SCANDINAVIAN JOURNAL OF UROLOGY
2021, VOL. 55, NO. 1, 27–32
https://doi.org/10.1080/21681805.2020.1849390

ARTICLE

# Postoperative change in Gleason score of prostate cancer in fusion targeted biopsy: a matched pair analysis

M. Apfelbeck[a], S. Tritschler[a,b], D.-A. Clevert[c], A. Buchner[a], M. Chaloupka[a], A. Kretschmer[a], A. Herlemann[a], C. Stief[a] and B. Schlenker[a]

[a]Department of Urology, LMU Klinikum, Ludwig-Maximilians-University Munich, Munich, Germany; [b]Department of Urology, Loretto Hospital, Freiburg, Germany; [c]Department of Clinical Radiology, Interdisciplinary Ultrasound-Center, LMU Klinikum, Ludwig-Maximilians-University Munich, Munich, Germany

**ABSTRACT**

**Objective:** To evaluate if MRI/ultrasound fusion based targeted biopsy (FBx) leads to a reduced rate of change in Gleason score (GS) compared to prostatectomy specimen.

**Methods:** The histopathological findings of the biopsy of the prostate and the radical prostatectomy (RP) specimen of 210 patients who were referred to our hospital between 2012 and 2017 were compared retrospectively in this study. One hundred and five patients who underwent FBx combined with ultrasound-guided 12-core biopsy of the prostate (SBx) were matched with 105 patients who underwent SBx only. This study evaluated the rate of up- or downgrading in the RP specimen in both groups and compared the results *via* matched pair analysis.

**Results:** Concordance in Gleason grade group (GGG) was found in 52/105 patients (49.5%) in SBx and in 49/105 patients (46.7%) with FBx ($p = 0.679$). The rate of downgrading was statistically significant ($p = 0.014$) and was higher in the FBx group (14/105 patients, 13.3%) than in the SBx group (4/105 patients, 3.8%). A higher rate of upgrading was seen in SBx (49/105 patients; 46.7%) compared to FBx (42/105 patients; 40%), with no statistical significance ($p = 0.331$). The change in GGG from biopsy to final pathology in patients with GGG 1 and 2 at biopsy level was not statistically significant ($p = 0.168$).

**Conclusion:** FBx does not decrease the rate of upgrading between biopsy and final pathology in RP specimens. Our results indicate that FBx tends to overestimate the final GGG compared to SBx.

**ARTICLE HISTORY**
Received 29 May 2020
Accepted 5 November 2020

**KEYWORDS**
Prostate cancer; Gleason score; upgrading; radical prostatectomy; MRI/ultrasound fusion-based targeted biopsy; 12-core random biopsy

## Introduction

New diagnostic approaches and the widespread use of prostate specific antigen (PSA) screening led to an increased incidence of low-risk tumors among prostate cancer (PCa). Therefore, new treatment options like active surveillance (AS) or focal therapy (FT) are gaining more importance as therapeutic options for low-risk PCa to avoid overtreatment and negative impact on quality-of-life caused by radical prostatectomy (RP) and radiotherapy.

Treatment selection for patients with PCa depends on the individual patient's risk stratification which is greatly based upon Gleason grade group (GGG) in biopsy, clinical T-stage and PSA level [1]. However, GGG upgrading is a well-known phenomenon, especially in low-risk tumors [2–5]. The identification of the accurate GGG in patients with low-risk tumor is gaining greater importance in the last years, with an increase in men undergoing AS instead of RP or external beam radiotherapy with the potential risk of undertreatment.

There are several studies evaluating clinical predictors of GGG upgrading in RP specimen [6,7]. Predictors associated with a higher risk of GGG upgrading include high PSA-levels, small prostate volume, PSA density, number of positive cores and patient age over 75 years [6–8]. However, only a few studies exist evaluating the risk of upgrading of GGG in MRI/ultrasound fusion-based targeted biopsy [9–12]. The efficiency of mpMRI is already proven as several studies could show a superiority of mpMRI to detect more clinically significant cancer compared to the systemic biopsy [13–15].

In the present study, we aimed to evaluate the risk of change in GGG in the MRI/ultrasound fusion-based targeted biopsy (FBx) of the prostate compared to the standard transrectal ultrasound guided 12-core biopsy (SBx) in the RP specimen. Various studies exist evaluating the change of GGG in patients undergoing a MRI-guided targeted biopsy of the prostate as well as SBx in the same patient. The unique characteristic of the presented study is that the patients with FBx were matched pairwise with patients who underwent SBx solely.

## Subjects and methods

### *Patient selection and data collection*

Out of a database with 2,585 patients between 2013 and 2017, 210 were diagnosed with PCa by either FBx or SBx and

CONTACT M. Apfelbeck Maria.Apfelbeck@med.uni-muenchen.de Department of Urology, LMU Klinikum, Ludwig-Maximilians-University Munich, Marchioninistr. 15, Munich 81377, Germany

received radical prostatectomy at our facility (Figure 1). We categorized patients into two groups based upon the diagnostic pathway: FBx or SBx. In each group, the histopathological findings of 105 patients were evaluated. In the FBx group, only patients with a positive mpMRI-targeted biopsy were included.

We reviewed clinical patient characteristics like patient age, PSA-level, prostate volume, number of cores taken in total and number of positive cores as well as preoperative GGG in prostate biopsy and pathologically data from RP specimen including GGG, T-, N-stage and surgical margin status.

### *mpMRI and MRI/ultrasound fusion-based targeted biopsy*

One hundred and five patients received an mpMRI due to clinical suspicion of PCa (elevated PSA and/or abnormal digital rectal examination) or after negative randomized 12-core transrectal ultrasound-guided biopsy of the prostate and persisting suspicion of PCa. Lesions in the mpMRI were classified according to the Prostate Imaging-Reporting and Data System (PI-RADS) version 2 [16]. Only patients with a PIRADS 3, 4 or 5 lesion underwent FBx. The mpMRI was performed by altogether 62 different referring radiologic institutes. All images were re-evaluated by a single radiologist with special expertise in mpMRI of the prostate. In every patient a randomized 12-core ultrasound-guided biopsy of the prostate was performed additionally to the FBx according to current guidelines [1]. The FBx as well as the SBx were performed transrectally using an end-fire probe.

Image fusion was done software-assisted using the Philips Percunav® device (Philips Medical Systems, Bothell, WA). The DICOM data set of the mpMRI was uploaded on the ultrasound device. Registration of the two image modalities was performed by plane wise fusion of the ultrasound and mpMRI. For image fusion the axial T2-weighted MRI-sequence was used. From every target lesion a minimum of two cores and a maximum of four cores were taken depending on the size of the target and the accordance of the two image modalities after fusion.

### *Standard 12-core randomized transrectal ultrasound-guided biopsy of the prostate*

Every patient included in the study underwent a SBx of the prostate. The SBx in the group without MRI-ultrasound fusion was performed transrectally using a biplanar probe with a BK ultrasound device. The cores in the random biopsy were gathered from the medial and lateral aspect of the base, mid and apical part of the prostate both for the left and right side.

### *Radical prostatectomy (RP)*

All patients underwent RP by either open retropubic (133/210 patients) or robot-assisted (77/210 patients) approach. Patients with intermediate or high risk PCa also underwent bilateral regional lymphadenectomy. Intermediate or high risk PCa was defined as Gleason score $\geq$ 7a or greater, more than three positive biopsy cores or a tumor infiltration of one core of more than 50% [17].

### *Pathological evaluation*

All RP specimen as well as the biopsy cores were sent to the same pathological institute and analyzed by an experienced uropathologist. The histopathological evaluation was done using the Gleason system according to the consensus recommendations of the International Society of Urological Pathology (ISUP) [18,19]. For every RP specimen the T-, N- and M- stage was specified using the TNM classification of malignant tumors by the Union for International Cancer Control (UICC).

Upgrading was defined as a change to a higher grade group in the GGG in the RP specimen compared to the preoperative biopsy. Downgrading was defined as a change to a lower grade group in the RP specimen compared to the preoperative biopsy.

### *Statistical analysis*

A matched pair analysis was performed between the FBx group and the SBx group. The matching was performed according to the following criteria: The maximum difference in PSA was no more than 2 ng/ml and the maximum difference in age no more than 2 years. Rates of postoperative upgrading or downgrading were evaluated comparing the histopathology of the biopsy of the two groups with the final histopathology of the RP specimen.

Statistical analyses were performed using the chi-squared test. A $p$-value $< 0.05$ was considered as statistically significant. The chi-squared test was used for categorial data and the Mann–Whitney test for continuous data. As software, MedCalc for Windows, version 18 (MedCalc Software, Ostend, Belgium) was used.

## Results

### *Patient demographics and clinicopathological characteristics*

The mean patients age at diagnosis was 67.1 (47–83) years. Median PSA-level was 9.9 ng/ml (1.9–36.1 ng/ml) and mean prostate volume was 54.3 ml (range = 22–172 ml). Biopsy prior to the RP was performed in 105 patients with image fusion of MRI and ultrasound with a minimum of 13 and maximum of 16 cores taken. The SBx was solely performed in 105 patients. A median of 5.7 cores were positive in the biopsy (range = 1–14) noted on pathologic review. Patient characteristics are outlined in Table 1, showing a statistically significant different distribution of GGG > 3 between the FBx and the SBx group.

### Tumor characteristics in biopsy cores

The distribution corresponding to GGG is outlined in Table 1. Most of the patients had GGG 2 (79/210; 37.6%) or GGG 1 (58/210; 27.6%) PCa after biopsy of the prostate. 34.7% (73/210 patients) had GGG 3 or higher prostate cancer.

### Tumor characteristics of post prostatectomy specimens

The GGG of the RP specimen are listed in Table 2. Similar to the biopsy group, most patients had GGG 2 (70/210; 33.3%) PCa. In contrast to tumor characteristics after biopsy, less patients had GGG 1 (30/210 patients; 14.3%) and GGG 3 (52/210 patients, 24.8%) PCa after RP.

Perineural invasion was found in 154/186 patients. Tumor invasion of the iliacal lymph nodes was diagnosed in 19/145 patients, and 58/208 patients had positive surgical margins.

### Rates of up- and downgrading

The change in GGG between FBx and SBx compared with the GGG of the RP specimen was significantly different ($p = 0.045$). The rate of downgrading was statistically significant ($p = 0.014$) as well and higher in the target biopsy group (14/105 patients,13.3%) compared to the random biopsy (4/105 patients; 3.8%) group (Figure 2).

The rate of upgrading was higher in the SBx group than in the MRI/ultrasound fusion biopsy group (49/105 patients, 46.7% vs 42/105 patients, 40%) with no statistical significance ($p = 0.331$) (Figure 3). Concordance of GGG in the biopsy and the RP specimen was found in 52/105 (49.5%) patients in the SBx group and in 49/105 (46.7%) patients with FBx, with no statistical significance ($p = 0.679$) (Figure 2). The change in GGG from biopsy to final pathology in patients with GGG1 or 2 at biopsy level also was not statistically significant ($p = 0.168$). Regarding the rate of upgrading or downgrading solely in patients with GGG 1 or 2 at biopsy level, the rate of upgrading was lower in the FBx group (20/105 patients, 19% vs 26/105 patients, 25%), with no statistical significance ($p = 0.318$), whereas the rate of downgrading was lower in the SBx group (2/105 patients, 2% vs 7/105 patients, 7%) with no statistical significance ($p = 0.089$). The results are outlined in Figure 3.

Table 1. Patient characteristics.

| | SBx ($n = 105$) | | FBx ($n = 105$) | | $p$-value |
|---|---|---|---|---|---|
| Age (years) | | | | | 0.966 |
| Median | 68 | | 68 | | |
| IQR | 62–73 | | 62–73 | | |
| PSA (ng/ml) | | | | | 0.790 |
| Median | 7.9 | | 8.2 | | |
| IQR | 5.8–12.4 | | 6.2–12.5 | | |
| Prostate volume (ml) | | | | | 0.294 |
| Median | 54 | | 51 | | |
| IQR | 44–62 | | 41–62 | | |
| | *n* | %* | *n* | %* | |
| Gleason grade group | | | | | 0.001 |
| 1 | 41 | 39 | 20 | 19 | |
| 2 | 39 | 37 | 40 | 38 | |
| 3 | 9 | 9 | 20 | 19 | |
| 4 | 8 | 8 | 21 | 21 | |
| 5 | 8 | 8 | 4 | 4 | |

*The sum differs from 100% due to rounded numbers.

## Discussion

The risk of Gleason upgrading in the RP specimen is a well-known phenomenon and often described in the literature [2–4,6,7]. The accurate knowledge of the exact GGG is essential to choose the right therapeutic option, especially for patients with low-risk tumors who are eligible for AS or FT as adverse pathological upgrading is associated with a higher risk of biochemical recurrence [20], progression of disease to distant metastasis and mortality [21].

In recent years, mpMRI of the prostate gained importance in the diagnostic pathway of PCa. Several studies could prove the efficiency of MRI/ultrasound fusion-based targeted biopsy of the prostate, especially in the detection of clinically significant PCa [13–15]. This raised the question if mpMRI-targeted biopsy may improve the concordance of GGG in the biopsy and the final pathology obtained after RP.

In this study, we evaluated the risk of upgrading to an adverse pathological outcome after RP in patients diagnosed with PCa by either FBx or SBx by matched pair analysis. According to current literature, most studies do not directly compare FBx with SBx but rather evaluate the change in GGG in the target as well as in the SBx within the same patient.

Although the superiority of FBx over the SBx approach is already proven [13,14], change of GGG from biopsy to RP specimen is still described in the literature [13]. The risk of GGG-upgrading for SBx is described between 29.7% and 56.7% [2,6,7,22], which is concordant to the findings in our study (46.7%). The existing literature based on the risk of GGG-upgrading after FBx is quite heterogeneous, describing rates of upgrading in the mpMRI-target lesion between 17% and 40.4% [9,11,14,23,24]. Data describing rates of up- and

Table 2. Upgrade and downgrade ratios of random biopsy (SBx) and fusion biopsy (FBx) results according to final radical prostatectomy (RP) pathology.

| | RP GGG 1 (%) | RP GGG 2 (%) | RP GGG 3 (%) | RP GGG 4–5 (%) | Upgrade (%) | Downgrade (%) | $p$-value |
|---|---|---|---|---|---|---|---|
| SBx GGG 1 | 18 (44) | 15 (37) | 4 (10) | 4 (10) | 56 | – | <0.001 |
| SBx GGG 2 | 0 (0) | 18 (46) | 13 (33) | 8 (21) | 54 | 0 | |
| SBx GGG 3 | 0 (0) | 2 (22) | 2 (22) | 15 (56) | 56 | 22 | |
| SBx GGG 4–5 | 0 (0) | 0 (0) | 1 (6) | 15 (94) | – | 6 | |
| FBx GGG 1 | 9 (45) | 10 (50) | 1 (5) | 0 (0) | 55 | – | <0.001 |
| FBx GGG 2 | 2 (5) | 19 (48) | 15 (38) | 4 (10) | 48 | 5 | |
| FBx GGG 3 | 1 (5) | 3 (15) | 11 (55) | 5 (25) | 25 | 20 | |
| FBx GGG 4–5 | 0 (0) | 3 (12) | 5 (20) | 17 (68) | – | 32 | |

GGG: Gleason Grade Group. The row total of percent differs from 100% due to rounded numbers in some cases.

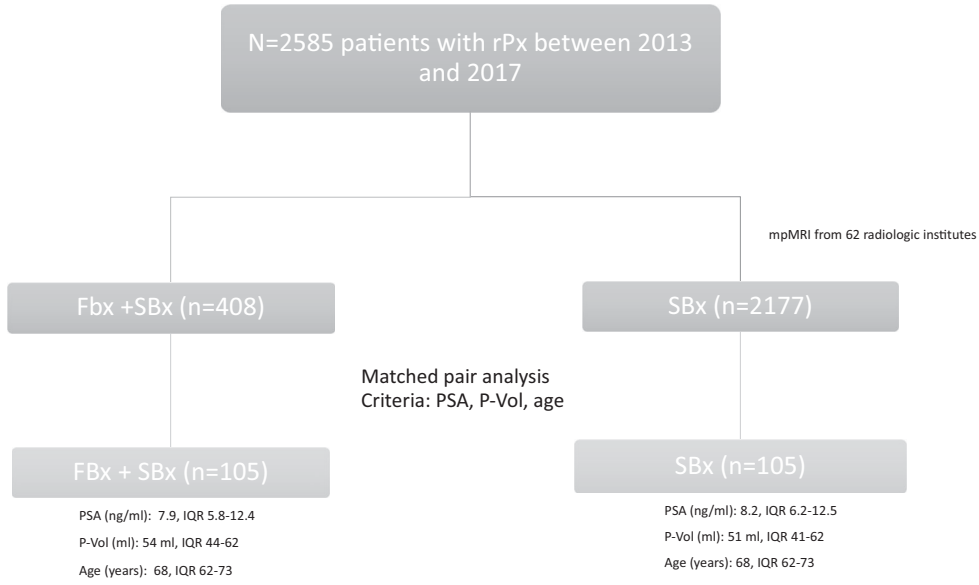


Figure 1. Patient selection.

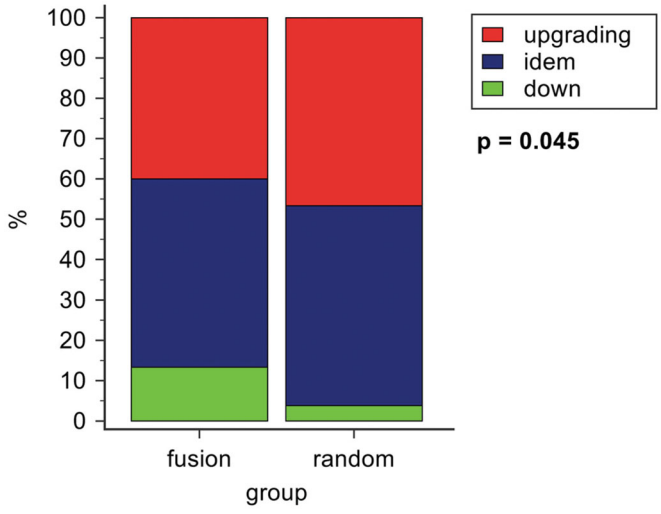


Figure 2. Rates of up- and downgrading between FBx and SBx.

downgrading for the target are quite rare with small patient cohorts.

A recent meta-analysis of Kasivisvanathan et al. [13] evaluated 76 studies focusing on mpMRI-targeted biopsy, but only one study also evaluated the rates of up-and downgrading. The PRECISION trial reported about the proportion of upgrading from biopsy to final histopathology for FBx as well as SBx. Although the number of patients with consecutive RP in this cohort was small, similar rates of up- and downgrading were described in both biopsy approaches. Rates of upgrading of 17% (5/30) in the FBx-group and 15% (4/27) in the SBx-group were reported, whereas downgrading was reported in 20% (6/30) and 15% (4/27), respectively [14].

The higher rates of upgrading in our cohort might be due to the fact that our data reflect a real-world setting with numerous referring radiologic institutes and various pathologists assessing the result.

Taking a closer look at low and intermediate risk PCa (Gleason 6 and 7a), upgrading rates between both biopsy approaches were similar in our study, with 19% (FBx) and 25% (SBx), respectively. Literature with subgroup analysis focusing on patients with GGG 1 or 2 PCa in the mpMRI-target are rare. In a series of 60 patients, Zhang et al. [25] described an upgrading-rate of the mpMRI-target lesion in 14/60 (23.3%) cases. In 10/60 (16.7%) patients downgrading was observed. Subgroup analysis in this cohort showed an upgrading from GGG 1 or 2 to a higher GGG in 12/60 (20%) patients [25].

Comparing the results with former data [4], it seems that concordance in GGG between biopsy and final histopathology did not change over the years and the implementation of mpMRI did not change the risk of upgrading. The great disparity between the studies and the remarkable rate of downgrading in our population leads to the assumption that interobserver variability might have the greatest influence on histopathological concordance. Interobserver variation in the assessment of GGG in biopsy is a commonly described phenomenon. Especially the differentiation between Gleason pattern 3 and 4 is challenging for the pathologist [26,27].

A major limitation of the present study is the retrospective character as well as the limited number of patients.

All in all, the results of our study indicate that mpMRI does not seem to have influence on the concordance of GGG between biopsy and RP specimens.

## Conclusion

MRI/Ultrasound fusion-based targeted biopsy does not lead to a reduction of GGG upgrading between prostate biopsy and RP specimen. The present findings might indicate that other factors like interobserver variability in pathological evaluation do have a greater impact on upgrading than the approach of prostate biopsy itself.

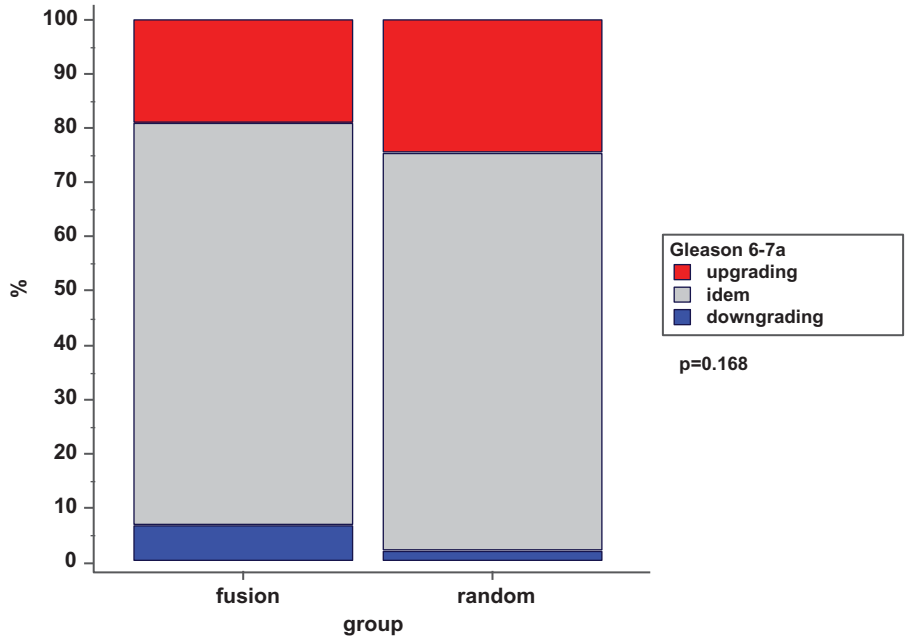


Figure 3. Rates of up- and downgrading between FBx and SBx related to GGG 1 and 2.

## Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Informed consent

Informed consent was obtained from all individual participants included in the study.

## Disclosure statement

The other authors declare that they have no conflict of interest.

## ORCID

A. Buchner http://orcid.org/0000-0001-7895-7070

## References

[1] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2017;71(4):618–629.

[2] Seisen T, Roudot-Thoraval F, Bosset PO, et al. Predicting the risk of harboring high-grade disease for patients diagnosed with prostate cancer scored as Gleason </= 6 on biopsy cores. World J Urol. 2015;33(6):787–792.

[3] Epstein JI, Feng Z, Trock BJ, et al. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol. 2012;61(5):1019–1024.

[4] Lellig E, Gratzke C, Kretschmer A, et al. Final pathohistology after radical prostatectomy in patients eligible for active surveillance (AS). World J Urol. 2015;33(7):917–922.

[5] Porcaro AB, Siracusano S, de Luyk N, et al. Low-risk prostate cancer and tumor upgrading in the surgical specimen: analysis of clinical factors predicting tumor upgrading in a contemporary series of patients who were evaluated according to the modified gleason score grading system. Curr Urol. 2016;10(3):118–125.

[6] Tilki D, Schlenker B, John M, et al. Clinical and pathologic predictors of Gleason sum upgrading in patients after radical prostatectomy: results from a single institution series. Urol Oncol. 2011;29(5):508–514.

[7] Herlemann A, Buchner A, Kretschmer A, et al. Postoperative upgrading of prostate cancer in men >/=75 years: a propensity score-matched analysis. World J Urol. 2017;35(10):1517–1524.

[8] Santok GD, Abdel Raheem A, Kim LH, et al. Prostate-specific antigen 10-20 ng/mL: a predictor of degree of upgrading to ≥8 among patients with biopsy Gleason score 6. Investig Clin Urol. 2017;58(2):90–97.

[9] Calio BP, Sidana A, Sugano D, et al. Risk of upgrading from prostate biopsy to radical prostatectomy pathology-does saturation biopsy of index lesion during multiparametric magnetic resonance imaging-transrectal ultrasound fusion biopsy help? J Urol. 2018;199(4):976–982.

[10] 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(11):1941–1948.

[11] Borkowetz A, Platzek I, Toma M, et al. Direct comparison of multiparametric magnetic resonance imaging (MRI) results with final histopathology in patients with proven prostate cancer in MRI/ultrasonography-fusion biopsy. BJU Int. 2016;118(2):213–220.

[12] Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. Eur Urol. 2013;64(5):713–719.

[13] Kasivisvanathan V, Stabile A, Neves JB, et al. Magnetic resonance imaging-targeted biopsy versus systematic biopsy in the detection of prostate cancer: a systematic review and meta-analysis. Eur Urol. 2019;76(3):284–303.

[14] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. 2018;378(19):1767–1777.

[15] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017;389(10071):815–822.

[16] Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS prostate imaging – reporting and data system: 2015, version 2. Eur Urol. 2016; 69(1):16–40.
[17] Epstein JI, Walsh PC, Carmichael M, et al. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA. 1994;271(5):368–374.
[18] Epstein JI, Allsbrook WC, Jr., Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol. 2005;29(9):1228–1242.
[19] Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol. 2016;40(2):244–252.
[20] Sved PD, Gomez P, Manoharan M, et al. Limitations of biopsy Gleason grade: implications for counseling patients with biopsy Gleason score 6 prostate cancer. The J Urol. 2004;172(1):98–102.
[21] Porter CR, Kodama K, Gibbons RP, et al. 25-Year prostate cancer control and survival outcomes: a 40-year radical prostatectomy single institution series. J Urol. 2006; 176(2):569–574.
[22] Evans SM, Patabendi Bandarage V, Kronborg C, et al. Gleason group concordance between biopsy and radical prostatectomy specimens: a cohort study from Prostate Cancer Outcome Registry – Victoria. Prostate Int. 2016;4(4):145–151.
[23] Arsov C, Becker N, Rabenalt R, et al. The use of targeted MR-guided prostate biopsy reduces the risk of Gleason upgrading on radical prostatectomy. J Cancer Res Clin Oncol. 2015;141(11):2061–2068.
[24] Le JD, Stephenson S, Brugger M, et al. Magnetic resonance imaging-ultrasound fusion biopsy for prediction of final prostate pathology. J Urol. 2014;192(5):1367–1373.
[25] Zhang Q, Wang W, Zhang B, et al. Comparison of free-hand transperineal mpMRI/TRUS fusion-guided biopsy with transperineal 12-core systematic biopsy for the diagnosis of prostate cancer: a single-center prospective study in China. Int Urol Nephrol. 2017;49(3):439–448.
[26] Berg KD, Toft BG, Roder MA, et al. Prostate needle biopsies: interobserver variation and clinical consequences of histopathological re-evaluation. APMIS. 2011;119(4–5):239–246.
[27] Meliti A, Sadimin E, Diolombi M, et al. Accuracy of Grading Gleason Score 7 prostatic adenocarcinoma on needle biopsy: influence of percent pattern 4 and other histological factors. Prostate. 2017;77(6):681–685.