Review – Prostate Cancer

Extended and Saturation Prostatic Biopsy in the Diagnosis and Characterisation of Prostate Cancer: A Critical Analysis of the Literature

Vincenzo Scattonia, Alexandre Zlottab, Rodolfo Montironic, Claude Schulmand, Patrizio Rigattia, Francesco Montorsi

aDepartment of Urology, University Vita-Salute, Scientific Institute San Raffaele, Milan, Italy
bDivision of Urology, Mount Sinai and Princess Margaret Hospitals, University of Toronto, Toronto, Ontario, Canada
cSection of Pathological Anatomy, United Hospitals, Marche Polytechnic University, Ancona, Italy
dDepartment of Urology, Erasme Hospital, University Clinics of Brussels, Brussels, Belgium

Abstract

Objective: To review and critically analyse all the recent literature on the detection and characterisation of prostate cancer by means of extended and saturation protocols.

Methods: A systematic review of the literature was performed by searching MedLine from January 1995 to April 2007. Electronic searches were limited to the English language, and the key words “prostate cancer,” “diagnosis,” “transrectal ultrasound (TRUS),” “prostate biopsy,” and “prognosis” were used.

Results: The prostate biopsy technique has changed significantly since the original Hodge sextant biopsy protocol. Several types of local anaesthesia are now available, but periprostatic nerve block (PPNB) has proved to be the most effective method to reduce pain during TRUS biopsy. It remains controversial whether PPNB should be associated with other medications. The optimal extended protocol (sextant template with at least four additional cores) should include six standard sextant biopsies, with additional biopsies (up to 12 cores) taken more laterally (anterior horn) to the base and medially to the apex. Repeat biopsies should be based on saturation biopsies (number of cores ≥20) and should include the transition zone, especially in a patient with an initial negative biopsy. As a means of increasing accuracy of prostatic biopsy and reducing unnecessary prostate biopsy, colour and power Doppler imaging, with or without contrast enhancement, and elastography now can be successfully adopted, but their routine use is still controversial.

Conclusion: Extended and saturation biopsy schemes should be performed at first and repeat biopsy, respectively. The widespread use of local anaesthesia makes the procedures more comfortable.

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1. Introduction

Widespread use of serum prostate-specific antigen (PSA) has certainly increased prostate cancer detection and resulted in considerable stage migration [1]. Such results would not have been achieved without the contemporary refinements of the technique of prostate biopsy (PBx). After the initial introduction of the sextant PBx technique proposed by Hodge, little refinement of the technique was made until Stamey [2] suggested directing the biopsies more laterally. It is now recognised that even lateral sextant biopsies can miss up to 30% of cancers because more extended prostatic biopsy (EPBx) schemes result in higher cancer detection rates [3–7]. As defined by the National Comprehensive Cancer Network, an EPBx is essentially a sextant template with at least four additional cores from the lateral peripheral zone as well as biopsies directed to lesions found on palpation or imaging.

At present, little controversy exists in the urologic community regarding the usefulness of EPBx compared with sextant biopsy in increasing the detection rate of prostate cancer. Data from both academic and community practices demonstrate a high cancer detection rate (42–44%) with a 12-core biopsy template in patients undergoing initial biopsy [8].

Nevertheless, prostate cancer detection is still an area currently fraught with many unanswered questions and significant controversy. Even if several different EPBx techniques have been recently presented, the optimal protocol needed to identify all patients with prostate cancer at the earliest stage possible for optimal treatment, outcome, and survival is still not known. Moreover, the significance of a PBx has changed over the years. Today, a PBx is not only a method to diagnose prostate cancer, but it has become an informative method for an accurate morphologic characterisation of prostate cancer, including its volume and Gleason score.

We have reviewed the available literature on this topic and compared the efficacy and safety of the different schemes with respect to the number of cores and sampling locations. A systematic review of the literature was performed by searching MedLine from January 1995 to April 2007. Electronic searches were limited to the English language, and the key words “prostate cancer,” “diagnosis,” “transrectal ultrasound (TRUS),” “prostate biopsy,” and “prognosis” were used.

2. Anaesthesia during transrectal prostate biopsy and antibiotic prophylaxis

2.1. Anaesthesia during TRUS

Anaesthesia during TRUS PBx is now considered the gold standard; it is recommended by recently published guidelines, and we are close to the point in which absence of anaesthesia would be considered malpractice [9].

Intrarectal local anaesthesia (IRLA) with lidocaine gel (2%) has had controversial results compared with placebo [10,11]. In a recent meta-analysis [12], five studies involving 466 patients and comparing IRLA with placebo showed that IRLA was associated with pain reduction, but the effect size was not statistically significant. Moreover, in randomised studies, IRLA was reported to be inferior to periprostatic nerve block (PPNB) with lidocaine injection [13–20].

In several articles, it has been shown that PPNB was superior to IRLA in reducing pain during PBx in different randomised studies (Table 1). Even if the superiority of PPNB versus IRLA is evident, it remains unclear which dosage and PPNB technique should be used.

As for the site and amount of anaesthetic infiltration, a study using a placebo and six groups of escalating doses of 1% lidocaine (2.5, 5, and 10 ml) infiltration revealed that the best pain relief was obtained with 10 ml lidocaine infiltrated solely at the neurovascular bundle region (single site) or to the neurovascular bundle and apical regions (double site). Therefore, the authors recommended single-site, 10-ml infiltration in the region of the neurovascular bundle [21].

Various infiltration sites have been described, including the apex only [22,23], bilateral neurovascular bundle regions only (defined variously as
<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Dose and type of drug</th>
<th>No. of core biopsies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matlaga et al. [13]</td>
<td>23 (PPNB) vs. 27 (GEL)</td>
<td>20 ml lidocaine 1% (10 ml to junction of seminal vesicle and prostate + 5 ml into genitourinary diaphragm + 5 ml between rectal wall and prostate) vs. 10 ml 2% lidocaine jelly intrarectally</td>
<td>8 up to 15 (mean 12)</td>
<td>Overall pain*: 0.5 vs. 4.2 (p &lt; 0.0001); biopsy pain 0.5 vs. 4.2 (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Adamakis et al. [14]</td>
<td>40 (sonographic gel) vs. 78 (GEL) vs. 80 (PPNB)</td>
<td>10 ml sonographic gel intrarectally vs. 10 ml 5% prilocaine-lidocaine cream (EMLA&lt;sup&gt;®&lt;/sup&gt;) vs. 10 ml 2% lidocaine to junction of seminal vesicle and prostate</td>
<td>10-core biopsies</td>
<td>Mean pain*: 5.1 vs. 4.8 vs. 2.5; statistically significant difference in group 3 and 1 (p &lt; 0.001) and in group 3 and 2 (p &lt; 0.001); no statistically significant difference in groups 1 and 2 (p = 0.18)</td>
</tr>
<tr>
<td>Lynn et al. [15]</td>
<td>30 (PPNB) vs. 27 (GEL) vs. 14 (gel-placebo) vs. 15 (placebo-injection)</td>
<td>10 ml 1% lignocaine periprostatic nerve plexus injection vs. 11 ml 2% lignocaine gel intrarectally vs. 10 ml gel-placebo rectally vs. 10 ml normal saline periprostatic nerve plexus injection</td>
<td>Sextant prostate biopsies</td>
<td>Mean pain*: 0.5 vs. 2.7 vs. 4.8 vs. 4.3; statistically significant difference in only group 1 (p &lt; 0.001)</td>
</tr>
<tr>
<td>Song et al. [16]</td>
<td>30 (GEL) vs. 30 (PPNB) vs. 30 (injection-placebo)</td>
<td>20 ml 2% lidocaine gel intrarectally vs. 5 ml 2% lidocaine to junction of seminal vesicle and prostate vs. 5 ml normal saline to junction of seminal vesicle and prostate</td>
<td>10-core biopsies</td>
<td>Biopsy pain*: 5.5 vs. 3.6 vs. 5.8; statistically significant difference in group 2 vs. group 3 (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Alavi et al. [17]</td>
<td>75 (PPNB) vs. 75 (GEL)</td>
<td>10 ml 1% injected into periprostatic nerve plexus vs. 10 ml 2% Turbojet lidocaine intrarectally</td>
<td>6–14 (average 6.8 vs. 6.6)</td>
<td>Mean pain*: 2.4 vs. 3.7 (p = 0.00002)</td>
</tr>
<tr>
<td>Stirling et al. [18]</td>
<td>50 (no anaesthetic) vs. 50 (PPNB) vs. 50 (GEL)</td>
<td>No anaesthetic vs. 5 ml 1% lidocaine periprostatic injection vs. 10 ml 2% lidocaine gel intrarectally</td>
<td>Minimum 8 (average 9.6 vs. 9.4 vs. 9.3)</td>
<td>Mean pain*: 3.8 vs. 2.6 vs. 3.1 (p &lt; 0.05)</td>
</tr>
<tr>
<td>Rodriguez et al. [19]</td>
<td>43 (GEL) vs. 53 (PPNB)</td>
<td>10 ml 2% lidocaine gel intrarectally vs. 10 ml 1% lidocaine solution injected at the prostate apex</td>
<td>6–14 (mean 7 vs. 8)</td>
<td>Mean pain*: 2.76 vs. 1.73* (p = 0.001)</td>
</tr>
<tr>
<td>Öbek et al. [20]</td>
<td>75 (no anaesthetic) vs. 75 (PPNB) vs. 75 (GEL + PPND) vs. 75 tramadol</td>
<td>No anaesthetic vs. 5 ml 2% lidocaine injection lateral to junction of seminal vesicle and prostate vs. 10 ml 2% lidocaine gel perianal/rectal + 5 ml 2% lidocaine periprostatic infiltration vs. tramadol 1.5 mg/kg e.v.</td>
<td>12-core biopsies</td>
<td>Mean pain*: 4.6 vs. 2.57 vs. 2.03 vs. 3.11; statistically significant difference only between group 3 and group 4 (p = 0.006).</td>
</tr>
</tbody>
</table>

PPNB = periprostatic nerve block; IRLA = intrarectal local anaesthesia; GEL = intrarectal anaesthetic gel; VAS = visual analog pain scale; TRUS = transrectal ultrasound.
basolateral, posterolateral, periprostatic nerve plexus, prostate-vesicular junction injections) \[17, 24, 25]\, and three locations (base, mid, and apex) posterolaterally \[26\] and lateral to the tip of the seminal vesicles \[27\] (Fig. 1). Even if infiltration of the neurovascular bundle region seems essential for effective anaesthesia, apical infiltration alone has been reported to provide significant pain relief \[22, 23\]. Recently, it has been demonstrated that the combination of PPNB and periapical local anaesthesia is not superior to PPNB alone in reducing pain during PBx \[28\].

The issue of whether PPNB should be associated with IRLA or oral medication has been recently discussed by some authors \[20, 29\]. Öbek et al \[20\] have demonstrated that the combination of PPNB and IRLA was superior to PPNB alone and concluded that this combined local anaesthesia could be considered a new gold standard. Pendleton et al \[29\] recently reported that oral administration of 75 mg tramadol/650 mg acetaminophen 3 h before PPNB appears to provide more effective pain control than PPNB alone without causing any additional complications.

There is no doubt that the introduction of PPNB has allowed EPBx to be performed easily in the office and, furthermore, the number of biopsies taken to be increased (from 10 to 18 or 20) without increasing the discomfort and pain of the patients. Despite the variability of location and dosage of infiltration, the PPNB is, nowadays, the most effective method to reduce pain during TRUS biopsy. It is controversial whether PPNB should be associated with IRLA or oral medication.

### 2.2. Antibiotic prophylaxis

Although published guidelines recommend prophylaxis for patients undergoing TRUS PBx because of the risk of urosepsis, the choice of antibacterial agent and duration of dosing are not consistent with the published recommendations and vary widely among urologists \[9\]. The antimicrobial prophylaxis is started the day before the EPBx and, in some cases, continued for 2–5 d \[9\]. The incidence of infection complications seems to be lower with longer duration of therapy in some but not all studies \[30–32\]. Schaeffer et al \[32\] have recently reported that a longer course (3 d) of antimicrobial prophylaxis (ciprofloxacin extended-release 1000) might be more beneficial than a short course (1–d).

### 3. Initial prostatic biopsy: from sextant to extended and saturation biopsy

Over the last few years, interest has increased in defining a more efficient biopsy scheme for detecting prostate cancer. Intuitively, adding more biopsies to prostatic areas not sampled by standard sextant schemes should increase the detection rate for prostate cancer. However, it is not clear whether the increased detection rate is simply due to the additional biopsies or to the location from which the cores are taken. Although biopsies of the transitional zone have been reported to add little to cancer detection \[33–42\], it would appear that the addition of far lateral biopsies improves the detection rate of adenocarcinoma (Fig. 2). Several researchers \[6–8\] have evaluated the diagnostic yield of lateral biopsies within an EPBx. It has been reported that laterally directed biopsies, which are aimed at sampling also the lateral horn, yield about a 25% increase in the ability to detect prostate cancer \[4, 7, 35\]. The apex and the base of the peripheral gland are the sites at which prostate cancer is most likely to be located and at which the biopsies should be directed, whereas the midline biopsies have been demonstrated to have the lowest probability of being positive \[7, 35\]. Most of the studies have demonstrated that EPBx has proven to be significantly superior to the sextant protocol in cancer detection, without significant morbidity and without increasing the number of insignificant cancer.

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**Fig. 2** – Histologic slide shows an intracapsular prostate cancer on the left side. The arrows show the directions of the biopsies. The classic Hodge biopsies as well as the Stamey biopsies (more lateral) are not in the optimal direction to detect the tumour that is localised very laterally in the subcapsular position. Only lateral biopsies are useful to detect the prostate cancer. LH = lateral horn, a site where the tumor is often situated; TZ = transition zone; T = prostate cancer.
cases [36]. There is no doubt that the direction and number of biopsies performed determine the procedure’s sensitivity. For these reasons the EPBx that optimises the detection rate should include six standard sextant biopsies with additional biopsies weighted more laterally at the base (lateral horn) and medially to the apex. The necessity of biopsying single hypoechoic lesions seems to be no longer necessary because the visible lesion itself is as likely to be the source of cancer as the next adjacent area [37].

More recently, some investigators have advocated even more aggressive biopsy schemes with >10–12 cores up to a saturation biopsy (≥24 cores) and reported even higher cancer detection rates [7,35].

Despite the use of an extended protocol, an increase in sampling error can occur in some patients, especially those with large prostate glands. It is well known that prostate volume is one of the factors that may influence the prediction of cancer at first biopsy and that a significant inverse relationship exists between the cancer detection rate and prostate volume [38]. Recently, it has been demonstrated that a scheme with eight cores turned out to be appropriate in patients with prostates < 30 cc. On the other hand, in prostates > 50 cc, an extended procedure with >12–14 cores was considered mandatory, even if the authors were not able to define the exact number of cores [39]. In a study of 303 patients comparing, directly in the same patient, the 6-, 12-, 18- and 21-core protocols, it was shown that a 21-sample needle biopsy procedure increased the prostate cancer detection rate [7]. The authors have reported a prostate cancer detection improvement of about 25% and 11% when 12- versus 6-core and 21- versus 12-core protocols were compared, respectively. Interestingly, they have demonstrated that the improvement was most marked in patients with a prostate volume of >40 cc. Unfortunately, these results should be interpreted with caution because most of the patients had already undergone a previous prostate biopsy. Recently, it was shown that 14-core biopsies are superior to 8-core biopsies for patients with prostate volumes of 30–40 cc. A core number > 14 may be needed to detect cancer for prostate volumes in excess of 40 cc [40]. In an EPBx that included lesion-directed biopsies plus a 14-core biopsy scheme, the difference in the cancer detection rates of the sextant and the 8-core biopsy schemes was larger in cases with prostate volumes < 50 cc than in those with prostate volumes > 50 cc, whereas the difference in the detection rates of 8-core and 14-core biopsies was smaller in patients with prostate volumes < 50 cc than in those with prostate volumes > 50 cc [41].

On the other hand, it has been demonstrated that the saturation technique as an initial PBx strategy does not improve cancer detection [42]. Jones et al [42] have suggested that further efforts at extended biopsy strategies beyond 10–12 cores are not appropriate as an initial biopsy strategy. In a recent systematic review, Eichler et al [43] have shown that there is no significant benefit in taking > 12 cores and that methods requiring ≥ 18 cores have a poor side-effect profile. Moreover, a transperineal (TP) 6-core biopsy has a detection rate similar to that of a 12-core biopsy in patients presenting with PSA levels > 10 ng/ml and abnormal digital rectal examination (DRE) findings [44].

In conclusion, it is now reasonable to consider a sampling with 12 cores of the peripheral gland as adequate even if limiting the number of cores to 12 in larger prostate is of concern.

4. The risk of over-diagnosis

The issue of nonsignificant prostate cancer is becoming more and more important because one possible disadvantage of the initial EPBx could escalate the risk of detecting small, possibly low-grade, and clinically insignificant cancers. Even if the definition of clinically insignificant prostate cancer is controversial and poorly defined, evidence in the literature suggests that EPBx has really contributed to the detection of more cancers of smaller volume and of little clinical relevance, with the potential for over-diagnosis or over-treatment. Nevertheless, the concern of over-detection must be weighed against the risk of missing clinically significant malignancy and cancer detection does not need necessarily a linked treatment because men with low-volume and low-grade diseases may also be managed expectantly.

There is no doubt that the recent stage migration of prostate cancer has been witnessed by regular increases in the proportion of patients with moderately differentiated low-volume tumour and a significant decrease in the volume of the cancers removed at surgery [45]. Recently, Master et al [46] demonstrated that a greater number of biopsies were associated with smaller tumour volumes at radical prostatectomy. Boccon-Gibod et al [47] have reported that 30% of patients with microfocal prostate cancer on EPBx have the risk of having insignificant tumour and of being over-treated. Moreover, no parameter was able to identify on an individual basis the patients harbouring a prostate
cancer potentially amenable to surveillance with delayed therapy.

Nevertheless, using an initial EPBx, Siu et al [36] have demonstrated that it is possible not only to enhance tumour detection but also to ultimately lead to the finding of clinically significant disease. Similarly, Singh et al [6] have shown no apparent significant association between the increased number of cores and the finding of smaller and clinically insignificant cancer. Meng et al [48] have recently demonstrated that performing more extensive biopsies does not significantly increase the number of lower-risk tumours identified. They have reported that there are no differences in disease characteristics and biochemical-free survival among men with a biopsy number between 6 and 17. Unfortunately, some methodologic flaws, such as a short median follow-up of just 2.2 yr, diminish the value of their results. Even if the authors concluded that increasing the number of cores does not affect the detection of lower-risk tumours, the usefulness of improved and earlier identification of cancers in altering the natural history remains uncertain.

Thus, even if the use of EPBx is recommended, the risk of detecting insignificant tumour should not be neglected. Nevertheless, saturation biopsies/rebiopsies, which are now used as part of active surveillance protocols, have recently proved to provide helpful information about quantitative and qualitative histology to predict the clinical significance of prostate cancer [49,50].

5. Repeat biopsy: from extended to saturation biopsy

The management of patients with persistently elevated levels of PSA in whom a first set of prostate biopsies has been negative for cancer is a daily problem for urologists. The cancer detection rate on repeat not-extended biopsy ranges between 10% and 20% [51]. Djavan et al [51] reported cancer detection rates on subsequent sets of biopsies one, two, three, and four of 22%, 10%, 5%, and 4%, respectively, in men with total serum PSA level of 4–10 ng/ml.

Recently, different researchers have demonstrated that saturation biopsy techniques aimed at greatly increasing the number of samples and varying the distribution of biopsy sites may provide a higher cancer detection rate (Table 2). The detection rate of prostate cancer ranged from 17% to 41%, and the likelihood of clinically insignificant cancers was not significantly increased compared with initial or repeat biopsy [52–58]. Saturation biopsies have a safe profile and are particularly useful in larger-volume prostates. Borboroglu et al [52] used an extensive TR saturation technique to obtain an average of 22.5 cores/patient and reported a cancer detection rate of 30%. A larger series with a different TR saturation biopsy scheme was reported by Stewart et al [53], who reported a cancer detection rate of 34%. Recently, Walz et al [57] reported a high prostate cancer detection rate of 41% with a 24-core protocol. Similarly to the initial biopsy protocol, it has been proven that more time and effort should be spent on lateral biopsies, which increase the cancer detection rate, whereas parasagittal biopsy provides a low yield on repeat PBx [56].

Although saturation biopsy is becoming more often the preferred repeat biopsy scheme, as yet no clear criteria indicate when to perform a rebiopsy in patients with persistently elevated levels of PSA.

6. Transrectal versus TP

The TP PBx is unusual, especially in the United States, even if some institutions in European and Asian countries perform TP PBx exclusively. Theoretically, the direction of the TP biopsies might be better than the transrectal (TR) route because they sample longitudinally the peripheral zone of the prostate. Initially the TP route was demonstrated to

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of patients</th>
<th>Mean/median PSA, ng/ml</th>
<th>No. of cores</th>
<th>Cancer detection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borboroglu et al.</td>
<td>2000</td>
<td>57</td>
<td>8.6</td>
<td>22.5</td>
<td>30%</td>
</tr>
<tr>
<td>Stewart et al.</td>
<td>2001</td>
<td>224</td>
<td>8.7</td>
<td>23</td>
<td>34%</td>
</tr>
<tr>
<td>Fleshner et al.</td>
<td>2002</td>
<td>37</td>
<td>22.4</td>
<td>32–38</td>
<td>13.5%</td>
</tr>
<tr>
<td>Rabets et al.</td>
<td>2004</td>
<td>116</td>
<td>9.2</td>
<td>22.8</td>
<td>29%</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>2004</td>
<td>100</td>
<td>9.4</td>
<td>20–24</td>
<td>25%</td>
</tr>
<tr>
<td>Pinkstaff et al.</td>
<td>2005</td>
<td>210</td>
<td>13.6</td>
<td>21.2</td>
<td>37%</td>
</tr>
<tr>
<td>Walts et al.</td>
<td>2006</td>
<td>161</td>
<td>9.4</td>
<td>24.2</td>
<td>41%</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen.
be less accurate than the TR approach in identifying all the hypoechoic lesions [59]. Subsequently, the same group of authors [60] also reported that TP-guided sextant biopsies were less accurate than TRUS-guided sextant biopsies in detecting prostate cancer. In a simulation experiment, Vis et al [61] have shown that the two approaches did not differ in prostate cancer detection. Emiliozzi et al [62] were the first to compare in vivo the two different approaches, and they have shown that the sextant TP biopsy seems superior to TR biopsy in detecting prostate cancer. The same authors [62] and Takeshita et al [63] have subsequently reported that the 12-core TP PBx is superior to 6-core biopsy and have shown that the number of cores may have a greater impact on cancer detection than the route of the PBx.

In the last few years, the concept of extended biopsies has been equally applied to the TP approach, with results similar to those achieved with the TR approach in patients undergoing biopsy procedures. The demonstration that the two approaches were equivalent in cancer detection was obtained only from reports of some Japanese urologists who had performed TR and TP biopsies in the same patients. Watanabe et al [64] compared 6-core TR and 6-core TP biopsies, and Kawakami et al [65] compared 12-core TR and 14-core TP biopsies. Both studies have shown that the overall cancer detection rate did not differ for the two approaches when the same number of cores were used, even if the two approaches combined were better than a single approach.

7. The role of nomograms

Detection of prostate cancer detection can be improved either with a better sampling of prostate cancer or by improving the indication for a PBx. The notion that combined input of multiple predictors usually exceeds that of most informative single variables has led to the development of artificial neural networks or nomograms to predict the probability of having cancer. Artificial neural networks have limited clinical applicability, and they have proven to be less accurate than nomograms in predicting the outcome of an initial biopsy [66]. Recently, different authors have reported nomograms based on extended biopsy protocol [66,67]. Chun et al [68] developed a useful nomogram based on a cohort of 2900 men exposed to ≥10 biopsy cores. Predictors included age, DRE, PSA, percent free PSA, and sampling density (ie, ratio of gland volume and the number of planned biopsy cores), which were included in multivariable logistic regression models predicting presence of prostate cancer. The nomogram was 77% accurate and also allowed the definition of the ideal ratio between gland volume and the number of planned biopsy cores that would yield the ideal biopsy rate.

Within the repeat biopsy setting, a novel nomogram including only patients undergoing extended biopsy schemes at final repeat biopsy has been reported with an accuracy of 77%, which exceeded the accuracies of previously published nomograms [69].

Therefore, nomograms represent a valid methodologic approach for detection of prostate cancer both at initial and repeat biopsy, if correct criteria are met. The availability of such high-quality predictive models should encourage the clinician to adopt these tools in everyday clinical practice.

8. Improving cancer detection by means of Doppler imaging

Standard grey-scale TRUS technology has limited specificity and sensitivity for prostate cancer detection because of its inability to detect isoechoic neoplasms. To increase its accuracy and utility, researchers have investigated a number of alternatives, including colour Doppler TRUS (CDUS), power Doppler imaging (PDI) with and without intravenous contrast administration, and, recently, elastography [65]. Increased microvasculature accompanies cancer growth, and neovascularity may be detectable by CDUS and PDI because of abnormal blood flow patterns in larger feeding vessels.

Some studies have shown that CDUS did not add significant information to grey-scale TRUS in detecting early stages of prostate cancer, whereas others have demonstrated varying degrees of benefit [70,71]. Overall, the sensitivity of CDUS for the diagnosis of prostate cancer ranged between 49% and 87%, and specificity ranged between 38% and 93% [71]. PDI is considered the next generation of colour Doppler imaging because it has the advantage of increased sensitivity for detecting small, low-flow blood vessels. Halpern et al [72] have shown that PDI may be useful for targeted biopsies when the number of biopsy passes must be limited but that there is no substantial advantage of PDI over CDUS. Remzi et al [73] have recently reported that PDI has a high negative predictive value and may help to reduce the number of unnecessary biopsies because a normal power Doppler TRUS signal might exclude the presence of a prostate cancer.
Contrast-enhanced colour Doppler (CECD) is an ultrasound-based technology for imaging of the prostate that is used after intravenous administration of gas-encapsulated microbubbles. This methodology allows for better prostate cancer visualisation and for targeted biopsies to isoechic areas that generally become hypervascular after contrast infusion. Halpern et al [74] have reported significantly improved sensitivity, from 38% to 65%, for detecting prostate cancer with preserved specificity at approximately 80%. Recently, different authors have demonstrated that targeted biopsy with CECD detects a number of tumours equal to that of systematic biopsies with less than half the number of cores [74–76]. Unfortunately, the poor discrimination of benign from malignant tissue, which is due to the CECD ultrasound signal arising from areas of benign disease such as benign prostatic hyperplasia, has diminished the specificity of this technology.

Recently, it has been reported that short-term oral therapy with a 5α-reductase inhibitor combined with dutasteride may improve prostate cancer detection if used with CECD ultrasound [77]. Despite these promising results, CECD has not yet gained popularity because of its low specificity, complexity, and high cost.

Some investigators [70] reported the use of sonography with manual compression of the prostate gland with the TR probe to generate elastograms. The basis for improved detection of cancer is that the elasticity of the neoplastic tissue is less compared with normal prostate tissue. The limited amount of data available on the ability of elastography to detect prostate cancer show that a targeted biopsy detects as many cancers as a systematic biopsy with less than half the number of biopsy cores, but more clinical trials are needed to determine the exact role of this advantage for TRUS [70].

9. Gleason concordance on EPBx

Different studies have demonstrated that the ability to predict the final Gleason score by means of standard sextant biopsy is quite poor with a concordance rate between the biopsy and prostatectomy Gleason scores of only 28–48% [78]. On average, the Gleason score is under-graded in 43% of cases (Table 3).

The use of EPBx has been beneficial in the pretreatment decision-making process because an increased number of biopsies increase the Gleason concordance. San Francisco et al [79] reported an improvement in the concordance rate from 63% to 72%. Mian et al [80] reported that the rate of upgrading to a worsening risk category was significantly reduced with EPBx. Numao et al [81] recently reported that a 26-core systematic biopsy can more accurately predict the presence of Gleason pattern 4/5 on surgical specimen compared with transrectal 12-core PBx.

### Table 3 – Grade of discordance, biopsy upgrading and downgrading with not-extended and extended protocols according to different authors

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>No. of cores taken</th>
<th>Grade of discordance</th>
<th>Biopsy upgrading</th>
<th>Biopsy downgrading</th>
</tr>
</thead>
<tbody>
<tr>
<td>San Francisco et al. [79]</td>
<td>2003</td>
<td>≤9, ≥10</td>
<td>37%, 24%</td>
<td>12%, 10%</td>
<td>25%, 14%</td>
</tr>
<tr>
<td>King et al. [78]</td>
<td>2004</td>
<td>6, 10</td>
<td>38%, 37%</td>
<td>25%, 12%</td>
<td>12%, 25%</td>
</tr>
<tr>
<td>Emiliozzi et al. [94]</td>
<td>2004</td>
<td>6, 12</td>
<td>51%, 30%</td>
<td>11%, 6%</td>
<td>39%, 24%</td>
</tr>
<tr>
<td>Coogan et al. [95]</td>
<td>2005</td>
<td>6, 8, 10</td>
<td>58.9%, 60%</td>
<td>19.6%, 23%</td>
<td>39.2%, 36.9%</td>
</tr>
<tr>
<td>Mian et al. [80]</td>
<td>2006</td>
<td>6, 12</td>
<td>52%, 32%</td>
<td>41%, 17%</td>
<td>31.5%, NR</td>
</tr>
<tr>
<td>Numao et al. [81]</td>
<td>2006</td>
<td>TP 14, TR 12, 3D 26</td>
<td>15%, 17%, 7.7%</td>
<td>NR, NR, 2%</td>
<td>51%, 48%, 26%</td>
</tr>
<tr>
<td>Elabbady et al. [5]</td>
<td>2006</td>
<td>6, 12</td>
<td>50%, 24.8%</td>
<td>NR, NR</td>
<td>NR, NR</td>
</tr>
</tbody>
</table>

NR = not reported; TP = transperineal; TR = transrectal; 3D = three-dimensional.
King et al distinguished between any upgrading and significant upgrading (Gleason sum increases either from ≤ 6 to ≥ 7 or from 7 to ≥ 8) and suggested that significant upgrading represents a clinically meaningful entity. Different authors [81–83] have demonstrated that, with more EPBx, the risk of significant upgrading decreases because of higher sampling density and more accurate pathologic biopsy evaluation. The two largest published cohorts [86,87] showed a rate of overall Gleason sum upgrading of 29.3% and 32.6% and a rate of significant upgrading of 32% and 28.2%, respectively. Because significant Gleason sum upgrading between biopsy and final pathology may have an impact on treatment decision-making, predictive nomograms have been developed as prognostic models capable of predicting the probability of significant upgrading [84,85].

10. Quantitative histology on EPBx

The amount of tumour in prostate needles can be expressed by the number of positive cores or by the amount of tumour per core. This parameter is an extremely important pathologic parameter and a predictor of a lethal phenotype of prostate cancer or a clinically insignificant cancer (Tables 4 and 5) [86,87]. The extent of involvement of needle cores by prostatic adenocarcinoma has been shown to correlate (albeit not perfectly) with the Gleason score, pathologic stage, surgical margins, but, especially, with tumour volume [88]. As the number of positive cores and the amount of tumour per core increase, the larger the tumour volume is likely to be. The extent of needle core involvement, including bilateral involvement, has also been shown to predict biochemical recurrence, postprostatectomy progression, and radiation therapy failure in univariate analysis and often in multivariate analysis [89,90]. It is a parameter included in some recent nomograms created to predict pathologic stage and seminal vesicle invasion after radical prostatectomy and radiation therapy failure. Although the correlation for high tumour burden in needle biopsies is directly proportional to the likelihood of an adverse outcome, low tumour burden in needle biopsies is not necessarily an indicator of low-volume and low-stage cancer in the prostatectomy specimen. For instance, an apparently favourable report with only one or two cores positive for cancer or a limited extent of < 3 mm of cancer does not act as a guarantee for either organ-confined prostate cancer or insignificant cancer after radical prostatectomy [91]. As with the other parameters, a combination of the extent of involvement of needle cores with the Gleason score, location of the tumour, and serum PSA levels increases the prognostic and predictive power of this parameter [91].

In one study [91], the percentage of cancer in biopsies from the base correlated with extraprostatic extension. In other studies, a Gleason score of 7–9 cancer in the midprostate or base biopsies correlated with the risk of seminal vesicle invasion and lymph node metastasis, and a tumour volume of > 50% in base biopsies correlated with a prediction of extraprostatic extension at the neurovascular bundle and posterior lateral region [92]. Moreover, the amount of cancer in apex biopsies has been shown to correlate with apical margin positivity [93]. The number and percentage of positive biopsy cores have also proven to improve the ability to predict lymph node invasion in patients undergoing radical prostatectomy and extended pelvic lymph node dissection (Table 6) [86].

There is lack of consensus in the literature with regards to the best method of reporting the extent of tumour involvement. It is recommended that the report should provide the number of involved cores. Typically, small foci are reported as < 1% or < 5%, and so forth, of needle core biopsies, and linear length is reported in increments of 0.5 mm. The correlation, as alluded to before with prognosis, is with greater involvement of the cores, and studies have shown various cut-off values (≤ 33%, 34–50%, and 51–100%,

Table 4 – Prostate biopsy reporting

<table>
<thead>
<tr>
<th>Parameters that should be reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Number and total length of the cores (exclude those &lt; 1 cm and those without epithelial component)</td>
</tr>
<tr>
<td>2. Number of cores with cancer (percentage of cores involved)</td>
</tr>
<tr>
<td>3. Longest single length of tumour (report also the location)</td>
</tr>
<tr>
<td>4. Total tumour length in all cores</td>
</tr>
<tr>
<td>5. Mean tumour length in all cores (reported as a percentage): total tumour length divided by total length of cores multiplied by 100 (ie, overall percentage of cancer in all biopsies)</td>
</tr>
<tr>
<td>6. Number of cores with perineural invasion (extent: focal, multifocal) and calibre of nerve bundles</td>
</tr>
<tr>
<td>7. Number of cores with vascular invasion</td>
</tr>
<tr>
<td>8. Composite (global) Gleason score for all cores for the patient</td>
</tr>
<tr>
<td>9. Number and location of cores with atypical glands, suspicious for cancer</td>
</tr>
<tr>
<td>10. HGPIN (extent; focality: focal or multifocal; number of cores involved; laterality: unilateral or bilateral)</td>
</tr>
</tbody>
</table>

Each core (slide) is reported individually (see the example below):

1. Prostate biopsy of 1.4 cm occupied for 7 mm (50% of the core length) by acinar adenocarcinoma, Gleason score 3 + 3 = 6. Perineural invasion is present.
2. Prostate biopsy of 1.3 cm with normal prostate tissue

HGPIN = high-grade prostatic intraepithelial neoplasia.
or ≤20%, 21–55% and >56%, etc) to be of significance [93]. Because literal translation of these findings to clinical cases would be difficult and not really necessary, reporting the percentage of cancer involvement in increments of 5% or 10% is appropriate.

### 11. Conclusions

Despite years of research, the exact number of biopsies to be taken to (1) detect significant prostate cancers, (2) predict the actual tumour volume, and (3) rule out insignificant prostate cancer is still largely unknown. Despite development of PDI, CDUS, and CECD, which allow performance of targeted biopsies, the current trend is to use, more and more often, EPBx (10- to 12-core biopsy without the transition zone) as the initial biopsy strategy. Moreover, the inability to better determine who needs to undergo biopsy and the reliance on Gleason score are the two main factors that contribute to the dependence on a greater number of biopsies. In men with persistent suspicion of prostate cancer after several negative biopsies, more extensive protocols (>12 cores) up to saturation biopsy represent a necessary diagnostic procedure that has proven to have a safe profile. The issue of whether an increase in number of biopsy cores taken results in the

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**Table 5 – Preoperative parameters predicting the presence of insignificant prostate cancer according to different authors**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Origin of cohort</th>
<th>% of IPCa</th>
<th>Biopsy protocol</th>
<th>Preoperative parameters predicting the presence of IPCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein et al. [96]</td>
<td>United States</td>
<td>26%</td>
<td>Sextant</td>
<td>• Gleason sum ≤ 6&lt;br&gt;• Adenocarcinoma present in fewer than 3 of 6 cores&lt;br&gt;• No more than 50% malignant involvement in each positive biopsy core&lt;br&gt;• PSA density &lt; 0.15 ng/ml/g</td>
</tr>
<tr>
<td>Goto et al. [97]</td>
<td>United States</td>
<td>10%</td>
<td>Sextant</td>
<td>• Quantitative analysis of the extent of cancer&lt;br&gt;• PSA, PSA density, and grade</td>
</tr>
<tr>
<td>Carter et al. [98]</td>
<td>United States</td>
<td>17%</td>
<td>Sextant</td>
<td>• PSA density&lt;br&gt;• Quantitative histology (number of cores involved with cancer and percentage of cancer within the core)</td>
</tr>
<tr>
<td>Epstein et al. [99]</td>
<td>United States</td>
<td>30%</td>
<td>Sextant</td>
<td>• Needle biopsy findings&lt;br&gt;• Free/total PSA levels</td>
</tr>
<tr>
<td>Kattan et al. [100]</td>
<td>United States</td>
<td>20%</td>
<td>≥6</td>
<td>• Nomograms incorporating pretreatment variables (clinical stage, Gleason grade, PSA, and the amount of cancer in a systematic biopsy specimen)</td>
</tr>
<tr>
<td>Ochiai et al. [101]</td>
<td>United States</td>
<td>22%</td>
<td>Extended (10–11 cores)</td>
<td>• Combination of tumour length &lt; 2 mm, Gleason score ≤ 3 + 4, and prostate volume &gt; 50 cc</td>
</tr>
<tr>
<td>Augustin et al. [102]</td>
<td>Europe</td>
<td>6%</td>
<td>Sextant</td>
<td>• PSA density&lt;br&gt;• Percent of cancer per biopsy</td>
</tr>
<tr>
<td>Chun et al. [68]</td>
<td>Europe</td>
<td>6%</td>
<td>≥6</td>
<td>• Preoperative nomograms (predictor variables: PSA, clinical stage, biopsy Gleason scores, core cancer length, and percent of positive biopsy cores)</td>
</tr>
<tr>
<td>Miyake et al. [103]</td>
<td>Japan</td>
<td>14%</td>
<td>8</td>
<td>• Gleason score &lt; 7&lt;br&gt;• Percent positive biopsy core &lt; 15%</td>
</tr>
</tbody>
</table>

IPCa = insignificant prostate cancer defined as tumour < 0.5 cc and no Gleason 4 and 5 at final pathology; PSA = prostate-specific antigen.

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**Table 6 – Importance of knowing the specific location of the biopsy and the location of cancer**

1. Tumour involvement of base biopsies may influence bladder-neck-sparing radical prostatectomy.
2. Extensive cancer in base biopsies correlates with extraprostatic extension.
3. Dominant side of prostate biopsy correlates with ipsilateral positivity of surgical margins and extraprostatic extension.
4. Knowledge of location of cancer may help target additional tissue or block sampling in cases with no apparent cancer in radical prostatectomy sections.
5. Knowledge of biopsy site helps recognise potential diagnostic pitfalls (eg, seminal vesicle epithelium or central zone epithelium, seen most frequently in base biopsies and the rare Cowper’s glands in apex biopsies).
6. Knowledge of biopsy site and location of cancer allows detailed correlation with digital rectal examination and imaging studies.
7. Laterality is useful in planning of nerve-sparing radical prostatectomy.
8. Map distribution of prostate cancer is useful for planning the field of radiation therapy (eg, in brachytherapy).
detection of more tumours with a lower-risk feature remains controversial.

Conflicts of interest

The authors have nothing to disclose.

References

[61] Vis AN, Boerma MO, Ciatto S, Hoedemaeker RF, Schroder FH, van der Kwast TH. Detection of prostate cancer: a comparative study of the diagnostic efficacy of sextant


[96] Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994;271:368–74.


