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Risk stratification of prostate cancer in the modern era

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Abstract

Purpose of Review—Novel tools have become available to the practicing urologist in recent years that endeavor to improve on commonly utilized prostate cancer (PCa) risk stratification techniques. In this review, we provide an overview of these modalities in the context of active surveillance.

Recent Findings—Multiparametric magnetic resonance imaging (MP-MRI) has a rapidly growing body of evidence that suggests it provides the necessary sensitivity and NPV to rule out clinically significant disease. MRI-guided targeted biopsy has the potential to improve detection of clinically significant cancers and for rebiopsy of patients with continued suspicion for PCa. PSA isoforms and Prostate Health Index (PHI) outperform PSA alone and improve risk stratification when combined with established criteria, but need further prospective studies using template and MRI-targeted biopsies. Urinary biomarkers tend to fall short in predicting adverse pathology when used alone, but improve risk-stratification when used in conjunction and with established criteria. Finally, tissue biomarkers and gene assays allow for patient-specific molecular and genetic characterization of cancer phenotype, showing significant promise in predicting adverse pathology and in some cases have already been incorporated into and altered clinical practice.

Summary—These novel modalities show remarkable promise in improving the risk-stratification of patients with PCa, and as the body of evidence grows will likely become incorporated into major oncologic guidelines and standard urologic practice. Further prospective clinical studies are needed, as well as analysis of cost-effectiveness.

Keywords

Prostate cancer; active surveillance; risk-stratification; biomarkers; MRI

Introduction

Active surveillance is a viable option in the management of low-risk prostate cancer (PCa). There remains today uncertainty in identifying patients suitable for active surveillance, which is a source of anxiety for urologist and patient alike. The commonly used risk-stratification methods incorporate PSA levels with random prostate biopsies and clinical

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staging. However, PSA levels are not cancer specific, and can lead to both false positives and negatives. Random biopsies can lead to sampling error, either missing the significant lesion or cancer completely. Even following strict criteria with 20 core biopsy, 20% of patients deemed suitable for active surveillance by Epstein criteria harbor higher risk disease^{1, 2}. As such, there is a need for new risk stratification tools that reduce the uncertainty of these commonly available methods and more accurately risk-stratify patients where PSA testing and random biopsies fall short.

The ideal risk stratification tool is one that can accurately and consistently identify patients harboring aggressive cancer phenotypes, and/or identify the transition from low- to higher-risk cancers in the natural progression of the disease while on active surveillance. In recent years, a plethora of new risk stratification modalities have become available to the practicing urologist, with the most recent and most studied reviewed below.

Magnetic Resonance Imaging and Targeted Prostate Biopsy

Multiparametric magnetic resonance imaging (MPMRI) is an attractive modality for use in the risk stratification of prostate cancer. Prostate MPMRI has the potential to detect and characterize cancers throughout the prostate and surrounding tissue, with multiple functional and anatomic parameters taken into account. MPMRI's role in active surveillance and risk stratification has not been clearly defined, and as such is not widely used for this purpose. However, with a rapidly growing body of evidence, MPMRI is becoming a validated and powerful risk stratification tool.

Detection of significant prostate cancer

In a recent prospective study, Thompson et al evaluated the accuracy of MPMRI imaging in detecting significant PCa in men with abnormal PSA and/or DRE, prior to saturation plus targeted prostate biopsy. 30 cores, systematic and targeted, were taken via a transperineal approach. Of the 150 men included in the study, MRI was positive for cancer in 66%. 61% had PCa on biopsy, with about 30–41% considered significant by various common criteria. Biopsy results were compared to radical prostatectomy specimens and found similar rates. The negative and positive predictive values for MRI detection of significant PCa were 100% and 71% respectively for higher risk patients (defined as PSA>10 with positive DRE) and 96% and 28% for lower risk patients. In their study, forgoing subsequent biopsy in patients with low risk MRI scores would have missed one Gleason 3+4 and no PCa higher grade than Gleason 3+4³.

In a retrospective study consisting of 115 patients who underwent MPMRI prior to RRP, our group recently evaluated the use of MPMRI combined with Epstein's criteria with and without the MPMRI parameter of apparent diffusion coefficient (ADC) to calculate the predictive values across the varying definitions of clinically significant cancer. Using Epstein's criteria alone, 12 patients were understaged (sensitivity 79%, NPV 68%). Adding ADC to Epstein's criteria improved the sensitivity and NPV to 93% and 84%, respectively⁴.

Turkbey et al evaluated 133 men who underwent MPMRI prior to RRP. MPMRI was retrospectively compared to various established definitions for predicating AS candidates. In

predicting insignificant disease, MRI had a sensitivity of 93%, PPV of 57% and accuracy of 92%, with 11 cases misclassified. MRI alone outperformed the established risk assessment criteria. Epstein biopsy criteria misclassified 16 patients (with 11 understaged). The inclusion of MRI corrected misclassification in 75% of these patients, with 8 of the 11 previously understaged no longer a candidate for active surveillance.⁵

The use of DWI in detecting significant PCa was recently evaluated in a prospective study of 111 men with bladder and/or PCa prior to RRP or cystoprostatectomy. The study had the benefit of including patients who were not known to have CaP prior to surgery. The sensitivity and specificity of T2WI and DWI combined was 89% to 91% and 77% to 81%, respectively. Of note, a false-positive rate of 17% was noted⁶.

Shukla-Dave et al. validated previously published risk-stratification nomograms that incorporated MRI or MPMRI and introduced a new nomogram incorporating MPMRI findings into clinical data. The MR-inclusive risk-stratification models performed significantly better than clinical-only models.⁷

MRI guided diagnostic biopsy

One of the downfalls of standard systematic biopsy is random sampling error inherent in the technique, with as much as 20% of clinically significant lesions missed on random biopsy¹. MRI guided biopsy, via various targeting modalities, combines the benefits of MR imaging with biopsy, and may improve the detection of clinically significant lesions. While the technology to biopsy under direct MRI guidance exists⁸, the time needed and impracticality limit the implementation in urologic practice. Systems that fuse MPMRI images with real-time ultrasound have been described that attempt to bring targeted biopsy to clinical practice^{9–11}.

We previously described the use of a MPMRI/transrectal ultrasound fusion biopsy system (Artemis) in clinic by a urologist, where stored MRI images were overlaid on real-time transrectal ultrasound images, affording the convenience and familiarity of the transrectal biopsy approach^{9, 12}. The use of MRI/transrectal ultrasound fusion biopsy in 105 men with prior negative biopsy with persistently elevated PSA was recently evaluated by our group. Targeted and systematic biopsies were obtained regardless of MRI results. Targeted biopsy revealed CaP in 34% of men of which 91% had significant cancer, compared to significant cancers in 54% of found on systematic biopsy. Degree of suspicion on MRI was the strongest predictor of significant cancer; 86% of subjects with high suspicion MRI target had clinically significant cancer¹³.

We recently examined the impact of MR imaging-ultrasound fusion prostate biopsy in predicting final surgical pathology. 54 men undergoing RRP at UCLA after fusion biopsy were included. 12 core systematic biopsies as well as MRI targeted biopsies were taken. Biopsy results were compared to whole mount pathology, with final Gleason score concordance being the primary end point. Highest Gleason pattern at prostatectomy was predicted by 54% of systematic biopsies, 54% of targeted biopsies, and 81% with targeted and systematic combined. Our results suggest that use of MRI-ultrasound fusion prostate

biopsy can increase biopsy detection of clinically significant lesions. Of note, 17% of cases were still understaged by systematic + fusion biopsy compared to whole mount pathology¹⁴.

About one quarter of prostate cancers are located in the anterior region¹⁵, which is notoriously difficult to access on standard TRUS biopsy. Volkin et al looked at the detection rate of anteriorly located prostate cancers using MRI/ultrasound fusion-guided biopsy compared to standard TRUS biopsy. All patients referred for biopsy underwent a 3T MPMRI screening and those with suspicious lesions in the anterior prostate were identified. All patients underwent a standard 12 core TRUS biopsy, followed by MRI/ultrasound fusion targeted biopsy of those suspicious anterior lesions. Out of 499 patients undergoing biopsy, 162 had anterior lesions on MPMRI with 121 of those lesions found to have prostate cancer. Of the anterior lesions, 25.7% were found positive on systematic biopsy whereas 40.2% were positive on targeted biopsy. In lesions that were positive on both targeted and systematic biopsy, the targeted lesions were 112% longer¹⁶.

Serum Biomarkers: [-2]proPSA, Free PSA, and Prostate Health Index (PHI)

Since the FDA approval of PSA in the early 1990s, different isoforms of PSA have been discovered and studied in an attempt to increase tumor specificity. [-2]proPSA is a molecular form of free PSA, with higher levels correlated with PCa aggressiveness^{17–19}. In 2012, [-2]proPSA was FDA approved for use in initial biopsy decision with men with PSA between 4–10 ng/ml and negative DRE. PHI is calculated value consisting of total, % free, and [-2]proPSA.

Tosoian et al. evaluated the use of PSA isoforms in patients on active surveillance. The relationship between unfavorable biopsy results and [-2]proPSA, %freePSA, and PHI was analyzed in 167 men previously enrolled in active surveillance. With a median follow-up of 4.3 years, [-2]proPSA and PHI were significantly associated with biopsy reclassification, being adjusted for age, date of diagnosis, and PSA density²⁰. These results were recently validated in 67 men on active surveillance who underwent protocol biopsy at 1 year. Reclassification rates were similar to the Tosoian study and regression analysis showed [-2]proPSA and PHI being independent predictive factors for reclassification one year after biopsy²¹. Similarly, in a recently published multicenter prospective trial following 658 men whom underwent prostate biopsy for PSA between 4–10 ng/mL with normal DRE, the investigators examined the ability of PSA, % free PSA, [-2]proPSA and PHI to predict biopsy results. PHI was significantly higher in men with significant cancer (AUC: 0.698) and outperformed %fPSA (AUC: 0.654), [-2]proPSA (AUC: 0.550), and total PSA (AUC: 0.549)²².

Urine Biomarkers: Prostate cancer gene 3 (PCA3) and TMPRSS2-ERG fusion

In 1999, Bussemaker et al discovered that a noncoding sequence of messenger RNA (now known as PCA3) was significantly overexpressed in PCa tissue²³. Further research demonstrated its presence in urine in PCa patients, leading to FDA approval of a commercially available PCA3 urinary assay indicated as a decision making aid for repeat

biopsy. In the first evaluation in an active surveillance cohort, Tosoian et al. examined the relationship between PCA3 and biopsy results in 294 men on active surveillance. The PCA3 score alone was not significantly associated with biopsy reclassification ($P=0.131$) or biopsy Gleason score ($P=0.304$)². However, samples were collected at various times following enrollment, which may have resulted in favorable biopsies being overrepresented. This is further supported by a rather low (12.9%) biopsy reclassification rate. Ploussard et al. prospectively examined preoperative PCA3 levels in 106 men who met active surveillance criteria but elected to undergo RP. A PCA3 level greater than or equal to 25 was significantly correlated with increased tumor volume (OR 5.4) and significant cancer (OR 12.7)²⁴. A recent prospective study conducted by the National Cancer Institute evaluated the diagnostic performance of PCA3 urinary assay in a cohort of 859 men screened with PSA either undergoing initial or repeat biopsy. PPV of PCA3 was 80% in the initial biopsy group with NPV 88% in the repeat biopsy group. This suggests that $PCA3 > 60$ significantly increases the likelihood of PCa being found on initial biopsy, whereas repeat biopsy patients with $PCA3 < 20$ could potentially forgo biopsy²⁵. In a large retrospective cohort, Chevli et al evaluated PCA3 levels in a retrospective cohort of 3,073 men undergoing initial prostate biopsy. PCA3 outperformed PSA in detecting overall PCa (AUC 0.687 vs 0.559, $p<0.01$) but not for high grade PCa (AUC 0.682 vs 0.679 $p=0.702$)²⁶.

TMPRSS2-ERG is another well studied urinary biomarker that holds promise in patient stratification. TMPRSS2-ERG fusion represents a rearrangement in TMPRSS2, an androgen related transcription promoter. It is detectable in urine post DRE and has a high specificity (93%) and PPV (94%) but low sensitivity (37%)²⁷. Given the low sensitivity, TMPRSS2-ERG fusion has been studied in conjunction with other biomarkers. TMPRSS2-ERG and PCA3 urinary levels were obtained at study entry in 387 men enrolled in the Canary Prostate Active Surveillance Study. Men were allowed to enroll regardless of PSA or Gleason score. PCA3 and TMPRSS2-ERG levels correlated with tumor volume (estimated by number of cores positive) and Gleason score on biopsy. Combined, AUC for high-grade disease (0.66) was smaller than PSA alone (0.68), with a combined AUC of 0.70²⁸. Expressed prostatic secretion (EPS) samples were obtained in 528 men prior to RP. 216 of those men were eligible for active surveillance by NCCN guidelines. PSA mRNA, TMPRSS2-ERG fusion mRNA and PCA3 mRNA were assayed. Of two high performing models that were identified, one decreased the risk of up-staging almost 8 fold and decreased the risk of up-staging plus Gleason upgrading about five fold, while doubling upstaging in the positive test group.²⁹

In comparing urinary and serum biomarkers to MPMRI, Porpiglia et al recently evaluated a prospective cohort of 107 men with initial negative biopsy and persistent suspicion for PCa. PHI and PCA3 tests along with MPMRI were done prior to repeat systematic biopsy, with the urologist blinded to MPMRI results. MPMRI provided the most significant contribution (AUC 0.963), which was greater than PHI+PCA3 ($p<0.001$). Decision curve analysis confirmed that MPMRI provided the most significant improvement in benefit³⁰.

Tissue Biomarkers

Tissue-based assays and biomarkers can potentially provide deeper insight into cancer phenotype and aid in risk stratification. Both assays discussed below are mentioned in NCCN prostate cancer guidelines, noting them as “further along in development and clinical use”³¹ compared to other novel modalities.

Oncotype DX (Genomic Health Inc) is a family of multi-gene real-time PCR based assays designed to analyze tumor biology in patient samples. The Oncotype DX Breast Cancer Assay has been clinically validated and incorporated into oncology practice guidelines in the treatment of breast cancer³². Oncotype DX PCa Assay was specifically developed to analyze small cores of paraffin embedded tissue obtained via prostate biopsy, analyzing the expression of 12 prostate cancer-related (and 5 control) genes. The test yields a Genomic Prostate Score ranging from 0 to 100³³. Oncotype DX is indicated for patients with Gleason grade 3+3 and small volume Gleason 3+4 disease on standard 12 core biopsy. The assay was recently validated in prospective clinical validation study in a cohort of 395 men with low to low-intermediate risk PCa who were candidates for active surveillance. GPS was an independent predictor of adverse pathology at RP (p=0.002). Each 20-point increase was associated with a 2.3-fold increased risk for high-grade disease, and 1.9-fold risk for non-organ confined disease. Adding GPS score to NCCN risk stratification criteria improved AUC, risk profiles, and decision-curve analysis in all counts, improving discrimination of PCa into very low, low, and modified intermediate risk groups³⁴. Of note, men with Gleason 3+4 were included as part of the AS cohort, and “high grade” was defined as primary Gleason 4 or any Gleason 5 pattern. As it is not known which Gleason grade 3+4, organ confined tumors are potentially lethal, Oncotype DX may not be completely suitable for selecting patients for surveillance.

Another promising risk-stratification tool is a tissue-based multigene assay (Prolaris, Myriad Genetics) that measures the expression of cell-cycle progression genes, yielding a Cell Cycle Progression (CCP) score³⁵. In a cohort of 349 men with localized PCa followed conservatively with needle biopsy, in multivariate analysis CCP score was the strongest predictor of death from PC, with a hazard ratio (HR) of 1.65 for each CCP score point increase³⁶. Note that this study was not one that would be considered representative of an active surveillance cohort; men with localized PCa were enrolled regardless of Gleason score, PSA, or clinical stage. More recently, whole-mount RP samples from 413 men were assayed for CCP score and results compared to post-prostatectomy outcomes (namely biochemical recurrence or need for salvage treatment). The CCP score was assessed for independent and combined prognostic utility. CCP score had significant prognostic accuracy, with the ability to further stratify patients with low clinical risk determined by previously established post-prostatectomy risk-stratification criteria (HR 1.7, 95% CI, 1.3 to 2.4)³⁷. These findings are consistent with a recently published systematic review of CCP score that found a pooled HR of for predicting biochemical recurrence following RP 1.88 in a univariate model and 1.63 in a multivariate model³⁸.

In an ongoing survey of physicians ordering CCP scores, CCP score altered PCa treatment in 65% of cases, with a 49.5% reduction in surgical interventions and 29.6% reduction in

radiation treatment. Third party audit showed an 80.2% concordance between post-CCP treatment recommendation and actual treatment³⁹. The study is limited by potential confounding factors that were not controlled, including patient input in therapeutic choice, and patient selection for CCP testing.

Discussion

While none of the above mentioned novel risk-stratification tools have yet to be incorporated into major oncologic guidelines, they hold significant promise. The body of evidence suggests that MPMRI has the sensitivity and NPV to rule out clinically significant disease and has promise in following patients on active surveillance. If further validated, MPMRI can potentially obviate the need for repeat biopsy in select patients. Targeted biopsy has the potential to improve detection of clinically significant cancers and for rebiopsy of patients with continued suspicion for PCa, especially when combined with systematic biopsy. PSA isoforms and PHI outperform PSA alone and improve risk stratification when combined with established criteria, but need further prospective studies using template and MRI-targeted biopsies. Urinary biomarkers fall short when used alone, but improve risk-stratification when used in conjunction and with established criteria. Finally, tissue biomarkers and gene assays allow for patient-specific molecular and genetic characterization of cancer phenotype, showing significant promise and in some cases have already been incorporated into and altered clinical practice.

At our center, patients deemed low risk by traditional means undergo prostate MPMRI for risk stratification purposes. If MPMRI is of intermediate suspicion or higher, an MRI/ultrasound fusion targeted prostate biopsy is obtained. If MPMRI is of low risk, the biopsy tissue is sent for Oncotype DX. If Oncotype DX results are low risk, the patient is enrolled in active surveillance.

Conclusion

MPMRI, urinary, serum and tissue biomarkers show remarkable promise in improving risk-stratification of patients with PCa, and as the body of evidence grows will likely become incorporated into major oncologic guidelines and standard urologic practice. Further prospective clinical studies are needed, as well as analysis of cost-effectiveness.

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Key Points

- There remains today a level of uncertainty in selecting patients with low-risk PCa for active surveillance utilizing PSA and systematic biopsy alone.
- New tools are being developed to detect more aggressive cancers missed with these traditional techniques, and to follow patients on active surveillance whose PCa may naturally progress
- Novel PCa risk stratification modalities studied and currently available include MP-MRI, MRI-targeted biopsy, and urine, serum, and tissue biomarkers.
- As the body of evidence grows, these tools will likely become incorporated into major oncologic guidelines, and in some centers have already become part of routine clinical practice.