Histopathological Analysis of False-positive Lesions in mpMRI/TRUS Fusion Prostate Biopsy

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Abstract. *Background/Aim:* Multi-parametric magnetic resonance imaging (mpMRI)/ultrasonography fusion prostate biopsy (FB) is a more accurate method of diagnosis than conventional prostate biopsy, but false-positive lesions still exist. Limited studies have examined the cause of false-positive lesions by histological analysis. *Patients and Methods:* We examined 322 patients who underwent mpMRI/transrectal ultrasonography (TRUS) FB. We classified prostate imaging-recording and data system (PI-RADS) 3 and PI-RADS 4-5 as low PI-RADS lesions and high PI-RADS lesions, respectively. In total, 105 lesions were identified as false-positive lesions. We performed histological analysis of atrophy, hyperplasia, and lymphocyte infiltration in these lesions, comparing low PI-RADS lesions and high PI-RADS lesions. *Results:* The frequencies of prostate hyperplasia and lymphocyte infiltration were higher in high PI-RADS lesions than in low PI-RADS lesions ($p=0.028$ and 0.024 , respectively). There was no significant difference regarding atrophy ($p=0.295$). *Conclusion:* Histopathological change may be one of the reasons for false-positive lesions.

The standard method of diagnosing prostate cancer (PCa) is transrectal ultrasonography (TRUS)-guided prostate biopsy (PB). However, TRUS-guided PB often fails to detect PCa

because of insufficient ability to distinguish malignant tissues from benign prostatic tissues (1). Furthermore, PB is a stressful and painful examination. To improve the accuracy of PCa detection and reduce unnecessary biopsies, multiparametric magnetic resonance imaging (mpMRI) has been used in the past decade (2). Further, for the standardised reporting of mpMRI, the Prostate Imaging-Recording and Data System (PI-RADS), was introduced in 2012 (3). Several recent clinical studies have shown that fusion-guided prostate biopsy (FB), which combines mpMRI with TRUS-guided PB, is a superior method compared to the conventional TRUS-guided PB (4, 5). Indeed, we previously reported that FB improved the accuracy of the detection of clinically significant PCa (6).

Although the accuracy of PB has improved, false-positive lesions exist that are suspicious for PCa on mpMRI but not diagnosed as PCa by PB. A recent study reviewed the technical reasons for false-positive lesions (7). Meanwhile, several studies reported the impact of histological alterations on the PI-RADS score. Recent studies showed that 18% of PI-RADS 5 lesions (18/98) were identified as non-cancerous lesions, and inflammatory changes were observed in 28% (5/18) of the false-positive lesions (8). One study reported that chronic inflammation and basal cell hyperplasia are associated with lesions falsely suspicious for PCa by comparing target biopsy tissues with standard biopsy tissues (9). Another recent study showed that histological changes such as stromal, glandular, vascular, and inflammatory alterations were observed in false-positive lesions by comparing target biopsy tissues with standard biopsy tissues (7). These findings indicate that histological alterations may influence the PI-RADS score. However, there are few reports on the histopathological analysis of false-positive lesions. Therefore, we focused on the histopathological changes in false-positive lesions comparing low PI-RADS lesions with high PI-RADS lesions. The pathological findings of atrophy, hyperplasia, and

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Key Words: Prostate cancer, fusion biopsy, PI-RADS, false positive.

Figure 1. Representative images of multiparametric MRI/ultrasonography fusion biopsy. Image of multiparametric MRI. Circle: region of interest. Line: biopsy line. (B) Image of transrectal ultrasonography. Circle: region of interest. Line: biopsy line.

lymphocyte infiltration are often observed in tissues from PB. Therefore, in this study, we performed histopathological analysis of the false-positive lesions to clarify the mechanism of the different findings between mpMRI and PB.

Patients and Methods

Patient characteristics. The patients with elevated prostate-specific antigen (PSA) levels were found to have lesions suspicious of PCa on mpMRI and subsequently received mpMRI/ultrasonography FB (Figure 1) together with additional 10-core systematic biopsies. Between February 2015 and January 2019, we performed mpMRI/ultrasonography FB in 322 patients at Hiroshima University Hospital. Two radiologists reassessed all MRI scans according to PI-RADS version 2.1 (10). We identified 322 PI-RADS scores in 322 patients. When multiple PI-RADS scores were found by mpMRI, we considered the highest PI-RADS score as the representative PI-RADS score in each patient. Seven urologists performed FB with the help of the Trinity® Image-Fusion system (Koelis, Grenoble, France). FB was performed with the patient in the lithotomy position by the transrectal approach under local anaesthesia. We punctured 2-4 cores per each representative PI-RADS 1-5 lesion. A single urologist (author) compared all specimens histopathologically, stained them with hematoxylin and eosin, and scored them in terms of atrophy, hyperplasia, and lymphocyte infiltration. They were rated using a three-grade scale: high, middle, and low.

Statistical analysis. All statistical analyses were performed using JMP Pro version 13 (SAS institute Inc, Cary, NC, USA). Comparisons between patient groups were assessed using the Chi-square test. p -Values <0.05 were considered significant.

Results

Among the 322 patients, 46 were excluded because they showed PI-RADS 1-2. Seventy-nine showed low PI-RADS

lesions, and 26.6% of them (21/79) were diagnosed as PCa. The other 73.4% (58/79) of the lesions were false-positive lesions. In contrast, 197 patients showed high PI-RADS lesions, and 76.1% of them (150/197) were pathologically diagnosed as PCa. The other 23.1% (47/197) of the lesions were false-positive lesions. In total, 105 lesions were identified as false-positive lesions (Figure 2). Table I shows the clinical features of the 105 false-positive lesions. The 47 high PI-RADS lesions included 37 PI-RADS 4 lesions and 10 PI-RADS 5 lesions. A comparison of the characteristics of the patients with high PI-RADS and low PI-RADS lesions showed median patient ages of 69 (range=37-86 years) and 69 (range=53-81 years), median patient PSA values of 7.9 ng/ml (range=0.6-31.4 ng/ml) and 6.1 (range=1.6-22.9 ng/ml), and median prostate volumes of 53.0 ml (range=25.3-128.2 ml) and 52.2 (range=24.4-138.5 ml), respectively. There were no significant differences in the values of age, PSA, and prostate volume between the patients with low PI-RADS lesions *versus* those with high PI-RADS lesions ($p=0.512$, 0.076 , and 0.336 , respectively).

We performed histopathological analysis of the false-positive lesions mainly focusing on atrophy, hyperplasia, and lymphocyte infiltration. Representative images of atrophy, hyperplasia, and lymphocyte infiltration are shown in Figure 3. We rated each lesion on a three-grade scale as high: 3 points, middle: 2 points, and low: 1 point. The results of the histopathological differences between the low PI-RADS lesions and high PI-RADS lesions are shown in Table II. The values for hyperplasia and lymphocyte infiltration were higher in the high PI-RADS lesions than those in the low PI-RADS lesions ($p=0.028$ and 0.024 , respectively). There was no significant difference for atrophy ($p=0.295$) between the two lesion types.

Figure 2. Flow chart of patient selection.

Table I. Clinical features of false positive lesions.

	PI-RADS low lesions	PI-RADS high lesions	<i>p</i> -Value
The number of patients	58	47	
PI-RADS 3	58		
PI-RADS 4		37	
PI-RADS 5		10	
Median age (range)	69 (53-81)	69 (37-86)	0.512
Median PSA value [ng/ml] (range)	6.1 (1.6-22.9)	7.9 (0.6-31.4)	0.076
Median prostate volume [ml] (range)	52.2 (24.4-138.5)	53.0 (25.3-128.2)	0.336

PI-RADS: Prostate Imaging-Recording and Data System.

Discussion

Although the PROMIS study, one of the key clinical trials, has shown that FB is more sensitive for the diagnosis of clinically significant cancer (93%) than conventional PB (41%) (4), false-positive lesions exist. Our report showed that the values for hyperplasia and lymphocyte infiltration were higher in high PI-RADS lesions than in low PI-RADS lesions. To the best of our knowledge, this study is the first to histopathologically analyse low PI-RADS lesions in comparison with high PI-RADS lesions in FB.

Prostatic intra-epithelial neoplasia (PIN) and proliferative inflammatory atrophy (PIA) are widely known to be precursors of PCa (11). Several studies have shown that disruption of the basal cell layer is indicated as a cause of

Table II. Average value of histopathological parameters in prostate with false-positive patients from FB.

	PI-RADS low lesions n=58	PI-RADS high lesions n=47	<i>p</i> -Value
Atrophy			
Low (1 points)	5	6	
Middle (2 points)	22	23	
High (3 point)	31	18	
Average value	2.448	2.255	0.295
Hyperplasia			
Low (1 points)	18	5	
Middle (2 points)	24	21	
High (3 point)	16	21	
Average value	1.966	2.340	0.028
Lymphocyte infiltration			
Low (1 points)	12	8	
Middle (2 points)	23	21	
High (3 point)	23	18	
Average value	1.810	2.213	0.024

PI-RADS: Prostate Imaging-Recording and Data System; FB: prostate biopsy.

cancer, inflammation, and high-grade PIN (12, 13). It has been shown that atrophy and inflammation can be the precursors of high-grade PIN and PCa (11). Hyperplasia and lymphocyte infiltration that is caused by chronic inflammation might also influence prostate carcinogenesis (11). These findings indicated that hyperplasia and lymphocyte infiltration may be possible precursors of PCa. In our study, the values of hyperplasia and lymphocyte infiltration were higher in the high PI-RADS lesions than in the low PI-RADS lesions,

Figure 3. Representative images of hematoxylin and eosin staining of atrophy, hyperplasia, and lymphocyte infiltration. (A) Atrophy. Grade 1: glands showing a lobular pattern. Grade 2: glands with partial atrophy. Grade 3: glands with atrophy. Magnification 40 $\times$. (B) Hyperplasia. Grade 1: uniform and less basophilic-appearing basal cells. Grade 2: variably sized basophilic glands. Grade 3: glands showing emphasised and darken basophilic basal cells. Magnification 40 $\times$. (C) Lymphocyte infiltration. Grade 1: low infiltration of inflammatory cells. Grade 2: inflammatory cells in the stroma. Grade 3: greater presence of inflammatory cells in stroma that are darker. Magnification 40 $\times$.

suggesting that hyperplasia and lymphocyte infiltration as precursors of PCa may affect the PI-RADS score.

PI-RADS includes scores of mpMRI of three images, T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced imaging (3). Considering the mechanism of MRI, the density of water molecules affects the score of DWI. Tissues with high water content cause an increased signal on T2 weighted imaging (14). One report showed that an open cellular architecture such as that in cribriform tumours could allow water molecules to move more easily (15). The status of a dense cellular pattern in hyperplasia and lymphocyte infiltration can also influence the score of DWI. These findings may help to explain the reason why the values of hyperplasia and lymphocyte

infiltration were higher in high PI-RADS versus low PI-RADS lesions.

This study has some limitations. First, this study is retrospective, and the number of specimens is limited. Second, multiple surgeons (seven urologists) performed FB. As mentioned in the introduction, technical errors influence the ratio of false-positive lesions. Lesions detected on mpMRI may not be perfectly comparable with those detected with FB.

Conclusion

Prostate hyperplasia and lymphocyte infiltration were more frequently observed in high PI-RADS lesions than in low PI-RADS lesions. Histopathological change might be one of the

reasons for false-positive lesions along with surgical proficiency, the context of the target biopsy of mpMRI, and other background factors.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

YS, and NH designed the study. TB, KK, HK, KI, KG, and TH provided patients' clinical information. RY, JT, YT, YH, and KA performed experiments and acquired data. YH and YT interpreted the results. RY drafted the manuscript. YS edited the article. All Authors approved the final content for journal submission and publication.

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