Prediction of treatment response using texture analysis on pharmacokinetic maps of dynamic contrast enhanced MRI in patients with head and neck cancer

Yonggang Lu[1], Jacobus F.A. Jansen[2], Gaorav Gupta[1], Nancy Lee[1], Hilda E. Stambuk[1], Yousef Mazaheri[1], Joseph O. Deasy[1], and Amita Shukla-Dave[1]
[1]Memorial Sloan-Kettering Cancer Center, NEW YORK, New York, United States, [2]Maastricht University Medical Center, Maastricht, Netherlands

Target audience: Researchers investigating imaging biomarkers in head and neck cancers.

Purpose: Advanced head and neck squamous cell carcinomas (HNSCC) are usually treated with concurrent chemoradiation therapy. Currently, there is significant clinical demand for reliable response indicator since maximum antitumor efficacy must be offset against minimization of morbidity and mortality. Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) allows for quantifying tumor vasculature and has shown its promise in tumor differentiation, treatment response assessment, and survival prediction in cancers. However, since HNSCC is very heterogeneous in nature, the summarizing tumor characteristics such as mean, median, or standard deviation may not reflect the underlying marked morphologic heterogeneity in HNSCC, resulting in unreliable prediction of treatment response. [1,2] Image texture analysis can be used to assess tissue heterogeneity, which may provide a more reliable imaging biomarkers for response prediction. [3,4] In this study, we assessed the merits of texture analysis of pharmacokinetic parametric maps derived from DCE-MRI in the prediction of treatment response in patients with HNSCC.

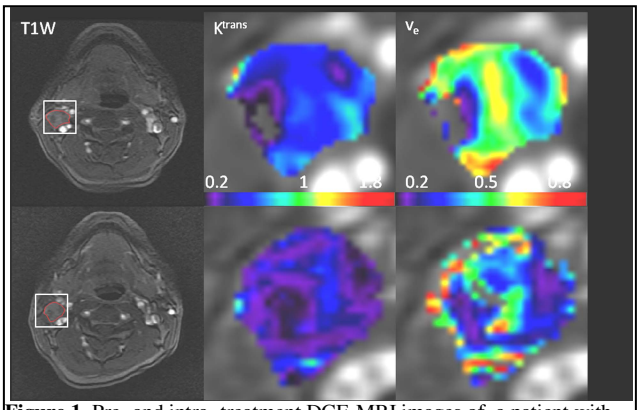

Figure 1. Pre- and intra- treatment DCE-MRI images of a patient with LF (male, 50y). The top row shows images of the pre-treatment study, and the bottom row shows images from the intra-treatment study.

Methods: *Human subjects:* Nineteen head and neck cancer patients with nodal metastases (M/F: 16/3; age: 58±8y; primary tumor site: oropharynx) with histopathologically confirmed HNSCC were recruited for this retrospective study which was approved by local institutional review board. All patients were treated with chemoradiation. Patient response assessment was performed after completing treatment, and the patients were grouped as those having loco-regional control (LC) or loco-regional failure (LF), which were determined by clinical and radiographic examination using established criteria with a median followup of 32 months. *DCE-MRI data acquisition:* Patients underwent examination with MRI before (pretreatment) and 10 to 14 days (intra-treatment) after the commencement of chemo-radiation treatment. MRI was performed on a 1.5-Tesla GE Excite scanner. The MRI protocol consisted of the standard anatomic MRI scans (T1/T2 weighted images) and DCE-MRI scans. A two-dimensional spoiled gradient echo (2D-SPGR) pulse sequence was used for DCE-MRI image acquisition with acquisition parameters of repetition time (TR) = 7.8 ms, echo time (TE) = 1.9 ms, temporal resolution = 6 s, phases = 50-60, number of excitation (NEX) = 1. Gd-DTPA (Gadopentetic Diethylene Triamine Penta Acetic acid) was delivered by antecubital vein catheters at a bolus of 0.1 mmol/kg and 2 cc/s, followed by saline flush. *Pharmacokinetic modeling:* Pharmacokinetic modeling was performed using the Tofts model,[1] generating voxelwise pharmacokinetic measures (K^{trans} (volume transfer rate), v_e (volume fraction of the extravascular extracellular space)) on three-dimensional regions of interest (ROIs) prescribed on metastatic nodes with summarizing measures such as average (mean) and standard deviation (std), as well as parametric maps of K^{trans} and v_e. *Image texture analysis:* Image texture analysis was performed on parametric maps of K^{trans} and v_e at the tumor's central slice based on a gray-level co-occurrence matrix (GLCM) scheme, yielding two texture measures: Energy (E) and Homogeneity (H). [3,4] *Statistical analysis:* The differences in these measures between pre- and intra- treatment DCE-MRI scans were tested using a paired Student's t-test. The non-parametric Mann-Whitney U test was performed to assess the metric differences between LC and LF groups. To determine the measures that provide the best prediction of outcome, a forward sequential feature selection algorithm was used, followed by logistic regression analysis, which determined the probability of prediction.

Table 1. Paired student's t test on K^{trans} and v_e between pretreatment and intra-treatment scans (n=19).

DCE-MRI Derived Parameters	Measures	Pretreatment (n=19) (mean±std)	Intra-treatment (n=19) (mean±std)	p values
K^{trans} (min^{-1})	mean	0.34± 0.18	0.37± 0.22	0.36
	std	0.25±0.11	0.25±0.11	0.99
	E (Energy)	0.34±0.14	0.38±0.19	0.18
	H (Homogeneity)	0.84±0.04	0.83±0.05	0.61
v_e	mean	0.29±0.12	0.34± 0.19	0.09
	std	0.15±0.04	0.17±0.07	0.26
	E (Energy)	0.30±0.11	0.41±0.22	0.04*
	H (Homogeneity)	0.84±0.04	0.83±0.06	0.78

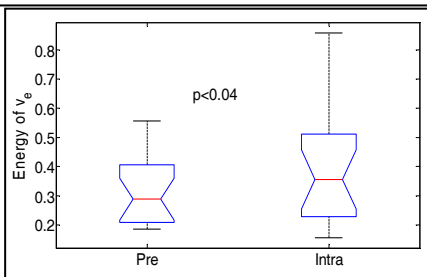

Figure 2. Box-and-whisker plot demonstrating the significant difference in the energy (E) of v_e between pretreatment (Pre) and intra-treatment (Intra) scans (p<0.04).

Results: The clinical outcome for 19 patients with cancer of the oropharynx was assessed: 17 patients had local control of the disease (LC), and 2 patients had local failure (LF). Figure 1 displays DCE-MRI images and derived parametric maps (K^{trans} and v_e) for one representative patient with LF (male, 50y). No significant changes were found for the common summarizing measures (mean and standard deviation) for K^{trans} and v_e (p>0.09). Texture analysis revealed that the energy (E) of v_e was significantly higher in the intra-treatment scans than in the pretreatment scans (0.41±0.22 vs.0.30±0.11; p<0.04), as shown in Table 1 and Figure 2. No significant difference was found when comparing the measures between the LC and LF groups, either in the pretreatment or intra-treatment scans. However, there was a trend towards greater elevation in the energy (E) of v_e in the LF patients after treatment, relative to the LC patients (0.37±0.23 vs. 0.07±0.16; p=0.07).

Discussion: The GLCM-derived parameter E can be interpreted as an inverse heterogeneity measure, in which lower values are indicative of greater heterogeneity. Hence, as the energy E of v_e was higher during treatment, compared with pretreatment, it seems that treatment reduces the heterogeneity of the tumor. However, the treatment-induced reduction in heterogeneity seems more pronounced for patients with local failure, rather than patients with local control, which might indicate that ineffective treatment counterintuitively yields more homogeneous, rather than heterogeneous, tumor characteristics. The low number of LF patients in this study is because at our Center, patients with advanced locoregional cancer of the oropharynx who undergo chemo-radiation treatment have an approximately 90% local control rate. Future studies would require larger patient populations. If treatment-induced reduction of tumor heterogeneity in patients with local failure is validated in subsequent studies, this finding may have implications for the future design of adaptive chemo-radiation therapy trials in advanced head and neck cancers.

Conclusion: We observed that chemo-radiation treatment significantly reduces the heterogeneity of tumors, and we found a trend that ineffective treatment leads to more homogeneous, rather than heterogeneous, tumor characteristics.

References: [1] Shukla-Dave A., et al. Int J Radiat Oncol Biol Phys. 2012; 82(5):1837-44. [2] Chawla S., et al. AJR Am J Roentgenol. 2013; 200(1):35-43. [3] Alic L., et al. Phys Med Biol. 2011; 56(6):1601-16. [4] El Naqa I., et al. Pattern Recognition. 2009; 42(6):1162-71.