

International Journal of Surgical Pathology

<http://ijs.sagepub.com/>

Clinicopathological Strategies to Identify Contralateral Prostate Cancer Involvement in Potential Candidates for Focal Therapy

Sonal Grover, Abhishek Srivastava, Gerald Tan, Prasanna Sooriakumaran, Majnu John, Kumaran Mudaliar, Youssef El-Douaihy, Robert Leung, Maria Shevchuk and Ashutosh Tewari
INT J SURG PATHOL published online 23 August 2010
DOI: 10.1177/1066896910379479

The online version of this article can be found at:
<http://ijs.sagepub.com/content/early/2010/08/18/1066896910379479>

Published by:



<http://www.sagepublications.com>

Additional services and information for *International Journal of Surgical Pathology* can be found at:

Email Alerts: <http://ijs.sagepub.com/cgi/alerts>

Subscriptions: <http://ijs.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

Clinicopathological Strategies to Identify Contralateral Prostate Cancer Involvement in Potential Candidates for Focal Therapy

International Journal of Surgical Pathology
XX(X) 1–9
© The Author(s) 2010
Reprints and permission: <http://www.sagepub.com/journalsPermissions.nav>
DOI: 10.1177/1066896910379479
<http://ijsp.sagepub.com>


Sonal Grover, MD¹, Abhishek Srivastava, MD¹,
Gerald Tan, MD¹, Prasanna Sooriakumaran, PhD¹,
Majnu John, PhD¹, Kumaran Mudaliar, MD¹,
Youssef El-Douaihy, MD¹, Robert Leung, MPH¹,
Maria Shevchuk, MD¹, and Ashutosh K. Tewari, MD¹

Abstract

Objective: To identify the magnitude and possible predictors of contralateral lobe involvement and contralateral extraprostatic extension (EPE) in prostatic biopsy-defined localized unilateral cancers. **Patients and Methods:** Between January 2005 and August 2009, 1861 patients underwent robotic-assisted radical prostatectomy at the authors' institution. A total of 1114 had unilateral disease on preoperative biopsy. Final histopathology reports of these patients were reviewed. **Results:** Of the 1114 patients with unilateral disease on biopsy, 867 (77.9%) had contralateral or bilateral disease on final histopathology. EPE was found in 132 patients (11.9%). Twenty patients (1.8%) had contralateral EPE involvement. High-grade prostatic intraepithelial neoplasm (HGPIN) on biopsy was the significant predictor of contralateral lobe involvement on both univariate ($P = .02$; odds ratio [OR] = 1.791) and multivariate analysis ($P = .004$; OR = 2.677). Clinical stage T2 was the significant predictor of contralateral EPE on both univariate ($P = .012$; OR = 5.250) and multivariate analysis ($P = .007$; OR = 8.656). **Conclusion:** HGPIN on biopsy significantly predicts for contralateral lobe involvement and should be considered an exclusion criterion for focal therapy in prostate cancer patients. Patients with palpable tumor on digital rectal examination should be advised in favor of radical treatment as these patients may harbor more aggressive tumors involving the contralateral side despite the biopsy findings.

Keywords

prostate cancer, focal therapy, extraprostatic extension, HGPIN, contralateral, multifocal

Introduction

Prostate cancer is the most commonly diagnosed nondermatological cancer in American men and is the second leading cause of cancer-related deaths.¹ Since 1989, the wide availability of total prostate-specific antigen (PSA) has revolutionized prostate cancer screening and has led to an increase in the number of men diagnosed with prostate cancer. There has also been a significant stage migration toward more localized and well-differentiated tumors—approximately 80% of prostate cancer cases diagnosed today are organ-confined cancers.² Radical prostatectomy (RP) and radiotherapy are established treatments for clinically localized prostate cancer. These 2 approaches often provide oncological control, but they are also accompanied by potential drawbacks such as incontinence³ and impotence.⁴

Recently, several new minimally invasive procedures have emerged as an alternative to RP and may have less morbidity with better continence and sexual function preservation. One of these is focal therapy, which involves subtotal ablation of the prostate with one of several energy sources, such as cryoablation, high-intensity focused ultrasound, photodynamic therapy, and radiofrequency ablation. The ideal candidates for focal therapy are supposed to be

¹Weill Cornell Medical College, New York, NY, USA

Corresponding Author:

Ashutosh K. Tewari, Director, Lefrak Center of Robotic Surgery, and Director, Prostate Cancer Institute, James Buchanan Brady Foundation Department of Urology, 525 East 68th Street Starr 900, New York, NY 10065, USA
Email: ashtewarimd@gmail.com

patients with low-risk, small-volume, unifocal, and unilateral tumors.⁵ However, a significant percentage of these potential focal therapy candidates harbor more aggressive features, which if known at the time of treatment selection would preclude them from the focal therapy protocols. Approximately 70% of patients with unilateral cancer on biopsy have contralateral lobe involvement on final histology and some of these actually have extraprostatic extension (EPE).⁶ Furthermore, approximately 40% of the cancers diagnosed on prostate biopsy undergo Gleason score upgrading on RP histopathology.⁶ Present staging tools, therefore, are inadequate in accurately identifying these focal therapy candidates. Even with the inclusion of elaborate staging approaches, including endorectal magnetic resonance imaging and magnetic resonance spectroscopy, understaging is still a problem.

There have been many studies in the past using various biopsy variables to establish selection criteria for focal therapy but not much has been reported regarding predictors of contralateral lobe involvement and contralateral EPE based on preoperative clinicopathological characteristics. The purpose of this study was to identify the magnitude and possible predictors of contralateral lobe involvement and contralateral EPE in biopsy-defined unilateral localized cancers. We present herein a cohort of 1114 patients with unilateral localized prostate cancer on transrectal ultrasound-guided prostate biopsy that has subsequently undergone RP.

Patients and Methods

Patient Population

Between January 2005 and August 2009, 1861 patients underwent robotic-assisted radical prostatectomy at our institution by a single surgeon (AT). Of these, 1114 patients were identified with unilateral disease on preoperative biopsy. These patients did not receive any adjuvant therapy before surgery. A written informed consent was obtained under a protocol reviewed and approved by the Weill Cornell New York-Presbyterian Hospital Institutional Review Board. The patients' charts were further reviewed to record clinical variables such as age, body mass index (BMI), preoperative PSA, and clinical stage.

Specimens

All the preoperative needle biopsies were retrospectively reanalyzed by one of our institutional uropathologists (MS). Pathology slides were rereviewed and additional blocks were analyzed wherever necessary for all the patients who had their biopsies done outside our institution. These uropathology reviews were focused at confirmation of the cancer diagnosis, accuracy of the Gleason grading, presence of

high-grade prostatic intraepithelial neoplasm (HGPIN) on biopsy, perineural invasion (PNI), number of positive cores, maximum percentage of positive cores, and laterality of the cancer involvement. The data from each analysis were transformed into a visual map. Of 1114 patients with unilateral cancer on biopsy, 106 men had preoperative biopsy cores of 6 or less, 207 men had biopsy cores of 7 to 11, and 735 men had biopsy cores numbering 12 or more. We did not have there data available on 66 patients.

The RP specimens were collected, processed, and evaluated according to a standard regimen performed at our institution. Each RP specimen was weighed, measured, inked in 2 colors to allocate right and left, and then fixed in 10% neutral formalin. After fixing, the distal 4 mm of the apex and the base were amputated and serially sectioned into 3-mm thin slices in a parasagittal plane. The remaining specimen was serially sectioned perpendicular to the long axis of the prostate from its apex to the tip of seminal vesicles and all the tissue was submitted for histological examination. The same uropathologist (MS) graded and staged the prostatectomy specimens without prior knowledge of biopsy findings. Particular attention was given to laterality and EPE in addition to other regular parameters such as Gleason score, percentage of tumor involvement, HGPIN on final pathology, PNI, pathological stage, positive surgical margins, and prostate volume. All the final pathology findings were documented on postoperative visual histopathology maps.

Patients with unilateral cancer on preoperative biopsy maps were selected and correlated with their corresponding postoperative histopathology visual maps. The tumor was classified as unilateral if all the foci of tumor were present on one side of urethra, which was taken as the midline in the sagittal plane.

Statistical Analysis

Statistical analysis was performed using PASW version 17.0 (SPSS, Inc, Chicago, IL). We used logistic regression (univariate analysis) to identify biopsy variables to predict contralateral lobe involvement and contralateral EPE on final histopathology. The following clinicopathological variables were treated as continuous variables: age, BMI, preoperative PSA, total number of positive cores, maximum percentage of cancer (max%) on biopsy, and prostate volume. Of these continuous variables, preoperative PSA and prostate volume did not have a normal distribution and were converted to their corresponding log values. Variables such as clinical staging, number of biopsy cores, biopsy Gleason score, HGPIN on biopsy, and PNI were treated as categorical variables. Number of biopsy cores was categorized into 6 or less cores, 7 to 11 cores, and 12 or more cores. Total biopsy Gleason score was grouped into ≤ 6 and ≥ 7 . The relationship

of all these clinical and biopsy variables was also studied using Backward Wald elimination (multivariate). Odds ratios were determined and statistical significance was set at $P < .05$.

We further stratified our cohort of 1114 men into those with Gleason ≤ 6 , Gleason ≥ 7 , clinical stage T1, clinical stage T2, clinical stage T1 with Gleason 6, and patients with total biopsy cores 12 or more. Univariate and multivariate analysis using Backward Wald was applied to determine predictors of increased risk of contralateral disease in these 6 groups on final histopathology.

Results

The preoperative clinicopathological characteristics of the cohort are summarized in Table 1. Of the 1114 patients with biopsy-proven unilateral disease, 867 (77.9%) actually had contralateral disease on final histopathology (Figure 1A, B, and C). EPE was found in 132 (11.9%) men. Univariate logistic regression analysis of pretreatment factors in our cohort demonstrated that presence of HGPIN on biopsy ($P = .02$; odds ratio [OR] = 1.791) in the biopsy specimen is associated with contralateral lobe involvement on RP specimen. Other biopsy variables such as age ($P = .708$; OR = 0.996), BMI ($P = .425$; OR = 1.015), preoperative PSA (log) ($P = .193$; OR = 1.469), total positive cores ($P = .287$; OR = 1.054), Gleason score ($P = .327$; OR = 1.791), max% ($P = .583$; OR = 1.002), PNI ($P = .251$; OR = 2.342), and prostate volume (log) ($P = .560$; OR = 0.776) did not predict for contralateral involvement (Table 2). Again, HGPIN on biopsy ($P = .004$; OR = 2.677) was the only independent predictor on multivariate analysis (Table 2).

EPE was present in 132 (11.9%) patients, and of these there were 20 (15.2%) cases with contralateral EPE on final histopathology (Figure 2A, B, and C). Univariate logistic regression analysis and multivariate analysis showed that the presence of clinical stage T2 significantly raised the risk of contralateral EPE on final histopathology. Other variables including Gleason score, preoperative PSA, and HGPIN on biopsy did not improve prediction of contralateral EPE (Table 3).

We further stratified our cohort into 6 groups based on clinical staging, biopsy Gleason score, and total biopsy cores 12 or more. Of the 761 men with Gleason score ≤ 6 and unilateral cancer on biopsy, 561 (73.7%) had contralateral involvement on final pathology. On both univariate and multivariate analysis, HGPIN on biopsy significantly improved the prediction of contralateral lobe involvement on RP specimens. There were 353 men with biopsy Gleason ≥ 7 , and 279 (79%) of these men actually had contralateral involvement. Univariate analysis determined the only significant variable to be clinical stage T2. However, on multivariate analysis it

Table 1. Preoperative Variables, Baseline Demographics, Systemic Biopsy, and Pathologic Data of the Cohort

Variable	Number of Patients (N = 1114)
Age (median, IQR)	60 (55, 65)
BMI (median, IQR)	26.40 (24.4, 29)
Preoperative PSA (median, IQR)	4.65 (3.6, 6.4)
Prostate volume (median, IQR)	47.85 (39, 61.6)
Clinical stage (%)	
T1	999 (89.7)
T2	115 (10.3)
Total number of biopsy cores (median, IQR), n = 1048	12 (10, 14)
≤ 6 (%)	106 (10.1)
7-11 (%)	207 (19.8)
≥ 12 (%)	735 (70.1)
Total number of positive cores (median, IQR)	1 (1, 3)
1 (%)	564 (50.6)
2 (%)	236 (21.2)
3 (%)	132 (11.8)
4 (%)	86 (7.7)
5 (%)	51 (4.6)
≥ 6 (%)	45 (4)
Biopsy Gleason (%)	
6 or less	761 (68.3)
7 or more	353 (31.7)
Biopsy HGPIN (%)	
Present	137 (12.3)
Absent	977 (87.7)
Biopsy PNI (%)	
Present	18 (1.6)
Absent	1096 (98.4)
Pathology Gleason (%)	
6 or less	445 (40)
7 or more	669 (60)
Pathology stage (%)	
T2	980 (87.9)
T3	134 (12.1)
Overall positive surgical margin (%)	79 (7.1)

Abbreviations: IQR, interquartile range; BMI, body mass index; HGPIN, high-grade prostatic intraepithelial neoplasm; PNI, perineural invasion.

was clinical stage T2 as well as number of biopsy cores 12 or more that showed notable association with increased risk of contralateral disease on final pathology (Table 4).

There were 999 men with clinical stage T1 and 115 men with stage T2; of these, bilateral disease was found in 524 (52.5%) and 83 (72.2%) patients, respectively. Biopsy Gleason ≥ 7 and HGPIN on biopsy were significant predictors of contralateral lobe involvement in patients with clinical

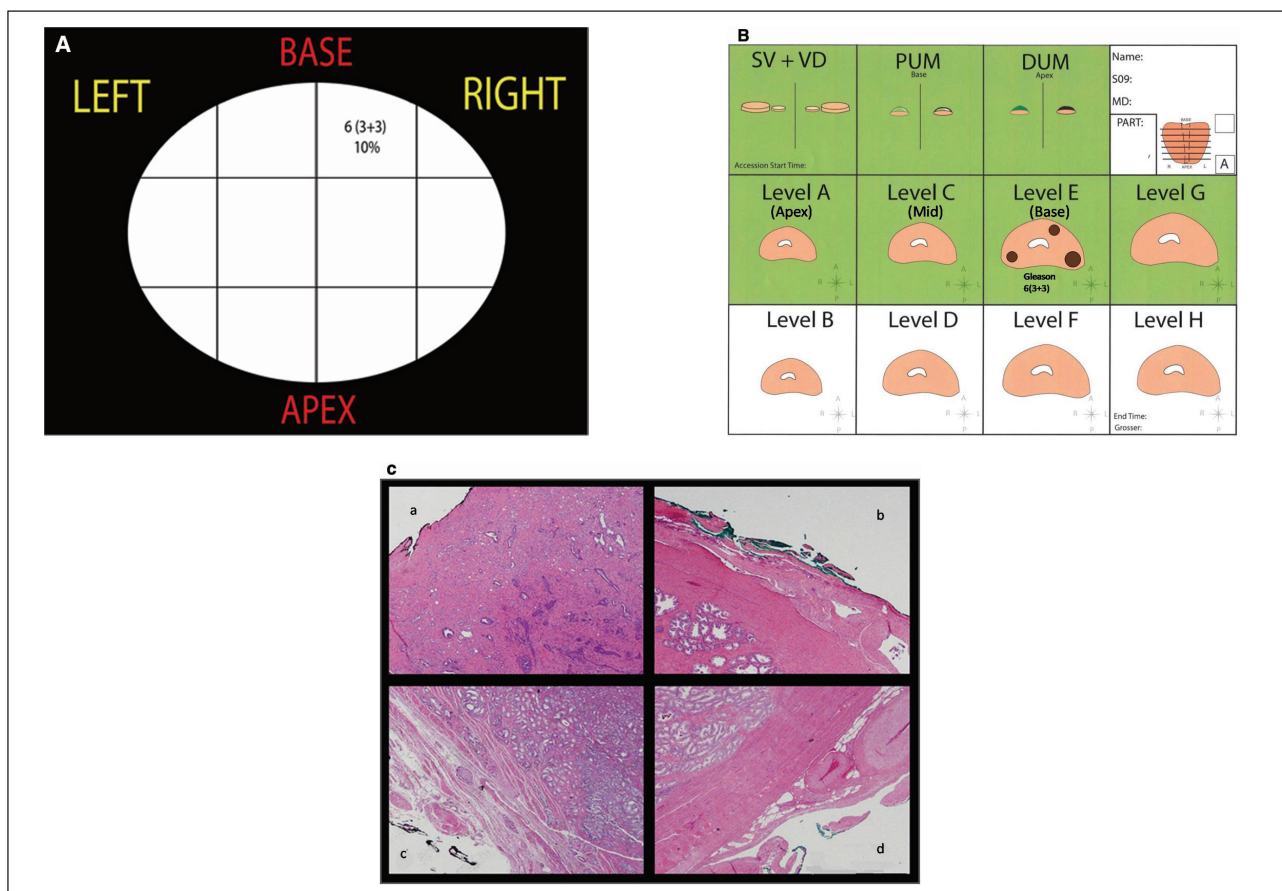


Figure 1. A, Twelve-core biopsy map showing right-sided tumor with Gleason score 6 (3 + 3). B, Postoperative visual histopathology maps showing both right and left prostate lobe involvement at the base. C, Final histopathology at the level of base showing the left anterior (a), left posterior (c), right posterior (d) tumor involvement. No tumor is present in the right anterior (b) quadrant

Table 2. Univariate and Multivariate Analysis of Clinicopathological Characteristics of the Whole Cohort for Predicting Contralateral Lobe Involvement of the Cancer on Final Histopathology

Variables	B	P	Exp(B)	95% CI
Univariate analysis				
Age	-0.004	.708	0.996	0.977-1.016
BMI	0.015	.425	1.015	0.979-1.052
Preoperative PSA(log)	0.385	.193	1.469	0.193-1.469
Total no. of positive cores on biopsy		.287	1.054	0.287-1.054
Maximum percentage of cancer on biopsy	0.002	.583	1.002	0.583-1.002
Clinical stage T1 (categorical)		Reference		
Clinical stage T2	0.339	.138	0.713	0.138-0.713
No. of biopsy cores ≤6 (categorical)		Reference		
No. of biopsy cores 7-11	0.202	.422	1.224	0.422-1.224
No. of biopsy cores ≥12	-0.071	.781	0.932	0.781-0.932
Total Gleason on biopsy ≤6		Reference		
Total Gleason on biopsy ≥7	0.155	.327	1.167	0.327-1.167
HGPIN on biopsy*	0.583	.02	1.791	0.020-1.791
PIN on biopsy	0.851	.251	2.342	0.251-2.342
Prostate volume (log)	-0.253	.560	0.776	0.560-0.776
Multivariate analysis^a				
HGPIN on biopsy*	0.985	.004	2.677	1.358-5.276

Abbreviations: CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen; HGPIN, high-grade prostatic intraepithelial neoplasm; PINI, perineural invasion.

^aMultivariate model obtained using Backward Wald elimination model.

*Significant P value.

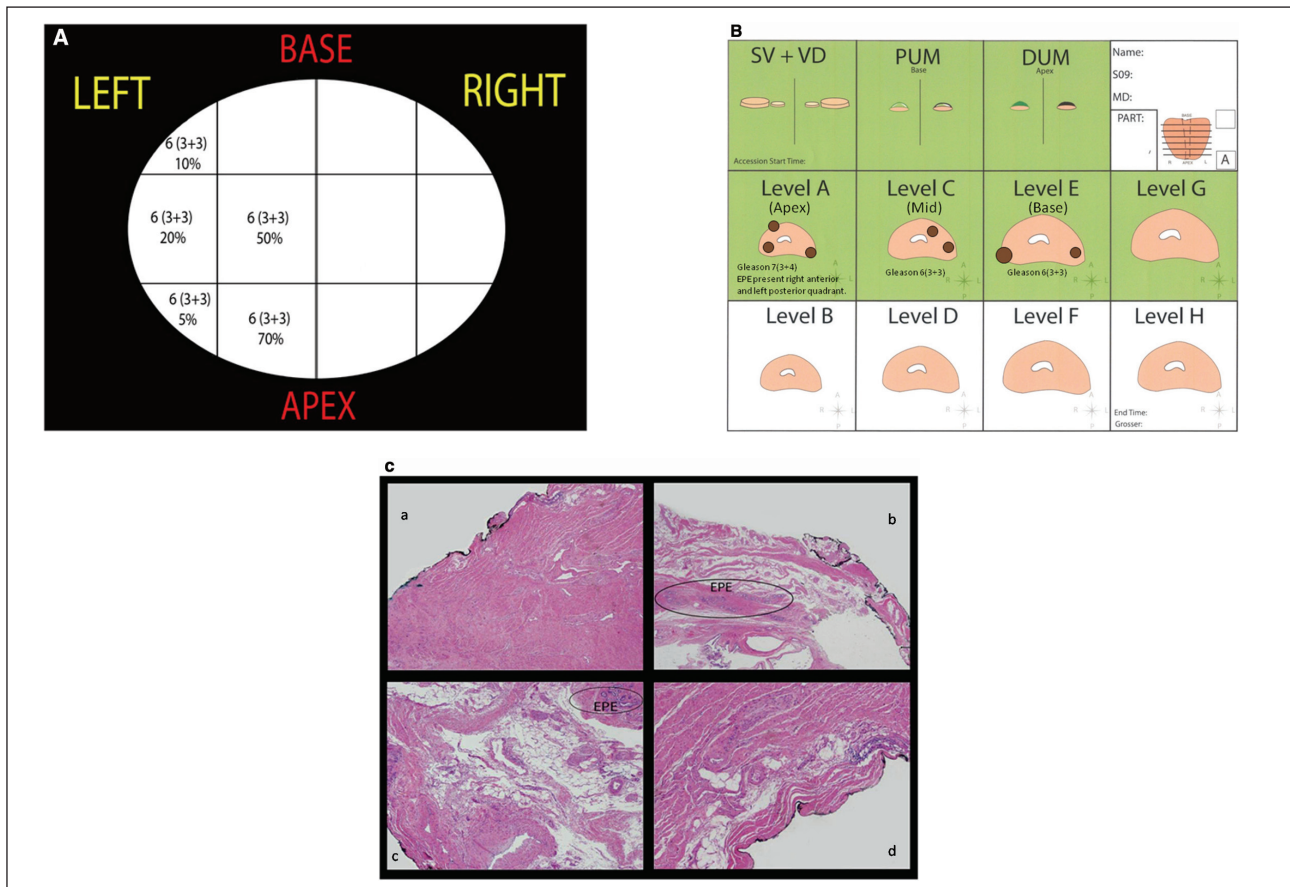


Figure 2. A, Twelve-core biopsy map showing left-sided tumor with Gleason score 6 (3 + 3). B, Postoperative visual histopathology maps showing both right and left prostate lobe involvement at the apex and base. C, Final histopathology at the level of apex showing EPE in left posterior (c) and right anterior (b) quadrants. No EPE is seen in left anterior (a) and right posterior (d) quadrants

Table 3. Univariate and Multivariate Analysis for Predicting Contralateral EPE on Final Histopathology

Variables	B	P	Exp(B)	95% CI
Univariate analysis				
Age	0.012	.755	1.012	0.940-1.88
BMI	-0.012	.858	0.989	0.871-1.122
Preoperative PSA(log)	0.083	.058	1.087	0.997-1.185
Total no. of positive cores on biopsy	-0.057	.687	0.945	0.716-1.247
Maximum percentage of cancer on biopsy	-0.004	.687	0.996	0.979-1.014
Clinical stage T1		Reference		
Clinical stage T2*	1.658	.012	5.250	1.442-19.110
No. of biopsy cores ≤6 (categorical)		Reference		
No. of biopsy cores 7-11	-0.076	.931	0.926	0.163-5.251
No. of biopsy cores ≥12	-0.174	.850	0.840	0.138-5.115
Total Gleason on biopsy ≤6		Reference		
Total Gleason on biopsy ≥7	-0.228	.670	0.796	0.278-2.278
HGPIN on biopsy	-1.031	.343	.357	0.042-2.999
PNI on biopsy	1.329	.199	3.778	0.497-28.697
Prostate volume (log)	0.009	.438	1.009	0.986-1.033
Multivariate analysis^a				
Clinical stage T2*	2.158	.007	8.656	1.803-41.563

Abbreviations: EPE, extraprostatic extension; CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen; HGPIN, high-grade prostatic intraepithelial neoplasm; PNI, perineural invasion.

^aMultivariate model obtained using Backward Wald elimination model.

*Significant P value.

Table 4. Univariate and Multivariate Analysis Showing the Significant Predictors of Contralateral Lobe Involvement in Different Subdivisions of the Cohort

Cohort Subdivision	Significant Predictors	B	P	Exp(B)	95.5% CI
Univariate analysis					
Clinical stage T1	1. Biopsy Gleason ≥ 7	0.486	.032	1.626	1.043-2.533
	2. Biopsy HGPIN	0.949	.009	2.584	1.262-5.291
Clinical stage T2	None	—	—	—	—
	Biopsy Gleason ≤ 6	1. Biopsy HGPIN	0.631	.041	1.879
Biopsy Gleason ≥ 7	1. Clinical stage T2	-0.962	.005	0.382	0.195-0.751
Multivariate analysis ^a					
Clinical stage T1	1. Biopsy Gleason ≥ 7	0.513	.028	1.670	1.058-2.634
	2. Biopsy HGPIN	0.958	.013	2.606	1.219-5.569
Clinical Stage T2	None	—	—	—	—
	Biopsy Gleason ≤ 6	1. Biopsy HGPIN	0.775	.050	2.170
Biopsy Gleason ≥ 7	1. Clinical stage T2	-0.870	.018	0.419	0.204-0.859
	2. Number of biopsy cores ≥ 12	1.428	.011	4.168	1.393-12.470

Abbreviations: CI, confidence interval; HGPIN, high-grade prostatic intraepithelial neoplasm.

^aMultivariate model obtained using Backward Wald elimination model.

stage T1 on both univariate and multivariate analyses. None of the clinicopathological variables were associated with contralateral lobe involvement on final pathology in patients with T2 cancers on both univariate and multivariate analyses (Table 4).

On analysis of 728 patients with clinical stage T1 and Gleason 6, we found that 555/728 (76.2%) patients had involvement of the contralateral lobe. On univariate analysis number of biopsy cores ≥ 12 showed significant association with increased risk of contralateral lobe involvement on final pathology. On multivariate analysis none of the clinical or pathological variables were significantly associated with involvement of the contralateral lobe (Table 5).

Furthermore, we analyzed 735 men who had ≥ 12 biopsy cores taken (the current accepted standard of diagnostic care) and found that 560 (76.1%) men had contralateral lobe involvement. On univariate analysis clinical stage T2 and Gleason score 7 were significant predictors of contralateral lobe involvement. On multivariate analysis clinical stage T2 and HGPIN on biopsy showed significant association with contralateral lobe involvement (Table 6).

Discussion

Focal therapy has recently emerged as an attractive alternative management option for localized cancer. Despite the increasing interest, the selection criteria for focal therapy still remain controversial. We evaluated the ability of standard diagnostic prostatic biopsy to accurately predict the laterality of tumor and contralateral EPE. We found 77.9% of patients with biopsy-proven unilateral cancer had contralateral disease. Contralateral EPE was found in 1.8% cases, which were previously reported to have unilateral

Table 5. Univariate and Multivariate Analysis for Predicting Contralateral Lobe Involvement in Men With T1 Clinical Stage and Gleason Score 6 on Biopsy

Variable	P	Exp(B)	B	95% CI
Univariate analysis				
Age	.182	0.975	-0.025	0.940-1.012
BMI	.221	0.960	-0.040	0.900-1.025
Preoperative PSA	.774	0.851	-0.161	0.282-2.566
No. of biopsy <6	.136	2.143	0.762	0.787-5.837
No. of biopsy 7-12	.142	1.461	0.379	0.880-2.423
No. of biopsy >12*	.030	0.560	-0.580	0.331-0.947
Total positive cores	.238	1.253	0.226	0.861-1.824
Max% of cancer	.231	1.014	0.013	0.992-1.036
Prostate volume	.361	0.522	-0.651	0.129-2.108
HGPIN	.162	1.940	0.663	0.766-4.912
PNI	.557	0.434	-0.834	0.027-7.025
Multivariate analysis				
None				

Abbreviations: CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen; HGPIN, high-grade prostatic intraepithelial neoplasm; PNI, perineural invasion.

^aMultivariate model obtained using Backward Wald elimination model.

*Significant P value.

tumor on preoperative biopsy. HGPIN on biopsy was the single most important predictor of contralateral involvement on final pathology. We also found that increasing the number of biopsy cores improves the prediction of tumor laterality in patients with biopsy Gleason ≥ 7 or in patients with clinical stage T1 and biopsy Gleason ≤ 6 . In particular, men with palpable tumor on digital rectal exam have a higher likelihood of harboring more aggressive tumors with sometimes extension of cancer beyond the prostate on the contralateral side (contralateral EPE). Therefore, all these preoperative

Table 6. Univariate and Multivariate Analysis for Predicting Contralateral Lobe Involvement in Men Who Had ≥ 12 Core Biopsy

Variables	B	P	Exp(B)	95% CI
Univariate analysis				
Age	0.007	.570	1.007	0.983-1.032
BMI	-0.026	.242	0.974	0.932-1.018
Preoperative PSA(log)	0.583	.093	1.792	0.908-3.538
Clinical stage T1		Reference		
Clinical stage T2*	0.783	.026	2.188	1.100-4.353
Total no. of positive cores on biopsy	0.111	.057	1.117	0.997-1.252
Maximum percentage of cancer on biopsy	0.005	.168	1.006	0.998-1.013
Total Gleason on biopsy ≤ 6		Reference		
Total Gleason on biopsy $\geq 7^*$	0.464	.018	1.591	1.084-2.336
HGPIN on biopsy	0.511	.069	1.666	0.961-2.890
PNI on biopsy	0.429	.582	1.536	0.333-7.081
Prostate volume (log)	-0.536	.322	0.585	0.203-1.688
Multivariate analysis				
Clinical stage T2*	0.851	.016	2.342	1.170-4.688
HGPIN on biopsy*	0.592	.020	1.808	1.036-3.155

Abbreviations: CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen; HGPIN, high-grade prostatic intraepithelial neoplasm; PNI, perineural invasion.

*Multivariate model obtained using Backward Wald elimination model.

*Significant P value.

variables should be taken into consideration, especially if opting for treatments other than RP.

Most clinicians would advocate low-risk parameters such as PSA < 10 , Gleason grade ≤ 6 , and clinical stage $\leq T2b$ as the best fit for focal therapy. However, insufficient correlation between biopsy and final histopathology has been shown in many studies.⁷⁻¹¹ Prostate cancer tends to be multifocal,^{12,13} a fact that makes selection for focal therapy challenging. Wise et al¹⁴ found that 83% of the prostate cancers have more than one focus. Apart from the index focus they found that on an average there were 2.9 nonindex foci of the cancer. In another series, Li et al¹⁵ found that the majority of small-volume prostate cancer are multifocal and often involve both sides of the prostate. In a comprehensive review Meiers et al¹⁶ reported multifocal prostate cancer in 67% to 80% of RP specimens.

Focal therapy may be appropriate for unilateral multifocal disease, which is confined to one side of the prostate but not for bilateral disease. Here again the accurate prediction of laterality on biopsy is questionable. Mouraviev et al¹⁷ studied 1186 RP specimens from patients with clinically localized cancer to establish the relation between biopsy and final pathology with regard to laterality of cancer and found that biopsy predicted unilateral cancers accurately in only 19.2% cases. Frota et al,¹⁸ from the Cleveland Clinic, studied the accuracy of preoperative biopsy in predicting the laterality of significant cancer. They reported only minor agreement between biopsy laterality and laterality on final pathology ($\kappa = .135$).¹⁸ Yoon et al¹⁹ evaluated 100 patients with unilateral disease on biopsy and found that 65% had contralateral lobe involvement on RP histology and 23% had a greater

tumor bulk on the contralateral side than on the biopsy-positive side. In our own series reported herein, 76% of men with T1 cancer and Gleason 6 on biopsy had contralateral lobe involvement on RP histology, and thus from our data as well as the other investigators' data quoted above, even low-risk disease on biopsy has a high likelihood of contralateral lobe involvement, making the rationale for focal therapy in these patients questionable.

Our findings that HGPIN on biopsy is associated with a worse prognosis and increased risk of contralateral disease is also well supported by the previously documented correlations between biopsy HGPIN and cancer outcomes. Qian et al²⁰ found a positive correlation between total volume of biopsy HGPIN with volume of cancer, pathological stage, and tumor grade. Tewari et al²¹ studied the racial differences between PSA doubling time and PSA recurrence and found that presence of biopsy HGPIN is independently associated with PSA recurrence irrespective of race. Recently, Pierorazio and colleagues,²² from Columbia University, studied 2133 RP specimens with HGPIN on biopsy and found presence of HGPIN on biopsy was associated with high-grade tumor, multifocality, PNI, and biochemical recurrence. In our study, HGPIN on biopsy was reported by our study pathologist (MS). However, one of the limitations of this study is that no mention of which core was affected, what percentage of the core(s) was affected, how many cores were involved, and whether the HGPIN was on the same side as the positive RP histology was mentioned. Indeed, many pathologists do not even report HGPIN on biopsy, especially if that core contains cancer. We thus do not know what the relationship is between location or volume of HGPIN on biopsy and

cancer on the RP specimen. This would be worth investigating in a future study, and we would recommend that all pathologists report HGPIN on biopsy whenever present.

In our study, the number of biopsy cores taken varied as the biopsies were not performed at a single institution. It is well accepted that the more biopsies that are taken the greater the likelihood of accurate diagnosis, with 12 or more cores being the current gold standard.²³ Hence, one of the weaknesses of our study, as with many tertiary referral practices, is that many of our patients had fewer than 12 cores taken at biopsy. Hence, we did a subgroup analysis on our cohort of 735 patients who had ≥ 12 cores taken at biopsy and found that more than three quarters had contralateral lobe involvement and that HGPIN was still a significant predictor for this. Hence, we do not believe our results are skewed by the fact that some patients did not have 12-core biopsies. Furthermore, given that our patient cohort had biopsies taken and reported on elsewhere in the main, all biopsy slides were reanalyzed by our study uropathologist (MS) in order to avoid interobserver variability. To this end, the same uropathologist analyzed all the RP specimen histologies as well.

Conclusion

We found, consistent with others, poor correlation between biopsy and final histopathology. The accuracy of biopsy in predicting tumor laterality is also questionable. Biopsy HGPIN was the only significant predictor of contralateral disease regardless of Gleason score, thus these patients should be investigated further before making management decisions regarding focal therapy. Patients with palpable tumor on digital rectal examination should be advised in favor of radical treatment as these patients may harbor more aggressive tumors involving the contralateral side despite the biopsy findings. We conclude that biopsy is an insufficient representation of tumor grade and extent of tumor involvement and cannot be considered fully representative of tumor pathology when making management decisions. This remains the case even when the current standard of care of ≥ 12 cores is taken. These considerations have significant implications in counseling patients toward focal/hemiablative therapies for apparently low-risk prostate cancer.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

Dr. Ashutosh Tewari discloses that he has received research grants from Intuitive Surgical and the Prostate Cancer Foundation; he is also the endowed Ronald P. Lynch Professor of Urologic Oncology and Director of the Lefrak Institute of Robotic Surgery, Weill Cornell Medical College.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin.* 2008;58:71-96.
2. SEER Cancer Statistics Review 1975-2006. http://seer.cancer.gov/statfacts/html/prost.html?statfacts_page=prost.html&x=13&y=16. Retrieved July 26, 2010.
3. Smither AR, Guralnick ML, Davis NB, See WA. Quantifying the natural history of post-radical prostatectomy incontinence using objective pad test data. *BMC Urol.* 2007;7:2.
4. Mettlin CJ, Murphy GP, Sylvester J, McKee RF, Morrow M, Winchester DP. Results of hospital cancer registry surveys by the American College of Surgeons: outcomes of prostate cancer treatment by radical prostatectomy. *Cancer.* 1997;80:1875-1881.
5. Jayram G, Eggner SE. Patient selection for focal therapy of localized prostate cancer. *Curr Opin Urol.* 2009;19:268-273.
6. Polascik TJ, Mayes JM, Schroeck FR, et al. Patient selection for hemiablativ focal therapy of prostate cancer: variables predictive of tumor unilaterality based upon radical prostatectomy. *Cancer.* 2009;115:2104-2110.
7. Fukagai T, Namiki T, Namiki H, Carlile RG, Shimada M, Yoshida H. Discrepancies between Gleason scores of needle biopsy and radical prostatectomy specimens. *Pathol Int.* 2001;51:364-370.
8. Altay B, Kefi A, Nazli O, Killi R, Semerci B, Akar I. Comparison of Gleason scores from sextant prostate biopsies and radical prostatectomy specimens. *Urol Int.* 2001;67:14-18.
9. Montesino Semper M, Jimenez Aristu J, Reparaz Romero B, et al. Correlation between Gleason score on prostate biopsies diagnostic of adenocarcinoma and radical prostatectomy specimens [in Spanish]. *Arch Esp Urol.* 2004;57:519-523.
10. Arellano L, Castillo O, Metrebian E. Concordance of Gleason histological scoring for prostatic cancer in needle biopsies and the surgical piece obtained during radical prostatectomy [in Spanish]. *Rev Med Chil.* 2004;132:971-978.
11. Cookson MS, Fleshner NE, Soloway SM, Fair WR. Correlation between Gleason score of needle biopsy and radical prostatectomy specimen: accuracy and clinical implications. *J Urol.* 1997;157:559-562.
12. Moore R. The morphology of small prostatic canceromas. *J Urol.* 1935;33:224.
13. Greene DR, Rogers E, Wessels EC, et al. Some small prostate cancers are nondiploid by nuclear image analysis: correlation of deoxyribonucleic acid ploidy status and pathological features. *J Urol.* 1994;151:1301-1307.
14. Wise AM, Stamey TA, McNeal JE, Clayton JL. Morphologic and clinical significance of multifocal prostate cancers in radical prostatectomy specimens. *Urology.* 2002;60:264-269.
15. Li TY, Lu XM, Su SW, et al. Detection of EBV-DNA, EBNA2 and LMP-1 in tumor tissues of han and uygur patients with nasopharyngeal carcinoma in Xinjiang [in Chinese]. *Lin Chuang Er Bi Yan Hou Ke Za Zhi.* 2000;14:76-77.

16. Meiers I, Waters DJ, Bostwick DG. Preoperative prediction of multifocal prostate cancer and application of focal therapy: review 2007. *Urology*. 2007;70:3-8.
17. Mouraviev V, Mayes JM, Sun L, Madden JF, Moul JW, Polascik TJ. Prostate cancer laterality as a rationale of focal ablative therapy for the treatment of clinically localized prostate cancer. *Cancer*. 2007;110:906-910.
18. Frota R, Stein RJ, Turna B, et al. Are prostate needle biopsies predictive of the laterality of significant cancer and positive surgical margins? *BJU Int*. 2009;104:1599-1603.
19. Yoon GS, Wang W, Osunkoya AO, Lane Z, Partin AW, Epstein JI. Residual tumor potentially left behind after local ablation therapy in prostate adenocarcinoma. *J Urol*. 2008;179:2203-2206.
20. Qian J, Wollan P, Bostwick DG. The extent and multicentricity of high-grade prostatic intraepithelial neoplasia in clinically localized prostatic adenocarcinoma. *Hum Pathol*. 1997;28:143-148.
21. Tewari A, Horninger W, Badani KK, et al. Racial differences in serum prostate-specific antigen (PSA) doubling time, histopathological variables and long-term PSA recurrence between African-American and white American men undergoing radical prostatectomy for clinically localized prostate cancer. *BJU Int*. 2005;96:29-33.
22. Pierorazio PM, Lambert SM, Matsukhani M, et al. High-grade prostatic intraepithelial neoplasia is an independent predictor of outcome after radical prostatectomy. *BJU Int*. 2007;100:1066-1070.
23. Durkan GC, Sheikh N, Johnson P, Hildreth AJ, Greene DR. Improving prostate cancer detection with an extended-core transrectal ultrasonography-guided prostate biopsy protocol. *BJU Int*. 2002;89:33-39.