Assessing Tumor Microenvironment in Head and Neck Squamous Cell Carcinoma: Pretreatment Multimodality Imaging with $^1$H-Magnetic Resonance Spectroscopy, Dynamic Contrast-Enhanced MRI and $^{18}$F-FDG PET

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Introduction
Multimodality imaging (MMI) allows the study of tumor microenvironment characteristics [1]. The goal of the present study was to correlate data from 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 nodal metastases of patients with head and neck squamous cell carcinoma (HNSCC) for assessment of tumor biology in vivo. Additionally, pretreatment MMI data was evaluated for its efficacy in predicting short-term response to treatment.

Methods
Metastatic neck nodes were imaged with $^1$H-MRS, DCE-MRI and $^{18}$F-FDG PET [Figure 1] in 29 newly diagnosed HNSCC patients before treatment. Short-term radiological response was evaluated at 3-4 months [2]. The correlations between $^1$H-MRS (choline concentration, Cho/W [3]), DCE-MRI (volume transfer constant, $K_{\text{trans}}$; volume fraction of the extravascular extracellular space, $v_e$; and redistribution rate constant, $k_{\text{ep}}$ [4]) and $^{18}$F-FDG PET (standard uptake value, SUV) were calculated using non-parametric Spearman rank correlation. Additionally, a one-way ANOVA was applied to assess the potential effect of necrosis. To predict the short-term response in 24 patients, logistic regression analysis was performed.

Results and Discussion
A significant positive correlation was found between Cho/W and TLG ($\rho = 0.661$, $p = 0.007$), suggesting that increased cellular proliferation requires increased glucose metabolism. Cho/W correlated negatively with heterogeneity measures std($v_e$) ($\rho = -0.532$, $p = 0.004$) and std($k_{\text{ep}}$) ($\rho = -0.516$, $p = 0.006$). Necrosis also had a significant effect on these measures (ANOVA, $p < 0.01$), suggesting that an increased cellular proliferation rate is related to lower heterogeneity (i.e., necrosis). SUV values correlated strongly with MRI tumor volume ($\rho = 0.691$, $p = 0.003$). A significant, positive correlation was found between $v_e$ and SUV ($\rho = 0.517$, $p = 0.028$). As it has been suggested that $v_e$ is a measure of cellularity [5], $^{18}$F-FDG uptake in HNSCC might reflect tumor aggressiveness, which is closely related to proliferative activity and cellularity [6]. Logistic regression indicated that std($K_{\text{trans}}$) and mean($k_{\text{ep}}$) were significant predictors of short-term response ($p < 0.09$). Patients with incomplete clinical response had higher std($K_{\text{trans}}$) and lower mean($k_{\text{ep}}$) values than did patients with complete response. The short-term responses of 21 (87.5%) of the 24 patients
included could be predicted correctly using the above two variables, and the area under the ROC curve was 0.76 [95% CI 0.56 0.97] [Figure 2].

**Conclusion**

Pretreatment multimodality imaging with $^1$H-MRS, DCE-MRI and $^{18}$F-FDG PET in HNSCC patients shows clear potential for facilitating patient-specific treatment. Furthermore, DCE-MRI provides predictive markers for short-term response to treatment which need to be validated in a larger patient population study.

**Figure 1.** Multiplanar MRI and $^{18}$F-FDG PET/CT images illustrating the right neck lymph node of a HNSCC patient (male, 37 years old, primary nasopharyngeal cancer). (A) Coronal T1-weighted, (B) axial short tau inversion recovery with $^1$H-MRS voxel overlaid, and (C) axial T1-weighted postcontrast MR images showing the anatomy of the neck. The node is indicated with a white arrow in (A) and (C). The voxel of interest for $^1$H-MRS is indicated in red in (B). In (D) the corresponding $^{18}$F-FDG intensity map is shown overlaid on a CT image, indicating $^{18}$F-FDG uptake in the node.

**Figure 2.** ROC curve constructed using the predicted probabilities of the logistic regression model for the prospectively obtained imaging parameters (significant predictors: std($K_{trans}$) and mean($k_{ep}$)). AUC: area under the curve.

**References**


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