

ORIGINAL ARTICLE



Repeatability of hypoxia dose painting by numbers based on EF5-PET in head and neck cancer

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ABSTRACT

Background: Hypoxia dose painting is a radiotherapy technique to increase the dose to hypoxic regions of the tumour. Still, the clinical effect relies on the reproducibility of the hypoxic region shown in the medical image. ¹⁸F-EF5 is a hypoxia tracer for positron emission tomography (PET), and this study investigated the repeatability of ¹⁸F-EF5-based dose painting by numbers (DPBN) in head and neck cancer (HNC).

Materials and methods: Eight HNC patients undergoing two ¹⁸F-EF5-PET/CT sessions (A and B) before radiotherapy were included. A linear conversion of PET signal intensity to radiotherapy dose prescription was employed and DPBN treatment plans were created using the image basis acquired at each PET/CT session. Also, plan A was recalculated on the image basis for session B. Voxel-by-voxel Pearson's correlation and quality factor were calculated to assess the DPBN plan quality and repeatability.

Results: The mean (SD) correlation coefficient between DPBN prescription and plan was 0.92 (0.02) and 0.93 (0.02) for sessions A and B, respectively, with corresponding quality factors of 0.02 (0.002) and 0.02 (0.003), respectively. The mean correlation between dose prescriptions at day A and B was 0.72 (0.13), and 0.77 (0.12) for the corresponding plans. A mean correlation of 0.80 (0.08) was found between plan A, recalculated on image basis B, and plan B.

Conclusion: Hypoxia DPBN planning based on ¹⁸F-EF5-PET/CT showed high repeatability. This illustrates that ¹⁸F-EF5-PET provides a robust target for dose painting.

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¹⁸F-EF5; hypoxia; dose painting; repeatability; radiotherapy; treatment planning system; positron emission tomography

Background

Dose painting is a radiotherapy (RT) technique to escalate the radiation dose to radioresistant regions of the tumour [1–3]. This technique is particularly relevant for head and neck cancers (HNC), as recurrences after radiotherapy are mainly localised within the primary tumour and involved nodes [4,5]. The main medical imaging modality in defining targets for dose painting is positron emission tomography (PET), although, e.g., diffusion-weighted magnetic resonance imaging has also been proposed [6,7]. Clinical results from dose painting of HNC based on PET with the metabolism tracer ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) are emerging, indicating high control levels but also rather high toxicity levels [8–11]. Still, patients with HNC treated with conventional RT have good treatment outcomes, especially those with HPV-positive disease in the oropharynx [12]. Moreover, the metabolic tumour volume based on ¹⁸F-FDG was recently shown to be prognostic only for patients with HPV unrelated disease [13]. Thus, for HNC, it may be preferable to employ dose painting of targets more closely linked to

radioresistance in selected patients with expected poor outcomes from conventional treatment.

Hypoxia is a known cause of clinical radioresistance in patients with HNC [14]. Several PET tracers have been suggested for hypoxia imaging [14,15], where ¹⁸F-fluoromisonidazole (¹⁸F-FMISO) is the most widely used. 2-(2-nitro-H-1-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)-acetamide (¹⁸F-EF5) is another hypoxia tracer for PET showing promising results for patients with HNC [16–18]. Previous studies utilising non-labelled ¹⁸F-EF5 have comprehensively demonstrated the hypoxia-avidity of this compound [19]. Compared to other hypoxia markers, such as ¹⁸F-FMISO and ¹⁸F-FAZA, ¹⁸F-EF5 has high lipophilicity and rapid clearance from normal neck tissues, resulting in higher or equal hypoxia-specific uptake [20]. This is an obvious advantage in HNC hypoxia dose painting, where the hypoxic regions of the tumour are targeted, thereby potentially increasing the likelihood of tumour control [21–24]. Currently, to the knowledge of the authors, there is one ongoing phase II hypoxia dose painting

trial of HNC, where an interim analysis has indicated no excess toxicity compared to conventional RT [25].

There are principally two different dose painting approaches dose painting by contours (DPBC) and dose painting by numbers (DPBN) [26,27]. DPBC requires thresholding of the hypoxic tumour sub-volume in the PET image and is technically the same as a simultaneous integrated boost. On the other hand, DPBN adapts the radiation dose distribution to a dose prescription map reflecting the voxel-by-voxel variation in hypoxia levels evident from the PET image. As such, DPBN is a more tailored treatment than DPBC and is more robust against variations in PET image reconstruction [28].

Although hypoxia dose painting is a promising approach, the treatment efficacy will depend on the geometrical stability of the targeted hypoxia within the tumour. It is common to plan the dose painting treatment based on one imaging session, acquired ~1 week before the start of treatment. Thus, image noise and potential temporal and spatial variations in tumour hypoxia are not considered. A diagnostic repeatability study indicated that the ^{18}F -EF5 distribution in HNCs was rather stable before treatment [18], but it is not clear how this impacts dose painting. This study aimed to investigate the robustness of ^{18}F -EF5-PET dose painting using a commercial treatment planning system [29] to repeat imaging and changes in ^{18}F -EF5 uptake over a few days. To our knowledge, no studies on EF5-based DPBN have previously been reported, and no studies have investigated the repeatability of DPBN based on a hypoxic PET tracer in general.

Material and methods

During 2013–2016, eight HNC patients who were enrolled in a diagnostic study before RT underwent two ^{18}F -EF5-PET/CT investigations a median of 7 days apart, in addition to standard RT planning with ^{18}F -FDG-PET/CT. All patients gave their signed consent to participate in the study. Patient inclusion criteria, as well as details on the imaging protocol, are found in the paper by Silvoniemi et al. [18]. Images were acquired on a GE D690 PET/CT (General Electric Medical Systems, Milwaukee, WI, USA) in the supine treatment position with thermoplastic mask fixation. Gross target volume (GTV) delineation was, according to current clinical practice, based on the RT planning ^{18}F -FDG-PET/CT images. The GTVs ranged between 9 and 94 cc with a mean of 50 cc (SD 33 cc). Tumour sites were the base of the tongue ($n=3$), nasopharynx (2), hypopharynx (1), oropharyngeal wall (1), and tonsillae (1). The T and N stages ranged from T2 to T4 and N0 to N3b, respectively (TNM 8th edition).

For this study, two repeat ^{18}F -EF5-PET/CT acquisitions were used. The first image series is referred to as EF5_A/CT_A and the second as EF5_B/CT_B. To manage the transfer of delineated contours from the planning CT as well as the dose recalculation between plans, all three CT image series were rigidly registered to each other in the Varian Eclipse Image Registration workspace version 13 (Varian Medical Systems Palo Alto, CA, USA). The CT series had a voxel size

of $1 \times 1 \times 2.5$ mm and a roughly 15 cm field-of-view (FOV) in the craniocaudal direction. The voxel size of the EF5-PET images was $3.65 \times 3.65 \times 3.27$ mm, which corresponds to a volumetric resolution of 0.04 cc. The DPBN treatment planning was performed according to the previous work by Arnesen et al. [29]. Briefly, a dose prescription matrix based on the ^{18}F -EF5 voxel uptake within the delineated GTV was generated. The dose prescription was based on a previously published linear formula relating the dose in a voxel to the corresponding PET intensity [1]. Assuming the treatment to be delivered in 35 fractions, the prescribed minimum, and maximum GTV dose was set to 70 Gy (standard dose from conventional RT) and 90 Gy, respectively. The inverse of the dose prescription matrix was then used as a mock base treatment plan for IMRT optimisation in dose summation mode. For treatment planning, 5–7 coplanar 6 MV IMRT treatment fields for a Varian TrueBeam with Millennium MLC were used. Optimisation and dose calculation were carried out with Eclipse (algorithms DVO 13.7.16 and AAA 13.7.16) with a dose matrix resolution of 0.25 cm. The high-risk CTV was created by a 5 mm expansion of the GTV excluding anatomic barriers. The corresponding PTV was generated by the addition of an isotropic 5 mm margin to the CTV, which resulted in PTVs between 50 and 251 cc (mean 157 cc). The prescribed dose to the PTV was 70 Gy and the GTV maximum was constrained to $V_{90\text{Gy}} \leq 2$ cc. No nodal or elective volumes were employed due to the limited craniocaudal FOV of the ^{18}F -EF5-PET/CT scans. The OAR dose constraints used were a spinal canal maximum of 40 EqD2Gy ($\alpha/\beta=0.9$ Gy), brainstem 54 EqD2Gy ($\alpha/\beta=3.0$ Gy), and optical nerves and chiasm 50 EqD2Gy ($\alpha/\beta=3.0$ Gy). For one patient with the tumour adjacent to the chiasm with optical nerves passing through it, the OARs were subtracted from the PTV such that the tolerance doses would not be exceeded. This patient treatment was also planned with seven fields, of which one had a couch angle of 270°.

A total of three DPBN plans were calculated for each patient: (a) DPBN_A based on the uptake in EF5_A, (b) DPBN_B based on EF5_B, and (c) DPBN_{A-B}, which was DPBN_A recalculated on CT_B. Voxel-by-voxel-based analysis of the GTV dose was carried out in Interactive Data Language (IDL 8.5, Harris Geospatial Solutions, Broomfield, CO, USA). To assess DPBN plan quality and repeatability, Pearson's correlations and quality factors (QFs) were calculated between the two EF5 sessions, treatment plans a–c, and the theoretical dose prescription derived from the EF5 uptakes. The quality factor QF was calculated as:

$$QF = \frac{1}{n} \sum_n \left| \frac{D_n}{(D_p)_n} - 1 \right|$$

where n is the total number of voxels within the GTV, D_n the planned dose in voxel n , and $(D_p)_n$ the prescription dose for voxel n [1]. For an ideal plan, QF equals 0.

To display voxel-by-voxel associations without showing an excessive number of data points, per-patient data was split into seven bins between the minimum and maximum dose value, and standard deviations and mean values were calculated within each bin. We stress that the binning was only

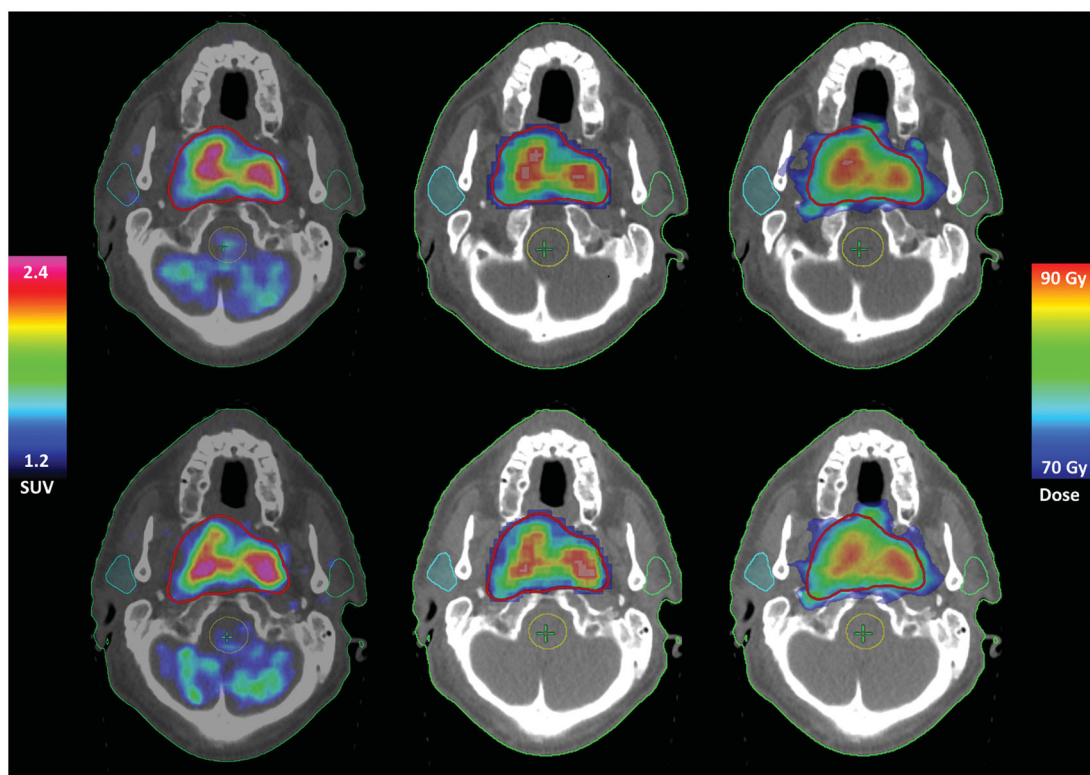


Figure 1. Example of PET uptake and dose distributions from repeat EF5-PET/CTs A and B (upper/lower row) for one patient. Left: ^{18}F -EF5 PET distributions; centre: corresponding DPBN prescribed doses; right: calculated doses.

Table 1. Pooled dose characteristics for the calculated DPBN plans.

	DPBN _A Dose Gy	DPBN _B Dose Gy	DPBN _{A-B} Dose Gy
Ipsilat. parotid gland Dmean ^a	15.7 (2.3–27.4)	16.0 (2.3–28.9)	16.0 (2.2–28.4)
Contralat. parotid gland Dmean ^b	6.1 (0.8–13.7)	6.3 (0.9–14.0)	6.3 (0.8–14.4)
Spinal canal D0.01 cc	43.8 (27.6–52.7)	43.5 (24.3–52.3)	43.4 (30.4–51.8)
PTV D98%	66.0 (63.6–67.4)	65.7 (62.4–67.0)	66.2 (63.1–67.2)
PTV Dmedian	72.3 (71.4–72.3)	72.4 (71.3–73.8)	72.8 (71.3–76.4)
GTV D98%	72.5 (70.9–75.7)	72.1 (70.5–73.3)	72.9 (71.2–75.0)
GTV D2%	90.6 (89.2–93.7)	90.3 (89.1–91.0)	91.1 (89.4–93.8)
GTV Dmedian	82.5 (78.9–87.0)	82.8 (79.9–87.4)	82.9 (79.1–87.0)

Parotids mean (range), spinal canal maximum (range) as well as PTV and GTV minimum, maximum, and median (range) doses are given.

^aMean of eight patients of whom two had medial tumours; in total 10 parotid glands.

^bMean of six patients, where the two patients with medial tumours were omitted.

performed for data display. All correlations and QFs were calculated for the full voxel-by-voxel distributions.

Results

An example of an EF5 distribution with the corresponding prescribed dose and the resulting optimised DPBN treatment plan is displayed in Figure 1. All DPBN plans, as well as the recalculated plan, had clinically acceptable and similar parotid and spinal canal doses as seen in Table 1. PTV minimum dose (D98%) varied between 62.4 and 67.4 Gy for all patients, which corresponded to 92–96% dose coverage of the prescribed dose, except for patient 2. For patient 2, who had a large tumour (84 cc), the PTV coverage ($D_{98} = 62.4$ Gy or 89%) was compromised by the OARs. All GTV dose distributions were well within the set maximum dose constraint $D_{2cc} \leq 90$ Gy, and despite patient-wise variations, there

were only small differences between the three sets of plans as seen from the population-based dose-volume histograms (DVHs) for GTV (Figure 2). GTV minimum doses (D98%) were between 72.1 and 72.9 Gy for all three plans and the maximum doses (D2%) between 90.3 and 91.1 Gy. A minor increase (0.6–0.9%) in GTV maximum dose for plan DPBN_{A-B} was found. The individually highest D2% of 93.8 Gy was found for one of the recalculated plans and corresponded to a volume of 0.2 cc.

Voxel-by-voxel analysis of GTV doses showed that DPBN treatment plans agreed well with the prescription doses in terms of correlation (R) and QFs, as seen from Table 2 and Figure 3. For a pooled population, the calculated dose DPBN_A was slightly higher than the prescription dose by 1–2% for low doses, while differences were <1% for doses higher than 80 Gy (Figure 3). The DPBN_B doses and prescribed doses were within 0.1–1% (data not shown). Despite the larger spread between DPBN_A and DPBN_B (Figure 3), a

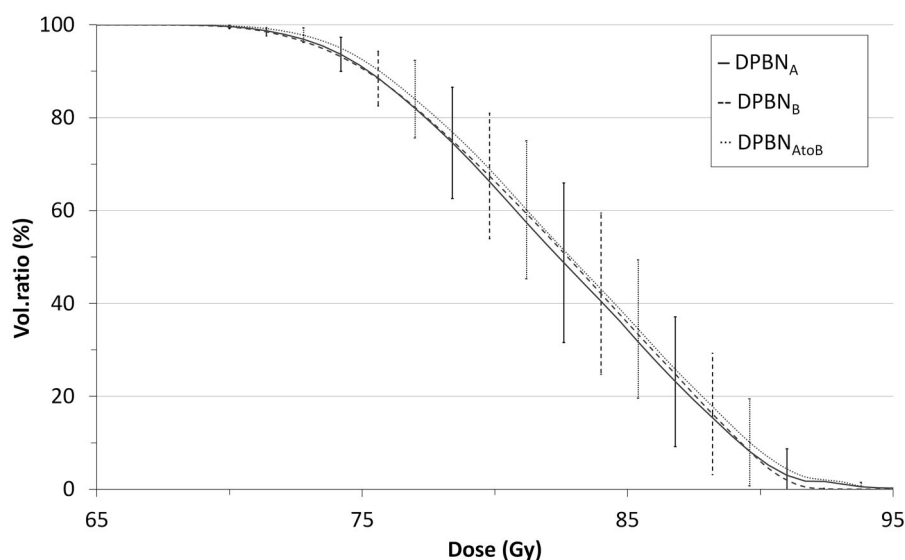


Figure 2. Zoomed mean GTV DVHs between 65 and 95 Gy overall patients for the DPBN plans based on EF5_{A/B} distributions: DPBN_A solid, DPBN_B dashed, and recalculated dose distribution DPBN_{A-B} dotted line. Error bars represent SDs.

Table 2. Mean (SD) correlation coefficients (R) and quality factors (QF) between EF5_A and EF5_B SUVs, EF5_{A/B} based prescriptions, and calculated doses (DPBN_{A/B}), as well as for the EF5_A based treatment plan recalculated on CT_B (DPBN_{A-B}) vs. the EF5_B based plan.

	R	QF
Prescription EF5 _A vs. calculated DPBN _A	0.92 (0.02)	0.02 (0.003)
Prescription EF5 _B vs. calculated DPBN _B	0.93 (0.02)	0.02 (0.002)
SUV EF5 _A vs. SUV EF5 _B	0.74 (0.14)	0.09 (0.02)
Prescription EF5 _A vs. prescription EF5 _B	0.72 (0.13)	0.04 (0.01)
DPBN _A vs. DPBN _B	0.77 (0.12)	0.03 (0.009)
DPBN _{A-B} vs. prescription EF5 _B	0.74 (0.08)	0.04 (0.005)
DPBN _{A-B} vs. DPBN _B	0.80 (0.08)	0.03 (0.005)

pooled comparison showed mean differences of <0.2%. Comparing the recalculated plans DPBN_{A-B} to DPBN_B, the differences were similar to that of DPBN_{A/B} and their prescription doses, which also is reflected by the QFs in Table 2 (0.03 vs. 0.02). Patient 6 was a slight outlier, with DPBN_{A-B} being 3–5% higher than DPBN_B, and this patient also had one of the largest GTVs (92 cc).

Discussion

We have investigated the temporal robustness and feasibility of ¹⁸F-EF5-based hypoxia dose painting of HNC. The results indicate that within one week before RT, the tumour hypoxia did not change in a way that would compromise DPBN delivery. The calculated treatment plans will effectively be smoothed by the MV photon dose deposition kernel relative to the raw PET-based prescription map. This is reflected in the slight improvements in both correlations and QFs when crosswise comparing recalculated dose distributions with SUV maps. Therefore, the DPBN plans are expected to be robust to minor changes over time in hypoxic volumes. The achieved quality factors (typically <0.03) are below the limit of 0.05 stated by Duprez et al. for clinically acceptable plans [30]. Although correlations were lower for the recalculated DPBN_{A-B} plans, the quality factors increased minutely and the plans were still within acceptable limits.

In line with the diagnostic imaging results from Silvoniemi et al. [18], the variations between the two ¹⁸F-EF5 PET uptake distributions were not pronounced and had only a limited effect on the resulting DPBN treatment plans. Previous studies on ¹⁸F-fluoromisonidazole (FMISO) PET has reported high reproducibility of SUVs when imaging head and neck [31,32] and lung cancer patients [33] 1–2 days apart. Considering dose painting, van Schie et al. [27] investigated repeat multiparametric MRI-based DPBN for prostate cancer patients with 21 days between imaging sessions. Both image sets were acquired before RT and showed good stability of DP with correlations between 0.82 and 0.98 and QFs of ~0.04 for the two sessions. In hypoxic HNC, with potentially acute and chronic hypoxic subvolumes, dose painting robustness and imaging accuracy are of even higher importance. For dose painting of HNC, Rasmussen et al. showed no relevant dosimetric impact of changes in ¹⁸F-FDG over time with a three-day interval between PET acquisitions [34]. Despite the small number of patients, our similar results for ¹⁸F-EF5-based DPBN imply that this is also the case when targeting hypoxia, indicating that spontaneous changes (before treatment) in acute and chronic hypoxia are not of great concern.

Since all imaging was performed before RT, we have no data on how, e.g., accelerated repopulation and revascularization affect acute and chronic hypoxic sub-volumes. These effects are thought to occur days to weeks after the start of radiotherapy [35]. Therefore, a possible workflow could be to start the treatment course with DPBN and acquire ¹⁸F-EF5-PET/CT control images after the first weeks of treatment. Thereafter, it could be decided whether to continue with the same DPBN, an adapted DPBN based on the new hypoxic sub-volumes, or a conventional approach with a homogeneous dose distribution in case the hypoxic subvolumes are inconsistent or absent [30]. The current work may serve as a guideline for when to adapt the treatment, as treatment-induced changes should be significantly greater than the variations seen before treatment.

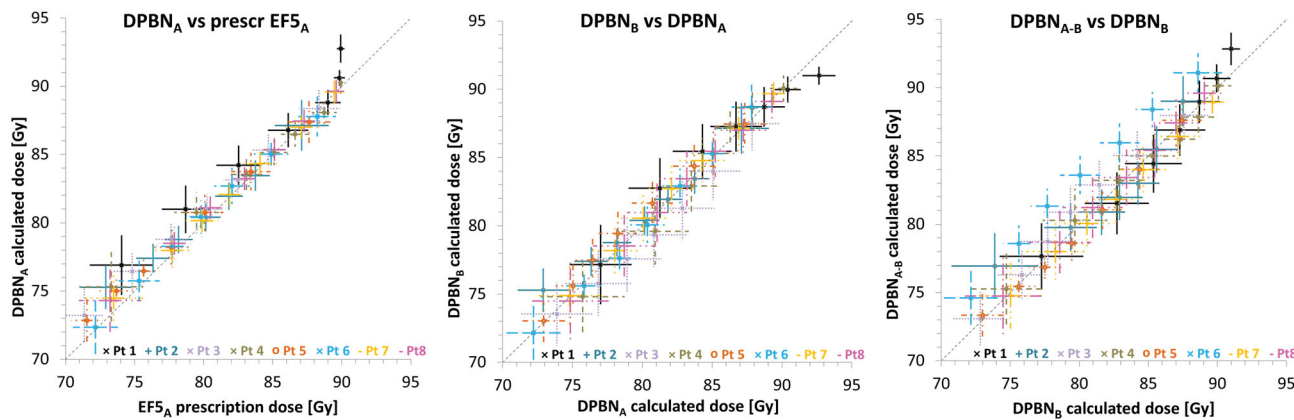


Figure 3. Binned paired data for GTV dose in $DPBN_A$ vs. prescription $EF5_A$ (left), $DPBN_B$ vs. $DPBN_A$ plan (middle), and recalculated plan $DPBN_{A+B}$ vs. $DPBN_B$ (right). The dotted line represents a perfect match $x = y$. For visualisation the data was split into seven bins, where each point represents the mean value within that bin while the horizontal and vertical lines are the ranges.

Olteanu et al. [8] reported late grade 4 mucosal ulcers after DPBN of HNC patients when the GTV dose was escalated to maximum $D2\% \geq 84$ Gy. Furthermore, patients with grade 4 ulcer had median tumour volumes of 17 cc, compared to 9 cc for those without grade 4 side effects. From a clinical point of view, especially for larger tumours it might be reasonable to either lower the allowed dose maximum of 90 Gy or decrease the DPBN prescription volume. In the current study, the clinical GTVs (based on FDG-PET and CT) were larger than the hypoxic sub-volumes from the ^{18}F -EF5 images. To reduce the dose-escalation volume, it might be sensible to choose a sub-GTV for dose painting based on e.g., $SUV^{18}F$ -FDG thresholding, similarly to the procedure of Welz et al. [25]. In their study on ^{18}F -FMISO dose painting, also for HNC patients, they concluded that a median of 77 Gy to an ~ 2 cc (range 0.3–49 cc) hypoxic tumour volume was well tolerated. In the current study, we obtained CTV median doses of 76–80 Gy (data not shown), which, however, is below the reported tolerated median CTV doses of 80.9 Gy by Madani et al. [9]. Correspondingly, also the reported GTV median doses of about 83 Gy are in line with the 85.9 Gy median dose reported by Madani. The studies by Olteanu [8], Madani [9], and Berwouts [11] all investigated parts of the same patient material and were based on ^{18}F -FDG-PET, which is indicative not of tumour hypoxia but of hypermetabolism. This is a general sign of malignancy (through the Warburg effect) and may as such include larger sub-volumes within the GTV compared to hypoxia. It is, therefore, possible that dose painting with a hypoxia tracer could focus the highest doses better to smaller but radioresistant parts of the tumour, and that the mucosa may thus tolerate ^{18}F -EF5-based DPBN at higher maximum doses than with ^{18}F -FDG-based DPBN.

Conclusions

In conclusion, the current work illustrates that hypoxia dose painting for HNC patients could be performed with ^{18}F -EF5-PET images acquired up to one week before the start of treatment. The DPBN plans were temporally robust,

indicating that baseline treatment planning using this hypoxia tracer is highly reliable.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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