Tumor metabolism and perfusion in head and neck squamous cell carcinoma: pretreatment multimodality imaging with 1H-MRS, DCE MRI and 18F-FDG PET: an exploratory study

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Introduction

The application of multimodality (MM) imaging is currently under investigation for the study of tumor microenvironment characteristics, such as metabolism and perfusion [1]. MM imaging combines functional and anatomical images to acquire biological data. This study focuses on pretreatment MM imaging data obtained with proton Magnetic Resonance Spectroscopy (^{1}H-MRS), Dynamic Contrast Enhanced MRI (DCE-MRI) and ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) in head and neck squamous cell carcinoma (HNSCC) patients with neck nodal metastases for more precise assessment of tumor biology in vivo. Additionally, pretreatment MM imaging data was evaluated for its efficacy in predicting short term response to treatment.

Material and Methods

Patients 29 newly diagnosed HNSCC patients with metastatic nodes (M/F: 25/4, age: 57±10y) were included (Table 1). Tumor metabolism and perfusion was assessed with ^{1}H-MRS, DCE-MRI and ^{18}F-FDG PET imaging prior to chemo-radiation therapy or surgery. After 3-4 months of treatment, a short term response assessment was performed based on WHO criteria. ***MRI*** MRI was performed on a 1.5 Tesla GE Excite scanner using a 4 or 8-channel neurovascular phased-array coil. The protocol consisted of standard clinical MR imaging covering the entire neck using T2-weighted and T1-weighted images. During ^{1}H-MRS, spectra were acquired on the tumor identified on T2- weighted images, and a volume of interest (>8cc) was placed over the node. Single voxel spectroscopy data (PRESS, TR/TE=1600/136 and 256 averages) was obtained. Additionally, a spectrum (16 averages) was recorded of unsuppressed water. DCE-MRI studies were acquired on the neck 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 neck 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*** PET examinations were performed on either GE or Siemens combined PET/CT scanners. Before the PET examination, patients fasted for at least 6 hours. Patients were injected with 12–15 mCi of ^{18}F-FDG intravenously. After a 45- to 60- minute uptake period, a PET/CT study was acquired with the patient in the same treatment position.

Analysis ^{1}H-MRS spectra were analyzed using LCModel (Version 6.2-1L) [2]. The metabolite basis set (PRESS, TE 136 ms, 1.5 T) including simulated macromolecule peaks was provided by Dr. Provencher. The ppm range included for analysis was 2.7 to 3.8 ppm. The standard 'only-cho-2' setting was used, which provides concentration estimates for choline. Concentrations are reported in arbitrary units, relative to water (Cho/W). Metabolite estimates were excluded from analysis, if the Cramer-Rao lower bounds (CRLB) exceeded the 50% range. MRI data was analyzed with IDL 5.4. ROIs were manually drawn by an experienced neuro-radiologist. The total number of pixels within the entire ROI was converted into the tumor volume (mm^3). Quantitative DCE-MRI analyses of the tumor tissue time course data was done using the two compartment Tofts model in all ROIs [3], as well as each pixel within the ROI using histogram analysis. A population based arterial input function was used [4]. The latter analyses calculated the pixel K^{trans} (volume transfer constant), v_e (extravascular-extra-cellular volume fraction), and k_{ep} (redistribution rate constant). A histogram analysis was performed on all pixels within the ROI, which yielded mean and standard deviation (std) of the distribution of all pixels. The std is indicative of the tumor heterogeneity [5]. ^{18}F-FDG images were transferred to a workstation for image analysis. ^{18}F-FDG uptake by the tumor was assessed by an experienced nuclear medicine physician. Semi-quantitative analysis included calculation of standardized uptake value (SUV) measurements and total lesion glycolysis (TLG, = SUV*volume). Correlations between ^{1}H-MRS, DCE-MRI and ^{18}F-FDG PET measures were calculated using Spearman correlation. Patients were divided into groups based on short term response assessment; complete response (no evidence of disease on clinical and imaging exam) and incomplete clinical response (measurable disease). Response was statistically tested using a 2-sided Student's t-test ($p<0.05$).

Subject	*Age / sex*	*Primary Cancer*	*Stage*	*Rs*	*FU (m)*
1	52 / m	Tonsil	IVa	CR	3
2	52 / m	Tonsil	IVa	ICR	3
3	41 / m	Tonsil	IVa	CR	4
4	49 / m	Tonsil	IVa	CR	5
5	50 / m	BOT	III	CR	3
6	60 / m	Unknown	IVa	CR	3
7	79 / m	Unknown	IVa	ICR	3
8	77 / f	Unknown	IVa	ICR	3
9	43 / m	Tonsil	IVa	ICR	3
10	48 / m	Unknown	IVa	CR	2
11	62 / m	BOT	IVa	CR	8
12	62 / m	Tonsil	IVa	ICR	6
13	44 / m	Tonsil	III	CR	4
14	53 / m	Larynx	IVa	ICR	3
15	59 / m	BOT	IVa	CR	4
16	61 / f	BOT	IVa	ICR	1
17	57 / f	BOT	IVa	CR	4
18	65 / m	BOT	IVa	CR	5
19	60 / m	BOT	IVa	CR	3
20	70 / m	BOT	IVa	ICR	4
21	66 / m	BOT	IVa	CR	3
22	68 / m	Tonsil	IVa	CR	6
23	51 / f	Tonsil	IVa	CR	4
24	37 / m	NPC	IVa	CR	3
25	55 / m	BOT	IVa	CR	3
26	50 / m	Tonsil	IVa	N/A	<3
27	62 / m	BOT	III	N/A	<3
28	48 / f	BOT	III	N/A	<3
29	61 / m	Tonsil	IVa	N/A	<3

Table 1: Patient characteristics and short term response assessment (Rs). FU = follow up (months), BOT = Base of Tongue, CR = complete response, ICR = incomplete clinical response.

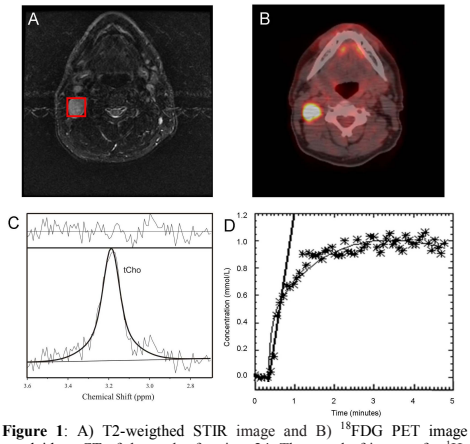

Figure 1: A) T2-weigthed STIR image and B) ^{18}FDG PET image overlaid on CT of the neck of patient 24. The voxel of interest for ^{1}H-MRS is indicated in red in A). C) LCModel analysis of the spectrum, highlighting the choline resonance. D) DCE-MRI signal, converted into Gd-DTPA concentrations, as function of acquisition time.

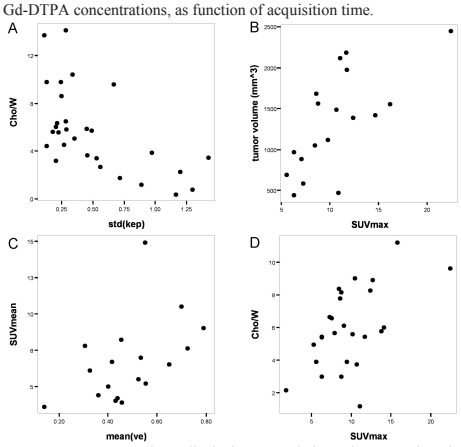

Figure 2: Scatter plots displaying correlations between imaging measurements. A) Cho/W concentrations as function of std(k_{ep}). B) MRI tumor volume as function of SUVmax value. C) SUVmean value as function of mean(v_e). D) Cho/W concentrations as function of ^{18}F-FDG uptake SUVmax values.

Results and Discussion

Out of 29 HNSCC patients, 27 patients were included for final retrospective ^{1}H-MRS analysis, and two patients were excluded due to high CRLB values. The median CRLB for Cho/W was 21 (range 5 to 43). The average voxel size was 8.5 ± 4.2 mL (mean ± SD). The DCE-MRI and ^{18}F-FDG PET data could be analyzed successfully for all 29 patients. Figure 1 shows the (1A) MRI and (1B) PET/CT series, (1C) the ^{1}H-MRS LCModel analysis, and (1D) the DCE-MRI contrast uptake obtained from the neck node of patient 24. A significant positive correlation was observed between Cho/W and TLG ($\rho = 0.661$) and a moderate positive correlation between Cho/W and SUV ($\rho = 0.443$), suggesting that increased cellular proliferation requires high glucose metabolism. Cho/W showed a moderate negative correlation with heterogeneity measures std(K^{trans}) ($\rho = -0.447$), and strong negative correlation with std(v_e) ($\rho = -0.516$), and std(k_{ep}) ($\rho = -0.534$). In this population, an increased cellular proliferation rate was related to a lower heterogeneity within these tumors. SUV values strongly correlated with the MRI tumor volume ($\rho = 0.673$). A moderate positive correlation was observed between v_e [6] and the parameters Cho/W ($\rho = 0.429$) and SUV ($\rho = 0.487$). Patients with incomplete response had significantly higher SUV values and larger tumors than patients with complete response ($p < 0.001$). This indicates that both an increased glucose metabolism and tumor volume are predictors for short term response. In a small patient population MR parameters did not predict short term response.

Conclusion

MM imaging using ^{1}H-MRS, DCE-MRI and ^{18}F-FDG PET in untreated HNSCC patients with nodal metastases yields complementary information, which is valuable for the precise assessment of tumor metabolism and perfusion in-vivo. Additionally, pretreatment MM imaging may provide a predictive marker for short term response to treatment.

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References

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