In vivo correlation of glucose metabolism, cell density and microcirculatory parameters in patients with head and neck cancer: initial results using an integrated PET/MRI tomograph.

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Aims and objectives

$^{18}$Fluor-Fluorodesoxyglucose Positron Emission Tomography with combined Magnetic Resonance Imaging ($^{18}$F-FDG-PET/MRI) seems to be a promising modality for imaging of head and neck squamous cell carcinoma (HNSCC) as in this type of malignancy the infiltration of surrounding structures is important for local staging and for surgical and radiotherapy planning [1].

With the high soft-tissue contrast of MRI and the superior ability of $^{18}$F-FDG-PET to detect nodal and distant metastatic tumour spread prior to morphological changes, the advent of combined PET/MRI will open new perspectives in non-invasive imaging [2]. The combination of PET with MRI also opens up numerous options to acquire multiple multimodal molecular imaging parameters simultaneously. This may contribute to a more detailed characterization of cellular and subcellular processes in vivo [3].

We hereby report about a study in which glucose metabolism (assessed by $^{18}$F-FDG-PET), tumour cellularity (measured by diffusion-weighted imaging - DWI) and microcirculatory parameters (estimated by T1-weighted dynamic contrast-enhanced MRI - T1w-DCE) were simultaneously acquired in patients with HNSCC.
Methods and materials

Patients

Patients with suspected malignancy of the upper aerodigestive tract or a cancer of unknown primary with cervical lymphadenopathy were scheduled to undergo $^{18}$F-FDG-PET computed tomography (PET/CT) for staging and treatment planning and thereafter, without additional radiopharmaceutical administration, an integrated simultaneous PET/MRI study. Patients were retrospectively included in the current study if they fulfilled the following inclusion criteria: (a) if a de-novo or recurring HNSCC of the upper aerodigestive tract was histopathologically proven either by biopsy or by resection within 2 weeks after imaging, (b) if a histopathological report including a tumour grading was available, (c) if a dedicated simultaneous PET/MRI of the neck including T1w-DCE and DWI sequences was performed with sufficient image quality not distorted by motion artefacts, (d) if no diagnostic or therapeutic intervention was performed on the tumour and (e) if a tumour was delineable in the imaging studies.

PET-imaging

Fasting of at least 6 hours prior to the investigation was ensured. After application of $^{18}$F-FDG dependent on body weight and an uptake time of 90 minutes (Lasix was given 5 minutes after admission of the radiotracer) a whole-body PET/CT was performed. Immediately afterwards, patients were transferred to the PET/MRI where whole-body and dedicated neck images where acquired without radiotracer reapplication.

Integrated PET/MRI tomograph

All examinations were performed on a combined simultaneous whole-body hybrid PET/MRI scanner (Siemens Biograph mMR; Siemens Healthcare, Erlangen, Germany). Detailed descriptions of the technical aspects were described in previous publications [4,5].

Simultaneous PET/MRI imaging protocol

Patients were placed in supine position with their arms beside the trunk. PET/MRI was conducted in two steps. After a whole body PET/MRI, a dedicated PET/MRI of the neck using a combined head & neck coil was performed, which included following sequences:

- a PET of the head & neck neck with 10 minutes of acquisition time
- an axial DWI-EPI sequence with b-values of 0 and 800 (TR/TE 8620/73 ms, slice thickness 4 mm, voxel size 3.2 x 2.6 x 4.0 mm)
- a dynamic T1-weighted contrast-enhanced sequence during the administration of 0.1 mmol Gadobutrol per kg of bodyweight (Gadovist®, Bayer Healthcare, Leverkusen, Germany) at a rate of 3 ml per second and flushing with 10 ml of normal saline using a power injector. This T1w-DCE sequence consisted of 40 subsequent scans at 6 seconds (40 slices per scan) with a TR/TE of 2.47/0.97 ms, a slice thickness of 5 mm, a flip angle of 8° and a voxel size of 1.2 x 1.0 x 5.0 mm. Contrast application was started after the fifth scan.

- a coronal T2-weighted TIRM
- an axial T2-weighted TSE sequence with fat suppression
- an axial T1-weighted turbo spin echo (TSE) without contrast medium followed by an axial and a coronal fat saturated T1-weighted TSE sequence after contrast application

**Image analysis**

For all tumours, mean and maximum standardized uptake values (SUV) were analyzed in the PET dataset of the neck with a nuclear medicine physician plotting an isocontour VOI around the tumour (SUVₘₐₓ threshold 40%).

T1w-DCE images were processed with a commercially available software module for tissue perfusion estimation (Tissue 4D, Siemens Medical Systems, Erlangen, Germany) as described previously [6]. The pharmacokinetic parameters $K^{\text{trans}}$, $k_{\text{ep}}$, $v_{\text{e}}$ and iAUC were calculated - scaling the arterial input function (AIF) in relation to the gadolinium dose and modelling it by a bi-exponential function - using the two-compartment model by Tofts and Kermode [7]. For each patient, these four parameter maps were projected onto the T2-weighted fat-suppressed TSE sequences and the tumour was manually delineated on each slice, resulting in mean values of $K^{\text{trans}}$, $k_{\text{ep}}$, $v_{\text{e}}$ and iAUC averaged over the complete tumour.

DWI images were transferred to a desktop computer with Mac OS X (Apple, Cupertino, California, USA) and an open-source freeware 4D DICOM viewer (OsiriX, Pixmeo, Geneva Switzerland). ROI's were manually drawn on the ADC maps along the contours of the tumour on each slice in conjunction with the complete MRI and PET datasets; mean and minimal ADC values (ADCₘₑᵃₘ and ADCₘᵢₙ) were then averaged for the whole tumour volume.

For an example see figure 1.

**Statistical analysis**
Statistical analysis and graphics creation was performed with SPSS 20 (IBM SPSS Statistics, Armonk, New York, USA). Values are presented as mean ± standard deviation (SD). Mean value comparison was carried out using the Mann-Whitney-U test. Spearman's non-parametric rank sum correlation coefficients were calculated between DCE parameters, SUV$_{\text{max}}$, SUV$_{\text{mean}}$, ADC$_{\text{mean}}$ and ADC$_{\text{min}}$. 0 - 0.2 was defined as poor, 0.2 - 0.4 as weak, 0.4 - 0.6 as moderate, 0.6 - 0.8 as strong and 0.8 - 1.0 as very strong correlation. Significance level was set at p # 0.05.
**Fig. 1:** Example of a 59 year old male patient depicting the different molecular parameters obtained by simultaneous PET/MRI. Note the biopsy-proven secondary squamous cell carcinoma of the base of the tongue on the right side. 23 months ago the patient was operated on a squamous cell carcinoma of the soft palate on the same side.

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Results

17 patients fulfilled all inclusion criteria (15 male, 2 female, mean age 57.7 ± 7.3 years; range 49 - 79 years, see Figure 2). Tumours were 11 primary cancers and 6 recurrent cancers, located in the oral cavity (n=4), in the oropharynx (n=8) or in the hypopharynx and larynx (n=5). In patients with recurrent HNSCC, mean time from the end of therapy to diagnosis of the recurring carcinoma was 46 months (range from 12 to 120 months).

Comparing primary and recurrent HNSCC, significantly higher $\text{SUV}_{\text{max}}$ (24.41 ± 6.52 vs. 12.93 ± 2.54; p # 0.01) and higher $\text{SUV}_{\text{mean}}$ values (15.01 ± 4.07 vs. 7.52 ± 1.56; p # 0.01) were observed in de-novo tumours. Furthermore higher values of $K^{\text{trans}}$ were observed in primary HNSCC (0.21 ± 0.49 vs. 0.15 ± 0.46; p # 0.01). The other DCE and DWI values did not differ between both groups (see table 1).

Significant correlations were observed between $\text{SUV}_{\text{max}}$ and $\text{SUV}_{\text{mean}}$ ($\# = 0.988; p # 0.01$), $\text{SUV}_{\text{mean}}$ and $K^{\text{trans}}$ ($\# = 0.425; p # 0.05$) and $k_{\text{ep}}$ ($\# = 0.444; p # 0.05$); between the microcirculatory parameters $K^{\text{trans}}$ and $k_{\text{ep}}$ ($\# = 0.532; p # 0.05$) and $\text{iAUC}$ ($\# = 0.640; p # 0.01$); and between $k_{\text{ep}}$ and $\nu_e$ ($\# = -0.743; p # 0.01$). Furthermore we noted trends towards an inverse correlation between $\text{SUV}_{\text{max}}$ and $\text{ADC}_{\text{min}}$ ($\# = -0.352; p = 0.083$) and towards a positive correlation between $\text{SUV}_{\text{max}}$ and the DCE parameters $K^{\text{trans}}$ ($\# = 0.37; p=0.072$) and $k_{\text{ep}}$ ($\# = 0.392; p = 0.060$). Also between $\text{ADC}_{\text{mean}}$ and $\text{ADC}_{\text{min}}$ ($\# = 0.364; p = 0.075$) and between $\text{ADC}_{\text{mean}}$ and $\nu_e$ ($\# = 0.401; p = 0.055$) trends towards positive correlations were apparent. Results are additionally depicted in figure 2 and table 2.
Fig. 1: Example of a 59 year old male patient depicting the different molecular parameters obtained by simultaneous PET/MRI. Note the biopsy-proven secondary squamous cell carcinoma of the base of the tongue on the right side. 23 months ago the patient was operated on a squamous cell carcinoma of the soft palate on the same side.

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Fig. 2: Statistically significant correlations are highlighted in red colour. Positive or negative correlations with a trend towards statistical significance are highlighted with blue colour in this figure.

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (n=17)</th>
<th>Primary HNSCC (n=11)</th>
<th>Recurrent HNSCC (n=6)</th>
<th>p value#</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{SUV}_{\text{max}}$</td>
<td>20.36 ± 7.78</td>
<td>24.41 ± 6.52</td>
<td>12.93 ± 2.54</td>
<td>0.005*</td>
</tr>
<tr>
<td>$\text{SUV}_{\text{mean}}$</td>
<td>12.27 ± 5.07</td>
<td>15.01 ± 4.07</td>
<td>7.25 ± 1.56</td>
<td>0.004*</td>
</tr>
<tr>
<td>$\text{ADC}_{\text{mean}}$</td>
<td>1287.23 ± 150.85</td>
<td>1284 ± 184.85</td>
<td>1291.6 ± 66.64</td>
<td>0.37</td>
</tr>
<tr>
<td>$\text{ADC}_{\text{min}}$</td>
<td>659.72 ± 175.64</td>
<td>646.02 ± 202.15</td>
<td>684.85 ± 125.78</td>
<td>0.48</td>
</tr>
<tr>
<td>$k_{\text{trans}}$</td>
<td>0.19 ± 0.06</td>
<td>0.21 ± 0.05</td>
<td>0.15 ± 0.05</td>
<td>0.02*</td>
</tr>
<tr>
<td>$k_{\text{ep}}$</td>
<td>0.41 ± 0.18</td>
<td>0.43 ± 0.14</td>
<td>0.36 ± 0.24</td>
<td>0.27</td>
</tr>
<tr>
<td>$v_e$</td>
<td>0.53 ± 0.13</td>
<td>0.53 ± 0.1</td>
<td>0.55 ± 0.19</td>
<td>0.69</td>
</tr>
<tr>
<td>iAUC</td>
<td>22.27 ± 12.19</td>
<td>23.89 ± 14.0</td>
<td>19.29 ± 8.17</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Table 1: Patient characteristics and comparison between primary and recurrent HNSCC. # comparing primary and recurrent HNSCC using the Mann-Whitney-U test; * p# 0.05

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**Table 2:** from 18F-FDG-PET, T1w-DCE and DWI using Spearman's non-parametric rank sum correlation coefficient. *p ≤ 0.05; **p ≤ 0.01

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Conclusion

The current study demonstrates that, by integrating advanced MRI techniques for tissue characterisation into a simultaneous PET/MRI protocol, the *in vivo* assessment of glucose metabolism, tissue cell density and microcirculatory parameters of the tumour’s vascular bed is feasible. It is demonstrated that - using PET/MRI - complex interactions between glucose metabolism and microcirculation (expressed by correlations between SUV and $K^{\text{trans}} / k_{ep}$), between glucose uptake and cellular density (depicted by correlations between SUV and ADC) and between cellularity and volume of the extravascular space (estimated by the correlation between ADC and $v_e$) can be displayed. As all correlations between the different molecular modalities were at best moderate, their combined acquisition seems to provide complementary and not redundant information; yet, they seem to be connected to a certain degree.

In the future, this could be of special interest for treatment planning and prognostic stratification. DWI and T1-DCE as well as $^{18}$F-FDG-PET were proven to be suitable for this purpose in patients with HNSCC prior to radiochemotherapy [8]; a satisfactory therapy response and a better prognosis is thought to be related to (a) higher $K^{\text{trans}}$ [9], (b) higher ADC$_{\text{mean}}$ and (c) lower SUV$_{\text{max}}$ values [9]. During successful radiochemotherapy, ADC values are increasing [10], whereas $^{18}$F-FDG uptake and $K^{\text{trans}}$ are known to decrease [11].

With PET/MRI and a combined acquisition of numerous parameters, further studies to investigate the most suitable modality for assessment and prediction of therapy response are possible. Moreover, by imaging only, the combination of a number of molecular imaging parameters could characterize the tumour biology and (sub)cellular tissue properties and contribute to the planning and adaptation of treatment plans with the aim of optimising patient outcomes.
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