Original Article

Detection of extraprostatic disease and seminal vesicle invasion in patients undergoing magnetic resonance imaging-targeted prostate biopsies

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Background: Finding incidental extraprostatic extension (EPE) or seminal vesicle invasion (SVI) by prostate cancer (PCa) is rare on standard prostate biopsy. We evaluated the clinical-pathologic features associated with EPE and SVI on multiparametric magnetic resonance imaging (MRI)/ultrasound (US) fusion-guided targeted biopsy (TB).

Methods: A retrospective review was performed from 2014–2017, selecting patients who had undergone TB. Clinical, pathologic, and radiologic features were evaluated.

Results: Five out of 333 (1.5%) patients who had PCa detected on TB had EPE and/or SVI. The average age and prostate-specific antigen (PSA) was 71 years and 17 ng/mL, respectively. The average number of cores taken on TB was 4.2. Two patients had a prior negative SB and two patients had a prior positive SB, one of which underwent radiation therapy. All patients had a PIRADSv2 suspicion score of 4 or 5. Four out of five (80%) patients underwent both SB and concurrent TB, of which 3/4 (75%) had EPE identified only on TB. One out of four (25%) patients also had both EPE and SVI, identified only on TB. One patient underwent only TB for MRI suspicion of SVI, which was pathologically confirmed on TB. On TB, one patient had Grade Group 3, two patients had Grade Group 4, and two patients had Grade Group 5 PCa. Perineural invasion (PNI) was present in 4/5 (80%) patients on TB.

Conclusions: Based on our small series, we hypothesize that MRI/US fusion TB outperforms SB in the identification of EPE and SVI. However, given the small sample size and the overall rarity of these pathologic findings on prostate biopsy, further validation is needed.

Keywords: Prostate cancer (PCa); cancer staging; cancer grading; multiparametric magnetic resonance imaging (MRI)

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Introduction

Although rare, both extraprostatic extension (EPE) and seminal vesicle invasion (SVI) by prostate cancer (PCa) can be identified on prostate needle core biopsy. In one large retrospective study, EPE was found in only 0.6% of prostate needle core biopsy cases (1). The majority of these cases were associated with perineural invasion (PNI) on standard biopsy (SB) as well as high-risk disease on follow up radical prostatectomy. Multiparametric magnetic resonance imaging/ultrasound (MRI/US) fusion targeted biopsy (TB) has been shown to more accurately identify

Table 1 Clinical and pathologic findings of patients with extraprostatic extension or seminal vesicle invasion on MRI/US fusion guided prostate biopsy

Case	Age	Race	Prior biopsy history	Highest PIRADS score	SVI suspected on MRI	EPE suspected on MRI	Prostate volume (cc)	PSA density (ng/mL/cc)	Prostate Cancer Grade Group on biopsy	PNI, SVI, and EPE status on biopsy
1	69	W	Yes, negative	5	Yes	Yes	78.0	0.5	SB: 2	SB: PNI
									TB: 5	TB: EPE, SVI, PNI
2	72	W	No	5	No	No	31.2	0.8	SB: 3	SB: EPE, PNI
									TB: 4	TB: EPE, PNI
3	66	W	Yes, positive*	4	No	No	29.0	0.1	SB: 4	SB: EPE, PNI
									TB: 4	TB: PNI
4	74	W	Yes, negative	5	Yes	Yes	41.4	0.2	SB: 3	SB: none
									TB: 3	TB: EPE, PNI
5	72	AA	Yes, positive#	5	Yes	Yes	22.2	0.4	SB: N/A	SB: N/A
									TB: 5	TB: EPE, SVI

*, history of radiation therapy; #, history of active surveillance. W, white; AA, African American; SB, standard biopsy; TB, targeted biopsy; PNI, perineural invasion; SVI, seminal vesicle invasion; EPE, extraprostatic extension; N/A, not applicable; PSA, prostate-specific antigen; MRI, magnetic resonance imaging; US, ultrasound.

higher grade PCas, compared to the standard extended prostate biopsy SB (2-5). TB has also been reported to have superior detection of poor prognostic features, such as PNI (6,7). We evaluated the clinical, pathologic, and radiologic features associated with EPE and SVI on TB.

Methods

An institutional review board approved (NO. X140724007) retrospective review of patients who had undergone MRI/US fusion TB was performed on our surgical pathology database from 2014–2017. Patients who had biopsy pathologic findings of EPE and/or SVI were included. Image processing and targeting was performed using DynaCad and UroNav, respectively (Phillips/InVivo, Gainesville, FL, USA). PI-RADS v2 scoring was assigned via a multidisciplinary consensus conference with fellowship-trained radiologists and oncologic urologists specializing in prostate MRI, all with >5 years of experience with prostate MRI. Two fellowship trained oncologic urologists at the University of Alabama at Birmingham performed all MRI/US fusion prostate biopsies.

All prostate biopsies were reviewed by a single genitourinary surgical pathologist. In each case, the overall Gleason score for each SB and TB was based on the core with the highest Gleason score. Prostate cancer Grade Groups, adopted by the International Society of Urological Pathology (ISUP) and World Health Organization (WHO), were also assigned to biopsy cores (8). EPE on prostate needle core biopsy was defined as tumor cells present within the periprostatic adipose tissue. All seminal vesicle tissue was labeled as "seminal vesicle" by the urologist performing the procedure and further confirmed as seminal vesicle by histologic examination. SVI was defined as tumor invasion within the smooth muscle wall of the seminal vesicle. Clinical, pathologic, and radiologic features were evaluated.

Results

We identified 333/593 (56.2%) patients who had cancer detected on MRI/US fusion TB. Of these, 5/333 (1.5%) patients were diagnosed with EPE and/or SVI (*Table 1*). The average age and prostate-specific antigen (PSA) of this subset was 71 years [median: 72 years; interquartile range (IQR): 5.5] and 17 ng/mL (median: 8.88 ng/mL; IQR: 27.2), respectively. The average prostate volume was 40.3 cc (median: 31.17 cc; IQR: 34.1). Two patients had a prior negative SB for PCa, two patients had a prior positive

biopsy for PCa and one patient was biopsy naïve. One patient had previously undergone radiation therapy for a PCa. All patients had a PIRADS score of 4 or 5. Four of five (80%) patients underwent both SB and concurrent TB, of which 3/4 (75%) patients had EPE identified only on TB and 1/4 (25%) patients had EPE identified only on SB. One of four (25%) patients also had concurrent SVI, identified only on TB. One patient underwent only TB for MRI suspicion of SVI, which was confirmed on TB. The average number of cores taken on TB was 4.2 (median: 4; IQR: 1.5). Prostate Grade Groups were as follows: 1/5 (20%) Grade Group 3, 2/5 (40%) Grade Group 4, and 2/5 (40%) Grade Group 5. Two of four (50%) patients had higher Grade Group PCa on TB compared to SB (Grade Group 2 to 5, 3 to 4). PNI was present in 4/5 (80%) patients on TB. Of the three patients with clinical follow-up, one completed radiation therapy and has remained disease free 3 years after his initial diagnosis. One patient is currently undergoing radiation and androgen deprivation therapy. The third patient, who had recurrent disease status post radiation therapy, underwent a salvage radical prostatectomy, with biochemical recurrence at 3 months follow-up.

Discussion

Approximately 30,000 men in the USA die from PCa annually, making it the second-leading cause of cancer-related mortality (9). Currently the standard of care in the diagnosis of PCa is a 12-core extended-sextant prostate biopsy. This procedure consists of systematic sampling of the prostate gland from six predetermined sections of the prostate. A major pitfall of this technique is that the samples are essentially taken at random from pre-defined quadrants and the accurate detection of cancer can be somewhat limited. In contrast, multiparametric MRI is a novel diagnostic tool that specifically evaluates tissue density and vascularity, allowing for more accurate detection of lesions suspicious for PCa (10). Use of MRI in conjunction with transrectal ultrasound results in real time electronically superimposed images, allowing for the collection of tissue from the most suspicious lesional areas (2). Recent studies have suggested TB can detect more clinically significant PCas and aid in accurate detection of higher staged disease (11-13). Siddiqui and colleagues evaluated 1,003 men undergoing both MRI/US-targeted biopsy and SB and found that MRI/US fusion TB was not only associated with increased detection of high-risk PCa, but was also better able to predict final pathology on follow-up radical prostatectomy (2). Gordetsky *et al.* evaluated 191 patients who had undergone MRI/US fusion TB with concurrent 12-core SB, and showed that there was no difference in the cancer detection rate between TB and SB (41.4% and 49.2%, respectively, P=0.15). In addition, the degree of detection of ≥ Grade Group 3 tumors significantly favored TB over SB (7). These results hold important implications for patient management, as the use of MRI/US fusion TB is able to provide more accurate diagnoses of high-grade PCa with sampling of fewer cores (9,14).

Identification of EPE is an important component of staging in PCa patients, and is defined by the American Joint Committee on Cancer (AJCC) TNM staging system as pT3a in the presence of extension into the periprostatic fat and as pT3b in the case of SVI (1,15,16). Although the presence of EPE on SB is a rare occurrence, a significant number of patients who undergo radical prostatectomy for presumed localized disease are found to have EPE, implying that its presence is being consistently under detected on SB (15). Although the presence of EPE can sometimes be captured on MRI, it is only with moderate sensitivity and specificity (72% and 65%, respectively), which is insufficient for confirmation of its presence. The presence of EPE in radical prostatectomy specimens has been extensively studied and has a well-established association with disease progression and positive surgical margins (15). However, due to its rarity on biopsy, little is known about biopsy detected EPE as a potential independent predictor of aggressive PCa. In a study by Fleshner *et al.*, 112/19,950 (0.6%) patients with PCa on SB had detection of EPE (1). Overall, we found EPE and/or SVI in 1.5% of patients with PCa who had undergone TB. In addition, of those who underwent both SB and concurrent TB, 75% had EPE identified only on TB. Although the numbers are too small for a definitive conclusion, the data suggests that TB may be detecting EPE at a higher frequency than SB alone.

The tracking of prostatic carcinoma along the perineural space is a known "path of least resistance" for cancer cells to extend beyond the prostate (15,17). Similar to the findings of Fleshner *et al.*, we found that nearly all our patients (4/5, 80%) with EPE/SVI also had concurrent PNI. PNI is believed to not only be a mechanism for PCa extension, but is also considered a marker for more aggressive neoplastic biology (18). Fromont *et al.* found that cancer cells in areas of PNI exhibited increased proliferation, as well as increased EGFR and CD74 expression (19). Recent radical prostatectomy, brachytherapy, and external beam radiotherapy series have found PNI to be independently associated with increased risk of biochemical relapse (9). In

one study, men with low-risk disease and PNI on prostate biopsy were shown to have a 4–5 times greater risk of harboring higher grade and/or higher volume disease than men without PNI on biopsy (15). DeLancey *et al.* reported on 3,226 patients who underwent radical prostatectomy, of which 20% had PNI on biopsy. Patients with PNI on biopsy were more likely to have EPE (35.9% *vs.* 12.8%), SVI (14.1% *vs.* 3.2%), positive surgical margins (26.5% *vs.* 16.4%), and positive lymph nodes (2.5% *vs.* 0.5%; all P<0.01) (20). Additionally, it has been found that men with PNI detected on biopsy tend to have more cores with cancer (9). PNI on prostate biopsy is also associated with a shorter time to disease progression on confirmatory biopsy, and failure of active surveillance (9). Although most studies involving PNI have been limited to biopsies obtained via standard techniques, a recent study showed greater detection of PNI by TB compared to SB (7). Another study showed the presence of PNI on TB to be associated with EPE on radical prostatectomy and early biochemical recurrence (6). Despite the association between PNI and high risk features there is still debate over its status as an independent risk factor for adverse pathologic features and worse survival outcomes after radical prostatectomy (18,21).

As might be expected, all five patients in our series with EPE/SVI identified on MRI/US fusion TB had associated preoperative high risk factors. The average PSA for our five patients was 17 ng/mL and 4/5 (80%) patients had Grade Groups 4 or 5 disease, which has a predicted 5-year biochemical risk-free survival of 48% and 26%, respectively (8,22,23). In addition, all patients had a PIRADS score of 4 or 5, indicating a high likelihood of clinically significant cancer (24). One of our patients underwent only TB due to MRI suspicion of SVI. In this case only four targeted cores were obtained and both EPE and SVI were diagnosed. These findings were confirmed on radical prostatectomy. This case illustrates the advantage of TB in diagnosing aggressive diseases while minimizing the number of cores and invasiveness of the biopsy procedure.

Limitations of this study include that it is retrospective in nature and presents data on a very limited number of patients. A multi-institutional study involving a larger cohort of patients who underwent both standard and TB would be ideal to assess the incidence of EPE and SVI detection using an MRI/US targeted technique.

Conclusions

Based on our small series, we hypothesize that MRI/US fusion TB outperforms SB in the identification of EPE and SVI. However, given the small sample size and the overall rarity of these pathologic findings on prostate biopsy, further validation is needed.

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None.

Footnote

Conflicts of Interest: JW Nix and S Rais-Bahrami serve as consultants for Philips/InVivo Corp.

Ethical Statement: The study was approved by the institutional review board of the University of Alabama at Birmingham (NO. X140724007) with approval of waiver of informed consent.

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