SPECT/CT-guided elective nodal irradiation for head and neck cancer is oncologically safe and less toxic: a potentially practice-changing approach

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Original Article

SPECT/CT-guided elective nodal irradiation for head and neck cancer is oncologically safe and less toxic: A potentially practice-changing approach

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ABSTRACT

Background and purpose: Bilateral elective nodal irradiation (ENI) remains the standard treatment for head and neck squamous cell carcinoma (HNSCC). Unilateral ENI could reduce treatment toxicity and improve health-related quality-of-life (HRQOL). This prospective proof-of-principle trial (NCT02572661) investigated the feasibility, safety and clinical benefits of SPECT/CT-guided ENI of the node-negative contralateral neck.

Materials and methods: Patients with lateralized T1-3N0-2bM0 HNSCC of the oropharynx, oral cavity, larynx and hypopharynx underwent SPECT/CT after peritumoral ^{99m}Tc-nanocolloid injection. Patients without contralateral lymph drainage received ipsilateral ENI only. If lymph drainage to only one contralateral hot spot was visible, ENI to the contralateral neck would be limited to only the level containing the hot spot. The primary endpoint was the incidence of contralateral regional failure (CRF) at 2 years. Toxicity and HRQOL were compared with a 1:1 matched historical cohort that received standard bilateral ENI (B-ENI) with identical planning and treatment techniques.

Results: Fifty patients were treated with SPECT/CT-guided ENI. After a median follow-up of 33 months (range 18–45), CRF was observed in one patient (2%; 95% confidence interval: 0–6%). Compared to the matched B-ENI group, patients treated with SPECT/CT-guided ENI had significantly lower incidences of grade $\geq$2 dysphagia (54% vs. 82%; $p < 0.001$), tube feeding (10% vs. 50%; $p < 0.001$) and late grade $\geq$2 xerostomia (9% vs. 54%; $p < 0.001$). Significant and clinically relevant HRQOL benefits of SPECT/CT-guided ENI were observed on the EORTC QLQ-C30 summary score, and QLQ-HN35 swallowing and dry mouth subscales.

Conclusion: SPECT/CT-guided ENI is associated with a low risk of contralateral regional failure. Compared to B-ENI, SPECT/CT-guided ENI significantly reduces dysphagia, feeding tube placement, and late xerostomia and improves HRQOL.

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The head and neck area has a rich lymphatic supply, and bilateral lymphatic drainage is thought to be common. Therefore, the great majority of patients with head and neck squamous cell carcinoma (HNSCC) receive bilateral elective nodal irradiation (ENI) as a standard part of radiotherapy treatment. Nonetheless, there is increasing evidence suggesting that the incidence of contralateral

Abbreviations: B-ENI, bilateral elective nodal irradiation; CRF, contralateral regional failure; CTCAE, Common Terminology Criteria for Adverse Events; DM, distant metastasis; ENI, elective nodal irradiation; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality-of-Life-Questionnaire; ES, effect size; EUA, endoscopy under anesthesia; HNSCC, head and neck squamous cell carcinoma; HRQOL, health-related quality of life; IMRT, intensity modulated radiotherapy; LDM, lymph drainage mapping; LF, local failure; ND, neck dissection; OS, overall survival; RF, regional failure; SG-ENI, SPECT/CT-guided elective nodal irradiation; SNP, sentinel node procedure; SPECT/CT, single-photon emission computed tomography/computed tomography; US-FNAC, ultrasound-fine needle aspiration cytology.

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regional failure (CRF) after unilateral ENI for HNSCC is very low [1]. Compared to bilateral ENI, unilateral ENI is associated with significantly less acute and late radiation-related toxicity and better health-related quality-of-life (HRQOL) [2–4]. Unilateral ENI thus seems to be an attractive way to de-escalate radiation treatment, and improve the therapeutic ratio.

We hypothesized that HNSCC patients with a lateralized tumor and no lymphatic flow to the node-negative contralateral neck would have a negligible risk of CRF after unilateral treatment. The SUSPECT study, a one-armed prospective proof-of-principle trial, investigated the feasibility, safety and clinical benefits of an image-guided approach, in which lymph drainage mapping (LDM) using single-photon emission computed tomography/computed tomography (SPECT/CT) guided the ENI of the contralateral neck. We present the oncologic outcome, acute and late toxicity, and HRQOL results.

Materials and methods

In 2015, we initiated the SUSPECT trial (ClinicalTrials.gov Identifier NCT02572661) in the Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital for patients with T1-3N0-2bM0 HNSCC of the oropharynx, oral cavity, larynx (with exception of T1) or hypopharynx (American Joint Committee on Cancer Staging Manual, 7th edition) planned for primary (chemo)radiotherapy. Eligible patients had a primary tumor not crossing the midline, N0-2b disease with $\leq$3 clinically involved lymph nodes, and no extracapsular extension. Exclusion criteria included previous head and neck radiotherapy, previous neck dissection (ND), other previous or current head and neck malignancies, or a history of cancer elsewhere (excluding basal cell carcinoma of the skin and in situ carcinoma of the cervix).

Work-up

The work-up included MRI scan for cancers of the oral cavity and oropharynx and CT scan for cancers of the larynx and hypopharynx, ultrasonography with fine needle aspiration cytology (US-FNAC) performed by a dedicated head and neck radiologist, endoscopy under anesthesia (EUA) and FDG-PET. On the day of the EUA, LDM using SPECT/CT was performed. Details of this procedure have been described previously [5]. Briefly, radiolabeled ^{99m}Tc-nanocolloid was injected during the EUA at 4 locations around the primary tumor at 3 mm distance from macroscopic tumor edges, and at a 5th location deep in the center of the tumor. Planar lymphoscintigraphic images and SPECT/CT of the neck were acquired 4 ± 1 h after administration using a dual-head SPECT/CT gamma camera (Symbia T, Siemens, Erlangen, Germany). The images were assessed for lymph drainage to both sides of the neck, and hotspots of tracer accumulation on SPECT/CT were denoted as draining neck nodes.

Treatment of the neck

Based on the LDM procedure, SPECT/CT-guided ENI (SG-ENI) was applied. Details of treatment have been described previously [6]. In brief, for patients with only ipsilateral lymph drainage on SPECT/CT, the ENI field included only the ipsilateral neck (levels delineated according to international guidelines [7]), thus excluding the contralateral neck. In case of contralateral lymph drainage to one draining area, only the contralateral neck level containing tracer accumulation was added to the ENI field. In case of $\geq$2 contralateral draining areas, patients underwent standard bilateral ENI (B-ENI) [7].

Radiotherapy planning

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. Gross tumor received 70 Gy in 35 fractions of 2 Gy, 6 fractions per week in case of radiotherapy alone and 5 fractions per week in case of concomitant chemoradiotherapy, old age (generally >70 years) or frailty. Elective irradiation fields received 54.25 Gy in 35 fractions of 1.55 Gy.

Response evaluation and follow-up visits

Tumor response evaluation, 12 weeks after end of treatment, consisted of physical examination of the neck and primary tumor site, including upper aerodigestive tract fibroscopy; US-FNAC; MRI scan or contrast-enhanced CT scan; an additional FDG-PET and EUA in case of any doubt about complete response at the primary tumor site or the neck. Standard oncologic follow-up visits were scheduled every 2–3 months during the first year, every 3–4 months during the second year, every 4 months during the third year and twice annually until 5 years of follow-up.

Toxicity and quality of life assessment

Treatment-related toxicity was graded weekly during treatment, and at each follow-up visit, by the treating radiation oncologist using Common Terminology Criteria for Adverse Events (CTCAE) version 4. HRQOL was measured at baseline, and at 3, 6, 12, and 18 months after treatment, using the European Organization for Research and Treatment of Cancer Quality-of-Life-Questionnaire-C30 (EORTC QLQ-C30) [8] and Head-and-Neck-35 (EORTC QLQ-HN35). HRQOL subscales were calculated according to EORTC guidelines [9].

Endpoints

The primary endpoint was the cumulative incidence of CRF at 2 years after treatment. Secondary endpoints were the incidence, duration and severity of common treatment-related side effects, and patient-reported HRQOL. We chose HRQOL scales relating to general health (QLQ-C30 Summary Score; QLQ-C30 revised physical functioning subscale) and symptom scales pertaining to the most relevant treatment side effects (QLQ-HN35 swallowing and dry mouth subscales). Although local failure (LF), regional failure (RF), distant metastasis (DM) and overall survival (OS) are not endpoints of this study, we report them for completeness.

Sample size calculation

The probability of CRF in patients with lateralized HNSCC treated to one side of the neck was estimated to be 2% at 2-years [1]. For patients treated in this study, we expected a similar rate of CRF. A 2-year probability of $\geq$15% was assumed to be unacceptable. To demonstrate a probability of <15%, approximately 40 evaluable patients are required (power = 0.80, α = 0.05, two-sided), if the true probability is 2%. Evaluable patients were those who received SG-ENI; thus excluding those with $\geq$2 contralateral draining areas who received B-ENI. We expected around 20% of included patients to be ineligible for endpoint analysis, either because of treatment with B-ENI or because of death during the first two years. Therefore, 50 patients were enrolled to ensure sufficient power for analysis of the primary endpoint.

Matching

In order to create a formal group for the comparison of toxicity and HRQOL, every evaluable study patient was matched to a patient treated outside the study framework with B-ENI [7]. Patients were matched for T- and N-classification, use of systemic therapy, tumor subsite, and (for oropharyngeal tumors) HPV-status. To ensure treatment planning and delivery techniques identical to the study cohort, only patients treated with B-ENI after January 2013 were eligible for matching. We identified suitable candidates backwards in time to find the most recent match per patient. If no complete match was available, a close match with more favorable characteristics was chosen (e.g. N0 instead of N1), to prevent any baseline differences favoring the SG-ENI trial group.

Statistical analysis

Cumulative incidences of LF, RF, CRF, DM and OS were estimated from the last day of (chemo)radiotherapy using the Kaplan-Meier method. In the analysis of LF, RF, CRF and DM, patients without events or with events other than the event of interest, were censored at the day of last follow-up. For OS, death from any cause was considered an event, and all other patients were censored at the day of last follow-up. Cumulative incidences of toxicities were estimated from the first day of (chemo)radiotherapy. The log-rank test was used to assess differences between groups.

Mixed effects modeling with a random intercept per patient was applied to assess differences in HRQOL from baseline. The best way to include time into the model was evaluated by entering it as a continuous variable with different shapes (linear, squared, or as a cubic polynomial) or as a discrete variable. Since a large proportion of participants in the matched group did not complete HRQOL questionnaires at all five time points, a variable indicating each individuals' missing data pattern and its interaction with treatment was tested. Differences in mean scores over time between groups were accompanied by Cohen's effect size (ES). An ES of 0.20 was considered small, 0.50 moderate and clinically significant, and 0.80 large [10]. Statistical analysis was performed in SPSS version 22. All tests were two-sided with an assumed significance level of $p < 0.05$.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the local research ethics committee (Medical Research Ethics Committee of the Netherlands Cancer Institute/Antoni van Leeuwenhoek, protocol ID: NL15706.031.14). Written informed consent was obtained from all individual SUSPECT trial participants before inclusion. For retrospective analysis of the matched patients treated with B-ENI, the local research ethics committee waived informed consent.

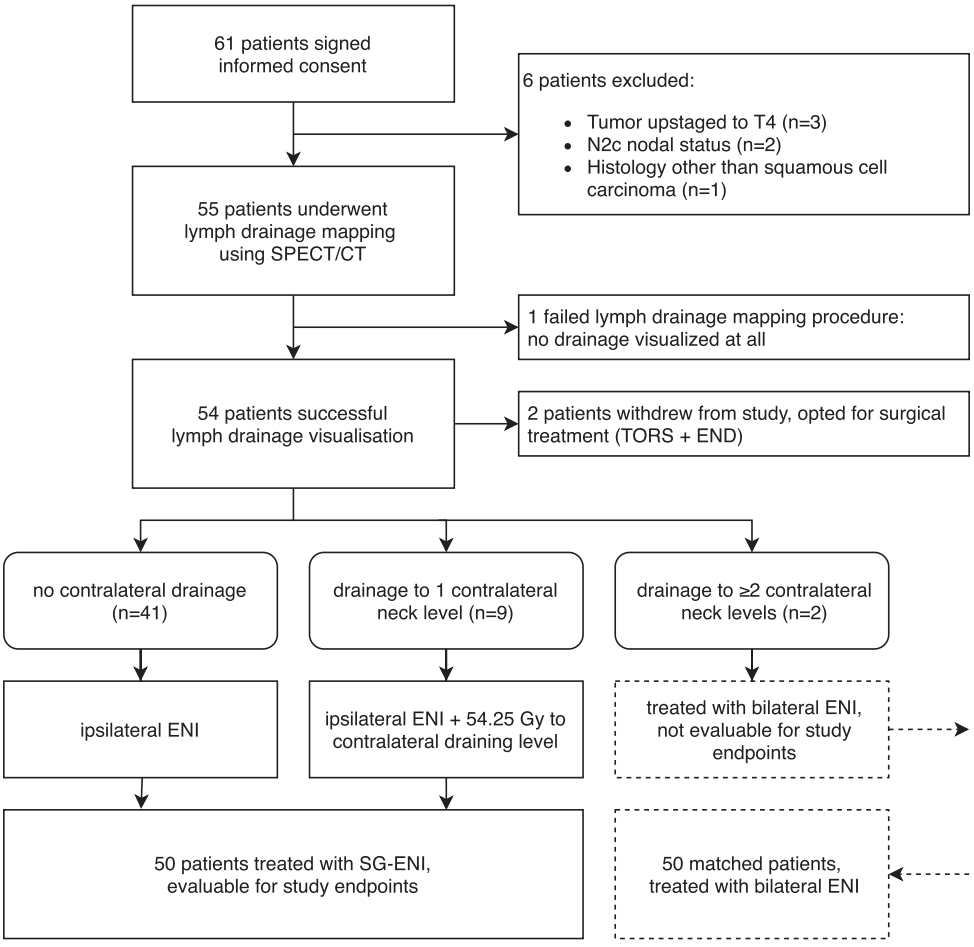

Fig. 1. Trial profile. Abbreviations: SPECT/CT: single proton emission computed tomography/computed tomography; TORS: transoral robotic surgery; END: elective neck dissection; SG-ENI: SPECT/CT-guided elective nodal irradiation.

Results

Between July 21, 2015 and Nov 1, 2017, 61 patients signed informed consent. A flow chart of the inclusion is shown in Fig. 1. Fifty-five patients underwent LDM by SPECT/CT [5]. In one patient, no drainage was visualized, and two patients had drainage to multiple contralateral neck levels and received B-ENI. Two patients opted for surgical treatment and withdrew from the study.

Fifty patients were treated with SG-ENI and are the subject of this analysis. Forty-one patients (82%) had drainage only to the ipsilateral neck and were treated with unilateral ENI. Nine patients (18%) had drainage to only one contralateral neck level and were treated with ipsilateral ENI and elective irradiation only to the contralateral level containing the tracer accumulation on SPECT/CT. All patients finished their radiotherapy course as planned.

Table 1
Patient characteristics and treatment details.

	SG-ENI	B-ENI	*p*-value*
	All		
Age in months: median (range)	61 (39–81)	61 (44–81)	0.619
Sex			
Male	41	34	0.106
Female	9	16	
Tumor sites and subsites			
Oropharynx	37	39	0.524**
Tonsillar fossa	24	18	
Soft palate	2	4	
Base of tongue	11	15	
Lateral pharyngeal wall	–	2	
Oral cavity	2	-	
Floor of mouth	2	-	
Larynx	6	7	
Glottic region	3	4	
Supraglottic region	3	3	
Hypopharynx	5	4	
Piriform sinus	5	4	
T-classification			
T1	10	12	0.643
T2	30	28	
T3	10	10	
N-classification			
N0	14	14	0.624
N1	13	16	
N2a	1	2	
N2b	22	18	
AJCC-stage (7th edition)			
I	2	2	0.743
II	10	9	
III	15	19	
IV	23	20	
HPV-status in OPC			
HPV-positive	22	25	0.488
HPV-negative	17	14	
Concurrent systemic treatment			
None	40	40	0.904
Cisplatin	5	6	
Cetuximab	5	4	
Accelerated radiotherapy			
Yes	37	35	0.656
No	13	15	
Median D_{mean} to organ at risk (in Gy)			
Contralateral parotid gland	3.7	19.9	**<0.001**
Contralateral submandibular gland	18.4	46.4	**<0.001**
Constrictor muscles	37.7	52.8	**<0.001**
Larynx	35.0	50.8	**<0.001**
Supraglottic larynx	37.9	52.9	**0.038**
Thyroid	30.4	47.2	**0.001**

Abbreviations: AJCC: American Joint Committee on Cancer; HPV: human papilloma virus; OPC: oropharyngeal carcinoma; D_{mean}: mean irradiation dose; Gy: gray.
* For age, follow-up time, T-classification, N-classification, AJCC-stage, and irradiation dose, the Mann-Whitney *U* test was used; for all other characteristics Pearson's chi-square tests were used. P-values <0.05 are shown in boldface.
** Test of distribution of general tumor sites, not subsites.

After a median follow-up time for alive patients of 33 months (range 18–45), the 2-year cumulative incidence of CRF was 2.0% (95%CI: 0–6%; events: 1, censored: 17) in the SG-ENI group. The only patient to develop CRF was a 57-year-old male who was treated unilaterally for T2N2b tonsillar fossa carcinoma. Three months after treatment a contralateral lymph node metastasis, 8 mm large, was found in level II. At that time, there was no evidence of LF or DM. He underwent a modified radical ND in which 3 metastases were found, and received postoperative irradiation. He was recently, 2.5 years after primary treatment, diagnosed with LF. Two-year cumulative incidence of LF, RF, and DM for the SG-ENI group were 4.3% (95%CI: 0–10%, events: 2, censored: 15), 4.0% (0–9%; events: 2, censored: 16), and 8.6% (0–16%; events: 4, censored: 13), respectively. Two-year OS was 81.6% (71–93%; events: 9, censored: 6).

The 50 SG-ENI patients were matched to 50 patients treated with standard B-ENI. With the exception of follow-up time, baseline characteristics did not differ significantly between both groups (Table 1). The median irradiation doses to all organs at risk were significantly lower in the SG-ENI group than in the B-ENI group (Table 1). Fig. 2 shows that for all toxicities, the prevalence was lower in the SG-ENI group at every time point. The SG-ENI group reported shorter median durations of grade 3 dermatitis, grade $\geq$2 and 3 mucositis and grade 2 dysphagia, compared to the B-ENI group (Table 2). At 90 days after end of radiotherapy, the cumulative incidences of acute mucositis (80% [95%CI: 65–89%] vs. 88% [85–94%] for SG-ENI and B-ENI groups, respectively) and dermatitis (56% [40–68%] vs. 66% [50–77%]) did not differ significantly between groups. In the SG-ENI group, we found significantly lower cumulative incidences of grade $\geq$2 dysphagia (54% [38–66%] vs. 82% [67–90%], $p < 0.001$); and feeding tube placement (10% [1–18%] vs. 50% [34–62%], $p < 0.001$). Two-year cumulative incidences of grade 2 xerostomia in the SG-ENI and B-ENI groups were 8.6% (95%CI: 0–16%; events: 4, censored: 17) and 54% (37–67%; events: 25, censored: 12), respectively ($p < 0.001$). No grade 3 xerostomia was reported.

Model-based mean scores for HRQOL scales of interest are shown in Table 3. Crude mean scores for all EORTC QLQ-C30 and HN35 scales are available in Supplementary Table 1. The course of HRQOL over time is plotted in Fig. 3. Compared to the bilaterally treated group, the SG-ENI group reported a significantly better summary score at 6 months after treatment (ES 0.81, $p = 0.011$). The SG-ENI group had significantly less swallowing complaints at 3 months after treatment compared to the B-ENI group (ES 0.72, $p = 0.015$), and significantly less complaints of dry mouth at 3, 6 and 12 months after treatment (ES 0.92, $p = 0.010$; ES 1.02, $p = 0.005$; and ES 0.94, $p = 0.006$, respectively). On the physical functioning subscale no significant differences were found between treatment groups.

Discussion

Our results suggest that SPECT/CT-guided ENI is safe in patients with lateralized HNSCC, as only one patient (2%) developed CRF. Furthermore, the incidence, severity and duration of radiation-related toxicity was significantly reduced, compared to a well-matched group treated bilaterally with identical planning and treatment techniques in the same institution. To the best of our knowledge, this is the first prospective trial where the ENI in lateralized HNSCC was guided by LDM using SPECT/CT.

CRF after B-ENI has a reported incidence of 2.8% [11]. The incidence of CRF after SG-ENI in our study (2%, 95%CI 0–6%) is comparably low. Moreover, it is in line with reported CRF incidence after

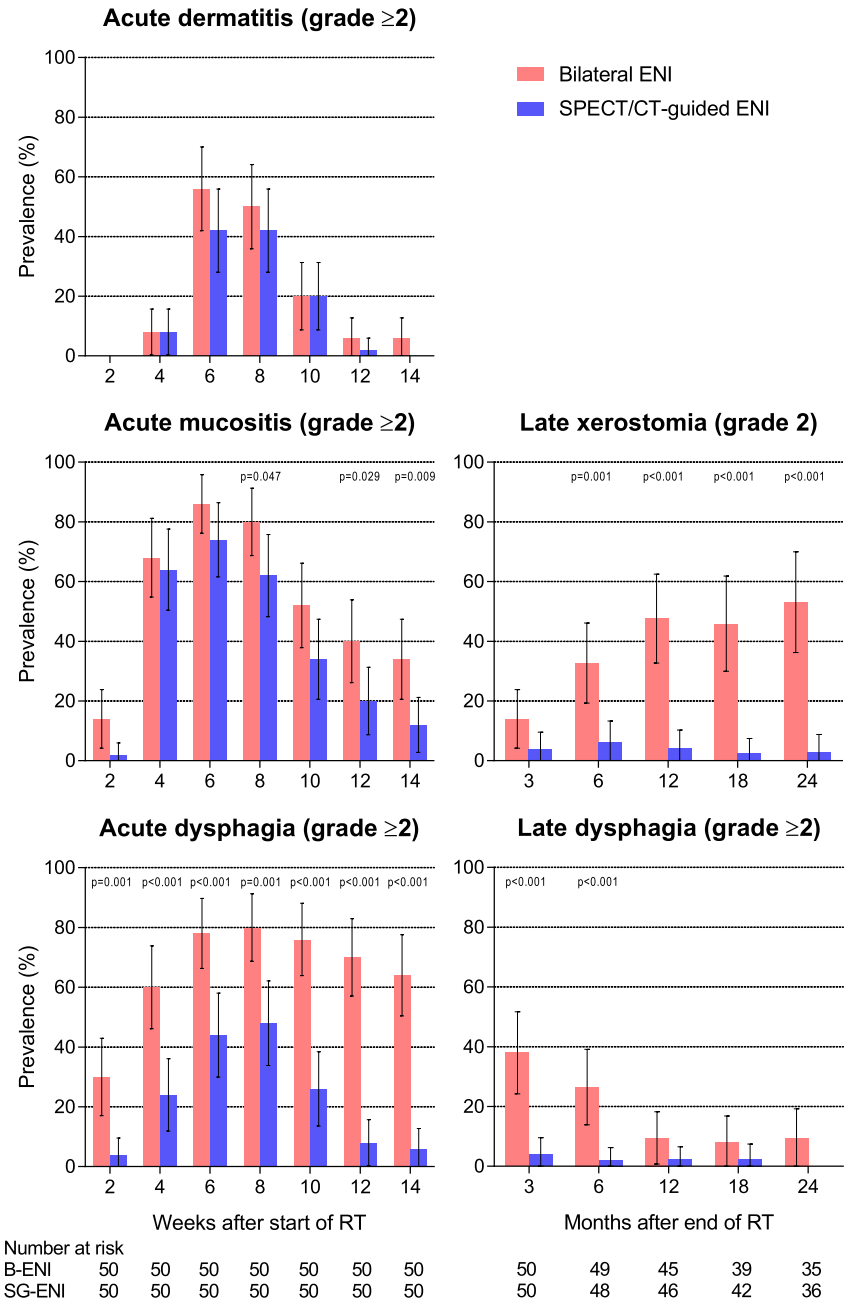

Fig. 2. Prevalence of radiation-related toxicities. Error bars represent 95% confidence intervals. Statistically significant differences between SG-ENI and B-ENI groups are indicated by *p*-values at that time point. Abbreviations: B-ENI: bilateral elective nodal irradiation; SG-ENI: SPECT/CT-guided elective nodal irradiation; RT: radiotherapy.

Table 2
Toxicity duration, in days.*

	SG-ENI		B-ENI		*p*-value**
	median	(range)	median	(range)	
Dermatitis grade ≥2	21	(12–51)	25	(10–154)	0.247
Dermatitis grade 3	14	(10–21)	21	(5–29)	0.152
Mucositis grade ≥2	40	(14–120)	50	(14–206)	**0.010**
Mucositis grade 3	26	(14–89)	51	(14–133)	**0.023**
Dysphagia grade ≥2	37	(13–150)	110	(12–155)	**<0.001**
Dysphagia grade 3 (tube feeding)	45	(34–118)	102	(15–155)	0.077

Abbreviations: SG-ENI: SPECT/CT-guided elective nodal irradiation; B-ENI: bilateral elective nodal irradiation.

* Only including patients that did have the toxicity. Treating radiation oncologists register toxicities at every follow-up visit according to CTCAE v4.0. Duration of all toxicities was based on 'start of toxicity' and 'end of toxicity' dates as entered in the electronic patient record.

** Mann-Whitney-*U* test. P-values <0.05 are shown in boldface.

Table 3
HRQOL results.

EORTC QLQ-C30 & HN35		Baseline	3 months				6 months				12 months				18 months			
				Between-group difference Baseline – 3 months				Between-group difference Baseline – 6 months				Between-group difference Baseline – 12 months				Between-group difference Baseline – 18 months		
		Mean (SD)	Mean (SD)	Mean change (SE)	*P*	ES	Mean (SD)	Mean change (SE)	*P*	ES	Mean (SD)	Mean change (SE)	*P*	ES	Mean (SD)	Mean change (SE)	*P*	ES
Summary score*	SG-ENI	87.5 (12.9)	85.9 (12.4)				88.1 (12.1)				91.2 (12.2)				90.6 (11.8)			
	B-ENI	85.5 (10.9)	80.5 (10.6)	−3.5 (3.5)	0.318	0.28	76.0 (10.7)	**−10.1 (3.9)**	**0.011**	**0.81**	85.3 (11.6)	−3.9 (4.0)	0.327	0.31	87.7 (9.9)	−0.9 (5.1)	0.864	0.07
Physical functioning*	SG-ENI	87.7 (17.3)	84.7 (16.4)				87.4 (16.4)				89.3 (16.7)				89.4 (16.3)			
	B-ENI	85.8 (15.1)	81.0 (15.2)	−1.8 (4.4)	0.687	0.11	75.7 (15.0)	−9.8 (5.4)	0.069	0.58	81.4 (15.8)	−6.0 (5.6)	0.291	0.35	81.9 (14.3)	−5.7 (7.3)	0.436	0.34
Swallowing**	SG-ENI	15.1 (18.9)	12.4 (18.8)				12.3 (18.3)				8.4 (18.4)				9.5 (18.1)			
	B-ENI	20.1 (17.7)	30.9 (17.4)	**13.4 (5.4)**	**0.015**	**0.72**	27.9 (17.0)	10.6 (6.4)	0.102	0.57	16.8 (18.0)	3.3 (6.4)	0.606	0.18	9.1 (16.9)	−5.5 (8.1)	0.499	0.30
Dry mouth**	SG-ENI	18.0 (28.0)	38.2 (27.9)				33.6 (27.5)				30.0 (27.2)				29.9 (26.7)			
	B-ENI	12.7 (26.3)	58.5 (26.6)	**25.6 (9.9)**	**0.010**	**0.92**	56.5 (26.7)	**28.1 (9.8)**	**0.005**	**1.02**	50.6 (27.2)	**25.9 (9.3)**	**0.006**	**0.94**	43.6 (26.0)	18.9 (12.0)	0.116	0.68

Reported means and effect sizes are model-based. Significant overall group-by-time interactions are shown in boldface ($p < 0.05$). In the analysis, contrasts were based on the between-group differences in mean change from baseline to follow-up (i.e., differences between the SG-ENI group and the B-ENI group in mean change from baseline to 3 months after treatment, baseline to 6 months after treatment, etc.). The statistical model did not compare mean change between individual time points after baseline.

* Higher score = better.

** Lower score = better.

unilateral treatment. Our own group recently reviewed 11 studies where 1116 patients with oropharyngeal cancer were treated unilaterally [12]. In many of these studies patients with a theoretically higher risk of CRF (e.g. with T3-4 or N2-3 disease, or tumors with midline invasion) were included. Nevertheless, the mean incidence of CRF was 2.4% (95%CI 1.6–3.5%). In this review, involvement of the midline showed the most significant correlation with the incidence of CRF; 12.1%, compared to 1.7% when the midline was free ($p = 0.001$). Furthermore, in surgical series where resection of T1-2 oropharyngeal cancer was combined with unilateral ND or sentinel node procedure (SNP), the incidence of CRF is comparable (0–2%) [13–16].

Although no follow-up data after unilateral or SNP-based treatment for hypopharyngeal and laryngeal cancer is available, the absence of CRF in these patients is in line with several surgical studies. Böttcher et al. [17], investigating patients with T2-4 laryngeal cancer treated with total laryngectomy and bilateral ND, reported 0% occult contralateral metastasis in patients with lateralized tumors, and 5 to 6% in tumors extending to or slightly beyond the midline. Other studies, combining SNP with bilateral ND, found occult nodal metastases in 0–3% of contralateral neck specimens [18,19].

A significant reduction of toxicity in patients treated unilaterally, compared to bilateral ENI, was found in a prospective study by Jensen et al.; 20% vs. 61% for grade ≥2 xerostomia and 10% vs. 22% for grade ≥2 dysphagia, respectively [20]. Similar results were reported by Liu et al. [21]. However, these series had a disbalance in disease stages between the unilaterally and bilaterally treated groups, and stem from before the era of intensity modulated radiotherapy (IMRT). In IMRT literature, high incidences of grade ≥2 dysphagia (85–90%) [22,23], feeding tube placement (29–70%) [22–24], feeding tube dependency at 1 year post-treatment (7–22%) [25–27], and late xerostomia (28–60%) [28] are reported. Unfortunately, these series include mostly locally advanced tumors, with corresponding high rates of concurrent chemotherapy use, making a direct comparison with our results difficult. In the RCT of Nutting et al., parotid-sparing IMRT was compared with conventional radiotherapy [29]. Concurrent chemotherapy was not given, though 43% received induction chemotherapy. Even in the parotid-sparing arm, the prevalences of grade ≥2 xerostomia at 12 and 24 months were 38% and 29%, respectively, compared to a 2-year cumulative incidence of 9% in our SG-ENI group.

The scarcity of series comparable to our own, with regard to patient population and detailed reporting on acute and late toxicity, was a compelling reason to create a 1:1 matched group of bilaterally treated patients. The results of this comparison show the clear benefit of SPECT/CT-guided treatment.

Bilateral ENI (compared to unilateral ENI) has been identified as a strong predictor for grade ≥2 dysphagia and xerostomia at 6 months after treatment [2,3], and worse HRQOL scores at the EORTC QLQ-HN35 dry mouth and swallowing subscales [4]. Our findings are in line with this. Notably, our study found differences of >10 points in favor of the SG-ENI group on the summary score (6 months post-treatment) and swallowing subscale (3 and 6 months post-treatment), a score difference that is often defined as clinically relevant [30]. On the dry mouth subscale, large differences of >20 points were observed. These statistically significant differences corresponded with moderate-to-large effect sizes, and coincided with a significant difference in dysphagia prevalence, and rising xerostomia prevalence (Fig. 3). This illustrates the previous finding that xerostomia and particularly late dysphagia have a significant impact on patient-reported HRQOL [31].

Besides significant reduction of toxicity, unilateral irradiation offers other important advantages. In case of contralateral

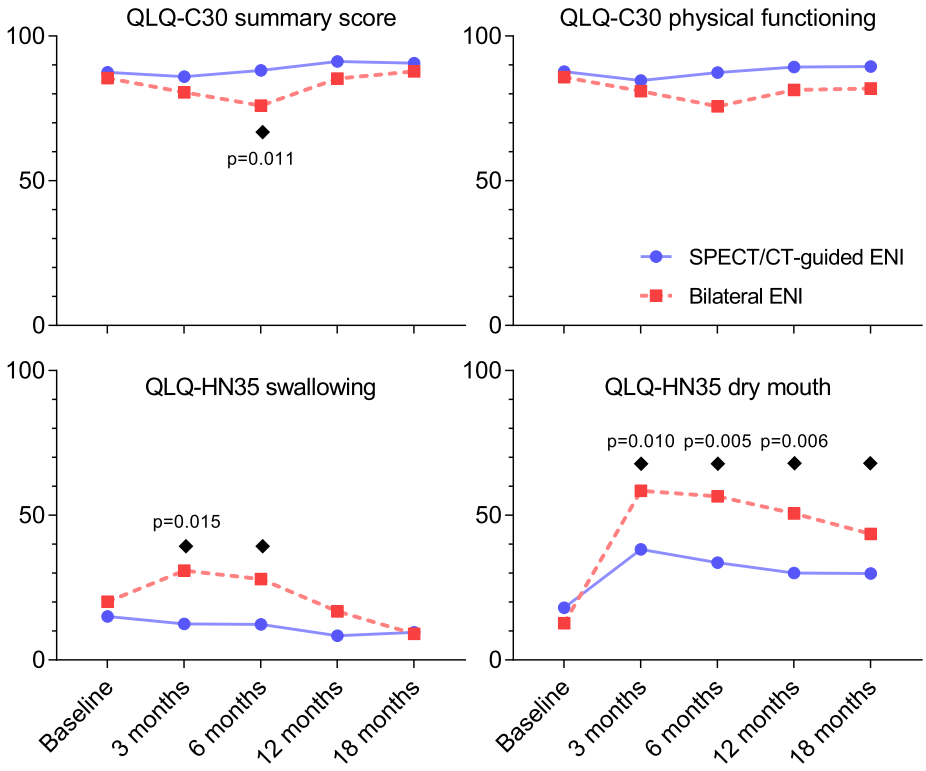

Fig. 3. Model-based mean scores for SG-ENI and B-ENI groups are plotted. Statistically significant differences between SG-ENI and B-ENI groups are indicated by *p*-values at that time point. An diamond indicates a clinically relevant difference of >10 points.

recurrence or a second primary tumor in the contralateral neck, the tolerance for re-irradiation is very limited after B-ENI. Even after an elective dose of 46–50 Gy, the cumulative irradiation dose of ≥100–110 Gy would be very toxic. Conversely, ND in a radiation-naive neck is related to less morbidity, and radiotherapy can easily be applied.

The limitations of the current study are well recognized by the authors. Although not randomized, it is a prospective study, and the formal group created for the comparison of toxicity and HRQOL results was well-matched with regard to known predictive factors for toxicity in HNSCC. Furthermore, in the current study nine patients had contralateral drainage and were treated to the ipsilateral neck and to the level containing the contralateral hot spot. Eliminating that contralateral level, mostly level II and III (91%) [5], would have further reduced the dose to the contralateral salivary glands, laryngeal structures and swallowing muscles. Most of these patients might still be overtreated, because we believe that only a minority of those contralateral hot spots will harbor occult metastases. Therefore, in the follow-up study (the SUSPECT2 trial, ClinicalTrials.gov Identifier: NCT03968679) [32] any contralateral sentinel node will be removed for pathological examination. Only when this node contains tumor cells, the patient will be treated bilaterally. In this way, we expect to further reduce the number of patients who are unnecessarily treated to the contralateral neck.

In conclusion, SPECT/CT-guided ENI is feasible and oncologically safe, as only one patient had contralateral regional failure. Compared to standard B-ENI, it results in clinically and statistically significant reductions of dysphagia, tube feeding placement, and late xerostomia, and substantial HRQOL improvement. These findings challenge the paradigm of B-ENI in HNSCC and should encourage the head and neck radiation oncology community to change practice towards lymph drainage mapping-based unilateral ENI for lateralized tumors.

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Contributors

AA conceived the study and was principal investigator. AA, EW, WV and MB designed the study. PV, WV, WS, CC, MD and AA contributed to data collection. PV, IW, EW and AA analyzed and interpreted the data and drafted the manuscript. All authors revised the manuscript and approved the submission.

Declarations of interest

Pieter de Veij Mestdagh has nothing to disclose.
Iris Walraven has nothing to disclose.
Wouter Vogel has nothing to disclose.
Willem Schreuder has nothing to disclose.
Erik van Werkhoven has nothing to disclose.
Casper Carbaat has nothing to disclose.
Maarten Donswijk has nothing to disclose.
Michiel van den Brekel has nothing to disclose.
Abrahim Al-Mamgani has nothing to disclose.

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Ethics committee approval

The study (ClinicalTrials.gov Identifier NCT02572661) was conducted in accordance with the Declaration of Helsinki. The study was approved by the local research ethics committee (Medical Research Ethics Committee of the Netherlands Cancer Institute/Antoni van Leeuwenhoek, protocol ID: NL68958.031.19). All patients were given oral and written information about the study, and were given sufficient time to consider participating. Written informed consent was obtained from each patient before inclusion.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.03.012.

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