Clinical staging of prostate cancer: a computer-simulated study of transperineal prostate biopsy

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OBJECTIVE

To identify the precise location of prostate cancer within the gland and thus possibly permit more aggressive therapy of the lesion, while potentially sparing the noncancerous gland from ablative therapy.

MATERIALS AND METHODS

Three-dimensional 'solid' computer models were reconstructed for 86 autopsy specimens and 20 stage T1c radical prostatectomy specimens. Transperineal biopsies were simulated for grid sizes of 5-mm (method A) and 10-mm (method B) with an 18 G, 23-mm long biopsy needle. One or two biopsies per grid point were obtained for a total of 12–108 biopsies, depending on the size of the prostate. Clinically threatening cancers were defined as having volumes of ≥ 0.5 mL or Gleason sum ≥7.

RESULTS

Method A detected significantly more carcinomas than method B in both the autopsy and prostatectomy specimens (autopsy, 72 vs 51; prostatectomy, 50 vs 32, both $P < 0.001$). Method A also detected more clinically threatening cancers found at autopsy (38/40 vs 31/40, $P = 0.008$). Among autopsy patients with negative sextant biopsies whose disease was localized to one side, method A detected 72% and method B detected 29–43% ($P < 0.001$).

CONCLUSIONS

The results of this computer simulation show that 5- and 10-mm grid biopsies detect three-quarters and a third, respectively, at autopsy, of patients with the disease localized to one side of the prostate, which may be useful when planning highly selective ablative treatments in the future.

KEYWORDS

prostate cancer, transperineal saturation biopsy, computer simulation, threatening carcinoma, ablative therapy

INTRODUCTION

In 2005 an estimated 232 090 men will be diagnosed with prostate cancer, and 30 350 men will die from this disease in the USA alone [1]. Due to intense early detection efforts, most cases of prostate cancer are diagnosed at a local, curable stage. The overall cancer detection rate of sextant biopsy techniques currently used in clinics is 25–30% [2]. Several alternative biopsy schemes targeting the posterolateral peripheral zone, the anterior transition zone superior and lateral to the urethra, the midline of the peripheral zone, and the inferior part of the anterior horn (where the peripheral zone wraps around the transition zone) have improved overall detection rates to >40% by obtaining an additional 2–16 biopsy cores [2–4].

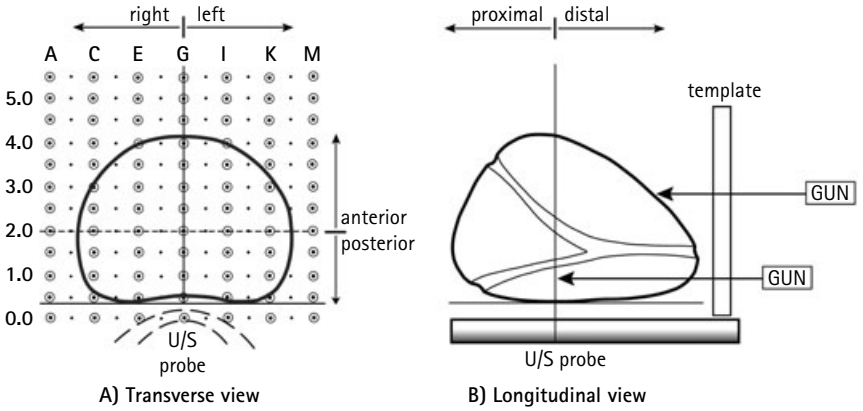
Patients with initial negative biopsies typically have repeated biopsies if they have increasing levels of PSA, a rapid PSA doubling time or a suspicious DRE. Therefore, it is important to obtain biopsy samples that are sufficient to determine the presence of clinically threatening carcinoma. The transrectal saturation biopsy protocol involves taking many biopsies (14–45) from various regions of the prostate while the patient is under either local or general anaesthesia [5–7]. Transrectal saturation biopsies have a cancer detection rate of 14–34% in men with previously negative sextant biopsies [7].

It is unfortunate that the definitive treatments for prostate cancer offered to a patient after positive biopsy findings (e.g. surgery, radiation and cryotherapy) are associated with some morbidity, including erectile dysfunction, incontinence, and complications of the bladder and rectum [8,9]. Although some patients with clinically insignificant or minimally threatening prostate cancer may be diagnosed, most American men with localized disease are treated after diagnosis [10]. By contrast, patients in Europe may be more likely to choose observation rather than intervention. In some cases, they may not even investigate a possible diagnosis of prostate cancer because of the morbidity associated with treatment or the possibility of over-treatment [11]. Clearly, a treatment with minimal morbidity would be a welcome addition to the therapeutic options.

The concept of 'highly selective' ablative procedures for prostate cancer is being considered in certain low-risk patients. This option would hypothetically result in a significant decrease in the morbidity associated with prostate cancer treatment, particularly erectile dysfunction. Our definition of highly selective ablation includes careful mapping to detect prostate cancer foci, followed by focused targeted treatment to only these locations. Even though the transrectal saturation biopsy protocol allows for such detailed mapping, subsequent treatment is somewhat difficult because there

are no proper landmarks to clearly identify specific locations. However, use of the brachytherapy template-guided transperineal saturation biopsy (TSB) scheme allows for systematic and comprehensive prostate biopsies in which specific locations can be targeted with far greater accuracy [12]. The present computer simulation was conducted to determine the feasibility of a template-guided TSB protocol as a preliminary step in highly selective ablative therapy. To consider such targeted therapy, the area(s) of the gland involved with prostate cancer must be accurately identified. This study was carried out to test the feasibility of identifying all areas of cancer in the gland which could potentially be clinically threatening.

FIG. 1. The system for obtaining template-guided TSBs.



MATERIALS AND METHODS

Two template-guided TSB protocols were tested on a set of autopsy specimens and subsequently validated on a set of T1c radical prostatectomy specimens. Both sets of prostate specimens were used previously for testing other biopsy protocols [4,13]. Briefly, 86 of 130 cancerous prostates selected from a consecutive series of 500 autopsies met the histopathological requirement for computer modelling (i.e. minimal autolysis, complete transverse sections and no previous TURP). None of the carcinomas histologically confirmed at autopsy were clinically apparent before autopsy. From a consecutive series of 120 radical prostatectomies at the University of Colorado Health Sciences Center between October 1992 and September 1997, 40 cases met the criteria for three-dimensional (3D) computer modelling and had not been previously incised or treated with neoadjuvant androgen deprivation [4]. Using the American Joint Committee on Cancer Staging Manual (Fifth Edition, 1997) classification guidelines, 20 of 40 patients were diagnosed with clinical stage T1c disease (impalpable). Analysis was limited to these T1c tumours, as patients with more advanced prostate cancer probably would not be considered for highly selective ablative prostate therapy.

Haematoxylin and eosin (H&E) sections were prepared from each prostate specimen for routine histological inspection [14]. On H&E sections, all tumours in each prostate were histologically graded using the Gleason system [15] and their locations classified according to McNeal's zonal anatomy [16].

The H&E sections were next transformed into solid 3D computer models using an algorithm with linear interpolation and extrapolation algorithms [17,18].

The template-guided TSB technique was simulated on all prostate specimens [12]; with a lithotomy position orientation, the simulation used a perineal template with either 5-mm (method A) or 10-mm (method B) grid of points (Fig. 1). Biopsies were simulated using an 18 G biopsy needle with a cutting length of 23 mm at each grid point (Travenol Laboratories, Deerfield, IL, USA). Depending on the prostate size, 12–108 transperineal biopsies were obtained to provide adequate sampling of the prostate from apex to base, left to right, and posterior to anterior. Horizontal grid points were denoted as A, B, C, etc., and vertical grid points as 0.0, 0.5, 1.0, etc.; grid co-ordinate A0.0 was located on the patient's right side at the bottom of the template. Two or more biopsies were taken from the same grid-point when a single biopsy was not sufficient to sample the length (from apex to base) of the prostate (denoted as distal C3.5, proximal C3.5). The urethra was approximately located at G2.0 in most cases and no biopsies were taken from this location and above.

Clinically threatening tumours were defined as all tumours identified with a Gleason sum of ≥7 or with a volume of ≥0.5 mL, as previously reported [19,20]. This volume was based on one tumour rather than an aggregate cancer volume in the gland. A patient was considered clinically threatened if at least one clinically threatening carcinoma existed in the prostate. Both the 5- and 10-mm sampling schemes were analysed to determine the efficacy of detecting all cancers, all high-grade cancers (Gleason patterns 4 and 5), and all clinically threatening cancers.

Sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were determined for each biopsy schema, with the results assessed statistically using McNemar's tests. Differences between groups were considered to be statistically significant for $P < 0.05$.

RESULTS

Table 1 shows the patient and tumour characteristics in the two groups of prostate specimens used. Compared with prostatectomy patients, autopsy patients were generally older, and had smaller prostates, smaller tumour volumes, a lower proportion of clinically threatening cancers, and a lower proportion of capsular perforation. Overall, method A detected significantly more patients with cancers at autopsy than method B ($P < 0.001$; Table 1).

Among autopsy patients, method A detected significantly more carcinomas than method B (method A, 123/161, 76%; method B, 72/161, 45%; $P < 0.001$). Method A also detected more tumours containing highest Gleason grade patterns 4/5 (method A, 23/30, 77%; method B, 12/30, 40%; $P < 0.001$). The total number of saturation biopsy cores obtained at each channel of the template for method A from the autopsy prostates is given in Table 2. Each alternate channel on horizontal (B, D, F, etc.) and vertical (0.0, 1.0, 2.0, etc.) axes corresponds to method B. The mean (median, range) number of biopsy cores for methods A

TABLE 1 Biomorphometric data for the patients and autopsy and radical prostatectomy specimens

Characteristic	Autopsy	Prostatectomy
N	86	20
Mean (SD, range):		
Age, years	67.4 (9.7, 36–87)	58.8 (6.8, 45–70)
Gland volume, mL	25.9 (10.6, 9.0–53.4)	40.0 (11.3, 31.3–67.0)
Tumour volume, mL	0.91 (2.1, 0.005–10.9)	2.29 (2.0, 0.43–7.7)
Total number of individual tumours	161	75
Mean (range) n tumours/prostate	1.9 (1–9)	3.8 (1–7)
Patients with:		
organ-confined cancer, %	80	50
clinically threatening cancer, %	37	85
N (%) of patients detected by:		
method A	74/86 (86)	20/20 (100)
method B	53/86 (61)	19/20 (95)

and B were 54 (54, 23–108) and 12 (12, 5–27), respectively. Only four of 86 (5%) autopsy specimens required >80 biopsy cores. The number of biopsy cores was evenly distributed except around the circumference of the prostatic urethra, and decreased towards the posterolateral peripheral zone. The number of biopsy cores that detected carcinoma at each channel is also given in Table 2.

According to the established definition, 25% of autopsy cancers were considered clinically threatening. Method A detected significantly more of these cancers than method B, at 38/40 (95%) and 31/40 (78%), respectively ($P = 0.008$). Notably method A also detected a significantly higher proportion of 121 clinically nonthreatening tumours than method B, at 85/121 (70%) and 41/121 (34%), respectively ($P < 0.001$). Most clinically threatening carcinomas were in the posterior peripheral zone and most nonthreatening carcinomas were in the anterior of the prostate. Using these data, the sensitivity, specificity, PPV and NPV can be calculated for detecting clinically threatening cancer in autopsy-detected prostate cancer cases. For method A, the sensitivity, the specificity of detecting clinically threatening cancer, PPV and NPV were 95%, 30%, 31% and 95%, respectively, and 78%, 66%, 43% and 90%, respectively, for method B.

In all, 75 separate tumours were identified in 20 patients with clinically detected, impalpable prostate cancer undergoing radical retropubic prostatectomy. Method A detected significantly more carcinomas than method B in this group, at 50 (66%) and 32 (42%), respectively ($P < 0.001$). In addition, method B failed to sample Gleason patterns 4/5 among four of 10 carcinomas, while method A consistently sampled the highest grade in every case ($P = 0.014$). Method B also missed three of 24 clinically threatening carcinomas, while method A missed only one of 24 ($P = 0.157$). Interestingly, method A also detected 27 of 51 (53%) clinically nonthreatening tumours, compared with 11 of 51 (22%) for method B ($P < 0.001$).

The main objective of highly selective ablative procedures is to focus treatment on one side of the prostate whenever possible. Some clinicians are recommending treatment on significant cancers on both sides of the gland. Therefore, the detection rates of TSB among autopsy patients with disease localized to a particular side (i.e. left/right or anterior/posterior) were examined. Fifty of 86 autopsy patients were identified with the disease localized to the left or right prostate, and another 50 as localized to the anterior or posterior gland. In the autopsy patients, methods A and B detected tumours in 38 (76%) and 22 (44%), respectively, with disease localized to the left or right side of the prostate (Table 3) and 39 (78%) and 24 (48%), respectively, with disease localized to the anterior or posterior gland (Table 2). Method A was significantly better than method B when detecting patients with the disease localized to the left/right or anterior/posterior (both $P < 0.001$). None of the 20 T1c patients had disease clearly localized to either left/right or anterior/posterior.

DISCUSSION

Highly selective prostate cancer ablation is a very new concept in the treatment of prostate cancer. Early treatments of this type may be focused on less aggressive cancers. It is imperative that clinicians identify the locations of all carcinomas if possible and specifically those that are clinically threatening, due to their high Gleason grades or volumes. Thus autopsy prostate specimens and clinical stage T1c radical prostatectomy specimens were used in the present study for accurate cancer staging.

Compared to the standard clinical screening procedure of six random systematic core biopsy (SRSCB) [13], TSBs in the autopsy group show that the latter detected significantly more carcinomas ($P < 0.001$). When compared to the modified fan-shaped biopsy (MFSB) technique (six laterally directed biopsies) [4], which has a higher overall detection rate than SRSCB, TSBs continued to be significantly more effective when detecting prostatic carcinoma ($P < 0.001$). From these findings we conclude that in clinical screening procedures, when initial and/or subsequent biopsies are negative but there is a suspicion that cancer is present, a certain subset of these patients are candidates for TSB (or transrectal) procedures.

Among autopsy patients previously undetected by SRSCB, method A detected 46/58 (79%) and method B 27/58 (47%) prostatic carcinomas ($P < 0.001$). Overall detection rates of TSB (47–79%) were significantly better than overall yields previously reported for transrectal saturation biopsies with either 24 or 14–45 cores (29% [5] and 34% [6], respectively). However, this improvement is at the price of more biopsies (14–45 vs 5–108).

In another study [21], 86 Japanese men with no previous biopsy and 27 with a previous negative sextant biopsy were subjected to extensive TSB using a combination of 5-mm (vertical axis) and 10-mm (horizontal axis) grid points. A mean (range) of 18.4 (9–33) biopsy cores were taken per patient and cancer was detected in 49/113 (43%) men. However, cancer was detected in 42/86 (49%) with no previous biopsy and seven of 27 (26%) with previous negative sextant biopsy. In the present simulations, this method detected 64/86 (74%) autopsy patients with cancers; among patients with previous

negative sextant biopsies, it detected 39/58 (67%). The lower clinical detection rate may be attributed to the presence of patients with benign disease. The higher detection rates in simulations may be due to smaller gland volumes of autopsy prostates.

Among the 20 T1c prostates at radical prostatectomy, there were no patients with the disease clearly localized to one side. As all of these cases were previously detected by initial sextant biopsies, there is a high probability that disease may have spread into more than one area. As the success rate of initial sextant biopsies in the general population is 25–30%, those with negative biopsies may still harbour small lesions that could warrant treatment [2]. Therefore, it can be argued that a subset of these patients may have incidental carcinoma 'similar' to what was found in the autopsy series.

Of the 50 of 86 autopsy patients with disease localized to either the left/right or anterior/posterior, method A detected 76–78% and method B 44–48%. Among eight patients who had a positive biopsy, both methods failed to detect all of the tumours on the side where the disease was localized. Failure to detect every tumour on one side is not an issue under the targeted-therapy guidelines, as these undetected tumours will also be eradicated during treatment. Sextant biopsies identified only 16% (eight of 50) of these patients with localized disease. Alternatively, among those autopsy patients with disease localized to one side of the prostate who had negative sextant biopsies, method A detected 71–73% and method B 29–43% ($P < 0.001$).

Patients suspected of having prostate cancer because they have a high serum PSA level and/or an abnormal DRE have TRUS-guided prostate biopsies. Whether it is the sextant biopsy protocol or the transrectal saturation biopsy protocol, many false-negative biopsies are obtained each year, resulting in additional prostate biopsies. In such situations, the use of new biomarkers such as $DD3^{PCA3}$ to confirm the undetected prostate malignancies is highly recommended [22]. The $DD3^{PCA3}$ transcript is, to date, the most specific marker for prostate cancer. Its expression is almost exclusively restricted to the prostate and it is highly overexpressed in >95% of prostate cancers [22,23]. After biomarker confirmation of prostate malignancies, template-guided TSBs can be taken to obtain tissue-based evidence of the disease.

TABLE 2 The number of TSB cores at each channel obtained from autopsy prostates, the number of cores that detected carcinoma at each channel, and those localized to the anterior or posterior of the prostate

cm	A	B	C	D	E	F	G	H	I	J	K	L	M	Sum
Total														
5.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4.5	0	0	0	0	1	1	0	1	1	0	0	0	0	4
4.0	0	0	0	1	5	7	0	6	3	1	0	0	0	23
3.5	0	0	1	8	19	30	0	25	15	9	1	0	0	108
3.0	0	1	9	28	53	70	0	72	54	27	10	1	0	325
2.5	0	2	21	57	100	129	0	130	99	62	27	3	0	630
2.0	0	2	42	96	144	162	0	161	145	99	43	5	0	899
1.5	0	4	57	125	151	161	164	163	151	123	56	4	0	1159
1.0	0	2	37	115	147	157	162	160	148	118	45	0	0	1091
0.5	0	0	9	56	74	81	82	82	75	54	14	0	0	527
0.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sum	0	11	176	486	694	798	408	800	691	493	196	13	0	4766
Biopsy cores with carcinoma														
5.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4.0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
3.5	0	0	0	0	2	1	0	0	1	1	0	0	0	5
3.0	0	0	2	3	5	11	0	2	2	1	0	0	0	26
2.5	0	0	0	3	11	19	0	12	6	1	0	0	0	52
2.0	0	0	2	6	9	15	0	16	10	5	1	0	0	64
1.5	0	0	3	14	15	11	9	11	12	11	3	0	0	89
1.0	0	0	5	19	22	18	11	13	17	17	3	0	0	125
0.5	0	0	2	12	27	21	15	20	22	16	0	0	0	135
0.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sum	0	0	14	57	92	96	35	74	70	52	7	0	0	497
Anterior														
5.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4.0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
3.5	0	0	0	0	2	1	0	0	1	1	0	0	0	5
3.0	0	0	2	2	2	4	0	1	1	1	0	0	0	13
2.5	0	0	0	0	3	6	0	4	1	0	0	0	0	14
2.0	0	0	0	0	0	1	0	3	1	0	0	0	0	5
1.5	0	0	0	0	0	1	0	2	0	0	0	0	0	3
1.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sum	0	0	2	2	8	13	0	10	4	2	0	0	0	41
Posterior														
5.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2.0	0	0	0	0	1	1	0	0	1	0	0	0	0	3
1.5	0	0	0	1	1	1	0	0	1	2	0	0	0	6
1.0	0	0	0	2	2	1	0	1	4	6	1	0	0	17
0.5	0	0	0	3	7	4	4	4	9	8	0	0	0	39
0.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sum	0	0	0	6	11	7	4	5	15	16	1	0	0	65

TABLE 3 The number of saturation biopsy cores that detected carcinoma localized to either the right (A–F) or the left (G–M) at each channel

cm	A	B	C	D	E	F	Sum	G	H	I	J	K	L	M	Sum
5.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4.0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0
3.5	0	0	0	0	1	0	1	0	0	1	1	0	0	0	2
3.0	0	0	1	1	3	4	9	0	0	0	0	0	0	0	0
2.5	0	0	0	0	4	6	10	0	2	0	0	0	0	0	2
2.0	0	0	0	0	1	1	2	0	1	1	0	1	0	0	3
1.5	0	0	1	2	2	1	6	0	1	1	1	0	0	0	3
1.0	0	0	1	4	3	3	12	1	1	3	3	0	0	0	7
0.5	0	0	1	4	6	4	15	2	4	5	4	0	0	0	15
0.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sum	0	0	4	11	21	19	56	3	9	11	9	1	0	0	33

The main advantage of TSBs over a transrectal approach is that the template allows needles to be accurately placed and highly selective treatments to be focused to localized areas of disease. TSBs can also target anterior tumours, including those located above the urethra in the transition zone, far more easily than SRSCB, MFSB or transrectal saturation biopsies. Furthermore, midline biopsies can be obtained through the perineum without risking injury to the prostatic urethra. Inserting a catheter with aerated gel makes it easy to identify the urethra, allowing biopsies to be directed away from it and minimizing any side-effects resulting from haematuria and dysuria. These biopsies do not cause severe rectal bleeding or discomfort to the patient, and reduce the risk of sepsis associated with transrectal biopsies.

Concerns include the clinical and pathological cost components, and the potential morbidity associated with the many biopsies required in TSB. The technique requires brachytherapy equipment, including a stepping unit and an ultrasound probe compatible with the metal template. To minimize the discomfort and to ensure proper set-up and calibration of the equipment, the transperineal approach requires the patient to be under regional or general anaesthesia.

In conclusion, using standard cryo- or brachytherapy grids to take TSBs at 5-mm intervals results in the detection of more cancers, both clinically threatening and nonthreatening, and is less likely to miss high-grade tumours. We think that a conservative 5-mm sampling approach should be maintained during the early investigative phase of highly selective prostate ablation; however, further investigation of more clinically detected prostate cancers may show that 10-mm intervals are adequate for detecting and treating clinically important tumours. Further studies evaluating template-guided TSBs and verification with more specimens will be helpful. Noninvasive techniques for accurate localization are needed. Only 60% of the patients in the autopsy series were potential candidates for treatment of the hemi-prostate and none qualified in the surgically treated group. Therefore, this approach will have significant challenges. Among autopsy patients with previously negative sextant biopsies, the 5-mm sampling method detected about three-quarters and the 10-mm sampling method about a third of patients whose disease was localized to just one side of the prostate, a justification that TSBs are better suited for highly selective or targeted therapy. With present knowledge and considering the limitations of our localization techniques, focal therapy is experimental and should be performed under a carefully constructed clinical protocol. The ultimate reward may be a less morbid procedure for a subset of patients diagnosed with prostate cancer. Ultimately outcome data for highly selective prostate ablation may be revolutionary.

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CONFLICT OF INTEREST

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Abbreviations: **TSB**, transperineal saturation biopsy; **H&E**, haematoxylin and eosin; **PPV**, positive predictive value; **NPV**, negative predictive value; **SRSCB**, six random systematic core biopsy; **MFSB**, modified fan-shaped biopsy.