Schema and cancer detection rates for transperineal prostate biopsy templates: a review

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Abstract: Prostate cancer (PCa) is the most common noncutaneous malignancy in men and is the second leading cause of cancer mortality in men in the United States. Current practice requires histopathological confirmation of cancer achieved through biopsy for diagnosis. The transrectal approach for prostate biopsy has been the standard for several decades. However, the risks and limitations of transrectal biopsies have led to a recent resurgence of transperineal prostatic biopsies. Recent studies have demonstrated the transperineal approach for prostate biopsies to be effective, associated with minimal complications and superior in several aspects to traditional transrectal biopsies. While sextant and extended sextant templates are widely accepted templates for transrectal biopsy, there are a diverse set of transperineal biopsy templates available for use, without consensus on the optimal sampling strategy. We aim to critically appraise the salient features of established transperineal biopsy templates.

Introduction

Prostate cancer (PCa) is the most common non-cutaneous malignancy in men and is the second leading cause of cancer mortality in men in the United States.[1,2] Approximately, 1 million prostate biopsies are performed in the United States on an annual basis and have continued to increase over recent years.[3] Prostate biopsy techniques have varied over the past century, undergoing many refinements in technique with the goal of improving cancer detection and risk stratification. The earliest efforts to sample prostate tissue involved biopsy of areas with palpable abnormalities. Systematic sampling of prostate became popular in the 1980s, as it would identify tumors previously missed by targeted sampling. Notably, transperineal biopsy (TP-Bx) was the prevailing method of choice for prostate gland access, until the establishment and popularity of the systematic sextant 12-core whole gland sampling via the transrectal route by Hodge *et al.* in 1989.[4,5] This

proposed technique, coupled with the introduction of the transrectal ultrasound (TRUS), displayed superior diagnostic accuracy and remains the standard of care today.[6] However, subsequent studies assessing transrectal biopsy (TR-Bx) in recent years have drawn attention to the higher risks of infectious complications, including hospital admissions due to sepsis.[7,8] In addition, a significant number of cancers can be missed by a transrectal approach, particularly in the antero-apical portions of the gland.[9,10] With improved access to hard-to-reach portions of the prostate gland and minimal infection rates, TP-Bx has re-emerged positioning itself as the solution to these problems.[11–14]

While TP-Bx is increasingly being used, there is a considerable variation in transperineal template-guided biopsy schemes used among clinicians. The absence of consensus highlights the need for evidence-based recommendations to optimize

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cancer detection. Several schemes have been described with varying combinations of regions sampled and cores obtained (Table 1). Both the mapping approach (Barzell) and the sector approach (Ginsburg) are examples of techniques that have been utilized with excellent results. Other schemes, such as the 10-sector, 12-core, and MUSIC (Michigan Urological Surgery Improvement Collaborative) approaches have also been routinely used. To our knowledge, while numerous approaches exist, there is a scarcity in literature regarding a review of these commonly used TP-Bx template types. Thus, our goal is to provide a brief overview of target zones and the effectiveness of the five commonly used TP templates, namely, (1) Barzell, (2) Ginsburg, (3) 12-core, (4) 10-sector, and (5) MUSIC.

Zonal anatomy of prostate

Transperineal templates are designed to systematically sample the prostate gland to maximize cancer detection rates (CDRs) and are based largely on the zonal anatomy of prostate. The prostate is divided into four zones: the central zone (CZ), transition zone (TZ), peripheral zone (PZ), and anterior fibromuscular stroma (Figure 1).[25] The CZ is derived from Wolffian duct, whereas the rest of the prostate is derived from urogenital sinus. In adult men, PZ comprises 70% of glandular tissue, whereas the CZ and the TZ comprise 25% and 5% of glandular tissues, respectively.[26,27]

As men age by the age of 60 years, the TZ and the PZ mainly contribute to prostate enlargement except that once the total volume of prostate exceeds 50 g, the growth is mainly accounted by TZ and may eventually lead to benign prostatic hyperplasia (BPH).[28] The PZ accounts for 75% of cancers; the TZ although enlarged in older males accounts for 20% of the cancer, while the CZ accounts for 5–8% of cancer. There is considerable evidence that cancers arising in the TZ are clinically and biologically different from PZ cancers.[29]

Barzell technique and its modifications

Sextant template biopsies using transrectal approach have been shown to undergrade and understage PCa.[30] In an effort to overcome the random and uneven sampling of all areas of the prostate, a systematic transperineal prostate biopsy using brachytherapy grid was proposed

that would later become known as the Barzell technique. Established in 2003 by Barzell and Whitmore,[15] the use of a grid in combination with TRUS was proposed to ensure reproducible and accurate systematic sampling of the prostate that would help minimize human error and provide precise localization of cancer foci. With this approach, a fixed set of reproducible coordinates would allow for accurate mapping of the lesions allowing for targeted therapy as a feasible option. Access to the antero-apical regions of the prostate was also a benefit of this approach given, it was to be performed through a transperineal approach.

In the Barzell template, the prostate is divided into eight sectors. A transverse plane separates prostate into proximal (base) and distal (apex) halves, a sagittal plane divides each half further into right and left lobes, and finally, a coronal plane divides into anterior and posterior regions (Figure 2). The resulting regions formed are as follows: left anterior apex (LAA), left anterior base (LAB), left posterior apex (LPA), left posterior base (LPB), right anterior apex (RAA), right anterior base (RAB), right posterior apex (RPA), and right posterior base (RPB).[31] The procedure is performed under general anesthesia or intravenous (IV) sedation anesthesia as it requires a significant number of cores. Local anesthesia has recently been utilized with success, allowing room for a speedier process and lower risk of complications that come with general anesthesia.[6] Using a bi-plane TRUS for guidance, four to eight cores are taken from each of the eight sectors in a craniocaudal fashion from apex to base, for a total of 32–64 biopsies depending on volume of prostate. Special care is taken in the anterior zone where biopsy gun can transverse through urethra and increase the risk of complications. In Barzell's description, oral antibiotics for 3 days were prescribed to all to prevent infection and sepsis, while most patients were given alpha-blockers to aid with voiding post catheter removal. In 65 patients, Barzell and Whitmore[15] demonstrated a 40% clinically significant cancer detection without major complications.

In 2008, Onik and Barzell[16] demonstrated increased reliability using the Barzell technique in the detection of clinically significant cancer if the prostatic tissue was sampled at intervals of every 5 mm as compared with an arbitrary 32/64 cores. The theory behind the proposed utilization of the 5 mm technique comes from the fact that fewer clinically significant cancers would be missed

Table 1. Summary table of templates.

Transperineal biopsy template type	Brief description	Median # cores	Cancer detection rates	Complication rates	Article
Barzell technique	Eight-sector template divided by three planes.—Four to eight cores are taken from each region for a total of 32–64 cores Eight-sector template, cores taken at every 5 mm; volume-dependent Twenty-sector template, modified Barzell created from two lateral sagittal sections per side (Modified Barzell)	32–64 46 (SD ±19) 40 (IQR = 22–53) N/A	Overall CDR: N/A, CsCDR: 40% (n = 65) Overall CDR: 78%, CsCDR: N/A (n = 110) Overall CDR: N/A, CsCDR: 62% (n = 182) Overall CDR: 71%, CsCDR: 40% (n = 576)	No major complications 8% catheter drainage, 2% had hematuria. 1% hospitalization No major complications	Barzell and Whitmore[15] Onik and Barzell[16] Kasivisvanathan *et al.*[17] Ahmed *et al.*[18]
Ginsburg protocol	Twelve-sector template, two cores/sector with two to four cores from targeted lesions for a total of 26–28 cores. More number of cores for larger prostates	28 28	Overall CDR: 96%, CsCDR: 97% (n = 120) Overall CDR: 75%, CsCDR: 45% (n = 487)	No major complications reported No serious complications or hospital readmissions	Radtke *et al.*[19] Hansen *et al.*[20]
10-sector template	Ten-sector template, targeting peripheral zones, one to two cores/sector	16 (IQR = 14–20) 20 for large prostate	Overall CDR: 70.9%, CsCDR: 51.3% (n = 117)	No major complications	Ristau *et al.*[21]
12-core template	Twelve-core peripheral template obtained in a fan-like pattern. Two cores from transition zone	12 (+2 if patient on surveillance)	Overall CDR: 49%, CsCDR: 16% (n = 43)	7% had CGII complications. 5% had AUR, 2% had hematuria	Meyer *et al.*[22]
MUSIC	Twelve core, omits midline cores of MB template, targets peripheral zone. Two of 12 sectors found in anterior zone	12	Overall CDR: 53%, CsCDR: 33.5% (n = 215) Overall CDR: 47.2%, CsCDR: 25% (n = 144)	0.17% had rates of infectious hospitalization No major complications were reported	Maruf *et al.*[23] Dupati *et al.*[24]

AUR, Acute urinary retention; CDR, cancer detection rate; CGII, Clavien–Dindo classification grade II; CsCDR, clinically significant cancer detection rate; IQR, interquartile range; MB, modified Barzell; MpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; SD, standard deviation; TRUS, transrectal ultrasound.

while allowing adequate sampling of larger prostates.[32] This theory was first reported using a computer simulation carrying out TP-Bx on 86 autopsy and 20 radical prostatectomy specimens. It demonstrated that the 5 mm protocol detected 95% (38/40) of clinically significant cancers.[33] This approach, aptly named as template prostate mapping (TPM) biopsy, achieved the maximal cancer detection for clinically significant cancer as lesions smaller than 5 mm would likely be clinically insignificant cancers. Also, 5 mm grid proved to be better for cancer detection over 10 mm grid, detecting cancer in 75%, an increase of 25% over
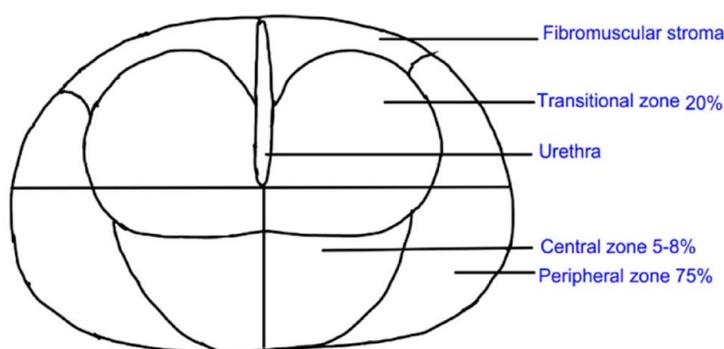
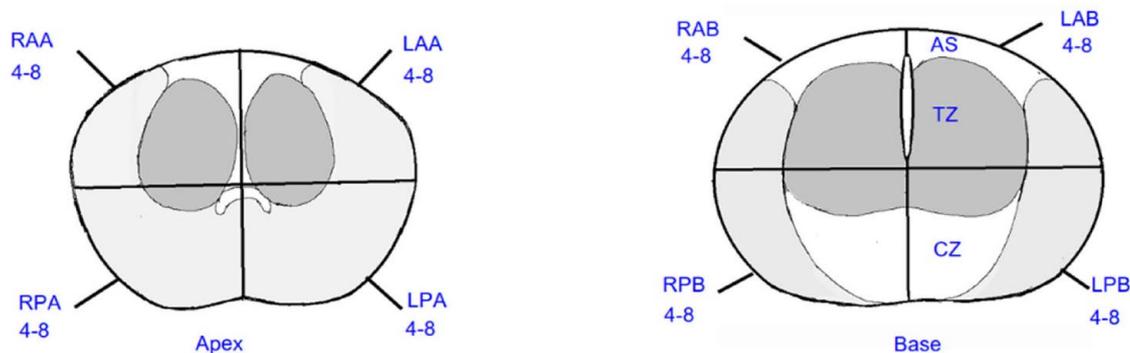**Figure 1.** Prostate anatomy zones with cancer frequency.

Figure 2. Eight-sector Barzell template.
AS, anterior fibromuscular stroma; LAA, left anterior apex; LAB, left anterior base; LPA, left posterior apex; LPB, left posterior base; PZ, peripheral zone; RAA, right anterior apex; RAB, right anterior base; RPA, right posterior apex; RPB, right posterior base; TZ, transition zone.

those with the 10 mm grid. Barzell and Onik carried out a study with similar parameters in 110 patients achieving a remarkably high positive biopsy rate of 78%.[16] The median number of cores taken in their study was 46 (SD ±19). Nine (8%) patients had urinary retention requiring short-term indwelling catheter drainage, two (1.8%) had hematuria, and one (0.9%) required hospital readmission for bladder irrigation. While a core-by-core coordinate yields most accurate information, there is a considerable excess cost and time associated with this approach. Some groups have proposed maintaining 5 mm sampling while grouping the cores geographically based on the Barzell zones. Such an approach would still facilitate a targeted prostate treatment while reducing the need for logistic and histopathological support. Researchers at the University College of London adopted the above approach by modifying the Barzell template into 20 separate sectors and renamed it as modified Barzell (MB) template (Figure 3).[31] In this modification, similar to original Barzell template, the prostate is divided into left and right halves, anterior and posterior prostate, and apex and base. The cores are obtained from medial to lateral sectors. On each side, the sectors are labeled as parasagittal anterior apex and base, parasagittal posterior apex and base, medial anterior apex and base, medial posterior apex and base, and lateral sectors. This modification also allowed for sampling of midline prostate using midline apex and midline base sectors. Kasivisvanathan *et al.*,[17] using the MB template, revealed a clinically significant CDR of 62% in 182 men with a median number of 40 cores. No major complications were reported. In the PROstate MR Imaging Study (PROMIS) trial, utilization of similar approach led to an overall CDR of 71% in 576 men, with 40% having cancer that was clinically significant.[18] The median number of cores were estimated to be in the 40–60 range as cores were taken at every 5 mm. Eight (1%) patients were reported to have sepsis secondary to urinary tract infection and 58 (10%) had urinary retention. These infections were likely confounded and not likely due to TP-Bx as this study had TR-Bx performed right after TP-Bx.

Excellent spatial localization is a major benefit in the use of this approach, appropriate for those patients who met the criteria for focal therapy intervention. However, given the high number of samples obtained, the technique is not without its drawbacks of increased costs and time required for pathology processing, increased risks of procedure-related morbidity, and possible findings of clinically insignificant cancers leading to overdiagnosis and potential overtreatment.[34–36] Thus, this template has mainly been utilized in those with prior-negative prostate biopsies and with persistent clinical suspicion. Complications associated with this technique have been higher rates of acute urinary retention and prostatic bleeding. While the exact mechanism behind the higher rates of urinary retention is not well known, it is thought that prostatic edema could be the cause. In attempt to find a solution to this problem, Bozlu *et al.*[37] demonstrated decreased incidence of acute urinary retention with the use of tamsulosin in the perioperative period. However, most of the associated complications of acute urinary retention have been transient, not requiring intervention as they often resolve on their own.
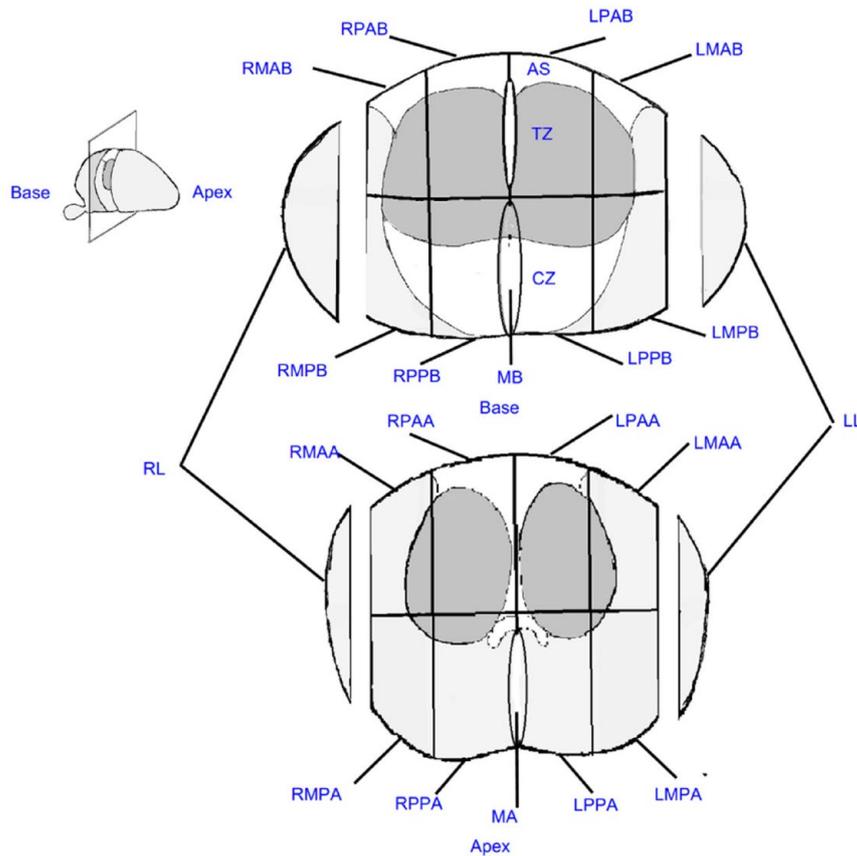
Figure 3. Twenty-sector modified Barzell.
AS, anterior fibromuscular stroma; LL, left lateral; LMAP, left medial anterior apex; LMAB, left medial anterior base; LMPA, left medial posterior apex; LMPB, left medial posterior base; LPAP, left parasagittal anterior apex; LPAB, left parasagittal anterior base; LPPA, left parasagittal posterior apex; LPPB, left parasagittal posterior base; MA, midline apex; MB, midline base; PZ, peripheral zone; RL, right lateral; RMAP, right medial anterior apex; RMAB, right medial anterior base; RMPA, right medial posterior apex; RMPB, right medial posterior base; RPAP, right parasagittal anterior apex; RPAB, right parasagittal anterior base; RPPA, right parasagittal posterior apex; RPPB, right parasagittal posterior base; TZ, transition zone.

Ginsburg protocol

While the Barzell technique has been well received for its reliability and accuracy, the high tissue sampling is thought to limit its utility and wider adoption. To standardize TP systematic biopsies and to encourage prospective studies and multicenter collaborative data analysis, the Ginsburg consensus discussed the definitions to be incorporated and minimal optimal requirements regarding data points to be included in a prospective TP-Bx database (Figure 4).[38] The panelists had a concern that while the Barzell technique showed significant diagnostic quality, it had substantial limitations. A consensus was reached that the increased side effects and the added burden of pathology having to process increased sample numbers was not justified leading to the proposed technique that would go on to become the Ginsburg Biopsy Scheme (GBS). It was recommended that this template should 'become the state of practice to be used by clinicians moving forward'.

The Ginsburg protocol is usually used in combination with magnetic resonance imaging/ultrasound (MRI/US) fusion to obtain tissue samples. This technique divides the prostate into 12 anatomical sectors, with two biopsies obtained from each sector in a craniocaudal fashion leading to a 24-core systematic sampling with two additional MRI-targeted biopsies (TBs) (lesions found on imaging) thought to deliver maximal PCa detection rates while minimizing post-procedural complications. The consensus of the group was that the peripheral and anterior zone should be preferentially targeted, as these are the areas
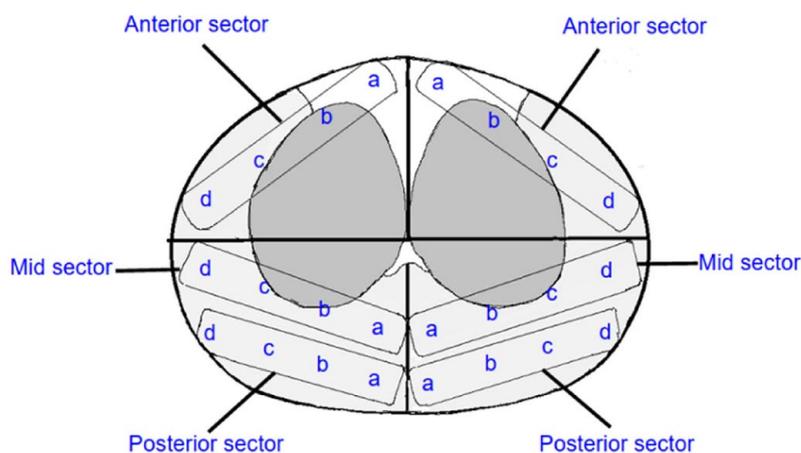
Figure 4. Ginsburg protocol template.

Table 2. Ginsburg protocol cores obtained according to prostate volume and length.

Prostate volume (ml)	Number of cores taken per sector (right + left)				Total number of cores
	Anterior	Mid	Posterior	Basal	
<30 ml	4 + 4	4 + 4	4 + 4	0	24
30–50 ml and >4 cm length	4 + 4	4 + 4	4 + 4	4 + 4	32
>50 ml and >4 cm length	5 + 5	5 + 5	5 + 5	4 + 4	38

most likely to harbor disease, thus, the prostate was divided into the anterior zone, apical (mid sector) PZ, and posterior PZ. A total of four to six cores are to be obtained from four equally spaced areas from medial to lateral in these zones for each side of the gland. For those with longer prostates >4 cm or volumes >50 ml, an additional basal PZ and posterior TZs are added. Overall, 24 total cores should be obtained in smaller prostates up to 30 ml, whereas the bigger prostates as previously mentioned would require up to 38 ml (Table 2). The TB is to be completed prior to systematic sampling to prevent movement of lesions localized on imaging and was added to the protocol. In a study by Radtke et al.,[19] the use of this template resulted in successfully detecting 96% of overall cancer with 97% of clinically significant PCa lesions. A median of 28 biopsies was taken per patient that was prostate volume adjusted and no major complications were reported. In a different study,

Hansen et al.[20] showed an overall detection rate of 75%, with 45% being clinically significant cancer in 487 men. No significant complications were reported.

While displaying satisfactory CDRs in the setting of reduced number of cores sampled, this protocol still has its shortcomings. GBS preferentially targets the PZ and systematically omits most of the transition and periurethral zones and thus risks missing cancers in these areas.[38] While the idea behind this approach is that most PCas occur around the PZ with minimal rates occurring elsewhere and the high risk of complications with sampling the omitted regions, a recent study published by Sigle et al.,[9] found significant lesions were missed in 3.6% of 1084 patients. However, there have been no increased risks of urinary retention and hematuria across most studies using these templates.[7]

12-core transperineal biopsy template

Another template, which has been popular in the outpatient office-based free-hand (FH) TP-Bx studies, is a 12-core biopsy template similar to the 12-core extended sextant template used in transrectal biopsies. Meyer et al.[22,39] performed an in-office 12-core US-guided prostate biopsy under local anesthesia using transperineal access system (such as PrecisionPoint). In this template, the PZ of prostate is divided into two anterior zones, namely, right and left PZ anterior (PZa), and four posterior zones, namely, right and left PZ posterior medial (PZpm), right and left PZ posterior lateral (PZpl) on either side (Figure 5). Using a fan-like pattern, 12 cores are sampled (two cores from each PZ of the prostate) (Figure 6). Patients who are under active surveillance underwent two additional cores from TZ either transitional zone anterior (TZa) or transitional zone posterior (TZp). The procedure can be completed in one to two access punctures on either side. The authors reported no periprocedural antibiotic use for this approach.

In their experience on 43 patients, 49% men were found to have PCa of which 16% were found to have clinically significant cancer with only using 12 cores. Seven percent of patients developed complication after biopsy, of which 4.7% required urethral catheterization for urinary retention and 2.3% patients developed gross hematuria that also required catheterization. None of the patients developed post biopsy infection.
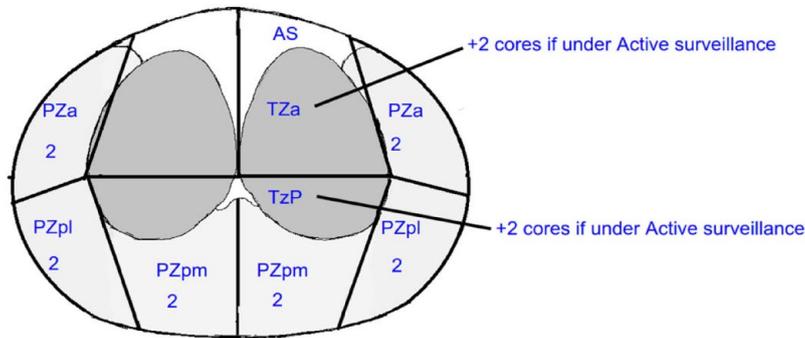
Figure 5. Transperineal 12-core biopsy template.
AS, anterior fibromuscular stroma; PZa, peripheral zone anterior; PZpl, peripheral zone posterior lateral; PZpm, peripheral zone posterior medial; TZa, transition zone anterior; TZp, transition zone posterior.
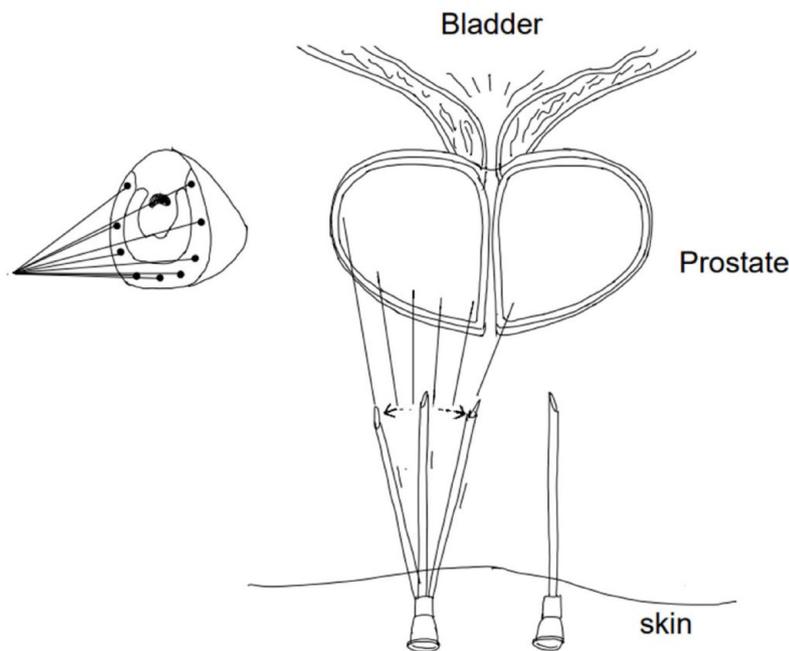

Figure 6. Fan technique method as described by Emiliozzi *et al.*[40]

Ten-sector template

In a retrospective single-institution study by Ristau *et al.*,[21] the authors suggested an alternative approach, proposing an outpatient FH transperineal prostate biopsy (fTP-Bx) using a 10-sector template. The 10-sector template involves dividing prostate into anterior and posterior halves (Figure 7). The anterior half is further divided into the right anterior lateral (RAL), right anterior medial (RAM), left anterior lateral (LAL), left anterior medial (LAM). The posterior half was divided into the right posterior lateral (RPL), right posterior medial (RPM), left posterior lateral (LPL) and left posterior medial (LPM). If prostate is large, then two additional sectors, namely, the right lateral base (RLB) and left lateral base (LLB), are biopsied at the base of the gland.

An advantage to utilizing this technique is that it can easily be used with MRI prostate sector maps utilized in the PRECISE recommendation.[41] Biopsy is performed in an FH manner using a transperineal access system (such as PrecisionPoint) which allows the biopsy needle to always be aligned to the sagittal plane of the probe. This obviates the need for brachytherapy steppers and grid as well as general anesthesia.
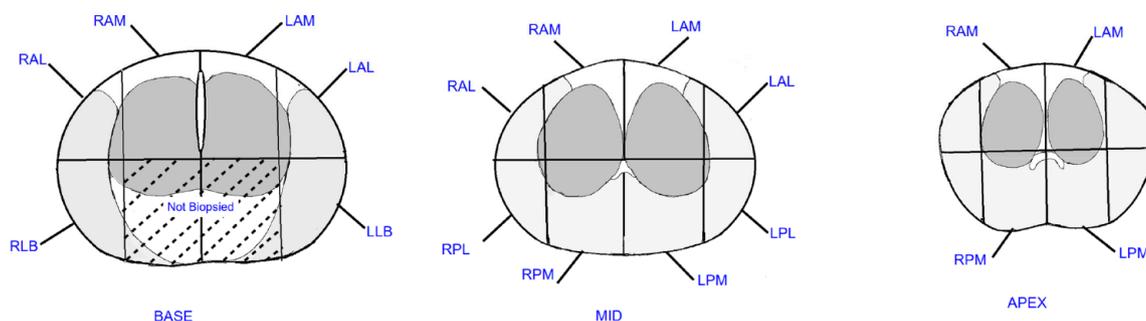
Figure 7. Ten-sector template.
LAL, left anterior lateral; LAM, left anterior medial; LLB, left lateral base; LPL, left posterior lateral; LPM, left posterior medial; RAL, right anterior lateral; RAM, right anterior medial; RLB, right lateral base; RPL, right posterior lateral; RPM, right posterior medial.

Of the 1000 fTP-Bx, 883 were performed using a 14-gauge hypodermic needle access system in a 'fan-like' method as described by Emiliozzi et al.[40] (Figure 6). In the other cohorts of 117 men, transperineal access system is used to take biopsies using the 10-sector template. The median core per prostate biopsy was 16 (IQR = 14–20) in the study. Total CDR with 10-sector template transperineal access system was more than 'fan like' pattern cohort (70.9% versus 59.3%) with similar findings for CDR for clinically significant GG ⩾ 2 (51.3% versus 38.8%). No major complications associated with this type of template biopsy. The potential shortcomings of both the 10- and 12-sector templates are lack of sampling of TZ and periurethral areas of prostate. However, by limiting the total number of cores to 12–16, these templates facilitate adoption of TP-Bx in the office setting and shorten the procedure times associated with other TP templates that plan for more extensive sampling.

Michigan Urological Surgery Improvement Collaborative

The MUSIC TP template was developed using core location-specific CDR data based on initial results from the adoption of MB template. It was developed to limit the overall number of cores obtained during TP sampling, while maintaining PZ sampling, where most of the cancers are commonly found (Figure 8). The template consists of obtaining biopsy from the six sectors of each prostate lobe, paramedian apex, paramedian base, posterior apex, posterior base, lateral, and anterior prostates. Each sector is biopsied once within each lobe, making it a 12-core biopsy and allowing a valid comparison with the 12-core transrectal biopsies.

A study done by Maruf et al.[23] comparing MUSIC with traditional TR-Bx demonstrated that the overall CDR is 53.0% for MUSIC template versus 55.3% for TR-Bx and the rate of ⩾ GG2 cancer was 33.5% for MUSIC template versus 38% for TR-Bx. Multivariate analysis showed no significant difference in the odds of detecting any cancer ⩾ GG2 cancer for MUSIC compared with TR-Bx. The rates of hospitalization due to infection were lower in MUSIC template than in TR-Bx, though it was not statistically significant, likely due to state-wide quality improvement efforts achieving rates approaching 0.6%. Another study by Dupati et al.,[24] found overall CDR of 47.2% with MUSIC template. CDR for clinically significant cancer was 25%. The study did not find any difference in CDR between MB and MUSIC templates, and noted that additional one to two midline core biopsies that were performed at apex and base did not improve in cancer diagnosis. Midline cores can potentially result in urethral injury and increased risk of hematuria, thus omitting those cores can potentially further reduce the risks associated with TP-Bxs.

Discussion

In this article, we describe some of the common TP-Bx templates. The clinical studies on these templates are heterogeneous and variable in the quality making direct comparison among these templates difficult. There is ample evidence that systematic saturation sampling of prostate, such as with Barzell or MB template, is reliable and
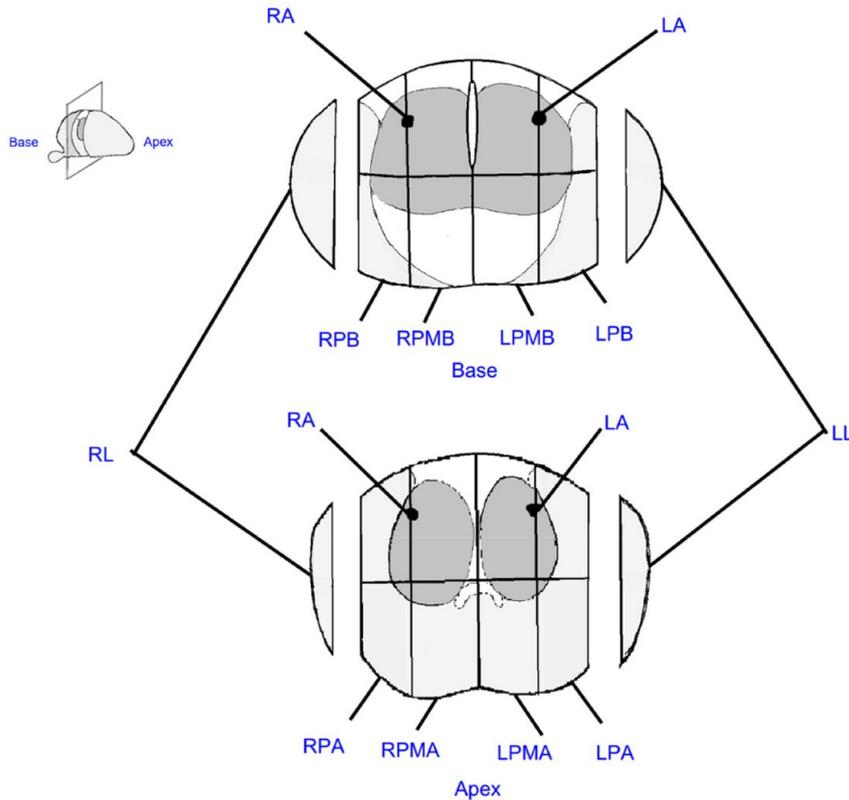
Figure 8. MUSIC template.
LA, left anterior; LL, left lateral; LPA, left posterior apex; LPB, left posterior base; LPMA, left paramedian apex; LPMB, left paramedian base; RA, right anterior; RL, right lateral; RPA, right posterior apex; RPB, right posterior base; RPMA, right paramedian apex; RPMB, right paramedian base.

accurate in detecting clinically significant PCa, however, a higher sampling leads to greater risk of complications as well as detection of clinically insignificant PCa due to higher biopsy density. Authors have significant experience with Ginsburg protocol that allows sampling from 12 sectors and with fixed number of cores range depending on prostate size. This template satisfactorily detects clinically significant cancer with a reduced number of cores by preferentially targeting peripheral and anterior zone where majority of cancer are present while misses cancer by omitting most of the transitional and periurethral zones. Currently, the authors utilize MUSIC template, most often as it has several advantages. First, it is a 12-core biopsy template, thus allowing valid comparison with 12-core transrectal sextant biopsies and easier adoption in office settings. It preferentially collects samples from PZ where majority of cancers are located as well as from anterior zone missed by traditional TRUS biopsy with a less thorough sampling of transitional zone. By avoiding sampling of the midline PZ like those

done by MB, it can reduce the risk of hematuria and urinary retention. In the past, increasing the number of prostate cores with larger prostate size made sense as seen with Barzell templates; however, the benefit of such an approach is limited in the age of prostate MRI, which can identify clinically significant PCa outside the traditional biopsy templates. Therefore, MUSIC template might serve as a good compromise between CDRs and burden on patients.

Conclusion
The mainstay of PCa diagnosis has been systematic sampling of the prostate gland via a transrectal approach. The transperineal approach for systematic sampling has demonstrated similar if not superior CDRs and infectious complications approaching zero. With innovations in imaging, such as multiparametric MRI showing promising results, the landscape of PCa diagnosis is rapidly changing; however, systematic sampling remains an accepted and essential component of biopsy.

The Barzell technique, the Ginsburg protocol, 12-core, the 10-sector, and MUSIC templates all represent excellent templates with data supporting their continued application. Studies done using these templates were conducted in different settings with nonhomogeneous patient populations, which make comparison between these templates very difficult. However, each template seems to have their relative advantages and shortcomings. Larger multi-institutional comparative studies will be needed to determine the relative efficacy, cancer detection, and complication rates of these templates. Until those data are available, physician discretion will likely dictate template selection during TP-Bx.

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Not applicable

Consent for publication
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