Original Article

^{18}F-FDG-PET/CT-based treatment planning for definitive (chemo) radiotherapy in patients with head and neck squamous cell carcinoma improves regional control and survival

Sven van den Bosch [a,*], Patricia A.H. Doornaert [b], Tim Dijkema [a], Ellen M. Zwijnenburg [a], Lia C.G. Verhoef [a], Bianca A.W. Hoeben [a], Nicolien Kasperts [b], Ernst J. Smid [b], Chris H.J. Terhaard [b], Johannes H.A.M. Kaanders [a]

[a] Department of Radiation Oncology, Radboud University Medical Center, Nijmegen; and [b] Department of Radiation Oncology, University Medical Center Utrecht, The Netherlands

ABSTRACT

Background and purpose: Multimodality imaging including ^{18}F-FDG-PET has improved the detection threshold of nodal metastases in head and neck squamous cell carcinoma (HNSCC). The aim of this retrospective analysis is to investigate the impact of FDG-PET/CT-based nodal target volume definition (FDG-PET/CT-based NTV) on radiotherapy outcomes, compared to conventional CT-based nodal target volume definition (CT-based NTV).

Materials and methods: Six-hundred-thirty-three patients treated for HNSCC with definitive (chemo) radiotherapy using IMRT/VMAT techniques between 2008 and 2017 were analyzed. FDG-PET/CT-based NTV was performed in 46% of the patients. The median follow-up was 31 months. Diagnostic imaging depicting the regional recurrence was co-registered with the initial CT-scan to reconstruct the exact site of the recurrence. Multivariate Cox regression analysis was performed to identify variables associated with radiotherapy outcome.

Results: FDG-PET/CT-based NTV improved control of disease in the CTV$_{elective-nodal}$ (HR: 0.33, p = 0.026), overall regional control (HR: 0.62, p = 0.027) and overall survival (HR: 0.71, p = 0.033) compared to CT-based NTV. The risk for recurrence in the CTV$_{elective-nodal}$ was increased in case of synchronous local recurrence of the primary tumor (HR: 12.4, p < 0.001).

Conclusion: FDG-PET/CT-based NTV significantly improved control of disease in the CTV$_{elective-nodal}$, overall regional control and overall survival compared to CT-based NTV. A significant proportion of CTV$_{elective-nodal}$ recurrences are potentially new nodal manifestations from a synchronous local recurrent primary tumor. These results support the concept of target volume transformation and give an indication of the potential of FDG-PET to guide gradual radiotherapy dose de-escalation in elective neck treatment in HNSCC.

Head and neck squamous cell carcinoma (HNSCC) has a substantial risk of cervical lymph node metastases [1]. For small nodal metastases, it is not uncommon that they remain undetected (i.e. occult) because they fall below the detection threshold of diagnostic imaging [1,2]. In a clinically negative neck (cN0) the prevalence of occult metastases ranges between 10% and 35%, depending on the primary tumor site and T-stage [2]. To eradicate potential occult nodal disease, elective irradiation (typically an equivalent dose of 45–50 Gy in 2-Gy fractions) to the clinically uninvolved nodal target volume (CTV$_{elective-nodal}$) is performed routinely in definitive (chemo)radiotherapy for HNSCC [2,3].

Detection of nodal metastases by computed tomography (CT) and magnetic resonance imaging (MRI) relies largely on non-specific anatomical criteria with limited abilities to differentiate between metastatic and non-metastatic lymph nodes of small size [4]. Ultra sound (US) with fine needle aspirated cytology (FNAC) can improve the accuracy, but there is a limit to the number of nodes that can be sampled as it is often burdensome for the patient [5]. Molecular imaging using ^{18}F-fluorodeoxy-D-glucose positron emission tomography (FDG-PET) provides non-invasive and quantitative assessment concerning the functional process of glucose metabolism [6]. Because an increased glucose metabolism is characteristic of SCC, good accuracy of FDG-PET in the detection of nodal metastases was shown, and superiority of integrated

* Corresponding author at: Radboud University Medical Center, Department of Radiation Oncology, Huispost 874, P.O. Box 9101, Nijmegen 6500 HB, The Netherlands.

E-mail address: Sven.vandenBosch@radboudumc.nl (S. van den Bosch).

FDG-PET/CT over conventional imaging was demonstrated [7–10]. In radiotherapy, defining the nodal target volume with FDG-PET/CT results in alteration of nodal treatment in approximately 1 out of 4 patients compared to conventional imaging; with nodal upstaging in 8–21% and down staging in 3–11% [11–15]. Increased FDG-accumulation in inflammatory cells, however, may cause false-positive nodal findings [7]. US-FNAC can provide pathologic confirmation, but sampling errors may also occur [5].

The potential impact of improved nodal detection by FDG-PET/CT on radiotherapy outcomes remains largely unresolved. This retrospective analysis investigates the effect of defining the nodal target volume with FDG-PET/CT compared to CT with endpoints recurrence and survival after definitive (chemo)radiotherapy for HNSCC.

Materials and methods

Patient selection

Clinical data of patients treated for HNSCC between 2008 and 2017 at the departments of Radiation Oncology of two tertiary head and neck cancer centers in The Netherlands were collected. Included were patients treated with definitive (chemo)radiotherapy for histologically proven SCC of the oropharynx, larynx or hypopharynx. Excluded were patients who had had previous oncologic treatment to the head and neck area, or who had no indication for elective neck irradiation. Individual patient data from a previously studied cohort was used and supplemented with patients for whom FDG-PET/CT was available for defining the nodal target volume [16]. A total of 633 patients with a median follow-up of 31 months (Range: 1–119 months) were included. Table 1 gives an overview of patient and tumor characteristics.

This analysis was conducted according to the ethical principles for medical research involving human subjects as stated in the Declaration of Helsinki and in the ICH Good Clinical Practice guidelines and was approved by the local review board (reference number 2018-4080). The need for written informed consent was waived because of the retrospective study design.

Diagnostic work-up and follow-up

Routine diagnostic work-up for the primary tumor involved physical examination including flexible endoscopy and histological biopsy. An MRI-scan of the head and neck area was acquired in case of oropharyngeal cancers (OPC), and a CT-scan in case of laryngeal and hypopharyngeal cancers. Evaluation of the neck was performed using US-FNAC. A chest x-ray was performed to screen for distant metastases and second primaries, and in case of extensive nodal disease a chest CT-scan or FDG-PET/CT-scan was acquired. HPV-status was available in 72% (262/365) of patients with OPC. All patients were evaluated and discussed by a multidisciplinary head and neck tumor board for tumor classification and treatment recommendations.

Routine evaluation for recurrence consisted of physical examination and flexible endoscopy and was performed every 2, 3, 4 and 6 monthly during the 1st, 2nd, 3rd and 4th–5th year after treatment, respectively. Additional diagnostic imaging and pathological sampling was acquired for confirmation when recurrence was suspected. Routine follow-up ended 5 years after treatment if there was no evidence of disease recurrence up to that date.

Imaging for radiation treatment planning

FDG-PET/CT-scans (46%, n = 290/633) or CT-scans of the head and neck area (starting from the lower border of the clavicle to cranium) were acquired in radiation treatment position using a customized thermoplastic head, neck and shoulders mask to immobilize patients during the scanning procedures and radiation treatment. CT-scans were acquired using an intravenous iodinated contrast agent. The majority (82%, n = 237/290) of FDG-PET/CT-scans were acquired in one session on EARL-accredited integrated PET/CT-scanners (BioGraph 40 mCT, Siemens Medical Solutions, Knoxville Tennessee, USA) and were acquired in Center 1 (43%, n = 124/290) or Center 2 (57%, n = 166/290). Image acquisition and reconstruction was performed applying the European Association of Nuclear Medicine (EANM) procedure guidelines for tumor PET imaging [6]. The EARL accreditation program comprises extensive image- and calibration quality control and (cross)calibrations between institutions, ensuring comparable scanner performance in a multicenter setting [17]. Evaluation of FDG-PET/CT-imaging was performed by the attending radiation oncologist and an experienced nuclear medicine physician. Study readings were performed by means of qualitative visual analysis. No standardized quantitative assessment of FDG-uptake was performed (e.g. thresholding).

Target volume definition and margins

The gross target volume (GTV) was delineated using information from clinical examination and diagnostic imaging and encompassed all overtly macroscopic disease. For CT-based nodal target volume definition (CT-based NTV), nodes were added to the GTV in case of central necrosis, loss of fatty hilum, or pathologic enlargement (short-axial diameter $\geq$10 mm, or $\geq$11 mm in case of subdigastric nodes) [18]. For FDG-PET/CT-based nodal target volume definition (FDG-PET/CT-based NTV), nodes were added to the GTV based on abnormal FDG-uptake (i.e. focal FDG-accumulation, notably above surrounding or expected normal metabolic tissue activity, no formal cut-off values were used) in combination with nodal appearance on CT-scan. Finally, nodes with positive US-FNAC were also added to the GTV. The CTV was created by three-dimensional expansion of the GTV by a margin of 10 mm, adjusted for anatomical borders.

The $CTV_{elective-nodal}$ was delineated according to international guidelines and encompassed levels II, III and IV [19]. Unilateral neck only was included in case of $cT_{1-2}N_{0-2a}$ tonsil cancers >1 cm from midline and limited invasion of the base of tongue, and bilateral neck for all other tumors. Based on individual local tumor extension or nodal involvement, additional levels (Ib, V, VI, VIIa, VIIb) were included [19]. A planning target volume (PTV) was created by 3D expansion of the CTV by a margin of 3–5 mm.

External beam radiotherapy

All patients were treated using intensity modulated radiotherapy (IMRT) (n = 490) or volumetric arc therapy (VMAT) (n = 143). Various fractionation schedules were used, all prescribing an equivalent dose in fractions of 2 Gy (EQD2) of 70–74 Gy to the GTV and 45–50 Gy to the $CTV_{elective-nodal}$. Eighty-seven percent of the patients was treated with 1 of the following fractionation schedules: an accelerated fractionation schedule prescribing 68/50.3 Gy in 2/1.48 Gy fractions with simultaneous integrated boost (SIB) in an overall treatment time (OTT) of 5.5 weeks (n = 439) or a conventional fractionation schedule prescribing 70/46 Gy in 2 Gy fractions with sequential boost in an OTT of 7 weeks (n = 114). Patients <70 years of age with stage III–IV disease received concurrent treatment with cisplatin 100 mg/m^2 every 3 weeks (n = 110) or 40 mg/m^2 weekly (n = 77), or with cetuximab if the patient was unfit for cisplatin (n = 51).

Recurrence in the elective nodal target volume

For all patients with a regional recurrence, the initial radiation treatment plans, including the planning (FDG-PET)CT-scan and

Table 1
Multivariate Cox regression analysis for recurrence in the CTV$_{\text{elective-nodal}}$.

Characteristic	No. of patients (n = 633) (%)	No. CT-based NTV (n = 343) (%)/events (n = 19)	No. FDG-PET/CT-based NTV (n = 290) (%)/events (n = 5)	Multivariate analysis	
				HR (95% CI)	P
Age at diagnosis (y)					
≤60	243 (38)	136 (40)/8	107 (37)/4	not in model*	0.350
>60	390 (62)	207 (60)/11	183 (63)/1		
Gender distribution					
Male	456 (72)	243 (71)/13	213 (73)/4	not in model*	0.777
Female	177 (28)	100 (29)/6	77 (27)/1		
Institution					
Center 1	467 (74)	343 (100)/19	124 (43)/1	not in model*	0.299
Center 2	166 (26)	–	166 (57)/4		
Primary tumor site					
Oropharynx	365 (58)	180 (53)/8	185 (64)/5	not in model*	0.947
Larynx	159 (25)	103 (30)/8	56 (19)/0		
Hypopharynx	109 (17)	60 (17)/3	49 (17)/0		
Stage					
I–II	153 (24)	104 (30)/6	49 (17)/2	not in model*	0.688
III–IV	480 (76)	239 (70)/13	241 (83)/3		
T classification					
T1–2	309 (49)	176 (51)/11	133 (46)/2	not in model*	0.491
T3–4	324 (51)	167 (49)/8	157 (54)/3		
N classification					
N0	239 (38)	154 (45)/11	85 (29)/2	not in model*	0.629
N1–3	394 (62)	189 (55)/8	205 (71)/3		
HPV-status (OPC only)±					
OPC HPV-negative	118 (19)	35 (10)/1	83 (29)/4	not in model*	0.877
OPC HPV-positive	144 (23)	68 (20)/4	76 (26)/0		
Other£	371 (58)	240 (70)/14	131 (45)/1		
NTV					
CT-based	343 (54)	343 (100)/19	–	Ref.	
FDG-PET/CT-based	290 (46)	–	190 (100)/5	0.33 (0.12–0.88)	**0.026**
Chemotherapy					
No	395 (62)	242 (71)/14	153 (53)/2	not in model*	0.592
Yes	238 (38)	101 (29)/5	137 (47)/3		
Local recurrence					
No	508 (80)	271 (79)/7¥	237 (82)/0	Ref.	
Yes	125 (20)	72 (21)/12¥	53 (18)/5¥	12.4 (5.1–30.0)	**<0.001**

Abbreviations: CTV = clinical target volume; HR = hazard ratio; CI = confidence interval; HPV = human papillomavirus; OPC = oropharyngeal cancer; FDG-PET = fluoro-2-deoxyglucose positron emission tomography; CT = computed tomography; NTV = nodal target volume definition.
* Variable removed from model by backward elimination due to insignificance (p > 0.157).
± HPV-status was available in 72% (262/365) of patients with OPC.
£ Cases with unknown HPV-status for cancers of the oropharynx (n = 103), larynx (n = 159) and hypopharynx (n = 109).
¥ All recurrences in the CTV$_{\text{elective-nodal}}$ were diagnosed synchronously with local recurrence of the primary tumor.

delineation, were imported into Pinnacle^3 version 9.10 (Philips Medical Systems, Best, The Netherlands). To reconstruct the projected site of the regional recurrences on the initial planning scan, co-registration was performed with diagnostic imaging depicting the recurrence. Reports from pathologic evaluation of salvage neck dissection specimens and US-FNAC, and reports of diagnostic imaging were combined to identify the lymph node recurrence on an individual basis. Based on the projected location on the initial planning scan, regional recurrences were categorized into three subtypes: within the initial nodal GTV, within the CTV$_{\text{elective-nodal}}$ or outside any radiotherapy target volume. For recurrences in the CTV$_{\text{elective-nodal}}$, pre-existing nodes on the exact same position of the recurrence were identified and delineated on the initial radiation planning (FDG-PET)CT-scan for analysis of morphology and FDG-uptake. FDG-uptake was reported as the tumor to cervical spinal cord standardized uptake ratio (SUR), as it was shown to have a better reproducibility in a multicenter setting than the standardized uptake value (SUV) [20].

Statistical analysis

Data characterized by normal distribution were expressed as mean with 95% confidence interval (95% CI) or as median with range if not. Comparison of groups with not normally distributed data was performed by applying the Mann-Whitney *U* test. Cramer's V was calculated to assess correlations between nominal variables. All reported data on recurrence and survival are actuarial rates, estimated using the Kaplan-Meier method. Time was calculated from histological diagnosis until an event. Statistical tests were two-sided and p-values of 0.05 or less were considered significant. All analyses were performed using SPSS version 25 for Windows (IBM Corporation, Armonk, NY, USA).

Multivariate Cox regression analysis was performed to estimate hazard ratios (HRs) with 95% CI. Variables associated with outcome were identified in a multivariate setting using backward elimination without univariate prefiltering [21]. In this method, all variables (age, gender, institution, tumor site, stage, T-classification, N-classification, HPV-status, NTV and chemotherapy) are entered in the multivariate model and significance is tested. In each subsequent iteration, the most insignificant variable is removed from the model and significance is recalculated. This process is repeated until all variables in the model meet the selection criterion to be retained in the model. A selection criterion of α ≤ 0.157 was chosen to reduce the possibility of missing variables associated with outcome [22].

Results

Model summaries of multivariate Cox regression analysis regarding local, regional and distant control, as well as overall survival are shown in Table 2 (for full models and univariate models

Table 2
Multivariate Cox regression analysis for radiotherapy outcome.

Local recurrence[a,*]			**Regional recurrence**[b,*]		
Characteristic	HR (95% CI)	P	Characteristic	HR (95% CI)	P
Gender distribution			Primary tumor site		
Male	Ref.		Oropharynx	Ref.	0.017
Female	0.67 (0.44–1.02)	0.059	Larynx	1.33 (0.63–2.83)	0.456
Primary tumor site			Hypopharynx	2.46 (1.24–4.86)	**0.010**
Oropharynx	Ref.	0.070	T classification		
Larynx	1.26 (0.73–2.17)	0.399	T1–2	Ref.	0.133
Hypopharynx	0.63 (0.32–1.24)	0.179	T3	0.58 (0.35–0.95)	**0.031**
T classification			T4	0.67 (0.40–1.12)	0.129
T1–2	Ref.	<0.001	N classification		
T3	1.51 (0.96–2.37)	0.072	N0	Ref.	<0.001
T4	3.13 (1.84–5.31)	**<0.001**	N1	1.27 (0.57–2.84)	0.565
HPV-status (OPC only)[±]			N2–3	4.34 (2.50–7.54)	**<0.001**
OPC HPV-negative	Ref.	0.088	HPV-status (OPC only)[±]		
OPC HPV-positive	0.54 (0.30–0.97)	**0.039**	OPC HPV-negative	Ref.	0.012
Other[£]	0.88 (0.50–1.55)	0.668	OPC HPV-positive	0.42 (0.22–0.78)	**0.006**
Chemotherapy			Other[£]	0.40 (0.19–0.84)	**0.016**
No	Ref.		NTV		
Yes	0.53 (0.33–0.85)	**0.008**	CT-based	Ref.	
			FDG-PET/CT-based	0.62 (0.40–0.95)	**0.027**
Distant recurrence[c,*]			**Overall survival**[d,*]		
Characteristic	HR (95% CI)	P	Characteristic	HR (95% CI)	P
Primary tumor site			Age at diagnosis (y)		
Oropharynx	Ref.	<0.001	≤60	Ref.	0.009
Larynx	5.76 (1.89–17.5)	**0.002**	60–70	1.23 (0.87–1.72)	0.237
Hypopharynx	7.28 (2.49–21.3)	**<0.001**	≥70	1.97 (1.28–3.01)	**0.002**
Stage			Primary tumor site		
I–II	Ref.	0.067	Oropharynx	Ref.	0.094
III	0.99 (0.36–2.71)	0.984	Larynx	1.27 (0.77–2.09)	0.347
IV	0.14 (0.02–0.97)	**0.047**	Hypopharynx	1.69 (1.04–2.72)	**0.033**
N classification			T classification		
N0	Ref.	<0.001	T1–2	Ref.	0.001
N1	0.94 (0.32–2.78)	0.905	T3	1.26 (0.86–1.84)	0.242
N2–3	23.2 (3.2–168)	**0.002**	T4	2.28 (1.47–3.54)	**<0.001**
HPV-status (OPC only)[±]			N classification		
OPC HPV-negative	Ref.	<0.001	N0	Ref.	<0.001
OPC HPV-positive	0.37 (0.19–0.70)	**0.002**	N1	0.98 (0.59–1.63)	0.934
Other[£]	0.12 (0.04–0.36)	**<0.001**	N2–3	1.86 (1.31–2.64)	**<0.001**
NTV			HPV-status (OPC only)[±]		
CT-based	Ref.		OPC HPV-negative	Ref.	0.022
FDG-PET/CT-based	0.67 (0.43–1.07)	0.091	OPC HPV-positive	0.52 (0.32–0.854)	**0.007**
Chemotherapy			Other[£]	0.60 (0.36–1.01)	0.053
No	Ref.		NTV		
Yes	1.81 (1.10-2.99)	**0.019**	CT-based	Ref.	
			FDG-PET/CT-based	0.71 (0.52–0.97)	**0.033**
			Chemotherapy		
			No	Ref.	
			Yes	0.66 (0.43–1.00)	0.051

Abbreviations: HR = hazard ratio; CI = confidence interval; HPV = human papillomavirus; OPC = oropharyngeal cancer; FDG-PET = fluoro-2-deoxyglucose positron emission tomography, CT = computed tomography, NTV = nodal target volume definition.

[*] Variables removed from model by backward elimination due to insignificance (p > 0.157).
[±] HPV-status was available in 72% (262/365) of patients with OPC.
[£] Cases with unknown HPV-status for cancers of the oropharynx (n = 103), larynx (n = 159) and hypopharynx (n = 109).
[a] Age (p = 0.675), institution (p = 0.403), stage (p = 0.314), N-classification (0.477), NTV (p = 0.333).
[b] Age (p = 0.830), gender (p = 0.794), institution (p = 0.336), stage (p = 0.500), chemotherapy (p = 0.832).
[c] Age (p = 0.765), gender (p = 0.648), institution (p = 0.893), T-classification (p = 0.823).
[d] Gender (p = 0.584), institution (p = 0.936), stage (p = 0.422).

see Supplemental Materials). Patients with FDG-PET/CT-based NTV had a significantly increased regional control (HR: 0.62, 95% CI: 0.40–0.95, p = 0.027), overall survival (HR: 0.71, 95% CI: 0.52–0.97, p = 0.033) and a trend towards increased distant control (HR: 0.67, 95% CI: 0.43–1.07, p = 0.091) compared to patients with CT-based NTV (Fig. 1). No statistically significant differences were observed between centers. Local control of the primary tumor was not different between patients who had FDG-PET/CT-based or CT-based NTV (p = 0.333). Correlations analysis demonstrated only weak correlations between (FDG-PET/)CT-based NTV and

tumor sites (e.g. oropharynx) (Cramer's V = 0.13; p = 0.005) or HPV-status (Cramer's V = 0.28; p < 0.001), indicating independent parameters (see Supplemental Materials).

For all regional recurrences (n = 98), the exact site of each recurrence could successfully be projected onto the initial planning scans. Recurrences were located within the nodal GTV in 77% (75/98), within the CTV$_{elective-nodal}$ in 24% (24/98), and outside any target volume in 7% (7/98) of the cases. For all patients with regional recurrences outside the elective target volume, the nodal levels treated were as per protocol (i.e. there were no regional
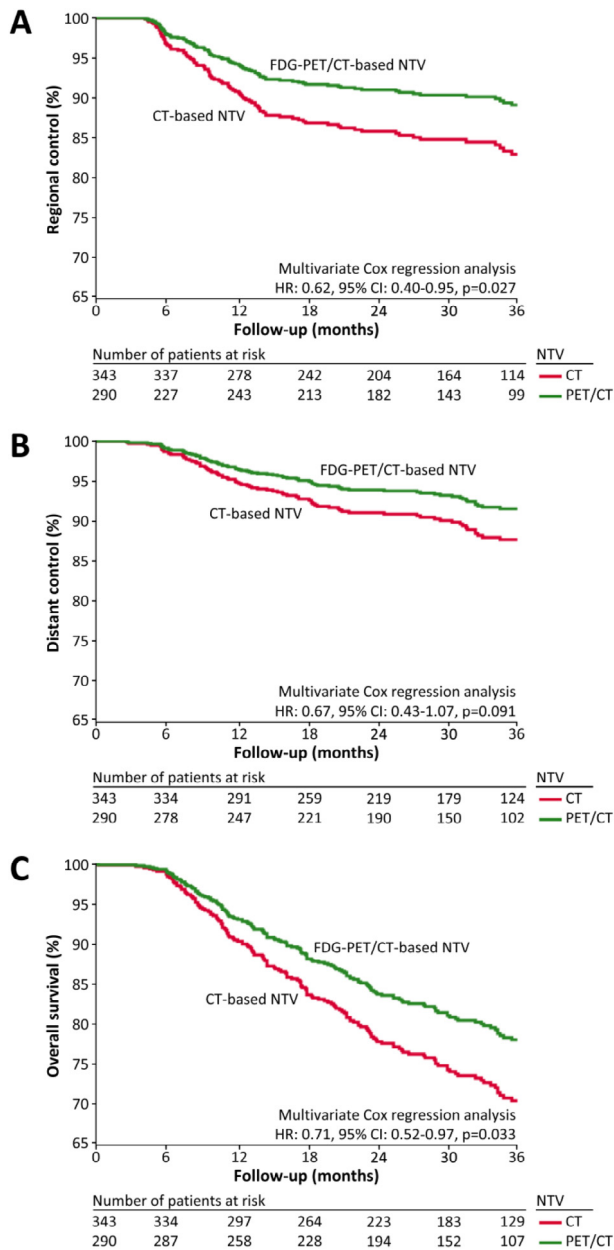
Fig. 1. Plots of multivariate Cox regression analysis showing actuarial radiotherapy outcomes stratified by FDG-PET/CT-based or CT-based NTV for (A) regional control, (B) distant control and (C) overall survival. Abbreviations: FDG-PET = 18F-fluorodeoxy-D-glucose positron emission tomography, CT = computed tomography, NTV = nodal target volume definition, HR = hazard ratio, CI = confidence interval.

Fig. 2. Plots of multivariate Cox regression analysis showing the actuarial rates of recurrence in the $CTV_{elective-nodal}$ stratified by (A) FDG-PET/CT-based or CT-based NTV and (B) presence of synchronous local recurrence of the primary tumor. *Abbreviations:* CTV = clinical target volume, FDG-PET = 18F-fluorodeoxy-D-glucose positron emission tomography, CT = computed tomography, NTV = nodal target volume definition.

examination of a neck dissection specimen (micro metastases) obtained at salvage surgery for the local recurrence, and thus was clinically occult (n = 2). For 1 patient, the local recurrent tumor was not recognized at the time of salvage treatment of the $CTV_{elective-nodal}$ recurrence (mucosal ulcer present), and was therefore diagnosed afterwards. For patients with synchronous local recurrence, FDG-PET/CT-based NTV did not reduce the rate of recurrence in the $CTV_{elective-nodal}$ (p = 0.27). For patients who remained free of local recurrence, not a single recurrence in the $CTV_{elective-nodal}$ was observed in case of FDG-PET/CT-based NTV (p = 0.01).

In 88% (21/24) of the patients with recurrence in the $CTV_{elective-nodal}$, pre-existing nodes on the exact same position of the recurrence could be identified on the initial planning scan. Critical revision of the images revealed that none of these pre-existing nodes were morphologically pathological (e.g. central necrosis or pathologically enlarged having a short-axis diameter ≥10 mm, or ≥11 mm in case of subdigastric nodes), and thus were not 'missed' in the GTV. These pre-existing lymph nodes had a significantly smaller volume (median: 0.46 cc versus 1.02 cc, p < 0.001) and short-axis diameter (median: 6 mm versus 8 mm, p = 0.05) (in transverse plane) in patients who had FDG-PET/CT-based NTV compared to those who had not (Fig. 3). FDG-uptake in pre-existing nodes was barely above background FDG-uptake, having a median SUR_{max} of 1.15 (range: 0.94–1.44). In cases of synchronous local recurrence of the primary tumor, pre-existing lymph nodes also had a significantly smaller volume (median: 0.76 cc versus 1.67 cc, p = 0.05) and short-axis diameter (median: 6 mm versus 8 mm, p = 0.04), compared to cases with isolated nodal recurrences (Fig. 3).

failures due to nodal levels erroneously not included in the elective volume). Recurrences in the $CTV_{elective-nodal}$ occurred within 2 years after treatment in 92% (22/24) of the cases.

Results of multivariate Cox regression analysis regarding recurrence in the $CTV_{elective-nodal}$ are shown in Table 1 and Fig. 2. Patients with FDG-PET/CT-based NTV had a significantly lower rate of recurrence in the $CTV_{elective-nodal}$ (HR: 0.33, 95% CI: 0.12–0.88, p = 0.026) compared to patients with CT-based NTV. Concurrent chemotherapy did not reduce this rate (p = 0.592).

In the entire patient group, the rate of recurrence in the $CTV_{elective-nodal}$ was significantly increased in case of synchronous local recurrence of the primary tumor (HR: 12.4, 95% CI: 5.1–30.0, p < 0.001). This means that regional recurrence was diagnosed during diagnostic work-up of the local recurrence or vice versa (n = 14), or that the regional recurrence was diagnosed by histopathological
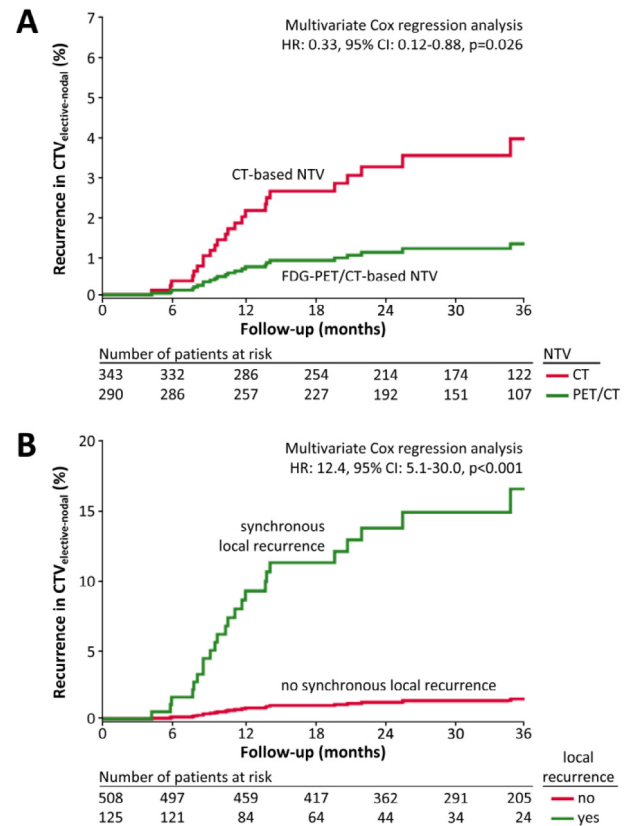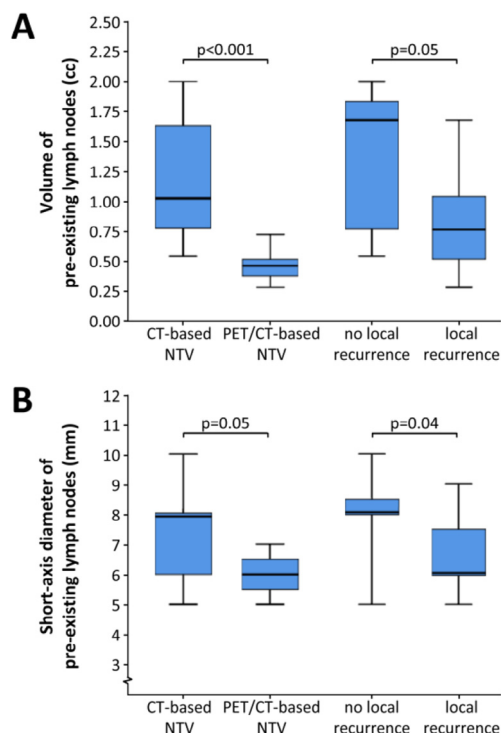
Fig. 3. Box plots showing the distribution of (A) volume and (B) short-axis diameter (in transverse plane) of pre-existing lymph nodes at the location of the CTV$_{elective-nodal}$ recurrence stratified by FDG-PET/CT-based or CT-based NTV, and synchronous local recurrence of the primary tumor. Abbreviations: FDG-PET = 18F-fluorodeoxy-D-glucose positron emission tomography, CT = computed tomography, NTV = nodal target volume definition.

Discussion

This retrospective analysis shows that FDG-PET/CT-based NTV significantly improves control of disease in the CTV$_{elective-nodal}$, regional control and overall survival, compared to CT-based NTV. These improved outcomes could not be attributed to HPV-effects as correlations analysis demonstrated independency between (FDG-PET/)CT-based NTV and tumor sites (e.g. oropharynx) or HPV-status. The results support the concept of target volume transformation and demonstrate the potential of FDG-PET to guide radiotherapy dose de-escalation in elective neck treatment in HNSCC [3]. In the following section, the concept of target volume transformation will be explicated and illustrated by clinical evidence provided in this paper.

It is well established that modern multimodality imaging including FDG-PET has improved the detection threshold of nodal metastases in HNSCC [9,10,15]. As a consequence, lymph nodes containing small tumorload that used to remain undetected and thus were included in the CTV$_{elective-nodal}$, are now detected and included in the GTV. This 'upgrading' of small nodal metastases from CTV$_{elective-nodal}$ to GTV is defined as target volume transformation (Fig. 4A) [3]. This is demonstrated in the current analysis by the smaller volume (0.46 cc versus 1.02 cc, p < 0.001) of pre-existing lymph nodes on the initial treatment planning CT-scan (at the locations of the CTV$_{elective-nodal}$ recurrences) in patients with FDG-PET/CT-based NTV. In an earlier comprehensive volumetric analysis of 1166 electively irradiated nodes in 264 patients of the current cohort with CT-based NTV, an increased risk of recurrence with increasing nodal volume was demonstrated (compared to nodes < 1.0 cc, HR = 5.4 for nodes 1.0–1.5 cc, and HR = 25.7 for nodes > 1.5 cc) [16]. A summed nodal short- and long-axis diameter was shown to be a good alternative for laborious volume calcu-
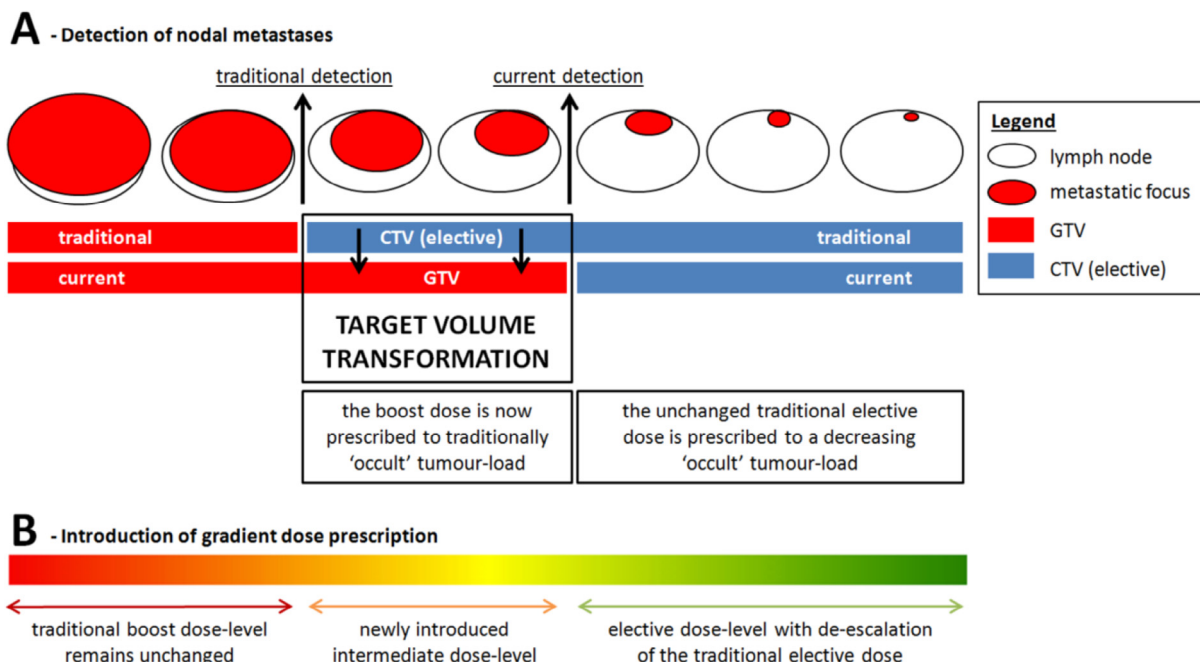

Fig. 4. Target volume transformation [3]. (A) Modern multimodality imaging employing FDG-PET has improved the detection threshold of small nodal metastases. As a result, borderline sized lymph nodes with metastases that used to remain undetected and were included in the CTV$_{elective-nodal}$, will nowadays be identified and included in the GTV. As a consequence of these target volume transformations, the GTV nowadays will more often contain low-volume disease (but is treated with the same high radiation dose) and the CTV$_{elective-nodal}$ will nowadays contain less tumorload (but is treated with the same elective radiation dose), which can be considered as overtreatment. (B) As such, the traditional binary dose prescription could be refined to a gradient dose prescription that is proportional to (occult) tumor volume. Abbreviations: FDG-PET = 18F-fluorodeoxy-D-glucose positron emission tomography, CTV = clinical target volume, GTV = gross tumor volume. Reproduced from [3] with permission.

lations, using ≥ 17 mm as cut-off (HR = 17.8). The significantly smaller volume (0.46 cc) of pre-existing lymph nodes in patients with FDG-PET/CT-based NTV suggests that borderline sized nodes carrying tumor deposits, but without pathological morphology, were identified by FDG-PET and added to the GTV. In the literature, several studies report nodal upstaging in 8–21% in patients with FDG-PET/CT-based NTV [11–15].

As a consequence of this improved detection, the GTV will more often contain low-volume disease, and the CTV$_{elective-nodal}$ will contain less occult disease (Fig. 4A). This has implications for treatment outcome, as is demonstrated in the current analysis by a significantly lower recurrence rate in the CTV$_{elective-nodal}$ in patients with FDG-PET/CT-based NTV (HR: 0.33, p = 0.026). While recurrence in the CTV$_{elective-nodal}$ is associated with synchronous local recurrence of the primary tumor (HR: 12.4, p < 0.001), the rate of local recurrences was not different between patients with FDG-PET/CT-based or CT-based NTV (p = 0.333) and thus could not explain the lower recurrence rate in the CTV$_{elective-nodal}$. The impact of FDG-PET/CT-based NTV on the recurrence rate in the CTV$_{elective-nodal}$ was most evident in patients without local recurrence, in whom not a single isolated recurrence in the CTV$_{elective-nodal}$ was observed.

There was also a significantly lower overall regional recurrence rate in patients with FDG-PET/CT-based NTV (HR: 0.62, p = 0.027). In the first place, this is a direct result of improved control of disease in the CTV$_{elective-nodal}$. Secondly, the addition of low-volume nodal disease to the GTV as a result of target volume transformation could also potentially have contributed to an increased control within the nodal GTV because treatment of low-volume disease to a high dose is expected to have a very high rate of control. Indeed, an increased overall survival was observed in patients with FDG-PET/CT-based NTV (HR: 0.71, p = 0.033). It is plausible that this is the result from the increased regional control in these patients, resulting in less distant metastases. In multivariate analysis on distant recurrence, a trend was observed towards less distant recurrences in patients with FDG-PET/CT-based NTV (HR: 0.67, p = 0.091).

As a consequence of the described target volume transformations, high-dose target volumes will more often contain low-volume disease (but are treated with the same high radiation dose), and elective volumes contain less tumorload (but are treated with the same elective radiation dose). This could be interpreted as an unintended dose escalation and thus as overtreatment, especially in the elective dose region (Fig. 4A) [3]. As such, this provides a window of opportunity for gradual de-escalation of radiation dose to lymph nodes proportional to the expected tumorload, aiming to maintain optimal tumor control with less treatment-related toxicity (Fig. 4B). FDG-PET is ideal for guidance of such dose de-escalation since it is a driving force for target volume transformation as FDG-uptake may be considered as a surrogate parameter for tumor cell density [23]. On the basis of nodal size and FDG-uptake, a graded dose prescription algorithm could be envisaged [16]. Morphologic pathological nodes and borderline sized nodes (e.g. summed diameter ≥ 17 mm) with high FDG-uptake receive the unchanged boost dose. Borderline sized nodes with intermediate FDG-uptake receive an intermediate dose. Nodes with low (normal) FDG-uptake are added to the low-risk volume (CTV$_{elective-nodal}$) and receive a de-escalated elective dose. Distinction between low-risk and intermediate-risk lymph nodes within the elective nodal target volume was recently recognized in the 2019 update for selection of lymph node target volumes in head and neck irradiation [24].

Currently, there is one ongoing multicenter randomized controlled trial that investigates the safety and long-term toxicity of this graded dose prescription concept [25]. In the UPGRADE-RT trial (NCT02442375), 300 patients with stage II-IV oropharyngeal, laryngeal and hypopharyngeal SCC will be randomized (ratio 2:1) to gradient dose prescription or to traditional dose prescription, irrespective of HPV-status. A FDG-PET/CT will be acquired for radiation treatment planning in all patients. In the intervention-arm, nodes are selected for treatment with an intermediate dose level of 60 Gy (EQD2) based on the previously mentioned risk-assessment algorithm using nodal size and FDG-uptake. Dose to the elective neck is de-escalated to 35 Gy (EQD2) versus 45 Gy (EQD2) in the control-arm. Dose to gross tumor will be 73 Gy (EQD2) in both treatment arms.

Another important observation in the current analysis is that the majority of recurrences in the CTV$_{elective-nodal}$ occurred synchronously with local recurrence of the primary tumor (17/24). FDG-PET/CT-based NTV did not reduce the recurrence rate in the CTV$_{elective-nodal}$ in patients *with* local recurrence (p = 0.27), while it was reduced to zero in patients *without* local recurrence (p = 0.01). This suggests that most of these recurrences may be new nodal metastases from the local recurrent primary tumor and do not result from failure of elective irradiation. This hypothesis is also supported by the observation that, in multivariate analysis, no benefit of concurrent chemotherapy was found on recurrence in the CTV$_{elective-nodal}$ (p = 0.592) while the radiosensitizing effect of chemotherapy is also expected to be effective for subclinical disease [26]. Finally, pre-existing lymph nodes at the location of the recurrence in the CTV$_{elective-nodal}$ had a substantially smaller volume in case of synchronous local recurrence (0.76 cc versus 1.67 cc, p = 0.05) compared to isolated nodal recurrences. The chance of harboring tumor rapidly decreases in nodes with decreasing size [4,5,27,28]. For such small tumor volumes, radiobiological models indicate very high tumor control probability (>98%) with current elective doses (45–50 Gy) [3]. Therefore, the 17.4% recurrence rate in the CTV$_{elective-nodal}$ in case of local recurrence cannot be solely explained by failure of elective irradiation.

While the observations mentioned above suggest that the majority of recurrences in the CTV$_{elective-nodal}$ are new nodal metastases from a synchronous local recurrence of the primary tumor, this study does not provide irrefutable evidence for this hypothesis. The gold standard to determine the presence or absence of occult nodal disease is histopathology, but obviously, this cannot be performed in retrospect [28]. Therefore, it is impossible to provide such evidence and the current results might be the best affirmation available. Other limitations of this study are the retrospective design, comparison with a single center cohort of CT-based NTV, and the low number of events. Due to the high efficacy of radiotherapy in eradicating occult disease, recurrence in the CTV$_{elective-nodal}$ was observed only in 24 of 633 patients. As a result, only the strongest predictors of recurrence in the CTV$_{elective-nodal}$, such as synchronous local recurrence and FDG-PET/CT-based NTV, could be identified in multivariate analysis. Potential but weaker associations with other patient or tumor characteristics were not found, but could not be excluded either.

In conclusion, this retrospective analysis shows that FDG-PET/CT-based NTV significantly improved control of disease in the CTV$_{elective-nodal}$, regional control and overall survival compared to patients with CT-based NTV. A significant proportion of CTV$_{elective-nodal}$ recurrences are potentially new nodal manifestations from a synchronous local recurrent primary tumor. These results support the concept of target volume transformation and give an indication of the potential of FDG-PET to guide gradual radiotherapy dose de-escalation in elective neck treatment in HNSCC. Results from randomized controlled clinical trials on FDG-PET guided dose de-escalation need to be awaited to evaluate safety and toxicity reduction.

Declaration of Competing Interest

All authors declare having no conflict of interest related to the content of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.07.025.

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