Defining Prostate Cancer at Favorable Intermediate Risk: The Potential Utility of Magnetic Resonance Imaging and Genomic Tests

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Abbreviations and Acronyms

AP = adverse pathology
AS = active surveillance
ECE = extracapsular extension
FIR = favorable intermediate risk
GGG = Gleason Grade Group
GPS = OncotypeDx Genomic Prostate Score®
IR = intermediate risk
LR = low risk
mpMRI = multiparametric MRI
MRI = magnetic resonance imaging
PCa = prostate cancer
PSA = prostate specific antigen
RP = radical prostatectomy
UIR = unfavorable intermediate risk
VLR = very LR

Purpose: We determined whether prostate multiparametric magnetic resonance imaging and genomic biomarkers might help further define patients with favorable intermediate risk prostate cancer which could safely be considered suitable for active surveillance.

Materials and Methods: From our institutional database we identified 509 patients who underwent radical prostatectomy with preoperative magnetic resonance imaging and a postoperative Decipher® prostate cancer test. According to the NCCN® (National Comprehensive Cancer Network®) risk stratification 125 men had favorable intermediate and 171 had unfavorable intermediate risk disease. Univariable and multivariable binary logistic regression analyses were done to test the utility of different variables in predicting adverse pathology, defined as Gleason Grade Group greater than 2, pT3b or pN1.

Results: On univariable analysis favorable intermediate risk, multiparametric magnetic resonance imaging and the prostate cancer test significantly predicted adverse pathology. On multivariable analysis favorable intermediate risk and the prostate cancer test maintained independent predictive value while multiparametric magnetic resonance imaging did not meet statistical significance ($p = 0.059$). The 19 patients at favorable intermediate risk with high genomic risk had an adverse pathology rate slightly higher than patients at unfavorable intermediate risk (42.1% vs 39.8%, $p = 0.56$). Those at low genomic risk had an adverse pathology rate slightly lower than patients at very low or low risk (7.5% vs 10.2%, $p = 0.84$). The 31 patients at favorable intermediate risk but at high multiparametric magnetic resonance imaging and genomic risk had an adverse pathology rate slightly lower than patients at unfavorable intermediate risk (25.8% vs 39.8%, $p = 0.14$). Those at low multiparametric magnetic resonance imaging and genomic risk had an adverse pathology rate slightly lower than

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patients at very low or low risk (8.5% vs 10.2%, p = 0.89).

Conclusions: Multiparametric magnetic resonance imaging and the Decipher test allowed us to better define the risk of adverse pathology in patients at favorable intermediate risk who were diagnosed with prostate cancer.

Key Words: prostatic neoplasms, magnetic resonance imaging, genomics, risk, pathology

PROSTATE cancer is the most commonly diagnosed cancer in men. Although it often has an indolent course, PCa represents the third leading cause of cancer death in men. Men diagnosed with localized disease, defined as no identifiable nodal involvement or distant metastasis, have 3 primary options, including AS, surgery and radiation therapy.[1]

To distinguish men who can safely be treated with AS from those more likely to benefit from immediate curative intervention patients are often classified into risk categories based on accepted clinical features such as the D'Amico criteria and the NCCN (National Comprehensive Cancer Network) risk groups.[2] According to the NCCN Guidelines® AS is deemed appropriate in patients at VLR and LR, and may be considered in those at FIR. However, in the latter scenario patients should be warned about the need to be closely monitored for progression.[2]

Several investigators have published studies on AS and delayed intervention in IR cases. Dall'Era and Klotz reviewed the results in patients at IR at 5 institutions.[3] They pointed out that although these men were at higher risk for eventually needing additional therapy, AS did not significantly compromise the chance of longer term cure.[3] On the other hand, Yamamoto et al noted that while AS appeared safe in patients with GGG 1 and PSA greater than 10 ng/ml, those with elements of Gleason pattern 4 were at increased risk for metastasis when treated with an initially conservative approach.[4]

Assuming that a subset of patients with FIR can safely undergo AS as first line treatment, there is no consensus on what should be considered FIR. The current AUA (American Urological Association) guidelines define FIR as cT1-T2a with GGG 1 and PSA 10 to 20 ng/ml or cT1-T2a with GGG 2 and PSA less than 10 ng/ml. Conversely UIR is defined as cT2b with GGG 2 and PSA less than 10 ng/ml or any cT1-2 with GGG 2 and PSA 10 to 20 ng/ml or cT1-2 with GGG 3 and PSA less than 20 ng/ml.[5] The EAU (European Organisation of Urology) guidelines define IR as cT2b or Gleason score 7, or PSA 10 to 20 ng/ml[6] but point out that the different prognostic impact of GGGs 2 and 3 support further distinction into FIR in GGG 2 and UIR GGG 3 cases.[7] The NCCN Guidelines define FIR as any of cT2b-c, GGG 2, PSA 10 to 20 ng/ml plus less than 50% positive biopsy cores.[2] Conversely 50% or greater positive biopsy cores and/or GGG 3 define UIR providing that cT2b-c and PSA 10 to 20 ng/ml are present.

The NCCN Guidelines indicate the possibility of using molecular or genomic tumor tests as additional tools in an effort to better define the different risk categories.[2] This suggests that men at FIR may undergo molecular markers testing if life expectancy is 10 years or greater, and genomic testing if there is a strong family history. However, there is no mention of whether such tests may improve the current stratification of patients at FIR and UIR. Moreover, none of the mentioned guidelines considers findings from prostate mpMRI in those stratifications of patients at IR.

Therefore, in the current study we aimed to determine the role of prostate mpMRI findings and molecular marker testing to further define the FIR category.

PATIENTS AND METHODS

After receiving Institutional Review Board approval we identified 520 patients in a prospectively maintained database who underwent robot assisted radical prostatectomy between October 2013 and August 2017 (IRB No. GCO 17-2084). All patients underwent mpMRI using 3 Tesla magnetic field strength and a pelvic phased array coil.[8] Documented loss of the prostate capsule and capsule irregularity were considered positive ECE findings. Prostate MRIs were interpreted by 1 of 6 fellowship trained radiologists, of whom all had at least 8 years of experience.

The Decipher® prostate cancer test was performed in the pathology specimen as previously described.[9] Patients who had previously undergone radiotherapy and/or androgen deprivation therapy were excluded from testing. A single dedicated fellowship trained uropathologist reviewed all slides of prostate biopsy and radical prostatectomy specimens. Biopsies done elsewhere were also reviewed before surgery and before entering the active surveillance protocol. Target biopsies of MRI lesions were performed with the Artemis device (Innomedicus, Cham, Switzerland) using a spring loaded biopsy gun and 18 gauge needles.

Eligible patients were classified by NCCN risk category[2] and evaluated for AP findings at RP, defined as GGG 3 or greater, seminal vesicle invasion (pT3b) or lymph node metastasis (pN1) since AS is considered inappropriate in patients with such features.[10] The ability of standard and novel variables (mpMRI and Decipher, respectively) to predict AP in patients at IR was tested by

univariable and multivariable logistic regression analyses. Finally, FIR cases were reclassified according to our novel variables and we reassessed the ability of such novel classifications to correctly assign cases to FIR or upgrade them to UIR.

Statistical Analysis

Continuous variables are reported as the median and IQR, and were tested by the Kruskal-Wallis test. Categorical variables are shown as the frequency and proportion, and were tested by the chi-square test. Univariable and multivariable binary logistic regression analyses were performed to test the impact of different variables on AP risk. ROC analyses were done to compare the predictive accuracy of different models. Statistical analyses were performed using Stata®, version 14 with significance considered at $\alpha = 0.05$.

RESULTS

Of the 509 eligible patients 59 met NCCN criteria for VLR and LR, 125 met criteria for FIR, 171 met criteria for UIR and 154 met criteria for HR and VHR.[2] The supplementary table (https://www.jurology.com) lists the descriptive characteristics of patients at VLR-LR, FIR and UIR.

On univariable analysis the differential criteria between FIR and UIR, namely GGG 3 and 50% or greater positive cores, did not independently predict AP in patients at NCCN IR.[2] Conversely the NCCN UIR category, mpMRI and Decipher significantly predicted AP (table 1). On multivariable analysis the UIR category and Decipher remained statistically significant predictors of AP while mpMRI was close to but did not maintain statistical significance (table 1).

ROC curve analyses demonstrated that a predictive model including mpMRI and Decipher findings performed significantly better than the base NCCN model to predict AP in patients at NCCN IR (ROC area 0.71 vs 0.66, p = 0.004, see figure).[2] Therefore, we reclassified patients at NCCN FIR to be at low and high genomic risk according to Decipher findings and compared the risk of AP with that of patients at NCCN VLR-LR and UIR (table 2). The 19 patients at high genomic risk and FIR had an AP rate slightly higher than that of patients at UIR (42.1% vs 39.8%, p = 0.56). Those at low genomic risk had an AP rate slightly lower than that of patients at VLR-LR (7.5% vs 10.2%, p = 0.84).

Finally we reclassified patients at NCCN FIR[2] into low and high risk FIR groups based on Decipher and mpMRI unfavorable findings (table 2). Of these men 31 were classified at high risk and FIR. The AP rate was slightly lower than in patients at UIR (25.8% vs 39.8%, p = 0.14). Conversely the 94 men at LR-FIR had an AP rate slightly lower than that of men at VLR-LR (8.5% vs 10.2%, p = 0.89).

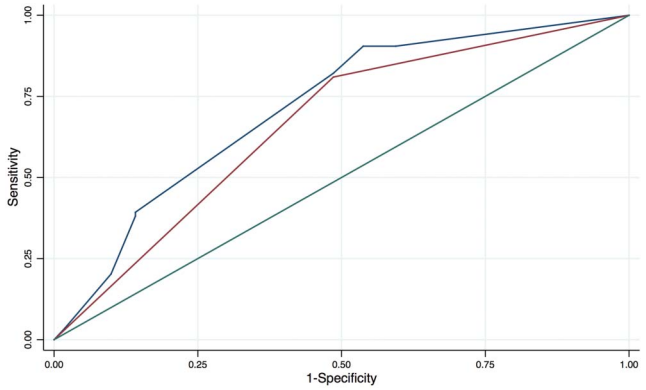
DISCUSSION

The current study demonstrates that using the NCCN risk classification[2] the incidence of AP at RP was 12.8% in patients at FIR and 10.2% in patients at VRL-LR. This could support the role of AS in patients at FIR. These finding differ from those of Patel et al, who compared the rates of AP in men at VLR and LR, and a subgroup of men at IR with low volume cancer (1 or 2 cores showing GGG 2).[11] Despite this more stringent definition of FIR approximately 1 of 4 men in this category were found to harbor AP findings. Furthermore, no clinical or pathological parameter identifies a population of men at IR with pathological outcomes comparable to those in the VLR or LR cohort.

This discrepancy is not surprising since the outcomes of IR PCa are heterogeneous. In a recent review Kane et al evaluated clinically relevant outcomes in men with IR PCa based on clinical and pathological features, and found that estimates of AP findings and

Table 1. *Univariable and multivariable log-binomial regression of adverse pathological finding predictors in NCCN intermediate risk group[2] of 296 patients*

	Univariable		Multivariable	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	1.03 (0.99–1.07)	0.118	–	–
Family history	0.66 (0.37–1.19)	0.168	–	–
Race (black vs other)	0.78 (0.30–2.03)	0.613	–	–
Biopsy Gleason Grade Group:			–	–
1	Referent			
2	0.45 (0.08–2.46)	0.360		
3	2.55 (0.47–13.71)	0.276		
Pos core:			–	–
Less than 50%	Referent			
50% or Greater	1.61 (0.89–2.88)	0.110		
Intermediate risk:			–	–
Favorable	Referent		Referent	
Unfavorable	4.50 (2.45–8.26)	<0.001	4.17 (2.25–7.72)	<0.001
MRI extracapsular extension	2.19 (1.13–4.23)	0.020	1.97 (0.97–3.97)	0.059
Genomic risk low-av vs high	2.38 (1.31–4.34)	0.005	2.26 (1.20–4.28)	0.012



ROC curve analysis in patients at intermediate risk shows added value of MRI ECE and Decipher test to NCCN risk classification[2] ($p = 0.004$). Blue curve indicates NCCN risk plus ECE on MRI plus Decipher test (ROC area 0.7137). Red curve indicates NCCN risk (ROC area 0.6618).

5-year disease progression rates were wide, ranging from 15% to 64% and 21% to 91%, respectively.[12] Clinical parameters and predictive nomograms refine these estimates but do not uniformly differentiate favorable and unfavorable IR PCa.

It is clear that the key to extending AS criteria lies in more precise risk classification possibly using novel and more precise tools. Berlin et al reported the accuracy of a 22-feature genomic classifier to predict disease recurrence in IR PCa cases treated only with dose escalated external beam radiotherapy.[13] In a recent multicenter study in 16,049 patients with LR or IR PCa, defined as PSA 20 ng/ml or less, ISUP (International Society of Urological Pathology) grade group 1-3 and clinical stage cT2b or less, a novel risk score was proposed for AS selection which yielded an absolute 10% increase in the number of patients eligible for this approach without increasing the risk of misclassification.[14]

Our study shows that the Decipher test was a statistically significant predictor of AP at radical prostatectomy in patients at NCCN IR.[2] We observed a similar trend for mpMRI but it did not reach statistical significance. Our findings are consistent with those of Kornberg et al, who tested the utility of the GPS and mpMRI to predict GGG upgrading in men on AS.[15] On subanalysis of 131 cases in which the GPS and mpMRI were done Kornberg et al found that only the GPS was associated with GGG upgrading, which added value to clinical covariates. Taken together the 2 studies support the genomic heterogeneity among tumors that are relatively homogeneous from a clinical standpoint[16] and the potential role of emerging tests based on an assessment of tumor RNA expression for predicting outcomes. Research is currently moving in this direction. It would be interesting to compare the performance of genomic tests with that of other emerging tests such as pentraxin 3[17] and ERG fusion.[18]

For the time being our study indicates that FIR and VLR-LR cases behaved similarly in terms of AP (12.8% and 10.2%, respectively). However, as many as 15% of FIR cases (19 of 125) at high genomic risk behaved like UIR cases. Therefore, those men would have been poor candidates for AS.

While molecular tests are not yet used in routine clinical practice, mpMRI is becoming widely available. As mentioned, mpMRI findings were close to but did not reach statistical significance. Nevertheless, as many as 25% of FIR cases (31 of 125) at high genomic risk and mpMRI risk behaved similarly to UIR cases. Therefore, these men would have been poor candidates for AS.

On the other hand, FIR cases at low genomic and mpMRI risk behaved like VLR-LR cases. This information can be useful when counseling such men about the possibility of undergoing AS and it promises to reduce the costs of care. Now mpMRI is affordable and usually reimbursed by insurance. Due to its high negative predictive value it can be done to follow patients on AS. Our protocol includes mpMRI

Table 2. *Adverse pathology rate according to genomic FIR classification, and MRI and genomic FIR classification*

		No. NCCN[2] Favorable Intermediate Risk (%)				
	No. Very Low-Low Risk (%)	Genomic Low Risk	Genomic High Risk	MRI + Genomic Low Risk	MRI + Genomic High Risk	No. NCCN Unfavorable Intermediate Risk (%)
Overall	59	106	19	94	31	171
No. Gleason Grade Group (%):						
1	11 (18.6)	4 (3.8)	0	3 (3.2)	1 (3.2)	3 (1.8)
2	42 (71.2)	95 (89.6)	13 (68.4)	84 (89.4)	24 (77.4)	107 (62.6)
3	6 (10.2)	7 (6.6)	6 (31.6)	7 (7.4)	6 (19.4)	54 (31.6)
4	0	0	0	0	0	4 (2.3)
5	0	0	0	0	0	3 (1.8)
No. pathological stage (%):						
pT2	51 (86.4)	85 (80.2)	11 (57.9)	75 (79.8)	21 (67.7)	110 (64.3)
pT3a	7 (11.9)	20 (18.9)	6 (31.6)	18 (19.1)	8 (25.8)	43 (25.1)
pT3b	1 (1.7)	1 (0.9)	2 (10.5)	1 (1.1)	2 (6.5)	18 (10.5)
pN1	1 (1.7)	0	0	0	0	2 (1.2)
No. any adverse pathological feature (%)	6 (10.2)	8 (7.5)	8 (42.1)	8 (8.5)	8 (25.8)	68 (39.8)

at 1 year and, if it is positive, a confirmatory targeted prostate biopsy. Decipher has a higher cost and should be performed only in select patients. If we had used this approach in every patient at NCCN FIR,[2] we could have avoided radical prostatectomy in 75% (94 of 125) without missing AP findings.

This study is not devoid of limitations. 1) AP served as a surrogate for oncologic outcomes but this bias is common to most studies as in the Western world patients at IR are usually offered curative therapy at diagnosis and sparse data are available on oncologic outcomes in patients at FIR who are on AS. 2) The tissue used for the Decipher test was obtained from the area with the highest Gleason finding in the pathology specimen and not from biopsy samples. However, the concordance rate between biopsy and RP samples reached 71% for the mean Decipher score of all biopsy cores, and 86% for the core with the highest sampled Gleason finding and percent of tumor involvement.[19,20] Finally, mpMRI findings involve a certain degree of inter-observer and intra-observer variability.[21]

CONCLUSIONS

To our knowledge the current study demonstrates for the first time that considering mpMRI and Decipher prostate cancer test findings allows for more precise classification of patients at FIR. Specifically individuals with mpMRI suspicious for ECE who are at high genomic risk should be considered to be at UIR and treated accordingly. Conversely those with low risk mpMRI who are at low genomic risk can be counseled about the possibility of safely undergoing AS.

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EDITORIAL COMMENT

There is strong evidence to support active surveillance in patients with low and very low risk prostate cancer, given 0.1% prostate cancer specific mortality at 10 years of followup.[1] However, in patients with

intermediate, low volume disease the risk increases, thus, calling for better tools to evaluate the presence of aggressive disease. Although mpMRI has proven to be of use when selecting candidates for active surveillance due to its approximately 90% high negative predictive value,[2] it is not a perfect method.[3] Falagario et al bring to the table the contemporary perspective that imaging techniques, although important, do not account for the genomic tumor heterogeneity known to have an important role in the biology of cancer.

The authors present their experience using the Decipher test when active surveillance was selected. They describe that when combined with mpMRI, this test outperformed the NCCN model (reference 2 in article) for predicting final pathology results (ROC area 0.71 vs 0.66, $p = 0.004$). In this way the authors shed light on the current issue of better stratifying patients with intermediate risk prostate cancer, assigning mpMRI a promising role in addition to the Decipher test in further risk stratifying those with ISUP 2 disease who might be safe candidates for active surveillance.

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