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Comparing Image-guided targeted Biopsies to Radical Prostatectomy Specimens for Accurate Characterization of the Index Tumor in Prostate Cancer

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Abstract. *Aim: To evaluate the accuracy of multiparametric magnetic resonance–transrectal ultrasound fusion targeted biopsy (TBx) in the characterization of the index tumor, as confirmed by association with radical prostatectomy (RP) specimens. Patients and Methods: A total of 152 patients with TBx-confirmed prostate cancer (PCa) underwent robot-assisted RP. Stained whole-mount histological sections were used as the reference standard. All lesions with a volume >0.5 ml and/or pathological Gleason score (GS) >6 were defined as clinically significant PCa. The index lesion was defined as the largest tumor focus within the prostate gland. Results: The pathological index tumours included: 147 lesions (96.7%) with a volume >0.5 ml and five (3.3%) with a volume ≤0.5 ml, but with a pathological GS ≥7; 135 (88.8%) were located in the peripheral zone. TBx accuracy in the detection of the correct site of the index lesion by reference standard was 82.2%. Sensitivity, specificity, positive and negative predictive value were: 82.3%, 50.4%, 82.8% and 49.7%, respectively. The primary/secondary Gleason grade and GS of the 152 index tumors were properly estimated in 130 (85.5%), 115 (75.6%) and 127 (83.6%) cases, respectively. The concordance of TBx with pathological GS was 83.6%. The rate of up-grading and down-grading of TBx Gleason sum was 12.2% and 4.2%, respectively. Conclusion: TBx has a high sensitivity for characterization of index lesions, with a good concordance for topographic and Gleason grading accuracy between biopsy and surgical specimens.*

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The development of multiparametric magnetic resonance (mpMRI) has changed the approach to prostate biopsy. MRI targeted biopsies (TBx) have been shown to detect more significant prostate cancer (PCa) than conventional transrectal ultrasound (TRUS)-guided ones (1-5). Although mpMRI improves the detection of aggressive tumors and reduces the overdiagnosis of indolent PCa, its role in the characterization of the index tumor is still debated (6, 7).

The index tumor in PCa is the largest tumor with the highest grade and is fundamental to prognosis. Recent studies demonstrated that TBx ensured a higher accuracy of PCa detection and reduced the risk of up-/downgrading of Gleason score (GS) at radical prostatectomy (RP) when compared to untargeted standard biopsy (8, 9).

TBx use is not widespread yet, with indications and techniques still under investigation. In particular, the ideal minimum number of samples to be taken and where to take them in order to better characterize the index lesion are unknown. With a homogenous MRI target, one TBx might be sufficient to detect PCa and accurately classify the highest GS. On the contrary, if there is significant intralesion heterogeneity, multipleTBx within the same area might be needed to determine the correct Gleason pattern.

Recently, we investigated the ideal number of cores, their spatial distribution and the GS bioptical heterogeneity within the same index lesion in order to maximize GS determination (10). We demonstrated that approaching TBx with a single core is inadequate; conversely, taking two cores in the central zone of the index lesion may provide more accurate cancer detection, optimizing the chances of detecting the region with highest GS (10). An important limitation of that study was that we did not perform a direct comparison to prostatectomy specimens.

The aim of the present study was to evaluate the sensitivity of fusion software TBx in the better characterization of the index tumor and in particular in the detection of highest Gleason pattern compared to RP specimen results.

Patients and Methods

The current study enrolled 152 patients with PCa who underwent robot-assisted RP at a surgical high-volume center (San Luigi Hospital, Orbassano, University of Turin, Italy) from June 2015 to January 2017. These 152 patients belong to a larger cohort of 327 consecutive patients with negative digital rectal examination, who underwent TBx after previous negative standard biopsy (12 samples) between January 2015 and September 2016, at San Luigi Hospital, Orbassano, Italy (10). All men had an ongoing suspicion for PCa (elevated or rising PSA) or one or more detectable lesions at mpMRI, performed at least 30 days before TBx. In these series, depending on the diameter of each region of interest (ROI) as ≤8 or >8 mm, four or six cores were, respectively, taken within the same index lesion, according to a well-determined sequence as previously reported by our group (10). Among these patients, 166 had a positive TBx (50.7%); their median age was 75 (range=46-85) years, while their median prostate specific antigen (PSA) was 7.5 (range=0.9-48) ng/ml.

We enrolled 152 out of the 166 patients; 14 men were excluded due to non-availability of reference standard since they had not undergone RP (13/166, 7.8%), or PCa foci were not found on the excised prostate (1/166, 0.6%). Prostate Imaging Reporting and Data System (PI-RADS) was missing for 44 men, being classified as "suspected lesion".

According to Italian law (Agenzia Italiana del Farmaco-AIFA, Guidelines for observational studies, 20 March 2008), no formal ethical approval was needed for this study.

Prostate mpMRI and fusion biopsy techinque. All patients underwent mpMRI according to the European Society of Urological Radiology guidelines; PI-RADS version 1 was used for scoring each reported lesion (11). mpMRI was centrally performed with a 1.5-T scanner using a 4-channel phase array coil combined with an endorectal coil. A PI-RADS grade from 1 to 5 was assigned for each patient, determined by the respective sum score. The size of the detected lesions was measured with a free hand ROI on axial T2-weighted (T2W) images (in mm^2) and each ROI was furthermore localized into 27 ROI models (11). Since men belonging to the indeterminate PI-RADS 3 subgroup also underwent biopsy, mpMRI was considered positive if final the PI-RADS was ≥3 while negative if <3.

In order to compare imaging with pathological data, peripheral zone (PZ) findings were classified as belonging to one of three axial levels, *i.e.* apex, mid-gland, and base; and to one of six additional regions, *i.e.* right anterior-lateral, right posterior-lateral, right posterior, left anterior-lateral, left posterior-lateral, and left posterior. Transitional zone (TZ) findings were classified as being either on the right or left side.

TBx was performed using the BioJet™ fusion system (D&K Technologies, Barum, Germany). The gland and the ROI were contoured, and the prostate contour was fused in real time with the TRUS image. Ultrasound was performed by a Hawk Ultrasound 2102 EXL scanner with a biplanar transducer (BK Medical, Herlev, Denmark). Biopsies were performed using a disposable 18-G biopsy gun with a specimen size of 18-22 mm by two senior urologists, having more than 20 years of experience in standard biopsy and more than 1 year in TBx (>100 procedures per urologist).

Transrectal or transperineal approach was based on the location of the ROI: transrectal for PZ ROIs, and transperineal for transition, central or anterior zone ROIs. For each patient, we identified the index lesion and one core was obtained every 2-3 mm along the longest axis of the lesion. For the transperineal approach, we used a brachytherapy grid linked to a stepper. In addition to samples every 5 mm made possible by the grid, additional sample went taken manually oriented after the skin passage, in order to sample every 2-3 mm approximately; such precision can be achieved thanks to the BioJet™ Fusion system s software's ability to mark the whole track of the needle for any core (stereotaxic registration).

The sampling of each core within each individual index lesion was performed according to a well-determined sequence: the first core was taken at the extreme medial site of the ROI, subsequent ones were taken moving progressively towards the extreme lateral site of the lesion (10).

Reference standard. Whole-mount histological sections resected from the RP specimens were used as reference standards. In detail, the prostate was cut into 3-mm thick sections; slices were obtained perpendicularly to the rear gland surface, with the same inclination as the axial T2W images. Conversely, bases and apices were sectioned longitudinally. Then, 5 μm sections were taken from each thick slice and stained with hematoxylin and eosin. All samples were then assessed for cancer foci by the same experienced uropathologist. The lesion volume was obtained by summing the area involved by the tumor on each contiguous slide. The pathologist also assessed the pathological GS for each focus and in multifocal cases recorded the index lesion location that was defined as the largest tumor focus within the prostate gland (6,12). Clinically significant PCa was defined as a tumor >0.5 ml or with or pathological GS>6; consequently, PCa foci with a volume <0.5 ml and GS <6 were defined as clinically non-significant (13).

Statistical analyses. The associations between categorical variables were estimated by the Fisher's exact test, while the Mann-Whitney test was used for continuous variables; the latter results were reported as median (range). All *p*-values were obtained by the two-sided exact method at the conventional 5% significance level. Data were analyzed as of November 2017 by R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

We enrolled 152 patients with positive TBx after previous negative standard biopsy who underwent robot-assisted RP at San Luigi Hospital, Orbassano-I. Patient characteristics and clinical information are reported in Table I. Median age and PSA were 66 (range=61-70) years and 6.8 (range=5.5-10.0) ng/ml, respectively. Around 60% of the whole cohort had lesion with PI-RADS >3 at mpMRI, PI-RADS grade 4 being the most common (40.8%). Eighty-eight percent of patients had only one ROI at MRI. Eighty-nine (58.5%) had an index lesion ≤8 mm and 63 (41.5%) patients one of >8 mm (maximum diameter 22 mm). Most patients (101/152, 66.4%) had PSA ≤10 ng/ml (61/89, 68.5% and 39/63, 61.9% among patients with ≤8 or >8 mm index lesion, respectively).

The location of the index tumor at TBx was in the PZ in 73% with a median volume of 0.6 ml. Index lesion biopsy GS was: ≤3+4 in 62.6%, 4+3 in 30.2% and ≥8 in 7.2%.

Overall, in the reference standard the pathologist identified 277 cancer foci, of which 179 (64.6%) were

Table I. *Patient characteristics and clinical information.*

Characteristic	Total
Number of patients included in study	152
Age at diagnosis, years (median/range)	66 (61-70)
PSA at diagnosis, ng/ml (median/range)	6.8 (5.5-10.0)
%fPSA at diagnosis (median/range)	14 (7-24)
Previous SBx sessions, n	1
MRI prostate volume, ml (median/range)	40.8 (11.5-158.6)
Location of index lesion, n (%)	
Posterior zone	111 (73.0)
Anterior (transition, central or anterior zone)	41 (27.0)
Volume of index lesion at MRI, ml (median/range)	0.6 (0.2-4.3)
PI-RADS v1 grade (total, %)	
3	18 (11.8)
4	62 (40.8)
5	28 (18.5)
missing	44 (28.9)
Index lesion GS at TBx (total, %)	
6	15 (10.0)
3+4	80 (52.6)
4+3	46 (30.2)
≥8	11 (7.2)
Time between TBx and surgery, days (median/range)	31 (22-47)

PSA, Prostate specific antigen; %fPSA, free/total prostate-specific antigen ratio; SBx, standard biopsy; MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging Reporting and Data System; GS, Gleason Score; TBx, targeted biopsy.

clinically significant lesions. Of the latter, 146 (81.5%) were located in the PZ and 33 (18.5%) in the TZ. Lesion distribution was as follows: one focus was detected in 55/152 patients (36.2%), two in 48 (31.5%), three in 40 (26.3%), and four in nine (6.0%); multifocal disease was therefore present in 63.8% of our series. The median tumor volume was 0.71 (range=0.07-19.51) ml.

The 152 pathological index tumors included: 147 lesions (96.7%) with a volume >0.5 ml and five lesions (3.3%) with a volume ≤0.5 ml but with a pathological GS ≥7. Among the above lesions, 135 (88.8%) were located in the PZ.

The accuracy of TBx in detecting the correct site of the index lesion by reference standard was 82.2%. Sensitivity, specificity, positive and negative predictive values in correct site evaluation were 82.3%, 50.4%, 82.8% and 49.7%, respectively.

Globally, 60 out of the 152 index lesions were pathological stage T3 (51 pT3a and 9 pT3b); the remaining 92 index lesions were pT2. The primary and secondary Gleason grade, and GS of the 152 index tumors were properly estimated in 130 (85.5%), 115 (75.6%) and 127 (83.6%) cases, respectively. The concordance of TBx with pathological GS was 83.6%. The rate of up-grading and down-grading in TBx Gleason sum was 12.2% and 4.2%, respectively.

Table II. *Pathological characteristics of index lesions according to Gleason Score (GS) and location by reference standard.*

	Number of index lesions (median volume, ml)			
Prostate site	GS 3+3	GS 3+4	GS 4+3	GS≥8
Posterior zone	3 (0.19)	69 (1.28)	47 (1.87)	16 (1.73)
Transition zone	4 (0.31)	7 (2.22)	5 (1.73)	1 (3.44)
Total	7 (0.23)	76 (1.32)	52 (1.84)	17 (1.78)

Pathological characteristics of index lesions according to GS and location by reference standard are reported in Table II. Gleason sum 3+3 tumors had a significant lower median volume (0.23 ml) than those with GS 3+4, 4+3 and ≥8 ($p<0.001$).

Lesions in the PZ of the prostate were more likely to be detected than those in the central zone [odds ratio (OR)=5.30, 95% confidence interval (CI)=1.40-23.0; $p=0.034$]. Finally, there was evidence of improved detection with increasing lesion volume (odds ratio=7.40, 95% confidence interval=2.20-24.60; $p<0.001$).

Discussion

Prostate cancer is predominantly a multifocal disease, consisting of an index lesion, defined as the lesion with the largest volume at pathology, and other satellite lesions (12). In almost 90% of patients with PCa, the total tumor volume is less than 10% of the prostate volume. The majority of the tumor volume (88%) was taken up by the index lesions (6, 12). Recent studies support the theory that PCa progression and metastasis are driven by the largest tumor focus (12, 14-16). According to this theory, therapeutic decision-making could be heavily influenced by the clinical relevance of index tumors, which therefore needs to be accurately assessed.

Some authors defined the index lesion as the lesion with the highest Gleason grade (17).

In a recent study, we evaluated the ideal number of cores, their spatial distribution and the GS biopsy heterogeneity within the same index lesion in order to optimize the chances of finding the highest GS within a target (10). We demonstrated that taking two cores in the central zone of the index lesion, rather than one, may provide more accurate cancer detection and GS classification (10). An important limitation of that study was that we did not perform a direct comparison with prostatectomy specimens but simply verified concordance of accuracy of topographic and Gleason grading.

We have now completed this investigation by having evaluated the same factors in the same cohort, comparing target biopsy with pathological specimens. This objective

was achieved using a well-standardized TBx technique and whole-mount histological sections, resected from the RP specimens as reference standard.

In our single-centre study, the index lesions site was correctly identified by TBx in 83%. Rosenkrantz *et al*. reported sensitivity and positive predictive values of 75.9% and 82.6%, respectively, for detecting index lesions (18). Moreover, a recent article by Russo *et al*. evaluated the sensitivity of mp-MRI for detecting PCa foci, including the largest (index) lesions in 115 patients, reporting an overall sensitivity of 90.4% and an index lesion sensitivity of 93.3% (19). We substantially confirmed these data: sensitivity and positive predictive value for index tumor detection by TBx were 82.3% and 82.8%, respectively.

Russo *et al*. showed that pathological GS (OR 11.7, p=0.003) and lesion volume (OR 4.24, p=0.022) were independently associated with the MRI detection of index lesions (19). In the present study, we observed improved detection with increasing lesion volume (OR 7.40, p<0.001). This is in agreement with the evidence that mpMRI is accurate in detecting large tumors but has limitations in identifying the smallest PCa foci (20-21). Similarly, others reported poor sensitivity for low-volume lesions (22).

Le *et al*. examined mp-MRI PCa detection, confirmed on whole-mount pathology; they reported an overall sensitivity of 47% and sensitivity of 80% for the index lesion (17). Due to the many missed index lesions, they highlighted the continuous need for systematic biopsy, despite a possible avoidance of biopsy with MRI screening. A possible explanation for the lower sensitivity reported by Le *et al*. might be due to their different definition of the index lesion, which they defined as the lesion with the highest Gleason grade at pathology (17). In their series, 14% of smaller secondary lesions had higher GS than the largest lesion, while in our study there were only five similar cases (3.3%). In the present study, the index lesion was defined as the lesion with the largest volume at pathology (12). As far as mpMRI detection of high GS tumor, literature data confirm that MRI is accurate in the identification of high Gleason pattern PCa (8-9, 23-24).

Recently, we demonstrated that TBx is more accurate than untargeted standard biopsy in the detection of the correct surgical GS (25). In the current series, we substantially confirm these data: primary Gleason grade and GS were determined accurately in about 85% of cases. As expected, high-grade lesions and large index lesions were more easily detected at TBx. The good detection rate for index lesions was counterbalanced by the very low sensitivity of mp-MRI for clinically insignificant lesions (18.4%). However, this evidence is in favor of mpMRI, because excluding clinically insignificant cancer could limit the performance of radical treatments and related complications, reduce patient anxiety of having cancer, and limit the costs resulting from overtreatment.

The strenghths of our study are the well-standardized TBx technique (10), and the simultaneous evaluation of topographic and biological features of each index lesion, through target biopsy and pathological specimens. Notably, this achievement was documented in the most common setting of TBx utilization: re-biopsy after a previous approach using standard biopsy.

However, our study is not devoid of limitations. Firstly, whole-mount histological sections resected from the RP specimens were used as reference standards unlike what actually happens when only a fraction of tissue is evaluated. Secondly, interobserver variability was not assessed as only one experienced radiologist reported on all mpMRI examinations; reader variability will be addressed in a future multi-reader trial. Finally, PI-RADS v1 and not the more recent v2 was used, potentially affecting the diagnostic accuracy, especially for the anterior ROI.

In conclusion, the present study confirms that mpMRI has a high sensitivity for detecting index lesions and most aggressive tumors (GS>6). We do recognize that in potential genomic or biological factors might increase the difference between biopsy and surgical GS. Considering that patient counseling and treatment decision-making depend predominantly on better characterization of the index tumor, our results need to be verified on larger surgically confirmed series.

References

1 De Rooij M, Hamon EH, Futterer JJ, Barentsz JO and Rovers MM: Accuracy of multiparametric MRI for prostate cancer detection: a meta analysis. AJR Am J Roentgenol *202*: 343-351, 2014.

2 Moore CM, Robertson NL, Arsanious N, Middleton T, Villers A, Klotz L, Taneja SS and Emberton M: Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol *63*: 125-140, 2013.

3 van Hove A, Savoie PH, Maurin C, Brunelle S, Gravis G, Salem N and Walz J: Comparison of image-guided targeted biopsies *versus* systematic randomized biopsies in the detection of prostate cancer: a systematic literature review of well designed studies. World J Urol *32*: 847-858, 2014.

4 Siddiqui MM, Rais-Bahrami S and Turkbey B, George AK, Rothwax J, Shakir N, Okoro C, Raskolnikov D, Parnes HL, Linehan WM, Merino MJ, Simon RM, Choyke PL, Wood BJ and Pinto PA: Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA *313*: 390-397, 2015.

5 Filson CP, Natarajan S, Margolis DJ, Huang J, Lieu P, Dorey FJ, Reiter RE and Marks LS: Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: the role of systematic and targeted biopsies. Cancer *122*: 884-892, 2016.

6 Rud E, Klotz D, Rennesund K, Baco E, Berge V, Lien D, Svindland A, Lundeby E, Berg RE, Eri LM and Eggesbø HB: Detection of the index tumor and tumor volume in prostate cancer using T2W and DW MRI alone. BJU Int *114*: E32-42, 2014.

7 Turkbey B, Mani H, Aras O, Rastinehad AR, Shah V, Bernardo M, Pohida T, Daar D, Benjamin C, McKinney YL, Linehan WM, Wood BJ, Merino MJ, Choyke PL and Pinto PA: Correlation of magnetic resonance imaging tumor volume with histopathology. J Urol *188*: 1157-1163, 2012.
8 Porpiglia F, Manfredi M, Mele F, Cossu M, Bollito E, Veltri A, Cirillo S, Regge D, Faletti R, Passera R, Fiori C and De Luca S: Diagnostic pathway with multiparametric magnetic resonance imaging *versus* standard pathway: results from a randomized prospective study in biopsy-naïve patients with suspected prostate cancer. Eur Urol *72*: 282-288, 2017.
9 Turkbey B, Mani H, Shah V, Rastinehad AR, Bernardo M, Pohida T, Pang Y, Daar D, Benjamin C, McKinney YL, Trivedi H, Chua C, Bratslavsky G, Shih JH, Linehan WM, Merino MJ, Choyke PL and Pinto PA: Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. J Urol *186*: 1818-1824, 2011.
10 Porpiglia F, De Luca S, Passera R, De Pascale A, Amparore D, Cattaneo G, Checcucci E, De Cillis S, Garrou D, Manfredi M, Mele F, Bollito E and Fiori C: Multiparametric magnetic resonance/ultrasound fusion prostate biopsy: number and spatial distribution of cores for better index tumor detection and characterization. J Urol *198*: 58-64, 2017.
11 Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, Rouviere O, Logager V and Fütterer JJ: ESUR prostate MR guidelines 2012. Eur Radiol *22*: 746-757, 2012.
12 Ahmed HU: The index lesion and the origin of prostate cancer. N Engl J Med *361*: 1704-1706, 2009.
13 Ploussard G, Epstein JI, Montironi R, Carroll PR, Wirth M, Grimm MO, Bjartell AS, Montorsi F, Freedland SJ, Erbersdobler A and van der Kwast TH: The contemporary concept of significant *versus* insignificant prostate cancer. Eur Urol *60*: 291-303, 2011.
14 Stamey TA, McNeal JM, Wise AM and Clayton JL: Secondary cancers in the prostate do not determine PSA biochemical failure in untreated men undergoing radical retropubic prostatectomy. Eur Urol *39(Suppl 4)*: 22-3, 2001.
15 Bott SR, Ahmed HU, Hindley RG, Abdul-Rahman A, Freeman A and Emberton M: The index lesion and focal therapy: an analysis of the pathological characteristics of prostate cancer. BJU Int *106*: 1607-1611, 2010.
16 Liu W, Laitinen S, Khan S, Vihinen M, Kowalski J, Yu G, Chen L, Ewing CM, Eisenberger MA, Carducci MA, Nelson WG, Yegnasubramanian S, Luo J, Wang Y, Xu J, Isaacs WB, Visakorpi T and Bova GS: Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nat Med *15*: 559-565, 2009.
17 Le JD, Tan N, Shkolyar E, Lu DY, Kwan L, Marks LS, Huang J, Margolis DJ, Raman SS and Reiter RE: Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Eur Urol *67*: 569-576, 2015.
18 Rosenkrantz AB, Deng FM, Kim S, Lim RP, Hindman N, Mussi TC, Spieler B, Oaks J, Babb JS, Melamed J and Taneja SS: Prostate cancer: multiparametric MRI for index lesion localization-a multiple-reader study. Am J Roentgenol *199*: 830-837, 2012.
19 Russo F, Regge D, Armando E, Giannini V, Vignati A, Mazzetti S, Manfredi M, Bollito E, Correale L and Porpiglia F: Detection of prostate cancer index lesions with multiparametric magnetic resonance imaging (mp-MRI) using whole-mount histological sections as the reference standard. BJU Int *118*: 84-94, 2016.
20 Villers A, McNeal JE, Freiha FS and Stamey TA: Multiple cancers in the prostate. Morphologic features of clinically recognized *versus* incidental tumors. Cancer *70*: 2313-2318, 1992.
21 Monni F, Fontanella P, Grasso A, Wiklund P, Ou Y, Randazzo M, Rocco B, Montanari E and Bianchi G: Magnetic Resonance Imaging In Prostate Cancer Detection And Management: A Systematic Review. Minerva Urol Nefrol *69*: 567-578, 2017.
22 Nakashima J, Tanimoto A, Imai Y, Mukai M, Horiguchi Y, Nakagawa K, Oya M, Ohigashi T, Marumo K and Murai M: Endorectal MRI for prediction of tumor site, tumor size, and local extension of prostate cancer. Urology *64*: 101-105, 2004.
23 Castellucci R, Linares Quevedo AI, Sánchez Gómez FJ, Díez Rodríguez J, Cogorno L, Cogollos Acuña I, Salmerón Béliz I, Muñoz Fernández de Legaría M, Martínez Piñeiro L: Prospective nonrandomized study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy to magnetic resonance imaging with subsequent MRI-guided biopsy in biopsy-naïve patients. Minerva Urol Nefrol *69*: 589-595, 2017.
24 Porpiglia F, De Luca S, Passera R, Manfredi M, Mele F, Bollito E, De Pascale A, Cossu M, Aimar R and Veltri A: Multiparametric-magnetic resonance/ultrasound fusion targeted prostate biopsy improves agreement between biopsy and radical prostatectomy Gleason Score. Anticancer Res *36*: 4833-4839, 2016.
25 Barentsz JO, Weinreb JC, Verma S, Thoeny HC, Tempany CM, Shtern F, Padhani AR, Margolis D, Macura KJ, Haider MA, Cornud F and Choyke PL: Synopsis of the PI-RADS v2 guidelines for multiparametric prostate magnetic resonance imaging and recommendations for use. Eur Urol *69*: 41-49, 2016.

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