Low accuracy of routine ultrasound-guided systematic 12-core biopsies in prostate tumor mapping

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Introduction: *To determine the accuracy of a 12-core biopsy protocol in assessing the location of prostate tumors within radical prostatectomy (RP) specimens.*
Materials and methods: *A consecutive series of patients with T1c stage prostate cancer who had undergone 12 ultrasound-guided prostate biopsies prior to RP was considered. The locations of the biopsies from prostate gland mapping were compared with the locations of tumor tissues obtained after analysis of the prostate specimens.*
Results: *Overall, 78 patients (27.4%) were included. The median PSA level was 6 ng/mL. The median prostate weight was 45 g (range 22 to 102). Overall, 936 biopsies were performed in the 78 men, of which 254 biopsies were positive. The mean number of positive biopsies per patient was 3.7 (range 1 to 12). Pathologic examination of the surgical specimens revealed that 58 (74.4%) patients had pT2 disease and 20 patients (25.6%) had locally advanced disease (pT3). The biopsy protocol's sensitivity, specificity and positive predictive value for tumor location were 0.34, 0.83 and 0.84. The performance of the protocol was modest in assessing the exact tumor location (area under curve (AUC) 0.581, 95% confidence interval (CI) 0.489-0.719).*
Conclusions: *Routine, ultrasound-guided, systematic 12-core biopsies lack precision in prostate tumor mapping.*

Key Words: prostatic neoplasms, prostate-specific antigen, prostate biopsy, diagnosis of transrectal ultrasound, radical prostatectomy, Gleason score

Introduction

Prostate cancer is the most commonly detected male cancer and is the second leading cause of male cancer deaths in the United States and in Europe.[1] However, the early and specific diagnosis of prostate cancer is difficult due to a lack of cancer-specific biomarkers.[2,3] The most commonly used marker is prostate-specific antigen (PSA), for which the specificity for disease is low, regardless of the threshold value (either 2.5 ng/mL or 4.0 ng/mL).[2,4] PSA may in fact be a better marker of benign prostate hypertrophy (BPH) than of prostate cancer. Markers that distinguish benign from clinically silent malignant disease are urgently needed to improve the care of men with prostate cancer and to reduce the number of unnecessary biopsies.[3,5]

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The introduction of PSA screening and the ease of sampling prostate tissue with transrectal ultrasound-directed prostate biopsy have contributed to an increase of small, localized prostate cancers considered as being "low risk".[6] Some of these cancers would have remained undetected throughout life without systematic screening.[7,8] A good biopsy mapping is crucial for treatment decision, however taking more cores also means detecting more prostate cancer and can lead, sometimes to systematic curative treatment in these small tumors which has been criticized and considered as over-treatment.

Prostate biopsy is an uncomfortable procedure with a non-negligible morbidity.[9] Initially proposed by Hodge,[10] ultrasound-guided sextant prostate biopsy has improved the diagnosis and management of prostate cancer, but it remains imperfect with regards to its accuracy and its ability to locate the tumor within the gland.[10,11] Thus, prostate biopsy protocols have evolved over the years toward protocols that propose either increasing numbers of biopsies (e.g., saturation) or biopsy techniques coupled with targeted MRI or even robots capable of guiding direction in some expert centers.[12-14] However, according to the most recent European guidelines, the current practice standard method to diagnose cancer remains ultrasound-guided prostate biopsy.[2,11] In daily practice, it is quite usual to propose prostate biopsy mapping of 10 cores, at least in the initial diagnosis of prostate cancer. Thus, the aim of our study was to determine the accuracy of our 12-core positive biopsy protocol in assessing the location of prostate tumors within radical prostatectomy (RP) specimens.

Materials and methods

Population

We collected data prospectively over 18 months (2008-2010) from 285 consecutive patients who underwent preoperative transrectal ultrasound (TRUS)-guided biopsy for the first time at our institution. Only patients with subsequent positive biopsies and who underwent a RP were included in the current study. The following data were collected: age at diagnosis, body mass index (BMI), preoperative PSA level, complications after biopsy, biopsy and pathological Gleason score and 2009 TNM stage, type of surgery and pathological data from the surgical specimen. Patients were selected and included on the basis of the following criteria: a normal digital rectal examination (i.e., clinical stage T1c: tumor identified by needle biopsy) and a PSA level > 4 ng/mL, biopsy-proven prostate cancer, a 12-needle ultrasound-guided biopsy protocol performed at our center, a treatment plan of RP performed within 2 months at our center, the patient having no history of the use of hormonal blockade prior to surgery.

Biopsy protocol

The biopsy protocol was an outpatient procedure, following rectal preparations the day before and the day of the examination. A fluoroquinolone antibiotic was prescribed in each case the day before the biopsies and the day of the biopsies according to French national guidelines.[15] The sterility of urine was checked before performing biopsies. Biopsies were performed in left lateral decubitus, under ultrasound guidance after local anesthesia, using 1% lidocaine and a 22-gauge needle. Twelve systematic prostate biopsies were taken, using 18-gauge biopsy needles and a spring-loaded biopsy gun with the aim to sample 17 mm long tissue cores. Additional sampling could be performed at the operator's discretion if an area was found to be suspicious on ultrasound. Two experienced operators were involved in the biopsy protocol, and they independently completed data sheets for each case and specified locations according to sextant mapping (divided into left lobe versus right lobe and anterior versus middle versus posterior). Thus, each prostate gland was divided into six distinct areas (three areas for each lobe). Twelve samples were systematically performed as follows: three lateral samples in each lobe (apex (n = 1), middle (n = 1), base (n = 1)) and three medial samples (apex (n = 1), middle (n = 1), base (n = 1)). Each sample was included separately and was then analyzed by our senior pathologist, who completed data sheets for each case and specified the location according to the map template used by biopsy operators.

Operative technique

The patients underwent either open retropubic prostatectomy or robot-assisted laparoscopic RP (with a 3-arm da Vinci surgical system and a transperitoneal approach with a six-port technique) as a first-line treatment for localized prostate cancer at the physician's discretion. Two seasoned surgeons were involved in each of these procedures.

Pathological finding

All biopsies/specimens were examined by one senior pathologist. Tumor differentiation was determined using the Gleason score as high (2 to 6), moderate (7) or poor (8 to 10). The 12 cores were immediately placed on sponge tissues in several cassettes and were individually inked with different colors to mark the sites from which they were collected. The cassettes were

soaked in glasses of Bouin solution for 1 s to fix the colors and then preserved in pots with 10% formalin. During macroscopic examinations, the entire surfaces of RP specimens were inked to accurately evaluate the surgical margins on histological slides. Surgical margins were positive when tumor foci were found upon microscopic examination. Briefly, all RP specimens were weighted, inked, fixed in formalin for 24-48 hours, and serially sectioned at 3 mm regular intervals perpendicularly to the urethra. The prostate slices were then subdivided in quadrants and labeled to allow for reconstruction as whole-mount sections, as described before.[16,17] The apex was firstly removed and sectioned parasagitally to start the process. Standard sections of the prostate, including the apical and bladder neck shave margins, the entire posterior peripheral zone, alternative sections of the anterior zone, and the base of the seminal vesicles were submitted for microscopic examination. The prostatic tissue submitted for microscopic evaluation in each case ranged from 70% to 100%. Blocks were embedded in paraffin and a 4 μm section from each block was stained with hematoxylin and eosin. Tumor foci on microscopic slides were circumscribed with a marker pen to determine the number and zone of origin of separate prostate cancer. The prostatectomy tumor mapping was done is the same way as the biopsy template. The presence or absence of tumor was determined on the basis of these matches for each positive biopsy marked on the initial mapping. All cases were reviewed by a single pathologist.

Statistical analysis

The sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy of the positive biopsies in the prediction of tumor location were evaluated. The locations of positive biopsies were compared to the location of the tumor. To determine how prostate weight influenced the results, we split our population into two groups, using a threshold of 45 g (i.e.; median prostate volume) for the analysis. The discrepancy for predictive accuracy between biopsy and specimen was evaluated by the concordance index presented by Harrell et al (kappa-index) for censored data (0.5: no discrimination; 1: perfect discrimination). The program SPSS 16.0 for Windows was used for descriptive and data analyses.

Results

Population

Overall, 78 patients with cT1 prostate cancer and a median age of 62 years were included in the current study. Patient characteristics are summarized in Table 1. The median PSA level was 6.2 ng/mL. The median prostate weight was 45 g (range 22 to 102). We found 15 patients (19%) with a family history of prostate cancer.

Few complications were reported after the biopsies and are listed as follows: persistent rectal bleeding and hematuria were common (n = 11), and infectious complications were rare, with three cases of fever and symptoms of prostatitis.

TABLE 1. **Main patient clinical characteristics in men with T1c prostate cancer who underwent ultrasound-guided prostate biopsies and radical prostatectomy (n = 78)**

	Prostate < 45 g	**Prostate ≥ 45 g**	**All**
No. of patients	38	40	78
Mean age (range)	62.3 yrs (45.5-72.4)	63.2 (47.7-73.2)	62.3 (45.5-73.2)
Family history of prostate cancer (%)	7 (18.4)	8 (20)	15 (19.2)
Mean body mass index (kg/m^2)	25.4	26.3	25.6
Mean prostate-specific antigen level (ng/mL)	5.7 (4-29)	7.4 (4-27)	6.6 (4-17)
Mean prostate weight (g)	33 (22-44)	57.5 (45-102)	45 (22-102)
Biopsy Gleason score (%)			
< 7	27 (71)	22 (55)	49 (62.8)
= 7	8 (21)	16 (40)	24 (30.8)
> 7	3 (8)	2 (5)	5 (6.4)
Mean Gleason score	6.5	6.2	6.4

TABLE 2. **Main pathological characteristics in men who underwent radical prostatectomy for positive prostate biopsies and T1c prostate cancer**

Variables	N (%)
TNM stage	
pT2a	3 (3.8)
pT2b	2 (2.6)
pT2c	53 (67.9)
pT3a	14 (18)
pT3b	6 (7.7)
Gleason score	
6 (3 + 3)	34 (43.6)
7 (3 + 4)	21 (26.9)
7 (4 + 3)	19 (24.4)
> 7	4 (5.1)
Mean Gleason score	6.8
Positive surgical margin	12 (15.4)
Prostate < 45 g	3
Prostate > 45 g	9

Biopsy findings

Overall, 936 biopsies were performed in the 78 men, of which 254 biopsies were positive. The median biopsy Gleason score was 6 (range 5 to 9). The mean number of positive biopsies per patient was 3.7 ± 1.2 (range 1 to 12). The mean length of tissue available for pathologic examination per core was 10 ± 3.6 mm (range 2 to 22).

Surgical pathologic findings

Pathologic examination of the surgical specimens revealed that 58 (74.4%) patients had disease confined to the prostate (pT2) and 20 patients (25.6%) had locally advanced disease (pT3). Detailed stages are provided in Table 2. The median biopsy Gleason score was 7 (range 6 to 9). Surgical margins were found to be positive in 12 cases (15.3%): 10 cases were in pT2 (17.2%), and two cases were in pT3 (16.7%). Half of the positive margins were located at the apex, five were in the medio-prostatic zona, and one was at the base of the prostate. The mean length of capsular penetration was 2.6 mm (range 1 to 9).

Tumor mapping

The degree of matching (overlap) between the locations of positive biopsies and the tumor (radical prostatectomy specimen) is shown in Table 3. After analysis of the surgical specimens, 637 tumor locations were found to match with positive biopsies in 214 cases, Table 4. The biopsy protocol's sensitivity, specificity and positive predictive value for tumor location were evaluated to be 0.34, 0.83 and 0.84. Indeed, 254 biopsy cores were positive and matched with 213 tumor sites on pathological specimens. Additionally, 682 biopsy cores were negative, and 254 were also actually negative in pathological specimens. Overall, 78 anterior tumors on the RP specimen were missed by prostate biopsies. The prostate weight did not significantly influence the interpretation of the results, as shown in Table 5. Overall, the ultrasound-guided 12-core biopsy protocol had a modest performance in assessing the exact tumor location in the gland (area under curve (AUC) 0.581, 95% confidence interval (CI) 0.489-0.719). The kappa-index for the assessment of tumor location agreement was 0.53. Among the 12 patients with positive surgical margins, nine (75%) had a positive biopsy in an area of the gland that matched the site of the margin within the prostatectomy specimen.

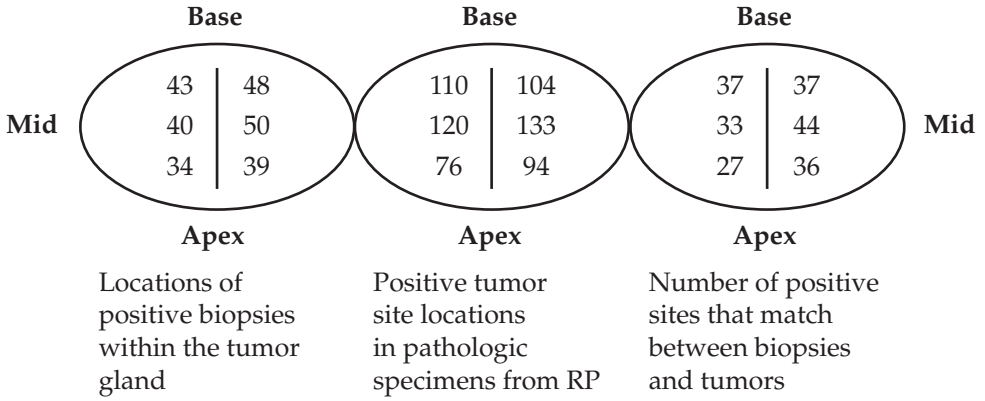
Discussion

In light of our data, it is evident that prostate cancer can be down-staged, with undetectable tumors on digital rectal examination (DRE) (T1c) (i.e., all patients

TABLE 3. **Contingency table for positive biopsies and positive tumor locations on pathologic specimens according to prostate weight**

	Prostate < 45 g		**Prostate > 45 g**		**All**	
	Positive tumor location	Negative tumor location	Positive tumor location	Negative tumor location	Positive tumor location	Negative tumor location
Positive biopsies	104	24	109	17	213	41
Negative biopsies	211	117	217	137	428	254
Total	315	141	326	154	637	299

TABLE 4. **Schematic distribution of the 254 positive biopsies in the prostate gland sites and overlap with the tumors on pathologic specimens after radical prostatectomy**



included herein) that are ultimately very significant in the surgical specimen. In fact, DREs appear to be poorly reproducible and highly variable among different examiners.[18,19] In addition, DREs are only of interest for voluminous tumors.[18,19] Several teams have advocated the use of high-resolution pelvic-phased MRI, which has presented promising results in staging prostate cancer and in accurately detecting extra-capsular extension.[20,21] Looking ahead, other teams are advocating the use of MRI to even define targets and guide biopsy protocols in the diagnosis of prostate cancer.[12,22] However, MRI is not currently available for the preoperative work up of prostate cancer in every center, and its costs/benefits should be evaluated. The current gold standard prostate biopsy is based on standard gray scale TRUS imaging. Although early investigations suggested that prostate cancer is seen as a hypoechoic lesion on TRUS, the reality today is that most PSA detected cancers have a highly variable appearance and do not demonstrate unique characteristics on gray scale imaging. Many imaging technologies have been studied to improve the biopsy yield. Color Doppler ultrasound enhanced prostate biopsy has limitations, but improvements are seen when combined with microbubble contrast agents.[23] Alternatively, elastography, also known as elastosonography, represents a newer TRUS based technique that relies on alterations in tissue stiffness that may indicate the presence of prostate cancer. In an initial promising elastography experience report, areas identified in the prostate with an abnormal elastography pattern were twice as likely to be prostate cancer compared to biopsies in areas of normal elasticity.[24]

Another goal of prostate biopsy is to stage the prostate cancer as precisely as possible, as the prognosis is directly related to the stage at diagnosis and treatment.[25] Thus, the mapping established by the prostate biopsy protocol is very important because the treatment decisions are mainly based on the Gleason score, the number of invaded cores, the ratio between the length of tissue invaded on a core and the total length of tissue, capsular extension, the pathological tumor type and, possibly, the invasion

TABLE 5. **Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of ultrasound-guided 12-core biopsy protocol in tumor location assessment**

	Prostate < 45 g	**Prostate > 45 g**	**All**
Sensibility	33	33.4	33.6
Specificity	83	90	83.3
Positive predictive value	81.2	86.5	84.3
Negative predictive value	35.7	38.7	37.9
Accuracy	48	51.3	50.5

of seminal vesicles. One cannot deny that the number of sites invaded within the gland and their locations have prognostic values, as prostate cancer is a multifocal disease. Several prediction tools have been developed in clinical use to help the clinician to assess the pathology outcome before biopsy or even the prognosis of the patient before treatment.[26-28] Accurate tumor mapping could also be useful in several upcoming focal therapies or protocols of active surveillance.[29]

However, our results showed that the performance of a routine 12-core ultrasound-guided biopsy protocol was lacking, with a sensitivity and NPV that were low and appeared to be imprecise. In previous studies obtained using sextant biopsies, the results were nearly identical.[11] However, in our study, prostate weight (threshold 45 g) had a lesser influence on the interpretation of the results than that reported for sextant biopsies.[11]

Thus, doubling the number of biopsies in daily practice led to a small improvement in the accuracy. Moreover, it has been previously established that saturation biopsies are not the solution to this problem, as such protocols did not increase the detection rate of prostate cancer in first intention against 10- or 12-biopsy protocols.[30,31] They do increase the detection rate in cases where sextant biopsies were performed and were negative. Indeed, a negative saturation biopsy cannot exclude the presence of cancer in the corresponding anatomic site.[16]

We demonstrated that a positive biopsy cannot accurately predict the presence of malignant tissue in the corresponding site on the RP specimen. Alternatively, a negative biopsy did not predict the absence of cancer in the prostatectomy specimen. In this study, all patients underwent RP as a first-line treatment of localized prostate cancer.[25] The aim of the surgery is to eradicate local cancer while maintaining continence and sexual function.[32-34] Nevertheless, the effectiveness of local tumor control after RP for localized prostate cancer is still a matter of debate.[35] Following primary curative treatment, approximately 35% (15% to 53%) of patients develop biochemical recurrence.[35] Thus, it is of crucial importance to avoid positive surgical margins. The maps obtained from biopsies are certainly the tools most frequently used nowadays to guide surgeons in the event that surgical treatments are chosen.[36] This map could also help physician with focal therapies in a near future.[37] Among our twelve patients with positive surgical margins, 75% had positive biopsies in the corresponding territories. The dissection during RP is not necessarily symmetrical and can move closer to the gland when possible (intrafascial) or away (extrafascial) when required by the biopsy findings.[38] Thus, the 12-biopsy protocol is inadequate, especially with tumor mapping becoming more and more important in guiding whether or not the chosen treatment is surgical. The role of transrectal saturation biopsy in tumor localization has also been questioned recently.[39] A flowchart has been proposed to identify the most advantageous set of sampling biopsy sites according to patients' characteristics.[40] Thus, we believe that further devices are necessary,[13,41,42] and we have already focused on tools that encourage abandoning this technique and gradually moving to more sophisticated and more accurate mapping.

Conclusion

Transrectal ultrasound-guided needle prostate biopsies remain nowadays the "practice standard" in diagnosing prostate cancer in daily practice. However, the routine ultrasound-guided systematic 12-core biopsy protocol does not adequately produce prostate tumor mapping and should be progressively abandoned for more appropriate and sophisticated tools. □

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