

# DCE-MRI as a predictor of outcome in head and neck squamous cell carcinoma patients with nodal metastases

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**Introduction:** The American Cancer Society estimates that approximately 48,010 new cases of oral cavity, pharyngeal and laryngeal cancers will be diagnosed, and 11,260 deaths will occur from the disease in 2009 in the United States [1]. Survival rates in head and neck squamous cell carcinoma (HNSCC) have remained relatively unchanged over the past 3 decades. Today with many treatment options available, it is important to have an a priori method to stratify good risk and poor risk categories to improve outcome and quality of life. The present study was designed to assess whether pretreatment DCE-MRI parameters can reliably predict outcome in HNSCC patients with advanced stage III/IV disease.

**Material and Methods:** A priori DCE-MRI was performed in 74 HNSCC patients with neck nodal metastases (median age 56 years; range 38-83 years; 63 males, 11 females; stage III n=12, stage IV n=62) prior to chemotherapy and radiation therapy or surgery. All diagnoses were histologically confirmed and all patients gave informed consent. MRI data were acquired on a 1.5 Tesla G.E. Signa scanner (GE, Milwaukee, WI). The study consisted of standard MRI of the neck using a neuro vascular phased array coil [2]. Antecubital vein catheters delivered a bolus of 0.1mmol/kg Gd-DTPA (Magnevist) at 2 ml/sec, followed by saline flush. DCE-MRI studies were acquired using a fast multi-phase spoiled gradient echo sequence. The entire node was covered contiguously with 5-7 mm thick sections yielding 4-6 slices depending on the size of the node. Acquisition parameters include a 9ms repetition time (TR), a 2ms echo time (TE), 30° flip angle, 15.63 kHz receive bandwidth, 18 cm field of view (FOV), 40-80 time points, and a 256x128 matrix. These parameters provided a temporal resolution between 4-6 sec/image which was sufficient to observe the initial uptake of Gd-DTPA into the region. MRI data was analyzed with IDL 5.4. ROIs were manually drawn on the neck nodal metastases by an experienced neuro-radiologist. Quantitative DCE-MRI analyses of the tumor tissue time course data were 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 [2,4]. The latter analyses calculated the pixel  $K^{trans}$  (volume transfer constant),  $v_e$  (extravascular-extracellular volume fraction), and  $k_{ep}$

(redistribution rate constant). A histogram analysis was performed on all pixels within the ROI, which yielded mean, standard deviation (std) and the skewness of the distribution of all pixels. The std describes the width of the distribution and skewness characterizes the asymmetry of the distribution. A minimum of 1 year clinical follow up was done for all the HNSCC patients. Patient's status on last follow up [range 14 months to 60 months] was no evidence of disease (NED), alive with disease (AWD), dead with disease (DOD) or dead of other causes (DOC). Prognostic significance was assessed using the log rank test for single variables. Significant variables were further considered in Cox proportional hazards regression for combination of variables. Kaplan and Meier product-limit method was used to display differences in progression free survival (PFS) or overall survival (OS), with continuous covariates dichotomized at the sample median. All statistical computations were done with SAS version 9.2 (SAS Institute, Cary, NC).

**Results:** Figure 1 shows the characteristic time intensity curves for neck nodal tissue after injection with Gd-DTPA. The figure displays the typical temporal resolution that was consistently obtained throughout all acquisitions. At last clinical follow-up, NED was observed in 55 patients, AWD=6, DOD=12 and DOC=1.

There was 100% PFS (i.e. no recurrence or death) among the twelve stage III patients. Hence, we limited further analyses of prognostic factors to the sixty two stage IV patients. In this cohort 49 patients were alive and 13 deceased. Figure 2 shows the average distribution plots of the calculated  $K^{trans}$  for the nodes of the deceased (black bars) and alive patients (white bars). The histograms depicting  $K^{trans}$  value of the nodes for deceased patients show shifts to lower  $K^{trans}$  values, indicative of lower perfusion in their tumors. Deceased patients have significantly higher  $K^{trans}$  skewness values (median=1.19) than alive (median=0.47) patients, which can be appreciated by a more skewed distribution in Figure 2. In stepwise Cox regression, skewness of  $K^{trans}$  was the strongest predictor for both PFS ( $p<0.001$ ) and OS ( $p<0.001$ ). Figure 3 and 4 shows the Kaplan-Meier plots when dividing the median 0.61 for both PFS ( $p<0.010$ ) and OS ( $p=0.019$ ) respectively.

**Discussion:** DCE-MRI has shown prognostic value in rectal, breast and head and neck tumors. In a recent study with 33 HNSCC patients it was observed that average pretreatment  $K^{trans}$  value for the complete response group was significantly higher ( $P = .001$ ) than that for the partial response group at six month follow-up [5]. It has been reported that imaging vascular heterogeneity by DCE-MRI at times is not best reflected by simple summary statistics like mean and median of the parameter but rather by the distribution of the parameter [6]. In the present study the skewness of  $K^{trans}$  was the strongest predictor of outcome in HNSCC patients with stage IV disease. A priori DCE-MRI parameters represent a non-invasive tool that may enhance prognostication in HNSCC patients with advanced disease and thus improve outcomes.

**References:** [1] Jemal, *et al.* CA Cancer J Clin. 2009;59: 225 [2] Shukla-Dave *et al.* BMC Med Phys 2009;9:4 [3] Tofts *et al.*, JMRI 1999, 10:223 [4] Parker *et al.*, MRM 2006, 56:993 [5] Kim *et al.*, AJNR 2009 [Epub ahead of print] [6] Jackson *et al.*, Clin Cancer Res 2007, 13:3449.

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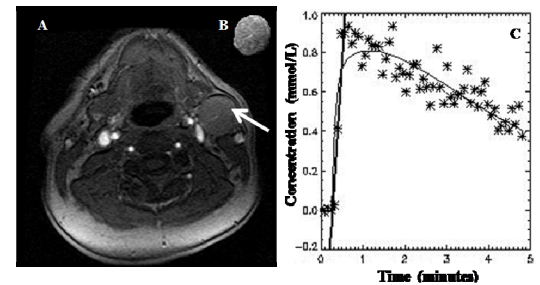


Figure 1: A) Post contrast MR image with arrow pointing to neck nodal metastasis [52 year old, male with primary tonsil cancer and stage IV disease]. The insert B) displays the calculated parametric  $K^{trans}$  map of the node. C) DCE-MRI signal (converted into Gd-DTPA concentration) over the acquisition time. Stars indicate the individual data points (averaged over the ROI), the thin black line is the fit, and the thick line indicates the slope.

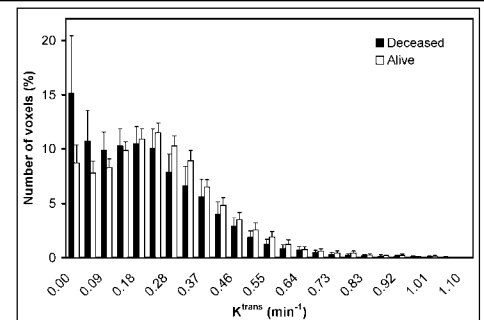


Figure 2: Average distribution histogram plot for the DCE-MRI parameter  $K^{trans}$  in all stage IV patients. The mean values for the nodes of the alive patients are shown in white bars and for the deceased patients in black bars. Error bars indicate the standard error of the mean.

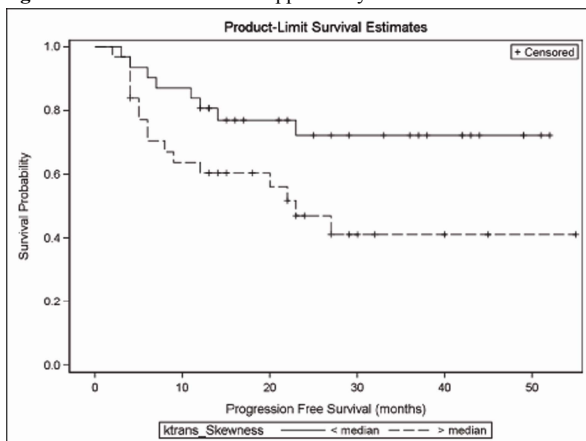


Figure 3: Kaplan-Meier progression free survival plot. Patients were stratified by median of  $K^{trans}$  skewness

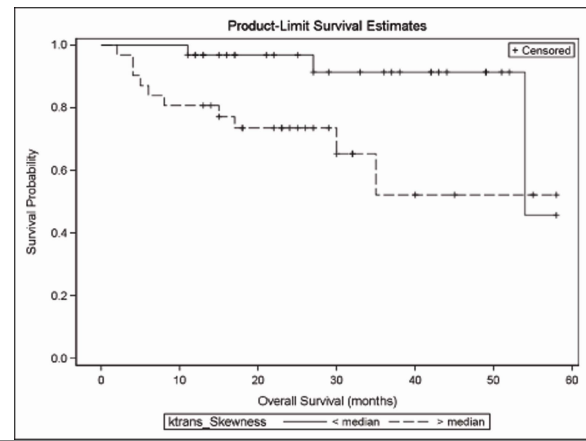


Figure 4: Kaplan-Meier overall survival plot. Patients were stratified by median of  $K^{trans}$  skewness