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Original Article

Current prostate biopsy protocols cannot reliably identify patients for focal therapy: correlation of low-risk prostate cancer on biopsy with radical prostatectomy findings

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Abstract: Focal therapy appears to be an attractive alternative approach for patients with localized prostate cancer (PCa). Identifying suitable candidates is crucial to the success of focal therapy. Currently, standard transrectal ultrasound (TRUS)-guided prostate biopsy remains the widespread approach to evaluate patient suitability. In this study, we evaluated the ability of current biopsy protocols to predict cancer characteristics in radical prostatectomy (RP) specimens. We reviewed 4437 cases from 2000 to 2008 in our PowerPath database, and identified 158 patients with low-risk cancer, defined as a pre-biopsy PSA level ≤ 10 ng/mL, unilateral, low tumor volume (≤5%) and low to intermediate Gleason score (GS≤6) on first positive prostate biopsy. The pathological characteristics of subsequent RP specimens were reviewed. We found that, of 158 patients with these criteria, 117 (74%) had bilateral cancer, 49 (31%) had increased tumor volume (≥ 10%), and 46 (29%) were upgraded to GS ≥ 7 at RPs. When patients were stratified by total biopsy core numbers, extended biopsy core protocols were not significantly more reliable in identifying unilateral and low volume prostate cancer patients. One core positive on biopsy was not significantly superior to ≥ 2 positive cores in predicting unilateral, low volume, low stage cancer at prostatectomy. These findings indicate that current standard prostate biopsy protocols have limited accuracy in identifying candidates for focal therapy.

Keywords: Prostate cancer, focal therapy, biopsy, prostatectomy

Introduction

Increasing evidence has shown an overdetection and overtreatment of low-risk prostate cancer since the introduction of PSA screening in the general population. Since prostate cancer is often multifocal and clonally heterogeneous, whole prostate treatments (radical prostatectomy, external beam radiotherapy and brachytherapy) are standard practice. However, the adverse effects and complications associated with current standard treatments remain challenging. It has been reported that 19-27% of prostatectomy specimens contain unifocal prostate cancer [1-3]. There is growing interest in focal therapy for prostate cancer to limit "collateral damage" and side effects.

Supporting studies have demonstrated that the largest tumor focus within the prostate (index lesion) predicts the outcomes of prostate cancer [4]. Recently, Liu and colleagues demonstrated that a single prostate cancer cell clone is responsible for disparate prostate cancer metastases in human body [5]. This discovery has encouraged focal therapy advocates. They speculate that if we could identify the aggressive clone or index lesion in the prostate, and destroy it, we may be able to control prostate cancer progression [6].

Focal therapy appears to be a logical and attractive alternative approach for not only unifocal, but also multifocal prostate cancer. Organ-sparing focal ablation therapies: cryosurgery, high-intensity focused ultrasound (HIFU), photodynamic therapy and radiofrequency therapy have emerged and are under development [7-10]. Appropriate identification of candidates and target lesion(s) in the prostate becomes crucial for successful focal therapy of prostate cancer. With the application of new biopsy

Table 1. Pathologic parameters of RP from 158 patients with GS≤6, unilateral, small volume of cancer on biopsy

Bx Core#	GS ≥ 7	Vol ≥10%	Bilateral*	EPE (T3a)	SVI (T3b)	SM+
≤7	5/22 (23%)	9/22 (41%)	20/22 (91%)	1/22 (5%)	1/22 (5%)	3/22 (14%)
8-9	22/59 (37%)	21/59 (36%)	42/59 (71%)	3/59 (5%)	0/59	6/59 (10%)
10-11	12/42 (29%)	10/42 (24%)	29/42 (69%)	1/42 (2%)	1/42(2%)	4/42 (9%)
12+	7/35 (20%)	9/35 (26%)	26/35 (74%)	2/35 (6%)	0/35	5/35 (14%)
Overall	46/158 (29%)	49/158 (31%)	117/158 (74%)	7/158 (4%)	2/158 (1%)	18/158 (11%)

RP, radical prostatectomy; GS, Gleason score; Vol, volume; Bilateral*, unilateral cancer in the biopsy and bilateral in prostatectomy; EPE, extraprostatic extension; SVI, seminal vesicle involvement, SM+, surgical margin positive; LN, lymph node; $p > 0.05$ (chi-square test) for GS, Vol and Bilateral between all four groups of different biopsy core number.

strategies and imaging technologies, more accurate localization of prostate cancer or the index lesion seems possible. At present, prostate biopsy remains the best means to evaluate patients who might be considered for focal therapy. We undertook an analysis to determine if current prostate biopsy strategies can reliably identify candidates for focal therapy.

Materials and methods

With University of Wisconsin (UW) Institutional Review Board (IRB) approval, we reviewed 4437 cases from 2000 to 2009 in our PowerPath database. We identified 158 patients with low-risk cancer, defined as a pre-biopsy PSA level ≤ 10 ng/mL, unilateral, low tumor volume (≤5%), and low to intermediate Gleason score (GS≤6) on first positive prostate biopsy. The biopsy cases selected were a mixed population of patients involving 136 patients' biopsies performed and diagnosed at UW and 22 were done at local community hospitals and reviewed at UW. Since the cases selected span 8 years, the biopsy strategies varied between 7 or less, 8-9, 10-11 and ≥ 12 core biopsies. These 158 patients underwent subsequent radical prostatectomy (RP) at UW Hospital and Clinics within 6 months after the positive prostate biopsy. None of these patients had any chemoradiation or hormonal therapies prior to the surgery. RP specimens were sampled, processed and evaluated following standard protocols [11, 12]. Briefly, the prostate was weighed, measured and inked with two colors (right, red; left, black). Apex (5-mm segment) was transected, radially sectioned and submitted. The bladder neck margin (3 mm) was shaved and submitted en face. The rest of the prostate was serially sectioned at 3-mm intervals parallel to the apical plane, into slices, the number of which varied according to the size of the prostate. Initially, only odd numbered slices (for example, slices 1, 3, 5 and 7) together with apical and bladder shave margins and representative sections of seminal vesicles were submitted for evaluation. If a small volume of tumor or no tumor was identified in the initially submitted sections, the remainder of the tissue (even slices) would then be submitted.

The pathologic parameters of the biopsy (tumor volume, total biopsy core number and positive core number) and corresponding prostatectomy (Gleason score, tumor volume, laterality, extraprostatic extension, margin positivity and involvement of seminal vesicles and lymph node status) were reviewed. Tumor volume of biopsy and RP specimens were estimated on slides. Chi-square test was used to detect group differences.

Results

The overall pathological parameters of corresponding RP specimens from the 158 patients who had small volume (≤5%), unilateral cancer on biopsy are summarized in **Table 1**. It has been reported that clinically insignificant prostate cancer was directly related to the number of positive cores [13]. We then divided the 158 patients into two groups according to positive core number. In group 1, 125 patients had 1 positive core in the biopsy samples. In group 2,

Table 2. Characteristics of two groups of patients with unilateral prostate cancer on first positive biopsy

Group	GS	#Pts	Mean age (y)	Mean PSA (ng/mL)	Tumor volume (%)	#positive core(s)
1	≤6	125	64	6.8	≤5	1
2	≤6	33	63	7.5	≤5	≥2

#Pts, number of patients; y, years; PSA, prostate specific antigen; GS, Gleason score

Table 3. Pathologic parameters of matching radical prostatectomy from group 1 (125) patients

Bx core#	Prostatectomy					
	GS ≥ 7	Vol ≥10%	Bilateral*	EPE (T3a)	SVI (T3b)	SM+
≤7	4/19 (21%)	7/19 (37%)	17/19 (89%)	1/19 (5%)	0/19	2/19 (10%)
8-9	16/45 (36%)	17/45 (38%)	31/45 (69%)	2/45 (4%)	0/45	5/45 (11%)
10-11	8/35 (23%)	8/35(23%)	23/35 (66%)	1/35 (3%)	1/35 (3%)	3/35 (9%)
12+	4/26 (15%)	5/26 (19%)	19/26 (73%)	2/26 (8%)	0/26	4/26 (15%)
overall	32/125 (26%)	37/125 (30%)	90/125 (72%)	6/125 (5%)	1/125 (1%)	14/125 (11%)

Bilateral*, unilateral cancer in the biopsy and bilateral in prostatectomy; Vol, tumor volume; EPE, extraprostatic extension; SVI, seminal vesicle involvement, SM+, surgical margin positive; LN, lymph node

33 patients had ≥ 2 positive core in the biopsy samples. The patients' pre-biopsy characteristics are summarized in **Table 2**. In group 1, a total of 125 patients were further stratified into 4 subgroups based on biopsies taken. Their RP pathological parameters are summarized in **Table 3**. In group 2, a total of 33 patients were also divided into 4 similar subgroups by biopsy protocol. Their RP pathological parameters are summarized in Table 4. Only 84 of the 158 patients had radical prostatectomy (with pelvic lymph node biopsy done at the time of prostatectomy). None of them had any positive lymph nodes.

Discussion

Transrectal ultrasound-guided prostate biopsy procedures have evolved greatly over time from the original sextant biopsy protocol [14]. Technological advances, better understanding of the zonal anatomy of the prostate, whole mount sectioning of radical prostatectomy specimens, and computer modeling of localized prostate cancers have all led to extended biopsy core protocols directed at the lateral zones of the gland [15-19]. These have increased the diagnostic accuracy of the needle biopsy and have become a standard practice.

So far, prostate biopsy is considered the best means to identify patients for focal therapy. Many investigators have suggested that ideal candidates for focal therapy are those with low-risk cancer, unilateral prostate cancer or dominant unilateral lesion and clinically insignificant contralateral lesion [20, 21].

In the present study, we found that of 158 patients with GS ≤ 6, small volume (≤5%) and unilateral cancer on biopsy, 117 (74%) had bilateral cancer, 49 (31%) had increased tumor volume (≥ 10%), and 46 (29 %) had upgraded GS (≥ 7) on RP specimens. Interestingly, when the patients were stratified by total biopsy core numbers, extended biopsy core protocols did not seem to be significantly more reliable in identifying unilateral and low volume prostate cancer patients (**Table 1**). We further stratified patients in this cohort by numbers of positive core. One positive core on biopsy did not seem significantly superior to two or more unilateral cores with tumor ($p>0.05$, chi-square test) in predicting unilateral, low volume, low stage cancer on prostatectomy in this highly selected group of patients (**Table 3** and **4**).

Other groups have reported comparable and incomparable data to the present study (**Table 5**) [1, 22, 23].

Recently, two similar biopsy techniques have

Table 4. Pathologic parameters of matching radical prostatectomy from group 2 (33) patients

Bx core#	Prostatectomy					
	GS ≥ 7	Vol ≥10%	Bilateral*	EPE (T3a)	SVI (T3b)	SM+
≤7	1/3 (33)	2/3 (67%)	2/3 (67%)	0/3	0/3	1/3 (33%)
8-9	6/14 (43%)	4/14 (29%)	11/14 (79%)	1/14 (7%)	0/14	1/14 (7%)
10-11	4/7 (57%)	2/7 (29%)	7/7 (100%)	0/7	0/7	1/7 (14%)
12+	3/9 (33%)	4/9 (44%)	7/9 (78%)	0/9	0/9	1/9 (11%)
overall	14/33 (42%)	12/33 (36%)	27/33 (82%)	1/33 (3%)	0/33	4/33 (12%)

Bilateral*, unilateral cancer in the biopsy and bilateral in prostatectomy; Vol, tumor volume; EPE, extraprostatic extension; SVI, seminal vesicle involvement; SM+, surgical margin positive; LN, lymph node

Table 5. Published data - PCa parameters of RP in patients with unilateral PCa on Bx

Study	#cases	Selection criteria	Case Source	Biopsy protocols (#cores)	Unilateral PCa on RP	RP GS upgrading	EPE	SVI
Our present data	158	Stage 1c, PSA<10 ng/mL, GS≤6	One center (UW)	≤7, 8-9, 10-11, ≥12	26%	29% (GS≥7)	4%	1%
Tareen et al[1] (2009)	342	Stage T1c, PSA<10 ng/mL, GS<7	One center (NYU)	<6, 6-12, >12	28.4%	-	-	-
Polascik et al[[22]] (2009)	382	Stage T1c-T2b, PSA<10 ng/mL, GS≤7	DPC Outcome Database	6-16	28%	4.7% (GS>7)	14.9 %	2.5%
Iczkowski et al[3] (2008)	245	Stage T1c, any PSA, any GS	Two centers (UCHSC and Baylor)	6-19	71-76%	-	-	-
Scales et al [23] (2007)	261	Stage T1c-T2b, PSA<10 ng/mL, GS≤6	SEARCH Database	>6 (median 8)	35.1	-	-	-

PCa, prostate cancer; RP, radical prostatectomy; GS, Gleason score; EPE, extraprostatic extension; SVI, seminal vesicle invasion; PSA, prostate specific antigen

been reported to identify candidates for focal therapy better than current standard biopsy protocols. Barzell et al. evaluated the usefulness of 3-dimensional extensive template guided transperineal mapping biopsy (3-DMP) of the prostate as a staging procedure in the appropriate selection of patients for treatment with focal cryoablation. A median of 38.75 biopsies were performed per side at 3-DPM, and 1.88 biopsies were completed per cubic centimeter of prostate. A total of 80 patients underwent 3-DPM, in conjunction with repeat TRUS-guided biopsies. Results of 3-DPM were compared with those of TRUS-guided biopsies to determine patient suitability for focal cryoablation. They demonstrated that 3-DPM was more accurately in identifying candidates for focal therapy than repeat TRUS-guided biopsies, and was able to precisely locate the site of the cancer to be selectively ablated [24].

Andriole et al. reported a 3-dimensional, template-guided, transrectal ultrasound-guided prostate biopsy device (TargetScan, Envisioneering Medical Technologies, St. Louis, MO). A 12-core TargetScan biopsy procedure was performed on 20 ex-vivo radical prostatectomy specimens. Simulated 12-core TargetScan biopsy was performed on all specimens, followed by complete embedding by a single pathologist. The simulated TargetScan biopsy detected prostate cancer in 16 prostates (80%) and only high-grade prostatic intraepithelial neoplasia (PIN) in 2 prostates. Of all missed tumors, 3 were judged to be histologically insignificant, and 1 was of small volume with a Gleason score of 7.

Because biopsies are performed in a template-guided manner and the location of the biopsy is more precisely characterized through the use of Cartesian coordinates, it is believed that the TargetScan biopsy approach offers improvements over conventional practice [25].

Increasing data have shown that a field effect or field cancerization exists in prostate cancer tissue. Aberrant changes occurring in tumor-adjacent histologically normal prostatic tissue are similar to those in cancer cells [26]. So far, field effects have been identified involving nuclear morphometric changes, gene expression, protein expression, gene promoter methylation, DNA damage and angiogenesis [26-33]. It seems promising that in the near future biomarkers of field cancerized prostatic tissues could be used to help locate cancer with biopsy cancer negative tissue, and to identify candidates for focal therapy.

Molecular imaging has made significant progresses in recent years. Most recent developments in imaging technologies, specifically in MRI, and the emergence of targeted imaging approaches with novel PET and gamma-emitting tracers could lead to significant improvements in both lesion detection and staging [34]. Recently, a new functional MRI spectroscopy technique using hyperpolarized ^{13}C-pyruvate has been developed to detect PCa and its aggressiveness [35]. Using metabolomic imaging approach, Wu et al recently demonstrated that prostate cancer metabolomic profiles could be obtained from previous intact tissue analyses, and the calculated malignancy index was linearly correlated with lesion size; the overall accuracy for detecting the presence of prostate cancer lesions was 93 to 97%. Their findings suggest metabolomic imaging could map cancer-specific biomolecular profile values onto anatomical structures to direct biopsy, and perhaps focal therapy [36].

Future development of new molecular imaging methods that not only locate prostate cancers or index lesions, but also interrogate the biologic function of cancers may aid risk assessment and therapy choices [37].

In conclusion, we believe that current standard prostate biopsy protocols have limited accuracy in identifying candidates for focal therapy. Unless we can develop better methods to locate cancer, or locate index lesions or the aggressive cancer clone in prostates with multifocal cancer, the efficacy of focal therapy of prostate cancer remains uncertain. Perhaps a combination of an optimized 3-D biopsy protocol, tissue biomarkers and molecular imaging technology can meet the challenge of identifying candidates for focal therapy.

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