Prostate Biopsy in Selecting Candidates for Hemiablative Focal Therapy

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Abstract

Focal therapy (FT) for the management of clinically localized prostate cancer (PCa) is growing from a concept to reality because of increased interest of both patients and physicians. Selection protocols, however, are yet to be established. We discuss the role of prostate biopsy in candidate selection for FT and highlight the different strategies and technical aspects of the use of prostate biopsy in this setting. In our opinion, prostate biopsy plays a major role in the selection process and tailoring appropriate treatment strategy to the patient. FT necessitates dedicated biopsy schemes that would reliably predict the extent, nature, and location of PCa in selected patients. Currently, there is insufficient scientific evidence to propose a specific biopsy scheme that could fit every candidate, providing accurate characterization of the disease in the individual patient. Further research is necessary to establish solid selection protocols that would reliably identify appropriate candidates for FT of PCa.

Introduction

Focal therapy (FT) for the management of clinically localized prostate cancer (PCa) is growing from a concept to reality because of increased interest of both patients and physicians. FT is an attractive option for appropriately selected patients because it may result in reduced morbidity and therefore better preserve quality of life compared with whole gland treatment. Appropriate candidate selection in this setting is paramount; however, the tools of selection are still debated as is their role in this setting.

Hemiablation is today the most established focal treatment technique that aims at destroying one half of the gland while preserving the contralateral side and its neurovascular bundle. Therefore, appropriate candidates for this approach are represented by patients with unilateral PCa and, possibly extending to include patients with clinically insignificant contralateral disease.

Prostate biopsy is a well-known tool in the decision-making process for the management of PCa and appears to be the most valuable criterion for selecting patients for FT. We discuss the role of prostate biopsy in candidate selection for FT and highlight the different strategies and technical aspects to propose evidence-based recommendations for the use of prostate biopsy in this setting.

Is Biopsy Necessary for Focal Therapy Candidate Selection?

Biopsy is not the only tool that plays an important role in the patient selection process for FT. Biopsy results need to be integrated with clinical, laboratory, and imaging data to be able to formulate a treatment plan. But can we avoid biopsy? Currently, PCa detection is largely based on biopsy results, because imaging tools are unable to be diagnostic and achieve appropriate sensitivity and specificity levels and confirmation of PCa on biopsy is a prerequisite to further steps in planning the treatment. Moreover, tissue diagnosis provides a list of useful prognostic variables (ie, Gleason score, percent of tumor involvement, distribution of cancerous tissue within the gland, molecular markers) that may modify the treatment strategy. In the FT setting, biopsy outcomes have been shown to be one of the strongest predictors of unilateral PCa.

At this time, it does not seem that biopsy can be avoided, and, therefore, the information obtained should be maximized to provide a truly useful tool for patient selection.

What Is the Appropriate Biopsy Strategy?

There is no agreement on the appropriate strategy to be used in patient selection protocols; however, it seems reasonable to suppose that the biopsy scheme used for FT patient
selection should be separate from the routine office-based cancer detection biopsy familiar to every urologist.

Standard prostate biopsies are simply aimed at detecting cancerous tissue, while the requirements for the FT setting include precise characterization and mapping of the lesion(s) within the prostate. These necessary prerequisites are unavailable with routine diagnostic biopsy. Moreover, prostate biopsy is a sampling technique, and, as such, suffers from sampling errors. These errors are unacceptable in the FT setting, emphasizing the need for extensive sampling and mapping to reduce the margins of error and underdetection.

The appropriate biopsy strategy for selecting patients for FT should therefore be sufficiently thorough to detect all significant cancer within the prostate, able to provide standard pathologic variables, such as Gleason grade and percent of tumor involvement per core, and able to identify core location for treatment decision and treatment planning.

From the above consideration, it is clear that the FT setting necessitates a specific and unique biopsy strategy that cannot be confused with the conventional routine cancer detection biopsy. Determining an appropriate biopsy scheme is an active field of research these days and will likely yield several options that may be safely used for the purpose of selecting candidates for FT.

**How many cores?**

The number of cores taken per biopsy is a crucial element for its diagnostic accuracy, given that biopsy is a sampling technique that estimates the reality and has the potential for sampling errors. Increasing the number of cores will definitely increase the diagnostic yield; however, the optimal number of cores per biopsy setting has not yet been defined.

Mayes and associates\(^6\) reported on the accuracy of routine office-based sextant biopsy in predicting unilateral PCAs in low-risk patients. The authors found sensitivity and a negative predictive value of unilaterally positive prostate biopsy of 86% and 91%, respectively, whereas specificity and positive predictive values were 39% and 24%. Routine sextant biopsy is clearly unable to reliably detect truly unilateral PCAs as determined by final pathologic analysis of radical prostatectomy specimens.

Another report compared the diagnostic accuracy of sextant vs extended biopsy schemes in all risk categories.\(^7\) It emerged that doubling the number of cores (from 6–9 in sextant to 10–20 in extended schemes) increases the diagnostic accuracy (overall correct predictions) from 45% to 59%. Similarly, biopsy specificity for detecting truly unilateral PCAs improved from 37% to 54%, respectively. Smaller diagnostic gains could be appreciated for sensitivity and negative predictive value. The extended biopsy scheme outperformed sextant biopsy with regard to indicating truly unilateral disease; however, the ability to exclude unilateral disease was similar for both biopsy schemes. In contrast, Tareen and colleagues\(^8\) reported that among patients with unilaterally positive prostate biopsy, the likelihood of pathologically proven unilateral PCAs did not vary significantly based on the number of cores obtained by biopsy.

Should the number of cores be adjusted to prostate size? The intuitive answer is yes, because biopsy is a sampling technique and the prostate gland is the pool—therefore, to accurately estimate the true variables, one needs more samples from a larger pool and fewer samples from a smaller pool. A recent study by our group, however, indicates that the relationship between prostate size\(^8\) and biopsy accuracy is not a linear one, with larger (>40 cc) prostates more frequently harboring unilateral disease enhancing biopsy performance (unpublished data), thereby suggesting that both sextant (6–9 cores) and extended (10–20 cores) biopsy techniques perform better in larger prostates with statistically significant improvement only in the latter case. More data are necessary to formulate an accurate scheme of adjustment of the number of cores to prostate size without increasing the invasiveness while maintaining diagnostic performance.

Mapping biopsy schemes that obtain an average of 50 cores have been reported\(^9\) and have been advocated as an essential tool in patient selection for FT. Obtaining these amounts of cores is likely to provide enhanced diagnostic performance of the biopsy; however, to date, there are no studies that report on diagnostic properties of these multicore techniques with radical prostatectomy specimens as the reference and no comparison with other biopsy techniques.

In summary, the optimal number of cores to be obtained on prostate biopsy to achieve adequate accuracy in detecting unilateral prostate cancer has yet to be determined. Routine office-based diagnostic biopsies did not prove reliable in predicting unilateral PCAs; however, they have an excellent power to exclude patients with bilateral disease, making these strategies appropriate for initial screening. Further research is needed to tailor the number of cores to the single patient, balancing the trade-off of diagnostic performance in detecting unilateral disease.

**Where to sample?**

Should prostate tissue sampling be random or should it be systematically guided by templates, and if so, which templates should be used? Unfortunately only scarce data are available on this topic in the FT setting, whereas most of the knowledge derives from routine cancer detection biopsies. Different sampling schemes have been proposed and reported in the literature. Onik and Barzel\(^10\) and Bott and co-workers\(^11\) proposed a random saturation sampling providing more than 50 cores per prostate using the standard 0.5 cm transperineal (TP) grid template. These random sampling techniques maximize the number of cores and represent the most thorough prostate sampling techniques that are currently available. On the other hand, these biopsies produce a large number of tissue samples that may have different *a priori* probabilities to harbor cancerous tissue.

An interesting and a more elegant approach has been reported by Narayan and colleagues\(^12\) who adapted a three-dimensional (3D) PCa atlas for an ultrasound-guided prostate biopsy. The atlas refers to patterns of likelihood to find PCa foci within the prostate according to 3D reconstructions of radical prostatectomy specimens.\(^12\) A further step in the same direction was reported by Ou and associates,\(^13\) who described the ability of the atlas-based biopsy schemes to estimate tumor volume and Gleason scores based on the location of positive biopsy by means of statistical models. This approach may reduce the random component of prostate biopsy and thus diminish the number of cores needed to reliably identify unilateral PCAs and enhance the information obtained from biopsy results. Clinical application of the statistical
model described needs to be validated in conjunction with other parameters in the setting of selecting appropriate candidates for FT, tailoring biopsy settings to the specific patient.

**Transrectal (TR) or TP?**

TR office-based biopsy is the standard approach, with decades of experience familiar to every urologist. TR biopsies are well-tolerated and are easily performed with the patient under local anesthesia. The current drawback is the number of cores that could be potentially obtained by a TR approach without compromising patient compliance.

The TP approach offers the possibility to obtain multicore biopsies but requires anesthesia or sedation typically performed in an ambulatory operating room and necessitates advanced equipment that may be reflected in procedure costs. Furthermore, it has been suggested that the TP approach may be more efficient in sampling the apical and anterior portions of the prostate. Moreover, there is less experience with the TP approach compared with the TR one; thus, urologists may be less familiar with this approach.

The morbidity profile of the TP approach differs from that of standard TR biopsies and may have a higher incidence of urinary retention episodes, this factor has to be taken into account as well. In a direct comparison between the two approaches, Kawakami and associates found no significance differences in the ability to detect and characterize PCa in contrast with Emiliozzi and coworkers, who reported on superiority of the TP approach. The conflicting conclusions reached by these investigators may be, at least in part, because of the different number of cores taken; while Emiliozzi and colleagues reported on six cores by each approach, Kawakami and coworkers obtained 12 and 14 cores by TR and TP approaches, respectively. These findings may suggest that the superiority of TP over the TR approach in detecting PCa may vanish when the number of cores is increased.

This hypothesis is further validated by Takenaka and associates, who could not find significant differences in cancer detection between the two 12-core biopsy approaches. Complications rates were compared by several authors, and no significant differences were found. A summarized comparison between the TR and TP approaches is reported in Table 1.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Anesthesia</th>
<th>Number of cores obtained</th>
<th>Sampling advantages</th>
<th>Complications rate</th>
<th>Cost</th>
<th>Insurance coverage</th>
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<tbody>
<tr>
<td>TR</td>
<td>Office-based</td>
<td>Typically ≤24</td>
<td>Peripherial</td>
<td>Low</td>
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<tr>
<td>TR</td>
<td>Ambulatory OR</td>
<td>Up to over 100</td>
<td>Transitional, anterior, apical</td>
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<td>≈ 10% urinary retention</td>
<td>High</td>
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<td>Sedation/general</td>
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<td>OR = operating room.</td>
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</table>

Currently, there are insufficient data to form a conclusion on the superiority of one approach over the other. The TR or TP approach may be favored based on the therapy technology used; if a TP treatment is chosen (eg, cryoablation), a TP biopsy technology may be integrated on the same platform to facilitate treatment planning. The future of the biopsy approach is likely to be integrated into the treatment devices.

**The Importance of Mapping Biopsies**

FT aims at focal destruction of known PCa foci; thus, it is mandatory to know the location of such foci to be able to target the therapy accurately for eradication of cancerous disease while preserving healthy surrounding tissues. In this view, biopsy results should be mapped to allow for a subsequent targeted therapy to be delivered into the afflicted zones. Mapping biopsies represent the cornerstone of FT. The question is, how precisely should we map? Should every core be analyzed separately or could more cores be batch together in zones for histopathologic evaluation?

The zonal approach, dividing the prostate into a variable number of zones and batch-analyzing the cores from these zones, has been successfully used by several investigators. Another possibility is creating mathematical models that predict the exact location of the needle and create a biopsy template. Such mapping reduces the possibility of mapping inaccuracy because of needle displacement by deflection or by deformation of tissues. A real-time registration of the needle position and thus the core location has been proposed with the same intent. The latter approaches necessitate separate pathologic evaluation of each core, gathering detailed information that, in turn, can be introduced into the mapping software and be used as a guide for targeted therapy. This approach is likely more expensive but provides additional information both for future research and for treatment decisions regarding the individual patient, enabling truly focal therapy that would treat precisely the involved portions of the gland.

A further advancement in optimizing the processing of the biopsy cores may help to maximize the information obtained from the tissue independent of the way biopsy cores are taken from the prostate. Stock and associates described the self-embedding technique for prostate biopsy specimens whereby each core is placed on a saline-tinctured tissue marking the proximal (apical) and distal (basal) end immediately after removing it from the biopsy needle. If the core is fragmented, the pieces are arranged in the appropriate order. Then they are covered with a second piece of saline-tinctured tissue and separately fixed in metal clamps to avoid shifting. The closed metal clips are placed together in a formalin-filled container to be sent to the pathologist. Embedding only minimally increases the effort necessary during the biopsy procedure. For the pathologist, the procedure simplifies the process with separated, preprocessed, and embedded cores.

This technique has clear advantages for mapping biopsies and precise localization of PCa within the gland. By knowing the orientation of the cores, one can easily reconstruct the correct alignment and map the cancer with extreme precision. This method maximizes the information that is obtained by biopsy and may be of particular advantage in TP grid-guided multicore biopsies where at least two (distal and proximal) cores are taken through one grid hole. In this setting, knowing
the orientation of the cores may provide valuable information about spatial localization and extent of PCa in evaluating potential candidates for FT. A summary of currently available dedicated 3D biopsy systems is provided in Table 2.

The recent technologic advances that propose image-guidance and therefore “targeted” biopsy are promising. Targeted biopsy would therefore sample zones with an increased chance of finding and characterizing PCa foci, somewhat like mathematical models discussed. Some of the technologies investigated in this setting are: Contrast-enhanced ultrasonography, elastography, and MRI/spectroscopy that have shown intriguing preliminary results. The implementation of targeted biopsies in the FT setting should be investigated and their potential scrutinized in larger, hopefully prospective, studies. Until these results are available, shifting from “blind” to “targeted” image-guided biopsy remains hypothetical.

Mapping biopsies are an essential prerequisite to FT implementation both today and especially in the future when more “focal” and targeted approaches may be implemented into clinical practice. For the advancement of FT and further acceptance into clinical reality of PCa treatments, mapping biopsies are essential, and detailed location of each core is recommended.

### Unilateral Versus Unilaterally Significant Prostate Cancer

Should hemiablation be reserved only for patients with unilaterally positive cores or could patients with insignificant contralateral cancer benefit safely from FT? The answer to this question is beyond the scope of this article; however, several considerations pertaining to biopsy strategies deserve mention.

Because of needle displacement, the true position of the biopsy needle in cores that are taken near the midline may be inaccurate and induce the error of diagnosing bilateral PCa. Assuming no software guidance for the biopsy needle, this event could be more likely to occur with the TR approach because of the trajectory of the needle. This error may be detected and may be avoided by recording the exact location of the core or by using mathematical models that accurately predict core location. In addition, if there is a positive contralateral core near the midline, can the ablation be extended beyond the midline and treat this focus effectively?

The same tools in use for whole gland decision-making, summarized by Bastian and coworkers, will likely be used to determine the insignificance of contralateral PCa. Biopsy variables are included in most of these criteria and will need to be adapted or reformulated considering multicore biopsy schemes in the FT setting.

### Conclusions

Defining appropriate patient selection protocols for FT is crucial to the success and acceptance of this approach. Prostate biopsy plays a major role in the selection process and tailoring appropriate treatment strategy to the patient. FT necessitates dedicated biopsy schemes that would reliably predict the extent, nature, and location of PCa in selected patients. Currently, there is insufficient scientific evidence to propose a specific biopsy scheme that could fit every candidate providing accurate characterization of the disease in the individual patient. It seems reasonable to suggest increasing the number of cores beyond the conventional 12-core scheme and tending toward a comprehensive systematic 3D mapping of the prostate in this setting. Although mathematical and “targeted” image-guided approaches to the development of efficient biopsy templates are intriguing, their clinical application has yet to be validated. Routine office-based prostate biopsy should not be relied on in selecting candidates but may serve as an initial “screening” tool that reliably identifies patients with bilateral disease.

For patients willing to embark on the option of FT, dedicated specific biopsy schemes should be requested in addition to the previously performed routine biopsy. Further research is necessary to establish solid selection protocols that would reliably identify appropriate candidates for FT of PCa.

### Disclosure Statement

No competing financial interests exist.

### References

5. Tareen B, Godoy G, Sankin A, et al. Can contemporary transrectal prostate biopsy accurately select candidates for...
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**Abbreviations Used**

FT = focal therapy
MRI = magnetic resonance imaging
PCa = prostate cancer
3D = three dimensional
TP = transperineal
TR = transrectal