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Clinical-Prostate cancer

Evaluation of MSKCC Preprostatectomy nomogram in men who undergo MRI-targeted prostate biopsy prior to radical prostatectomy

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Abstract

Introduction: The Memorial Sloan Kettering Cancer Center (MSKCC) Preprostatectomy nomogram is a widely used resource that integrates clinical factors to predict the likelihood of adverse pathology at radical prostatectomy. Adoption of magnetic resonance imaging targeted biopsy (TB) permits optimized detection of clinically-significant cancer over systematic biopsy (SB) alone. We aim to evaluate the prognostic utility of the MSKCC Preprostatectomy nomogram with TB pathology results.

Methods: Men who underwent SB and magnetic resonance imaging TB who later underwent radical prostatectomy at our institution were included. Patient information was entered into the MSKCC Preprostatectomy nomogram using 5 biopsy reporting schemes with TB reported by both individual core (IC) and aggregate group (AG) methods. The likelihood of extraprostatic extension, seminal vesicle invasion, and lymph node involvement as predicted by the nomogram for each biopsy reporting schema were compared to radical prostatectomy pathology.

Results: We identified 63 men from January 2014 to November 2017. On receiver operating characteristic analysis, IC-TB, AG-TB, SB plus IC-TB, and SB plus AG-TB exhibited similar, if not improved, area under the curve compared to SB alone in predicting extraprostatic extension (0.671, 0.674, 0.658, and 0.6613 vs. 0.6085). This was similarly observed for seminal vesicle invasion prediction using SB plus IC-TB compared to SB alone (0.727 vs. 0.733). For lymph node involvement, superior but nonsignificant area under the curve was observed for AG-TB (0.647) compared to IC-TB (0.571) and SB alone (0.524)

Conclusions: Using TB pathology results either alone or combined with SB pathology results as input to the MSKCC Preprostatectomy nomogram appears comparable for prognosticating adverse pathology on radical prostatectomy compared to SB alone, but robust validation is warranted prior to adoption into clinical practice. © 2019 Elsevier Inc. All rights reserved.

Keywords: Magnetic resonance imaging; Radical prostatectomy; Fusion biopsy; Prostate cancer; Risk calculator

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Conflicts of interest: Jeffrey W. Nix and Soroush Rais-Bahrami serve as consultants to Philips/InVivo Corp.

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1. Introduction

In 2018, nearly 165,000 American men will be newly diagnosed with prostate cancer (CaP) [1]. Among men with newly diagnosed clinically-significant localized disease, radical prostatectomy is considered a standard-of-care approach to primary definitive treatment with curative intent [2]. However, surgical intervention is not without recognized potential morbidity and may not yield durable cure in select circumstances. As such, clinical risk stratification tools such as the Memorial Sloan Kettering Cancer Center (MSKCC) Preprostatectomy nomogram are widely relied upon to guide shared decision-making in this pretreatment setting [3]. While historically useful, these nomograms were developed and validated on systematic extended-sextant biopsy schema but not extensively studied or validated in the era of advanced imaging for prostate cancer detection as well as image-targeted biopsy (TB) of suspicious lesions.

Multiparametric magnetic resonance imaging (mpMRI) with fusion-TB has become increasingly utilized for the detection and localization of CaP. Robust evidence suggests this approach superiorly detects clinically-significant cancer foci using fewer cores compared to systematic biopsy (SB) [4−8]. While recently proposed nomograms that account for degree of cancer suspicion on mpMRI and TB pathology have been developed, incorporation of TB pathology into a previously validated, and widely accepted clinical tool such as the MSKCC Preprostatectomy nomogram has not been evaluated [9−13] Since many urologists currently refer to this nomogram in routine clinical practice, understanding the prognostic utility of TB in place of, or in conjunction with, SB pathology from which the nomogram was largely derived has potentially broad and impactful implications. Furthermore, urologists would not be tasked with incorporating the often complex and sometimes unavailable lesion parameters on MRI that are required for use of the novel TB nomograms [9−10].

Additionally, defining the best method of pathologic reporting for prostate biopsy cores sampled from a MRI-targeted lesion for use with this nomogram has yet to be determined. It has been proposed that reporting the aggregate group (AG) of pathologic findings from multiple cores sampled from a single target as a composite grade and percentage of cancer involvement better correlates with true tumor volume and the finding of extraprostatic extension (EPE) on radical prostatectomy than an individual core (IC) method [14]. Herein, we aim to evaluate the MSKCC Preprostatectomy nomogram with inclusion of TB pathology according to both IC and the proposed AG histologic reporting schemas in conjunction with SB findings and in isolation compared to SB pathology findings alone.

2. Methods

2.1. Patient selection and imaging

After obtaining institutional review board approval, our prospectively maintained patient database was accessed for men who underwent SB and TB and later elected for radical prostatectomy at our institution. A mpMRI was performed on all men using a 3 Tesla MRI scanner. Images were reviewed and interpreted by an abdominopelvic radiologist with at least 3 years of experience and subspecialization in genitourinary MRI. A multidisciplinary prostate imaging conference comprised of abdominopelvic radiologists, genitourinary pathologists, and urologic oncologists then reviewed each suspicious lesion, and assigned a Prostate Imaging Reporting and Data System (PI-RADS) v2 suspicion score for target designation as previously described [13].

2.2. Biopsy protocol and surgery

For biopsy naïve men, SB was performed concurrently at the time of TB. For men with a prior SB history, repeat SB was conducted at the time of TB in some cases based upon shared decision-making model between the patient and urologist. TB acquisition was performed using the UroNav system (Philips Medical Systems/InVivo, Gainesville, FL). At least 2 needle cores were obtained for each suspicious focus. Biopsy pathology was discussed in clinic where the options of active surveillance (AS), surgery, radiation therapy, and other treatment modalities were presented. All men who opted for surgery underwent robotic assisted laparoscopic radical prostatectomy with or without bilateral pelvic lymph node dissection based on preoperative clinical staging, patient counselling, and available adjunct data. TB, preoperative counseling, and surgery were performed by 1 of 2 fellowship-trained urologic oncologists who performed all TB cases. The decision to perform pelvic lymph node dissection was based on shared decision-making as well as a ≥2% chance of lymph node involvement (LNI) on the MSKCC Preprostatectomy nomogram as recommended by the NCCN guidelines [15]. All biopsy and final surgical pathology were reviewed and reported by a single fellowship-trained genitourinary surgical pathologist. The TB cores were given Gleason score/Grade Groups and percentage of tissue involved with CaP from 1 of 2 reporting methods as previously described [14]. In brief, the IC technique reported Gleason score/Grade Group and percent core involvement for each individual biopsy core irrespective of the number of cores samples from any given MRI-targeted lesion. The AG method reported the composite Gleason score/Grade Group and percent tissue involved with CaP assuming that all biopsy cores from the same MRI-targeted lesion was 1 tissue sample (Fig. 1).

2.3. Nomogram prognostication

In order to compare the prognostic utility of entering TB pathology into the MSKCC Preprostatectomy nomogram either in place of, or in conjunction with, SB pathology, 5 biopsy pathology schemas were generated based on SB and TB core data: SB alone, IC from TB alone, AG from TB

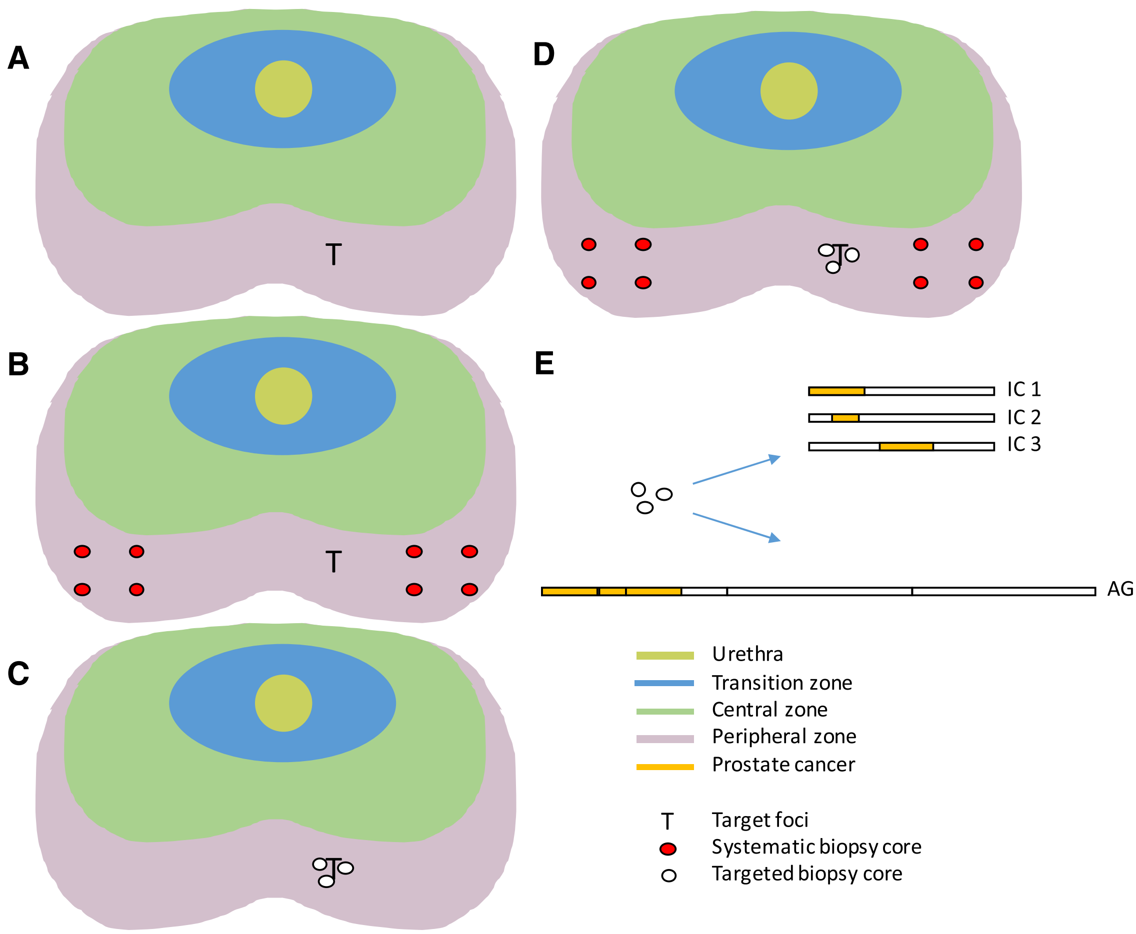

Fig. 1. Overview of biopsy acquisition and pathologic reporting schemas for a prostate with a single target (T) identified via mpMRI (A). Biopsy reporting consisted of systematic cores only (red, B), target cores only (white, C), or a combination (D). Target cores were then reported as individual cores (IC) or as aggregate groups (AG, E). (Color version available online.)

alone, SB plus IC from TB, and SB plus AG from TB. Patient clinical and demographic information was entered into the MSKCC Preprostatectomy nomogram using each biopsy schema [3]. The likelihood of organ-confined disease, EPE, seminal vesicle invasion (SVI), and LNI as predicted by the nomogram were compared to final surgical pathology from radical prostatectomy.

2.4. Statistical analysis

Descriptive statistics were formulated for demographic and other clinical/pathologic characteristics. The receiver operating characteristic (ROC) curves, area under the curve (AUC) analyses, were used to compare the prognostic accuracy of the nomogram with input from each of the 5 biopsy reporting schemas compared to final surgical pathology from radical prostatectomy. DeLong methodology was performed for statistical comparisons of the ROCs [16]. Statistical significance was considered if P values were less than a predetermined threshold of 0.05. All analyses were conducted using SAS v9.4 (SAS Institute, Cary NC).

3. Results

From January 2014 to November 2017, 644 men underwent prostate mpMRI followed by fusion TB. Among these, 63 (9.8%) pursued radical prostatectomy in the same time frame at our institution. Available clinical and demographic information are summarized in Table 1. Median age was 65 years. Our cohort consisted of 51/63 (81%) white men and

Table 1
Baseline patient characteristics.

No. of patients	63
Median age (IQR)	65 (60−69)
Ethnicity (%)	
White	51 (81.0)
Black	11 (17.5)
Other	1 (1.5)
Median PSA (IQR)	7.43 (5.2−10.1)
Clinical stage (%)	
T1c	54 (85.7)
T2a	8 (12.7)
T2b	1 (1.5)

Table 2
Standard and targeted prostate biopsy pathology.

Systematic biopsy Grade Group (%)	
No cancer	24 (39.3)
1	22 (36.1)
2	8 (13.1)
3	6 (9.8)
4	0 (0)
5	1 (1.6)
No systematic biopsy	2 (3.2)
No. targets (%)	
1	20 (31.7)
2	24 (38.0)
3	12 (19.0)
4	2 (3.2)
>4	5 (7.9)
Median no. cores (IQR)	4 (3.5−6)
Target biopsy Grade Group (%)	
No cancer	3 (4.8)
1	11 (17.5)
2	20 (31.7)
3	13 (20.6)
4	12 (19.0)
5	4 (6.3)
De novo CaP or Grade Group upgrade (%)	46 (73)

CaP = prostate cancer.

Table 3
Final radical prostatectomy surgical pathology.

Median prostate weight (g)	48.15
Grade Group (%)	
1	2 (3.2)
2	26 (41.3)
3	23 (36.5)
4	5 (7.9)
5	7 (11.1)
Extraprostatic extension (%)	34 (54.0)
Seminal vesicle invasion (%)	6 (9.5)
Lymph node dissection performed (%)	49 (77.8)
Lymph node invasion (%)	7 (11.1)

11 (17%) African American men. Preoperative disease characteristics included a median prostate specific antigen (PSA) of 7.43 (IQR 5.2−10.1), 54/63 (85.7%) with cT1c disease, and no men had undergone previous oncologic intervention.

All but 2 men underwent SB prior to or at time of TB. On SB, cancer was not identified in 24/61 (39.3%) men, and Grade Group 1, 2, and 3 CaP was identified in 22 (36.1%), 8 (13.1%), and 6 (9.8%) men, respectively (Table 2). All 63 men underwent mpMRI and subsequent TB. A majority of men (88.7%) had 1 to 3 suspicious prostatic foci which were sampled by a median of 4 (IQR 3.5−6) total target cores. De novo cancer detection or Grade Group upgrade occurred in 46 (73%) of men following TB. All men included in this study analysis underwent radical prostatectomy. A majority of men harbored Grade Group 2 ($n = 26$, 41.3%) or 3 ($n = 23$, 36.5%) disease on final surgical pathology (Table 3). EPE and SVI were identified in 34 (54%) and 6 (9.5%) of men, respectively. LNI was identified in 7 (11.1%) of the 49 (77.8%) men who underwent lymph node dissection.

On ROC analysis, likelihood of EPE, SVI, and LNI as predicted by the MSKCC Preprostatectomy nomogram using 1 of 5 biopsy pathology reporting schemas were individually compared to final surgical pathology. For prediction of EPE, using IC alone, AG alone, SB plus IC, and SB plus AG exhibited higher absolute AUCs to SB alone (0.671, 0.674, 0.658, 0.661 vs. 0.609, though not statistically significant: $P > 0.05$, Fig. 2). For SVI, the AUC for AG plus SB was comparable to SB alone (0.727 vs. 0.733, $P > 0.05$), and IC alone, AG alone, IC plus SB exhibited inferior absolute AUCs (0.428, 0.630, 0.699, $P > 0.05$, Fig. 2). Following ROC analysis of LNI, IC alone, and AG alone demonstrated higher absolute AUCs to SB alone (0.571, 0.647 vs. 0.524, $P > 0.05$), and IC plus SB as well as AG plus SB had inferior absolute AUCs (0.472 and 0.472, $P > 0.05$, Fig. 2).

4. Discussion

Performing mpMRI and subsequent TB during the diagnostic workup of CaP has become commonplace, and is recommended by the National Comprehensive Cancer Network in the setting of a prior negative biopsy and/or suspicion of aggressive disease [15,17]. Recent evidence demonstrates this diagnostic modality optimally detects significant cancer requiring fewer cores than traditional SB [4,7,18]. Moreover, men eligible for AS may be more likely to pursue this when TB is obtained in addition to SB, thus avoiding a potentially unnecessary radical intervention [19].

Among the 644 men who underwent mpMRI and TB, just 9.8% pursued radical prostatectomy during the same study period at our institution. This is likely multifactorial and could be due to having persistently benign prostatic tissue on TB following a prior negative SB, which is a common occurrence [19,20]. Alternatively, a significant proportion (>50% in this study) of men considering or already enrolled in AS elected to continue with this surveillance strategy following a stable risk assessment rendered based upon TB results as previously observed by Lai et al. [13] Lastly, men may have elected to pursue definitive surgical or nonsurgical intervention at another center.

Prognostic tools such as the MSKCC Preprostatectomy nomogram facilitate the discussion of surgery with patients and offer insight as to the likelihood of adverse pathological outcomes [3]. The likelihood of biochemical recurrence and disease progression using this formula was designed, validated, and revalidated in an era prior to the widespread adoption of MRI-directed TB sampling [21−23]. While providers may already enter targeted core pathology into the Preprostatectomy nomogram, evaluation of the algorithm in this high-yield biopsy setting is warranted to ensure patients are not receiving misguided preoperative counseling.

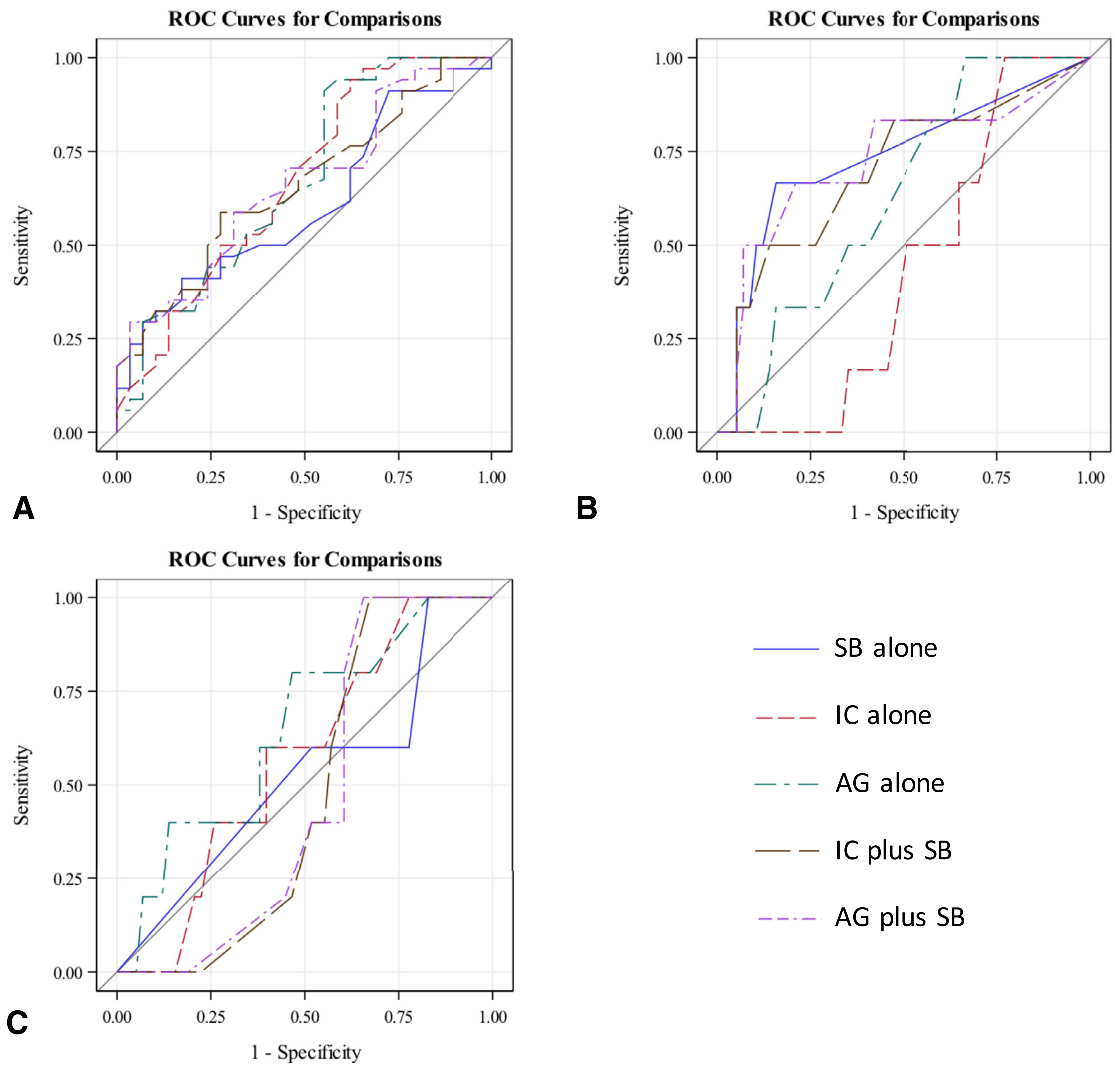

Fig. 2. ROC curves for predicting (A) EPE, (B) SVI, and (C) LNI using various biopsy reporting schemas compared to final surgical pathology according to the MSKCC Preprostatectomy nomogram.

While several preoperative nomograms incorporating mpMRI and TB pathology do exist, robust validation and incorporation into routine practice present considerable barriers [9,10,24]. Moreover, detailed imaging information required for these nomograms such as lesion size and clinical stage on MRI may not readily be available to the clinical urologist, can vary across institutions based on the MRI magnet strength, sequences used and the experience of the reporting radiologist. This is the first study to assess the prognostic reliability of an already existing, previously externally validated, widely used and user-friendly nomogram with TB pathology. These findings suggest using TB pathology alone or in conjunction with SB cores predicts final surgical pathology at least comparably to SB pathology alone.

In order to adequately sample a region of interest during a TB session, multiple cores are usually acquired from each target. For nomograms originally designed to prognosticate standard template biopsies, this could be problematic as more than 1 positive core from the same suspicious foci could skew the algorithm. Therefore, reporting the overall yield from an aggregate of cores from 1 suspicious imaging focus may better reflect the true pathologic cancer burden. Gordetsky et al. recently evaluated this reporting method in a cohort of men who underwent TB and subsequent radical prostatectomy. Interestingly, the AG method demonstrated greater concordance with tumor lesion volume, lesion density, and the presence of EPE on mpMRI compared to standard IC reporting [14]. This study is among the first to utilize this novel AG reporting method in a standardized manner [14]. Superior prediction of surgical pathology using the AG method was not demonstrated in the present study. However, this should bring to light the lack of a discipline-wide consensus on TB pathology reporting, and the potential impact on patient care given the variability in reporting methodologies across institutions and even individual pathologists.

Our study has several acknowledged limitations. This represents a single institution, retrospective study lacking long-term follow-up to evaluate biochemical recurrence and overall survival which were also prognostic read-outs of the MSKCC Preprostatectomy nomogram. The cohort size precludes the establishment of both superiority and inferiority regarding biopsy core reporting, and is considerably smaller than the patient populations used to generate MSKCC Preprostatectomy and more recent Gandaglia et al. nomograms [3,9]. In addition, the clinical course of men who underwent mpMRI and subsequent TB but did not pursue radical prostatectomy at our institution was not captured in the present study. Lastly, LNI could not be evaluated in the 14 men where a pelvic lymph node dissection was not performed. Whether or not the lymph node pathology would have impacted the overall findings of this study is unknown. Future multi-institutional studies may allow for larger patient populations and normalization across institutional variability to potentially validate the current study findings. Subsequent long-term follow-up of these patients will permit evaluation of important outcomes such as biochemical recurrence and survival.

5. Conclusions

Using TB pathology either alone or combined with SB pathology results for the MSKCC Preprostatectomy nomogram appears comparable for prognosticating adverse pathologic features on radical prostatectomy. Continued use of this nomogram may be a pragmatic alternative to the complex nomograms recently proposed for this setting, but robust validation is warranted before adopting this into routine clinical practice.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
[2] Martin G. Sanda MRCC, MD; Tony Crispino; Stephen Freedland, MD; Kirsten Greene, MD; Laurence H. Klotz, MD; Danil V. Makarov, MD; Joel B. Nelson, MD; James Reston, PhD; George Rodrigues, MD; Howard M. Sandler, MD; Mary Ellen Taplin, MD; Jeffrey A. Cadeddu, MD. CLINICALLY LOCALIZED PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE. In: Association AU, editor. AUA Guidelines 2017.
[3] Memorial Sloan Kettering Cancer Center. Prediction Tools/Prostate Cancer Nomograms: Pre- Radical Prostatectomy. Memorial Sloan Kettering Cancer Center; 2018.
[4] Yarlagadda VK, Lai WS, Gordetsky JB, et al. MRI/US fusion-guided prostate biopsy allows for equivalent cancer detection with significantly fewer needle cores in biopsy-naive men. Diagn Interv Radiol 2018;24:115–20.
[5] Siddiqui MM, George AK, Rubin R, et al. Efficiency of prostate cancer diagnosis by MR/ultrasound fusion-guided biopsy vs standard extended-sextant biopsy for MR-visible lesions. J Natl Cancer Inst 2016;108. https://academic.oup.com/jnci/article/108/9/djw039/2499548.
[6] Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol 2015;68:438–50.
[7] Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015;313:390–7.
[8] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767–77.
[9] Gandaglia G, Ploussard G, Valerio M, et al. A novel nomogram to identify candidates for extended pelvic lymph node dissection among patients with clinically localized prostate cancer diagnosed with magnetic resonance imaging-targeted and systematic biopsies. Eur Urol 2018;75:506–14.
[10] Rayn KN, Bloom JB, Gold SA, et al. Added value of multiparametric magnetic resonance imaging to clinical nomograms in predicting adverse pathology in prostate cancer. J Urol 2018;200:1041–7.
[11] Bjurlin MA, Rosenkrantz AB, Sarkar S, et al. Prediction of prostate cancer risk among men undergoing combined MRI-targeted and systematic biopsy using novel pre-biopsy nomograms that incorporate MRI findings. Urology 2018;112:112–20.
[12] Truong M, Wang B, Gordetsky JB, et al. Multi-institutional nomogram predicting benign prostate pathology on magnetic resonance/ultrasound fusion biopsy in men with a prior negative 12-core systematic biopsy. Cancer 2018;124:278–85.
[13] Lai WS, Gordetsky JB, Thomas JV, et al. Factors predicting prostate cancer upgrading on magnetic resonance imaging-targeted biopsy in an active surveillance population. Cancer 2017;123:1941–8.
[14] Gordetsky JB, Schultz L, Porter KK, et al. Defining the optimal method for reporting prostate cancer grade and tumor extent on magnetic resonance/ultrasound fusion-targeted biopsies. Hum Pathol 2018;76:68–75.
[15] Prostate Cancer. NCCN Clinical Practice Guidelines in Oncology. Version 4.2018 ed.
[16] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.
[17] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.
[18] Radtke JP, Schwab C, Wolf MB, et al. Multiparametric magnetic resonance imaging (MRI) and MRI-transrectal ultrasound fusion biopsy for index tumor detection: correlation with radical prostatectomy specimen. Eur Urol 2016;70:846–53.
[19] Gordetsky JB, Saylor B, Bae S, et al. Prostate cancer management choices in patients undergoing multiparametric magnetic resonance imaging/ultrasound fusion biopsy compared to systematic biopsy. Urol Oncol 2018;36:241 e7- e13.
[20] Bjurlin MA, Renson A, Rais-Bahrami S, et al. Predicting benign prostate pathology on magnetic resonance imaging/ultrasound fusion biopsy in men with a prior negative 12-core systematic biopsy: external validation of a prognostic nomogram. Eur Urol Focus 2018. https://doi.org/10.1016/j.euf.2018.05.005.
[21] Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. J Clin Oncol 1999;17:1499–507.
[22] Kattan MW, Vickers AJ, Yu C, et al. Preoperative and postoperative nomograms incorporating surgeon experience for clinically localized prostate cancer. Cancer 2009;115:1005–10.
[23] Stephenson AJ, Scardino PT, Eastham JA, et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Clin Oncol 2005;23:7005–12.
[24] Feng TS, Sharif-Afshar AR, Wu J, et al. Multiparametric MRI improves accuracy of clinical nomograms for predicting extracapsular extension of prostate cancer. Urology 2015;86:332–7.