Evaluating limited biopsy templates for men with markedly elevated PSAs

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Introduction: *To define the smallest prostate needle biopsy (PNB) template necessary for accurate tissue diagnosis in men with markedly elevated PSA while decreasing procedural morbidity.*

Materials and methods: *We performed a chart review of 80 men presenting with a newly elevated PSA >100 ng/mL who underwent biopsy (PNB or metastatic site). For patients who underwent a full 12-core biopsy, simulated templates of 2- to 10-cores were generated by randomly drawing subsets of biopsies from their full-template findings. Templates were iterated to randomize core location and generate theoretical smaller template outcomes. Simulated biopsy results were compared to full-template findings to determine accuracy to maximal Grade Group (GG) diagnosis.*

Results: *Amongst those that underwent PNB, 93% had GG 4 or 5 disease. Twenty-two (40%) underwent a full 12-core biopsy, 20 (37%) a 6-core biopsy, and only 8 (15%) had fewer than six biopsy cores sampled at our hospital. Simulated templates with 2-, 4-, 6-, and 8-cores correctly diagnosed prostate cancer in all patients, and accurately identified the maximal GG in 82%, 91%, 95%, and 97% of patients, respectively. The biopsy locations most likely to detect maximal GG were medial mid and base sites bilaterally. A 4-core template of these sites would have accurately detected the maximal GG in 95% of patients relative to a full 12-core template.*

Conclusions: *In men presenting with PSA > 100 ng/mL, decreasing from a 12-core to a 4-core prostate biopsy template results in universal cancer detection and minimal under-grading while theoretically decreasing procedural morbidity and cost.*

Key Words: PSA, prostate cancer, prostate biopsy, metastatic prostate cancer

Introduction

Prostate cancer is the most common malignancy among American men, with 299,010 men receiving a new diagnosis in 2024.[1] Even with the growing use of the trans-perineal approach, today the vast majority of men are diagnosed by transrectal ultrasound-guided prostate needle biopsy (TRUS-PNB). From the very first transrectal prostate biopsy by Astraldi in 1937 to the work of Eskew et al in the late 1990s, urologists have come to agree upon a standard 12-core prostate biopsy template as a balance between diagnostic yield and procedural morbidity.[2,3]

One of the risks of a standard TRUS-PNB is post-procedural sepsis. The 2016 AUA White Paper on The Prevention and Treatment of the More Common Complications Related to Prostate Biopsy cites a 5%-7% post-procedural infection risk with 1%-3% of individuals requiring inpatient care. The rising risk of serious infection over recent years has been driven in part by the rise of fluoroquinolone resistance in enteric flora.[4]

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Given this risk of potential peri-procedural morbidity, the role of performing a TRUS-PNB in men presenting with markedly elevated prostate specific antigen (PSA) levels and clinically presumed high risk and/or metastatic prostate cancer can be questioned. However, many oncologists will not initiate therapy without a tissue diagnosis, and the advent of targeted therapies has made tissue sampling increasingly important for genetic oncotyping, even when the diagnosis of prostate cancer is clear.[5]

In the pursuit to decrease post-biopsy infection risk, there has been mixed evidence suggesting a relationship between the number of sampled cores and risk of post-procedural infection, with the rational thought that fewer transrectal needle passages could decrease bacterial seeding and thus infection risk.[6-8] There is clear logic that taking fewer biopsy cores decreases procedure duration and patient discomfort as well as the healthcare costs of materials and pathologic analysis.

Given this, we aim to determine the minimum necessary number of biopsy cores that can be performed for men with clinically presumed prostate cancer with the goal of decreasing peri-procedural morbidity while retaining the diagnostic sensitivity and tissue procurement of biopsy.

Materials and methods

We performed a retrospective chart review to identify all men with a PSA value greater than 100 ng/mL and no previously known diagnosis of prostate cancer who presented to our 731-bed county hospital, Santa Clara Valley Medical Center over a 10-year period (2010-2020). A PSA threshold of 100 ng/mL was chosen based on evidence showing an overwhelming probability of high-risk prostate cancer in this population.[9-11] Of 125 men presenting to our institution with a PSA > 100 ng/mL, 45 were excluded due to incomplete follow up or declined work up/biopsy. For the remaining 80 men included in the study, demographics (age, gender, ethnicity) and pre-biopsy characteristics (digital rectal exam (DRE) findings, PSA, imaging, and TRUS prostate volume) were collected. For men who underwent prostate biopsy, the number of cores taken, location of positive biopsy and biopsy core Grade Group (GG) was recorded.

TRUS-PNB procedures were performed by one of three board-certified urologists following standard protocol and biopsy specimens were reviewed by genitourinary pathologists.[12] Biopsies of metastatic lesions were performed by interventional radiologists and reviewed by the same pathology staff. Data were gathered from the electronic health record in a retrospective fashion using RedCap (Research Electronic Data Capture, Stanford University).[13] Statistical analysis including association testing was performed using JMP Statistical Software (Version 16.0.0. SAS Institute Inc., Cary, NC, USA).

The investigation of limited alternative biopsy templates was simulated using MatLab (2018. Mathworks Inc., Natick, MA, USA). For each patient in our cohort who had undergone a full 12-core PNB, simulated smaller templates of 2- to 10-cores were generated by randomly drawing a symmetric subset of biopsy cores from their standard template biopsy findings. To remove the variable of core location, this random drawing process was repeated over 10,000 iterations, generating an array of theoretical smaller biopsy template outcomes for each proposed patient. Finally, each simulated template was compared to the patient's gold-standard 12-core biopsy findings to calculate overall cancer detection and accuracy to maximal Grade Group diagnosis.

Results

In our study cohort of 80 men undergoing biopsy workup for a PSA value > 100 ng/mL, the median age was 65 years,

TABLE 1. **Demographics and findings of prostate cancer work up for patients undergoing biopsy**

Variable	n (%)
Age (years, range)	65 (43-95)
Ethnicity	
White/Caucasian	19 (24%)
Hispanic/Latino	22 (28%)
African American	7 (9%)
Other/Unknown	32 (40%)
PSA at presentation (ng/mL, range)	560 (100-11700)
< 500	38 (47%)
500-1000	14 (18%)
> 1000	28 (35%)
DRE findings	
Benign	7 (9%)
Abnormal	56 (70%)
Unknown	17 (21%)
Metastases identified	
Yes	73 (91%)
No	7 (9%)
Biopsy type performed	
PNB	56 (70%)
Metastasis	24 (30%)

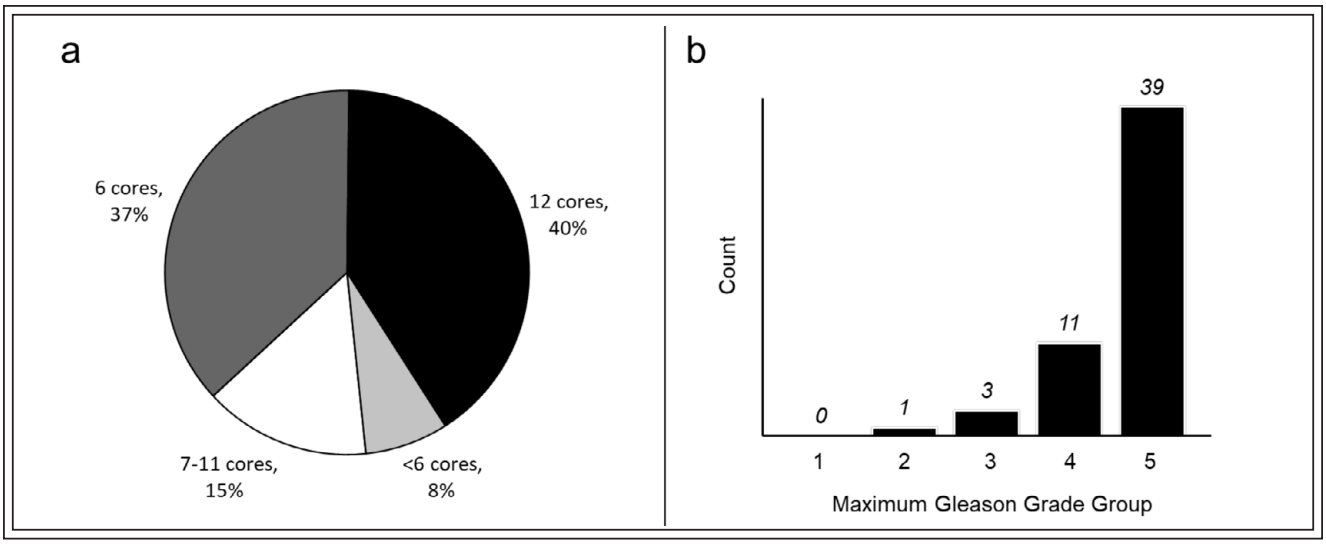

Figure 1. Relative distribution of biopsy templates utilized in this cohort **(a)** and maximal Gleason Grade Group identified on prostate biopsy **(b).**

with a median presenting PSA of 560 ng/mlL, Table 1. In these men, 56 (70%) had a documented abnormal DRE, and 73 (91%) were found to have metastatic disease on either cross-sectional abdominal imaging or bone scintigraphy. Twenty-six men (32%) underwent biopsy of a metastatic lesion while the remaining 54 (68%) underwent TRUS-PNB. Association testing showed no independent relationship between age, ethnicity, PSA, DRE findings, or presence of metastases with the choice between metastatic biopsy or TRUS-PNB. All metastatic biopsies showed adenocarcinoma consistent with prostate origin with

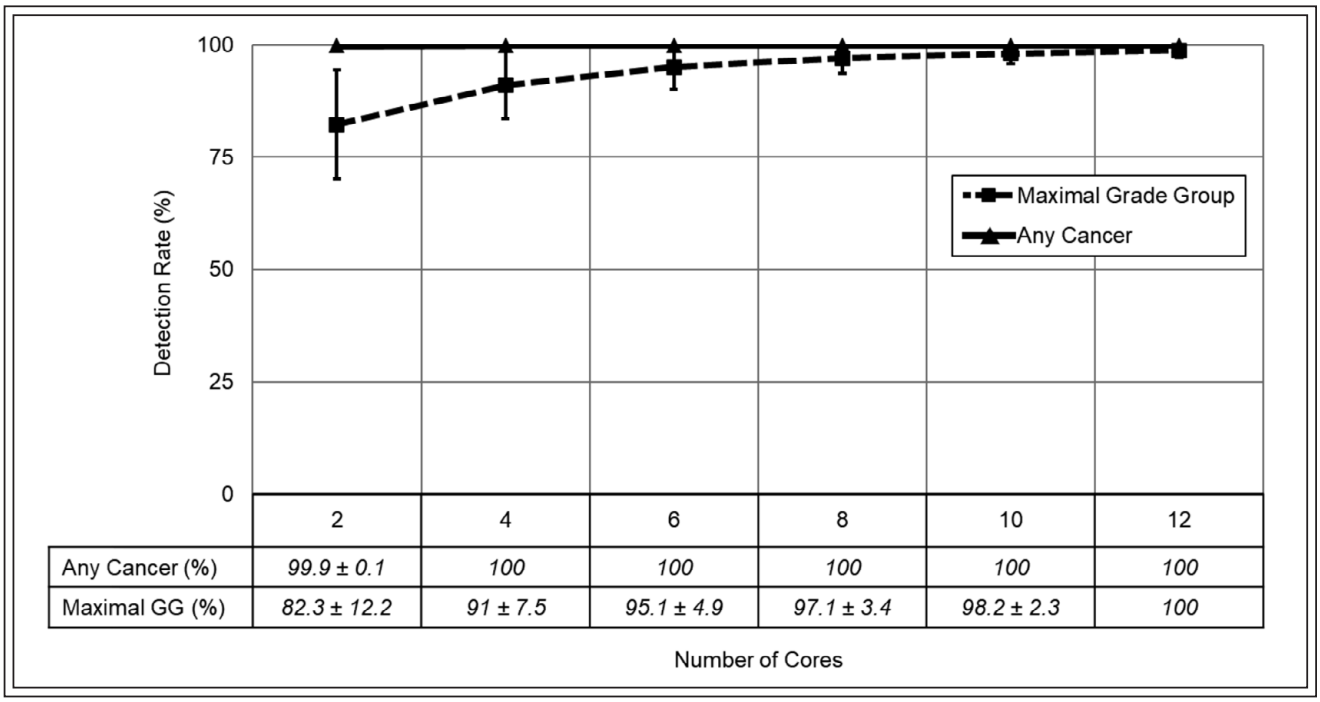

Figure 2. Simulated cancer detection and Grade Group (GG) findings from alternate biopsy templates showing retained overall cancer detection and subtly decreased maximal Grade Group detection rates with more limited templates.

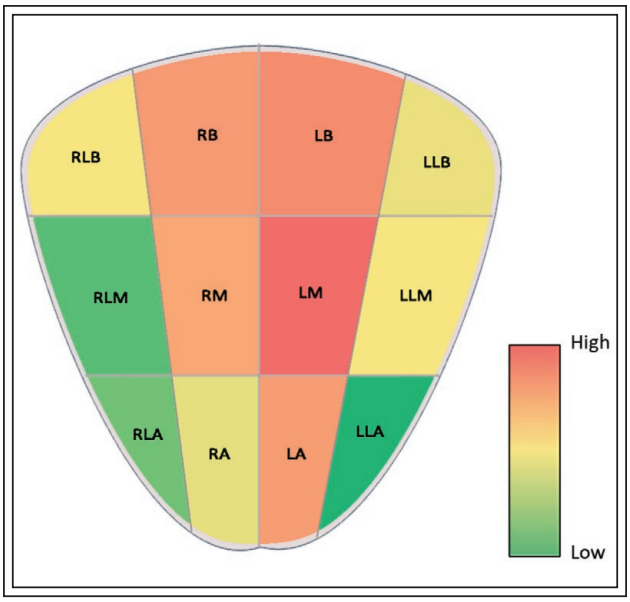

Figure 3. Relative likelihood of sampling the maximal Grade Group by core location. Color scheme reflects a normalized scale.

the most commonly sampled sites being bone (54%) and nodal tissue (31%). Amongst men undergoing TRUS-PNB, 22 (40%) underwent a full 12-core biopsy, 20 (37%) a 6-core biopsy, and only 8 (15%) had fewer than six biopsy cores sampled, Figure 1a. Prostate cancer was found in all men undergoing TRUS-PNB, with 50/54 (92.6%) of men having GG 4 or 5 disease, Figure 1b. Association testing showed no independent relationship between age, ethnicity, PSA, TRUS volume, DRE findings, or presence of metastases on the number of cores taken or the maximal GG identified on biopsy.

Using the smaller template simulations as described above, templates ranging from the traditional 12-core down to just 2-core accurately detected prostate cancer in 99.9% of simulations. Comparing the simulated templates to the gold-standard 12-core biopsy data showed a subtle loss of sensitivity for maximal GG as template size decreased. Templates with 2-, 4-, 6-, and 8-cores accurately identified the maximal GG in 82, 91, 95, and 97% of simulations respectively, Figure 2.

Biopsies taken from the medial mid and base sites were most likely to capture the maximal GG in our cohort, Figure 3. A template comprised of these four biopsy sites would have detected the maximal GG in 95% of patients relative to the full 12-core template, versus 91% maximal GG detection with a random 4-core biopsy.

Discussion

Our group is far from the first to propose alternatives to the standard 12-core biopsy template for specific populations suspected of having prostate cancer. Increasingly, more urologists are using limited TRUS-PNB templates in this patient population, though our data shows that over the past decade, 85% of men at our hospital with PSA > 100 ng/mL still had at least six cores sampled. Just as we have changed our workflow for men with mild PSA elevations, incorporating prostate MRI to increase diagnostic yield, this work strives to develop a similarly optimized biopsy workflow for men on the other end of the diagnostic spectrum with markedly elevated PSA (> 100 ng/mL) and presumed high risk prostate cancer.

It can be argued that one option for this subset of men is to forego any biopsy and initiate oncologic therapies on a clinical diagnosis. Indeed, all members of this cohort were found to have cancer on either metastatic or prostate biopsy. However, while foregoing biopsy entirely may seem ideal from a risk mitigation perspective, there are two reasons tissue procurement is still often performed in this population. First, many oncologists hesitate to start treatment without tissue diagnosis due to apprehension of delivering harmful and costly oncologic agents for a possibly benign process. Second, tissue from biopsy is now commonly helpful for oncologic genotyping which can inform personalized therapies and improve treatment outcomes.[5]

In cases where a biopsy is desired, one option is sampling of a metastatic lesion. In our cohort this was successful as all biopsies of metastases did demonstrate prostate cancer. Unfortunately, biopsies of metastatic lesions carry their own risks: they can be difficult to sample adequate tissue for genetic analysis, bone biopsies are notoriously painful and inaccurate, and metastatic soft tissue lesions are often difficult to access (especially when compared to the prostate).[14]

Given the potential for an ongoing role of prostate biopsies in our high-risk population with a PSA > 100 ng/mL on presentation, it is essential to minimize peri-procedural risk, chiefly infection. To that end, numerous recommendations have been made including tailoring antibiotic prophylaxis based on pre-procedural rectal swab cultures, using disposable biopsy needles, performing alcohol or formalin rinses between needle insertions, and even considering bactericidal enemas in high-risk patients.[15] Template size has been implicated in infection risk after biopsy.[6-8] Using the widely accepted hypothesis that infection after TRUS-PNB stems from bacterial

seeding of prostate tissue with enteric flora during needle insertion, one can surmise that minimizing the number of biopsy cores could lower the risk of infectious complications. While this hypothesis is met with mixed opinion, some of the strongest evidence to support it comes from a study of more than 2,000 men in which patients who had just eight or ten cores sampled had a statistically significant 35% lower risk of post-procedural infectious complications compared to men who had 12 cores taken.[8]

Limited biopsy templates also hold potential to reduce the healthcare costs associated with TRUS-PNB. Weiner et al recently reported that the cost of an office based prostate biopsy averages $1,740, with that cost rising significantly to $4,060 when one complication occurred.[16] Nearly half of all costs annually for PNB were related to complications, thus all interventions that can reduce the morbidity of the procedure without compromising diagnostic yield must be prioritized. Limited templates also lead to shorter procedural duration, less patient discomfort, and decrease the costs of materials and pathologic analysis.

Our study provides evidence that smaller biopsy templates (as few as four total cores) for men with markedly elevated PSAs can still accurately diagnose prostate cancer while decreasing procedural duration, discomfort, and potentially the risk of post-procedural infectious complications. While we report an inverse relationship between core number and sensitivity of maximal GG diagnosis, this decrease appears slight, with a four-core random biopsy still accurately detecting maximal GG in 91% of our simulations (and notably detecting cancer in all patients). In the pursuit of maximizing the oncologic yield of less extensive, and potentially safer templates, our data also shows that medial mid and base biopsy sites are most likely to capture the maximal GG diagnosis. Utilizing a four-core biopsy template of these sites further increases the diagnosed maximal GG to 95% of patients compared to a less systematic four-core biopsy.

There are several limitations to this study. First, it is underpowered to report on post-procedural complication rates within our cohort and therefore we can offer no conclusions on the association between template size and post-procedural infection risk beyond what is already suggested in the literature. Second, this study assumes 100% sensitivity of the standard 12-core biopsy for its ground truth use in our statistical analysis, though we recognize that pathologic upgrading, as seen in studies comparing TRUS-PNB to radical prostatectomy specimens may have occurred.[17] Third, our analysis of optimal template size and core location does not factor in palpable nodules on DRE (which may substantially increase the yield of a biopsy in a certain location), as the detail of DRE descriptions varied in this retrospective chart review. Fourth, pathology specimens were reviewed by multiple genitourinary pathologists which could lead to some variability in Gleason grading. Finally, we are limited in the fact that only 40% of men undergoing TRUS-PNB underwent a full 12-core biopsy template and therefore comparisons of simulated smaller templates to gold-standard data could only be made for this subset of men.

This study does succeed in identifying and analyzing a large cohort of men at their initial presentation with clinically presumed metastatic prostate cancer. As men continue to present with markedly elevated PSAs, especially in communities with limited access to healthcare resources, optimal biopsy strategies can potentially reduce morbidity and lower costs without compromising outcomes. This study succeeds in identifying a cohort of these patients from a community-based practice and using iterative modeling techniques to simulate thousands of alternative biopsies, ultimately identifying an optimum of diagnostic sensitivity and template size. Our findings also demonstrate a need to standardize biopsy techniques for men with clinically presumed high-risk prostate cancer, with 40% of patients in this category undergoing a full 12-core biopsy template and only 15% having less than six cores sampled at our institution.

Conclusion

Decreasing from a standard 12-core template to as little as a four-core TRUS-PNB in men presenting with a PSA greater than 100 ng/mL detected prostate cancer in all cases with more than 90% of four-core biopsies returning an accurate maximal Gleason GG. Reducing the number of prostate cores taken results in minimal under-grading while theoretically decreasing procedural morbidity and cost in men with clinically presumed metastatic prostate cancer. □

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