Original Article

# Prostate cancer detection using MRI ultrasound fusion-guided biopsy compared with saturation biopsy in patients with prior negative biopsies in King Chulalongkorn Memorial Hospital

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Magnetic resonance imaging ultrasound fusion-guided prostate biopsy,
Prostate cancer,
Saturation biopsy,
Prior negative biopsy

## Abstract

**Objective:** To compare prostate cancer (PCa) detection between MRGB and SB in patients with a history of at least one prior negative prostate biopsy and prostate-specific antigen (PSA) ≥4 ng/ml.

**Material and Method:** Between November 2015 and December 2018 a total of 82 men with prior negative biopsies and persistent elevated PSA underwent MRGB combination with subsequent SB in our institution. Their charts were retrospectively reviewed. In our institution, MRGB was performed on the lesions that scored 3-5 by Prostate Imaging Reporting and Data System (PI-RADS) on MRI. The primary outcome was PCa detection. Secondary outcomes were the detection rate of significant PCa (Gleason ≥7), histopathologic details of biopsy, and complication rate. Sensitivity, specificity, negative predictive values (NPVs), and positive predictive values (PPVs) were reported.

**Result:** Of 82 men, 39 (47.6%) had PCa. Overall the PCa detection rate was 37.8% by MRGB and 31.7% by SB (95% confidence interval for the difference, -6.0% to 18.1%; p = 0.27). The estimated sensitivity of MRGB and SB for overall PCa detection was 79.5% and 66.7%, respectively. The highest positive rate was among PI-RADS with a score of 5 (80%), followed by a score of 4 (26%) and 3 (12%).

**Conclusion:** In a repeat biopsy setting, PCa detection rate by MRGB was better than SB insignificantly in our institution. MRGB was also found to have better sensitivity to overall PCa detection than SB.

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## Introduction

Prostate cancer (PCa) incidence is highly variable around the world. In Thailand, PCa is the fourth most common cancer in men[1]. PCa is clinically suspicious in men who have had an abnormal digital rectal examination (DRE), or have elevated serum prostate-specific antigen (PSA). Definite diagnosis of PCa still requires tissue for pathological verification. Transrectal ultrasound (TRUS)-guided biopsy, which typically obtains 10-12 cores of prostate tissue, was once accepted by urologists as the standard technique[1]. PCa detection rate by an initial TRUS-guided biopsy is about 30-50%[2-4]. Nevertheless, a significant proportion of men with previous negative biopsies and persistently elevated serum PSA still have a concern for PCa. This situation is a common scenario which typically causes a dilemma for urologists.

Saturation biopsy (SB) is similar to TRUS-guided biopsy, except total cores obtained from SB are typically more than twelve[5]. This concept has been proposed with an intention to improve PCa detection by increasing the total core numbers. SB was reported to improve the PCa detection rate[5]; in contrast, some researchers have reported opposite results[6].

In recent years, multiparametric magnetic resonance imaging (mpMRI) has emerged as a new diagnostic tool that improves PCa detection ability. Consequently, MRI-guided targeted biopsy has recently become an alternative approach to standard TRUS-guided biopsy in the setting of repeat biopsy. Many guidelines suggest the use of MRI-guided targeted biopsy in men with persistently elevated PSA despite prior negative biopsies[7,8]. At the present time, there are 3MRI techniques for guided targeted biopsy: (1) Direct “In bore” MRI-guided biopsy; (2) Cognitive fusion guided biopsy; and (3) MRI ultrasound fusion-guided biopsy (MRGB)[9,10].

At our institution, we have used MRGB combined with SB in the setting of repeat biopsy. However, comparative efficacy between both techniques remains unclear. Therefore, this retrospective study was designed to compare the PCa detection rates between these two approaches.

## Material and Method

### Study Design and Study Population

We retrospectively reviewed charts between November 2015 and December 2018.A total of 105 men with elevated PSA (≥4 ng/ml) had MRI ultrasound fusion-guided prostate biopsy with subsequent saturation biopsy. All patients who had at least one negative prostate biopsy and persistently elevated serum PSA values ≥4 ng/ml were enrolled in this study. Patients were excluded from the study if they (1) were known PCa, (2) had no history of previous prostate biopsy, (3) had MRI ultrasound fusion guided biopsy in either PI-RADs score 1 or 2 lesions detected from MRI, (4) had no subsequent saturation prostate biopsy after MRI ultrasound fusion guided biopsy and (5) total core number of saturation biopsy ≤12 cores. The 82 patients who met these criteria constituted our analytic dataset.

### Study Endpoints

The primary outcome was the overall PCa detection rate. Secondary outcomes included (1) the distribution of the highest Gleason scores; (2) the detection rate for significant PCa, defined as PCa with Gleason score ≥7; (3) the positivity rate among lesion scores detected bympMRI; (4) the statistical performance of MRGB and SB; (5) the complication rate.

### Imaging

Subjects in our study underwent mpMRI performed with a 3 Tesla without endorectal coil. The imaging protocol included T1 and T2 weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast enhanced (DCE) imaging. Lesions that were detected from mpMRI were scored by the radiologists using the Prostate Imaging Reporting and Data System (PI-RADS) version 2 classification: from 1 (low) to 5 (high) according to the likelihood of PCa being present[11]. From our review, only 2 radiologists performed the scoring in our study.

### Interventions

Subjects that met our study criteria were hospitalized before the operation date at least one day. General anesthesia or regional anesthesia by spinal block was chosen for the procedure by the anesthetists. Subjects were placed in the lithotomy position. MRGB was performed initially. SB was performed afterwards. MRGB was performed on lesions with PI-RADS version 2 scores from 3 to 5.

SB was then performed with at least 10 cores for each prostatic lobe, 20 cores totally. Urethral catheter was indwelt in all of the subjects and removed on the next day.

### Histology

Gleason scoring of the subjects in our study was performed independently by 3 experienced pathologists and followed the recommendations of the 2005 consensus conference of the International Society of Urological Pathology.

### Statistical Analysis

The data analysis was performed using Stata version 15.1 (Stata Corp., College Station, TX, USA). For the descriptive analysis, the frequencies of categorical variables were calculated, while the median, interquartile range (IQR) or mean and standard deviation (SD) were calculated for continuous variables as appropriate. Median and mean between the 2 groups were compared and evaluated using the Wilcoxon rank sum test or the independent two-sample t-test as appropriate, and the Chi square test for categorical data. The sensitivity, specificity, PPV, NPV and ROC area with 95% confidence intervals (CI), were calculated for the MRGB and SB using prostate cancer detection as the gold standard. We comparedthe ROC area between MRGB and SB using the chi-square test. We compared dis-concordance between MRGB and SB using McNemar's test. Youden's index was estimated for the probability of an informed decision for MRGB and SB. P-Values of less than 0.05 were considered statistically significant.

## Result

### Patient Baseline Characteristics

A total of 82 men were enrolled in our study for analysis: 39 men were found to have prostate cancer by either MRI ultrasound fusion-guided biopsy (MRGB) or saturation biopsy (SB). All patients were Thai, except for one Cambodian. Mean age (SD) at the time of biopsy was 66.9 (6.5) years. Median serum PSA and PSA density (PSAD) were 13.1 ng/ml (interquartile range [IQR]: 10.5-17.5) and 0.34 ng/ml$^2$ (IQR: 0.26-0.47), respectively. Median prostate volume was 59.5 ml (IQR: 41.8-82.3). Most men included in our study had a history of negative biopsy, 1-2 times and most had 1-2 suspicious lesions for PCa on mpMRI. Other baseline characteristics are listed in Table 1.

### Primary Outcomes (Overall PCa Detection Rate)

MRI ultrasound fusion-guided biopsy (MRGB) did not significantly improve the overall PCa detection rate compared to saturation biopsy (SB) (MRGB vs. SB; 37.8% vs 31.7%, p=0.27). Nevertheless, MRI ultrasound fusion-guided biopsy (MRGB) with subsequent saturation biopsy did significantly improve the overall PCa detection rate when compared with both biopsy techniques (MRGB+SB vs. MRGB; 47.6% vs 37.8%, p=0.008), (MRGB+SB vs. SB; 47.6% vs 31.7%, p<0.001). Comparison of the ROC area between MRGB and SB is shown in Figure 1.

### Secondary Outcomes

### Distribution of the Highest Gleason Scores by Each Technique

Prostate cancer was detected in 39 men by either MRGB or SB, with 4 (10%) men classified as low-risk, 27 (70%) men classified as intermediate risk, and 8 (20%) men classified as high risk. Overall percentage distribution of the highest Gleason scores by MRGB alone or SB alone or MRGB + SB is shown in Table 2. For overall PCa detection, MRGB alone missed 8 (20%) tumors, whereas 13 (33%) tumors were missed by SB alone. The concordance between MRGB and SB was 62.2 % (51/82), as shown in Table 3.

**Table 1.** Patient baseline characteristics.

| | Total (N=82) | No PCa (N=43) | PCa (N=39) | p=value |
|---|---|---|---|---|
| Mean (SD) Age at biopsy (years) | 66.9 (6.5) | 66.1 (6.7) | 67.9 (6.2) | 0.21 |
| Median (IQR) PSA before operation | 13.1 (10.5-17.5) | 13.3 (9.2-22.7) | 12.9 (10.5-17.5) | 0.82 |
| Median (IQR) PSAD | 0.34 (0.26-0.47) | 0.34 (0.24-0.58) | 0.33 (0.27-0.45) | 0.83 |
| Prostate volume | | | | <0.001 |
| <30 ml | 9 (11) | 1 (2.3) | 8 (20.5) | |
| 30-50 ml | 21 (25.6) | 6 (14) | 15 (38.5) | |
| >50 ml | 52 (63.5) | 36 (83.7) | 16 (41) | |
| Previous negative biopsy (n) | | | | 0.13 |
| 1 | 34 (41.5) | 13 (30.2) | 21 (53.9) | |
| 2 | 31 (37.8) | 20 (46.5) | 11 (28.2) | |
| 3 | 13 (15.9) | 8 (18.6) | 5 (12.8) | |
| 4 | 3 (3.7) | 2 (4.7) | 1 (2.6) | |
| 6 | 1 (1.2) | 0 (0) | 1 (2.6) | |
| Target lesions (n) | | | | 0.03 |
| 1 | 23 (28.1) | 7 (16.3) | 16 (41) | |
| 2 | 37 (45.1) | 21 (48.8) | 16 (41) | |
| 3 | 18 (22) | 11 (25.6) | 7 (18) | |
| 4 | 4 (4.9) | 4 (9.3) | 0 (0) | |
| Median (IQR) Total cores (n) | 36 (30-40) | 35 (31-41) | 34 (30-40) | 0.42 |

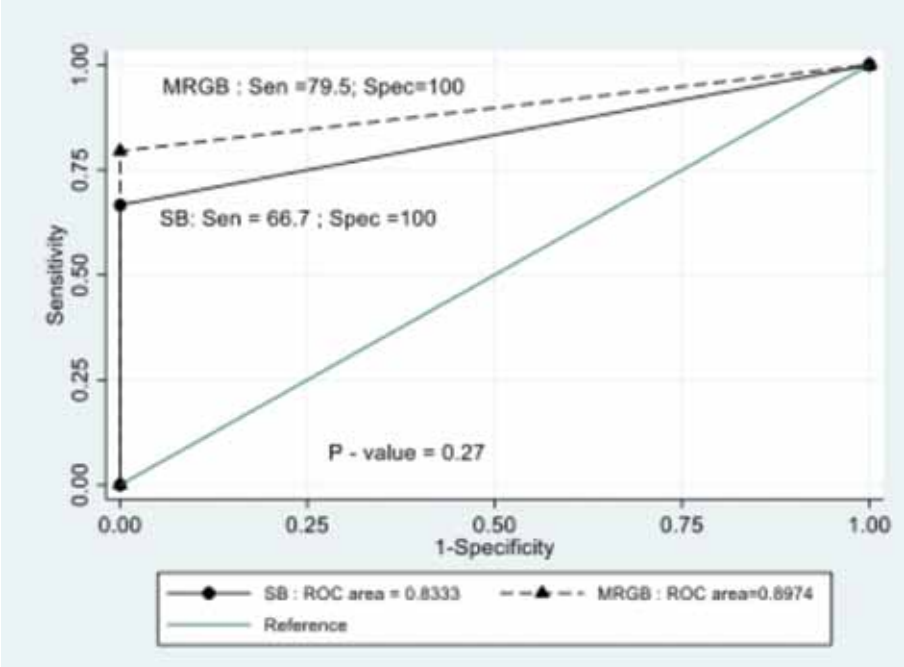


**Figure 1.** Comparison of the ROC area between MRGB and SB for overall PCa detection.

**Table 2.** Percentage distribution of the highest Gleason score by MRGB vs. SB vs. MRGB+SB.

| Gleason score | Frequency, % (n/N) | | |
|---|---|---|---|
| | MRGB | SB | MRGB + SB |
| 3 + 3 (Grade group 1) | 25.8 (8/31) | 34.6 (9/26) | 30.8 (12/39) |
| 3 + 4 (Grade group 2) | 48.4 (15/31) | 34.6 (9/26) | 38.5 (15/39) |
| 4 + 3 (Grade group 3) | 16.1 (5/31) | 19.2 (5/26) | 17.9 (7/39) |
| 4 + 4 (Grade group 4) | 6.5 (2/31) | 3.9 (1/26) | 7.7 (3/39) |
| 9 - 10 (Grade group 5) | 3.2 (1/31) | 7.7 (2/26) | 5.1 (2/39) |

MRGB = MRI ultrasound fusion-guided biopsy; SB = saturation biopsy

**Table 3.** Concordance between MRGB & SB.

| SB | MRGB | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | No cancer | GS 3 + 3 | GS 3 + 4 | GS 4 + 3 | GS 4 + 4 | GS 4 + 5 | GS 5 + 4 | GS 5 + 5 | |
| No cancer | 43 | 5 | 6 | 1 | 1 | 0 | 0 | 0 | 56 |
| GS 3 + 3 | 6 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 9 |
| GS 3 + 4 | 1 | 2 | 5 | 1 | 0 | 0 | 0 | 0 | 9 |
| GS 4 + 3 | 1 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 5 |
| GS 4 + 4 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| GS 4 + 5 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 2 |
| GS 5 + 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| GS 5 + 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 51 | 8 | 15 | 5 | 2 | 1 | 0 | 0 | 82 |

Concordance between MRGB and SB = 51/82 = 62.2%

MRGB detect cancer, but SB cannot detect cancer = 13/39 = 33.3%

MRGB cannot detect cancer, but SB detect cancer = 8/39 = 20%

MRGB detect lower grade cancer than SB = 7/39 = 18%

MRGB detect higher grade cancer than SB = 3/39 = 7.7%

**Significant PCa Detection Rate**

Significant prostate cancer (Gleason ≥7) was detected by either MRGB or SB in 27 (70%) men. The detection rate for significant PCa between MRGB and SB were comparable (MRGB vs SB; 28.1% vs 20.7%, *p*=0.11). Comparison of the ROC area between MRGB and SB for significant PCais shown in Figure 2.

**Positivity Rate Among Lesions With PI-RADS Score of 3-5 on mpMRI**

There were a total of 127 lesions classified as PI-RADS V2 score 3-5 detected on mpMRI. The highest percentage of prostate cancer was among lesions with PI-RADS V2 score of 5 (80%), followed by a score of 4 (26%), and those with a score of 3 (12%) (Figure 3). Percentage of clinically significant prostate cancer was highest among lesions with a PI-RADS V2 score of 5 (60%), followed by a score of 4 (18%). The lowest was among lesions with a PI-RADS V2 score of 3 (12%), as shown in Figure 4.

**Statistical Performance of MRGB and SB**

For overall PCa detection and significant PCa detection, the sensitivity, specificity and other parameters are shown in Table 3 and Table 4, respectively.

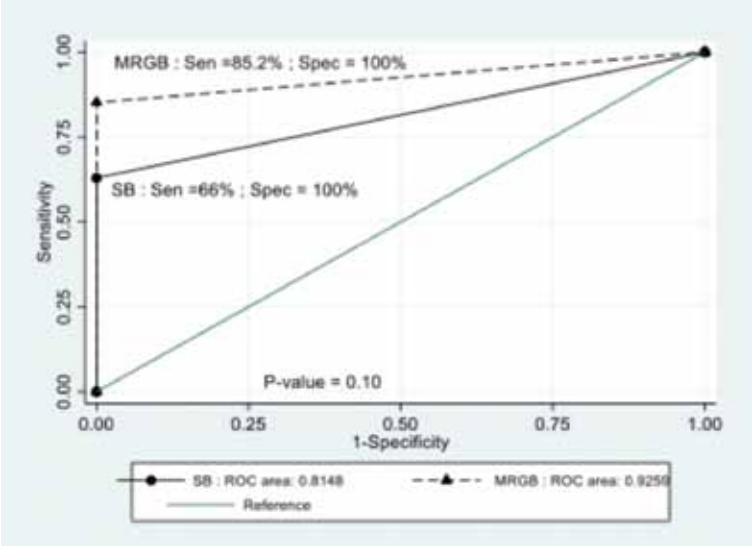


**Figure 3.** Positivity rate among lesions with PI-RADS score of 3-5 on mpMRI[1].

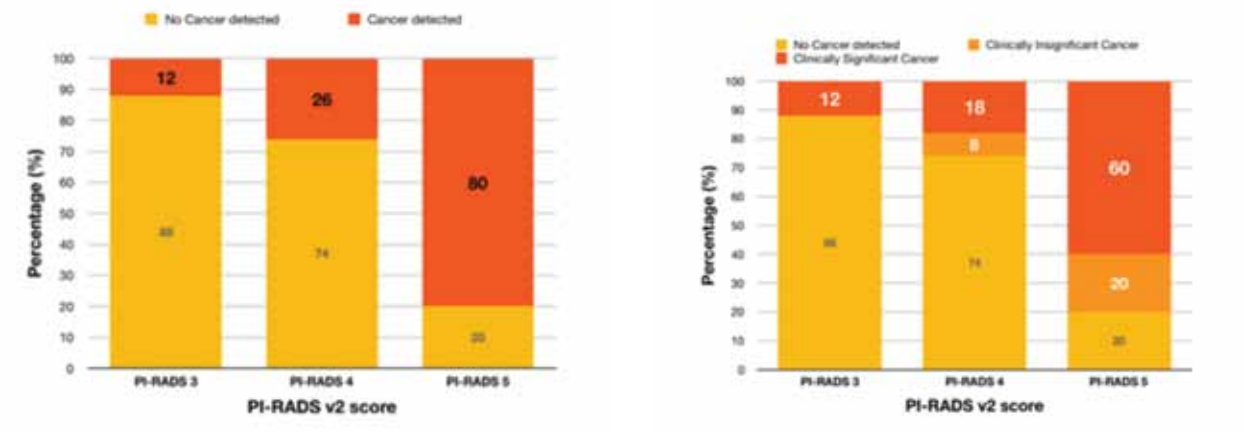


**Figure 4.** Positivity rate among lesions with PI-RADS score of 3-5 on mpMRI[2].

**Table 3.** Statistical performance of MRGB and SB to overall PCa detection.

| Parameter | Estimate | 95% confidence interval |
|---|---|---|
| Sensitivity: MRGB | 0.795 | 0.635 - 0.907 |
| Sensitivity: SB | 0.667 | 0.498 - 0.809 |
| Specificity: MRGB | 1.00 | 0.918 - 1.00 |
| Specificity: SB | 1.00 | 0.918 - 1.00 |
| PPV: MRGB | 1.00 | 0.888 - 1.00 |
| PPV: SB | 1.00 | 0.868 - 1.00 |
| NPV: MRGB | 0.843 | 0.714 - 0.930 |
| NPV: SB | 0.768 | 0.636 - 0.870 |

MRGB = MRI ultrasound fusion-guided prostate biopsy; SB = saturation biopsy;
PPV = positive predictive value; NPV = negative predictive value.

**Table 4.** Statistical performance of MRGB and SB to significant PCa detection.

| Parameter | Estimate | 95% confidence interval |
|---|---|---|
| Sensitivity: MRGB | 0.852 | 0.663 - 0.958 |
| Sensitivity: SB | 0.630 | 0.424 - 0.806 |
| Specificity: MRGB | 1.00 | 0.935 - 1.00 |
| Specificity: SB | 1.00 | 0.935 - 1.00 |
| PPV: MRGB | 1.00 | 0.852 - 1.00 |
| PPV: SB | 1.00 | 0.805 - 1.00 |
| NPV: MRGB | 0.932 | 0.835 - 0.981 |
| NPV: SB | 0.846 | 0.735 - 0.924 |

MRGB = MRI ultrasound fusion-guided prostate biopsy; SB = saturation biopsy;
PPV = positive predictive value; NPV = negative predictive value.

### Complication Rate

Three (4%) men were reported to develop sepsis after the biopsy. Two (2.4%) men were reported to have epididymo-orchitis. Urinary retention was reported to develop in 7 men after removing the urethral catheter on post-operative day 1. No prostatic abscesses, major bleeding, or other severe complications that required surgical interventions occurred.

## Discussion

Our study results have failed to prove the benefit of MRGB over SB with the overall PCa detection rate by MRGB and SB equal to 37.8% and 31.7%, respectively. The explanation concerning why the result was not as we expected: SB in our institution performed subsequent to MRGB by the same operators caused bias. Nevertheless, when we compared the PCa detection rate using a combination of both MRGB and SB with either MRGB or SB alone, a combination of both techniques was significantly superior to either MRGB or SB alone.

Many recent studies have shown that MRGB has a higher PCa detection rate for significant PCa compared with the standard random prostate biopsy, but a lower detection rate for insignificant PCa.[12,13] In contrast, our study results show that MRGB and SB are comparable in detecting significant PCa.

Many urologists at out institution question the necessity of performing MRGB with subsequent SB.In our experience, when men are diagnosed with low-grade PCa or clinically insignificant PCa, a large proportion of themare prone to choose an aggressive radical surgery rather than active surveillance, despite the urologist's advice. As a consequence, data from recent studies have shown that MRGB can miss low-grade PCa[12,13]; we performed subsequent SB after MRGB to eliminate the possibility of missing low-grade PCa as much as we could.

Our study showed that the highest positivity rate was among PI-RADS with a score of 5 (80%), followed by those with a score of 4 (26%), and those with a score of 3 (12%). In contrast, PRECISION trial has reported the data differently: the highest percentage of men with PCa among men with a PI-RADS score of 5 (94%), followed by those with a score of 4 (69%), and those with a score of 3 (34%)[14]. Interestingly, the positivity rates among PI-RADS with a score of 3 and 4 from the PRECISION trial were markedly higher than the results from our study. Thus, 2 questions have come into view. First, do we really need to perform the targeted biopsy at the lesions classified as PI-RADS with a score of 3? Second, why were the positivity rates among PI-RADS with a score of 4 lesions so different?

Our study has a lot of limitations. First, performing MRGB prior to SB undoubtedly had an influence on the diagnostic performance of SB. The bleeding areas from MRGB might have guided the operator to target SB, especially at these areas. Second, the operators who performed MRGB and subsequent SB were the same persons. These factors can explain why there was no significant difference in overall PCa detection between MRGB and subsequent SB. Third, there was a marked variation of sites where SB was performed among the operators. And lastly, our study was retrospective in nature.

Data from our study showed no benefit of MRGB over SB in the overall PCa detection rate. Further prospective studies should be conducted in order to eliminate the risk of bias in the near future.

## Conclusion

In a repeat biopsy setting, the PCa detection rate by MRGB was better than SB insignificantly. MRGB was also found to have better sensitivity to overall PCa detection than SB.

## Conflict of interest

The authors declare no conflict of interest.

### References

1. Lojanapiwat B. Urologic cancer in Thailand. Jpn J Clin Oncol 2015;45:1007-15.
2. Serag H, Banerjee S, Saeb-Parsy K, Irving S, Wright K, Stearn S, et al. Risk profiles of prostate cancers identified from UK primary care using national referral guidelines. Brit J Cancer 2012;106:436-9.

3. Cormio L, Scattoni V, Lorusso F, Perrone A, Di Fino G, Selvaggio O, et al. Prostate cancer detection rates in different biopsy schemes. Which cores for which patients? World J Urol 2014;32:341-6.
4. Arsov C, Rabenalt R, Blondin D, Quentin M, Hiester A, Godehardt E, et al. Prospective Randomized Trial Comparing Magnetic Resonance Imaging (MRI)-guided In-bore Biopsy to MRI-ultrasound Fusion and Transrectal Ultrasound-guided Prostate Biopsy in Patients with Prior Negative Biopsies. European Urology 2015;68:713-20.
5. Stewart CS, Leibovich BC, Weaver AL, Lieber MM. Prostate cancer diagnosis using a saturation needle biopsy technique after previous negative sextant biopsies. J Urology 2001;166:86-91.
6. Ashley RA, Inman BA, Routh JC, Mynderse LA, Gettman MT, Blute ML. Reassessing the diagnostic yield of saturation biopsy of the prostate. European Urology 2008;53:976-83.
7. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 2014;65:124-37.
8. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. European Urology 2017; 71:618-29.
9. Logan JK, Rais-Bahrami S, Turkbey B, Gomella A, Amalou H, Choyke PL, et al. Current status of magnetic resonance imaging (MRI) and ultrasonography fusion software platforms for guidance of prostate biopsies. BJU International 2014;114:641-52.
10. Raskolnikov D, Rais-Bahrami S, Turkbey B, Rastinehad AR, Choyke PL, Wood BJ, et al. Current Ability of Multiparametric Prostate Magnetic Resonance Imaging and Targeted Biopsy to Improve the Detection of Prostate Cancer. Urol Pract 2014;1:13-21.
11. Barentsz JO, Weinreb JC, Verma S, Thoeny HC, Tempany CM, Shtern F, et al. Synopsis of the PI-RADS v2 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging and Recommendations for Use. Eur Urol 2016;69:41-9.
12. Fütterer JJ, Briganti A, De Visschere P, Emberton M, Giannarini G, Kirkham A, et al. Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance Imaging? A Systematic Review of the Literature. European Urology 2015;68:1045-53.
13. Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015;313:390-7.
14. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. New England Journal of Medicine 2018;378:1767-77.