Biopsy of the prostate – the urge to search for a new standard

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ABSTRACT

Although the worldwide urological community generally accepts the existing protocol of TRUS-guided (transrectal ultrasound-guided) random prostate biopsy, there is strong evidence that sextant, extended, and saturation protocols are not sufficiently accurate (with ranges from 28-78%). Moreover, the number of repeated biopsies remains extremely high (33%) as a consequence of using an imperfect diagnostic tool. An overview of current literature concerning common practice in prostatic biopsies has revealed discrepancies in indications, technique, number of cores collected, and pathological examination standards. This fact has prompted many authors to search for methods of improving the existing standard. The latest developments in the field are primarily related to MRI-guided (magnetic resonance-guided) targeted prostate biopsy, which is currently a promising tool in diagnosing prostate cancer. However, genetically supported molecular biopsy seems to be a highly promising avenue for developing the future biopsy standard.

Diagnosis of prostate cancer (PCa)

The incidence of adenocarcinoma of the prostate (PCa) in Europe is very high: it is the third most common neoplasm in men [1]. Moreover, 11% of men suffering from a neoplasm are PCa patients. PCa prevalence in Europe affects approximately 2.6 million males. In recent years PCa incidence has increased in Poland, while the standardized incidence rate has risen from 12.2 in 1991 to 27.2 in 2006. The standardized mortality rate in the same period increased from 10.1 to 12.9. In 2006, 7,154 individuals were diagnosed with PCa in Poland, while 3,681 PCa – related deaths were recorded [1].

Histologic examination of prostatic tissue is the only method of confirming the existence of PCa. The vast majority of patients undergo a transrectal random biopsy protocol in order to obtain representative prostatic tissue. Nowadays, only 2-4% of cases of PCa are diagnosed as a result of routine examination of the specimen obtained during prostate surgery (TURP – transurethral resection of prostate, open prostatectomy). This decrease in diagnosing pT1a/b prostate cancer is due to a suggestive trend of performing early prostate biopsy for the purpose of ruling PCa out in patients undergoing minimally invasive benign prostate treatment (e.g. laser treatment) [2].

TRUS-guided needle prostate biopsy is a standard method for diagnosing PCa with a positive predictive value (PPV) ranging from 0.27 to 0.73 [3-5]. As it is simple to perform, safe and accessible, the standard biopsy has become the most common urological diagnostic procedure around the world. However, the negative predictive value (NPV) of prostate biopsy has been challenged with a false negative rate of up to 25-30% and the frequency of re-biopsy to the extent of 20-40% has been reported [6-9]. Another drawback of the transrectal biopsies is the strong evidence that in about half of all cases (41-62%) the Gleason grade is underestimated based on biopsy results when compared with the final post prostatectomy pathological report [10-13]. In the present paper an overview of the current literature (2004-2010) that was based on search in medical literature databases was presented, concerning common practice in prostatic biopsies.

Economic considerations

Prostate biopsies are performed either as an outpatient procedure or as a procedure during a one day hospitalization, involving both a urologist and a pathologist. To perform a standardized procedure to collect 8 to 12 cores, one needs an ultrasound machine with a high-frequency transrectal probe, a biopsy needle and a biopsy gun or a disposable device. An experienced uro-pathologistis is also preferable. In Poland, a 10-14-day delay is usually needed in order to obtain a final written report. However, in many European countries the delay is much shorter.

Authors estimate that in Europe that over 3 million biopsies are performed annually. In Poland, the statistics are as follows: approximately 6,000 to 8,000 patients are diagnosed annually with newly diagnosed prostate cancer with about 30,000 biopsies being performed. Nowadays, the National Health Fund (NHF) assigns 12-14 points to a biopsy when encoded as an ambulatory procedure and 22 points when encoded as a procedure involving one day hospitalization. Since one point is worth 51 PLN (NHF 2009-2010), the reimbursement is 1,122 PLN. This means that the annual cost of prostate biopsy procedures in Poland is around 33 million PLN (8 million Euro). The data support the importance of this subject both from a clinical and a health economic point of view.

Timeline of prostate biopsy

For over 100 years urologists have not managed to conclude definitively, which approach should be chosen as the most preferable to collect prostate samples for histologic examination. At the beginning of the 20th century, an open biopsy was applied for the first time [14]. In the 1930s, transperineal needle aspiration became the standard, while in 1937 transrectal biopsy was described by Franzen (oligobiopsy). This approach did not receive general acceptance because of fear for fecal contamination [15]. Until the end of the 1980s, a digitally-guided transperineal biopsy was performed [16]. It was not until the transrectal ultrasound examination (TRUS) was introduced in 1986 and the zonal structure of the prostate was described in 1989 that the next major advancement in needle biopsy, i.e. the TRUS-guided needle biopsy became popular [17, 18]. In the 90's systematic sextant prostate biopsy was developed and

established [19]. This technique entailed 6 sampling areas in anatomic sites of the prostate: the apex, middle, and base of each lobe, parasagittally. In practice, this protocol was embraced as standard procedure at the onset of the 21st century. Protocols of biopsies of the prostate according to different authors are presented in Figure 1 [17, 20-27].

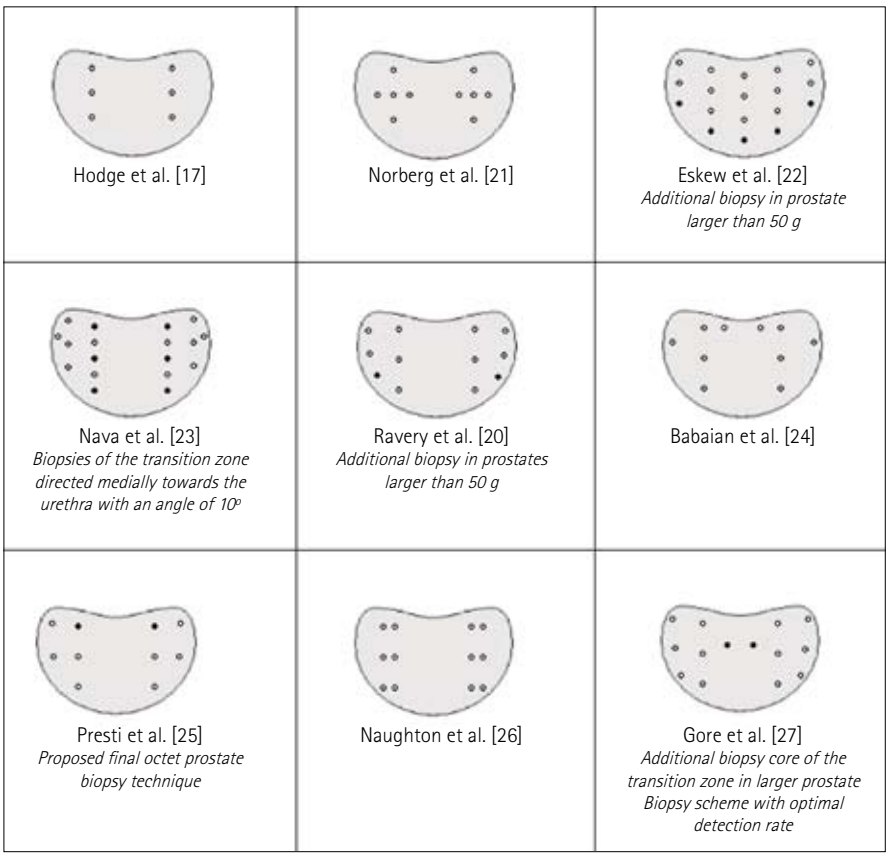

Fig. 1. Prostatic biopsy schemes according to different authors, grouped and presented by Scattoni et al. [52].

Prostate biopsy standard 2000

This new prostate biopsy standard was established by the American Urologic Association in editorials published in the Journal of Urology in the year 2000. In the representative article 'TRUS-guided prostate biopsy – defining a New Standard', the position is taken that TRUS guided prostate biopsy is an essential tool for the diagnosis and staging of PCa [28]. However, it should be emphasized that sextant biopsies alone may miss half of all existing cancers in men with a normal DRE (digital rectal examination) and PSA higher than 4 ng/mL and an extended biopsy technique, including more laterally directed biopsies, is necessary for improved detection [28].

Many urologists have adopted the leaders' tips for a more lateral approach, and for an increase in the number of prostate needle biopsies to 8, 10, or even 12 cores [18, 29]. The individualization of prostate biopsy schemes in different urological centers continued along with the individualization of the indications for performing this procedure. As a result, different approaches were performed in different ways and, what is even more important, in patients at different stages of PCa and with different PSA serum levels.

Non-standardized indications

Even though, according to the EAU Guidelines updated in 2010, elevated PSA (prostate specific antigen) and/or suspicious DRE are indications for biopsy one should be aware of the fact that the first elevated PSA reading does not always prompt an immediate biopsy. The PSA has to be verified after the elapse of several weeks in standard conditions (no ejaculation, no UTI, no local maneuvers, such as DRE, cystoscopy, TUR, TRUS, etc.) in the same laboratory using the same biochemical test [30]. In the study of Pepe et al., it was found that only 25-30% of prostate cancers are detected in patients with a PSA level of 2.5-4 ng/mL with most of these cancers being clinically significant [31]. In the NCCN (national comprehensive cancer work) Clinical Practice Guidelines in Oncology, one can find an algorithm that can be used in defining the indications for prostate biopsy [32, 33]. First, DRE and PSA determination should be performed in patients over 40 years of age. In patients with a PSA >0.6 ng/mL or with a family history of PCa, annual follow-up is recommended, while in patients with a PSA <0.6 ng/mL it should be repeated at the age of 45. Finally, one should consider a biopsy in men either with a PSA >2.5 ng/mL or a PSA Velocity >0.35 ng/mL/year or in whom DRE is positive.

According to the findings of the control arm of the Prostate Cancer Prevention Trial (PCPT), in which more than 5,000 men were biopsied independently of their PSA status, a PSA cut-off value of 4.0 ng/mL, a commonly used biopsy indicator, missed about 75% of all biopsy sdetectable cancers [34]. On the other hand, sextant biopsies performed in all men led to a detection rate of 21.9% and evidence of PCa diagnosis was present in many cases in which otherwise one would never have found any clinical signs of prostate cancer (over-diagnosis). The European Randomized Study of Screening for Prostate Cancer (ERSPC) offers an opportunity to postpone the biopsy until PSA exceeds the cut-off value of 3.0 ng/mL [35].

It was proven in PSA-based screening studies that approximately 9% of all men have elevated serum PSA values, but cancer is detectable in an initial biopsy in only about one third of them [36, 37]. The question is whether the group of 66% of the men with an initially negative prostate biopsy have an elevated serum PSA value because of benign prostatic hyperplasia [38]. To increase the sensitivity and specificity of PSA screening, %free PSA, PSAD (PSA density), and PSA-TZ (prostate specific antigen adjusted for the transition zone volume) were examined to determine whether the PSA derivatives can be useful in PCa diagnosis [39]. It was found that total PSA, PSAD, and PSA-TZ were all significantly higher in subjects diagnosed with PCa in initial and repeat biopsy ($p < 0.01$). In further studies, free PSA (cut-off 0.3) performed better than PSA-TZ (cut-off 0.26 ng/mL/cc) for PCa detection in repeat biopsy [40-42]. The free PSA/complexed PSA ratio ensured a reduction in negative biopsies in the PSA gray zone 4-10 ng/mL [43]. The suggestion was made to substitute the free PSA/total PSA ratio with the free PSA/complexed PSA ratio in patients with a PSA level between 4 and 10 ng/mL. Moreover, complexed PSA can be an alternative to total PSA as the first screening test due to the fact that a substantial number of men with PCa are currently diagnosed with a total PSA value higher than 10.0 ng/mL [44]. Complexed prostate specific antigen density might be a better initial test than PSA for prostate cancer detection, as it

was found to be better than other PSA derivatives for detection of prostate cancer in men with a total PSA ranging from 2.5 to 20 ng/mL [45]. A recent study suggested that the lower cancer detection rate for men with large prostates may be due to a decrease in the use of elevated serum PSA for prostate cancer detection in larger prostates in addition to other factors such as sampling error [46]. Elevated serum PSA levels in larger prostates may also be due to non-malignant sources such as benign prostatic hyperplasia.

The new prostate specific marker, PCA3, is thought to have both higher sensitivity and specificity [30]. The PCA3 urine sediment level is influenced neither by prostate volume nor prostatitis, but it is still unclear whether there is a correlation between tumor aggressiveness and PCA3 level. Nowadays, it should be treated as an experimental model although some authors claim that it has a potential to identify prostate cancer in individuals with an elevated PSA and with initial negative biopsies.

Digital rectal examination (DRE) has long been the only method of physical examination of the prostate. Nodularity, firmness, or irregularity of DRE have led clinicians to perform a biopsy of the prostate to determine the presence or absence of carcinoma [18]. Weaver et al. described the use of TRUS versus digitally directed needle biopsy in patients with abnormal DRE findings [47]. Digitally directed biopsy missed more than 50% of PCa in comparison with TRUS-directed biopsy. Finally, PCa is present in over 25% of the cases when DRE is negative and PSA is 4-20 ng/mL [48].

The physician dependent strategy

Prostate volume is the most relevant variable in planning the optimal number of cores in the extensive first biopsy set [49]. One of the models for prostate biopsy was the Vienna nomogram that was based on patient age and gland volume in those with a PSA in the range of 2-10 ng/mL (Table 1) [38]. The data were derived from the European Prostate Cancer Detection Study (EPCDS) and the three-dimensional model of virtual biopsies taken from prostatectomy specimens [38].

As the majority of prostate cancer originates in the peripheral zone, some researchers began exploring alternative biopsy schemes to the sextant procedure. One of the studies demonstrated an inverse relationship between prostate gland size and PCa detection determined by sextant biopsy [50]. It was subsequently revealed that sextant biopsy can miss up to 30% of the cases of cancer [5]. Most researchers are of the opinion that a 10 to 12-core scheme is optimal in initial and repeat biopsy patients [29].

However, the available recommendations differ among European centers, e.g. in the Netherlands 8- is thought to be as good as a 12-core scheme. Italy applies a 12-14-core scheme, Austria applies an 8-18-core scheme, and France applies a 20-21-core scheme. In turn, Poland applies a 6-21-core biopsy scheme [51-53]. According to the French 21-core standard, patients with suspected localized prostate cancer should be offered at least 12 biopsies in the peripheral zone and the far lateral peripheral zone, while TZ biopsies have to be considered having in mind improvement of the diagnostic yield [51]. Italian clinicians claim, however, that the optimal sampling scheme for initial prostate biopsy varies according to the clinical characteristics of each patient [52]. Furthermore, in the study of Mamoulakis et al., it was stated that the 8 and 12-core biopsy protocols showed similar diagnostic performance, while transition zone biopsies contributed to PCa detection in a repeat biopsy protocol. However, it should be emphasized that the accuracy of the procedure measured by PPV is influenced strongly by the sampling strategy [52]. The biopsy scheme should be heavily weighted towards the lateral aspect and the apex of the prostate to maximize peripheral zone sampling [29]. The fact that the increase in the number of cores does not lead to significant morbidity nor to an increase in the number of insignificant cancers is worth emphasizing [54]. Some authors have suggested that the 10 core biopsy protocol should be used in all groups of patients, except in those with a prostate volume of 14.9 to 35 cm^3 [55], in whom the 8 core biopsy protocol consisting of the apex, mid gland, lateral mid gland, and lateral base can be advised, since it produces similar results. On the other hand, the 14-core prostate needle biopsy protocol is recommended by some authors as a method of detecting prostate cancer in a large-volume prostate gland over 30 cm^3 without increasing the risk of complications [49, 56]. In patients with a prostate volume ranging from 30.1 to 50 cm^3, a 12 peripheral core biopsy produces results equivalent to the most extended sampling [49]. However, in prostates larger than 50 cm3, an even more extensive procedure is mandatory, considering the low detection rate offered by the 14-core scheme. In the study of Eskew et al., it was suggested that an additional biopsy should be considered in prostates larger than 50 cm^3 [22]. Generally, there is a significant sampling error in prostate glands over 50 cm^3, therefore a re-biopsy is needed when the initial one shows no PCa [57]. By performing two sets of sextant biopsies the probability of detecting prostate cancer in patients with prostates over 50 cm^3 doubles. Moreover, small volume cancers are more frequent in larger prostates. Even though the classic sextant biopsy protocol by some authors is thought to be inadequate for all prostate volumes [55], it may be implemented in patients with very small prostates or very high PSA and very firm prostate on DRE. Additionally, transrectal ultrasound directed lesion biopsies may be omitted when using 10 core biopsy protocols, since the yield of these biopsies was lower than 2%. Moreover, the procedure of lateral peripheral zone biopsies increases the sensitivity for cancer detection while nearly eliminating the need for lesion directed biopsies [58]. Evidence does not support the use of routine midline peripheral zone needle biopsies in the initial biopsy to enhance the detection of PCa [51]. Finally, TURP with biopsy-proven prostate cancer has a low accuracy of 5-12% in patients whose PSA levels are steadily rising [59].

Table 1. Vienna Nomogram after Djavan [38]: number of cores per biopsy in order to obtain 90% accuracy of cancer detection while taking into consideration prostate volume and patient's age.

Size (cc)	Age (years)			
	<50	50-60	60-70	>70
20-29	8	8	8	6
30-39	12	10	8	6
30-49	14	12	10	8
50-59	16	14	12	10
60-69	–	16	14	12
>70	–	18	16	14

Non-reproducible re-biopsy protocols

According to the EAU Guidelines 2010, rising and/or persistent PSA, suspicious DRE, and atypical small acinar proliferation (ASAP) are indications for re-biopsy. PIN is no longer an indication for repeated biopsy (level of evidence 2a) unless it is extensive and occurs in multiple biopsies [30].

Patients who have undergone a negative prostate biopsy often return to the doctor's office for further evaluation because of a persistently elevated or rising PSA or change in the digital rectal examination. The finding of high-grade intraepithelial neoplasia or atypia on an initial biopsy may warrant a repeat biopsy [29]. Some researchers have advocated more aggressive biopsy schemes in patients un-

dergoing repeat biopsy, including saturation biopsy performed under anesthesia as an outpatient procedure [29]. Cancers that were found in re-biopsy protocols, were located in apical/dorsal areas, the anterior horn, or in the anterior area of the prostate [57]. Detailed maps of consecutive radical prostatectomies show that the directions of prostate cancer expansion are primarily transverse across the posterior surface of the capsule and cephalocaudal [19]. Directing the biopsies more laterally to the mid-parasagittal plane may support sampling of a large group of cancers located more laterally in the PZ (peripheral zone). Routine TZ biopsies are not justified in light of low detection rates under 15% [3]. While cancers detected in an initial biopsy are distributed homogeneously over the entire prostate, cancers in a repeat biopsy are found in a more apical-dorsal location [60]. This is why the re-biopsy should be modified and needles should be directed to a more apical-dorsal location. To define such a scheme, site-specific cores had to be individually labeled so as to identify both overall and unique cancer detection rates for a specific site [29]. In a recent study of Hong et al., it was found that cancer detection rates tended to be higher in patients who had undergone a prior sextant biopsy compared to a prior extended biopsy scheme [61]. Apically and laterally directed biopsies had higher overall and unique cancer detection rates in patients who had undergone a prior negative sextant biopsy. Anterior directed biopsies had a low unique cancer detection rate in all patients. Clinicopathologic features of cancers detected in a repeat biopsy tend to be worse in patients who have undergone a prior negative sextant biopsy compared to a negative prior extended biopsy. In an another recent study, Djavan et al. presented the results of a prospective study of the pathological features found in first, second, third, and fourth prostate biopsy [57]. Despite differences in location and multifocality, the pathological and biochemical features of cancer detected on biopsies 1 and 2 were similar, suggesting comparable biological behaviors. Cancer detected on biopsies 3 and 4 had a lower grade, stage and volume compared with biopsies 1 and 2. Morbidity was similar in biopsies 1 and 2, while biopsies 3 and 4 had a slightly higher complication rate. Therefore, biopsy 2 in all cases of a negative finding on biopsy 1 appears justified. However, biopsies 3 and 4 should only be obtained in selected patients with a high suspicion of cancer and/or poor prognostic factors on biopsy 1 or 2. Rabets et al. stated that a saturation biopsy can be performed safely and effectively in the doctor's office with a significant diagnostic yield, even in patients with previous extended biopsy schemes and consequently should be the next diagnostic step after an initial negative biopsy in patients in whom suspicion for the diagnosis of prostate cancer is high [62]. However, positive results were found only in 35-48% of the cases. The cancer detection in a re-biopsy was determined by Chun et al. and the predictors of prostate cancer in a repeat biopsy were as follows: patient age, DRE, PSA, percent of free PSA, number of previous negative biopsy sessions, and sampling density [63]. Relative to the previous nomograms (10 predictors or 71% accuracy) the tool relied on fewer variables (6) and showed superior accuracy in European men in comparison with accuracy in American men. It was commented that racial, clinical, and biochemical differences may underline the observed discrepancy in predictive accuracy.

In the study performed by Loch to compare the diagnostic yield of computerized transrectal ultrasound (C-TRUS) guided biopsies in the detection of prostate cancer in a group of men with a history of multiple systematic random biopsies with no prior evidence of prostate cancer, the question was raised whether one can detect cancer using a C-TRUS in cases in which multiple systematic biopsies have failed to detect cancer [64]. There were 132 men who had a history of prior negative systematic random biopsies (median: 12 cores) with a median PSA of 9.01 ng/mL. Cancer was found in 66 men (50%) using a C-TRUS (computerized transrectal ultrasound) with only 5 cores in suspect areas.

Variability of Visualization Techniques

Recently, significant achievements have been made in the visualization of the prostate with respect to biopsy, especially in ultrasound imaging, MRI, and specific biopsy devices and robotic equipment. Due to the lack of specificity and variability in the ultrasonic appearance of tumors, TRUS alone performs poorly for prostate cancer identification [65]. Even though some prostatic tumors may be visualized due to a hypoechoic appearance distinguishable from the normal homogeneous isoechoic parenchyma, most hypoechoic lesions are not cancers [66]. Moreover, many early stage cancers are isoechoic and are not distinguishable from the surrounding benign tissue [52]. One of the controversial issues is whether it is necessary to take samples from a TRUS visible lesion area in addition to systematic biopsies or simply to add more biopsies to the standardized sextant biopsy scheme in order to increase the prostate cancer detection rate [52]. Hypoechoic prostatic lesions are more than twice as likely to have cancer on biopsy than isoechoic prostatic tissue [67]. Because only 60% of clinically diagnosed prostate cancer is hypoechoic [66] and since transition zone cancers are generally concentrated in the farthest anterior areas of the prostate near the midline, TRUS lesion-guided biopsies would detect only about 50% of all prostate cancers [68] and, as a result, are not recommended. Nowadays, lesion-guided biopsies only play a role in the combination of systematic biopsies in prostates with visible lesions [52]. All in all, it seems wise to add one single biopsy targeted at the peripheral hypoechoic lesions located outside the standard biopsy location. Due to the multifocality of prostate cancer, in the future it is probable that, by adding more biopsies to the sextant standard scheme, the necessity of biopsying single small hypoechoic lesions will no longer be necessary [52]. In the study of Mitterberger et al., contrast enhanced color Doppler targeted biopsy detected cancers with higher Gleason scores and more cancer than systematic biopsy [69]. As a consequence, contrast enhanced color Doppler seems to be helpful in grading prostate cancer, which is important for defining the prognosis and determining the treatment protocol. In another study of Remzi et al., Power Doppler enhanced transrectal ultrasound (PD-TRUS) combined with guided prostate biopsies were performed in men with PSA levels between 2.5 and 10 ng/mL to evaluate its impact on PCa detection in men undergoing first and repeat biopsies [70]. Eight of nine patients with cancer had positive Power Doppler findings, while one of 18 patients had cancer without generating a Power Doppler signal. A normal TRUS including Power Doppler meant a 94.4% chance of a benign biopsy. A negative PD-TRUS signal was capable of precluding most patients without PCa in the PSA range of 2.5-10 ng/mL. As an additional tool at TRUS biopsy PD-TRUS had a high negative predictive value and may help to reduce the number of unnecessary biopsies. Furthermore, it was found that 3D-ultrasound is better for staging than diagnosis, and isoechoic images on 2D are isoechoic on 3D, as well. When TRUS and elastography are combined, the sensitivity per patient reached the level of 84-86%, with a sensitivity per core of 51-66% [71]. PPV per patient was 0.616 and NPV – 0.914. Sonoelastography findings showed a robust correlation with systematic biopsy results [71]. The best sensitivity and specificity were found in the apex region.

HistoScanning™, an ultrasound-based technology, was introduced to distinguish cancerous and noncancerous tissues in solid organs with the use of computer-aided analysis that quantifies tissue disorganization induced by malignant processes [72]. The new device is able to visualize specific changes in the tissue morphology by extracting and quantifying statistical features from back-scattered ultrasound data. It uses 'characterization algorithms' applied on backscattered ultrasound data before they are transformed into

the grey-scale video image. Importantly, the algorithms may be applied in so called 'discrete regions of interest' throughout the prostate and by doing so one can specify the presence or absence of prostate cancer within small volumes of prostatic tissue. In the papers of Braeckman et al. the reports on preliminary studies were published, in which one compared HistoScanning findings (detection, localization, and estimation of the cancer extension) with pathologic radical prostatectomy specimens [72, 73]. HistoScanning accurately detected cancer foci of ≥0.50 mL. The determination of multifocality and unilateral/bilateral disease between HistoScanning and pathological findings was 100% and, therefore, authors concluded that the precision of the technology appeared to be high enough to be implemented as a triage test for men at risk of prostate cancer and who wish to avoid prostate biopsy.

The other new visualizing technique based on ultrasound imaging is the TargetScan – a method of systematic, template-guided, 3D transrectal ultrasound-guided prostate biopsy [74]. In the beginning, a 3D map of the prostate is created and subsequently a computer algorithm calculates an optimum biopsy scheme using the measured dimensions of the prostate [75]. The system then uses a fixed template that allows the physician to biopsy the prostate at specific locations. The exact location of each specimen is defined by 2 coordinates: depth in centimeters proximal from the apex of the prostate and degree of rotation (clockwise or counterclockwise from 12 o'clock) [74]. The instrument can be used for 12-core template biopsy or for targeted and saturation biopsy if indicated, and what is more, to target the same region of the prostate in the future if needed, which is particularly useful in patients with suspicious histology [76]. Template-guided biopsy potentially produces a higher cancer detection rate and more accurate assessment of grade. In the study of Megwalu et al. cancer was detected in 50 (35.7%) of the 140 patients biopsied, including 39 (47.6%) with no previous biopsies [75]. The biopsy predicted the prostatectomy Gleason score in 12 patients (52%), overestimated in two (9%), underestimated in eight (35%), and biopsy Gleason score could not be assigned in one (4%). In the other preliminary study of Bullock et al. several important observations suggested the potential efficacy of the system [77]. First, the number of cores with cancer was greater than that observed with the preoperative conventional biopsy, suggesting efficacy in detection. Second, cancer was identified in 16 of 20 patients and in 31 of 64 prostate quadrants on whole mount. Finally, the correlation of Gleason score between biopsy was better with the TargetScan system than conventional biopsy. The following advantages of the TargetScan are mentioned: reliable localization of prostate zones, recording of biopsy sites for future reference, intra-operator and inter-operator reproducibility of biopsy techniques, better spatial mapping of cancer volume, better cancer detection, and better localization of disease for potential focal therapy [76].

As far as diagnostic magnetic resonance imaging (MRI) is concerned, it provides more accurate selection of regions in which tumors are suspected [78]. In open MRI scanners, pre-biopsy images often must be registered against real-time biopsy images because open MRI scanners do not provide optimal tissue contrast; thus, the patient must first be examined in a closed MRI scanner and then biopsied in an open scanner. The advantage of open MRI over closed MRI is that the physician has easier patient access. With special equipment, prostate MRI-guided biopsy is also possible in a closed system. Closed MR scanners can be used for the pre-biopsy scan as well as for the biopsy procedure.

In the study of Beyersdorff et al., the authors evaluated a MRI – compatible biopsy device comprising a needle guide that can be visualized with MRI and manipulated mechanically from outside the MRI unit [79]. This device was tested in 12 patients by using a closed 1.5-T MR unit and a body phased-array coil. Patients had elevated PSA levels (6-60 ng/mL) and one or more areas in the prostate suspected of carcinoma in pre-biopsy MR (magnetic rezonance) imaging. A biopsy was performed with transrectal access and with the patient prone. A 16-gauge MRI–compatible needle was successfully positioned with the device, and six to nine tissue cores were obtained from each patient. Histologic analysis showed prostate cancer in five patients and prostatitis in six. The device enabled MRI-guided core-needle biopsy of prostate areas suspected of cancer on MR images.

In another study done by DiMaio et al., an integrated system for planning and performing percutaneous procedures with robotic assistance under MRI guidance was described [80]. A graphical planning interface allows the physician to specify the set of desired needle trajectories, based on anatomical structures and lesions observed in the patient's registered pre-operative and pre-procedural MR images, immediately prior to the intervention in an open-bore MRI scanner. All image-space coordinates are automatically computed, and are used to position a needle guide by means of an MRI-compatible robotic manipulator, thus avoiding the limitations of the traditional fixed needle template. Automatic alignment of real-time intra-operative images aids visualization of the needle as it is manually inserted through the guide.

Based on the findings mentioned above, clinical and commercial use of MRI-guided prostatic biopsy became available in 2009 in the USA. The first example was the installation of this advanced technology in the Fox Chase Cancer Center in Philadelphia offering a robot-assisted percutaneous intervention in an open-MRI.

Mapping biopsy in focal treatment

The aim of focal therapy of the prostate is to perform ablation of the gland leading to the eradication of unifocal low-risk prostate cancer, and preserving uninvolved (peri-) prostatic tissue and therefore quality of life [81]. The main arguments against focal therapy are the risk of under-staging and cancer multifocality [82]. Thus, all the focal therapies require correct localization of the lesion that is possible in either transperineal mapping biopsy or MRI of the prostate. While current evaluation with 12 to 18 core biopsies may be adequate to determine the index lesion, transperineal 3D mapping biopsy of the prostate should be performed if greater accuracy is necessary. Transperineal 3D mapping biopsy of the prostate is a well tolerated procedure, providing superior staging information in comparison with TRUS biopsy, and it should be an essential component in selecting patients for focal prostate cancer therapy [83]. Recently, a joint committee of urologic surgeons, radiation oncologists, radiologists, and histopathologists from North America and Europe participated in a workshop on focal therapy for prostate cancer, the aim of which was to establish a consensus in relation to case selection, conduct of therapy, and outcomes that are associated with focal therapy for men with localized prostate cancer [84]. Based on the report, the best method to ascertain the key characteristics for men who are candidates for focal therapy is exposure to transperineal template mapping biopsies. MRI of the prostate using novel techniques such as dynamic contrast enhancement and diffusion weighed imaging are increasingly being performed to diagnose and stage primary prostate cancer with excellent results. However, these new techniques require validation in prospective clinical trials. As a consequence, it seems that MRI will remain an investigative tool in assessing eligibility of patients for focal therapy, till the reports coming from the trials are available.

Pain control gains popularity

In order to reduce patient discomfort, it is advisable to reduce the number of systematic biopsies to a minimum. Most protocols

including 10 to 12 cores appear to be safe and well-tolerated with an acceptable discomfort rate which can be further improved by using local anesthesia [52]. More than 25% of the men stated that during the prostate biopsy procedure they felt moderate or severe pain. This percentage was even higher in the population of males under 60 years of age. Furthermore, 19% of the men experienced severely negative pain-related feelings causing them to refuse consent to undergo a prostate biopsy. Although the peri-prostatic nerve block (PPNB) is currently considered the gold standard for pain control during PBx (prostate biopsy), it does not alleviate probe-related anorectal discomfort and may even add significant pain due to transcapsular infiltration by the local anesthetic [85]. The combination of perianal-intrarectal lidocaine-prilocaine cream and peri-prostatic nerve block provided better pain control than separate stand alone modalities during the sampling part of the transrectal ultrasound guided prostate biopsy with no increase in the complication rate. The magnitude of this effect was higher in younger men, men with a larger prostate, and men with lower anorectal compliance.

Some authors suggest that caudal anesthesia may be a reliable anesthetic procedure for transrectal prostate biopsy in patients with anal-rectal disorders (such as hemorrhoids, anal stenosis, and chronic anal fissure) [86]. According to them, individuals with caudal nerve blockade experienced decreased pain during probe insertion, with probe manipulation and prostate biopsies. The relaxation of the anal sphincter made TRUS-guided biopsy far more comfortable for the urologist, and it allowed one to assess the entire prostate gland for hardness and nodules on its surface, as well.

Occasional complications

As with any surgical procedure, complications can occur (Table 2). The European Prostate Cancer Detection Study prospectively analyzed complications and adverse events resulting from TRUS-guided biopsy in a first and second biopsy setting in which patients were given oral fluoroquinolones 1 day before biopsy and 4 days afterwards [18]. Early complications such as rectal bleeding, vasovagal episodes, and urinary retention that required either observation or intervention were rare in the primary biopsy setting. However, mild hematuria requiring observation or intervention occurred in 62% of the cases in the primary biopsy setting. Delayed complications such as urinary tract infections, fever, sepsis, and recurrent mild hematuria occurred in 10.9%, 2.9%, 0.1%, and 15.9%, respectively [18, 87]. No deaths were noted among the 1,051 subjects. However, in the case report of Weber et al., a 58-year-old physician presented with an elevated PSA, who developed severe septic shock following a repeat transrectal prostate biopsy despite standard preoperative prophylactic protocol [88]. As far as anticoagulants are concerned, the recommendation states that one should cease giving anticoagulants 5 days prior to the procedure, unless contraindicated and no NSAIDs (non-steroidal antiinflammatory drugs) should be administered 2 days before.

Pathological assessment

Little was reported on the differences in pathological stage, grade, and behavior of cancers detected on initial and repeat prostate biopsy. Djavan et al. concluded that cancers detected on repeat biopsy exhibit similar characteristics to initially detected cancers [39]. Thus, repeat biopsies detect significant cancers, and a repeat biopsy policy should be advocated in cases demonstrating a negative initial biopsy. High grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) in the sextant biopsy had been associated with a high risk of prostate cancer [89]. HGPIN found in the contemporary extended biopsy does not warrant repeat biopsy. ASAP continues to be associated with a high risk of cancer and requires at least 1 repeat biopsy using the extended biopsy scheme. To survey current European practices in handling and reporting of radical prostatectomy (RP) specimens, a European Network of Uropathology (ENUP) was organized for the dissemination of information, survey studies and research collaborations [90]. In the study of Stock et al., a systematic biopsy protocol was proposed consisting of 12 cores in a fan-shaped arrangement originating from the apex [91]. Self-embedding of the biopsy cores is a simple new way of processing that provides additional information for the operating urologist (e.g. exact localization of the tumor and the distance of the carcinoma from the capsule if a nerve-sparing procedure is planned). In large glands, the procedure has proved to be useful to expand this protocol by taking additional cores. Self-embedding of the biopsy cores provides the maximum information from biopsy core distribution. At an International Society of Urological Pathology (ISUP) consensus conference in 2005 the Gleason grading system for prostatic carcinoma underwent its first major revision [92]. It is not the aim of this review to individually describe all of the features included in the 2005 ISUP Modified Gleason System [93]. The major changes are summed up in the Table 3 adapted from Uemura et al. [94]. Overall, the recommendations follow a trend towards the use of higher grades than before and it is clearly defined how to classify rare forms of prostatic carcinoma. Moreover, small cell carcinoma should not be graded according to the Gleason system.

In the study of Billis et al., the concordance pattern and change of prognostic groups for the conventional and the modified Gleason grading were compared and the discriminative power of modified Gleason grading was checked [92]. The greatest impact of the ISUP consensus recommendations for Gleason grading was seen on the secondary pattern exhibiting the lowest percentage of concordance and was reflected in a change toward higher Gleason prognostic groups. Revised Gleason grading identified a higher number of patients in this series in the aggressive prognostic group with a Gleason score of 8-10 who had a significantly shorter time to biochemical progression-free outcome after radical prostatectomy (log rank p = 0.011).

Table 2. Complications of prostatic biopsy as reported in the literature, irrespective of the number of cores [18, 30, 87].

Complications	% of biopsies
Rectal bleeding	2.2%
Hematospermia	37.4%
Urinary retention requiring observation/intervention	0.2%
Mild hematuria requiring observation/intervention	14.5-62%
Epididymitis	0.7%
Prostatitis	1.0%
Urinary tract infections	10.9%
Fever	0.8-2.9%
Sepsis	0.1%-03%
Recurrent mild hematuria	15.9%
Severe complications: death, meningitis, epidural abscess, acute endocarditis	<1% of cases, reported in the literature

Future developments await

To limit the morbidity of prostate biopsy, research is underway to develop less invasive techniques to diagnose PCa [18]. Molecular diagnosis may be made e.g. by employing ProteinChip array technology or reverse transcriptase-polymerase chain reaction (RT-PCR).

PCa presents two characteristic features: epithelial-mesenchymal interactions, which play a pivotal role for tumor development and the prevalent occurrence of clinically manifest cancers in prostate properly compared to a minority of tumors developing in the transitional zone [95]. Deciphering the epithelial-mesenchymal cross talk and identification of molecular peculiarities of the sub-populations of cells in different zones can therefore help us understand carcinogenesis and develop new, non-invasive tools for the diagnosis and prognosis of prostate carcinomas, an endeavor that has remained a challenge until today [95, 96]. ProteinChip array technology (SELDI = surface enhanced laser desorption ionization) has been developed recently by Ciphergen Biosystems enabling analysis and profiling of complex protein mixtures using just a few cells [96]. It should be underlined that this technology exhibits vast potential to comprehend pathogenesis better and identify potential candidates for new specific biomarkers in general, which could help screen for and distinguish disease entities, i.e. between clinically significant and insignificant carcinomas of the prostate [95, 96].

Moreover, there is hope to differentiate prostate cancer and normal prostatic tissue samples taken from adjacent sites using reverse transcriptase-polymerase chain reaction (RT-PCR) [97]. A total of 19 diagnostic genes for either PCa or benign prostatic tissue have been reported in published studies, of which 11 were represented on the profiling platform for the initial training test. Six of these genes were expressed at high levels in benign tissue and five were expressed at high levels in PCa. On calculation of expression ratios (expression of a benign tissue marker divided by the expression of a prostate cancer marker), a value higher than 1 signified the presence of benign tissue, and a value lower than 1 signified the presence of prostate cancer. Ninety percent of the samples were accurately identified as either PCa or benign prostate tissue using RT-PCR gene expression ratios, with no false negative findings noted; a 100% PCa detection rate.

Changes in some genes expression of a significant rate have been detected in PCa, i.e. GSTP1, PTEN, NKX3.1, TP53, AR, CDH1, and CTNNB1 [98]. By microarray gene expression profiling, a discovery of PCa biomarkers: AMACR, EZH2, TMPRSS2-ERG, mi-R-221, and miR-141 was possible [99]. The question that remains is how to use that knowledge to develop better treatment protocols. Moreover, some authors claim the existence of numerous associations between BPH and PCa, among them of anatomic, pathologic, genetic, and, finally, epidemiologic origins [100]. As a result, some patients may have PCa with a pre-existing BPH. In the future this may lead to shared prophylactic and therapeutic management for BPH and PCa.

Proposal of the standard 2009/2010

The preferred PSA cut-off should be 2.5-3 ng/mL (repeated result). TRUS-guided technique using side-fire and/or end-fire probe seems to be the most common procedure. The number of cores is minimally 8, and steadily grows to 16 in cases of prostate enlargement to 60 cm^3. The maximum number of cores is 24 in the saturation re-biopsy protocol. Local anesthesia is accepted worldwide in greater than 8-core biopsy. Doubt remains on who should perform the invasive prostate biopsy procedure [101].

Table 3. Changes in the original Gleason system after the 2005 International Society of Urological Pathology (ISUP): 2005 ISUP Modified Gleason System. Adapted from Uemura et al. [94].

Original Gleason system	2005 ISUP Modified Gleason System
A diagnosis of GS <4 is possible on NB.	GS of NB specimens <4 is rarely if ever made.
A partial cribriform pattern or large cribriform are diagnosed as Gleason pattern 3.	Most cribriform patterns would be diagnosed as Gleason pattern 4; specimens with only rare cribriform lesions would satisfy the diagnostic criteria for cribriform pattern 3.
The same GS is used for NB and RP specimens.	Different GS is used for NB and RP specimens.
High-grade tumor of small quantity (<5%) on NB should be excluded based on GS (5% threshold rule).	High-grade tumor of any quantity on NB should be included within the GS.
Tumors on NB should be graded by listing the primary and secondary patterns (ie, excluding tertiary pattern).	For the tertiary pattern on NB specimens, both the primary pattern and the highest grade should be recorded.
The GS of RP specimens should be assigned based on the primary and secondary patterns.	For RP specimens, the pathologist should assign the GS based on the primary and secondary patterns with a comment on the tertiary pattern.
Separate or overall scoring is used to assess all grades of NB specimens.	When NB specimens show different grades in separate cores, individual GS should be assigned to these cores (separate scoring).
The grade of the largest portion should be assigned even if the second largest portion is of higher grade.	When RP specimens show different grades in separate tumor nodules, a separate GS should be assigned to each of the dominant tumor nodules.

GS = Gleason score; NB = needle biopsy; RP = radical prostatectomy

CONCLUSIONS

In the context of a biopsy of the prostate, there is no gold standard that would be applicable to indications that are currently non-standardized (PSA level) and very subjective (DRE) or to strategy (number of cores, needle placement map, etc.). Pathology of the biopsy specimen is the most standardized issue, but until automated computer assisted microscopic analysis becomes common practice, it will continue to be a very subjective issue with adverse repercussions. Better visualization of the targeted foci of the suspect organ is expected to improve accuracy and some progress has been made in ultrasound technology, although it is presently restricted only to experimental use. Recently, some centers have successfully developed MRI-guided biopsy protocols with an extremely high accuracy rate of more than 80%. Robotic MRI-guided transperineal targeted biopsy of the prostate has the potential to become the next globally-approved standard. If this happens, the urologist may cease to be involved. One should expect evolution from multiple-random to targeted sampling, whose consequence would be a dramatic reduction in the number of cores collected. Urologists have to be prepared for the future; otherwise, they will relinquish their position as the leader in prostate biopsy – a genuinely urological procedure.

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