

D'Amico Risk Stratification Correlates With Degree of Suspicion of Prostate Cancer on Multiparametric Magnetic Resonance Imaging

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Purpose: We determined whether there is a correlation between D'Amico risk stratification and the degree of suspicion of prostate cancer on multiparametric magnetic resonance imaging based on targeted biopsies done with our electromagnetically tracked magnetic resonance imaging/ultrasound fusion platform.

Materials and Methods: A total of 101 patients underwent 3 Tesla multiparametric magnetic resonance imaging of the prostate, consisting of T2, dynamic contrast enhanced, diffusion weighted and spectroscopy images in cases suspicious for or with a diagnosis of prostate cancer. All prostate magnetic resonance imaging lesions were then identified and graded by the number of positive modalities, including low—2 or fewer, moderate—3 and high—4 showing suspicion on multiparametric magnetic resonance imaging. The biopsy protocol included standard 12-core biopsy, followed by real-time magnetic resonance imaging/ultrasound fusion targeted biopsies of the suspicious magnetic resonance lesions. Cases and lesions were stratified by the D'Amico risk stratification.

Results: In this screening population 90.1% of men had a negative digital rectal examination. Mean \pm SD age was 62.7 ± 8.3 years and median prostate specific antigen was 5.8 ng/ml. Of the cases 54.5% were positive for cancer on protocol biopsy. Chi-square analysis revealed a statistically significant correlation between magnetic resonance suspicion and D'Amico risk stratification ($p < 0.0001$). Within cluster resampling demonstrated a statistically significant correlation between magnetic resonance suspicion and D'Amico risk stratification for magnetic resonance targeted core biopsies and magnetic resonance lesions ($p < 0.01$)

Conclusions: Our data support the notion that using multiparametric magnetic resonance prostate imaging one may assess the degree of risk associated with magnetic resonance visible lesions in the prostate.

Key Words: prostate, prostatic neoplasms, biopsy, magnetic resonance imaging, ultrasonography

PROSTATE cancer is the leading cause of cancer in American men with 217,730 new cases in 2009 and the second most

common cause of cancer related death.¹ Since 1986, the landscape of prostate cancer has changed significantly in re-

Abbreviations and Acronyms

DCE = dynamic contrast enhanced
DRE = digital rectal examination
MP = multiparametric
MR = magnetic resonance
MRI = MR imaging
PSA = prostate specific antigen
TRUS = transrectal US
T2W = T2-weighted
US = ultrasound

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gard to screening, age at diagnosis, incidence and stage at diagnosis. Inherent bias is introduced when transrectal US guided biopsy is used to screen and diagnose patients with prostate cancer due to sampling error.² We evaluated MP endorectal coil MRI and its correlation with prostate biopsy findings.

Initially prostate MRI was not considered for routine clinical practice.³ However, adding an endorectal coil probe, functional imaging and a 3 Tesla magnet has dramatically improved its clinical and diagnostic usefulness.^{4,5} Wefer et al reported an early series that combined T2 MR, MR spectroscopy and TRUS guided biopsy, and achieved 98% specificity for identifying patients with prostate cancer.⁶ These initial observations helped set the foundation for using MRI in patients with suspected prostate cancer.

We believe that the underlying motivation for imaging in prostate cancer cases is to obtain a more complete pretreatment clinical picture with the possible but unproven goal of achieving better tailored treatment in our cases since 1/5 is up-graded after radical prostatectomy.⁷ This is even more relevant with the increased use of radiation therapy and focal or whole gland ablation to treat patients with prostate cancer. Unfortunately one will never be able to assess whether these cases were under graded at treatment. The overall effect on clinical outcome is unclear but prostate cancer imaging and its impact on clinical outcomes merit continued research.

To meet this challenge of using MR images but moving biopsy out of the MR gantry a custom platform was developed at National Institutes of Health that fuses real-time TRUS with previously obtained prostate MR images using an electromagnetic tracking system. The urologist can then perform image guided transrectal prostate biopsy of MR identified areas suspicious for prostate cancer (targets), in addition to standard 12-core biopsy, with the ease and familiarity of the real-time TRUS prostate biopsies that urologists already perform. The technical aspects of this platform were previously described.^{8,9} We now report the correlation between MP MRI suspicion for prostate cancer and biopsy results using the D'Amico risk stratification.

The D'Amico risk stratification was applied due to its clinical usefulness. It is a confirmed, validated method to determine patient pretreatment prostate cancer specific mortality.¹⁰ This stratification was applied to specific biopsy data on MRI visible lesions in the prostate due to the possibility of assessing the aggressiveness of an index lesion, which may help guide future care.

MATERIALS AND METHODS

All patients were counseled and informed consent was obtained with the supervision of the National Cancer Institute institutional review board, which approved this prospective trial. From March 2007 to June 2009, 101 consecutive patients entered the protocol and underwent 3 Tesla MP endorectal coil MRI of the prostate, followed by biopsy under monitored anesthesia care. Study patients were referred to the National Cancer Institute with suspicion or a previous diagnosis of prostate cancer. All patients with previous prostate cancer treatment were excluded from study.

MP endorectal coil MRI of the prostate was performed with triplane T2W, DCE, diffusion-weighted and proton MR spectroscopy images obtained. If patients had undergone previous biopsy, imaging was delayed for at least 8 weeks to decrease the effect of post-biopsy hemorrhage on MRI. These images were interpreted by 2 radiologists (PC and BT) with expertise in reading prostate MRI. Intraprostatic MRI lesions were identified and then scored by the number of modalities positive on MRI in nonweighted fashion, including low—2 or fewer of 4, moderate—3 of 4 or high suspicion—4 of 4 on MRI for prostate cancer (fig. 1).

Before biopsy each patient received a cleansing Fleet® enema and standard antibiotic prophylaxis. The protocol required each patient to undergo standard 12-core TRUS biopsy, followed by MRI/US fusion biopsy of suspicious MR lesions using a custom prototype prostate navigation system that has Food and Drug Administration 510(K) clearance. Details of this novel biopsy platform were described previously.^{8,9}

Preoperatively MR images were imported directly from the picture archiving and communication system. An electromagnetic field generator was placed above the pelvis, which allows real-time tracking of a custom biopsy needle guide embedded with a miniature electromagnetic tracking sensor.

A 2-dimensional prostate sweep was done manually to render a 3-dimensional US image, which was then registered and fused to preoperative prostate MR images.⁹ The endorectal coil used in conjunction with MRI improves image quality. Also, there is a slight distortion of the prostate, similar to the effects of the TRUS probe used during the 2-dimensional prostate sweep, possibly aiding image fusion. Tracking also allows motion compensation to improve image registration. The real-time TRUS images were fused to the axial T2W MR images and selected MRI lesions were labeled for tracking (fig. 2). The physician manually guided the biopsy gun to the highlighted lesion visualized on MR and US fused images. After alignment 2 biopsies were done per lesion with a minimum of 1 biopsy in the axial and sagittal planes. To ensure core length greater than 5 mm occasionally additional biopsies were taken (up to 4). Each specimen was sent in a separate container for pathological evaluation.

Descriptive statistics are used to describe patient characteristics, including age, prebiopsy PSA, DRE, prostate volume and previous biopsy data. A statistician (JS) performed all study calculations. All pathological findings were reviewed by a single pathologist. Results

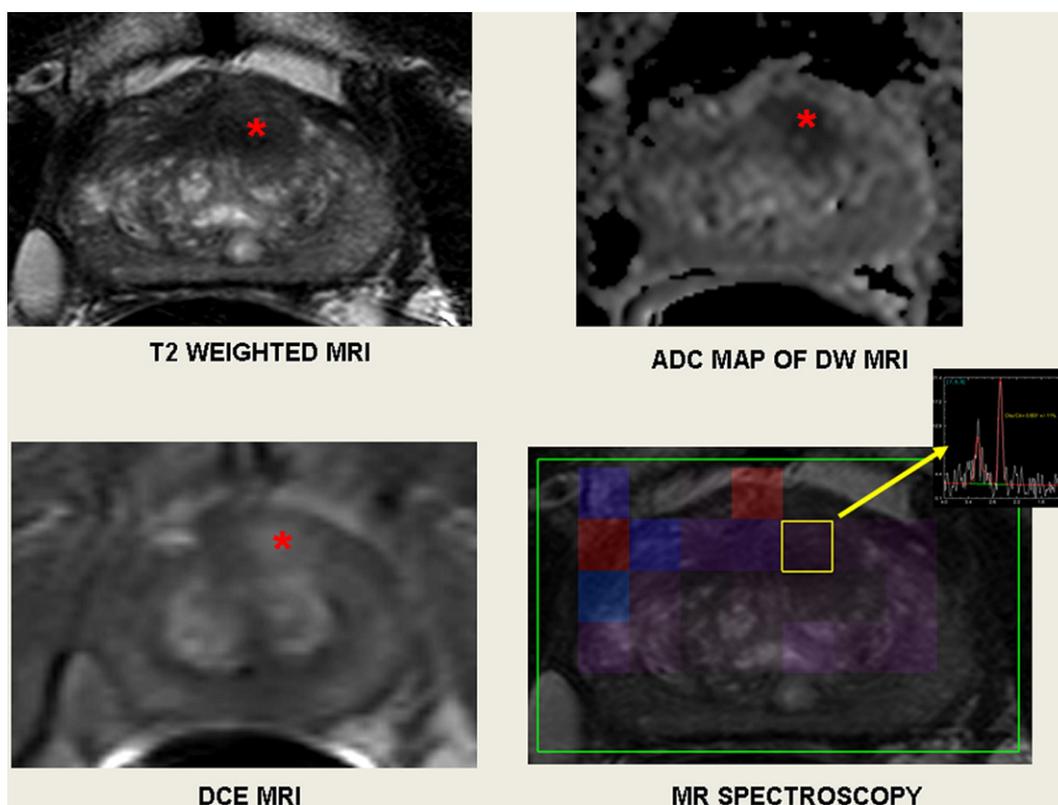


Figure 1. Four positive imaging modalities resulted in high MR suspicion lesion in 55-year-old male with serum PSA 3.33 ng/ml. Axial T2W MRI shows round, low signal intensity lesion (asterisk) at anterior mid gland. On corresponding apparent diffusion coefficient (ADC) map lesion (asterisk) appears hypointense. DW, diffusion weighted. DCE MRI reveals increased enhancement at lesion (asterisk). MR spectroscopy shows increased choline-to-citrate ratio in lesion (inset).

of fusion biopsies were stratified according to the pre-operative MRI scoring system as low, moderate or high, as described. The D'Amico risk stratification was calculated at biopsy using stage, Gleason score and PSA as low—Gleason T1c, T2a, score 6 or less, or PSA 10 ng/ml or less, intermediate—T2b, Gleason score 7, PSA

greater than 10, or 20 ng/ml or less and high risk—T2c, Gleason score 8 or greater, or PSA greater than 20 ng/ml.¹¹ Chi-square analysis was used to determine whether there was a correlation between the degree of MRI suspicion and the D'Amico risk stratification in patients. The within cluster resampling technique was

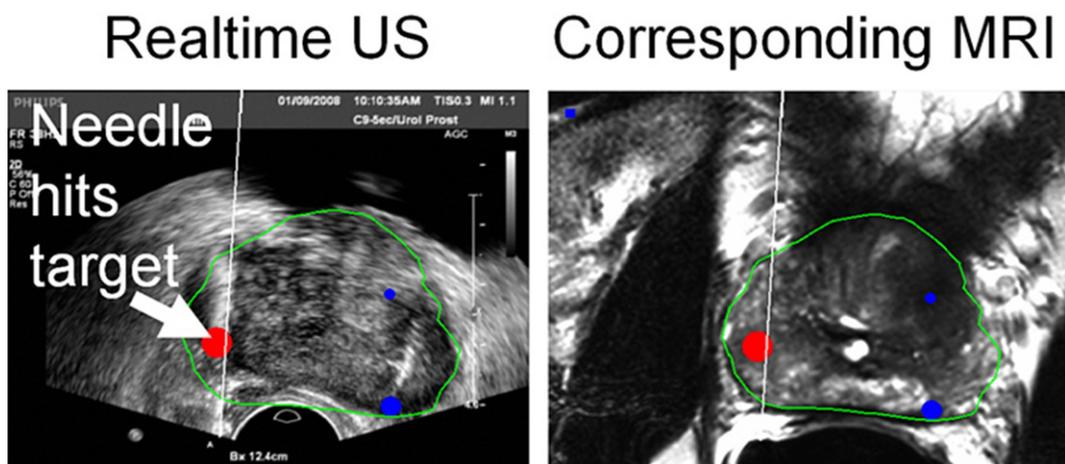


Figure 2. Combined real-time US and corresponding multiplanar reconstruction of co-registered preprocedural MRI with superimposed MRI based prostate segmentation (green outline) and MRI identified targets (red and blue areas).

used to account for the correlation between repeated measures in each patient. This was done to assess the correlation between MRI suspicion and D'Amico risk stratification for MR lesions and each MR targeted core biopsy.

RESULTS

A total of 101 patients with a mean \pm SD age of 62.7 ± 8.3 years (range 41 to 82) and mean PSA 8.3 ± 11.8 ng/ml (median 5.8, range 0.2 to 103) were included in the study. Of the patients 91 (90.1%) had negative DRE and the remaining 10 had positive DRE. Before entering the protocol 36 patients had undergone no prior prostate biopsy while 29 and 36 had had a previous negative and positive prostate biopsy, respectively. On MP MRI a mean of 2.6 lesions (median 3, range 1 to 7) were suspicious for cancer.

Median time between MRI and protocol biopsy was 20.0 days. Of the 101 cases 55 were positive for prostate cancer on standard or MR targeted core biopsy, including 35 positive on MR targeted core biopsy and on standard biopsy, 10 positive only on MR targeted core biopsy and the remaining 10 positive only on standard 12-core extended biopsy. A mean of 2.6 MRI lesions (range 1 to 7) was identified per patient. We obtained 252 standard cores, of which 149 (11.0 %) were positive for prostate cancer.

Chi-square analysis was used to determine whether there was a correlation between MRI suspicion for prostate cancer and D'Amico risk stratification (see table). The within cluster resampling technique was also used to compare the MRI suspicion level and D'Amico risk stratification for MRI targeted core biopsies and MRI lesions. All tests were statistically significant ($p < 0.01$, see table).

Multiple MRI targeted core biopsies were taken from each MRI lesion. MRI lesions were labeled

positive for statistical analysis if at least 1 MRI targeted core biopsy was positive for cancer. This secondary analysis was done due to the possibility of inadequate sampling of the MRI lesion. The MRI lesion could have been missed during 1 MRI targeted core biopsy due to the inherent limitations of manually guided biopsy or to the spatial accuracy of the system. There were 588 MRI targeted core biopsies of a total of 264 MR lesions. This method of using MRI targeted core biopsies vs lesions increased the biopsy yield only an average of 7.4%, which did not alter our study conclusions. An average of 2.2 MRI targeted core biopsies per lesion were performed with at least 1 core biopsy in the axial and sagittal planes.

DISCUSSION

Prostate cancer is the most common cancer and the second most common cause of cancer related mortality in American males. Prostate cancer diagnosis has gone through significant improvements, resulting in a 5-year relative survival rate of 100% for local or regional stages.¹ As urologists, we have adapted our treatment paradigm using a multidisciplinary approach (urologists, diagnostic radiologists, radiation oncologists, pathologists, interventional radiologists and medical oncologists). During the evaluation of patients with prostate cancer practitioners must determine prostate cancer specific mortality and tailor treatment accordingly. Using this rationale we applied the D'Amico risk stratification to each patient to determine whether there was a correlation with MP endorectal coil MRI.

There was a statistically significant association between the degree of MR suspicion for prostate cancer and the D'Amico risk stratification for each patient, MR targeted core biopsy and MR lesion ($p < 0.01$, fig. 3). This is consistent with data correlating whole mount prostate specimens to prostate MP MR images.¹² In our series when patients with only a low suspicion level on MRI were compared to patients with moderate and highly suspicious lesion(s) on MP MRI, there was an absolute 38.8% and 61.6% increase in prostate cancer detected, respectively, using our protocol ($p < 0.0001$). Also, using prostate MRI one may quantitatively predict the aggressiveness (Gleason score) associated with specific MRI lesions in the prostate.¹³ Unfortunately this was not available at the beginning of our study and we are currently investigating the application in our patients.

There are several limitations of this study. Our study population may be biased since all patients were characterized as at low risk in regard to clinical stage. This may reflect stage migration due to the increased

Positive biopsy results

| MR Suspicion | No. D'Amico Risk Stratification | | |
|----------------------------|---------------------------------|--------------|------|
| | Low | Intermediate | High |
| Low: | | | |
| Pts | 10 | 1 | 1 |
| MR lesions | 17 | 2 | 4 |
| MR targeted core biopsies | 23 | 3 | 7 |
| Moderate: | | | |
| Pts | 10 | 15 | 1 |
| MR lesions | 10 | 15 | 4 |
| MR targeted core biopsies | 13 | 25 | 8 |
| High: | | | |
| Pts* | 2 | 6 | 9 |
| MR lesions† | 2 | 6 | 16 |
| MR targeted core biopsies† | 3 | 12 | 34 |

* $p < 0.0001$.

† $p < 0.01$.

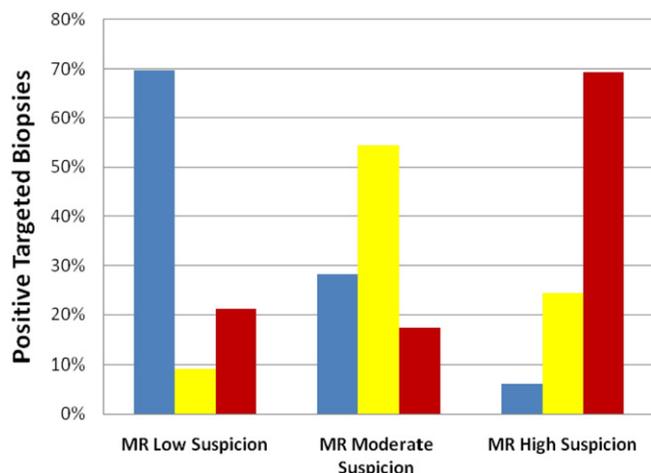


Figure 3. Correlation of MRI suspicion of MR targeted core biopsies with D'Amico risk stratification ($p < 0.01$). Percents were calculated using total number of positive targeted biopsies per MR suspicion category, stratified by D'Amico risk stratification. Blue bars represent low risk. Yellow bars represent intermediate risk. Red bars represent high risk.

use of PSA for prostate cancer screening.¹⁴ An additional limitation of this platform is that prostate MRI still cannot detect all cancerous lesions (less than 3 mm). Recently our histopathological correlation with MP (T2W MRI, DCE MRI and MR spectroscopy) MRI for lesions in the peripheral zone revealed 94%, 55% and 32% sensitivity, and 84%, 97% and 99% specificity, respectively.¹²

Using the nonweighted grading technique to assess MR suspicion may place unneeded emphasis on functional imaging in regard to MR spectroscopy. Spectroscopy especially is a functional imaging sequence that may not add a large amount of clinical information for lesion detection compared to the other modalities. This is partly due to the fact that spectroscopy requires a minimum of an approximately 0.6 cc lesion to adequately assess the choline-to-citrate ratio. Moreover, voxels may possibly include normal prostate tissue if the lesion is small and has a lower Gleason score. Thus, intuitively

larger lesions and possibly more aggressive ones would be observed using this modality. Possibly one could use fewer sequences to achieve a similar correlation with Gleason score.¹³

A concern with active surveillance is under grading cases. In the last 20 years there has been a significant decrease in Gleason score upgrading of prostatectomy specimens. Historically the rate of pathological upgrading on radical prostatectomy specimens is 54%.¹⁵ Most recently Gofrit et al at University of Chicago reported that 20.3% of cases were upgraded after prostatectomy.⁷ We are currently investigating whether our platform can further decrease the number of cases up staged after surgery (local regional staging) to overcome the inherent biases of TRUS guided biopsy, which may under sample tumor volume and grade.¹⁵

Finally, this platform may be used in the emerging field of focal prostate therapy. In addition to improving prostate cancer quantification, this platform may also guide the treatment of focal areas of the prostate and allow close followup of treated lesions and rebiopsy, as indicated.

CONCLUSIONS

MP MRI assessment of patients with lesions positive for prostate cancer resulted in a statistically significant correlation with the MRI detected lesion suspicion level and the D'Amico risk stratification. There was a statistically significant association of cancer detected with increasing MR suspicion level. These MP MRI data were used to guide prostate biopsies with a custom MRI/TRUS fusion guided biopsy platform. Interval imaging to assess the lesion(s) may obviate the need for multiple biopsies and the associated morbidity in patients undergoing long-term watchful waiting.¹⁶ While a larger prospective trial and further evaluation are certainly needed, MP MRI assessment may provide insight into which patients may be eligible for active surveillance vs other treatment options.

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EDITORIAL COMMENT

MP prostate MRI is becoming an important diagnostic tool for prostate cancer detection, localization and local staging. Increasing evidence demonstrates that MRI performance is improving with the combined use of different functional MR techniques.^{1,2} This will probably create the bridge to tailored prostate cancer management, ie image guided and focal therapy. However, to reach this point these authors introduced a scoring system for prostate MRI. They report the correlation between D'Amico risk stratification and the degree of suspicion of prostate can-

cer on MRI. The study is based on 101 patients at a single institution. They concluded that there is a statistically significant association of cancer detected with increasing MR suspicion. Future clinical trials must focus on validating these scoring systems. Furthermore, it is essential to define how to perform and report prostate MRI.

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