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Review

Italian Prostate Biopsies Group: 2016 Updated Guidelines Insights

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Abstract. *Aim: To present a summary of the updated guidelines of the Italian Prostate Biopsies Group following the best recent evidence of the literature. Materials and Methods: A systematic review of the new data emerging from 2012-2015 was performed by a panel of 14 selected Italian experts in urology, pathology and radiology. The experts collected articles published in the English-language literature by performing a search using Medline, EMBASE and the Cochrane Library database. The articles were evaluated using a systematic weighting and grading of the level of the evidence according to the Grading of Recommendations Assessment, Development and Evaluation framework system. Results: An initial prostate biopsy is strongly recommended when i) prostate specific antigen (PSA) >10 ng/ml, ii) digital rectal examination is abnormal, iii) multiparametric magnetic resonance imaging (mpMRI) has a Prostate Imaging Reporting and Data System (PIRADS) ≥4, even if it is not recommended. The use of mpMRI is strongly recommended only in patients with previous negative biopsy. At least 12 cores should be taken in each patient plus targeted (fusion or cognitive) biopsies of suspicious area (at mpMRI or transrectal ultrasound). Saturation biopsies are optional in all settings. The optimal strategy for reducing infection complications is still a controversial topic and the instruments to reduce them are actually weak. The adoption of Gleason grade groups in adjunction to the Gleason score when reporting prostate biopsy results is advisable. Conclusion: These updated guidelines and recommendations are intended to assist physicians and patients in the decision-making regarding when and how to perform a prostatic biopsy.*

Prostate biopsy is a common urological office-based procedure because prostate cancer (PCa) has become the first

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Abbreviations: mpMRI: Multiparametric magnetic resonance imaging; LMWH: low-molecular weight heparin; DWI: diffusion weighted imaging; DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; MRSI: magnetic resonance spectroscopic imaging; ECE: extraprostatic extension; SVI: seminal vesicles invasion; TRUS: transrectal ultrasound.

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tumor with regards to incidence in men and the second leading cause of cancer death (1).

PCa represents a spectrum that ranges from non-aggressive and slow-growing disease that does not require treatment to aggressive and fast-growing disease that requires radical treatment. In recent years, the most appropriate treatment of the individual patient has greatly changed and an improvement of the prostate biopsy approach was necessary in order to reduce overdiagnosis, the risk of overtreatment and the side-effects of inappropriate therapies. There is, nowadays, the need to diagnose, but at the same time to define PCa aggressiveness in order to establish appropriate treatment. In this context, prostate biopsy and histological report play a key role in the management of PCa. Moreover, the introduction into clinical practice of multiparametric magnetic resonance imaging (mpMRI) has completely revolutionized the approach to prostate biopsy. This study updates the guidelines of Italian Prostate Biopsies Group (IPBG) (2) following the best recent literature evidence.

Materials and Methods

The IPBG consisted of 14 Italian experts (eight urologists, two pathologists, three radiologists and one methodologist). The panel was supported by the Italian Society of Uro-Oncology and the Italian Society of Ultrasound in Urology and Nephrology. Four experts in urology of the core group were delegates of the corresponding cancer societies.

The Commission defined the scope of the guidelines, the clinical questions, other relevant aspects (populations, interventions, outcomes, acceptable study designs *etc*.), and literature search strategies. Two or three experts were grouped for each topic after reviewing the literature from January 2012 to December 2015.

The experts collected articles published in the English-language literature by performing both a computerized search using Medline, EMBASE and the Cochrane Library database, and manual search through the reference lists from each article. Studies in languages other than English were excluded due to lack of funding and resources for translation. Complete eligibility assessment was performed independently by two investigators who independently extracted data for each selected study using a standardized data extraction sheet defined a priori by the study team.

Flow charts were defined for decision-making that described the current standard therapeutic pathways at the commencement of work to update the guidelines; this enabled identification of decision points, and the definition of relevant clinical questions based on the Population, Intervention, Comparison, Outcome of interest, Type of study (PICOT) system (Tables I-III). Outcomes were identified and their importance classified as important and essential (score 7-9), important but not essential (score 4-6), or not important (score 1-3) based on the votes of the core panel. On the basis of this classification, outcomes were given greater or lesser consideration in the literature review and subsequent formulation of recommendations. For each intervention, the commission voted on the strength of recommendation (applying previously published rules) (3) and also the benefit/risk ratio (Table III). A total of 1328 articles were identified by the literature search: 1190 of these were extracted, 857 were eliminated with reason, and 333 were finally assessed.

Table I. *Controversies regarding prostate biopsy (division in groups).*

	Topic
1	Indication for biopsy and re-biopsy
2	mpMRI and TPBx
3	Biopsy approach and technique
4	Number of cores required to perform a biopsy
5-6	How to reduce infection and optimize preparation to reduce complications
7	Pathological issues

mpMRI: Multiparametric magnetic resonance imaging; TPBx: targeted biopsy.

Subsequently, the articles were evaluated using a systematic weighting and grading of the level of evidence according to the Grading of Recommendations Assessment, Development and Evaluation framework (GRADE) (4). The two investigators independently extracted data for each selected study using a standardized data extraction sheet defined a priori by the study team.

Lastly, the final report was prepared according to the recommendations of the Conference on Guidelines Standardization (5).

At the end of this phase, the panel organized a Consensus Conference supported by the above mentioned Italian Scientific Societies, which took place in Bologna in December 2015.

Outcomes of the guidelines were determined and reflected the consensus of the panel of experts, resulting from the literature review. The guidelines underwent revision by a multidisciplinary group of professionals (recognized as experts in their respective fields) who had not participated in their development, including urologists, geriatricians, general practitioners and health economists. The final version was approved by the two Italian Scientific Societies that supported the panel.

Results

The IPBG clinical guidelines insights are statements of consensus of the Authors regarding their views of current accepted approaches to performing a prostatic biopsy. The IPBG insights highlighted important changes to the recommendations from previous versions. A full version of the IPBG compendium is available online (www.siuro.it).

Discussion

The major issues discussed by the panel are discussed in the following sections.

1 Indication for Prostate Biopsy

Recommendation 1: A prostatic biopsy is strongly recommended with a

- PSA >10 ng/ml
- Positive digital rectal examination (DRE)

Table II. *Grade system used to rate the quality of evidence and the strength of recommendations.*

Evidence level	
High quality	Further research very unlikely to change confidence in estimate of effect
Moderate quality	Further research likely to have an important impact on confidence in estimate of effect and may change estimate
Low quality	Further research very likely to have an important impact on confidence in estimate of effect and likely to change estimate
Very low quality	Any estimate of effect is very uncertain
Strength of recommendations	
Strongly positive	The examined treatment is the first-choice therapeutic option (favorable benefit/risk ratio)
Weakly positive	Consider the examined therapeutic strategy as the first option, realizing there are alternatives that could have similar or more appropriate indications in different settings
Weakly negative	The examined treatment is not excluded, but its use is limited to carefully selected cases; the clinical decision must be thoroughly discussed and shared with the patient
Strongly negative	The examined treatment should be avoided (unfavorable benefit/risk ratio or lack of scientific evidence)

- mpMRI Prostate Imaging Reporting and Data System (PIRADS) ≥4 (even if not recommended in biopsy-naive patients).

The need for prostate biopsy is based on prostate-specific antigen level (PSA) with or without suspicious DRE (6). PSA testing should be offered to patients following detailed counseling on the potential risks and benefits. Moreover, an individualized risk-adapted strategy for early detection of PCa should be performed for those with life expectancy >10-15 years, comorbidity, family history of PCa, Afro-American race (PSA evaluation starting from 45 years of age). Data in the literature indicate that age alone is not but rather comorbidities are the major factors that should be considered when performing a biopsy to detect PCa (7-9). It seems necessary to consider patient age and comorbidities with the use of validated instruments such as the Charlson comorbidity index (CCI) to assess life expectancy. CCI has been validated in men with PCa and has been shown to have a relatively high predictive accuracy that can be used in daily routine. The current guidelines on the diagnosis of PCa recommend PSA testing in men who have a life expectancy >10 years and to consider comorbidities and fragilities before performing a biopsy (7-9).

Limited PSA elevation alone should not prompt immediate biopsy (6). The PSA level should be verified after a few weeks using the same assay under standardized conditions (*i.e.* no ejaculation, manipulation, or urinary tract infection) in the laboratory using the same testing standard (11). Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA level should not be undertaken even if it is common in current clinical practice (11).

PSA should be considered as a continuous parameter (12). The higher the value, the more likely is the existence of PCa. However, a value of >4 ng/ml according to Hybritech

Table III. *Definitions of the different benefit/risk ratios.*

Risk/benefit ratio	Definition
Favorable	Benefits clearly outweigh risks and burdens
Uncertain	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced
Unfavorable	Risks clearly outweigh benefits and burdens

standard (Beckman Coulter, USA) is still a recommendation for performing prostate biopsy. In our review, we considered the Hybritech as standard calibration since it has been the clinical standard used for biopsy recommendations since 1994, the beginning of PSA screening. If the laboratory test used the World Health Organization (WHO) criteria (13) we should consider PSA >3 ng/ml as cut-off for a recommendation to perform prostate biopsy. In young men with a family history of prostate cancer, the cut-off level should be established at 2.5 ng/ml (2).

Even if the free/total PSA ratio (%FPSA) has been demonstrated to reduce the number of unnecessary biopsies, %FPSA (cut-off of 25%) in men with PSA between 2.5 and 10 ng/ml has demonstrated low overall diagnostic accuracy (14). Thus, %FPSA usage should be considered optional in the evaluation of patients for an initial biopsy. Since the probability of finding PCa with a value of %FPSA <10% is relatively high, this cut-off value has remained an indication to perform a biopsy, as shown in the previous guidelines (2).

Several studies have shown that men with PSA density >0.15 ng/ml are significantly more likely to have PCa, but the level of evidence is low (15-17).

This indication has not changed according to the 2007 guidelines. Moreover, PSA velocity and doubling time are

of limited value in supporting indications for biopsy due to several unsolved issues. Prospective studies have not shown that these measurements can provide additional information compared with use of PSA alone (18). No change has been performed comparing with the 2007 guidelines. The use of risk calculators including more clinical parameters have provided good accuracy and could be offered for men with PSA values between 2.5 and 10 ng/ml. Nevertheless, no studies have confirmed the real utility or improvement in the diagnostic process in that clinical setting. Thus, both these parameters are considered optional in the decision-making (19).

Although DRE has a low sensitivity in diagnosing PCa, the presence of an abnormal DRE is associated with an increased risk of PCa with a high Gleason score. A positive DRE remains a strong indication to perform a biopsy independently of the PSA value (2).

Prostate biopsy should be performed if there is suspicion for PCa and if the treatment decision might be changed by PCa diagnosis (patients eligible for surgery for benign prostatic hyperplasia).

The most controversial topic discussed by the Committee was the role of mpMRI in the initial setting. mpMRI has recently gained growing importance in the diagnosis of clinically significant PCa. The estimated mpMRI sensitivity and specificity for PCa detection varies between 57% and 100% *vs*. 44% and 96%, respectively (20-23).

Nowadays, it is advisable to use mpMRI targeted biopsy (TPBx) since it has the potential to reduce the sampling error through localization of disease, increasing the clinically significant PCa detection (24-28). The high negative predictive value of mpMRI is important because it can be used to rule-out significant disease. This may result in fewer or even no biopsies in patients with PSA suspicious for PCa but a negative mpMRI. Moreover, the PIRADS score used to convey the degree of suspicion on mpMRI seems to be the strongest predictor of the presence of clinically significant PCa (24-28).

Nevertheless, the role of mpMRI in the initial setting in the literature is controversial. In general, the results of the mpMRI in PCa detection differs among various series; a recent meta-analysis showed a pooled sensitivity of 0.74 [95% confidence interval (CI)=0.66-0.81], specificity of 0.88 (95% CI=0.82-0.92), negative predictive value ranged from 0.65 to 0.94 and positive predictive value from 0.31 to 0.95, for detection of clinically significant PCa (GS ≥7; volume ≥0.5 cc) (29). The PIRADS categories 4 and 5 are associated with high probability of the presence of clinically significant PCa, while the percentage of such PCa in the PIRADS 3 category is variable from 15% to 29%. Rarely, small foci of csPCa can be present even in PIRADS 1 and 2 categories, but usually tumor missed at mpMRI represents indolent disease (30-32).

There are few studies on this topic. Mozer *et al*. reported the outcomes of comparing TPBx with extended 12-core systematic biopsy (SPBx) in men with no previous biopsies. In a cohort of 152 men, overall cancer detection was lower for TPBx than for SPBx (54% *vs*. 57%). There was almost no difference in the detection of Gleason score 7 or higher between the two techniques in their biopsy results (21.7% *vs*. 22.4%). However, when categorized as clinically significant disease *vs*. clinically insignificant disease, TPBx detected more significant cancers than did SPBx (43.4% *vs*. 36.8%) (33).

Delongchamps *et al*. also reported outcomes of pre-biopsy mpMRI and TPBx *vs*. SPBx in 391 men who presented for the first biopsy. TPBx demonstrated higher Gleason score 7 and overall PCa detection than SPBx. In these two groups, but not in the visual co-registration group, TPBx also yielded higher overall cancer detection than SPBx (34).

Pokorny *et al*. reported the results of TPBx *vs*. SPBx in biopsy-naive men. Of 142 men with abnormal mpMRI, defined as a PIRADS score of 3 or greater, PCa was detected by SPBx in 101 (71.1%) *vs*. 99 (69.7%) by TPBx. However, TPBx detected more high-risk cancer than did standard biopsy (65.5% *vs*. 52.1%) (22).

Nevertheless, Schoots *et al*., in a recent meta-analysis, showed that in men with clinical suspicion of PCa and a suspicious lesion observed on mpMRI, TPBx and SPBx did not differ in overall detection of PCa. However, TPBx had a higher rate of detection of clinically significant PCa and a lower rate of detection of insignificant PCa compared to SPBx (29). Subgroup analysis showed that TPBx improved the detection of clinically significant PCa in men with a previous negative biopsy, rather than in men with an initial biopsy. Moreover, in a randomized Finnish clinical trial, addition of mpMRI prior to prostate biopsy, appeared to offer similar diagnostic accuracy compared with routine systematic 12-cores SPBx in the diagnosis of PCa, since similar number of cancer were detected with and without mpMRI (35).

On the contrary, recently, Mendhiratta *et al*. reported the largest reported cohort of biopsy-naive men undergoing TPBx and SPBx. By yielding a lower rate of overall cancer detection, but a higher rate of Gleason score 7 or greater cancer detection compared to SPBx, their TPBx outcomes reflected the trends reported in other mpMRI-guided prostate biopsy trials. They also demonstrated a significant reduction in low-risk PCa detection with TPBx (36-37).

A great relevance has been given to these results of Mendhiratta *et al*.: Out of 34 clinically insignificant cancers detected by SPBx and missed by TPBx, 24 (70.1%) were detected in men with PIRADS less than 4 (36-37). They concluded that mpMRI is able to provide added ability to predict the risk of Gleason score 7 or greater PCa, with a negative predictive value of >80% for detecting Gleason score 7 or greater PCa in men with PIRADS ≤3 and a positive predictive value of about 70% in men with a

maximum level of suspicious of 4/5. Thus, it may be possible to further optimize the balance between high-grade PCa detection and avoidance of low-risk disease. The authors concluded that pre-biopsy mpMRI followed by TPBx and avoidance of SPBx in select men, especially those with PIRADS 2 or 3, may provide the greatest potential to limit the detection of low-risk cancer while maximizing the detection of high-grade disease.

Based on these observations, the Committee concluded that mpMRI is not mandatory in the initial setting, but when performed, only patients with a PIRADS 4 or 5 should be submitted to prostate biopsy.

2 Indication for re-biopsy

Recommendation 2: A prostatic re-biopsy is strongly recommended with a

- PSA rising above 10 ng/ml
- Positive DRE or DRE modifications
- Inadequate first biopsy set, with or without ASAP finding, with or without multifocal high-grade prostatic intraepithelial neoplasia (HGPIN)
- Positive mpMRI PIRADS ≥3

There is no consensus regarding the need for repeat biopsy in men with previous negative sampling except for those with abnormal histology [*i.e.*, >3 cores with HGPIN, atypical small acinar proliferation (ASAP)], or inadequate initial prostate biopsy and persistence of an elevated PSA level (38).

HGPIN is considered a precursor for PCa development (39, 40). The median risk recorded in the literature for cancer following the diagnosis of isolated HGPIN on needle biopsy is 24.1%, which is not much higher than the risk reported in the literature for a repeat biopsy (39, 40). Current recommendations for isolated HGPIN diagnosis suggest follow-up and the panel was in agreement to consider this approach a strong recommendation. The meaning of multifocal HGPIN is biologically different (41-43); current recommendations for extensive HGPIN (multiple biopsy sites, *i.e.* ≥3) diagnosis suggest repeating the biopsy within 12 months of the initial biopsy. The Committee is also in agreement to strongly consider re-biopsy in this situation.

ASAP is a diagnosis that occurs in about 1-2% of prostate biopsies (44-47). The term ASAP, first defined by Bostwick, represents suspicious glands without adequate histological atypia for a definitive diagnosis of prostate adenocarcinoma (57). Previous studies have suggested that 17-90% of patients with ASAP have adenocarcinoma present on subsequent prostate biopsies. This would most likely represent under sampling rather than disease progression. Current recommendations (59-66) for ASAP diagnosis suggest repeating the biopsy within 3-6 months of the initial biopsy. The panel of experts has not modified the previous version of guidelines (45-48).

2.1 Prostate cancer markers and indication for re-biopsy. The prostatic cancer gene 3 (PCA3) score which is obtained after massage of the prostate and is measured in the urinary sediment, has been shown to be superior to PSA and the %FPSA in early detection. Univariate analyses have shown that PCA3 and PSA had an Area Under the Curve (AUC) of 0.69-0.76 and 0.68-0.73, respectively, *vs*. 0.54-0.65 and 0.52-0.58, respectively, in the initial and repeated setting, respectively (49-56). This molecular marker may help in the decision-making process with regard to a repeat biopsy in men with a negative first biopsy but a persistent suspicion of prostate cancer. Unfortunately, no consensus has been reached about the most helpful cut-off. The majority of studies recommend a threshold value of 35 as providing a better balance between sensitivity and specificity. Recently, the literature has compared the cutoff value of 35 with a lower one (*e.g.* 20), reporting an improvement of the performance of the test. In patients undergoing a repeat biopsy, sensitivity and specificity of 93% and 64%, respectively, have been reported (49-56). On the basis of the quality of the evidence in the literature, the IPBG Committee has therefore stated a very weak recommendation against the use of PCA3 score as an indication for first biopsy, and a weak recommendation in favor of the use of PCA3 score as an indication for a re-biopsy in patients with persistently elevated PSA.

The Prostate Health Index (PHI) represents a mathematical formula that includes −2proPSA, total PSA and free PSA. Different prospective trials showed the superiority of the PHI compared to PSA and PSA derivatives, mainly, at first biopsy. The AUC ROC curve values range between 0.70 and 0.88 for PHI, between 0.50 and 0.53 for PSA and between 0.58 and 0.68 for %FPSA (58-65). The PHI also seems to correlate with biological aggressiveness of cancer, the risk of progression in case of active surveillance, and the tendency to metastasize (58-65). In the case of the first set of biopsies, both in univariate and multivariate analysis, PCA3 was found to provide a better global diagnostic accuracy (AUC 0.71 *vs*. 0.65), while PHI was a superior predictor of clinically significant PCa, with an AUC of 0.80 *vs*. 0.55 (58-67). The Committee stated a weak positive recommendation for the use of PHI in the management of the first biopsy; on the other hand it stated a weak recommendation against its use as an indication for a re-biopsy.

2.2 Prostate cancer Imaging and indication for re-biopsy. In the diagnostic workup of patients with suspected PCa, mpMRI represents the second and probably the second most important step after one (or more) prior negative biopsies. In the literature, there is an overall consensus that mpMRI is useful in candidates for repeat biopsy and the detection rate for PCa in these patients ranges between 39% and 59%, with an incidence of cancer located only in the anterior zone of 20% (68-73). Porpiglia *et al*. demonstrated that mpMRI is significantly superior to PCA3

and PHI in predicting the outcome of a prostatic biopsy after an initial negative result (74). In a recent meta-analysis, mpMRI was shown to have the potential to accurately exclude significant PCa and reduce biopsy burden (29). Fourteen articles reporting the outcomes of 15 studies were included. Valerio *et al*. reported that TPBx detected more clinically significant PCa (median: 33.3% *vs*. 23.6%; range: 13.2-50% *vs*. 4.8-52%) using fewer cores (median: 9.2 *vs*. 37.1) compared with SPBx, respectively. Some studies showed a lower detection rate of all cancer (median: 50.5% *vs*. 43.4%; range: 23.7-82.1% *vs*. 14.3-59%). TPBx was able to detect some clinically significant PCa that would have been missed by using only SPBx (median: 9.1%; range: 5-16.2%). Fusion TPBx detected more clinically significant PCa than visual-cognitive TPBx in the only study reporting this outcome (20.3% *vs*. 15.1%).

Cash *et al*. showed that detection of clinically significant PCa is correlated with the PIRADS score (32). Their analysis included 408 consecutive men who underwent TPBx and 10-core SPBx. The overall cancer detection rate was 56% (227/408). The cancer detection rates correlated with PIRADS 2, 3, 4 and 5 and were 16% (5/32), 26% (29/113), 62% (94/152) and 89% (99/111), respectively. They concluded that cancer detection rate was strongly correlated with a rising PIRADS score, values of 4 and 5 increasing the detection of clinically significant PCa and leading to a higher histological stage after surgery.

The results described above are supported by the high negative predictive value of mpMRI on a patient-by-patient basis and a sufficient accuracy on a lesion-by-lesion basis. Nonetheless, current reported figures for the negative predictive value for mpMRI range from 60% to 100% (29); this wide range is due to the lack of standardized criteria for reporting mpMRI results, defining clinically significant PCa, population features, analysis methods and, last but not least, radiologist expertise, between different studies. The reliability of a negative mpMRI is a key clinical metric. It is, therefore, important for an mpMRI to accurately exclude tumor, and a low false-negative rate is a key determinate of whether this approach is clinically feasible.

The Committee has defined the mandatory technical requirements and the reporting system that should always be adopted (74). In particular, it is suggested to report the detection and measurements of all abnormal prostatic lesions with the identification of the index lesion, the localization of the lesion according to the Dickinson scheme, and the probability of extraprostatic extension. The suspicious lesions should be scored according to the PIRADS v.2 system (74-76).

The Committee concluded that mpMRI is necessary in most cases after an initial negative biopsy, and a TPBx (cognitive or software-based, as well as fusion) should be performed in case of PIRADS 4 or 5. TPBx in PIRADS 3 foci may be considered according to clinical parameters. The expertise of the radiologist in the interpretation of mpMRI seems to be a key factor.

3 Number of cores to be taken when performing a biopsy

Recommendation 3: At least 12 cores should be taken in each patient plus targeted (fusion or cognitive) biopsies on suspicious area [at mpMRI or transrectal ultrasound (TRUS)]. Saturation biopsies are optional in all settings. Both peripheral and anterior zone should be always sampled.

Optimizing PCa detection rate in clinical practice translates into defining the ideal number and location of biopsy cores to maximize detection of clinically significant PCa, minimize detection of clinically insignificant PCa, and reduce the necessity for repeat biopsy. The SPBx scheme (sextant template plus laterally directed sampling from each sextant template) has become the most widely accepted method in the initial procedure (15, 77-80). Some authors emphasize the need to sample the apical and far-lateral regions as these appear to increase the detection rate for PCa. However,transition-zone sampling does not improve PCa detection at initial biopsy (78-81). In candidates for surgery for benign prostate hyperplasia (*i.e*. prostate laser vaporization), prostate biopsies of the anterior zone are recommended even if not mandatory. A potential drawback of increasing the core number at the time of initial prostate biopsy is the increased likelihood of detecting insignificant PCa, especially when sampling the anterior region of the prostate.

The panel of experts did not support the recommendations to use saturation biopsy (≥20 cores) in biopsy naive men even if they suggested to consider more aggressive scheme than the classical extended 12-core scheme. However, the number and location of cores may vary according to some modulatory factors such as prostate volume (≥60 cc), patient features (*i.e*. age, comorbidities *etc*.), suspicious areas on imaging. The search for and targeting of hypoechoic lesions on TRUS remain controversial but, nowadays, only suspicious areas at mpMRI (in particular area classified as PIRADS 4 or 5) have been demonstrated to have a high degree of correlation with clinically significant PCa and can be used to define a targeted area before prostate biopsy (82).

A repeat biopsy strategy may include extended prostate biopsy (>12 cores), saturation biopsy, or image (mpMRI) guidance to improve the detection rate (15, 82). Overall, when performing repeat prostate biopsy, it is mandatory to increase the number of cores compared to the initial setting (82); moreover, it is important to recognize that regions of the prostate such as the anterior apex, the peripheral midline and far anterior zone are under-sampled at initial biopsy (77-80). Saturation prostate biopsy may be considered in men with a prior negative biopsy and persistent suspicion of prostate cancer. Nowadays, it is advisable to use TPBx for the repeat session, indeed, it has the potential to reduce the sampling error through localization of disease, increasing the detection of clinically significant PCa.

The optimal technique for TPBx is still a matter of debate. Two recent trials compared the diagnostic accuracy of

software-based biopsy to cognitive (visual) biopsy and failed to detect a significant difference in the overall detection of clinically significant PCa (83-84). Nevertheless, the Committee did consider that there may be some differences in the respective abilities of these techniques to detect PCa in different locations of the prostate.

4 Biopsy approach and technique

Recommendation 4a: Transrectal and transperineal prostate biopsy procedures are recommended with the same level of evidence.

Although the majority of the Urological Centers perform biopsy *via* the transrectal approach, in recent years, the transperineal prostate biopsy has gained popularity due to its lower incidence of sepsis (71), higher detection rate for anterior PCa (15-20% of the cases) and the opportunity to perform template-guided prostate biopsy (85-87). Transrectal and transperineal prostate biopsy procedures are recommended with the same level of evidence (76) and provided a similar detection rate for PCa in initial (34%-40%) and repeat procedures (22-43%) with at least 12 (extended biopsy) and 20 (saturation biopsy) cores, respectively (85-87) (Table I).

Recommendation 4b: The Committee has recommended extended biopsy schemes be combined with TPBx in the reclassification of men under active surveillance.

The prostate biopsy is the gold standard in the reclassification of men enrolled in active surveillance. Confirmatory repeat biopsy, which is generally performed after 1 year of enrollment, is the most important instrument to define unfavorable quantitative histological results (25-30% of the cases) and probably progression (*i.e.*, Gleason score >6, number of positive cores >2, greatest percentage of cancer >50%) (88-90). The optimal number of biopsy cores (extended *vs*. saturation *vs*. template-guided schemes) and biopsy approach (transrectal *vs*. transperineal) have not been established, while the transperineal biopsy seems more accurate at identifying the PCa risk class of the patients enrolled in active surveillance protocols (88-90). The committee has recommended to perform extended (or even saturation prostate) biopsy schemes combined with TPBx in order to obtain the highest accuracy in diagnosing csPCa in the reclassification of men in active surveillance. Finally, transperineal prostate biopsy greatly reduces the incidence of sepsis (strong recommendation) secondary to antibiotic resistance (range: 0-0.07% of cases), which in men submitted to a transrectal approach could reach 1-2.5% of the cases (88-90).

5 How to reduce infections

Recommendation 5: In men at high risk of sepsis (*i.e.* recurrent prostatitis, recurrent urinary tract infection, hospitalization), rectal culture or transperineal approach are strongly recommended. Changing or use of double antibiotic drugs is optional.

Clinical complications and hospital admissions following prostate biopsy have increased during the past 10 years primarily due to an increasing rate of infection (87). Although antibiotic prophylaxis following prostate biopsy is mandatory, there are no definitive data to confirm that long-course (>3 days) are superior to short-course antibiotic treatments (1 day) (87); in order to achieve an optimal therapeutic level of antibiotic, the drug should be administered 2-3 hours prior to the biopsy. The risk of sepsis following transrectal biopsy reached 1-2.5% of cases, mainly due to multidrug-resistant *Escherichia coli* (86, 91-92). To date there is no strong evidence for factors associated with infective complications; fecal carriage of fluoroquinolone-resistant *E. coli* strains represents a significant risk factor classifying patients into a high-risk group for infective complications after transrectal prostate biopsy (93).

Various strategies have been reported to reduce infectious complications. One strategy is rectal cleansing with povidone-iodine prior to transrectal biopsy, but this failed to reduce infection significantly (94). Many studies have investigated switching or expanding the antimicrobial regimen, performing rectal swab cultures and using different techniques for biopsy. Patients with ciprofloxacin-sensitive bacteria can then receive ciprofloxacin prophylaxis, while culture results can guide an alternative selection for those with resistance. Although a positive rectal swab culture is a risk factor for infection after transrectal biopsy, the presence of resistant organisms does not necessarily translate into clinical infection. Most studies have shown that there is no evident superiority in antibiotic prophylaxis and its disadvantages, such as possible increase in side-effects, cost effectiveness and the drawback of increasing future antimicrobial resistance are of great concern (94-96). It is noteworthy that according to recent randomized trials, fosfomycin before transrectal prostate biopsy led to a lower rate of infective complications when compared with standard therapy with fluoroquinolone drugs, thus representing a strong alternative for antibiotic prophylaxis, in particular in populations where fluoroquinolone resistance is common (98). To date, there are no randomized studies showing that targeted prophylaxis using rectal swabs reduces infection and cost compared with standard or expanded prophylaxis. In clinical practice, enema containing iodine-povidone or clorexidine is used in most centers using the transrectal approach. Even if weak scientific evidence supports this procedure, an antibacterial enema performed immediately before transrectal biopsy is recommended according to expert opinion.

The Committee stated that all men undergoing transrectal prostatic biopsies should receive antimicrobial prophylaxis, should be warned about the increasing risk of infection, and told to seek prompt medical care in case of signs of systemic infection. In men at risk of sepsis (*i.e.* those with recurrent prostatitis, recurrent urinary tract infection, prior hospitalization for sepsis at initial biopsy) culture based on rectal swab or transperineal approach are suggested.

6 How to optimize prostate biopsy preparation in order to reduce complications

Recommendation 6: In order to reduce risk of bleeding, when possible, anticoagulant or anti-aggregant drugs should be stopped 7 days before biopsy.

Biopsy is typically well tolerated, with a low risk of major complications. However, minor complications such as bleeding and pain are frequent.

One of the most frequent and bothersome complications of transrectal biopsy is bleeding (87), such as hematuria, hematospermia, and hematochezia, or rectal bleeding.

One contentious area is the discontinuation of anticoagulant therapy before biopsy, which involves a balance of risks between cardiovascular or thromboembolic events when stopping anticoagulation *versus* the risk of bleeding and associated complications with continuation. Various reports have described bleeding complications in men taking warfarin and aspirin.

A systematic review and meta-analysis of aspirin use and bleeding following transrectal biopsy found higher rates of hematuria with use of anticoagulant. In total, 3218 men were identified in reports from 1990-2011, and the risk of hematuria increased 1.36-fold with aspirin use (99-100). Rectal bleeding and hematospermia were not statistically increased. The authors concluded that continuing aspirin did not increase the risk of moderate and severe hematuria after transrectal biopsy, thus stopping aspirin is unnecessary.

Giannarini *et al*. prospectively assigned 196 men to continue aspirin, replaced it with low molecular-weight heparin or discontinued aspirin without replacement for transrectal biopsy. There was no difference in the overall bleeding rate among groups. Although no severe bleeding complications occurred, men on anticoagulant reported bleeding for a longer duration. The authors concluded that aspirin did not increase mild bleeding but did prolong its duration (101).

The Committee concluded that whenever possible, anticoagulant or anti-aggregant drugs should be stopped 7 days before the procedure (102).

Local anesthesia using 10 mg of lidocaine to perform the periprostatic block is, nowadays, mandatory. In the case of transperineal saturation, template biopsy or fusion procedure, locoregional or even general anesthesia are recommended.

7 Pathological issues

Recommendation 7: If the length of the fresh specimen is less than 1 cm, one more biopsy core in the same sampling is recommended. Biopsy specimens should be collected single or grouped (no more than 2 or 3), labeled separately per zone (base, mid, apex, anterior zone) and collected by pre-embedded sandwich technique. The new definition of grading patterns for PCa suggesting five prognostic grade groups should always be adopted in addition to the Gleason scoring system.

The average length of prostatic tissue per biopsy core should be >10 mm, if the length of the fresh specimen is less, one more biopsy core in the same sampling is recommended. Biopsy specimens should be collected as single or grouped (no more than 2 or 3), labeled separately per side (right and left) and area (base, mid, apex, anterior zone) and collected by pre-embedded sandwich technique (103). Recently, the International Society of Urological Pathology (ISUP) stated a new definition of grading patterns for Prostate cancer suggesting five prognostic Grade Groups. The new grades would, for the foreseeable future, be used in conjunction with the Gleason system (*i.e*. Gleason score 3+3=6, Grade group 1). The new grading system and the terminology Grade Groups 1-5 have also been accepted by the World Health Organization (appendix I-III) (104).

Conclusion

These updated guidelines and recommendations are intended to assist physicians and patients in decision-making regarding when and how to perform a prostatic biopsy.

References

1 Siegel RL, Miller KD and Jemal A: Cancer statistics. CA Cancer J Clin *65*: 5-29, 2015.

2 Bertaccini A, Fandella A, Prayer-Galetti T, Scattoni V, Galosi AB, Ficarra V, Trombetta C, Gion M and Martorana G: Italian Group for Developing Clinical Practice Guidelines on Performing Prostate Biopsy: Systematic development of clinical practice guidelines for prostate biopsies: a 3-year Italian project. Anticancer Res *27*: 659-666, 2007.

3 Schünemann H, Jaeschke R, Cook D, Bria W, El-Solh A and Ernst A: An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med *174*: 605-614, 2006.

4 Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P and Schünemann HJ: GRADE Working Group: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ *336*: 924-926, 2008.

5 Shiffman R, Shekelle P, Overhage J, Slutsky J, Grimshaw J and Deshpande A: Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Ann Intern Med *139*: 493-498, 2003.

6 Prayer-Galetti T, Ficarra V, Franceschini R, Liguori G, Martino P and Schiavina R: Gruppo Italiano Biopsia Prostatica: When to carry out prostate biopsy. Arch Ital Urol Androl *77*: 3-16, 2005.

7 Liss MA, Billimek J, Osann K, Cho J, Moskowitz R, Kaplan A, Szabo RJ, Kaplan SH, Greenfield S and Dash A: Consideration of comorbidity in risk stratification prior to prostate biopsy. Cancer *13*: 2413-2418, 2013.

8 Sammon JD, Abdollah F, D'Amico A, Gettman M, Haese A, Suardi N, Vickers A and Trinh QD: Predicting Life Expectancy in Men Diagnosed with Prostate Cancer. Eur Urol *68*: 756-765, 2015.

9 Daskivich TJ, Kwan L, Dash A, Greenfield S and Litwin MS: Weighted *versus* unweighted Charlson score to predict long-term other-cause mortality in men with early-stage prostate cancer. Eur Urol *66*: 1002-1009, 2014.

10 Park YH, Lee JK, Jung JW, Lee BK, Lee S, Jeong SJ, Hong SK, Byun SS and Lee SE: Prostate cancer detection rate in patients with fluctuating prostate-specific antigen levels on the repeat prostate biopsy. Prostate Int *2*: 26-30, 2014.

11 Busato WF, Almeida GL, Geraldo J and Busato FS: Does PSA reduction after antibiotic therapy permits postpone prostate biopsy in asymptomatic men with PSA levels between 4 and 10 ng/mL? Int Braz J Urol *41*: 329-336, 2015.

12 Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS and Parnes HL: Prevalence of prostate cancer among men with a prostate-specific antigen level ≤4.0 ng per milliliter. N Engl J Med *350*: 2239-2246, 2004.

13 Stamey TA: Second Stanford Conference on international Standardization of Prostate-Specific Antigen Immunoassays: September 1 and 2, 1994. Urology *45*: 173-184, 1995.

14 Bruzzese D, Mazzarella C, Ferro M, Perdonà S, Chiodini P, Perruolo G and Terracciano D: Prostate health index *vs*. percent free prostate-specific antigen for prostate cancer detection in men with "gray" prostate-specific antigen levels at first biopsy: systematic review and meta-analysis. Transl Res *164*: 444-445, 2014.

15 Scattoni V, Maccagnano C, Capitanio U, Gallina A, Briganti A and Montorsi F: Random biopsy: When, how many and where to take the cores? World J Urol *32*: 859-869, 2014.

16 Amini E, Pishgar F, Ayati M, Jamshidian H, Arbab A, Gooshe M and Nowroozi MR: Transition zone prostate-specific antigen density could better guide the rebiopsy strategy in men with prostate inflammation at initial biopsy. Urology *86*: 985-990, 2015.

17 Teoh JY, Yuen SK, Tsu JH, Wong CK, Ho BS, Ng AT, Ma WK, Ho KL and Yiu MK: The performance characteristics of prostate-specific antigen and prostate-specific antigen density in Chinese men. Asian J Androl. 2015, doi: 10.4103/1008-682X.167103.

18 Heidegger I, Klocker H, Pichler R, Horninger W and Bektic J: PSA isoform velocities for early diagnosis of prostate cancer. Anticancer Res *35*: 3567-3570, 2015.

19 Tormey WP: Prostate cancer risk calculators using ERSPC-derived data underestimate the risk if the WHO IRP 96/670 standard is used in prostate-specific antigen analysis. Eur Urol *68*: 541-542, 2015.

20 Fütterer JJ, Briganti A, De Visschere P, Emberton M, Giannarini G, Kirkham A, Taneja SS, Thoeny H, Villeirs G and Villers A: Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. Eur Urol *68*: 1045-1053, 2015.

21 Valerio M, Donaldson I, Emberton M, Ehdaie B, Hadaschik BA, Marks LS, Mozer P, Rastinehad AR and Ahmed HU: Detection of clinically significant prostate cancer using magnetic resonance imaging-ultrasound fusion targeted biopsy: a systematic review. Eur Urol *68*: 8-19, 2015.

22 Renard Penna R, Mozer P, Cornud F, Barry-Delongchamps N, Bruguière E, Portalez D and Malavaud B: Prostate Imaging Reporting and Data System and Likert scoring system: multiparametric MR imaging validation study to screen patients for initial biopsy. Radiology *275*: 458-468, 2015.

23 Pokorny MR, de Rooij M, Duncan E, Schröder FH, Parkinson R, Barentsz JO and Thompson LC: Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy *versus* magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. Eur Urol *66*: 22-29, 2014.

24 de Rooij M, Hamoen EH, Fütterer JJ, Barentsz JO and Rovers MM: Accuracy of multiparametric MRI for prostate cancer detection: a meta-analysis. Am J Roentgenol *202*: 343-351, 2014.

25 Baco E, Rud E, Eri LM, Moen G, Vlatkovic L, Svindland A, Eggesbø HB and Ukimura O: A randomized controlled trial to assess and compare the outcomes of two-core prostate biopsy guided by fused magnetic resonance and transrectal ultrasound images and traditional 12-core systematic biopsy. Eur Urol *69*: 149-156, 2016.

26 Junker D, Schäfer G and Edlinger M: Evaluation of the PI-RADS scoring system for classifying mpMRI findings in men with suspicion of prostate cancer. Biomed Res Int doi: 10.1155/2013/252939, 2013.

27 Itatani R, Namimoto T, Atsuji S, Katahira K, Morishita S, Kitani K, Hamada Y, Kitaoka M, Nakaura T and Yamashita Y: Negative predictive value of multiparametric MRI for prostate cancer detection: outcome of 5-year follow-up in men with negative findings on initial MRI studies. Eur J Radiol *83*: 1740-1745, 2014.

28 Barentsz JO, Richenberg J and Clements R: ESUR prostate MR guidelines 2012. Eur Radiol *22*: 746-757, 2012.

29 Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW and Hunink MG: Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol *68*: 438-450, 2015.

30 Harada T, Abe T, Kato F, Matsumoto R, Fujita H, Murai S, Miyajima N, Tsuchiya K, Maruyama S, Kudo K and Shinohara N: Five-point Likert scaling on MRI predicts clinically significant prostate carcinoma. BMC Urol *4;15*: 91, 2015.

31 Costa DN, Lotan Y, Rofsky NM, Roehrborn C, Liu A, Hornberger B, Xi Y, Francis F and Pedrosa I: Assessment of Prospectively Assigned Likert Scores for Targeted Magnetic Resonance Imaging-Transrectal Ultrasound Fusion Biopsies in Patients with Suspected Prostate Cancer. J Urol *195*: 80-87, 2016.

32 Cash H, Maxeiner A, Stephan C, Fischer T, Durmus T, Holzmann J, Asbach P, Haas M, Hinz S, Neymeyer J, Miller K, Günzel K and Kempkensteffen C: The detection of significant prostate cancer is correlated with the Prostate Imaging Reporting and Data System (PIRADS) in MRI/transrectal ultrasound fusion biopsy. World J Urol *34*: 525-532, 2016.

33 Mozer P, Rouprêt M, Le Cossec C, Granger B, Comperat E, de Gorski A, Cussenot O and Renard-Penna R: First round of targeted biopsies using magnetic resonance imaging/ultrasonography fusion compared with conventional transrectal ultrasonography-guided biopsies for the diagnosis of localised prostate cancer. BJU Int *115*: 50-57, 2015.

34 Delongchamps NB, Peyromaure M, Schull A, Beuvon F, Bouazza N, Flam T, Zerbib M, Muradyan N, Legman P and Cornud F: Prebiopsy magnetic resonance imaging and prostate cancer detection: comparison of random and targeted biopsies. J Urol *189*: 493-499, 2013.

35 Tonttila PP, Lantto J, Pääkkö E, Piippo U, Kauppila S, Lammentausta E, Ohtonen P and Vaarala MH: Prebiopsy multiparametric magnetic resonance imaging for prostate cancer diagnosis in biopsy-naive men with suspected prostate cancer based on elevated prostate-specific antigen values: results from a randomized prospective blinded controlled trial. Eur Urol *69*: 419-425, 2016.

36 Mendhiratta N, Rosenkrantz AB, Meng X, Wysock JS, Fenstermaker M, Huang R, Deng FM, Melamed J, Zhou M, Huang WC, Lepor H and Taneja SS: Magnetic resonance imaging-ultrasound fusion targeted prostate biopsy in a consecutive cohort of men with no previous biopsy: reduction of overdetection through improved risk stratification. J Urol *194*: 1601-1606, 2015.

37 Mendhiratta N, Meng X, Rosenkrantz AB, Wysock JS, Fenstermaker M, Huang R, Deng FM, Melamed J, Zhou M, Huang WC, Lepor H and Taneja SS: Prebiopsy MRI and MRI-ultrasound fusion-targeted prostate biopsy in men with previous negative biopsies: impact on repeat biopsy strategies. Urology *86*: 1192-1198, 2015.

38 Ukimura O, Coleman JA, de la Taille A, Emberton M, Epstein JI, Freedland SJ, Giannarini G, Kibel AS, Montironi R, Ploussard G, Roobol MJ, Scattoni V and Jones JS: Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. Eur Urol *63*: 214-230, 2013.

39 Herawi M, Kahane, H, Cavallo C and Epstein JI: Risk of prostate cancer on first re-biopsy within 1 year following a diagnosis of high-grade prostatic intraepithelial neoplasia is related to the number of cores sampled. J Urol *175*: 121-124, 2006.

40 Merrimen JL, Jones G, Walker D, Walker D, Leung CS, Kapusta LR and Srigley JR: Multifocal high-grade prostatic intraepithelial neoplasia is a significant risk factor for prostatic adenocarcinoma. J Urol *182*: 485-490, 2009.

41 Eminaga O, Hinkelammert R, Abbas M, Titze U, Eltze E, Bettendorf O and Semjonow A: High-grade prostatic intraepithelial neoplasia (HGPIN) and topographical distribution in 1,374 prostatectomy specimens: existence of HGPIN near prostate cancer. Prostate *73*: 1115-1122, 2013.

42 Roscigno M, Scattoni V, Freschi M, Raber M, Colombo R, Bertini R, Montorsi F and Rigatti P: Monofocal and plurifocal high-grade prostatic intraepithelial neoplasia on extended prostate biopsies: factors predicting cancer detection on extended repeat biopsy. Urology *63*: 1105-1110, 2004.

43 Taneja SS, Morton R, Barnette G, Sieber P, Hancock ML and Steiner M: Prostate cancer diagnosis among men with isolated high-grade intraepithelial neoplasia enrolled onto a 3-year prospective phase III clinical trial of oral toremifene. J Clin Oncol *31*: 523-529, 2013.

44 Montironi R, Scattoni V, Mazzucchelli R, Lopez-Beltran A, Bostwick DG and Montorsi F: Atypical foci suspicious but not diagnostic of malignancy in prostate needle biopsies (also referred to as 'atypical small acinar proliferation suspicious for but not diagnostic of malignancy'). European Urology *50*: 666-674, 2006.

45 Scattoni V, Roscigno M, Freschi M, Briganti A, Fantini GV, Bertini R, Salonia A, Montorsi F and Rigatti P: Predictors of prostate cancer after initial diagnosis of atypical small acinar proliferation at 10 to 12 core biopsies. Urology *66*: 1043-1047, 2005.

46 Dorin RP, Wiener S, Harris CD and Wagner JR: Prostate atypia: does repeat biopsy detect clinically significant prostate cancer? Prostate *75*: 673-678, 2015.

47 Leone A, Rotker K, Butler C, Mega A, Li J, Amin A, Schiff SF, Pareek G, Golijanin D and Renzulli JF: Atypical small acinar proliferation: repeat biopsy and detection of high grade prostate cancer. Prostate Cancer doi: 10.1155/2015/810159, 2015.

48 Chun FK, de la Taille A, van Poppel H, Marberger M, Stenzl A, Mulders PF, Huland H, Abbou CC, Stillebroer AB, van Gils MP, Schalken JA, Fradet Y, Marks LS, Ellis W, Partin AW and Haese A: Prostate cancer gene 3 (PCA3): development and internal validation of a novel biopsy nomogram Eur Urol *56*: 659-668, 2009.

49 Marks LS, Fradet Y, Deras IL, Blase A, Mathis J, Aubin SM, Cancio AT, Desaulniers M, Ellis WJ, Rittenhouse H and Groskopf J: PCA3 molecular urine assay for prostate cancer in men undergoing repeat biopsy. Urology *69*: 532-535, 2007.

50 Haese A, de la Taille A, van Poppel H, Marberger M, Stenzl A, Mulders PF, Huland H, Abbou CC, Remzi M, Tinzl M, Feyerabend S, Stillebroer AB, van Gils MP and Schalken JA: Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy. Eur Urol *54*: 1081-1088, 2008.

51 Wei JT, Feng Z, Partin AW, Brown E, Thompson I, Sokoll L, Chan DW, Lotan Y, Kibel AS, Busby JE, Bidair M, Lin DW, Taneja SS, Viterbo R, Joon AY, Dahlgren J, Kagan J, Srivastava S and Sanda MG: Can urinary PCA3 supplement PSA in the early detection of prostate cancer? J Clin Oncol *32*: 4066-4072, 2014.

52 Pepe P and Aragona F: Prostate cancer detection rate at repeat saturation biopsy. PCPT risk calculator *versus* PCA3 score *versus* case-finding protocol. Can J Urol *20*: 6620-6624, 2013.

53 Bollito E, De Luca S, Cicilano M, Passera R, Grande S, Maccagnano C, Cappia S, Milillo A, Montorsi F, Scarpa RM, Papotti M and Randone DF: Prostate cancer gene 3 urine assay cut-off in diagnosis of prostate cancer: a validation study on Italian patient population undergoing first and repeat biopsy. Anal Quant Cytol Pistol *34*: 96-104, 2012.

54 Capoluongo E, Zambon CF, Basso D, Boccia S, Rocchetti S, Leoncini E, Palumbo S, Padoan A, Albino G, Todaro A, Prayer-Galetti T, Zattoni F, Zuppi C and Plebani M: PCA3 score of 20 could improve prostate cancer detection: results obtained on 734 italian individuals Cl Chim *428*: 46-50, 2014.

55 Merola R, Tomao L, Antenucci A, Sperduti I, Sentinelli S, Masi S, Mandoj C, Orlandi G, Papalia R, Guaglianone S, Costantini M, Cusumano G, Cigliana G, Ascenzi P, Gallucci M and Conti L: PCA3 in prostate cancer and tumor aggressiveness detection on 407 high risk patients: a National, Cancer Institute experience. J Exp Clin Res *34*: 15, 2015.

56 Filella X, Foj L, Augé JM, Molina R and Alcover J: Clinical utility of %p2PSA and prostate health index in the detection of prostate cancer. Clin Chem Lab Med *52*: 1347-1355, 2014.

57 Bostwick DG and Cheng L: Precursor of prostate cancer. Hystopathology *60*: 4-27, 2012.

58 Perdonà S, Bruzzese D, Ferro M, Autorino R, Marino A, Mazzarella C, Perruolo G, Longo M, Spinelli R, Di Lorenzo G, Oliva A, De Sio M, Damiano R, Altieri V and Terracciano D: Prostate health index (PHI) and prostate cancer antigen 3 (PCA3) significantly improve diagnostic accuracy in patients undergoing prostate biopsy. Prostate *73*: 227-235, 2013.

59 Lazzeri M, Briganti A, Scattoni V, Lughezzani G, Larcher A, Gadda GM, Lista G, Cestari A, Buffi N, Bini V, Freschi M, Rigatti P, Montorsi F and Guazzoni G: Serum index test %[-2]proPSA and Prostate Health Index are more accurate than prostate specific antigen and %fPSA in predicting a positive repeat prostate biopsy. J Urol *188*: 1137-1143, 2012.

60 Ito K, Miyakubo M, Sekine Y, Koike H, Matsui H, Shibata Y and Suzuki K: Diagnostic significance of [-2]pro-PSA and prostate dimensionadjusted PSA-related indices in men with total PSA in the 2.0-10.0 ng/ml range. World J Urol *31*: 305-311, 2013.

61 Ng CF, Chiu PK, Lam NY, Lam HC, Lee KW and Hou SS: The Prostate Health Index in predicting initial prostate biopsy outcomes in Asian men with prostate-specific antigen levels of 4-10 ng/ml. Int Urol Nephrol *46*: 711-717, 2014.

62 Guazzoni G, Lazzeri M, Nava L, Lughezzani G, Larcher A, Scattoni V, Gadda GM, Bini V, Cestari A, Buffi NM, Freschi M, Rigatti P and Montorsi F: Preoperative prostate-specific antigen isoform p2PSA and its derivatives, %p2PSA and prostate health index, predict pathologic outcomes in patients undergoing radical prostatectomy for prostate cancer. Eur Urol *61*: 455-466, 2012.

63 Heidegger I, Klocker H, Steiner E, Skradski V, Ladurner M, Pichler R, Schäfer G, Horninger W and Bektic J: [-2]proPSA is an early marker for prostate cancer aggressiveness. Prostate Cancer Prostatic Dis *17*: 70-74, 2014.

64 Seisen T, Rouprêt M, Brault D, Léon P, Cancel-Tassin G, Compérat E, Renard-Penna R, Mozer P, Guechot J and Cussenot O: Accuracy of the prostate Health Index *versus* the urinary prostate cancer antigen 3 score to predict overall and significant prostate cancer at initial biopsy. Prostate *75*: 103-111, 2015.

65 Scattoni V, Azzeri M, Lughezzani G, De Luca S, Passera R, Bollito E, Randone D, Abdollah F, Capitanio U, Larcher A, Lista G, Gadda GM, Bini V, Montorsi F and Guazzoni G: Head-to-head comparison of prostate health index and urinary PCA3 for predicting cancer at initial or repeat biopsy. J Urol *190*: 496-501, 2013.

66 Lazzeri M, Haese A, de la Taille A, Palou Redorta J, McNicholas T, Lughezzani G, Scattoni V, Bini V, Freschi M, Sussman A, Ghaleb B, Le Corvoisier P, Alberola Bou J, Esquena Fernández S, Graefen M and Guazzoni G. Serum isoform [-2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2-10 ng/ml: a multicentric European study. Eur Urol *63*: 986-994, 2013.

67 Cantiello F, Russo GI, Cicione A, Ferro M, Cimino S, Favilla V, Perdonà S, De Cobelli O, Magno C, Morgia G and Damiano R: PHI and PCA3 improve the prognostic performance of PRIAS and Epstein criteria in predicting insignificant prostate cancer in men eligible for active surveillance. World J Urol *34*: 485-493, 2016.

68 Osses DF, van Asten JJ, Kieft GJ and Tijsterman JD: Prostate cancer detection rates of magnetic resonance imaging-guided prostate biopsy related to Prostate Imaging Reporting and Data System score. World J Urol, 2016.

69 Haider MA, Yao X, Loblaw A and Finelli A: Multiparametric magnetic resonance imaging in the diagnosis of prostate cancer: a systematic review. Clin Oncol *28*: 550-567, 2016.

70 Kongnyuy M, Sidana A, George AK, Muthigi A, Iyer A, Fascelli M, Kadakia M, Frye TP, Ho R, Mertan F, Minhaj Siddiqui M, Su D, Merino MJ, Turkbey B, Choyke PL, Wood BJ and Pinto PA: The significance of anterior prostate lesions on multiparametric magnetic resonance imaging in African-American men. Urol Oncol *34*: 15-21, 2016.

71 De Visschere PJ, Briganti A, Fütterer JJ, Ghadjar P, Isbarn H, Massard C, Ost P, Sooriakumaran P, Surcel CI, Valerio M, van den Bergh RC, Ploussard G, Giannarini G and Villeirs GM: Role of multiparametric magnetic resonance imaging in early detection of prostate cancer. Insights Imaging *7*: 205-214, 2016.

72 Thompson JE, van Leeuwen PJ, Moses D, Shnier R, Brenner P, Delprado W, Pulbrook M, Böhm M, Haynes AM, Hayen A and Stricker PD: The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer. J Urol *195*: 1428-1435, 2016.

73 Porpiglia F, Russo F, Manfredi M, Mele F, Fiori C, Bollito E, Papotti M, Molineris I, Passera R and Regge D: The roles of multiparametric magnetic resonance imaging, PCA3 and prostate health index – Which is the best predictor of prostate cancer after a negative biopsy? J Urol *192*: 60-66, 2014.

74 Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, Margolis D, Schnall MD, Shtern F, Tempany CM, Thoeny HC and Verma S: PIRADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol *69*: 16-40, 2016.

75 Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ, Heijmink SW, Hoskin PJ, Kirkham A, Padhani AR, Persad R, Puech P, Punwani S, Sohaib AS, Tombal B, Villers A, van der Meulen J and Emberton M: Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol *59*: 477-494, 2011.

76 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.

77 Cormio L, Scattoni V, Lorusso F, Perrone A, Di Fino G, Selvaggio O, Sanguedolce F, Bufo P, Montorsi F and Carrieri G: Prostate cancer detection rates in different biopsy schemes. Which cores for which patients? World J Urol *32*: 341-346, 2014.

78 Somford DM, Vreuls W, Jansen TS, van Basten JP and Vergunst H: Incremental value of transition zone and midline apical biopsy at baseline TRUS-guided biopsy for prostate cancer detection. World J Urol *32*: 461-467, 2014.

79 Pepe P, Dibenedetto G, Pennisi M, Fraggetta F, Colecchia M and Aragona F: Detection rate of anterior prostate cancer in 226 patients submitted to initial and repeat transperineal biopsy. Urol Int *93*: 189-192, 2014.

80 Pepe P, Pennisi M and Fraggetta F: Anterior prostate biopsy at initial and repeat evaluation: is it useful to detect significant prostate cancer? Int Braz J Urol *41*: 844-888, 2015.

81 Bjurlin MA, Wysock JS and Taneja SS: Optimization of prostate biopsy: review of technique and complications. Urol Clin North Am *41*: 299-313, 2014.

82 Scattoni V, Raber M, Capitanio U, Abdollah F, Roscigno M, Angiolilli D, Maccagnano C, Gallina A, Saccà A, Freschi M, Doglioni C, Rigatti P and Montorsi F: The optimal rebiopsy prostatic scheme depends on patient clinical characteristics: results of a recursive partitioning analysis based on a 24-core systematic scheme. Eur Urol *60*: 834-841, 2011.

83 Lee DJ, Recabal P, Sjoberg DD, Thong A, Lee JK, Eastham JA, Scardino PT, Vargas HA, Coleman J and Ehdaie B: Comparative effectiveness of targeted prostate biopsy using magnetic resonance imaging ultrasound fusion software and visual targeting: a prospective study. J Urol *196(3)*: 697-702, 2016.

84 Wysock JS, Rosenkrantz AB, Huang WC, Stifelman MD, Lepor H, Deng FM, Melamed J and Taneja SS: A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. Eur Urol *66*: 343-351, 2014.

85 Pepe P and Aragona F: Morbidity following transperineal prostate biopsy in 3,000 patients submitted to 12 VS 18 VS more than 24 needle cores. Urology *81*: 1142-1146, 2013.

86 Abdollah F, Novara G, Briganti A, Scattoni V, Raber M, Roscigno M, Suardi N, Gallina A, Artibani W, Ficarra V, Cestari A, Guazzoni G, Rigatti P and Montorsi F: Trans-rectal *versus* trans-perineal saturation rebiopsy of the prostate: Is there a difference in cancer detection rate? Urology *77*: 921-925, 2011.

87 Loeb S, Vellekoop A, Ahmed HU, Catto J, Emberton M, Nam R, Rosario DJ, Scattoni V and Lotan Y: Systematic review of complications of prostate biopsy. Eur Urol *64*: 876-892, 2013.

88 Abdi H, Pourmalek F, Zargar H, Walshe T, Harris AC, Chang SD, Eddy C, So AI, Gleave ME, Machan L, Goldenberg SL and Black PC: Multiparametric magnetic resonance imaging enhances detection of significant tumor in patients on active surveillance for prostate cancer.Urology *85*: 423-428, 2015.

89 Schoots IG, Petrides N, Giganti F, Bokhorst LP, Rannikko A, Klotz L, Villers A, Hugosson J and Moore CM: Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. Eur Urol *67*: 627-636, 2015.

90 Ouzzane A, Renard-Penna R, Marliere F, Mozer P, Olivier J, Barkatz J, Puech P and Villers A: Magnetic resonance imaging targeted biopsy improves selection of patients considered for active surveillance for clinically low risk prostate cancer based on systematic biopsies. J Urol *194*: 350-356, 2015.

91 Pinkhasov GI, Lin YK and Palmerola R: Complications following prostate needle biopsy requiring or emergency department visits – experience from 1000 consecutive cases. BJU Int *110*: 369-374, 2012.

92 Roberts MJ and Doi SA: Prostate biopsy, targeted prophylaxis and infectious complications: A critique of methods used. BJU Int *117*: 719-721, 2016.

93 Wagenlehner FME, Van Oostrum E, Tenke P, Tandogdu Z, Çek M, Grabe M, Wullt B, Pickard R, Naber KG, Pilatz A, Weidner W and Bjerklund-Johansen TE: Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections In Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. Eur Urol *63*: 521-527, 2013.

94 Taylor AK and Murphy AB: Preprostate biopsy rectal culture and postbiopsy sepsis. Urol Clin North Am *42*: 449-458, 2015.

95 Cussans A, Somani BK, Basarab A and Dudderidge TJ: The role of targeted prophylactic antimicrobial therapy before transrectal ultrasonography-guided prostate biopsy in reducing infection rates: a systematic review. BJU Int *117*: 725-731, 2016.

96 Summers SJ, Patel DP, Hamilton BD, Presson AP, Fisher MA, Lowrance WT and Southwick AW: An antimicrobial prophylaxis protocol using rectal swab cultures for transrectal prostate biopsy. World J Urol *33*: 2001-2007, 2015.

97 Fahmy AM, Kotb A, Youssif TA, Abdeldiam H, Algebaly O and Elabbady A: Fosfomycin antimicrobial prophylaxis for transrectal ultrasound-guided biopsy of the prostate: A prospective randomised study. Arab J Urol *14*: 228-233, 2016.

98 Volkan S, Ozgu A, Ibrahim HB, Tarik Y, Pinar S, Salih P, Tansu D and Deniz B: The use of prophylactic single-dose fosfomycin in patients who undergo transrectal ultrasound-guided prostate biopsy: A prospective, randomized, and controlled clinical study. J Can Urolog Assoc *9*: 863-867, 2015.

99 Carmignani L, Picozzi S and Bozzini G: Transrectal ultrasoundguided prostate biopsies in patients taking aspirin for cardiovascular disease: a meta-analysis. Transfus Apher Sci *45*: 275-280, 2011.

100 Wang J, Zhang C, Tan G, Chen W, Yang B and Tan D: Risk of bleeding complications after preoperative antiplatelet withdrawal *versus* continuing antiplatelet drugs during transurethral resection of the prostate and prostate puncture biopsy: a systematic review and meta-analysis. Urol Int *89*: 433-438, 2012.

101 Giannarini G, Mogorovich A and Valent F: Continuing or discontinuing low-dose aspirin before transrectal prostate biopsy: results of a prospective randomized trial. Urology *70*: 501-505, 2007.

102 Culkin DJ, Exaire EJ, Green D, Soloway MS, Gross AJ, Desai MR, White JR and Lightner DJ: Anticoagulation and antiplatelet therapy in urological practice: ICUD/AUA review paper. J Urol *192*: 1026-1034, 2014.

103 Galosi AB, Dellabella M, Polito M, Yehia M, Dell'Atti L, Montironi R and Muzzonigro G: A new method to embedd fragments of prostate biopsy: the "Sandwich" technique, preliminary experience. Urologia *2*: 170-174, 2001.

104 Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR and Humphrey PA: Grading Committee. 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 *40*: 244-252, 2016.

105 Loeb S, Montorsi F and Catto JW: Future-proofing Gleason grading: what to call Gleason 6 prostate cancer. Eur Urol *68*: 1-2, 2015.

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