Can Confirmatory Biopsy be Omitted in Patients with Prostate Cancer Favorable Diagnostic Features on Active Surveillance?

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Abbreviations and Acronyms

AS = active surveillance

DWI = diffusion weighted imaging

MR = magnetic resonance

MRI = magnetic resonance imaging

PSA = prostate specific antigen

T2WI = T2-weighted images

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Editor's Note: This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 232 and 233.

Purpose: We evaluated whether initial diagnostic parameters could predict the confirmatory biopsy result in patients initiating active surveillance for prostate cancer, to determine whether some men at low risk for disease reclassification could be spared unnecessary biopsy.

Materials and Methods: The cohort included 392 men with Gleason 6 prostate cancer on initial biopsy undergoing confirmatory biopsy. We used univariate and multivariable logistic regression to assess if high grade cancer (Gleason 7 or greater) on confirmatory biopsy could be predicted from initial diagnostic parameters (prostate specific antigen density, magnetic resonance imaging result, percent positive cores, percent cancer in positive cores and total tumor length).

Results: Median patient age was 62 years (IQR 56–66) and 47% of patients had a dominant or focal lesion on magnetic resonance imaging. Of the 392 patients 44 (11%) had high grade cancer on confirmatory biopsy, of whom 39 had Gleason 3+4, 1 had 4+3, 3 had Gleason 8 and 1 had Gleason 9 disease. All predictors were significantly associated with high grade cancer at confirmatory biopsy on univariate analysis. However, in the multivariable model only prostate specific antigen density and total tumor length were significantly associated (AUC 0.85). Using this model to select patients for confirmatory biopsy would generally provide a higher net benefit than performing confirmatory biopsy in all patients, across a wide range of threshold probabilities.

Conclusions: If externally validated, a model based on initial diagnostic criteria could be used to avoid confirmatory biopsy in many patients initiating active surveillance.

Key Words: prostatic neoplasms, biopsy, watchful waiting

Current protocols for monitoring men on AS involve repeat digital rectal examination, PSA and repeat prostate biopsy.[1–3] Given that systematic biopsy may miss Gleason pattern 4 disease,[4–7] confirmatory biopsy has become a mainstay of AS. However, there are several reasons why avoiding repeat biopsy would be desirable. Prostate biopsy is an invasive procedure, is sometimes poorly tolerated, and is commonly associated with hematospermia, hematuria and transient worsening of lower urinary tract symptoms.[2] While the majority of these complications are benign and self-limiting, the rates of severe sepsis requiring hospitalization have

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increased in recent years as a result of emerging antimicrobial resistance.[8] The risk of infectious complications increases with each additional biopsy.[9]

Using clinical and tumor characteristics, attempts have been made to identify those patients at risk for biopsy progression. Men with a higher PSA density,[10,11] positive confirmatory biopsies[10] and a higher number of positive cores[11] have been shown to carry an increased risk of progression on AS. We sought to determine whether clinical predictors of progression, including imaging in the form of MRI, could predict the results of the confirmatory biopsy with sufficient accuracy to allow some patients to avoid biopsy.

MATERIALS AND METHODS

Patient Population

A review of our institutional database identified 583 patients on AS from December 2007 to December 2013 who underwent MRI and a confirmatory biopsy. These patients came from across the United States, consistent with our role as a dedicated cancer hospital. Inclusion criteria for AS at our institution are clinical stage T2a or less, Gleason score 3+3=6 or less, PSA 10 ng/ml or less, and 3 or fewer positive cores with 50% or less positivity in a single core. To maintain consistency with these criteria we excluded 3 patients who chose AS despite an initial biopsy score of 4+3, 31 patients with Gleason 3+4 and 35 with a baseline PSA greater than 10 ng/ml. We also excluded 5 patients missing baseline PSA and 93 missing complete initial biopsy information. Three patients were excluded for whom more than 14 months had elapsed between the diagnostic and confirmatory biopsy. Lastly, we excluded 22 patients who underwent MRI after confirmatory biopsy and 4 who underwent MRI more than 1 year before confirmatory biopsy. This left a final cohort of 392 patients.

MRI Protocol and Analysis

We used whole body MRI units (GE Healthcare, Waukesha, Wisconsin) at 1.5T (62 patients) and 3T (305 patients). An endorectal coil was used in 370 cases. Data on MRI acquisition parameters were not available for 25 patients. MRI parameters varied with time as clinical protocols at our institution evolved with new developments. Twenty studies involved anatomical T2WI alone. Of the multiparametric MRI studies 281 used DWI and dynamic contrast enhanced imaging in addition to T2WI. DWI and T2WI were used in 75 cases, dynamic contrast enhanced imaging and T2WI in 11 cases, and the combination of DWI, T2WI and magnetic resonance spectroscopy in 6 cases. A total of 29 MRI studies were performed elsewhere. MRIs reporting a dominant prostatic lesion were considered positive studies for this project. We defined a dominant lesion on MRI as a nodule demonstrating reduced signal intensity on T2WI, restricted diffusion on DWI and/or early enhancement or rapid washout compared to adjacent prostate tissue on dynamic contrast enhanced imaging. In cases for which these sequences were unavailable, MRI positivity was determined as a score greater than 3 on a Likert-type scale. Similar to the PI-RADS (Prostate Imaging Reporting and Data System) score, this corresponds to a greater than 50% likelihood of prostate cancer.

Biopsy Protocol

All patients underwent systematic peripheral and transition zone sampling under local anesthesia at the time of confirmatory biopsy. In those cases in which the surgeon used MRI to help target confirmatory biopsies, such targeting was cognitive. MR fusion guidance systems were not used in this cohort.

Statistical Analysis

We assessed whether initial diagnostic parameters could predict confirmatory biopsy results. Thus, we used univariate and multivariable logistic regression to determine whether any grade of prostate cancer and high grade prostate cancer (Gleason 7 or greater) on confirmatory biopsy could be predicted from PSA density (initial PSA in ng/ml divided by MRI prostate volume in cm^3), MRI results (presence/absence of dominant lesion) and initial biopsy results (percent positive cores out of all cores, percent cancer in all positive cores and total tumor length from all positive cores). If 2 areas in the same core contained cancer, then the length of each segment was added, with the exclusion of intervening normal tissue. Biopsy parameters were analyzed as continuous variables. The area under the receiver operating curve was used to assess the discrimination of the model. We also performed decision curve analysis for the outcome of high grade cancer to assess whether our model would be clinically useful in deciding whether to perform confirmatory biopsy.[12] We used tenfold cross-validation to address overfit. The decision curve was assessed up to a threshold probability of 15%, as this was viewed as the highest threshold risk of high grade cancer for which a physician would forgo a confirmatory biopsy. All statistical analyses were conducted using Stata® 13.0.

Table 1. *Patient characteristics*

Baseline or initial biopsy results		
Median pt age (IQR)	62	(56–66)
No. clinical stage (%):		
T1	348	(89)
T2	44	(11)
Median ng/ml PSA (IQR)	4.5	(3.4–5.9)
Median ng/ml/cm^3 PSA density (IQR)	0.10	(0.07–0.14)
Median total biopsy cores (IQR)	12	(12–13)
Median % pos cores from all cores (IQR)	8.3	(8.3–16.7)
Median mm total tumor length from all pos cores (IQR)	1.5	(0.7–3.5)
Median % Ca from all pos cores (IQR)	10.0	(5.0–20.0)
No. MRI result (%):		
No dominant/focal tumor	208	(53)
Dominant/focal tumor	184	(47)
Confirmatory biopsy result		
No. Gleason score (%):		
No Ca on biopsy	135	(34)
6	213	(54)
3+4	39	(10)
4+3	1	(0.3)
8	3	(0.8)
9	1	(0.3)