Correlation between pretreatment MRI/MRSI data and tissue molecular marker levels for characterization of prostate cancer and prediction of disease recurrence

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Introduction

Prostate cancer (PCa) screening has led to increased detection of small-volume, low-grade and organ-confined tumors (1). Many of these cancers are pathologically insignificant and are not life-threatening (1). Accurate pretreatment distinction between low-risk and more advanced disease remains challenging. The determination of prognosis and the selection of treatment are based on clinical variables such as biopsy Gleason score, clinical stage and prostate-specific antigen levels, which have known limitations. Additional biomarkers are needed to better characterize insignificant PCa and predict which cancers may recur after initial treatment. The present study was designed to assess whether pretreatement MR imaging/MR spectroscopic imaging (MRI/MRSI) data and the expression levels of selected molecular markers in surgical speimens correlate with pathologically insignificant PCa. Furthermore, we assessed whether the above biomarkers alone or in combination can predict disease recurrence. Three molecular markers (Ki-67, phoshpo-Akt and Androgen Receptor (AR)) were selected based on their association with PCa progression (2).

Materials and Methods

Eighty-nine patients with biopsy-proven PCa underwent combined MRI/MRSI before radical prostatectomy. Pretreatment MRI/MRSI data were acquired on a 1.5 Tesla G.E. Excite scanner (GE, Milwaukee, WI). The study consisted of MR imaging using a pelvic phased array and expandable endorectal coil followed by 3D ^{1}HMRSI with voxel size of 0.24 to 0.33 cm^3 (3). MRSI data was overlaid on the corresponding T2-weighted images. Based on the metabolic (choline+polyamine+creatine/citrate) ratios, the spectroscopist identified the voxels suspicious for cancer; the MRSI data were then provided to the radiologist. Both MRI and MRSI data were analyzed based on established criteria (3, 4). The radiologist scored MRI/MRSI data on a scale of 0 to 3 for the likelihood of insignificant PCa (3) based on tumor volume: 0, definitely insignificant PCa; 1, probably insignificant PCa; 2, indeterminate; and 3, definitely significant PCa. During the same session, the radiologist also scored MRI/MRSI data for the likelihood of recurrence on a scale of 1 to 7 based on TNM staging: 1, no tumor seen; 2, tumor seen no extra capsular extension (ECE); 3, tumor seen ECE can not be ruled out; 4, unilateral ECE; 5, bilateral ECE; 6, seminal vesicle invasion (SVI) and 7, lymph node metastasis (LNM). Immunohistochemistry (IHC) assays were performed on all surgical specimens by the pathologist. Well-characterized antibodies and standard IHC protocols were used (2). IHC data were analyzed by scoring % of positive tumor cells. Surgical pathology was used as the standard of reference (3) for pathologically insignificant PCa (organ-confined cancer with tumor volume ≤0.5cc and no patterns of Gleason 4 or 5). Disease recurrence was defined as a serum PSA value of 0.4 ng/ml or greater, secondary therapy or clinical recurrence (5). The correlation between MRI/MRSI data and marker levels was assessed using Spearman's correlation. Receiver operating characteristic (ROC) curves were used to see how well both techniques did in differentiating between insignificant and significant PCa. The concordance index was calculated to assess whether the two methods could predict recurrence. Cox proportional hazard models were built to assess the incremental value of molecular markers data to MRI/MRSI findings. Kaplan-Meier graphs were used to examine time to recurrence.

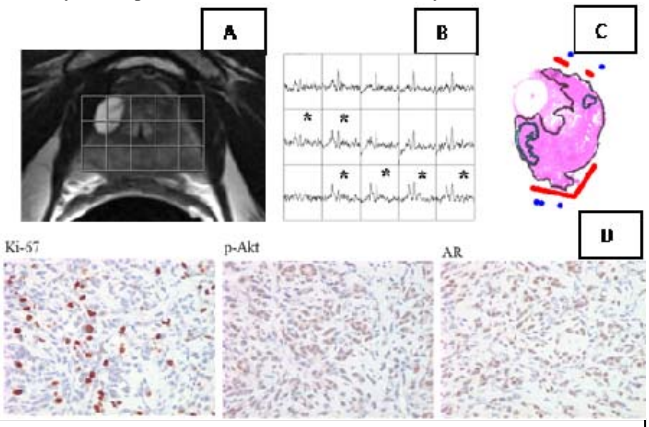

Figure 1: MRI/MRSI, histopathologic whole mount step-section and IHC staining data from a PCa patient A) MRSI grid superimposed on a T2 weighted MR image B) Corresponding spectroscopic grid showing voxels suspicious for cancer (marked by asterisks) C) Histopathologic section showing Gleason score 7 tumor and D) IHC staining from tissue section in (C) for, left to right, Ki-67, p-Akt and AR.

Results

At pathology, twenty-four percent of the patients had insignificant and 76% had significant PCa. Figure 1 shows an example of a pathologically significant PCa that received an MRI/MRSI score of 3 (definitely significant PCa). The correlations between the MRI/MRSI score (0-3 scale) and the molecular markers levels (%) ranged from 0.52 to 0.60 ($p<0.0001$). These numbers indicate moderately strong positive correlations and suggest that as MRI/MRSI scores for significance increased, so did the marker levels. In differentiating between insignificant and significant PCa, the area under the ROC curve (AUC) for Ki-67 was 0.75, the AUC for AR was 0.78, the AUC for phospho-Akt was 0.80 and the AUC for MRI/MRSI was 0.91. The AUC for the model that incorporated all the molecular markers and MRI/MRSI data was 0.93.

Thirty-one percent of the patients had recurrence while 69% did not. The correlation coefficients for MRI/MRSI score (1-7 scale) and molecular marker levels (%) ranged from 0.58 to 0.67 ($p<0.0001$). The concordance indices for prediction of recurrence were 0.78 for Ki-67, 0.81 for phospho-Akt, 0.85 for AR, and 0.89 for MRI/MRSI. The concordance index for the model with molecular markers and MRI/MRSI was 0.91. Kaplan-Meier (K-M) graphs for prediction of time to recurrence by Ki-67, AR, phospho-Akt and MRI/MRSI score were constructed using selected cutoffs (15% for Ki-67, 60% for both AR and phosho-Akt, and score 2 for MRI/MRSI). All the graphs showed clear separation at these cutoffs between patients that had recurrence versus those that did not. Figure 2 shows K-M graphs for AR and MRI/MRSI score.

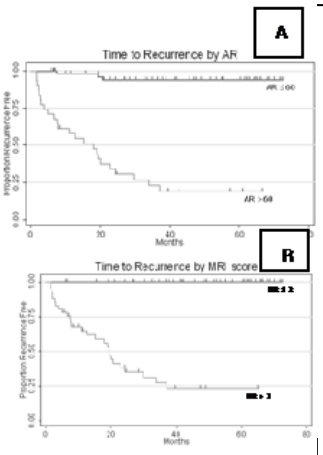

Figure 2: Kaplan-Meier graphs showing A) time to recurrence by AR expression levels using cutoff of 60 and B) time to recurrence by MRI/MRSI score using cutoff of 2

Discussion

The results show that MRI/MRSI findings and molecular marker levels correlated with each other and with pathologically insignificant and significant PCa. The results also showed that both imaging and molecular markers were significant predictors of recurrence after radical prostatectomy. The results suggest that pretreatment MRI/MRSI findings and molecular marker analyses of biopsy samples could help differentiate between insignificant and significant PCa and predict recurrence to favorably impact treatment selection.

References (1) Klein EA Cancer 2004, 101:1923; (2) Cordon-Cardo C et al J Clin Invest 2007, 117:1876; (3) Shukla-Dave A et al BJU Intl 2007, 99:786; (4) Jung JA et al Radiology 2004, 233:701; (5) Stephenson AJ et al J Clin Oncol 2006, 24:3973.