Predictors of pathologically aggressive prostate cancer and surgical management

Scott M. Brockman, Srinivas Vourganti

Department of Urology, Rush University Medical Center, Chicago, IL, USA

Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Srinivas Vourganti, MD. Department of Urology, Rush University Medical Center, 1725 W. Harrison St. #970, Chicago, IL 60612, USA. Email: Srinivas_Vourganti@rush.edu.

Abstract: Prostate cancer is the leading cause of solid organ malignancy in American men with over 33,330 men predicted to die of prostate cancer in 2020 by the American Cancer Society. An increase in PSA screening has led to an increased number of men being diagnosed with both clinically significant and insignificant disease. Such an increase in detection has made selecting patients who would benefit from more aggressive treatment modalities with surgery or radiation as opposed to watchful waiting more complex. Several predictive models have been developed which utilize well established diagnostic risk factors aimed to predict which patients are at highest risk of disease progression and thus require more aggressive treatment modalities i.e., radical prostatectomy (RP). This comprehensive review article will discuss how such risk stratification models along with biochemical markers and imaging modalities can be used to predict which patients may harbor pathologically aggressive prostate cancer and would benefit from surgical intervention.

Keywords: Prostate cancer; prostate biopsy; pathologic predictors

Received: 16 April 2020; Accepted: 20 July 2020; Published: 25 March 2021.

doi: 10.21037/amj-20-82

View this article at: http://dx.doi.org/10.21037/amj-20-82

Introduction

Prostate cancer is the leading cause of solid organ malignancy in American men and remains the second leading cause of cancer-related deaths in this population. Indeed, the American Cancer Society predicts that 33,330 men will die of prostate cancer in 2020 (1). Coincident with an increase in routine prostate cancer screening since the 1990's, more men are being diagnosed at earlier stages with lower PSA levels, a trend which resulted in an increase in the incidence of clinically insignificant prostate cancer. Physicians are increasingly being faced with the task of deciding between noninvasive management strategies such as watchful waiting or active surveillance and more definitive treatment approaches i.e., surgery or radiation therapy which, while generally effective in oncologic control, can carry significant morbidity. In order to help guide clinical recommendations and shared decision making, several predictive models have been developed which utilize well established diagnostic risk factors aimed to predict which patients are at highest risk of disease progression and thus require more aggressive treatment modalities i.e., radical prostatectomy (RP). We will discuss such models and how they can be implemented to predict which patients most likely harbor pathologically aggressive prostate cancer who could realize the greatest potentially benefits from surgical management approaches.

Prostate cancer can be characterized as clinically localized, locally advanced, or metastatic disease that is either castration-sensitive or resistant. Clinically localized cancer is defined as organ-confined disease without lymph nodal involvement or metastatic spread. Patients with clinically localized disease may be optimal surgical candidates, but must weigh the risk of mortality from

prostate cancer relative to other competing risks of death when choosing this option. Additionally, a patient's baseline urinary, sexual, and bowel function must be considered as many definitive treatments (surgery or radiation therapy) can have a significant impact on quality of life. As the number of patients being diagnosed with prostate cancer continues to increase, identifying patients who may benefit from curative surgery from those who can be managed with active surveillance or watchful waiting has become a focus of urologic research.

Clinical guidelines and predictive nomograms to optimize prostate cancer treatment pathways

Numerous statistical methodologies have been implemented in the form of nomograms to provide accurate tools to identify patients with aggressive disease that are at high risk of poor outcomes. These nomograms utilize clinical and pathologic variables assigned a value to indicate prognostic significance on an outcome of interest. One such nomogram, the Kattan nomogram, also known as the Memorial Sloan Kettering Cancer Center Pre-Prostatectomy nomogram, was developed to predict the extent of cancer and long-term prognosis of patients diagnosed with prostate cancer prior to undergoing radical prostatectomy (2). Variables included in this nomogram are patient's age, PSA prior to prostate biopsy, Gleason pattern and score, clinical tumor stage by DRE and number and percentage of biopsy samples positive for cancer. This widely utilized nomogram was created using data from greater than 10,000 patients diagnosed with prostate cancer on systematic sextant prostate biopsy compared to pathology at time of surgery and their outcomes, but was recently further validated using data from MRI-targeted biopsy which showed comparable predicted outcomes (3). This tool offers a probability of both cancer-specific survival and progression-free probability after surgery as well as a probability percentage of disease extent. One inherent limitation of nomograms is that their development is mostly based upon the most common combinations of clinical features of disease making it not always accurate in predicting rare disease cases, however, the Kattan nomogram has been shown to predict actuarial survival across all risk-groups including those at the extremes of the patient spectrum (4).

Risk stratification has been implemented by the AUA and NCCN to help clinicians identify patients at risk of disease progression or biochemical recurrence after definitive treatment. Risk stratification utilizes clinical staging based on digital rectal examination (DRE), prostate specific antigen (PSA) level, PSA density, prostate needle biopsy results including Gleason Grade Grouping, amount of cancer by percentage of cores and total number of cores positive. As a tool to predict disease aggressiveness, PSA levels are associated directly with pathologic stage and tumor extent (5). For example, one study showed that 80% of men with a PSA less than 4.0 ng/mL were found to have pathologically confined organ disease while 75% of those with PSA level greater than 50 ng/mL are found to have pelvic lymph node involvement (6). Free PSA or PSA not complexed to proteases is enzymatically inactive and generally lower in men with prostate cancer then men without (7). The amount of free PSA can improve accuracy of SA in men with serum PSA 4–10 ng/mL with negative DRE. While free PSA is most notably useful in determining whether patient should undergo prostate biopsy, it may also provide prognostic information as an independent association between lower percentage free PSA and biochemical recurrence has been shown in men who underwent surgery for clinically localized prostate cancer (8). PSA dynamics including PSA velocity (the change in PSA per year) and PSA density (total PSA divided by prostate volume) have been investigated as predictors of aggressive disease. While PSA velocity has been shown to have minimal use in prostate cancer screening, its use in predicting reclassification in the active surveillance setting is still being determined (9). PSA density helps to adjust PSA for prostate size and can help distinguish an elevated PSA caused by benign prostatic hyperplasia (BPH) from those caused by prostate cancer. PSA density has been shown to associated directly with prostate cancer aggressiveness and may be utilized to determine the eligibility for active surveillance among men with prostate cancer (10,11). DRE is a less sensitive tool for detecting cancer and may not independently predict disease aggressiveness but is important for clinical staging. A palpable lesion on DRE is associated with local disease extent and contributes to the T stage such that a palpable tumor confined to the prostate is deemed cT2, while tumor beyond the prostate invading the seminal vesicles is deemed cT3. When complemented with PSA, DRE increases the likelihood of detecting prostate cancer and may detect different cancer than those detected by PSA alone. To trigger a prostate biopsy, digital rectal examination findings and PSA levels are generally used in a complimentary manner. PSA testing has been shown to improve the positive predictive value of DRE and when used together have higher detection rates of prostate cancer than

with either individually (12). Furthermore, PSA has been shown to increase the detection of organ-confined disease when compared to detected cancer without PSA. The probability of cancer detection has been shown to increase directly with increasing level of PSA (13). Once prostate biopsy has been performed, Gleason score is the greatest predictor of outcome for any man with prostate cancer (14). Prostate needle biopsy and Gleason Grade Grouping provides the histologic diagnosis that is paramount to predicting disease aggressiveness and prognosis. There have been numerous refinements to Gleason classification over the years, but the contemporary system is comprised of 5 grade groups with Grade Group 1 defined as Gleason 3+3=6 to Grade Group 5 defined as patients with Gleason sums 9 and 10. The Grade groupings have been shown to predict chance of biochemical recurrence progression and were also predictive of biopsy grade following RP or radiation therapy.

The NCCN and AUA risk stratification divides patients into very low/low, intermediate, and high-risk groups (15). Patients stratified into very low/low risk group are defined as those with PSA less than 10 ng/mL, Gleason Grade Group 1 and clinical stage T1-T2a. In order to be considered very low risk, fewer than 34% of biopsy cores may be positive, no core may exhibit greater than 50% cancer involvement, and PSA density may not exceed 0.15 ng/mL/cc. In this very low risk group, such men have a very favorable outcome with a low probability of adverse pathology at surgery and low rate of metastatic disease when managed with active surveillance. Differentiating those with very low and low risk from those men with higher risk disease is based on a large body of evidence supporting active surveillance in such men. While those with very low risk disease treated with active surveillance have been found to have less than 1% metastatic progression rate at 15 years, those in the low risk category face a small chance of metastasis or prostate cancer specific mortality on active surveillance found to be roughly 3% as shown in the PIVOT and ProtecT trials (16). The role of surgical management in low risk patients is dependent on shared decision making with patient's performance status, baseline urinary, bowel, or sexual function, and overall life expectancy. In this patient population, the clinical predictors which have been shown to increase risk of higher-grade disease and progression at subsequent biopsy are PSA density exceeding 0.15, obesity (measured by BMI), African American race, and extensive cancer on systematic biopsy cores (17).

RP in the management of aggressive prostate cancer

Patients in the intermediate-risk or high-risk category of clinically localized prostate cancer should be offered surgery or radiation therapy with or without androgen deprivation therapy as treatment options. Those with intermediate risk disease are defined as PSA 10–20 ng/mL, Gleason Grade Group 2–3, or clinical stage T2b-c. Patients with intermediate-risk are further divided into favorable *vs.* unfavorable groups with those in the favorable group being Grade Group 1 with PSA 10–20 ng/mL or Grade Group 2 with PSA <10 ng/mL. Unfavorable intermediate risk disease is defined as Grade Group 2 with PSA 10–20 ng/mL or clinical stage T2b-c or Grade Group 3 with PSA <20. In this risk category, several studies including the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) and PIVOT have shown both higher overall survival and prostate cancer-specific survival among patients who underwent RP at 10 years follow-up (18,19). In this classification scheme, high-risk category is defined as PSA greater than 20 ng/mL or Gleason Grade Group 4–5 or clinical stage T3). In unfavorable intermediate or high-risk groups, at time of RP an extended pelvic lymph node dissection (PLND) is commonly completed with the rationale being a greater amount of nodal tissue results in an increased identification of potential lymph node metastases (20). The therapeutic benefit of using an extended template map (removing the obturator, external, and internal iliac nodes) compared to a standard PLND (obturator and external iliac) is not conclusive (21).

RP has historically been offered to patients with pathologically confirmed cancer clinically confined within the prostate or cancer that extends beyond the margins of the prostate but would still be amenable to a wide resection. The role of surgery in locally advanced disease is less certain in comparison to more localized and lower risk disease states, however, many studies have shown that surgery may offer suitable oncologic control by decreasing tumor burden and allow accurate and precise pathologic staging with the need for more definitive treatment (22). Previously, outcomes after RP for clinical stage T3a showed that men with lower-volume disease may benefit as local control and complete excision of cancer is possible. However, a minority of patients who undergo RP for clinically localized disease will be found to have pathologic spread outside of the prostate either with extracapsular extension, seminal vesicle invasion or lymph node metastasis. Those diagnosed with

varying degrees of pathologic spread at time of RP were found to have significantly worse 5-year PSA-free survival with the highest risk being presence of a positive surgical margin (23). Surgery in management of node-positive disease has become an interest of researchers. Ga-PSMA-11 positron emission tomography (PET) scan which has been used to detect soft tissue and bony metastases in the setting of biochemical recurrence has been increasingly utilized pre-operatively in high risk patients to identify those with high risk of biochemical progression (24). Those found to have oligometastatic disease on PET may benefit from oncologic and symptomatic control with RP as surgery in this population can be done with appropriate morbidity (25) while receiving neoadjuvant systemic therapy has not shown to increase the risk of perioperative complications (26). Overall, the rationale and oncologic benefit from surgery in these high-risk populations remain the study of ongoing clinical trials including the ongoing Southwest Oncology Group (SWOG) 1802 trial, Surgery in Metastatic Carcinoma of Prostate (SIMCAP) trial, Testing RP in men with prostate cancer and oligoMetastases to the bone (TRoMbone), and others.

Clinical imaging in the diagnostic prediction of prostate cancer

Over time, improvement in prostate imaging modalities has improved the ability to detect clinically significant disease during the diagnostic phase of management. Transrectal ultrasound-guided prostate biopsy became widely used in 1989 when a systematic sextant (six-core) biopsy protocol was created (27). Since then, refinements in sampling templates which led to an increase in systematic core biopsies to 12 as well as the use of PSA screening has increased the number of men being diagnosed with prostate cancer. Most recently, the development of multiparametric MRI (mpMRI), which is standard anatomical T1 and T2-weighted imaging supplemented with additional imaging sequences most typically dynamic contrast-enhanced (DCE) and/or diffusion-weighted imaging (DWI), has led to improved prostate cancer detection (28). A Prostate Image Reporting and Data System (PIRADS) was developed to standardize the interpretation and reporting of mpMRI prostate scans which assigns a score 1 to 5 with higher numbers indicating an increased risk for clinically significant malignancy. In general, MRI cannot detect all prostate tumors and has poor sensitivity for low volume Gleason 3+3 disease which lends credence to its use in predicting aggressive tumors while focusing attention away from these smaller more occult tumors. Because of this, mpMRI may safely allow men without imaging-based suspicion to avoid biopsy (and associated morbidity) and the resultant risk of incidental detection of very low and risk occult malignancy (29). The adoption of TRUS/MRI fusion prostate biopsy which utilizes real-time TRUS guidance familiar to most urologist with superimposed mpMRI images has further improved the concordance of biopsy results to true pathologic findings on RP (30). MRI fusion biopsy has been increasingly utilized in a wide variety of clinical scenarios including initial evaluation of elevated PSA, repeat biopsy after previous negative TRUS biopsy in patients with persistently elevated PSA, as well as active surveillance. While MRI fusion biopsy has shown promising and favorable results in identifying potentially aggressive cancers, other studies have noted out a persistent false negative rate in missing potentially significant disease (31). MRI may offer an additional benefit in detecting extraprostatic extension (EPE) and seminal vesicle invasion which is important in informing surgical technique. Although compared to other preoperative parameters mpMRI is the best predictor of extraprostatic extension at RP, its overall ability to detect EPE remains relatively limited. Furthermore, preoperative MRI has been shown to be even more challenged in the detection of seminal vesicle invasion (32). Instead of using mpMRI to directly visualize EPE in binary terms (present *vs.* absent), several mpMRI features been found to be associated with likelihood of EPE on pathology at time of surgery. These features include curvilinear contact length with the capsule, capsular bulge, direct visualization of EPE on MRI, obliteration of the rectoprostatic angle, and neurovascular asymmetry. A grading system developed by Mehralivand *et al.* demonstrated that when combined with clinical parameters, these imaging findings improved the diagnostic ability of MRI to detect EPE and therefore, better predict extent of disease (33). Seminal vesicle invasion is associated with an increased risk of lymph node metastasis and tumor recurrence and is therefore important in assessing treatment options for patients (34). MRI evidence of seminal vesicle invasion (or EPE at the prostate base transition) has been shown to be significantly associated with seminal vesicle invasion confirmed at time of surgery on pathology, and may inform when it is appropriate to biopsy SV for treatment planning and may adjust treatment planning (i.e., resection planes and radiation plans) (35). Depending on the risk category of disease, surgeons are faced with balancing

clinical outcomes (i.e., neurovascular bundle sparing RP) with adequate oncologic control in high-risk groups (i.e., wide resection). Further research is needed to determine whether or not mpMRI is able to decrease the positive surgical margin rate at time of RP (32).

The development of specialized PET scan with tracers specific for prostate cancer cells has been increasingly adopted into practice to detect metastasis in the setting of biochemical recurrence as well as to potentially inform pre-operative planning for RP. One such FDA approved tracer for imaging of in the setting of biochemical recurrence is 18F-fluciclovine (Axumin) which has high diagnostic accuracy in post-treatment cases. Due to its ability to characterize lymph nodal and distant metastases, its use in initial workup and restaging of prostate cancer is likely in the future and will play a role in imaging high-risk patients (36). As noted above, PSMA PET is increasingly utilized in this space, and an FDA approved application is anticipated.

Emerging surgical techniques in management of locally advanced prostate cancer

An increasing number of urologists are utilizing mpMRI in order to inform surgical planning, especially in cases of high-risk or locally advanced disease (37). Despite this widespread adoption, positive surgical margins (PSM) rates in this group continue to be high, which has been shown to increase the risk of biochemical recurrence (38). In order to improve oncological safety margins, new techniques are emerging including a super-extended robotic assisted RP (seRARP) with resection of Denonvilliers fascia and dissection down to perirectal fat (39). Dell'Oglio *et al.* described this technique in two patients with posterior T3a or T3b prostate cancers where mpMRI demonstrated PI-RADS 5 lesions involving the seminal vesicles. Operative times and estimated blood loss were comparable in these cases to those who undergo standard robotic RP and both patients had uneventful post-operative courses lending credence to its feasibility in this risk category (39). With a focus on improving clinical outcomes including continence rate and erectile function preservation, a Retzius-sparing approach to robotic assisted RP (rsRARP) has been shown to be clinically feasible and oncologically safe in low and intermediate risk patients (40). With more studies demonstrating a role for RP in high-risk and locally advanced disease, one group performed rsRARP in these groups and the results demonstrated comparable PSM to conventional RARP with earlier continence recovery (41). However, long-term oncological outcomes and data addressing the probability of biochemical recurrence after 12 months is still pending.

Genomic testing in the prediction of prostate cancer biology

With advancement in molecular engineering technology such as next-generation sequencing, the role of genomics in predicting aggressive prostate cancer has been increasingly studied and utilized. Commercially available genomic tests such as the Oncotype Dx Genomic Prostate Score (GPS), Prolaris and Decipher tests have been used to provide prognostic information from adverse pathology at RP, and even prior to surgery with prostate biopsy tissue samples. Oncotype Dx Genomic Prostate Score uses a 12-gene panel from genes used in various molecular pathways to compile a GPS score from 0–100 that corresponds to the aggressiveness of the tumor at time of prostatectomy (42). This test has been shown to help management decisions in patients regarding active surveillance or primary treatment and has been extensively validated for its clinical outcome (43-45). Prolaris assesses 31 cell cycle progression genes and 15 housekeeping genes and has been shown to be an independent predictor of prostate cancer specific death (46). The Decipher assay is a 22-marker genomic classifier which has been independently associated with the development of metastatic disease and prostate cancer-specific mortality in patients with high-risk disease and those with biochemical recurrence (47). While these genomic tests may help guide clinical decision making, one disadvantage of these tests is the inability to take in to account tumor multifocality and heterogeneity. One analysis showed that scores of low-grade prostate cancers derived from the above genomic tests could not predict the concomitant presence of an unsampled high-grade cancer from the same patient (48). It should be mentioned, however, that most of these genomic studies were done prior to the widespread use of mpMRI which has increased the detection of clinically significant prostate cancer. Furthermore, while tissue-based biomarkers can be helpful in stratifying patients based on risk, they should only be used in situations where clinical decision making may be influenced by their results, as the above biomarkers have not undergone prospective testing or been shown to improve long-term clinical outcomes (49).

Conclusions

Prostate cancer is a complex disease in which predicting which patients are at risk of progression and thus will require curative treatment becomes paramount in clinical decision making. While RP has been shown to prevent disease progression in patients with intermediate or high-risk clinically localized cancer, there may be some role in surgery in patients with locally advanced disease and regionally advanced as well. Risk stratification methodologies consider numerous clinical and pathologic factors including digital rectal examination, PSA level, histology on prostate needle biopsy as well as radiologic imaging with mpMRI. In the future, blood and urine-based biomarkers are showing potential in detecting prostate cancer with greater sensitivity and specificity than traditional PSA. Furthermore, tissue-based genomic classifiers from prostate biopsy samples are being increasingly utilized in improving the prognostic potential of prostate-needle biopsy. More studies are needed to validate the use of these new molecular markers in the clinical environment. Lastly, improved imaging techniques with mpMRI, and prostate-cancer specific tracers for PET scans are promising tools that will not help detect clinically significant cancer, but also help identify high-risk patients with locally or regionally advanced disease that may benefit from surgery.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Simon P. Kim) for the series "Surgical Management of Genitourinary Malignancies" published in *AME Medical Journal*. The article has undergone external peer review.

Peer Review File: Available at https://amj.amegroups.com/article/view/10.21037/amj-20-82/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.com/article/view/10.21037/amj-20-82/coif). The series "Surgical Management of Genitourinary Malignancies" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. No ethics approval was necessary for the preparation of this manuscript as the article was done by literature review and involved no human subjects research. Written informed consent was not obtained for publication of this study.

References

1. American Cancer Society. Facts & Figures 2020. Atlanta, Ga: American Cancer Society, 2020.
2. Kattan MW, Eastham JA, Stapleton AM, et al. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. J Natl Cancer Inst 1998;90:766-71.
3. Glaser ZA, Gordetsky JB, Bae S, et al. Validation of MSKCC pre-prostatectomy nomogram in men who undergo MRI-targeted prostate biopsy prior to radical prostatectomy. Urol Oncol 2019;37:970-5.
4. Korets R, Motamedinia P, Yeschina O. Accuracy of the Kattan nomogram across prostate cancer risk-groups. BJU International 2011;108:56-60.
5. Stamey TA, Yang N, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317:909-16.
6. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320-8.
7. Catalona WJ, Beiser JA, Smith DS. Serum free prostate specific antigen and prostate specific antigen density measurements for predicting cancer in men with prior negative prostatic biopsies. J Urol 1997;158:2162-7.
8. Shariat SF, Abdel-Aziz KF, Roehrborn CG, et al. Pre-operative percent free PSA predicts clinical outcomes in

patients treated with radical prostatectomy with total PSA levels below 10 ng/mL. Eur Urol 2006;49:293-302.
9. Cooperberg MR, Brooks JD, Faino AV, et al. Refined analysis of prostate-specific antigen kinetics to predict prostate cancer active surveillance outcomes. Eur Urol 2018;74:211-7.
10. Bul M, Zhu X, Valdagni R, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. Eur Urol 2013;63:597-603.
11. Tseng KS, Landis P, Epstein JI, et al. Risk stratification of men choosing surveillance for low risk prostate cancer. J Urol 2010;183:1779-85.
12. Gosselaar C, Roobol MJ, Roemeling S, et al. The role of the digital rectal examination in subsequent screening visits in the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam. Eur Urol 2008;54:581-8.
13. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med 2004;350:2239-46.
14. Chun FK, Epstein JI, Ficarra V, et al. Optimizing performance and interpretation of prostate biopsy: a critical analysis of the literature. Eur Urol 2010;58:851.
15. National Comprehensive Cancer Network: 2017 NCCN guidelines for treatment of prostate cancer. Available online: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
16. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. J Clin Oncol 2015;33:3379.
17. Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2016;375:1425-37.
18. Wilt TJ, Brawer MK, Jones KM. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-13.
19. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2011;364:1708-17.
20. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: Risk stratification, shared decision making, and care options. J Urol 2018;199:683-90.
21. Fossati N, Willemse PM, Van den Broeck T, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. Eur Urol 2017;72:84-109.
22. Nazim SM, Abbas F. Role of Surgery in locally advanced prostate cancer. Pak J Med Sci 2015;31:710-6.
23. Hull GW, Rabbani F, Abbas F, et al. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol 2002;167:528-34.
24. Gorin MA, Pomper MG, Pienta KJ, et al. Defining the clinical utility of PSMA-targeted PET Imaging of prostate cancer. BJU International 2017;120:160-1.
25. Heidenreich A, Pfister D, Porres D. Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. J Urol 2015;193:832-8.
26. Williams SB, Davis JW, Wang X, et al. Neoadjuvant systemic therapy before radical prostatectomy in high-risk prostate cancer does not increase surgical morbidity: contemporary results using the Clavien system. Clin Genitourin Cancer 2016;14:130-8.
27. Hodge KK, McNeal JE, Terris M, et al. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol 1989;142:71-4.
28. Turkbey B, and Choyke PL. Multiparametric MRI and prostate cancer diagnosis and risk stratification. Curr Opin Urol 2012;22:310-5.
29. Kasivisvanathan V, Rannikko A, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med 2018;378:1767-77.
30. Ahdoot M, Wilbur A, Reese S. MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis. N Engl J Med 2020;382:917-28.
31. Borofsky S, George AK, Gaur S, et al. What are we missing? false-negative cancers at multiparametric MR imaging of the prostate. Radiology 2018;286:186-95.
32. Kozikowski M, Malewski W, Michalak W, et al. Clinical utility of MRI in the decision-making process before radical prostatectomy: Systematic review and meta-analysis. PLoS One 2019;14:e0210194.
33. Mehralivand S, Shih JH, Harmon S, et al. A Grading System for the Assessment of Risk of Extraprostatic Extension of Prostate Cancer at Multiparametric MRI. Radiology 2019;290:709-19.
34. Ohori M, Scardino PT, Lapin SL, et al. The mechanisms and prognostic significance of seminal vesicle involvement by prostate cancer. Am J Surg Pathol 1993;17:1252-61.
35. Gold SA, Shih JH, Rais-Bahrami S, et al. When to Biopsy the Seminal Vesicles: A Validated Multiparametric Magnetic Resonance Imaging and Target Driven Model to Detect Seminal Vesicle Invasion in Prostate Cancer.

J Urol 2019. [Epub ahead of print]. doi: 10.1097/JU.0000000000000112.
36. Songmen S, Nepal P, Olsavsky T, et al. Axumin Positron Emission Tomography: Novel Agent for Prostate Cancer Biochemical Recurrence. J Clin Imaging Sci 2019;9:49.
37. Baack Kukreja J, Bathala TK, Reichard CA, et al. Impact of preoperative prostate magnetic resonance imaging on the surgical management of high-risk prostate cancer. Prostate Cancer Prostatic Dis 2020;23:172-8.
38. Silberstein JL, Eastham JA. Significance and management of positive surgical margins at the time of radical prostatectomy. Indian J Urol 2014;30:423-8.
39. Dell'Oglio P, Brook N, Turri F, et al. Super-extended robotic-assisted radical prostatectomy for locally advanced prostate cancer. J Urol 2019;201:e1120.
40. Galfano A, Ascione A, Grimaldi S, et al. A new anatomic approach for robot-assisted laparoscopic prostatectomy: a feasibility study for completely intrafascial surgery. Eur Urol 2010;58:457-61.
41. Nyarangi-Dix JN, Görtz M, Gradinarov G, et al. Retzius-sparing robot-assisted laparoscopic radical prostatectomy: functional and early oncologic results in aggressive and locally advanced prostate cancer. BMC Urol 2019;19:113.
42. Knezevic D, Goddard AD, Natraj N, et al. Analytical validation of the Oncotype DX prostate cancer assay – a clinical RT-PCR assay optimized for prostate needle biopsies. BMC Genomics 2013;14:690.
43. Cullen J, Rosner IL, Brand TC, et al. A biopsy-based 17-gene genomic prostate score predicts recurrence after radical prostatectomy and adverse surgical pathology in a racially diverse population of men with clinically low- and intermediate-risk prostate cancer. Eur Urol 2015;68:123-31.
44. Eure G, Germany R, Given R, et al. Use of a 17-gene prognostic assay in contemporary urologic practice: results of an interim analysis in an observational cohort. Urology 2017;107:67-75.
45. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol 2014;66:550-60.
46. Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol 2011;12:245-55.
47. Karnes RJ, Bergstralh EJ, Davicioni E, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. J Urol 2013;190:2047-53.
48. Hovelson D, Salami SS, Kaplan JB, et al. Integrative molecular profiling challenges robustness of prognostic signature scores in multifocal prostate cancer. J Clin Oncol 2018;36:96.
49. Eggener SE, Rumble RB, Armstrong AJ, et al. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. J Clin Oncol 2020;38:1474-94.

doi: 10.21037/amj-20-82
Cite this article as: Brockman SM, Vourganti S. Predictors of pathologically aggressive prostate cancer and surgical management. AME Med J 2021;6:7.