

Review

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¹⁸F-FDG-PET/CT-guided radiotherapy of cervical lymph nodes in head and neck squamous cell carcinoma

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Abstract

The use of positron emission tomography with fluor-18-fluorodeoxyglucose (FDG-PET) in clinical practice for patients with head and neck squamous cell carcinoma (HNSCC) has expanded rapidly, with implications for diagnostic staging, radiotherapy planning, adaptive radiotherapy, and post-therapy evaluation. The implementation of FDG-PET/CT in radiation treatment planning not only has consequences for target volume definition and dose prescription but is also associated with an increased overall survival in patients with HNSCC. FDG-PET/CT-guided gradient dose prescription provides a window of opportunity for treatment de-intensification of the neck in order to decrease treatment-related toxicity without compromising oncological outcome. Further, interim FDG-PET/CT during radiotherapy can be useful to assess metabolic tumor response and enables opportunities for adaptive treatment strategies. The goals are to increase treatment effectivity in poor responders and reduce unnecessary toxicity in patients with good early tumor response. Further prospective trials investigating adaptive radiotherapy based on interim PET-evaluation are needed, especially regarding human papilloma virus-negative HNSCC and patients treated with primary radiotherapy.

Keywords: Head and neck cancer, radiotherapy, FDG-PET, imaging, nodal metastases



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INTRODUCTION

In a majority of patients with head and neck squamous cell carcinoma (HNSCC), treatment consists of radiotherapy, and if possible, combined with chemotherapy for locally advanced disease^[1-3]. Current dose prescription in curative (chemo)radiotherapy [(C)RT] for HNSCC consists of two dose levels. A high “boost dose”, of around 70 Gy in fractions of 2 Gy (or biologically equivalent: EQD2), is delivered to tumor that can be detected during diagnostic work-up (i.e., macroscopic disease). A lower “elective dose” of 45-50 Gy (EQD2) is delivered to the so called elective clinical target volume (CTV_{elective-nodal}). This often encompasses large anatomical volumes of the neck containing the lymphatic drainage system and lymph nodes, that are presumed to harbour tumor deposits that are too small to be detected by diagnostic imaging (i.e., “microscopic”, “subclinical”, or “occult” disease). This concept originates from the 1950s and, remarkably, has not changed to date^[4]. At that time, assessment of macroscopic tumor extension was limited to physical examination. Therefore, defining the primary tumor was much less accurate, and small lymph node metastases (short-axis diameter < 10-15 mm) often remained undetected.

In the past few decades diagnostic imaging techniques have evolved rapidly, contributing to a better nodal staging of the neck in HNSCC. The criterion for pathologic lymph nodes on computed tomography (CT) was limited to a nodal short-axis diameter \geq 10 mm, because of a rapidly decreasing specificity for smaller nodes^[5]. With the use of magnetic resonance imaging (MRI), the detection threshold could be reduced to 7-10 mm, when assessing morphological features such as border irregularity and inhomogeneity^[6]. Ultrasound-guided fine needle aspirated cytology (US-FNAC) further improved the detection of smaller lymph node metastases, mainly based on the excellent specificity of pathological examination, but with limited sensitivity and inherent inter-operator variability and practical limitations in the number of evaluable nodes^[7,8].

Finally, the introduction of positron emission tomography with fluor-18-fluorodeoxyglucose (FDG-PET) imaging enabled quantitative functional evaluation of lymph nodes in addition to morphologic evaluation. Since the beginning of this century, the use of FDG-PET/CT in clinical practice for patients with HNSCC has expanded rapidly, being far more than only a diagnostic tool for disease staging. This review discusses the role of FDG-PET/CT in radiotherapy of the neck in HNSCC, with implications for diagnostic staging, dose prescription, adaptive radiotherapy, and post-therapy evaluation.

FDG-PET/CT FOR DIAGNOSTIC EVALUATION, CURRENT PRACTICE

Pre-treatment nodal staging

FDG-PET has the unique ability to perform a quantitative functional evaluation of tissues, as FDG-uptake reflects the metabolic activity of tumor cells and can be considered as a surrogate for tumor burden^[9]. Especially in HNSCC, FDG-PET/CT is commonly used for diagnostic evaluation of lymph nodes. Several large meta-analyses demonstrate a superior accuracy of FDG-PET/CT for lymph node assessment, in comparison with stand-alone conventional anatomic imaging^[10-13]. There are few studies reporting on the detection threshold of FDG-PET for nodal metastases in HNSCC using histopathological validation. Roh *et al.*^[14] examined 4378 lymph nodes in 93 HNSCC patients, finding a mean size of true-positive nodes of 12.4 ± 6.7 mm *vs.* 5.7 ± 4.5 mm for false-negative nodes. Similar results were reported in another study, suggesting a FDG-PET detection threshold of 5-10 mm^[15]. Functional and anatomical imaging modalities are considered complementary to a certain extent and, when used together, can lower the diagnostic threshold of nodal tumor deposits to about 5 mm^[16].

FDG-PET-guided surveillance of the neck

In addition to pre-treatment staging, FDG-PET/CT plays an important diagnostic role in follow-up after (C)RT for HNSCC. The main focus of post-therapy FDG-PET is the detection of residual disease in cervical lymph nodes. Multiple studies confirm that FDG-PET/CT has a high negative predictive value (> 93%) in the evaluation of residual nodal disease after (C)RT^[17-20]. However, there are indications that post-therapy response evaluation with FDG-PET/CT may be less reliable in human papilloma virus (HPV)-positive HNSCC^[19]. FDG-uptake as a result of inflammatory response to irradiation of the neck usually declines within weeks, allowing an accurate evaluation at approximately 10-12 weeks after the end of (C)RT^[21]. The PET-NECK trial demonstrated that survival was similar among advanced nodal stage HNSCC patients (N2/N3) who underwent PET/CT-guided surveillance 12 weeks after (C)RT, and those who underwent planned neck dissection. However, PET/CT-guided surveillance resulted in sparing of neck dissection in 80% of patients^[22]. Occasionally, increased FDG-uptake in certain areas of the neck may persist for months after (C)RT, without evidence of residual disease^[23]. The underlying causes include inflammation or ulceration^[18]. Correlation with clinical evaluation, anatomical imaging, histopathological validation, and discussion within a multidisciplinary board are critical to correctly differentiate persistent cancer from non-malignant pathology.

FDG-PET/CT-GUIDED RADIOTHERAPY, A NEW ERA

Impact on outcome

The better identification of lymph node metastases by FDG-PET not only has consequences for the radiotherapy target volume, but also has prognostic implications for HNSCC patients treated with (C)RT. Defining the nodal target volume based on FDG-PET/CT results in alteration of nodal radiation treatment in approximately 1 out of 4 patients compared to conventional imaging, with nodal up-staging in 8%-21% and down-staging in 3%-11%^[14,24-27]. Recently, van den Bosch *et al.*^[28] described the clinical impact of target volume transformation on radiation treatment outcomes using FDG-PET/CT-based treatment planning. They retrospectively analysed 633 HNSCC patients treated with definitive (C)RT. In 46% of the patients, a diagnostic iodine contrast enhanced FDG-PET/CT in treatment position was acquired for radiotherapy planning. If patients developed a recurrence in the neck after treatment, the exact site of the recurrence was reconstructed by performing co-registration of the diagnostic images showing the recurrence with the initial treatment planning scan. It was demonstrated that FDG-PET/CT-assisted radiation treatment planning is associated with a significantly lower rate of recurrence in the CTV_{elective-nodal} (HR = 0.33; *P* = 0.026), increased overall regional control (HR = 0.62; *P* = 0.027), and higher overall survival (HR = 0.71; *P* = 0.033), compared with CT-only radiotherapy planning^[28].

Target volume transformation

Combining FDG-PET/CT with conventional anatomical imaging significantly improves the detection rate of lymph node metastases, which has important consequences for radiotherapy target volume and dose [Figure 1]^[29]. Small metastases that remained subclinical in the past can nowadays be detected and thus are included in the gross tumor volume (GTV), which is treated to a high dose (≥ 70 Gy EQD2). Consequentially, the GTV covers a larger area and will more often contain small lymph nodes with relatively low-volume disease. As a result, the CTV_{elective-nodal} harbors less lymph nodes with smaller tumor load. This “shift” of lymph nodes between target volumes results in a decreased overall tumor burden in the CTV_{elective}, but also increases the number of nodes with low-volume disease in the GTV.

This nodal target volume transformation imposes changes in radiotherapy dose levels that need to be prescribed to these volumes. Moreover, this provides a window of opportunity for treatment de-intensification of the neck in order to decrease treatment-related toxicity without compromising oncological outcome.

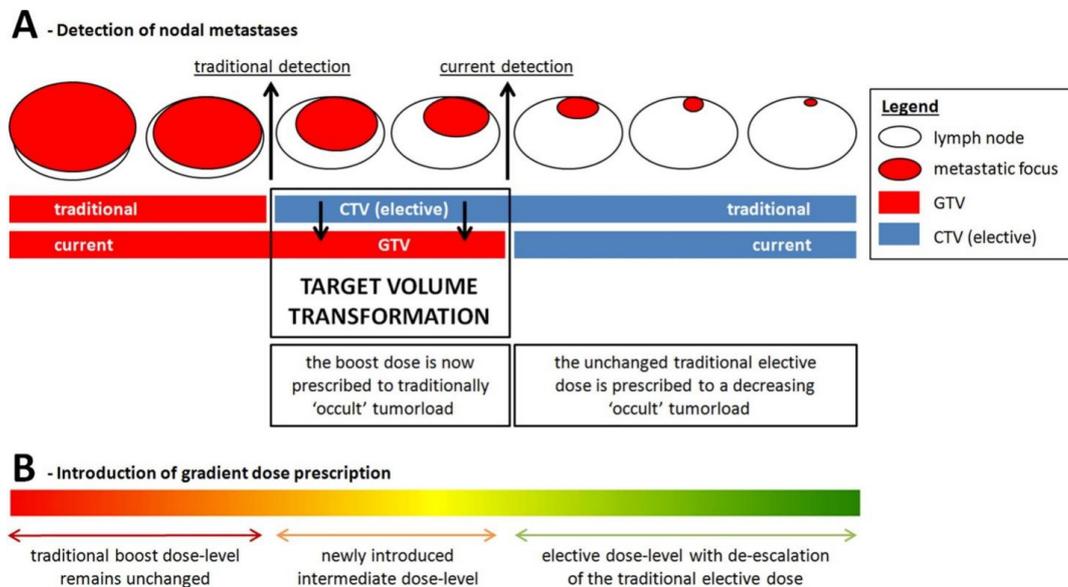


Figure 1. Target volume transformation. Nodal target volume transformation is defined as “upgrading” lymph node metastasis from the elective CTV to GTV based on their increased detectability resulting from improved diagnostic imaging techniques. Target volume transformation may result in overtreatment of both volumes. First, the boost-dose is now prescribed to small lymph node metastases that would have traditionally been treated with the elective dose. Second, the traditional elective dose is prescribed to the elective CTV while the occult tumor volume within the elective CTV is decreased as a result of improved diagnostic imaging (A). By refining traditional binary dose prescription to a gradient dose prescription that is proportional to (occult) tumor volume, the current overtreatment can be addressed in order to decrease treatment-related morbidity without compromising efficacy (B). Reprinted from van den Bosch et al.^[29], with permission from Elsevier. CTV: Clinical target volume; GTV: gross tumor volume.

Intermediate dose level

First, small nodal metastases that previously remained undetected and used to be part of the CTV_{elective-nodal} will currently be irradiated with a high boost dose of 70 Gy (EQD2) because they are now included in the GTV, which may be unnecessarily high for the relatively low tumor burden in these lymph nodes. Studies investigating recurrence in the electively irradiated neck have identified selection criteria for lymph nodes that can be treated with intermediate dose. An analysis of 1166 electively irradiated lymph nodes in 264 HNSCC patients identified nodal size (summed long- and short-axis diameter ≥ 17 mm) as an important risk factor for nodal failure after elective irradiation with 45 Gy (EQD2)^[30]. However, a relevant proportion of nodes with a summed diameter ≥ 17 mm turns out to be false positive, which confirms the need for additional parameters to facilitate adequate risk assessment of lymph nodes^[30]. Because FDG-uptake reflects the metabolic activity of tumor deposits it can be used as a surrogate measure of tumor load. FDG-PET/CT has the potential to discriminate between nodes with low, moderate, or high tumor burden using standardized nodal FDG-uptake thresholds^[9,31].

By combining nodal size and FDG-uptake as a parameter for tumor load, a nodal risk assessment algorithm for standardized evaluation of lymph nodes could be defined^[30-32]. For selected metastases with moderate tumor burden, an intermediate dose level of 60 Gy (EQD2) may be sufficient, as no recurrences in electively irradiated lymph nodes were observed above this dose in the previously mentioned retrospective analysis [Figure 2]^[30]. Radiobiological evaluations also show a high tumor control probability of occult metastatic nodes < 10 mm at the 60 Gy dose level^[29,33].

Elective dose and volume de-escalation

Another consequence of this target volume transformation is that the CTV_{elective-nodal} will contain lower

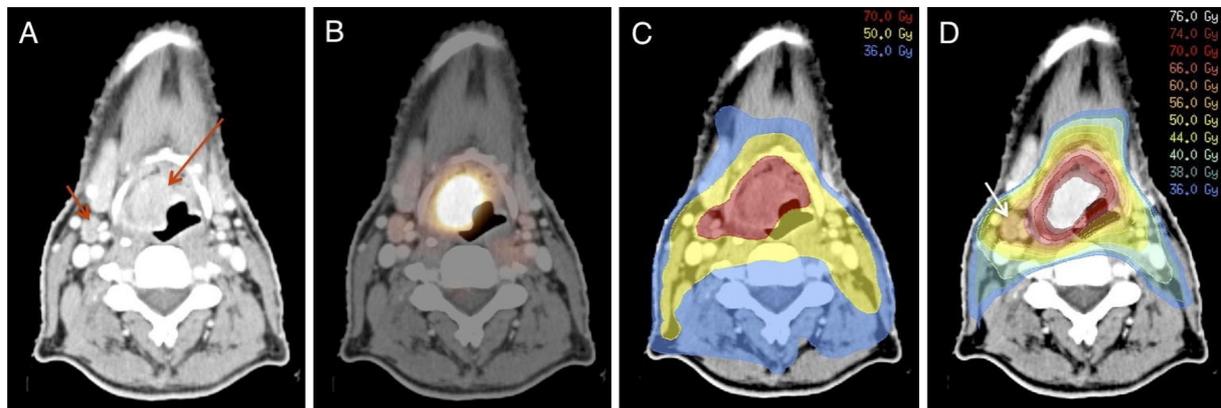


Figure 2. Patient with T3N1M0 squamous cell carcinoma of the supraglottic larynx. CT-scan showing primary tumor (long arrow) and small metastatic node (short arrow) (A). FDG-PET/CT scan showing high FDG-uptake in the primary tumor and moderate uptake in the lymph node indicating low tumor load in this node (B). Conventional radiotherapy dosing; 70 Gy to primary tumor and metastatic node and 50 Gy to elective lymph node regions (C). Gradient radiotherapy dosing; dose escalation (76 Gy) to gross tumor with high FDG-uptake in primary location, 70 Gy to peripheral zone, intermediate dose (60 Gy) to low volume tumor deposit with intermediate FDG-uptake (arrow), and low dose (36-40 Gy) to elective lymph node regions (D). Reprinted from Kaanders *et al.*^[34], with permission from Elsevier. FDG-PET: Fluor-18-fluorodeoxyglucose positron emission tomography.

disease volume, while it is nowadays still treated with the unchanged elective dose of 50 Gy (EQD2) originating from more than half a century ago. There is increasing evidence that lymph nodes that contain only very low-volume deposits of metastatic squamous cell carcinoma can be eradicated with doses well below 50 Gy^[29,33,35,36].

Deschuymer *et al.*^[35] performed a multicenter randomized controlled trial comparing an equivalent dose of 50 Gy with 40 Gy to the elective neck in 200 HNSCC patients treated with definitive (C)RT. After 5 years of follow up, no difference in elective neck failures between the dose levels were reported (2 elective-only recurrences in each arm) and no effect on overall survival was observed. The lower elective dose of 40 Gy resulted in a significant reduction of xerostomia and a trend toward less dysphagia at 6 months^[35,37,38]. However, in the 40 Gy arm, additional dose constraints were set to the swallowing apparatus, which potentially biases the toxicity outcomes of the trial. Furthermore, the dysphagia outcome scale of the RTOG-EORTC late toxicity scoring was used, which is quite a crude scale (e.g., ability to eat solid *vs.* semi-solid *vs.* only liquid foods), and may therefore be unable to detect subtle differences.

A single-arm phase 2 study using 36 Gy electively in 54 patients with locally advanced HNSCC showed no elective volume recurrences after a median follow-up of 36 months in surviving patients^[39]. Notably, 54% of these patients had HPV-positive oropharyngeal cancer, which is considered to be more radiosensitive and all patients received concurrent chemotherapy. At the Memorial Sloan Kettering Cancer Center, current clinical practice is to de-escalate the dose of the elective neck to 30 Gy (EQD2), albeit only in HPV-positive oropharyngeal cancer receiving concomitant platinum based chemotherapy^[40].

Recently the single-arm INFIELD trial investigated the possibility to improve acute and late morbidity of patients with oropharyngeal and laryngeal cancer, both by tailoring the elective irradiation only to regions with a legitimate risk of recurrence (> 5%) and by lowering the elective dose to 40 Gy^[36]. Following an “involved node” approach, nodal levels III and IV were only electively irradiated if the immediate proximal level contained pathologic lymph nodes. Irradiation of level IB and V was only performed in case of suspicious lymph nodes in these levels. Ninety percent of the patients received concurrent chemotherapy. At a median follow-up of 24.7 months for surviving patients, there were no solitary recurrences in electively

irradiated lymph nodes. Seven of 72 patients developed a nodal recurrence, 5 of which were in-field and 2 occurred in electively irradiated nodes with synchronous in-field recurrence. Patient-reported outcomes assessment at 1 year showed superior or equivalent outcomes compared with baseline, except for saliva and taste measures.

The above findings strongly suggest that the biologically equivalent dose of 36-40 Gy is sufficient to eradicate occult nodal disease after state-of-the-art assessment of the neck. In fact, this dose appears to be sufficient in both radiosensitive non-smoking, HPV-associated oropharyngeal cancer and higher-risk HPV-negative HNSCC. The concept of FDG-PET-guided gradient dose prescription is solely based on the estimation of tumor burden, and de-escalation of the elective dose is performed independent of tumor radiosensitivity. This concept may apply to many other tumor types in which routine treatment includes elective irradiation of nodal areas, such as cancers of the breast, cervix, prostate, rectum and bladder^[29]. The effect of dose de-escalation on toxicity may vary according to the anatomical location of target volumes and surrounding organs at risk. However, in all of the aforementioned dose de-escalation studies in HNSCC, a majority of patients received concurrent chemotherapy, which may compensate for a (too) low elective dose because of its radiosensitizing effect. Currently, the ongoing UPGRADE-RT trial (NCT02442375) is the first multicenter randomized controlled trial investigating the safety and efficacy of FDG-PET-guided dose de-escalation in HNSCC patients treated with primary radiotherapy, without the use of concomitant chemotherapy^[32]. The primary endpoint of the UPGRADE-RT trial is dysphagia, measured on a 10-step “normalcy of diet” scale from the performance status scale for patients with head and neck cancer. Three-hundred patients will be randomized and accrual is expected to be complete by the end of 2021, and first results to be reported in 2022.

Gradient dose concept

Implementing FDG-PET in radiation treatment planning, enables the opportunity to replace the current two-dose-level practice for a “gradient dose” concept, in which dose is prescribed proportional to tumor burden and the estimated risk of occult disease [Table 1]^[29]. In the intervention arm of the UPGRADE-RT trial, only a partial implementation of the gradient dose concept is being evaluated^[32]. For dose prescription to lymph nodes, an ordinal scale consisting of three dose levels is used, based on a risk assessment algorithm combining nodal size and metabolic activity on FDG-PET/CT as a surrogate for nodal tumor burden. To bring the gradient dose concept further, dose prescription to lymph nodes should ideally be done on a continuous scale, attuned to tumor burden per individual node. The ultimate implementation of this concept would imply selective irradiation of individual lymph nodes harbouring metastases, instead of elective irradiation of complete anatomical nodal levels. There are several innovative diagnostic techniques emerging that could support this implementation, such as ultra-small superparamagnetic iron-oxide nanoparticle (USPIO)-enhanced MRI and sentinel lymph node detection using SPECT/CT^[41]. However, the exact diagnostic value of these techniques in the detection of very small nodal tumor deposits is still under investigation, impeding implementation of the gradient dose concept to its full extent at this point.

Interim treatment evaluation by PET

Despite treatment with concomitant (C)RT, loco-regional disease relapse occurs within the first 2 years in 30%-50% of patients with locally advanced HNSCC, mostly in initially involved sites^[42]. It would be of great help if subgroups of patients that are poor responders to (C)RT can be identified before or early during the treatment. Performing FDG-PET/CT during radiotherapy can be useful to assess metabolic tumor response in addition to volume-based assessment by anatomical imaging. Several studies aimed to identify early prognostic imaging biomarkers using interim FDG-PET, enabling on-treatment decisions to be made regarding modification of treatment strategy (e.g., early dose de-escalation or switch to a different treatment modality)^[43-46]. The goals are to increase treatment effectivity in poor responders and reduce unnecessary

Table 1. Overview of current and future concepts in radiotherapy for HNSCC

Concepts	Currently	Near future	Distant future
RT dose/volume	- Traditional binary dose prescription - Large elective irradiation volumes	- FDG-PET guided gradient dose prescription - Sentinel lymph node procedure	- On individual basis, elective volumes will be largely reduced or completely abandoned - Selective irradiation of sentinel lymph node(s) only
FDG-PET for radiotherapy planning	- Increasingly used, but not in a systematic manner	- Algorithms for risk assessment of lymph nodes and segmentation of PET-signal	- Biological target volumes based on more specific PET-tracers
Interim PET response evaluation	- Not widely implemented in clinical practice	- Dose adaptive RT (e.g., escalation/de-escalation) - Anatomically adaptive RT	- Biological tumor profiling with various PET-tracers to guide patient tailored treatment

HNSCC: Head and neck squamous cell carcinoma; RT: radiotherapy; FDG-PET: fluor-18-fluorodeoxyglucose positron emission tomography.

toxicity in patients with good response.

Prognostic PET-biomarkers

Timing is of crucial importance when determining the value of interim FDG-PET/CT for various reasons. First, radiotherapy-induced mucositis occurring mostly in the second half of the treatment course could complicate the interpretation of images. Secondly, evaluation should not be done too early because it takes time to develop a response. And third, the earlier response prediction can be done, the more time remains to modify the treatment strategy. There are good indications that week 2-3 of radiotherapy, corresponding to a delivered dose of about 20 Gy, seems the most favourable time-point for interim PET-evaluation^[44,45,47].

In a meta-analysis, pre-treatment high metabolic tumor volume, defined as the sum of the volume of voxels in a tumor with standardized uptake value (SUV) surpassing a certain threshold value, was significantly associated with a worse loco-regional control and overall survival^[46]. Several studies reported that a lower total lesion glycolysis (i.e., the product of SUVmean and metabolic tumor volume) at 3 weeks into treatment was predictive for loco-regional control and overall survival in patients with HNSCC^[45,48-50]. Metabolic tumor volume and SUVmax reduction during treatment seem also prognostic for loco-regional control^[45,51,52]. Hentschel *et al.*^[47] found in a retrospective analysis that patients with a reduction of SUVmax $\geq 50\%$ within the first 2 weeks of (C)RT, showed significantly higher 2-year overall survival rates (88% vs. 38%; $P = 0.02$) and 2-year loco-regional control rates (88% vs. 40%; $P = 0.06$) compared to patients with a SUVmax reduction $< 50\%$. However, evidence regarding this issue remains equivocal. At present, no firm conclusions can be drawn about the optimal metabolic parameter to predict outcome early during treatment using FDG-PET, nor the corresponding threshold values.

PET-guided adaptive radiotherapy

Early response evaluation with PET imaging could open a window of opportunity for adaptive treatment strategies [Table 1]^[53]. First, there is the possibility to refine the target volume during the course of radiation therapy based on changes in FDG-uptake, which would allow for a reduction of the treated volume and thus facilitate healthy tissue sparing. Already in 2007, Geets *et al.*^[54] found that, using a gradient-based algorithm on five FDG-PET scans performed before and during radiotherapy, PET-segmented target volumes could be reduced by 15%-40% compared to baseline CT-planning. Other studies have demonstrated a reduction of the mean parotid dose with CT-based re-planning during the course of radiation for a selected group of patients, which resulted in a significantly lower risk of xerostomia^[53,55]. The main difficulty of anatomically adaptive radiotherapy is the fact that re-simulating, re-contouring, and re-planning of patients remains highly time-consuming^[56]. Besides, there is no clear consensus about clinical or dosimetric criteria to select patients who benefit most from re-planning. However, we envisage that this process will be largely automated in the near future, based on technological advancement such as synthetic CT generation from

daily cone-beam computed tomography and auto-contouring using artificial intelligence^[57,58]. Though CT-based automated re-planning could theoretically be performed on a daily basis, this is not realistic for FDG-PET-guided re-planning. FDG-PET should be reserved for re-planning based on metabolic tumor response once or twice during a course of radiotherapy^[44].

Second, there is the strategy of radiotherapy dose (de-)escalation during treatment. Several studies confirmed the feasibility of FDG-PET-guided “dose painting by numbers”, where voxel-wise dose escalation is related to FDG-uptake to produce a non-uniform dose distribution^[59-61]. Currently two randomized controlled phase II trials are investigating whether radiotherapy dose escalation based on interim FDG-PET/CT can improve loco-regional control compared to standard radiotherapy (NCT01341535 & NCT01504815). However, in this era of concomitant chemotherapy, immunotherapy, and targeted therapy, it is debatable if radiotherapy dose escalation is a reasonable approach to improve outcome, especially since it may increase the risk of severe late toxicity such as mucosal ulcers^[62]. Therefore, we believe it is important to keep the high dose volume (e.g., > 70 Gy) to a minimum. When using modern imaging, the target definition is more accurate and GTV-CTV_{gross} margins can be tighter^[63-65]. Also, the traditional dose of 70 Gy may be unnecessarily high for microscopic local tumor spread. Applying an intermediate dose of approximately 50-60 Gy to the periphery of the tumor may be adequate to eradicate small tumor extensions. This opens an opportunity for dose escalation to smaller, but highly active metabolic tumor volumes, or small tumor volumes that show residual FDG uptake towards the end of the radiation course, without increasing the risk of late sequelae. In the future of HNSCC treatment, it remains highly important to explore the landscape of patient tailored radiotherapy-drug combinations and how PET-based early response assessment, next to genetic and biological tumor profiling, can steer this process^[66].

Opposite to radiotherapy dose intensification, interim PET treatment evaluation enables the opportunity for dose de-escalation in patients with favourable prognosis and excellent intra-treatment tumor response in order to decrease radiotherapy related morbidity. Clinical evidence regarding interim PET-guided dose de-escalation in well-responding patients remains scarce, especially in HPV-negative HNSCC and patients treated with primary radiotherapy^[67]. Recently, a non-randomized controlled trial has been initiated to evaluate the safety of radiotherapy dose de-escalation in HPV-associated oropharyngeal cancer, based on interim evaluation with FDG-PET/CT in week 2 of (C)RT (NCT04667585). Besides FDG, there are several other PET-tracers that can be useful for intra-treatment tumor response evaluation and adaptive radiotherapy, such as fluorothymidine (FLT), fluoro-ethyl-tyrosine (FET), fluoromisonidazole (FMISO) and fluoroazomycin-araboside (FAZA)^[21,44,67-69]. Similar to FDG, week 2-3 of radiotherapy seems to be the optimal time-point for interim PET-evaluation with these tracers. Further discussion of these tracers is outside the scope of this review.

CONCLUSION

The use of FDG-PET/CT in patients with HNSCC has major implications for diagnostic staging and radiotherapy. High sensitivity of FDG-PET/CT for identification of smaller lymph node metastases not only has consequences for radiotherapy target volume definition and dose prescription, but also has prognostic implications. The use of FDG-PET/CT in radiotherapy planning opens a window of opportunity for treatment de-intensification of the neck in order to decrease toxicity without compromising oncological outcome. This concept is currently being investigated in the randomized controlled UPGRADE-RT trial. Further prospective trials investigating adaptive radiotherapy based on interim PET-evaluation are needed, especially regarding HPV-negative HNSCC and patients treated with primary radiotherapy.

DECLARATIONS

Authors' contributions

Performed the literature search and drafted and revised the manuscript: Cox MC, van den Bosch S
Critically reviewed and edited the manuscript: van den Bosch S, Dijkema T, Kaanders JHAM
Supervised the writing process: Kaanders JHAM
Approved the final version of the report: Cox MC, van den Bosch S, Dijkema T, Kaanders JHAM

Availability of data and materials

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Conflict of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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