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MISO PET in head and neck

Serial [18F]-fluoromisonidazole PET during radiochemotherapy for locally advanced head and neck cancer and its correlation with outcome

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ABSTRACT

Purpose: The aim was to assess changes of tumour hypoxia during primary radiochemotherapy (RCT) for head and neck cancer (HNC) and to evaluate their relationship with treatment outcome.

Material and methods: Hypoxia was assessed by FMISO-PET in weeks 0, 2 and 5 of RCT. The tumour volume (TV) was determined using FDG-PET/MRI/CT co-registered images. The level of hypoxia was quantified on FMISO-PET as TBRmax (SUVmaxTV/SUVmean background). The hypoxic subvolume (HSV) was defined as TV that showed FMISO uptake $\geqslant$1.4 times blood pool activity.

Results: Sixteen consecutive patients (T3–4, N+, M0) were included (mean follow-up 31, median 44 months). Mean TBRmax decreased significantly ($p < 0.05$) from 1.94 to 1.57 (week 2) and 1.27 (week 5). Mean HSV in week 2 and week 5 (HSV2 = 5.8 ml, HSV3 = 0.3 ml) were significantly ($p < 0.05$) smaller than at baseline (HSV1 = 15.8 ml). Kaplan–Meier plots of local recurrence free survival stratified at the median TBRmax showed superior local control for less hypoxic tumours, the difference being significant at baseline and after 2 weeks ($p = 0.031$, $p = 0.016$).

Conclusions: FMISO-PET documented that in most HNC reoxygenation starts early during RCT and is correlated with better outcome.

Hypoxia is a characteristic feature in HNC and has been identified as a factor negatively correlated with prognosis [1–3]. Tumour hypoxia is known to increase radiation resistance, has been identified as a key factor in triggering hypoxia-mediated gene expression and was found to be associated with a more aggressive tumour phenotype [1]. There are a significant number of trials showing that hypoxia-PET may serve as a tool to identify patients potentially at increased risk of local failure [3]. However, the question whether hypoxia-PET may serve as a basis for radiation treatment planning by dose painting in intensity modulated radiation therapy (IMRT) is still open [2–6]. A central problem is the poor knowledge regarding the variation of tumour hypoxia during R(C)T and the possible implication of this variation on radiation treatment planning.

There are only limited data on the temporal changes of hypoxia based on PET imaging during R(C)T and its correlation with clinical outcome. Eschmann et al. [7] investigated 14 patients with HNC on FMISO-PET before and under radiotherapy and observed a significant tumour reoxygenation under treatment (ca. 45 Gy), suggesting a correlation with a better tumour control but without statistical significance. The group of Leuven [8] assessed the variation of hypoxia on FMISO-PET in 15 HNC patients. They also described a significant re-oxygenation during RCT. Additionally they showed that hypoxia is one of the most important factors affecting RCT treatment resistance: not only the pretreatment level of hypoxia but also the extent during radiotherapy (30 Gy) correlated significantly with disease control. Zips et al. [9] investigated the temporal changes of tumour hypoxia in 25 HNC patients treated with RCT. In an exploratory prospective trial the authors showed that FMISO-PET in the first or second week of RCT has a strong prognostic value for diagnosing patients with high risk of tumour recurrence. Interestingly, PET before treatment was not as strong in comparison. The authors postulate that different treatment related tumour reoxygenation profiles lead to differences in treatment response. A prospective hypoxia imaging study

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including 50 patients is on-going. The group of Aarhus [10] investigated on FAZA-PET/CT 40 patients with HNC cancer included in the DAHANCA 24 trial. In 13/40 patients a FAZA-PET/CT was performed about 14 days after the start of RCT. The HSV during treatment became significantly smaller and was located in the same region assessed at the first and second PET investigation. The authors observed a higher recurrence rate in the hypoxic group (4/6 patients) in comparison to the group showing no hypoxia under treatment (2/7 patients), however statistical significance was not reached.

Our group assessed the distribution of hypoxia in HNC on FAZA-PET [4], showing that in the majority of patients the hypoxic tissue was located in a single confluent region and therefore a HSV for radiation treatment planning could be delineated based on hypoxia-PET. Only in a small number of cases hypoxia was diffusely dispersed or the tumours were not hypoxic. In a more recent study [11] we have evaluated the changes in the location of the HSV on FMISO-PET during RCT and have concluded that in patients with persistent hypoxia after 2 weeks of treatment, the HSV is topographically relatively stable.

The goal of this prospective feasibility study was to evaluate the temporal changes of tumour hypoxia during RCT, to correlate these data with the clinical outcome and, considering our results and published data, to discuss their possible impact on the design of new treatment strategies.

Materials and methods

Patients' characteristics

Sixteen consecutive patients undergoing definitive RCT for locally advanced HNC (squamous cell carcinoma) were enrolled. Inclusion criteria were histologically confirmed T3/4, N+, M0 squamous cell carcinomas of the oral cavity, oropharynx, hypopharynx, and larynx and age $\geqslant$18.

Study design

A prospective feasibility FMISO-PET imaging monocentric study was conducted. The institutional review board approved the study and all participants provided written informed consent. Tumour hypoxia was assessed by FMISO-PET prior to (FMISO1) and during the course of RCT, at weeks 2–3 (FMISO2) and weeks 5–6 (FMISO3).

All patients received planning CT, MRI (MRI1) and [^{18}F]-fluorodeoxyglucose (FDG)-PET imaging prior to RCT. MRI was repeated in treatment weeks 5–6 (MRI2).

Radiation treatment was delivered as conformal IMRT (2 Gy/d, 5×/week; total dose to macroscopic tumour 70 Gy). Cisplatin was administered in weeks 1, 4, 7 (100 mg/m^2). For follow-up, patients were evaluated clinically and by MRI every 3 months.

PET/CT

[^{18}F]-MISO and [^{18}F]-FDG production met standard quality criteria. For FMISO-PET, one bed position, covering the head and neck region examined 150 min after injection of approx. 400 MBq [^{18}F]-MISO. Scan duration was 35 min (3 frames at 10 min, followed by a 5 min transmission scan). For quantitative analysis, three attenuation corrected frames were summed after excluding frames with patient movement. Planning CT images were acquired in 2-mm slice thickness. For FDG-, FMISO-PET and CT, patients were immobilized identical to the radiation position with a head and neck mask.

Image analysis

PET data were iteratively reconstructed to voxels of $4.3 \times 4.3 \times 3.4\,mm^3$ using an ordered-subset expectation–maximization (OSEM) reconstruction algorithm. Scatter and attenuation correction was applied. Hypoxic volumes were determined using PMOD software (PMOD-Group, Switzerland). Tumour volume (TV) delineation, separately for primary tumour and pathological lymph nodes, was performed on FDG-PET/CT/MRI co-registered images. In accordance with the literature, the TV was determined on FDG-PET by a 40% threshold of the maximum standardized uptake values (SUVs) within TV.

The intensity of FMISO uptake was assessed quantitatively by calculating the ratio of the maximum SUV in the tumour (TV) to the mean SUV in contralateral neck musculature (TBRmax). By visual assessment, a TBRmax of $\geqslant$1.4 was considered most appropriate to define a tumour as being hypoxic. For statistical analysis, median TBRmax values were applied to split according to oxygenation status (median TBRmax for FMISO 1, 2, 3: 2.02, 1.26, 1.24).

The HSV was determined by normalizing against blood activity concentration by counting all voxels within the TV for which the tumour to blood ratio on FMISO-PETs was $\geqslant$1.4 [12]. The blood activity concentration was determined from a region of interest in the left ventricle. The HF was defined as the ratio of HSV/TV.

Statistical analysis

Statistical analyses were performed using SPSS (v. 15.0.1.) and Stata/IC 12. p-values <0.05 were considered statistically significant. Comparison of continuous outcomes between subgroups is based on paired Wilcoxon-tests. The Wilcoxon matched-pairs signed-ranks test was used to compare TBRmax and HSVs between PET scans. The Mann–Whitney-*U* test was applied to compare mean TBRmax between recurrent and non-recurrent tumours. The association of various PET parameters with the time to recurrence was assessed using Kaplan–Meier plots based on splitting the values at the median, together with *p*-values from a log-rank test.

Results

15/16 patients (94%) showed hypoxic tumour tissue on the baseline FMISO-PET scan: 11 in the primary tumour only, 2 in lymph nodes only, 2 in both. The number of patients with hypoxic lesions decreased to 5/14 (36%) at the second and to 3/11 (27%) at the third FMISO-PET investigation. Mean TBRmax significantly decreased from 1.94 (pre-treatment) to 1.57 (week 2, $p = 0.035$) and 1.27 (week 5, $p = 0.003$) (Table 1, Fig. 1). The median TBRmax dropped from 2.02 (pre-treatment) to 1.26 (week 2) and 1.24 (week 5).

Mean and median TV assessed by FDG-PET/CT/MRI and HSV, HF on FMISO-PET at baseline and in week 2 and 5 are presented in Table 2.

Mean follow-up was 31 months (median 44, range 1–53 months). The time course of FMISO TBRmax was strikingly different for patients with and without recurrence (Figs. 1 and 2, Table 1). While patients without tumour recurrence demonstrated a rapid and continuous decrease in the TBRmax, the decline was slower in patients with recurrence and some patients even showed an increase in tumour hypoxia at the time of the second FMISO-PET. No local recurrence occurred if there was at least one negative FMISO scan (TBRmax < 1.4, Fig. 1).

For the three consecutive FMISO-PET scans, patients with tumour recurrence were found to have higher mean TBRmax compared to patients without tumour recurrence: mean TBRmax over all time points: 2.15 vs. 1.45, (Mann–Whitney-*U*-Test, $p = 0.002$).