Assessment of tumor microenvironment using DCE MRI and 18Fluoromisonidazole PET imaging in neck nodal metastases

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Introduction

Most malignant tumors develop regions of hypoxia during growth, and usually occur in regions with poor blood perfusion and/or high cell density [1]. The tumor microenvironment in head and neck (HN) cancers plays a critical role in malignant tumor progression and treatment resistance [1]. In particular, tumor hypoxia can cause resistance to radiation- and chemo-therapy, and may promote malignant progression [2]. Gadopentetate dimeglumine (Gd-DTPA)-based dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has been suggested to be a useful noninvasive method for characterizing the pathophysiological microenvironment of tumors [3]. With proper compartmental modeling, the data may yield results on tumor-vessel permeability, tumor perfusion, and extracellular-extravascular volume fraction, i.e. data relating to the tumor microenvironment. Targeting hypoxia as a marker of outcome in HN cancer has shown its promises as well as challenges. Radiopharmaceuticals containing nitroimidazole moieties such as ^{18}F-misonidazole (^{18}F-MISO) show promise as potential agents for hypoxia imaging [4]. The present study has been designed to compare perfusion and hypoxic status of the neck nodal metastasis in HN cancer using DCE-MRI and ^{18}F-MISO PET imaging.

Material and Methods

Patients 13 newly diagnosed head and neck cancer patients with metastatic nodes (M/F: 13/0, age: 58±9y, primary cancer: 7 base of tongue, 5 tonsil, 1 larynx) were included. Tumor perfusion and hypoxia was assessed using DCE-MRI and ^{18}F-MISO PET imaging prior to chemotherapy and radiation therapy. ***MRI*** MRI was performed on a 1.5 Tesla GE Excite scanner using a 4-channel neurovascular phased-array coil. The protocol consisted of MR imaging covering the entire neck or oral cavity/tongue or larynx using T2-weighted and T1-weighted images. Dynamic perfusion studies were acquired on the nodes using a fast multi-phase spoiled gradient echo sequence. Antecubital vein catheters delivered a bolus of 0.1mmol/kg Gd-DTPA (Magnevist) at 2 cc/s, followed by saline flush. The entire node was covered contiguously with 5-7 mm thick slices, zero gap, yielding 3-6 slices with 3.75-7.5 sec temporal resolution. Acquisition parameters included TR 9 ms, TE 2 ms, flip angle 30°, bandwidth 15.63 kHz, FOV 18-20 cm, time course data points 40-80, and matrix 256x128. ***PET*** For ^{18}F-MISO PET imaging, F18-fluoride was produced by the cyclotron by proton irradiation of an enriched O-18 water target in a small-volume titanium chamber. 11.0 mCi of ^{18}F-MISO was administered by IV and image acquisition at the PET/CT scanner started after 2 hours of the injection. PET/CT images were reconstructed with the standard reconstruction array processor and corrected for attenuation. ***Analysis*** MRI data was analyzed with IDL 5.4 (Research Systems Inc., Boulder Co). ROIs were manually drawn by an experienced neuro-radiologist. Quantitative DCE-MRI analyses of the tumor tissue time course data was done using the two compartment Tofts model in all ROIs [5], as well as each pixel within the ROI using histogram analysis. A population based arterial input function was used [6]. The latter analyses calculated the pixel K^{trans} (distribution rate constant), v_e (extravascular-extra-cellular volume fraction), and k_{ep} (redistribution rate constant). ^{18}F-MISO images were transferred to a workstation for image analysis.^{18}F-MISO uptake by the tumor was scored: no uptake (score 0) or moderate-severe uptake (score 1), using visual analysis by an experienced nuclear medicine physician. This was followed by the evaluation of CT and PET/CT images. Further semi-quantitative analysis included calculation of tumor-to-muscle ratios as standardized uptake value (SUV) measurements. Whole blood samples collected from each patient were counted in a calibrated multichannel gamma well counter and the blood activity was expressed in as µCi/ml, decay corrected to time of injection. Differences in DCE parameters between nodes with ^{18}F-MISO uptake and nodes without uptake were statistically tested using a 2-sided Student's t-test, with $p<0.05$. All patients had clinical follow up.

Subject	Tumor site	Follow Up / Response	Node	FMISO / SUV	K^{trans}	v_e	k_{ep}
1	Tonsil	42/ CR	L	N / 1.0	0.55	0.76	0.73
			R	N / 1.0	0.50	0.69	0.73
2	Tonsil	Deceased	R	Y / 3.2	0.36	0.88	0.41
3	Tonsil	40 / CR	L	Y / 2.0	0.21	0.67	0.31
			R	N / 1.0	0.23	0.51	0.47
4	BOT	35 / CR	L	Y / 2.0	0.27	0.54	0.49
5	BOT	35 / CR	L	Y / 2.1	0.17	0.67	0.26
			R	Y / 2.4	0.20	0.67	0.29
6	Tonsil	26 / CR	R	Y / 2.8	0.29	0.55	0.53
7	BOT	34 / CR	L	Y / 2.6	0.27	0.38	0.76
8	BOT	32 / CR	L	N / 1.0	0.43	0.46	0.92
			R	N / 1.0	0.43	0.44	0.98
9	Tonsil	31 / CR	L	Y / 2.4	0.14	0.62	0.22
10	BOT	22 / CR	L	Y / 4.2	0.24	0.55	0.42
11	BOT	15 / CR	R	Y / 4.2	0.30	0.53	0.61
12	BOT	6 / CR	L	N / 1.0	0.04	0.11	0.40
13	Larynx	10 / NR	R	N / 1.8	0.27	0.75	0.37

Table 1: Patient characteristics and results, BOT: base of tongue. Follow Up (months), CR: complete responder, NR: non-responder, Node: (L: left, R: right), FMISO: uptake (Y: yes, N: no), SUV: standardized uptake value, K^{trans}: distribution rate constant (min^{-1}), v_e: extravascular-extracellular volume fraction, k_{ep}: redistribution rate constant (min^{-1}).

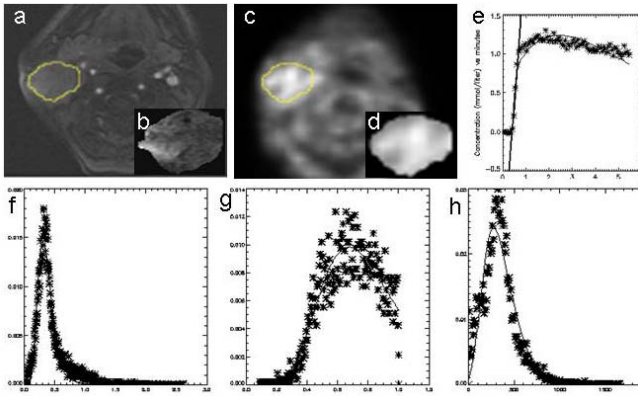

Figure 1: a) Post contrast T1w-image of patient 2 with node outlined in yellow, b) parametric image of the node showing K^{trans} map, c) ^{18}F-MISO PET image with node marked, d) ^{18}F-MISO uptake in the node, e) DCE-MRI signal change over time with fit, and histogram distributions for f) K^{trans}, g) v_e, and h) k_{ep}.

Results and Discussion

For the 13 patients, a total of 17 nodes were analyzed (Table 1). All 17 nodes studied had perfusion and hypoxia data measured by DCE-MRI and ^{18}F-MISO signal intensity, respectively. Figure 1 displays the results from the two compartment analysis (DCE-MRI) and FMISO uptake (PET) for the right hypoxic node of patient 2. For the nodes that showed no hypoxia on PET imaging (n=7), the mean (±SD) values were: ^{18}F-MISO SUV (1.1 ± 03), K^{trans} (0.33 ± 0.18), v_e (0.53 ± 0.23), and k_{ep} (0.66 ± 0.25). For the nodes that showed moderate to severe ^{18}F-MISO uptake (n=10) the values were: ^{18}F-MISO SUV (2.8 ± 08), K^{trans} (0.24 ± 0.07), v_e (0.61 ± 0.13), and k_{ep} (0.43 ± 0.17). A Student's t-test yielded significant lower k_{ep} for nodes with ^{18}F-MISO uptake (p=0.042, figure 2). K^{trans} and v_e were not significantly different in the whole population ($p > 0.1$). Table 1 shows patient 12 to have an extremely low value for v_e (the value is between an interquartile range of 1.5 and 3 [7]), therefore this node can be regarded as an outlier for a subset analysis. This yields significant lower k_{ep} (p=0.021) and K^{trans} (p=0.005) for nodes with ^{18}F-MISO uptake. Clinical follow-up information is available over a range of period (6 to 42 months, Table 1).

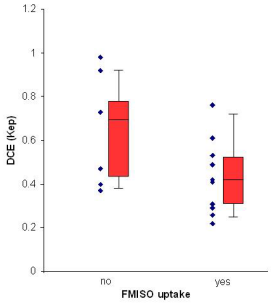

Figure 2: Individual k_{ep} redistribution rate constants (min^{-1}) of the nodes versus the ^{18}F-MISO PET uptake score (yes or no) for the nodes p=0.042. Box-plots are shown in red, displaying minimum, first quartile, median, third quartile, and maximum.

Conclusion

This initial evaluation of the preliminary result supports the hypothesis that the hypoxic nodes are poorly perfused nodes (lower k_{ep} and K^{trans} values) compared to the nodes that had no hypoxia.

References

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