Amide Proton Transfer MRI Evaluation of Bladder Cancer Neoadjuvant Chemotherapy

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Introduction

Bladder Cancer is the 5th most commonly diagnosed cancer in the United States (1). Neoadjuvant chemotherapy prior to radical cystectomy can improve oncologic outcomes and overall survival. However not all patients respond to chemotherapy allowing greater time for the primary tumor to grow and possibly progress before surgery (2). Amide proton transfer (APT) MRI has recently emerged as a new molecular-MRI technique in which the contrast is determined by a change in water signal intensity due to chemical exchange with saturated amide protons (3.5 ppm) in protein backbones (3). This study is to evaluate whether APT-MRI can improve the assessment of bladder tumor response to neoadjuvant chemotherapy.

Materials and methods

This HIPAA-compliant Phase I trial received institutional review board approval, and written informed consent was obtained from all 36 bladder cancer patients included. All patients received cisplatin-based therapy for a period of three months (four 21 day cycles). All patient scans were performed on a 3T MRI system (Achieva, Philips Healthcare). APT-MRI was based on 2D single-shot single-slice TSE sequence with the pre-saturation pulse composed of a train of sixteen block pulses (B_1 = 4.0 μT, duration = 0.5 sec). Z-spectra with the pre-saturation pulse at 33 frequency offsets (-8 to 8 ppm, interval 0.5 ppm) were acquired in a transverse slice covering suspected bladder tumors. B_0 field map was acquired using a dual-echo FFE sequence. MTR_{asym}(3.5ppm) based on the asymmetric signal at 3.5 ppm was defined to quantify cellular mobile protein and peptide levels. ΔMTR_{asym}(3.5ppm), defined as MTR_{asym}(3.5ppm) in baseline scan (B01) subtracted from MTR_{asym}(3.5ppm) in mid-cycle follow-up (F01), was used to differentiate the neoadjuvant chemotherapy responders from non-responders.

Results

Tumor characterization In order to facilitate the region of interest (ROI) placement of thin normal bladder wall (NBW), a total of 14 APT-MRI scans with little or no motion artifact were analyzed (Figure 1). MTR_{asym}(3.5ppm) was 3.2% ± 1.6% in tumor regions, -0.13% ± 1.6% in normal bladder wall, 3.1% in one metastasized lymph node, 10.0% ± 2.1% in seminal vesicles, 10.3% ± 2.6% in uterus. Tumor showed significantly higher (3.4% ± 1.6%) in MTR_{asym}(3.5ppm) than normal bladder wall ($p < 0.001$). Tumor showed significantly lower (-7.3% ± 2.0%) in MTR_{asym}(3.5ppm) than seminal vesicles or uterus ($p < 0.001$) after adjusting for multiplicity using Bonferroni method.

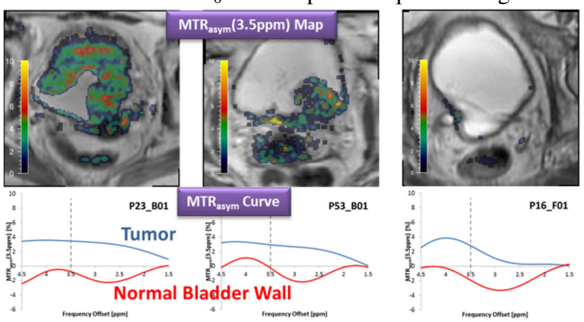

Figure 1. APT-MRI can depict bladder cancer region by mapping the elevated mobile protein level in cancerous tissues.

Therapy response At the end of the neoadjuvant chemotherapy, 12 out of 17 patients were defined as responders, and the remaining 5 patients (non-responders) were defined as stable, or exhibiting progressive disease. All tumors in baseline imaging were shown to have MRI-detectable cellular protein levels (Figure 3). There was no significant difference in baseline MTR_{asym}(3.5ppm) between the responders (4.1 ± 1.5%) and the non-responders (3.3 ± 2.0%, $p = 0.41$). Tumor mobile protein levels in the chemotherapy responders exhibited a decrease from baseline to mid-cycle follow-up scan (ΔMTR_{asym}(3.5ppm) = -2.9 ± 2.2%). The tumors in the non-responders were shown to be stable or increasing in mobile protein levels (ΔMTR_{asym}(3.5ppm) = 1.5 ± 1.3%). There was a significant difference in tumor ΔMTR_{asym}(3.5ppm) between the responders and the non-responders ($p < 0.001$).

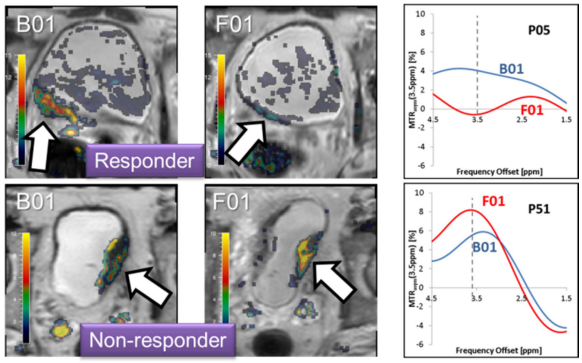

Figure 2. Typical baseline and mid-cycle APT-MRI scans from a chemotherapy responder and a non-responder.

Discussions and conclusion

APT-MR imaging was evaluated in a Phase I trial with the goal to improve imaging and characterization of bladder lesions. This trial is the first application to clinical bladder cancer imaging. APT-MR revealed increased MRI-detectable mobile proteins in cancerous bladder lesions. Successful neoadjuvant chemotherapy induced decreased protein level detected by APT-MRI. Non-responders showed stable or progressive disease with constant or increasing MRI-detectable mobile protein levels. In conclusion, the APT-MRI signal-based detection and quantification of endogenous cellular protein concentrations has shown to be a promising marker in improving chemotherapy response assessment. Dedicated Phase II trials to appropriately assess the efficacy of this novel molecular approach will now be undertaken.

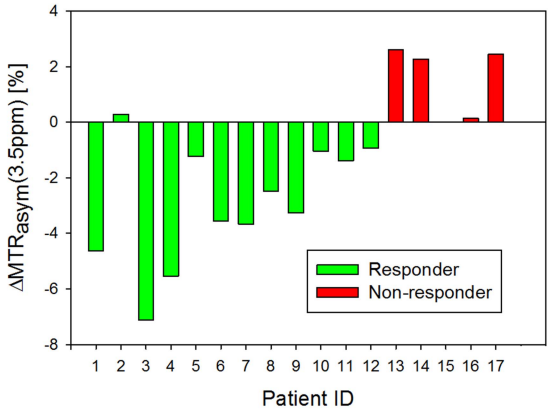

Figure 3. The responders exhibited decreases in MTR_{asym}(3.5ppm) from B01 to F01. However, the non-responders showed increases in MTR_{asym}(3.5ppm) from B01 to F01. The changes were significantly different ($p < 0.01$)

References

1. http://www.bcan.org/about/press/facts/. 2. Grossman HB, et al. N Engl J Med 349:859-66 (2003). 3. Jia G, et al. J Magn Reson Imaging 33:647-654 (2011).