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Can transrectal needle biopsy be optimised to detect nearly all prostate cancer with a volume of ≥0.5 mL? A three-dimensional analysis

Kent Kanao*†, James A. Eastham†, Peter T. Scardino†‡, Victor E. Reuter*§ and Samson W. Fine*

*Departments of *Pathology and †Surgery, Urology Service, Memorial Sloan-Kettering Cancer Center, and Departments of ‡Urology and §Pathology, Weill Cornell Medical Center, New York, NY, USA*

Objective

- To investigate whether transrectal needle biopsy can be optimised to detect nearly all prostate cancer with a tumour volume (TV) of ≥0.5 mL.

Materials and Methods

- Retrospectively analysed 109 whole-mounted and entirely submitted radical prostatectomy specimens with prostate cancer.
- All tumours in each prostate were outlined on whole-mount slides and digitally scanned to produce tumour maps. Tumour map images were exported to three-dimensional (3D) slicer software (http://www.slicer.org) to develop a 3D-prostate cancer model.
- In all, 20 transrectal biopsy schemes involving two to 40 cores and two to six anteriorly directed biopsy (ADBx) cores (including transition zone, TZ) were simulated, as well as models with various biopsy cutting lengths.
- Detection rates for tumours of different volumes were determined for the various biopsy simulation schemes.

Results

- In 109 prostates, 800 tumours were detected, 90 with a TV of ≥0.5 mL (mean TV 0.24 mL).
- Detection rate for tumours with a TV of ≥0.5 mL plateaued at 77% (69/90) using a 12-core (3 × 4) scheme, standard 17-mm biopsy cutting length without ADBx cores. In all, 20 of 21 (95%) tumours with a TV of ≥0.5 mL not detected by this scheme originated in the anterior peripheral zone or TZ.
- Increasing the biopsy cutting length and depth/number of ADBx cores improved the detection rate for tumours with a TVof ≥0.5 mL in the 12-core scheme.
- Using a 22-mm cutting length and a 12-core scheme with additional volume-adjusted ADBx cores, 100% of ≥0.5 mL tumours in prostates ≤ 50 mL in volume and 94.7% of ≥0.5 mL tumours in prostates > 50 mL in volume were detected.

Conclusions

- Our 3D-prostate cancer model analysis suggests that nearly all prostate cancers with a TV of ≥0.5 mL can be detected by 14–18 transrectal needle-biopsy cores.
- Using longer biopsy cutting lengths and increasing the depth and number of ADBx cores (including TZ) according to prostate volume are necessary as well.

Keywords

prostate cancer, biopsy, simulation, anterior, transition zone

Introduction

TRUS-guided prostate biopsy is the 'gold standard' for the diagnosis of prostate cancer. Over the past decade, several extended and saturation biopsy schemes [1–3] showing improved sensitivity for prostate cancer detection have been introduced; however, the optimal number and location of prostate biopsies is still debated [4]. A major concern with transrectal biopsy is that even with newer biopsy schemes, the procedure may still miss 'clinically significant' prostate cancers, generally defined as those with tumour volume (TV) of ≥0.5 mL [5,6]. Another concern is that the anterior portion of the gland, including the anterior peripheral (PZ) and transition zones (TZ) is difficult to target by standard transrectal biopsy, in particular with larger glands [7].

While many studies have evaluated the detection rate of prostate cancer for various biopsy schemes, including the transperineal approach, few have investigated the detection of clinically significant cancers using various biopsy schemes. In addition, the influence of biopsy cutting length and method of anterior gland sampling on the detection rate of clinically significant cancer in prostate glands of various sizes have hardly been evaluated.

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Several studies have assessed simulated biopsy schemes using three-dimensional (3D) reconstructions of actual prostate cancer specimens [8,9]. In these studies, the volume of multiple tumours could be analysed independently. As a 3D-prostate cancer model can more accurately identify: (i) the original tumour from which a positive simulated biopsy is taken and (ii) any tumours missed by biopsy, it is likely that properly constructed 3D-prostate biopsy simulations will have clinical relevance [8]. However, the detection of clinically significant tumours and targeting of the anterior prostate have not been fully evaluated using a 3D-prostate cancer model. Using such a model, we evaluated various simulated biopsy schemes and investigated whether transrectal needle biopsy can be optimised to detect prostate cancers with a TV of ≥0.5 mL.

Materials and Methods

Development of a 3D-prostate Cancer Model

In all, 109 patients with prostate cancer who had undergone biopsy and radical prostatectomy (RP) at our institution were retrospectively analysed. All patients were initially diagnosed by standard TRUS-guided 12-core biopsy (apex, mid-gland, and base by lateral and medial in both lobes) with the addition of two TZ-directed cores. For RP specimens, the intact prostate and seminal vesicles were inked in two colours (right, green; left, blue) in the fresh state and the superficial fragments of muscular tissue surrounding the proximal urethra (i.e. bladder neck) were shaved. To permit assessment of the inked apical margin, the most apical 3 mm of the gland were sectioned, segmented sagittally in a cone-like fashion and embedded. Seminal vesicles were amputated at the junction with the prostate and submitted separately. Finally, the remaining bulk of the gland was sectioned from apex to base at 3–5 mm intervals, whole-mounted and entirely submitted.

Digitised tumour maps were created, colour-coded by grade and stage (Fig. 1A) and these images were captured and used for computed analysis (Fig. 1B). The segmented sections were stacked and manually aligned using Photoshop CS5 (Adobe Systems, San Jose, CA, USA). For alignment, we used the border of the slices (i.e. the prostate capsule) and any additional tissue landmarks, if present [10]. Portions of the apical and bladder neck margins of resection were sectioned separately and not represented in the reconstructed computer models. A factor of 1.5 was used to compensate for tissue shrinkage [11]. The images of planimetry regions were transferred to DICOM images and exported to a 3D-software program, 3D slicer (http://www.slicer.org), which reconstructed the regions from which the 3D-prostate cancer model was developed (Fig. 1C). All prostate tumours were individually identified by the software and zonal origins were determined. Tumour and overall prostate volumes were calculated using the 3D-slicer program.

Fig. 1 (A) Digitised tumour maps: tumour and prostate capsule are outlined on slides and images of these regions are captured and used for computed analysis. Images of planimetry regions (B) were transferred to a 3D-software program from which the 3D-prostate cancer model (C) was developed.

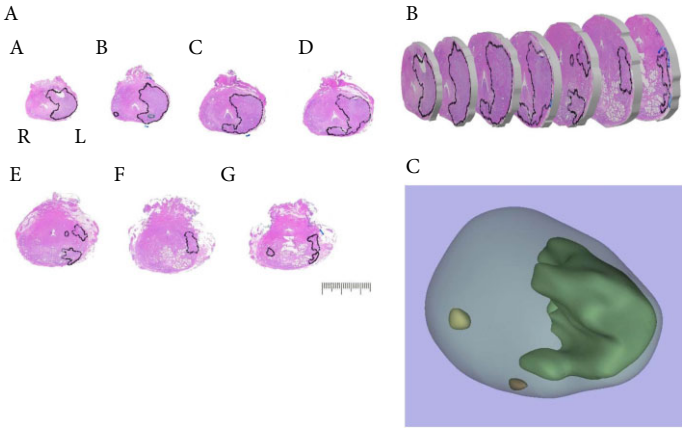
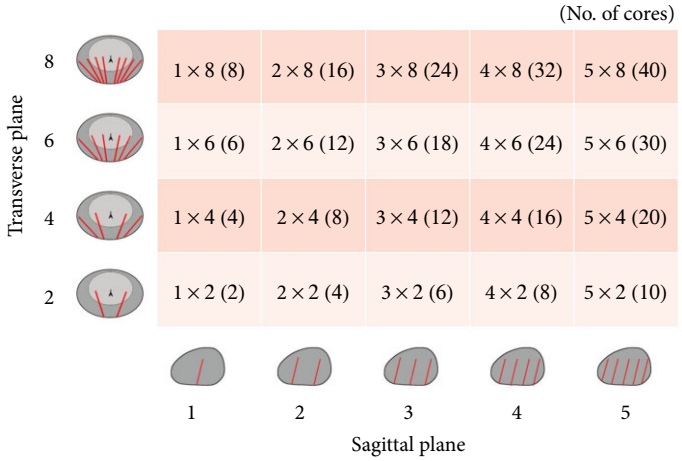


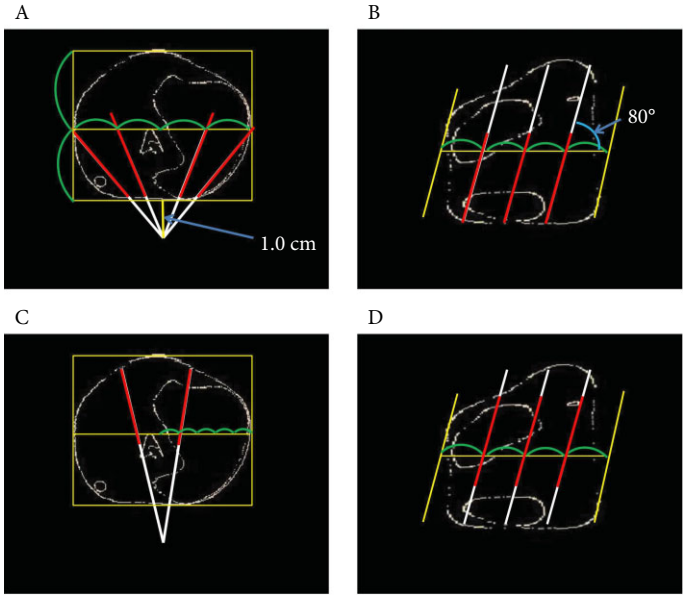
Fig. 2 In all, 20 transrectal prostate biopsy schemes involving 2–40 cores were simulated for the 3D model. The 3 × 4 scheme is generally used in 12-core biopsies.



Simulation Biopsies for 3D-prostate Cancer Model

In all, 20 transrectal prostate biopsy schemes (Fig. 2) involving 2–40 cores (1–5 cores in the sagittal plane by 2–8 cores in the transverse plane) were simulated for each 3D model and tumours detected by each scheme were noted. Figure 3A and B demonstrate a 3 × 4 scheme (apex, mid-gland, and base by lateral and medial in both lobes). The maximum transverse (Fig. 3A) and sagittal (Fig. 3B) diameters were divided into four equidistant parts. Simulated biopsy needles were placed 1.0 cm below the inferior border of the prostate oriented/angled towards each division (Fig. 3A, arrow). Simulated biopsy cores were then directed from the spot where the simulated needle contacted the inferior prostate, following its trajectory toward the line demarcating the

Fig. 3 (A) An example of the 3 × 4 scheme (apex, mid-gland, and base by lateral and medial in both lobes); (B) Maximum transverse and sagittal diameters are divided into four; simulated needles are placed 1.0 cm below the inferior prostatic border to each divided border and cross-sections were tilted 80 °. ADBx cores (C–D) were also simulated in the sagittal plane at apex, mid-gland, and base. White lines indicate the direction of the simulated needle, while red lines indicate the portion taken as a sample in simulation biopsy.



maximum diameter. Sagittal cross-sections were tilted 80 ° (Fig. 3B, arrow). Next, anteriorly directed biopsies (ADBx), including the TZ, were simulated in the apex, mid-gland, and base sagittal planes as shown in Fig. 3C and D.

Evaluation of the Various Biopsy Schemes

Using the simulated biopsies, we investigated the detection rates of various tumour volumes (i.e. 'clinically significant' vs not) by different zonal origins, prostatic volumes and biopsy cutting lengths. Figure 4A shows what is meant by biopsy cutting length. Using simulated biopsies, including ADBx, we further evaluated the influence of: (i) ADBx core depth, (ii) the number of cores, and (iii) biopsy cutting length on detection rate for cancer with a TV of ≥0.5 mL. Figure 4B and C show the approach to depth and number of the ADBx. Specifically, 'shallow' ADBx refer to medially oriented cores in the transverse plane with the simulated needles placed in a similar fashion to the 3 × 4 scheme described above (Fig. 4B, left). In contrast, for 'deep' ADBx, simulation was accomplished by estimating the anterior–posterior prostatic length (as by ultrasonography in the clinical realm) from which the biopsy device cutting length was subtracted. The difference represents the distance to indent the gland with the biopsy device such that the remainder of the anterior–posterior diameter is sampled (Fig. 4B, right). While clinical TZ biopsies are

Fig. 4 Parameters investigated to increase detection rate for anterior tumours: (A) cutting length of the biopsy device; (B) depth of ADBx cores, shallow (left) and deep (right); (C) number of ADBx cores.

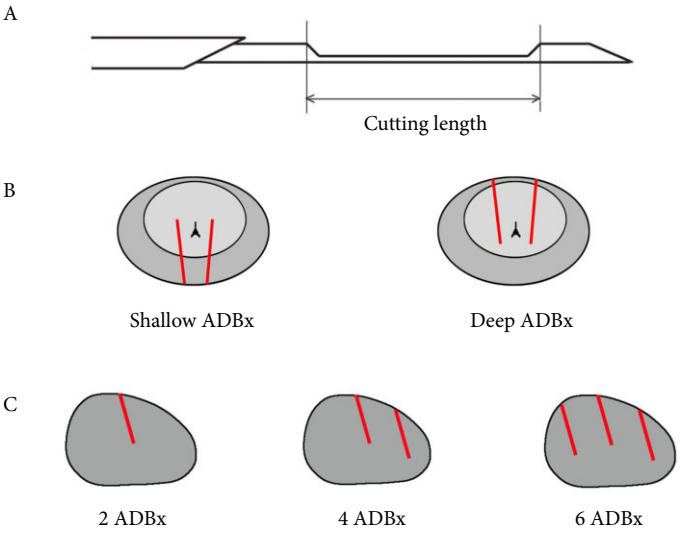


Table 1 Characteristics of the RP specimens for 109 patients.

Characteristic	Value
Mean (SD, range):	
Age, years	61.9 (1.6, 42–81)
PSA level, ng/mL	6.4 (0.9, 1.1–40.3)
N (%):	
Pathological stage:	
pT2	82 (75.2)
pT3	27 (24.8)
Gleason score:	
3 + 3	18 (16.5)
3 + 4	71 (65.1)
4 + 3	15 (13.8)
≥8	5 (4.6)
Mean (SD, range):	
Prostate volume, mL	45.9 (0.9, 19.5–208)
Prostate *anterior–posterior diameter* on mid-plane, cm	3.84 (6.2, 2.8–6.2)

oriented to the mid-gland alone, we evaluated schema using ADBx of the apex, mid-gland and base (Fig. 4C). Finally, the detection rate for cancer with a TV of ≥0.5 mL was compared for prostates of differing sizes, using combinations of the aforementioned schemes.

Results

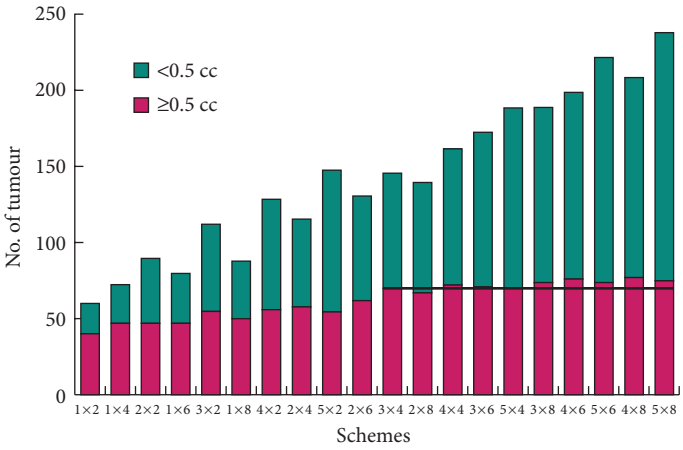
Patient Characteristics and the Distribution of Tumours

Table 1 shows the characteristics of the patients considered for the 3D analysis. Overall, the 3D model detected 800 tumours in 109 prostates for which the distribution of TV and zonal origin are shown in Table 2. In all, 90 tumour nodules had a TV of ≥0.5 mL, while 710 had a TV of <0.5 mL; the mean (range) TV was 0.24 (2.4×10^{-5} to 12.8) mL.

Table 2 The volume and zonal origin of all detected tumours (n = 800).

Tumour zone of origin, n (%)	Tumour volume, mL				
	<0.005 (n = 197)	0.005–0.05 (n = 306)	0.05–0.5 (n = 207)	0.5–5 (n = 80)	≥5 (n = 10)]
Posterior PZ (n = 466)	124 (15.5)	181 (22.6)	116 (14.5)	41 (5.1)	4 (0.5)
Anterior PZ (n = 182)	40 (5.0)	70 (8.8)	51 (6.4)	18 (2.3)	3 (0.4)
TZ (n = 152)	33 (4.1)	55 (6.9)	40 (5.0)	21 (2.6)	3 (0.4)

Fig. 5 Tumours detected among the 20 schemes without ADBx cores using a 17-mm cutting length.



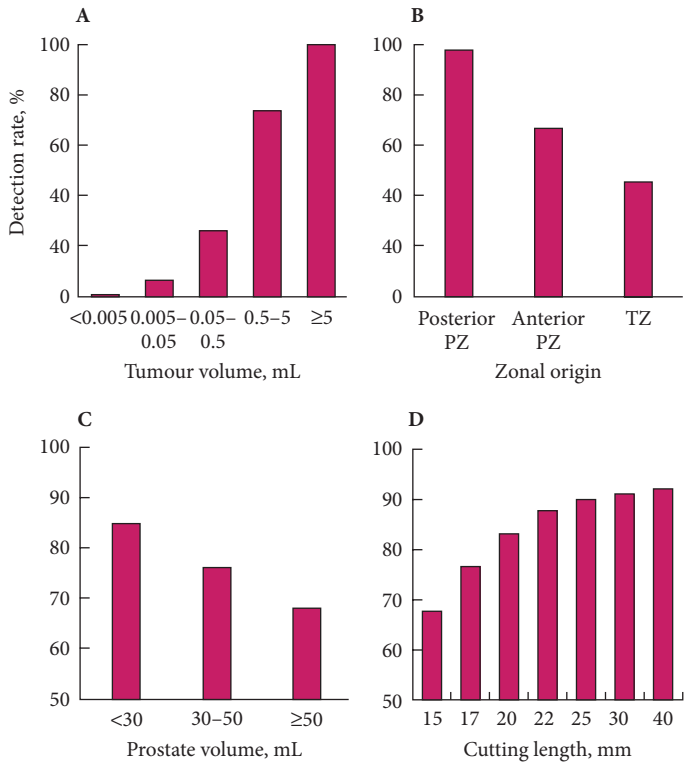
Detection Rate for Tumours in Various Schemes without ADBx

Comparing the number of tumours detected among the 20 schemes (Fig. 2) using a standard 17-mm biopsy cutting length, we found that an increase in the number of biopsy cores resulted in a higher tumour detection rate. However, without using ADBx, the detection rate of tumours with a TV of ≥0.5 mL plateaued at 77% (69 of 90) for the 3 × 4 (12 core) scheme (Fig. 5).

Detection Rate for Tumours using the 3 × 4 (12 Core) Scheme

Figure 6 depicts the detection rate for tumours in the 3 × 4 (12 core) scheme. The detection rate as a function of TV for a 17-mm biopsy cutting length is shown in Fig. 6A. The results clearly show that the larger the TV, the higher the detection rate for this scheme. All tumours with a TV of ≥5.0 mL were detected using the 3 × 4 scheme, while the detection rate for tumours with a TV of 0.5–5 mL was 74%. Figure 6B and C show the detection rate for tumours with a TV of ≥0.5 mL for different zonal origins and prostate volumes using the 17-mm biopsy cutting length. The detection rate for tumours with a TV of ≥0.5 mL originating in the posterior PZ, anterior PZ and TZ were 96%, 70%, and 46%, respectively (Fig. 6B). In all, 20 of 21 (95%) tumours not detected by the 3 × 4 scheme originated in the anterior PZ and TZ. Increasing prostate

Fig. 6 Detection using 3 × 4 (12 core) scheme: (A) detection rate for various TVs using 17-mm cutting length; (B) detection rate for tumours with a TV of ≥0.5 mL originating in the posterior PZ, anterior PZ, and TZ; (C) detection rate in prostates with volume of <30, 30–50, and ≥50 mL; (D) detection rate for tumours with a TV of ≥0.5 mL detected by various cutting lengths.



volume also decreased the detection rate for tumours with a TV of ≥0.5 mL (Fig. 6C), as the detection rates in prostates with volume of <30, 30–50, and >50 mL were 85%, 77%, and 68%, respectively.

Figure 6D highlights the improved detection rate for tumours with TV of ≥0.5 cc using the 3 × 4 scheme that may be achieved by increasing biopsy cutting lengths.

Detection Rate for Tumours with a TV of ≥0.5 mL in the 3 × 4 (12 core) Scheme with ADBx Cores

Figure 7 shows the detection rate for tumours with a TV of ≥0.5 mL in the 3 × 4 (12 core) scheme with the addition of

Fig. 7 Detection rate for tumours with a TV of ≥0.5 mL in the 3 × 4 (12 core) scheme with ADBx cores: (A) detection rate in schemes with two shallow or two deep ADBx cores at mid-gland; (B) detection rate in schemes with two to six deep ADBx cores; (C) detection rate for various cutting lengths in schemes with six deep ADBx cores.

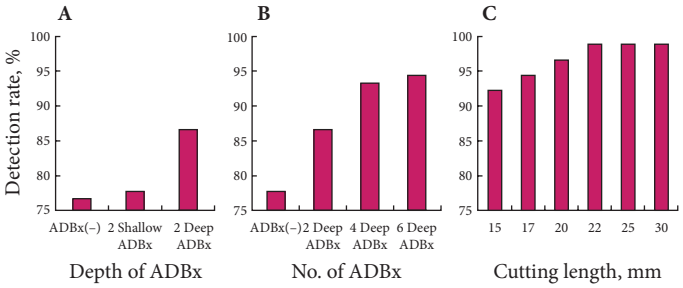
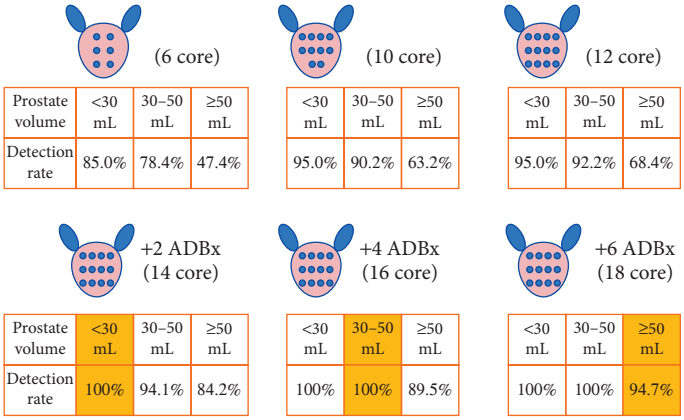


Fig. 8 Detection rates for various combinations of schemes at various prostate volumes using a 22-mm cutting length.



Prostate volume	<30 mL	30–50 mL	≥50 mL
Detection rate	85.0%	78.4%	47.4%

<30 mL	30–50 mL	≥50 mL
95.0%	90.2%	63.2%

<30 mL	30–50 mL	≥50 mL
95.0%	92.2%	68.4%

Prostate volume	<30 mL	30–50 mL	≥50 mL
Detection rate	100%	94.1%	84.2%

<30 mL	30–50 mL	≥50 mL
100%	100%	89.5%

<30 mL	30–50 mL	≥50 mL
100%	100%	94.7%

ADBx cores. Adding two shallow ADBx, the detection rate for tumours with a TV of ≥0.5 mL is nearly identical to a scheme without ADBx (78% vs 77%, Fig. 7A); however, adding two deep ADBx increases the detection rate for clinically significant tumours to 87%. Figure 7B shows that increasing the number of deep ADBx (two, four and six) improved the detection rates to 87%, 93%, and 94%, respectively. The detection rate for tumours with a TV of ≥0.5 mL for different biopsy cutting lengths in schemes containing six ADBx cores is shown in Fig. 7C. Increasing the cutting length in a 3 × 4 (12 core) scheme with an additional six ADBx cores is still beneficial for increasing the detection rate; a plateau is seen at 22-mm cutting length (for tumours with a TV of ≥0.5 mL).

Detection Rate for Tumours with a TV of ≥0.5 mL in Various Prostate Volumes and Biopsy Schemes

Figure 8 shows the detection rate of various combinations of biopsy schemes with a 22-mm biopsy cutting length for different prostate volumes. Adding deep ADBx cores based on the prostate volume improved tumour detection. All tumours with a TV of ≥0.5 mL could be detected by adding either two deep ADBx cores for prostates with a volume of <30 mL or by adding four deep ADBx cores for prostates with a volume of 30–50 mL (Fig. 8, lower left and centre). About 95% of all tumours were detected with six deep ADBx cores for prostates with a volume of ≥50 mL (Fig. 8, lower right).

Discussion

Over the past decade, a large number of studies have investigated the effect of biopsy scheme on prostate cancer detection rate [1–3]. However, none of these studies revealed how many cancers were missed by the schemes investigated and most did not determine the detection rate for clinically significant cancers (TV of ≥0.5 mL). The present study, which analysed 800 tumours from 109 prostates, investigated all simulated biopsy cores individually using a 3D model such that both detected and undetected tumours could be calculated using the various biopsy schemes. Although we investigated only 109 patients, all of whom were initially diagnosed with prostate cancer by transrectal biopsy, the 3D model enabled study of many more tumours in the anterior PZ and TZ than would have been detected by the clinical biopsy session alone. Therefore, the implications of the present study may address current concerns about transrectal biopsy including detection of clinically significant tumours and targeting of the anterior prostate.

Herein, we further confirm the notion that increasing the number of biopsy cores can increase the detection of tumours but also show that the detection of tumours with a TV of ≥0.5 mL plateaued at 12-core biopsies in schemes without ADBx cores. This result is consistent with those of several other studies that have compared the detection rate for various schemes [1,12,13] and found 12 cores to be optimal and most effective. However, the present findings go further, showing that 21 of 90 (23%) tumours with a TV of ≥0.5 mL were missed by a 12-core scheme without ADBx cores, using 17-mm biopsy cutting length. The overwhelming majority (20 of 21) of these undetected tumours originated in the anterior prostate, either anterior PZ or TZ, strongly suggesting that adding biopsies directed to these regions coupled with longer cutting length may increase the detection of tumours.

The present study also shows that simulating deep ADBx proved beneficial in increasing the detection rate for tumours with a TV of ≥0.5 mL. A recent reconsideration of prostate anatomy showed that the PZ encompasses the posterior, lateral, and majority of the anterolateral tissue in the normal prostate gland [14]. This is especially true for the apex where the PZ constitutes nearly all glandular tissue in the region. In recent years, we and other authors have reported that anterior-predominant tumours are increasingly common [15–17]. Al-Ahmadie et al. [16] analysed a large series of dominant anterior tumours and reported that more (49%)

were of anterior PZ origin than of TZ origin (36%). They further highlighted the finding that anterior fibromuscular stroma, a region likely to be sampled by the ADBx cores simulated in this study, is involved by ≈75% of TZ dominant tumours and ≈50% of anterior PZ tumours. This collective evidence suggests that biopsies of the anterior gland would be beneficial for increasing the detection rate. In the present study, deep ADBx cores were designed for both the TZ and the anterior PZ in an effort to decrease the number of undetected prostate cancer in this region.

Interestingly, we showed that adding two shallow ADBx cores does not increase the detection rate for tumours with a TV of ≥0.5 mL (compared with schemes without ADBx). Conversely, adding two deep ADBx cores increased the detection rate. The current trend in prostate cancer detection is to use extended prostatic schemes (10–12 core biopsies without TZ-directed cores) as the initial biopsy strategy [4]. Several studies have suggested that including TZ-directed core(s) at the time of initial biopsy is of little value, while others argue for the use of TZ-directed biopsies only in patients with prior negative biopsies and persistently elevated serum PSA levels [12,18,19]. The method of obtaining TZ cores is not well defined in many studies, although Fleshner et al. [20] described TZ biopsies obtained by triggering the gun once the needle had been advanced to the junction of the PZ and TZ. In the single study to correlate positive TZ-directed biopsy cores with findings at RP, Haarer et al. [21] reported that such biopsies uncommonly sample clinically relevant prostate cancer from the TZ. To our knowledge, no study has thus far assessed the depth of TZ or ADBx cores in transrectal biopsy. The present results indicate that depth of ADBx, using the difference of anterior–posterior diameter and biopsy cutting length to determine the distance to advance the biopsy needle before triggering, might significantly affect the efficacy of such cores. These findings imply that more attention paid to the depth of ADBx may well reduce the incidence of clinically significant tumours missed in the anterior PZ and TZ.

The role of prostate volume in choosing an appropriate biopsy scheme remains controversial [12]. Several studies have shown a significant inverse relationship between the cancer detection rate and prostate volume [22–24]. Similarly, the present simulated biopsy findings confirm that an increase in prostate volume decreased the detection rate for tumours with a TV of ≥0.5 mL. However, it is not entirely clear how additional cores should be oriented in larger prostates to increase the detection rate. In the present study, we showed that adding ADBx cores to a standard 12-core scheme increased the detection rate for tumours with a TV of ≥0.5 mL and that this effect is maximised by increasing the number of ADBx cores in a prostate volume-adjusted fashion, supporting the results of a recent study [25]. Although further investigation is necessary for prostates with a volume of ≥50 mL, the present results suggest that volume-adjusted ADBx would be beneficial.

Few prior studies compare prostate cancer-detection rate using different biopsy cutting lengths [26,27]. Intuitively, a longer biopsy cutting length should improve prostate cancer detection. Fink et al. [26] compared the detection rate by an end-cutting technique (i.e. cores obtained at the tip of the biopsy needle) with 19- and 29-mm cutting lengths and concluded that a 29-mm cutting length led to a significant improvement in cancer detection. However, most of the biopsy instruments on the market are suitable for biopsies of 17- to 22-mm cutting length and conventionally operate with a side-cutting technique [28]. In the present simulation, we showed that increasing the cutting length resulted in increased detection rates for tumours using a 12-core scheme and that the detection rate plateaus at 22-mm cutting length for detection of tumours with a TV of ≥0.5 mL. At that longer biopsy cutting length, adding volume-adjusted deep ADBx cores can aid in detection of nearly all (95%) tumours with a TV of ≥0.5 mL. It is intriguing to note that Moussa et al. [29] have shown that adding two extreme anterior apical biopsies to a standard 12-core biopsy achieves the highest rates of cancer detection when compared with ≤12-cores schema. This approach may be akin to the present simulated ADBx cores directed toward the apex, which were shown to increase detection of clinically significant prostate cancer.

In recent years, several groups have reported that a transperineal biopsy approach may result in a significantly higher prostate cancer detection rate than the standard transrectal approach, especially for anterior tumours [7,30–32]. However, little data is available about the efficacy of transperineal biopsy for detecting prostate cancer with a TV of ≥0.5 mL and the transperineal approach may have increased association with adverse effects, e.g. urinary retention, erectile dysfunction, bleeding and LUTS, when compared with transrectal biopsies. The present study, while using biopsy simulation, strongly suggests that transrectal biopsy has the potential to detect nearly all prostate cancers with a TV of ≥0.5 mL. Yet, there are some limitations to the present study. While we showed an 'optimal' simulated-biopsy scheme, our conclusions are based on only 109 RP specimens. To validate this simulated scheme, it may be necessary to apply the present findings to an additional set of computer-modelled prostate phantoms. Furthermore, at least one recent study has suggested that biopsy schemes applied in virtual models will not necessarily produce equivalent results when applied in the clinic. Han et al. [33] have reported how poorly freehand prostate biopsy patterns compare with planned patterns and advise that robot assistance for TRUS needle biopsy may improve and standardise these biopsy schemes in the clinic. Overall, robust clinical investigation of these proposed biopsy schemes with correlation to pathological outcomes at RP will be necessary to confirm the present findings.

In conclusion, the present 3D-prostate cancer model analysis suggests that nearly all prostate cancer with a TV of ≥0.5 mL can be detected by 14–18 cores in TRUS needle biopsies. Longer biopsy cutting length and the use of deep ADBx cores (including the TZ) adjusted for prostate volume will be necessary to maximise detection.

Conflict of Interest

None declared.

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Correspondence: Samson W. Fine, Department of Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue Room C513, New York, NY 10065, USA.

e-mail: fines@mskcc.org

Abbreviations: ADBx, anteriorly directed biopsies; PZ, peripheral zone; 3D, three-dimensional; TZ, transition zone; TV, tumour volume.