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Dose painting

FDG-PET and diffusion-weighted MRI in head-and-neck cancer patients: Implications for dose painting

Antonetta C. Houweling, Anne Lisa Wolf, Wouter V. Vogel, Olga Hamming-Vrieze, Corine van Vliet-Vroegindeweij, Jeroen B. van de Kamer, Uulke A. van der Heide *

Department of Radiotherapy, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

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ABSTRACT

Purpose: The purpose of this study was to investigate if FDG-PET and DWI identify the same or different targets for dose escalation in the GTV of HN cancer patients. Additionally, the dose coverage of DWI-targets in an FDG-PET-based dose painting plan was analyzed.

Materials and methods: Eighteen HN cancer patients underwent FDG-PET and DWI exams, which were converted to standardized uptake value (SUV)- and apparent diffusion coefficient (ADC)-maps. The correspondence between the two imaging modalities was determined on a voxel-level using Spearman's correlation coefficient (ρ). Dose painting plans were optimized based on the 50% isocontour of the maximum SUV ($SUV_{50\%max}$). Dose coverage was analyzed in three different SUV- and three different ADC-targets using the mean dose and the near-minimum and near-maximum doses.

Results: The average maximum SUV was 13.9 and the mean ADC was $1.17 \cdot 10^{-3}$ mm^2/s. The average ρ between SUV and ADC was −0.2 (range: −0.6 to 0.4). The ADC-targets were only partly overlapping the $SUV_{50\%max}$-target and the dose parameters were significantly smaller in the ADC-targets compared to the $SUV_{50\%max}$-target.

Conclusions: FDG-PET and DWI contain different information, resulting in different targets. Further information about failure patterns and dose relations can be obtained by adding DWI to currently ongoing dose painting trials.

The feasibility and benefit of dose painting in the head-and-neck (HN) area are being investigated in several clinical trials [1–3]. In these trials, dose painting is based on a single imaging modality, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). FDG-PET identifies aggressive or radiation resistant subvolumes, as it represents the cumulative effects of multiple adverse tumor characteristics, such as high cell metabolism, proliferation, expression of key oncogenes, and hypoxia [1,4]. In principle, other PET tracers and functional magnetic resonance imaging (MRI) techniques are also available to visualize the complex and heterogeneous biology of the tumor [5–8].

Diffusion-weighted MRI (DWI) is an MRI technique that reflects the microanatomy of the tissue. Water diffusion in and between cells is restricted by increased cellularity, which is frequently observed in tumors [9]. Wang et al. reported a more severe restriction in malignant tumors compared to benign solid masses [10].

While both FDG-PET and DWI could be candidates to define subvolumes within the GTV for dose painting in HN cancer, it is not obvious how to convert image values into dose. For PET, typically areas with a standardized uptake value (SUV) above 50% of the maximum SUV in the GTV are boosted [1–3]. For DWI, the relation between the apparent diffusion coefficient (ADC) and the required dose is not clear. While a low ADC value is indicative of tumor presence [10], Hatakenaka et al. [11] reports that a higher ADC within the tumor is associated with worse outcome.

Therefore, the purpose of this study was to investigate whether FDG-PET and DWI identify the same or different targets for dose escalation within the GTV. Furthermore, the dose coverage of DWI targets in FDG-PET-based dose painting was analyzed.

Materials and methods

Patients

Eighteen consecutive patients with HN cancer referred to our department for radiotherapy between May 2010 and August 2011, were included in this study (Table 1). No patients were previously treated for cancer.

* Corresponding author. Address: Department of Radiotherapy, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands.
E-mail address: u.vd.heide@nki.nl (U.A. van der Heide).

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Table 1
Patient characteristics.

Tumor location	T-stage	Number of patients
Oral cavity	T2	1
	T3	2
	T4a	2
Oropharynx	T2	5
	T3	1
	T4a	2
Nasopharynx	T1	1
	T3	3
	T4	1

Imaging

The planning CT scan, PET/CT and MRI exam were performed within 2 weeks.

The planning CT scan (Somatom Sensation Open, Siemens Healthcare) was performed using intravenous contrast, patients were positioned in their five-point radiotherapy mask. The scan was acquired using an in-plane voxel size of $1 \times 1\ mm^2$ and 3 mm thick slices.

Patients received a FDG-PET/CT exam (GEMINI TF, Philips Healthcare) and were positioned in their five-point radiotherapy mask. The CT scan was acquired for attenuation purposes using 40 mAs, 140 kV, and $2 \times 2 \times 2\ mm^3$. The FDG-PET scan was performed 1 h post-injection of 190–240 MBq of FDG. Data were acquired for 3 min per bed position. Patients were well hydrated, fasted for 6 h and glucose levels were below 10 mmol/l. The images were reconstructed to $2 \times 2 \times 2\ mm^3$ voxels using attenuation correction. The FDG-PET images were converted to SUV maps.

The MR images were acquired (3.0T Achieva, Philips Healthcare) using a 16-element neurovascular receive coil. The MRI scans used in this study were a transversal T1-weighted MRI and the DWI images, both part of the standard clinical MRI protocol.

The T1-weighted MRI was acquired with a 3D turbo field echo (TFE) technique with gadolinium enhancement. The scan had acquired and reconstructed voxels of $0.8 \times 0.8 \times 0.8\ mm^3$, a repetition time (TR) of 5.0 ms, an echo time (TE) of 2.2 ms, a flip angle of 10°, a TFE factor of 90, and fat suppression using spectrally selective attenuated inversion recovery (SPAIR).

The DWI images were acquired using single-shot spin-echo echo-planar imaging (EPI) with an acquisition matrix of 112×89, a FOV of 230 (AP) $\times$ 230 (RL) mm^2, reconstructed voxels of $0.9 \times 0.9\ mm^2$, 35 slices of 4 mm, sensitivity encoding (SENSE) with a factor of 2, TR/TE of 3815/45 ms, fat suppression using a spectral fat saturation inversion recovery (SPIR) technique, and a bandwidth of 30.2 Hz/pixel. The *b*-values were 0 and 1000 s/mm^2, with a number of averages of 1 and 3, respectively. The ADC map was calculated on the scanner (software version 3.2.1).

Standard clinical delineation of the GTV was performed by an experienced radiation oncologist on the conventional CT, FDG-PET and T1-weighted MRI scans according to local hospital guidelines.

Image registration

For this study, all images were registered to the planning CT using in-house developed software with a region of interest defined around the GTV [12]. The quality of the image registration was verified by visual inspection.

The PET/CT scan was rigidly registered to the planning CT using a normalized correlation coefficient algorithm. The T1-weighted MRI scan was rigidly registered to the planning CT using mutual information [13]. Before applying the same transformation to the DWI images, distortions due to susceptibility artefacts [9] were corrected using deformable registration of the DWI images ($b = 0\ s/mm^2$ image) to the T1-weighted MRI [14]. The deformable registration was performed using a 6-step multiresolution strategy based on mutual information, a gradient based optimizer and a global smoothness penalty [15]. The resulting deformation field was applied to the ADC-map.

FDG-PET based dose painting

The dose painting treatment plans were generated for this planning study only (Pinnacle^3, version 9.2, Philips Healthcare) according to the guidelines of the ARTFORCE trial [1]. These VMAT plans were acquired using a simultaneous integrated boost (SIB) technique. In short, a subvolume was defined within the clinical GTV as the 50% isocontour of the maximum SUV ($SUV_{50\%max}$), which was expanded with a margin of 3 mm to the PET-PTV. The prescribed mean dose to the primary PTV, lymph nodes and the elective PTV was 67, 70 and 54.25 Gy respectively, delivered in 35 fractions. The dose to the PET-PTV was escalated to a maximum dose of 84 Gy, with a minimum of 70 Gy and a mean dose of 77 Gy. The dose constraints to the organs at risk were a maximum normalized total dose (NTD) of 55 Gy for the brainstem and of 50 Gy for the spinal cord ($\alpha/\beta = 2$). We aimed to obtain a mean physical dose to at least one parotid gland below 26 Gy.

Data analysis

For each patient, the correspondence between the SUV- and ADC-maps was investigated on a voxel-level within the GTV. The Spearman's correlation coefficient (ρ) of all corresponding voxels within the GTV was calculated. Spearman's ρ does not require a linear relation between the values as the more often used Pearson's ρ does. Instead, a monotonic relation is required, which includes linear relations.

To evaluate the dose coverage of the FDG-PET dose painting plan, target volumes had to be defined. For the FDG-PET based dose painting, the target was defined as the area with a SUV-value above the $SUV_{50\%max}$ threshold, comparable to other dose painting studies [1–3]. To investigate the influence of the threshold, target volumes $SUV_{60\%max}$ and $SUV_{40\%max}$ were generated comparably.

For the ADC, an often used measure to report ADC values within a tumor is the mean ADC in a region [16]. However, large variations in threshold values have been reported in the HN area, ranging from $0.4 \cdot 10^{-3}\ mm^2/s$ to $1.4 \cdot 10^{-3}\ mm^2/s$ [17]. Additionally, a low ADC is indicative of tumor presence, but a higher ADC within the tumor is associated with worse outcome [11]. Therefore, we segmented the areas within the GTV with an ADC below the mean ADC ($ADC_{<mean}$), below the mean ADC minus the standard deviation ($ADC_{<mean-SD}$) and above the mean ADC ($ADC_{>mean}$) as ADC-targets.

The percentage overlap of these target volumes with the target volume used for the dose painting plans ($SUV_{50\%max}$) was calculated. For the purpose of this study, the dose parameters were evaluated in the target volumes and not in PTVs. The mean dose (D_{mean}), the near-minimum dose ($D_{98\%}$) and the near-maximum dose ($D_{2\%}$) [18] were determined for all targets. A Wilcoxon signed-rank test was used to test for statistical difference in the dose coverage.

Results

The volume of the GTV was 36.7 ml on average (range: 5.7–118.7 ml). The average maximum SUV and mean ADC were 13.9 and $1.17 \cdot 10^{-3}\ mm^2/s$, respectively. The voxelwise Spearman's ρ between the SUV and ADC ranged from −0.63 to 0.36 (Fig. 1), which indicates that FDG-PET and DWI contain different information in the majority of the patients (Figs. 2 and 3).