one patient. The D_{mean} of the bilateral plan is represented on the X-axis, the D_{mean} of the SSG plan on the Y-axis. Thus, the ΔD_{mean} can be read as the vertical distance between the reference line ($y = x$) and the colored dot.

Table 3
Comparison of median NTCP values (%).

	Bilateral plan	SSG plan	p-value*	Median ΔNTCP
Xerostomia (patient reported)				
All patients	43.3	22.0	<0.001	−19.7
Only ipsilateral lymph drainage**	43.7	22.1	<0.001	−21.4
Limited contralateral lymph drainage***	41.6	22.0	0.043	−16.6
OPC and OCC	48.1	23.1	<0.001	−22.5
HPC and LC	35.3	21.0	0.012	−14.4
Parotid function (contralateral)				
All patients	14.5	1.0	<0.001	−13.5
Only ipsilateral lymph drainage	16.5	1.0	<0.001	−15.0
Limited contralateral lymph drainage	14.0	1.0	0.025	−8.5
OPC and OCC	16.5	1.0	<0.001	−15.0
HPC and LC	10.0	1.0	0.005	−9.0
Dysphagia				
All patients	18.1	6.8	<0.001	−10.2
Only ipsilateral lymph drainage	17.7	6.2	<0.001	−10.5
Limited contralateral lymph drainage	32.7	23.8	0.050	−1.9
OPC and OCC	16.5	5.7	<0.001	−10.2
HPC and LC	38.9	27.7	0.013	−10.0
Hypothyroidism				
All patients	44.4	20.2	<0.001	−20.3
Only ipsilateral lymph drainage	46.8	21.3	<0.001	−23.5
Limited contralateral lymph drainage	35.1	19.9	0.036	−4.5
OPC and OCC	44.6	19.0	<0.001	−22.4
HPC and LC	44.4	26.2	0.013	−10.2
Laryngeal edema				
All patients	24.0	7.0	<0.001	−4.5
Only ipsilateral lymph drainage	24.0	1.0	<0.001	−6.5
Limited contralateral lymph drainage	56.0	53.0	0.167	−1.0
OPC and OCC	10	1.0	<0.001	−7.5
HPC and LC	97.5	97.0	0.276	0.0

Abbreviations: NTCP: normal tissue complication probability; SSG: selective SPECT/CT-guided; OPC: oropharyngeal carcinoma; OCC: oral cavity carcinoma; HPC: hypopharyngeal carcinoma; LC: laryngeal carcinoma.
* Wilcoxon signed rank test, two-sided.
** These patients had lymphatic drainage only to the ipsilateral neck ($n = 32$).
*** These patients had also contralateral lymphatic drainage, limited to one neck level ($n = 8$).

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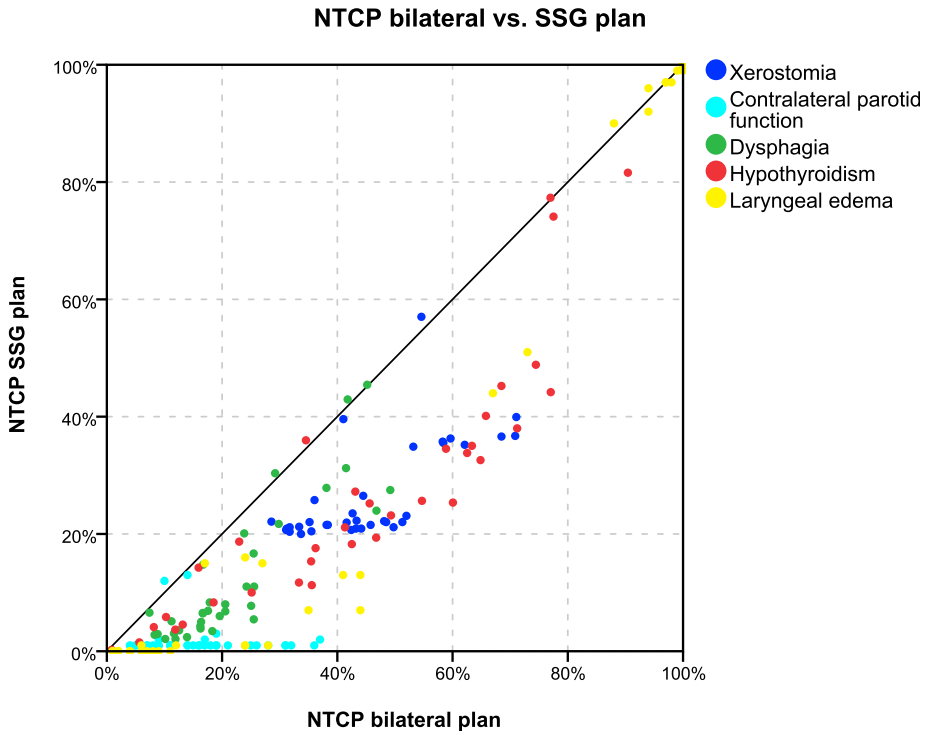

Fig. 2. NTCP values, for individual patients, per toxicity category. Per toxicity, every colored dot represents one patient. The NTCP-value of the bilateral plan is represented on the *X*-axis, the NTCP-value of the SSG plan on the *Y*-axis. The ΔNTCP for an individual patient can be read as the vertical distance between the reference line ($y = x$) and the colored dot. A moderate-to-large xerostomia NTCP reduction for all but two patients is visible. For dysphagia, a moderate NTCP reduction is visible for all but three patients. For hypothyroidism a large NTCP reduction is visible for most patients. For laryngeal edema, two distinct groups can be identified: the LC and HPC patients, all with NTCP values >90% for both plans, and the OPC and OCC patients for whom the SSG plan constitutes a moderate-to-large NTCP reduction as compared to the bilateral plan.

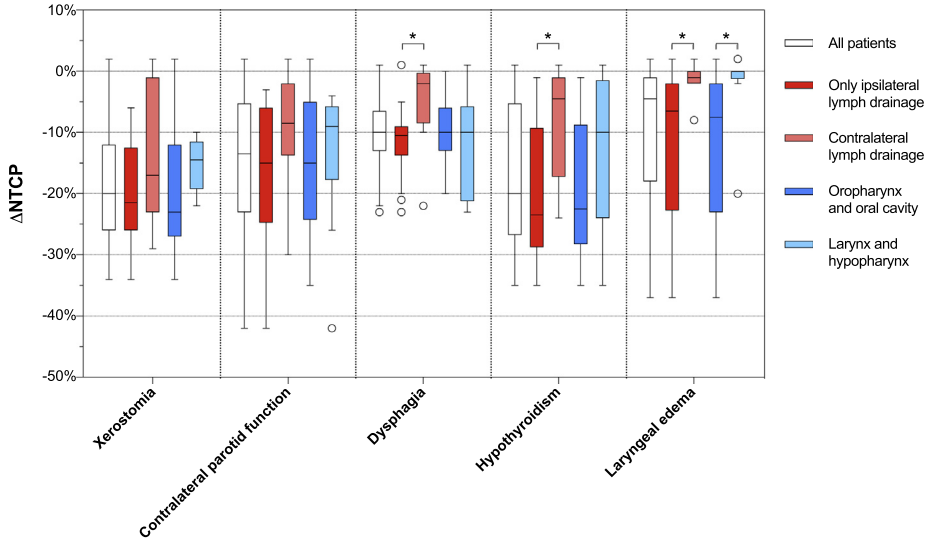

Fig. 3. Boxplot of ΔNTCP values per toxicity. Results shown for all patients (white); stratified by SPECT/CT result, thus comparing 'pure' unilateral ENI vs. selective bilateral ENI (shades of red); and stratified by primary tumor site (shades of blue). Significant differences are indicated with an asterisk. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

than in the group that also had contralateral lymph drainage ($p = 0.010$, $p = 0.009$ and $p = 0.009$, respectively). For laryngeal edema, a similar NTCP reduction in favor of OPC/OCC patients was found, compared to LC/HPC patients ($p < 0.001$).

Discussion

The current study investigated the potential dosimetric benefits which might be obtained by the implementation of selective SPECT/CT-guided ENI in patients with lateralized T1-3N0-2b HNSCC with limited or no contralateral lymph drainage seen at lymph drainage mapping using SPECT/CT. Significant reductions of the mean radiation dose were achieved to different OARs (salivary glands, swallowing muscles, larynx, supraglottic region, and thyroid gland). Using NTCP models [15–19], moderate to large NTCP reductions were seen for all toxicities. As expected, the largest NTCP reductions were seen in patients treated only to the ipsilateral neck ($n = 32$), compared to those who had limited

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contralateral drainage to one neck level and were also treated to that level ($n = 8$). Similarly, the largest NTCP reduction for laryngeal edema and hypothyroidism was seen in patients with OPC and OCC, compared to HPC and LC (Table 3), simply because the structures involved belong to the high-risk volume in case of LC or HPC.

Because considerable gains have been achieved over the last few decades with regard to loco-regional control and overall survival in patients with HNSCC, improving toxicity profiles and QoL after treatment become increasingly important. Not in the least because of the increasing incidence of HPV-related OPC among young patients [23], for whom the current treatment paradigm might be overtreatment and unnecessarily toxic.

Several studies investigated the dose–effect relationship for different types of toxicity after radiotherapy for HNSCC. In terms of salivary flow rate, steep dose–response relationships have been described, with the TD_{50} (the mean parotid gland dose with a 50% complication probability) for >75% flow rate reduction ranging from 28 Gy [24] to 38 Gy [25]. In the present study, the reduction of median contralateral parotid gland dose from 23.3 Gy to 3.3 Gy implies, for most patients, a leftward shift out of the steep part of the NTCP curve, preserving function of at least one parotid gland [16]. Using Beetz's model for patient-reported xerostomia, it means the fraction of patients with a D_{mean} to the contralateral parotid gland above the TD_{50} (approximately 30 Gy for patients with no xerostomia at baseline, and approximately 15 Gy for patients with mild xerostomia at baseline) decreases from 34% to 0%. The reduction of median NTCP for xerostomia from 43.3% to 22.0% would predict a clinically relevant improvement of QoL for a substantial proportion of patients treated within the framework of the current study. Furthermore, reduction of xerostomia will result in subjective improvements in radiation-related swallowing problems. Teguh et al. [26] reported on the significant correlation between dysphagia, xerostomia, and sticky saliva as important items of the EORTC H&N 35 QoL questionnaires.

While different dose–effect relationships have been described for various dysphagia-related end-points [27,28], the D_{mean} to the superior pharyngeal constrictor muscle and supraglottic larynx were the most important predictors for physician-rated swallowing dysfunction in the predictive model by Christianen et al. [17]. In their validation study, mean NCTPs of 27.5% ('standard' intensity modulated radiotherapy [IMRT] treatment plan) and 22.6% ('swallowing-sparing IMRT' plan, a further optimized treatment plan with additional constraints for OARs involved in the swallowing process) matched the actual prevalence of ≥grade 2 dysphagia at 6 months (27.9% and 22.6%) almost perfectly [29]. This suggests that the reduction of median NTCP achieved in the current study (from 18.1% to 6.8%) will translate into a clinically relevant reduction in ≥grade 2 dysphagia.

Boomsma et al. [18] found thyroid volume and D_{mean} to be the two most important predictors of hypothyroidism. The reduction of thyroid gland median D_{mean} from 48.3 to 29.5 Gy in our group will mean a leftward shift on the steepest part of the NTCP curve for most patients, as 75% of them had a thyroid volume of <20 cc. This translates into a ΔNTCP of −24.2%. Moreover, the proportion of patients with a D_{mean} above the dose constraint for 25% risk of hypothyroidism, according to the model developed by Rønjom et al. [30], was 72% for the bilateral plan and 32% for the SSG plan.

To minimize the risk of ≥grade 2 laryngeal edema, Sanguineti et al. [31] advocated to keep the D_{mean} to the larynx below 43.5 Gy. In the current study, the D_{mean} to the larynx was kept under this threshold in 73% of the SSG plans and in 40% of the bilateral plans. Using the NTCP model of Rancati et al. [19], a reduction of median NTCP from 24.0% to 7.0% is achieved in our patient population. While laryngeal edema is regarded as an early morphological change that may be correlated with a late effect like swallowing problems [32], we found a marked difference between the laryngeal edema ΔNCTP for HPC and LC patients (−0.5%, compared to −17.0% for the whole group) and the dysphagia ΔNCTP (−11.2%, compared to −11.3% for the whole group).

A limitation of the study is the lack of external validation for four of the five NTCP models, three of which (Boomsma, Rancati and Dijkema) include a considerable proportion (11–67%) of patients treated with 3D-conformal radiotherapy (3D-CRT). The model of Christianen was validated with good model performance, but Beetz's model was expressly developed in an IMRT cohort because a previous 3D-CRT-based model performed significantly worse with IMRT-treated patients. However, we don't believe that a possible suboptimal model performance will influence the clinical validity of our results.

In conclusion, selective SPECT/CT-guided ENI seems promising, as significant reductions can be achieved in the mean radiation dose to different OARs. According to the used NCTP models, this is likely to result in significant reductions in the incidence and severity of different troublesome radiation-related toxicities such as xerostomia, dysphagia, laryngeal edema, and hypothyroidism, with subsequent improvement of the QoL of these patients. The clinical impact of selective SPECT/CT-guided ENI on tumor control and toxicity will be assessed in ongoing studies.

Conflicts of interest

The authors declare that they have no conflict of interest.

Funding

This research was partially funded by a *Top Consortium Knowledge and Innovation of the sector Life Sciences & Health* (LSH-TKI Foundation) public–private partnership grant (LSHM15036) in collaboration with Elekta (SE). The funding source had no involvement in study design; collection, analysis and interpretation of data; writing of the report; or decision to submit the article for publication

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2018.07.023.

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