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Cribriform pattern and perineural invasion on MR/US fusion biopsy predict failure of selection criteria for prostatic hemigland ablation

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Abstract

Objectives: To assess clinicopathologic factors on MR/US fusion biopsy that might predict failure of theoretical selection criteria for prostatic hemigland ablation (HA).

Subjects and methods: A retrospectively maintained single institution multiparametric MRI database ($n = 1667$) was queried to identify 355 patients who underwent MR/US fusion biopsy, including both targeted biopsy and concurrent systematic biopsy from December 1, 2014 to June 1, 2018. Clinical, pathological, and imaging variables were assessed on fusion biopsy (Table 1) to determine who met theoretical selection criteria for HA, defined as unilateral intermediate-risk prostate cancer per NCCN criteria (Grade Group [GG] 2 or 3 with prostate-specific antigen <20) and no evidence of extraprostatic extension (EPE) on multiparametric MRI. Predictors of selection criteria failure were then assessed in patients who also underwent radical prostatectomy (RP). Failure of the theoretical HA selection criteria was defined as presence of GG $\geqq$ 2 on the contralateral (untreated) side, or the presence of high-risk disease (any GG $\geqq$ 4 or EPE) in the RP specimen.

Results: Of the 355 patients who underwent fusion biopsy, 84 patients met the theoretical selection criteria for HA. Of those patients eligible, 54 underwent RP, 37 (68.5%) of which represented unsuccessful HA selection criteria. Patients no longer met HA selection criteria on the basis of upgrading alone in 6/54 (11.1%), EPE alone in 9/54 (16.7%), bilateral GG 2 or 3 in 16/54 (29.6%) or combined EPE and bilateral GG 2 or 3 in 6/54 (11.1%) cases. In the HA selection failures due to upgrading, three also had EPE, one of whom also had missed contralateral GG $\geqq$ 2 disease. The only factor independently associated with HA failure was any presence of cribriform pattern (HR 7.01, $P = 0.021$). Perineural invasion on systematic biopsyalso appeared to improve the performance of our multivariable model (HR 5.33, $P = 0.052$), though it was not statistically significant when using a cutoff of <0.05. Accuracy for predicting successful HA was 0.32 and improved to 0.74 if PNI or cribriform were excluded and 0.84 if both were excluded.

Conclusions: In a retrospective analysis of RP patients who underwent preoperative MRI/US fusion biopsy, current selection criteria for prostatic HA based on NCCN intermediate-risk stratification failed to accurately identify appropriate candidates in 68.5% of patients. Cribriform pattern and PNI detected on biopsy reduced the failure of hemigland selection criteria to 43%. These criteria should be routinely reported on biopsy pathology and taken into consideration when selecting patients for HA in prospective clinical trials.

Keywords: Prostate cancer; Cribriform; Focal therapy; Perineurial invasion; MR/US Fusion Biopsy; Selection criteria

1. Introduction

Focal therapy for the treatment of prostate cancer (CaP) is becoming more prevalent, as men are seeking less invasive treatment options with potentially decreased urinary and sexual morbidity. It is appealing to think that a therapy could be tailored to the extent of the patient's CaP, such that hemigland ablation (HA), quadrant ablation or even more selective ablation could be used instead of whole gland therapy. However, the ideal selection criteria for focal therapy in CaP remain unclear [1,2]. While studies have shown the safety and feasibility of multiple modalities for

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focal therapy, such as cryotherapy, electroporation, high-intensity focused ultrasound, radiofrequency ablation, laser ablation and photodynamic therapy, data regarding long-term oncologic outcomes is not yet mature. Furthermore, many of these modalities have been studied in patients with low-risk CaP who could potentially have durable oncologic outcomes with surveillance alone [3].

A key impediment to the greater adoption of focal therapy has been a lack of universally accepted selection criteria despite the work of numerous committees and working groups [1,2]. MR/US fusion biopsy (FB), which includes targeted biopsy (TB) and systematic biopsy (SB) is believed to be an accurate method for selecting patients for definitive primary treatment of CaP [4]. However, significant CaP can still be missed by mpMRI due to small lesion size, reduced visibility of cribriform lesions, and inherent sampling limitations of most biopsy techniques [5,6]. In studies using selection criteria for focal therapy based on unilateral intermediate-risk disease (NCCN classification), FB did not reliably identify patients who would be safe for focal therapy, as evidenced by the rates of upgrading and greater tumor extent found at the time of radical prostatectomy (RP) [7,8].

Further risk stratification is needed to optimally select CaP patients for focal therapy. In this study, we assessed the performance of theoretical selection criteria for prostatic HA and factors on biopsy that may improve the accuracy of these criteria in patients with unilateral intermediate-risk disease at the time of FB.

2. Patients and methods

2.1. Study population

After Institutional Review Board approval, a retrospectively maintained single institution multiparametric MRI (mpMRI) database ($n = 1{,}667$) was queried to identify 355 patients who underwent MR/US FB, including both TB and concurrent SB from December 1, 2014 to June 1, 2018. Clinical and pathological variables were assessed on FB to determine who met selection criteria for HA, defined as unilateral intermediate-risk CaP per NCCN criteria (Grade Group [GG] 2 or 3 with prostate-specific antigen [PSA] <20) [8]. We chose to examine HA because it is a focal therapy template that has the advantage of ensuring an adequate margin with still minimal morbidity [9]. In addition, patients eligible for quadrant and selective ablation should often also be eligible for HA.

Patients with the presence of GG 1 disease on the contralateral side were considered eligible. Selection criteria performance was then assessed by examining pathologic specimens in those patients who had undergone RP. HA selection failure was defined on RP specimen and included GG ≥ 4) or extraprostatic extension (EPE). Cases with contiguous lesions that crossed the midline of the RP specimen were classified as bilateral disease.

2.2. Prostate mpMRI acquisition and MRI/ultrasound FB

Two 3 Tesla Magnetom Skyra scanners were used to perform mpMRI with a pelvic phased array coil. The mpMRI protocol at our institution was previously described [5]. DynaCAD software (InVivo) was applied for postprocessing contrast kinetics to assess for rapid contrast wash in and target marked regions of interest. PI-RADS, version 2 was scored by 2 fellowship trained radiologists who had more than 4 years of experience with mpMRI. FB was performed by 6 urologists using the UroNav (Phillips) software-based FB platform. All patients underwent TB and concurrent 12-core SB under transrectal US guidance. At least 2 TB cores (median 4, IQR 3-5) were obtained from each mpMRI lesion.

2.3. Pathological review

Prostate pathology from all biopsy and RP tissues was reviewed by a single genitourinary pathologist (HM) blinded to mpMRI results. RP specimens were sectioned at 3-5 mm intervals from apex to base. Tumor foci were individually reviewed and evaluated for location, size, GG, pattern 4 morphology and the presence of EPE**.** GGs were assigned to each positive biopsy core in accordance with International Society of Urologic Pathology 2014 guidelines. The index lesion on biopsy and RP specimen was considered to be the lesion with the highest proportion of the highest GG, or, if GG was equal between lesions, then size was the determining factor. In patients found to have bilateral disease on RP specimen that was missed on biopsy, a review was carried out to determine if the contralateral "untreated" side contained the RP index lesion.

2.4. Statistical analysis

The Mann-Whitney *U* test was used to compare medians of continuous variables between patients who had HA selection failure on RP specimen and those who were successfully selected. The chi-square test was applied to compare the distribution of independent categorical variables between these groups. Multivariable logistic regression was performed using forward entry with a P value cutoff of $P < 0.1$. A P value of <0.05 was considered statistically significant. The following variables were entered into the multivariable model: age, BMI, prostate volume on MRI, PSA, PIRADS score, SB PNI present, TB PNI present, SB + TB PNI present, SB cribriform present, TB cribriform present, SB + TB cribriform present, MRI abutment present, number of prior TRUS biopsies, index lesion size (mm), no. of TB cores, no. positive SB cores, PSAD, DRE, and Gleason score. All statistical analyses were done using IBM SPSS, version 24.

3. Results

The detailed overall distribution of normal, PIRADS 3, 4, and 5 of patients undergoing mpMRI at our institution was previously published by Truong et al. [10]. Of the 355 patients who underwent FB, 84 patients met the selection criteria for HA. Of those patients eligible for HA on FB, 54 underwent RP, 37 of which had HA selection failure after review of the RP specimen (Fig. 1). Among the 54 patients considered HA candidates, contralateral GG ≥ 2 alone was found in 16/54 (29.6%) cases, EPE alone in 18/54 (33.3%) cases, and both EPE and contralateral GG ≥ 2 in 6/54 (11.1%) cases. In 6/54 (11.1%) cases, patients had GG ≥ 4 that was missed on biopsy, 3 of who also had EPE and 1 who had contralateral GG ≥ 2.

Patient clinical, imaging, and pathological characteristics are summarized in Table 1. Univariable analysis found no significant difference between patients who had success or failure of HA selection criteria based on RP with regards to age (64.0 vs. 64.6 years, $P = 1$), PSA (6.0 vs. 7.3, $P = 1$), PSA density (0.14 vs. 0.16, $P = 0.558$), GG (0.191) or digital rectal exam ($P = 0.487$). Similarly, indicators of tumor extent including index lesion size and capsular abutment were not significantly associated with HA selection failure on RP.

The only factor on biopsy predictive of HA selection failure on univariable analysis was presence of cribriform pattern on SB + TB ($P = 0.030$). On multivariable analysis, cribriform pattern on SB + TB (HR 7.01, $P = 0.021$) and) improved the performance of our model. PNI on SB also appeared to improve the performance of our model, however this was not significant using a cutoff of <0.05 (HR 5.33, $P = 0.052$) (Table 2).

Of the 18 patients theoretically eligible for HA on FB who also had cribriform, upon examining the RP specimen, 16 (88.9%) had selection criteria failure due either to contralateral GG ≥ 2 CaP in 7/18 (38.9%) cases (Fig. 2), EPE in 11/18 (61.1%) cases or missed ipsilateral GG ≥ 4 disease in 3/18 (16.6%). In the 15 patients who had perineural invasion (PNI) on SB, 13 (86.7%) patients had selection failure. Out of 15, 8 (53.3%) had contralateral GG ≥ 2 CaP, 5/15 (33.3%) had EPE, and 2/15 (13.3%) had missed GG ≥ 4 disease.

Table 3 shows performance of our theoretical selection criteria. Accuracy was 0.59, with a sensitivity of 0.94 and specificity of 0.52 (Table 3). Accuracy improved to 0.84 when patients with cribriform morphology and PNI both were excluded, with corresponding decrease in sensitivity and increase in specificity.

In 3 cases, the pathological index lesion found on RP specimen was distinct from and involved the side contralateral to the biopsy index lesion. Two of these RP index lesions shared the same GG as the biopsy index lesion, but were larger, while a third RP index lesion had a higher GG.

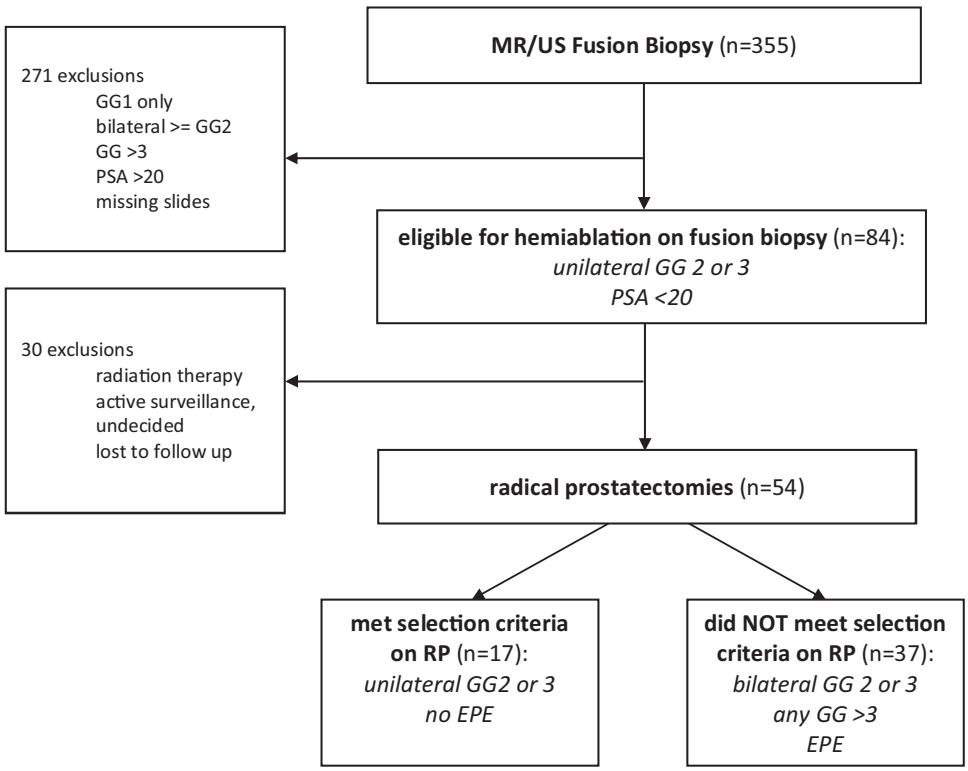

Fig. 1. Application of theoretical focal therapy criteria for prostate cancer using MR/US fusion biopsy with verification in available radical prostatectomy specimens.

Table 1
Clinical, pathological, and imaging variables available after fusion biopsy assessed for correlation with performance of theoretical hemiablation selection on radical prostatectomy specimen.

	Successful HA selection on RP (IQR)	Failed HA selection on RP (IQR)	*P*
n	17	37	
Age, median years	64.0 (61.6,68.0)	64.6 (61.0,68.3)	1*
BMI (kg/m^2)	28.0 (26.6,31.1)	28.3 (25.4,30.4)	0.558*
PSA (ng/ml)	6.0 (5.4,9.3)	7.3 (5.8,9.5)	1*
PSAD (ng/ml/ml)	0.14 (0.10,0.20)	0.16 (0.11, 0.26)	0.558*
DRE, *n*			0.366***
Normal	14	34	
Abnormal	3	3	
MRI prostate volume, median ml	38.0 (31.5, 72.0)	44.3 (34.0,52,6)	1*
PIRADS, *n*			0.497**
3	2	2	
4	9	17	
5	6	18	
Number of prior biopsies	1.0 (1.0,2.0)	1.0 (1.0,1.0)	0.335*
Index lesion size, median mm	15.0 (11.0, 20.0)	14.0 (11.0, 18.3)	0.711*
MRI capsular abutment, *n*			1***
No	14	30	
Yes	3	7	
Overall grade group on FB (*n*)			0.336***
2	14	24	
3	3	13	
Number of TB cores	2.0 (2.0,3.0)	2.5 (2.0,3.3)	1*
Cribriform present (SB), *n*			0. 470***
No	15	28	
Yes	2	9	
Cribriform present (TB), *n*			0.106***
No	15	24	
Yes	2	13	
Cribriform present (SB + TB), *n*			0.030**
No	15	21	
Yes	2	16	
PNI present (SB), *n*			0.106***
No	15	24	
Yes	2	13	
PNI present (TB), *n*			0. 470***
No	15	28	
Yes	2	9	
PNI present (SB + TB), *n*			0.135***
No	13	19	
Yes	4	18	

BMI = body mass index; DRE = digital rectal exam; HA = hemigland ablation; IQR = interquartile range; PSA = prostate-specific antigen; PSAD = PSA density; PNI = perineural invasion; RP = radical prostatectomy; SB = systematic biopsy; TB = targeted biopsy.

*Mann-Whitney *U*, **chi-square, ***Fisher's exact.

Table 2
Multivariate model for predicting failure of hemiablation selection criteria.

Variable	B	SE	Wald	OR	95% CI	*P*
PNI (SB)	1.673	0.860	3.788	5.330	0.998 −28.740	0.052
Cribriform (SB + TB)	1.958	0.846	5.354	7.084	1.349 −37.201	0.021

CI = confidence interval; OR = odds ratio; SB = systematic biopsy; TB = targeted biopsy.

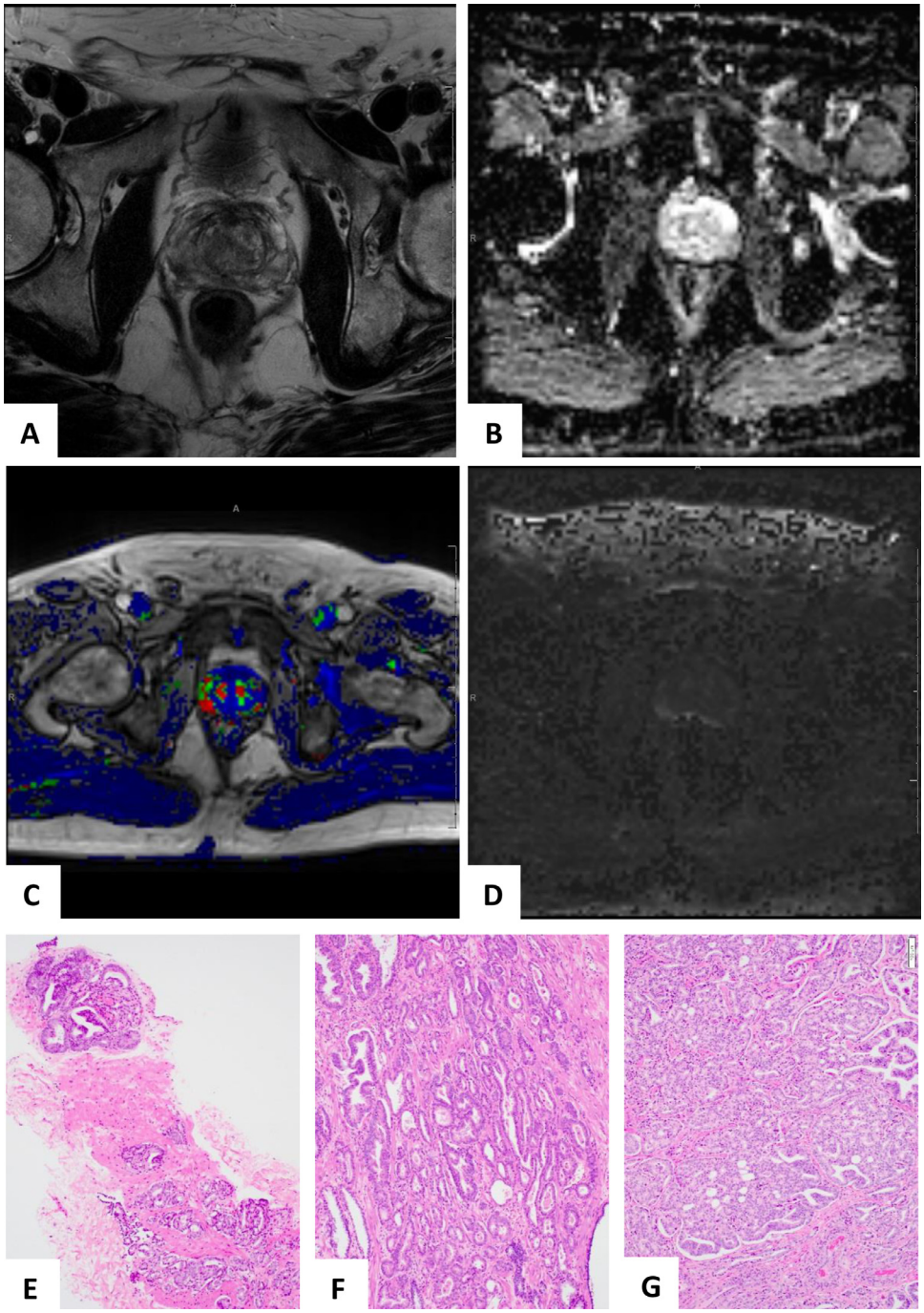

Fig. 2. Prostate imaging and pathology. mpMRI: A PIRADs 5 lesion was seen in the left prostate on T2 weighted imaging (A), ADC map (B), dynamic contrast-enhanced imaging (C), and diffusion-weighted imaging with high B zero of 1600 (D). Pathology (100×): MR/US fusion biopsy showed GG 2 disease harboring cribriform pathology only on the right side (E). On RP specimen, GG>=2 disease was found in both the left gland (F) and right gland(G).

4. Discussion

Focal therapy holds promise as a way to reduce the sexual and urinary morbidity associated with CaP treatment, but its exact role is yet to be defined [1]. Focal therapy has been proposed as both a substitute for active surveillance in low-risk CaP and a definitive treatment for intermediate-risk CaP. Despite a paucity of long-term oncologic data, multiple focal therapy technologies are available for use today and some are even considered an option for treatment of localized CaP according to AUA guidelines [3,11]. There is no current consensus on the selection of patients ideally suited for focal therapies, including HA, for the definitive treatment of CaP, though multiple groups have been working toward this goal [1,2]. Current criteria used to select patients for focal therapy rely on risk stratification data has

Table 3
Performance of theoretical hemiablation selection criteria with and without additional exclusions.

HA selection criteria	HA eligibility		Sensitivity	Specificity	Accuracy
Unilateral GG 2 or 3, PSA < 20					
	RP eligible	RP ineligible			
Biopsy eligible	17	37	0.94	0.51	0.59
Biopsy ineligible	1	38			
PNI (SB+TB) excluded					
	RP eligible	RP ineligible			
Biopsy eligible	13	19	0.72	0.75	0.74
Biopsy ineligible	5	56			
No Crib (SB+TB) excluded					
	RP eligible	RP ineligible			
Biopsy eligible	15	21	0.83	0.72	0.74
Biopsy ineligible	3	54			
PNI and Crib (SB + TB) excluded					
	RP eligible	RP ineligible			
Biopsy eligible	12	9	0.67	0.88	0.84
Biopsy ineligible	6	66			

GG = grade group, HA = prostatic hemigland ablation, PNI = perineural invasion, PSA = prostate specific antigen, RP = radical prostatectomy, SB = systematic biopsy, TB = targeted biopsy.

largely been developed from the use of whole gland therapies, the rationale for this being that the index lesion is likely the primary driver of CaP outcomes. The index lesion hypothesis has been supported by studies showing that size of the highest risk foci of disease can predict progression-free survival just as well as total cancer volume [12]. Such studies must be translated to focal therapy planning with caution, however, as they are comprised of patients who ultimately underwent whole gland therapy, thereby having all of their nonindex lesions treated as well.

Despite the significant improvements in detection and characterization of the index lesion by mpMRI and FB, the risk of missing clinically significant CaP remains real. In the largest study to date using prostate specimens to assess mpMRI performance, mpMRI missed a clinically significant lesion in 45% of patients with multifocal CaP and 34% overall [13]. Even after saturation biopsy of the index lesion, a risk of upgrading of 20% has been reported [14]. This may have to do with the biology of CaP itself; the cribriform subtype of Gleason pattern 4 disease is poorly detected by MRI and smaller lesions <0.5 ml may harbor Gleason pattern 4 disease at rates as high as 16% [5,15]. Nevertheless, MR/US FB remains the best tool for identifying clinically significant CaP and its performance with regards to focal therapy patient selection must continue to be evaluated.

Ideally, the improved accuracy of detecting clinically significant CaP with MR/US FB would translate to improved focal therapy selection criteria. Nassiri et al. recently showed that while FB showed an accuracy of 75% for assessing focal therapy eligibility, the rate of missed clinically significant cancer was concerning [7]. In patients who underwent FB and were selected for definitive focal therapy, the corresponding RP specimen harbored clinically significant CaP that would have gone untreated by the proposed focal therapy strategy in 13 of 25 cases. Our findings reinforce such concerns with selection of patients for HA, as 37 of the 54 patients who met our selection criteria based on FB had HA selection failure on RP specimen. Even more alarming, we found 3 cases in which an index lesion newly identified on RP would have gone untreated via HA. These findings highlight the need for better HA selection criteria incorporating more than imaging, PSA and Gleason score if we are to move away from more aggressive biopsy strategies such as saturation biopsy.

To our knowledge, ours is the first study to examine PNI, cribriform morphology and PIRADS score on biopsy as they relate to performance of selection criteria for prostatic HA. Moreover, no other pathologic factors have been previously identified that predict HA or focal therapy failure. We found that cribriform on FB predicted HA selection failure on analysis of RP specimen. Of the 18 patients in our study theoretically eligible for HA on FB who also had cribriform, 16 (87%) had HA selection failure on the basis of untreated GG $\geq$ 2 (Fig. 2), EPE or missed GG $\geq$ 4 disease.

Cribriform pattern has been associated with increased rates of metastasis and CaP-specific death [16,17]. In fact, recent pathologic studies suggest that cribriform morphology may be a more important predictor of post-RP outcomes than Gleason pattern 4 disease without cribriform [17,18]. Our group recently showed that cribriform morphology is the Gleason pattern 4 subtype most associated with EPE in the RP specimen while at the same time being poorly detected via MRI [5]. Though our current study did not show any factors to be predictive of missed cribriform at biopsy, it is concerning that 15 out of the 37 patients who

no longer met selection criteria on RP specimen had cribriform in the contralateral "untreated" gland. Cribriform on biopsy should warrant added caution when considering focal therapies.

In addition to cribriform pattern, we found that though it was not significant based on the cutoff of $P < 0.05$, when combined with cribriform on pathology, PNI on SB appeared to improve the accuracy or our selection criteria (0.84, Table 3). PNI is the invasion of tumor into nerves and a route of potentially distant metastasis in multiple different malignancies [19]. PNI on SB is a well-known predictor of poorer oncologic outcomes in CaP, such as nonorgan confined disease including EPE, seminal vesical invasion and positive lymph nodes, and worse biochemical-free survival [20,21]. In men with intermediate-risk or higher disease, PNI has been associated with increased risk of upgrading [22]. One study has specifically examined PNI on TB in depth and found it to be associated with both EPE and early biochemical recurrence, though this was not the case in our results [23].

Overall, the results of our study are consistent with findings suggesting that patients with either cribriform or PNI found on biopsy could have foci of more advanced disease that is being missed at the time of biopsy. When combined with prior evidence suggesting that PNI and cribriform pattern are prognostic of poorer oncologic outcomes after RP, our data suggest that that these pathologic features should be taken into consideration when selecting patients for HA based on FB.

In this study, pathologic analysis could only be conducted on the 93 patients who also underwent RP after undergoing mpMRI/US FB. We found an accuracy of only 0.59 for patients with unilateral GG2 or 3 disease on biopsy and PSA < 20. The accuracy improved to 0.84 and the specificity to 0.88 when patients with cribriform and PNI on SB were both excluded, though only 21 total patients remained eligible for HA at biopsy and the sensitivity dropped to 0.67 from 0.94. As such, our most restrictive criteria for HA utilizing MRI, TB, SB, and pathologic indicators of aggressiveness, multifocality, and metastasis still misclassified 43% of patients as appropriate for HA (Table 3), though it suggests that the addition of select clinico-pathologic criteria may enhance current selection criteria.

It must be acknowledged that the significance of untreated lesions in the contralateral lobe is yet to be determined and that such lesions do not necessarily compromise oncologic outcomes. However, the histopathological end points used in our study (GG ≥ 2 and EPE) were strong risk factors of prostate cancer-specific mortality at 29 years of follow-up [24]. We were able to identify patients who would be at risk of missed bilateral disease and might warrant consideration for definitive whole gland therapy or potentially closer surveillance. It was not possible to evaluate all definitions of selection criteria failure within the scope of this study, though we acknowledge that our results may differ with variations in PSA cutoffs, incorporation of lesion size criteria, or even the potential targeting of EPE via extraglandular ablation strategies.

A strength of our study was central imaging and pathology reviews by highly experienced genitourinary radiologists and pathologists whose performance has previously been published and found to be on par with high-volume institutions [25]. A limitation is that there may have been a selection bias in evaluating only patients who underwent RP, which is inherently a higher risk group. However, the evaluation of RP specimens is still the gold standard for determining the presence of CaP missed on biopsy. The total number of patients undergoing RP was also limited by the selection of alternative modalities such as active surveillance and radiation therapy. Our single center design is a limitation due to variability in techniques across institutions that might affect FB performance.

5. Conclusions

In a retrospective analysis of RP patients who underwent preoperative MRI/US FB, current selection criteria for prostatic HA based on NCCN intermediate-risk stratification failed to accurately identify appropriate candidates in 68.5% of patients. Cribriform pattern and PNI detected on biopsy reduced the failure rate of hemigland selection criteria to 43.0%. These criteria should be routinely reported on biopsy pathology and taken into consideration when selecting patients for HA in prospective clinical trials.

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