



## Prostate Cancer

# Systematic Assessment of the Ability of the Number and Percentage of Positive Biopsy Cores to Predict Pathologic Stage and Biochemical Recurrence after Radical Prostatectomy

Alberto Briganti<sup>b,1</sup>, Felix K.-H. Chun<sup>c,1</sup>, Georg C. Hutterer<sup>a,d</sup>, Andrea Gallina<sup>b</sup>, Shahrokh F. Shariat<sup>e</sup>, Andrea Salonia<sup>b</sup>, Vincenzo Scattoni<sup>b</sup>, Luc Valiquette<sup>f</sup>, Francesco Montorsi<sup>b</sup>, Patrizio Rigatti<sup>b</sup>, Markus Graefen<sup>c</sup>, Hartwig Huland<sup>c</sup>, Pierre I. Karakiewicz<sup>a,f,\*</sup>

<sup>a</sup>Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Quebec, Canada

<sup>b</sup>Department of Urology, Vita-Salute University San Raffaele, Milan, Italy

<sup>c</sup>Department of Urology, University Medical Centre Eppendorf, Hamburg, Germany

<sup>d</sup>Department of Urology, Graz Medical University, Graz, Austria

<sup>e</sup>Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA

<sup>f</sup>Department of Urology, University of Montreal, Montreal, Quebec, Canada

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### Abstract

**Objectives:** We hypothesized that the number and/or percentage of positive cores, proxies of tumor volume, could improve the ability to predict pathologic stages and/or biochemical recurrence (BCR). To test this hypothesis, we examined radical retropubic prostatectomy (RRP) data from three centers on two continents.

**Material and methods:** Clinical data from men undergoing RRP at three different institutions were used to predict pathologic stages and BCR. Univariable and multivariable logistic analyses and Cox regression analyses were used. Predictive accuracy (PA) was assessed with the area under the receiver operating characteristics curve estimates, which were subjected to 200 bootstraps to reduce overfit bias. The statistical significance of PA gains was assessed with the Mantel-Haenszel test.

**Results:** The number and the percentage of positive cores were independent predictors of virtually all pathologic stage outcomes and of BCR. In PA analyses, the percentage of positive cores improved the PA of pathologic stage predictions and of BCR predictions between 0.06% and 1.49%. Conversely, the number of positive cores improved the PA of pathologic stage predictions and of BCR predictions between 0.36% and 1.14%.

**Conclusions:** The information derived from biopsy cores is important and can improve the ability to predict pathologic stage and BCR. It appears that the percentage of cores is most helpful in stage predictions. Conversely, the number of cores appears to improve mostly BCR predictions. Consideration of both variables might not be helpful because of the similarity of information they encode.

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\* Corresponding author. Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center (CHUM), 1058, Rue St-Denis, Montreal, Quebec, Canada, H2X 3J4. Tel. +1 514 890 8000 35336; Fax: +1 514 412 7363. E-mail address: [pierre.karakiewicz@umontreal.ca](mailto:pierre.karakiewicz@umontreal.ca) (P.I. Karakiewicz).

<sup>1</sup> Both authors contributed equally to the manuscript.

## 1. Introduction

In recent years, numerous regression model-based nomograms have been introduced to predict either pathologic stage or cancer control outcome after radical prostatectomy on the basis of pretreatment tumor characteristics [1-9]. Because of their inability to perfectly predict the targeted outcome, the search for additional predictors continues.

Recent studies suggest that the amount of cancer and high-grade cancer in diagnostic systematic biopsies of the prostate may improve the accuracy of predictive and prognostic models [6,7,10-14]. The predictive ability of these two variables defined by the number and the percentage of positive cores has been suggested by some investigators [4-20], but was also refuted by others [15,21,22]. The reason for this discrepancy stems from the fact that no study compared the predictive accuracy (PA) of these two variables in a head-to-head fashion. Similarly, no previous single study assessed the effect of these two variables on several simultaneous outcomes, such as their effect on all pathologic stages, as well as on the rate of biochemical recurrence (BCR). Therefore, it is difficult to reconcile some of the conflicting results of these reports [6-20].

To address this issue, we performed a systematic and comprehensive analysis of the ability of either the number of positive cores or the percentage of positive cores to predict the pathologic stage and the rate of BCR. Our study spanned a period of over a decade, during which time the biopsy schemes drastically changed. This is reflected by a wide range of the number of biopsy cores that were obtained (2-36). Detailed information about the distribution of the number of biopsy cores taken are shown in Table 1.

## 2. Material and methods

Table 2 shows patient characteristics of each cohort enrolled. Patients with pretreatment prostate specific antigen (pPSA) values >50 ng/mL were excluded. All preoperative biopsies were performed under transrectal ultrasound guidance. PSA failures were defined as a value of  $\geq 0.1$  ng/ml and rising. None of the patients received neoadjuvant therapy or adjuvant treatment before evidence of recurrence. Patients without biochemical failure were censored at the date of last available pPSA value.

We focused on prediction of six different end points: organ confinement (OC), extracapsular extension (ECE), seminal vesicle invasion (SVI), lymph node invasion (LNI), the rate of BCR predicted with clinical variables, as well as the rate of BCR predicted with pPSA and pathologic variables. The prediction of BCR with clinical variables henceforth will be referred to as preoperative prediction of BCR. Conversely, the prediction of BCR with pPSA and pathologic variables henceforth will be referred to as postoperative prediction of BCR. Each end point was addressed in a separate analysis. Since the number of missing fields varied from one analysis to another, six different cohorts were developed. These ranged in size from 1783 to 3374 patients. Details about the exclusion of patients because of missing data are shown in Table 3. All patients were treated with radical retropubic prostatectomy (RRP) for  $cT_{any}N_0M_0$  prostate cancer at two European and one North American institution between January 1992 and July 2005.

In all six models, the main predictors of interest consisted of the number and the percentage of positive biopsy cores. The percentage of positive cores was defined as the sum of all cores that contained invasive cancer divided by the sum of all cores that were taken. The contribution of these variables to multivariable (MVA) models represented the focal point of all analyses. Statistical tests were performed with S-PLUS Professional, version 1. Two-sided tests with significance at 0.05 were used. Logistic regression models tested the added value of the variables of interest to pPSA, clinical stage, and biopsy Gleason sum, and were complemented with models

**Table 1 – Distribution of the number of biopsy cores taken according to different cohorts**

Variable	OC	ECE	SVI	LNI	BCR predicted with clinical variables	BCR predicted with pPSA and pathologic variables
Total no. of cores taken						
Mean (median)	8.4 (7.0)	8.4 (7.0)	8.4 (7.0)	8.4 (7.0)	7.4 (6.0)	7.4 (6.0)
Range	2.0-36.0	2.0-36.0	2.0-36.0	2.0-36.0	4.0-24.0	4.0-24.0
2-5	52 (1.6%)	52 (1.5%)	52 (1.6%)	52 (1.5%)	1 (0.1%)	1 (0.1%)
6-8	2090 (62.3%)	2095 (62.2%)	2071 (62.2%)	2097 (62.2%)	1361 (76.3%)	1365 (75.0%)
9-36	1211 (36.1%)	1220 (36.3%)	1203 (36.2%)	1225 (36.3%)	421 (23.6%)	454 (24.9%)
Total no. of patients included	3353 (100%)	3367 (100%)	3326 (100%)	3374 (100%)	1783 (100%)	1820 (100%)

OC = organ confinement; ECE = extracapsular extension; SVI = seminal vesicle invasion; LNI = lymph node invasion; BCR = biochemical recurrence; pPSA = pretreatment prostate-specific antigen.

BCR predicted with clinical variables. Predictors in the base model included pPSA, clinical stage, biopsy Gleason sum and either number or percentage of positive cores or both.

BCR predicted with pPSA and pathologic variables. Predictors in the base model included pPSA, ECE, SVI, LNI, surgical margin status (SM), pathologic Gleason sum.

**Table 2 – Patient characteristics and descriptive statistics**

Variable	OC	ECE	SVI	LNI	BCR predicted with clinical variables	BCR predicted with pPSA and pathologic variables
<b>pPSA</b>						
Mean (median)	8.9 (6.8)	8.9 (6.8)	8.8 (6.8)	8.9 (6.8)	9.4 (7.2)	9.3 (7.2)
Range	0.1–50.0	0.1–50.0	0.1–50.0	0.1–50.0	0.1–50.0	0.1–50.0
<b>Clinical stage</b>						
T1c	2163 (64.5%)	2169 (64.4%)	2156 (64.8%)	2174 (64.4%)	1097 (61.5%)	
T2	1152 (34.4%)	1159 (34.4%)	1138 (34.2%)	1160 (34.4%)	663 (37.2%)	
T3	38 (1.1%)	39 (1.2%)	32 (1.0%)	40 (1.2%)	23 (1.3%)	
<b>Biopsy Gleason sum</b>						
2–5	241 (7.2%)	241 (7.2%)	241 (7.2%)	243 (7.2%)	69 (3.9%)	
6	1942 (57.9%)	1944 (57.7%)	1938 (58.3%)	1946 (57.7%)	1044 (58.5%)	
7	1026 (30.6%)	1037 (30.8%)	1007 (30.3%)	1038 (30.8%)	602 (33.8%)	
8–10	144 (4.3%)	145 (4.3%)	140 (4.2%)	147 (4.4%)	68 (3.8%)	
<b>Total no. of cores taken</b>						
Mean (median)	8.4 (7.0)	8.4 (7.0)	8.4 (7.0)	8.4 (7.0)	7.4 (6.0)	7.4 (6.0)
Range	2.0–36.0	2.0–36.0	2.0–36.0	2.0–36.0	4.0–24.0	4.0–24.0
<b>No. of positive cores</b>						
Mean (median)	2.9 (2.0)	2.8 (2.0)	2.8 (2.0)	2.9 (2.0)	2.6 (2.0)	2.6 (2.0)
Range	1.0–19.0	1.0–19.0	1.0–19.0	1.0–19.0	1.0–8.0	1.0–8.0
<b>Percentage of positive cores</b>						
Mean (median)	36.2 (33.4)	36.2 (33.4)	36.0 (33.4)	36.2 (33.4)	37.3 (33.4)	36.5 (33.4)
Range	2.8–100.0	2.8–100.0	2.8–100.0	2.8–100.0	4.2–100.0	4.2–100.0
Organ-confined status	2285 (68.1%)					
Presence of ECE		731 (21.7%)				401 (22.0%)
Presence of SVI			351 (10.6%)			230 (12.6%)
Presence of LNI				132 (3.9%)		63 (3.5%)
Positive surgical margin						385 (21.2%)
<b>Pathologic Gleason sum</b>						
2–5						192 (10.6%)
6						600 (33.0%)
7						993 (54.6%)
8–10						35 (1.9%)
BCR predicted with clinical variables					365 (20.5%)	
BCR time (yr)						
Mean (median)					Not reached (7.9)	
Range					0.01–10.8	
BCR predicted with pPSA and pathologic variables						369 (20.3%)
BCR time (yr)						
Mean (median)						Not reached (7.9)
Range						0.01–10.8
Total no. of patients included	3353 (100%)	3367 (100%)	3326 (100%)	3374 (100%)	1783 (100%)	1820 (100%)

OC = organ confinement; ECE = extracapsular extension; SVI = seminal vesicle invasion; LNI = lymph node invasion; pPSA = pretreatment prostate-specific antigen; BCR (biochemical recurrence) predicted with clinical variables. Predictors included in the base model: pPSA, clinical stage, biopsy Gleason sum, and either the number or percentage of positive cores or both.

BCR predicted with pPSA and pathologic variables. Predictors in the base model included pPSA, ECE, SVI, LNI, surgical margin status (SM), pathologic Gleason sum.

consisting of pPSA, clinical stage, and biopsy Gleason sum, in prediction of pathologic stages at RRP: OC, ECE, SVI, and LNI.

Cox regression models relying on pPSA, clinical stage, and biopsy Gleason sum were used for preoperative prediction of BCR. Conversely, logistic regression models relying on pPSA, clinical stage, and biopsy Gleason sum were used for

postoperative prediction of BCR. PA of the MVA models was assessed by calculation of the area under the receiver operating characteristics curve (AUC). We used 200 resamples to reduce overfit bias and to internally validate the MVA estimate of PA. In Cox regression models, the AUC was substituted with Harrell's concordance index. A value of 100%

**Table 3 – Description of the exclusion of patients in the different cohorts because of missing data**

		OC	ECE	SVI
Original data set (no. of patients)		5921	5921	5921
Exclusions because of missing data	OC	97	—	—
	No. of positive cores	2288	2328	2257
	No. of total cores	1	1	1
	pPSA	70	72	68
	Clinical stage	27	27	26
	Biopsy Gleason sum	85	87	84
	ECE SVI	— —	39 —	— 159
Total no. of patients		3353 (100%)	3367 (100%)	3326 (100%)
		LNI	BCR predicted with clinical variables	BCR predicted with pPSA and pathologic variables
Original data set (no. of patients)		5921	5921	5921
Exclusions because of missing data	OC	—	—	—
	No. of positive cores	2330	1174	1174
	No. of total cores	1	—	—
	pPSA	72	51	53
	Clinical stage	29	16	—
	Biopsy Gleason sum	86	45	—
	ECE	—	—	2
	SVI	—	—	17
	LNI	29	—	—
	Event of BCR	—	946	946
	Time to BCR	—	1906	1906
	SM	—	—	1
	% of positive cores >100	—	—	2
Total no. of patients		3374 (100%)	1783 (100%)	1820 (100%)
<p>OC = organ confinement; ECE = extracapsular extension; SVI = seminal vesicle invasion; LNI = lymph node invasion; BCR = biochemical recurrence; pPSA = pretreatment prostate-specific antigen; SM = surgical margin status.</p> <p>BCR predicted with clinical variables. Predictors in the base model included pPSA, clinical stage, biopsy Gleason sum, and either number or percentage of positive cores or both.</p> <p>BCR predicted with pPSA and pathologic variables. Predictors in the base model included pPSA, ECE, SVI, LNI, surgical margin status (SM), and pathologic Gleason sum.</p>				

indicates perfect predictions, while 50% is equivalent to a toss of a coin. The statistical significance of the increment in PA related to the addition of the variable(s) of interest was tested with the Mantel-Haenszel test.

### 3. Results

The descriptive variables of the six cohorts are shown in Table 2. Of all patients, 2285 of 3353 (68.1%) had OC, 731 of 3367 (21.7%) had ECE, 351 of 3326 (10.6%) had SVI, and 132 of 3374 (3.9%) had LNI. Mean pPSA ranged from 8.8 to 9.4 (0.1–50.0) ng/ml. Clinical stage distribution was T1c in 61.5–64.8%, T2 in 34.2–37.2%, and T3 in 1.0–1.3% of the patients, according to the end point being analyzed. Biopsy Gleason sum of 2–5 was found in 3.9–7.2%, 6 in 57.7–58.3%, 7 in 30.3–33.8%, and 8–10 in 3.8–4.3% of the patients.

The biopsy core information was distributed as follows. The mean number of total cores taken ranged from 7.4 to 8.4 (2–36), and the mean number

of positive cores ranged from 2.6 to 2.9 (1.9), while the mean percentage of positive cores ranged from 36.0% to 37.3% (2.8–100%). BCR was diagnosed in 365 of 1783 (20.5%) patients included in the cohort who were used for the preoperative prediction of BCR (median follow-up: 7.9 yr), and in 369 of 1820 (20.3%) patients included in the cohort who were used for postoperative prediction of BCR (median follow-up: 7.9 yr). Pretreatment PSA, clinical stage, and biopsy Gleason sum (base model) were independent predictors of pathologic stages ( $p < 0.001$ ). Moreover, when the base variables were complemented with either the number (base model + number of positive cores) or the percentage of positive cores (base model + percentage of positive cores) or with both (base model + number and percentage of positive cores), they maintained independent predictor status in all pathologic stage predictions ( $p \leq 0.001$ ).

In MVA analyses, when the variable that defined the number of positive biopsy cores was added to the

**Table 4 – Univariable and multivariable models predicting organ confinement (OC) and extracapsular extension (ECE) with corresponding predictive accuracies (PAs)**

Predictor	OC						ECE					
	Univariable		Multivariable				Univariable		Multivariable			
	OR; p value	PA (%)	Base model*	Base model + no. of positive cores	Base model + % of positive cores	Base model + no. and % of positive cores	OR; p value	PA (%)	Base model	Base model + no. of positive cores	Base model + % of positive cores	Base model + no. and % of positive cores
			OR; p value	OR; p value	OR; p value	OR; p value			OR; p value	OR; p value	OR; p value	
pPSA	0.9; <0.001	<b>66.5</b>	0.9; <0.001	0.9; <0.001	0.9; <0.001	0.9; <0.001	1.0; <0.001	<b>59.8</b>	1.0; <0.001	1.0; <0.001	1.0; 0.001	1.0; <0.001
Clinical stage	—; <0.001	<b>64.9</b>	—; <0.001	—; <0.001	—; <0.001	—; <0.001	—; <0.001	<b>61.2</b>	—; <0.001	—; <0.001	—; <0.001	—; <0.001
T2 vs. T1c	0.3; <0.001		0.4; <0.001	0.4; <0.001	0.4; <0.001	0.4; <0.001	2.6; <0.001		2.2; <0.001	2.2; <0.001	2.1; <0.001	2.0; <0.001
T3 vs. T1c	0.04; <0.001		0.1; <0.001	0.1; <0.001	0.1; <0.001	0.2; <0.001	3.4; <0.001		1.8; 0.09	1.8; 0.1	1.6; 0.2	1.5; 0.2
Biopsy Gleason sum	—; <0.001	<b>67.5</b>	—; <0.001	—; <0.001	—; <0.001	—; <0.001	—; <0.001	<b>61.1</b>	—; <0.001	—; <0.001	—; <0.001	—; <0.001
6 vs. 2–5	0.9; 0.5		0.8; 0.3	0.8; 0.2	0.9; 0.4	0.9; 0.6	1.2; 0.4		1.2; 0.3	1.2; 0.3	1.2; 0.4	1.1; 0.5
7 vs. 2–5	0.2; <0.001		0.3; <0.001	0.3; <0.001	0.3; <0.001	0.3; <0.001	2.8; <0.001		2.4; <0.001	2.3; <0.001	2.1; <0.001	2.1; <0.001
8–10 vs. 2–5	0.1; <0.001		0.2; <0.001	0.2; <0.001	0.2; <0.001	0.2; <0.001	3.7; <0.001		2.8; <0.001	2.7; <0.001	2.5; <0.001	2.4; 0.001
No. of positive cores	0.8; <0.001	<b>64.4</b>		0.9; <0.001		1.1; 0.009	1.1; <0.001	<b>59.0</b>		1.0; 0.2		0.9; 0.02
Percentage of positive cores	1.0; <0.001	<b>67.5</b>			1.0; <0.001	1.0; <0.001	1.0; <0.001	<b>61.8</b>			1.0; <0.001	1.0; <0.001
Multivariable PA (%)			<b>76.5</b>	<b>77.0</b>	<b>77.9</b>	<b>77.9</b>			<b>67.9</b>	<b>68.3</b>	<b>68.7</b>	<b>68.9</b>
PA gain relative to base model (%)				+0.5%	+1.4%	+1.4%				+0.4%	+0.8%	+1.0%

OR = odds ratio; pPSA = pretreatment prostate-specific antigen.  
 \* Predictors in base model included pPSA, clinical stage, biopsy Gleason sum.

**Table 5 – Univariable and multivariable models predicting seminal vesicle invasion (SVI) and lymph node invasion (LNI) with corresponding predictive accuracies (PAs)**

Predictors	SVI						LNI					
	Univariable		Multivariable				Univariable		Multivariable			
	OR; p value	PA (%)	Base model <sup>*</sup>	Base model + no. of positive cores	Base model + % of positive cores	Base model + no. and % of positive cores	OR; p value	PA (%)	Base model	Base model + no. of positive cores	Base model + % of positive cores	Base model + no. and % of positive cores
			OR; p value	OR; p value	OR; p value	OR; p value			OR; p value	OR; p value	OR; p value	OR; p value
pPSA	1.09; <0.001	<b>68.8</b>	1.07; <0.001	1.07; <0.001	1.06; <0.001	1.06; <0.001	1.1; <0.001	<b>71.1</b>	1.05; <0.001	1.05; <0.001	1.0; <0.001	1.0; <0.001
Clinical stage	—; <0.001	<b>64.0</b>	—; <0.001	—; <0.001	—; <0.001	—; <0.001	—; <0.001	<b>67.3</b>	—; <0.001	—; <0.001	—; <0.001	—; <0.001
T2 vs. T1c	2.9; <0.001		2.02; <0.001	1.9; <0.001	1.8; <0.001	1.8; <0.001	2.7; <0.001		1.6; 0.02	1.5; 0.06	1.3; 0.2	1.3; 0.2
T3 vs. T1c	10.9; <0.001		3.1; 0.006	2.8 0.014	2.3; 0.05	2.3; 0.05	40.9; <0.001		13.3; <0.001	11.1; <0.001	8.9; <0.001	8.9; <0.001
Biopsy Gleason sum	—; <0.001	<b>70.0</b>	—; <0.001	—; <0.001	—; <0.001	—; <0.001	—; <0.001	<b>78.7</b>	—; <0.001	—; <0.001	—; <0.001	—; <0.001
6 vs. 2–5	0.9; 0.8		0.9; 0.9	1.0; 1.0	0.9; 0.8	0.9; 0.8	0.9; 0.9		0.8; 0.8	0.9; 0.9	0.8; 0.8	0.8; 0.8
7 vs. 2–5	4.2; <0.001		3.3; <0.001	3.2; <0.001	2.8; 0.001	2.7; 0.001	11.6; 0.001		8.6; 0.003	7.9; 0.004	6.7; 0.009	6.8; 0.008
8–10 vs. 2–5	8.9; <0.001		5.5; <0.001	5.2; <0.001	4.4; <0.001	4.3; <0.001	24.7; <0.001		11.9; 0.001	11.2; 0.001	9.5; 0.003	9.6; 0.003
No. of positive cores	1.2; <0.001	<b>66.0</b>		1.1; <0.001		1.0; 0.4	1.3; <0.001	<b>71.9</b>		1.2; <0.001		1.0; 0.6
Percentage of positive cores	1.03; <0.001	<b>68.9</b>			1.0; <0.001	1.02; <0.001	1.0; <0.001	<b>74.2</b>			1.0; <0.001	1.02; <0.001
Multivariable PA (%)			<b>78.1</b>	<b>78.7</b>	<b>79.6</b>	<b>79.5</b>			<b>85.0</b>	<b>86.2</b>	<b>86.4</b>	<b>86.4</b>
PA gain relative to base model (%)				+0.6%	+1.5%	+1.4%				+1.2%	+1.4%	+1.4%

OR = odds ratio; pPSA = pretreatment prostate-specific antigen.  
<sup>\*</sup> Predictors in base model included pPSA, clinical stage, biopsy Gleason sum.

**Table 6 – Univariable and multivariable models predicting biochemical recurrence (BCR) with clinical variables and models predicting BCR with pretreatment prostate specific antigen (pPSA) and pathologic variables with corresponding predictive accuracies (PAs)**

Predictor	BCR predicted with clinical variables						BCR predicted with pPSA and pathologic variables					
	Univariable		Multivariable				Univariable		Multivariable			
	RR; p value	PA (%)	Base model*	Base model + no. of positive cores	Base model + % of positive cores	Base model + no. and % of positive cores	Base model	Base model + no. of positive cores	Base model + % of positive cores	Base model + no. and % of positive cores		
			RR; p value	RR; p value	RR; p value	RR; p value					RR; p value	RR; p value
pPSA	1.06; <0.01	<b>64.8</b>	1.04; <0.01	1.04; <0.01	1.04; <0.01	1.04; <0.01	1.06; <0.01	<b>64.9</b>	1.03; <0.01	1.03; <0.01	1.03; <0.01	1.03; <0.01
Clinical stage	—; <0.01	<b>58.7</b>	—; 0.04	—; 0.09	—; 0.1	—; 0.09						
T2 vs. T1c	1.9; <0.01		1.3; 0.01	1.3; 0.03	1.3; 0.03	1.3; 0.04						
T3 vs. T1c	4.0; <0.01		1.2; 0.6	1.0; 0.9	1.0; 1.0	1.0; 1.0						
Biopsy Gleason sum	—; <0.01	<b>66.7</b>	—; <0.01	—; <0.01	—; <0.01	—; <0.01						
6 vs. 2–5	0.9; 0.7		0.9; 0.8	0.9; 0.6	0.8; 0.6	0.8; 0.6						
7 vs. 2–5	3.07; 0.001		2.6; 0.004	2.2; 0.02	2.2; 0.02	2.2; 0.02						
8–10 vs. 2–5	8.9; <0.01		6.7; <0.01	6.0; <0.01	6.0; <0.01	6.0; <0.01						
ECE (yes vs. no)							2.0; <0.01	<b>55.8</b>	2.1; <0.01	2.1; <0.01	2.07; <0.01	2.1; <0.01
SVI (yes vs. no)							5.0; <0.01	<b>63.5</b>	3.3; <0.01	3.2; <0.01	3.2; <0.01	3.2; <0.01
LNI (yes vs. no)							6.7; <0.01	<b>55.8</b>	2.4; <0.01	2.3; <0.01	2.3; <0.01	2.3; <0.01
SM (yes vs. no)							3.1; <0.01	<b>61.8</b>	1.8; <0.01	1.7; <0.01	1.7; <0.01	1.7; <0.01
Pathologic Gleason sum							—; <0.01	<b>68.4</b>	—; <0.01	—; <0.01	—; <0.01	—; <0.01
6 vs. 2–5							0.9; 0.8		1.2; 0.5	1.3; 0.5	1.3; 0.5	1.3; 0.5
7 vs. 2–5							5.8; <0.001		3.8; <0.001	3.8; <0.001	3.8; <0.001	3.8; <0.001
8–10 vs. 2–5							26.0; <0.001		8.7; <0.001	9.1; <0.001	8.9; <0.001	9.2; <0.001
No. of positive cores	1.3; <0.001	<b>63.0</b>		1.1; <0.001		1.1; 0.4	1.3; <0.001	<b>63.1</b>		1.1; 0.04		1.1; 0.1
Percentage of positive cores	1.0; <0.001	<b>62.0</b>			1.0; <0.001	1.0; 0.4	1.0; <0.001	<b>61.8</b>			1.0; 0.1	1.0; 0.5
Multivariable PA (%)			<b>70.9</b>	<b>72.0</b>	<b>71.8</b>	<b>72.0</b>			<b>78.9</b>	<b>79.2</b>	<b>78.9</b>	<b>79.1</b>
PA gain relative to base model (%)				+1.1%	+0.9%	+1.1%				+0.3% <sup>a</sup>	+0.0%	+0.2%

RR = relative risk; ECE = extra-capsular extension; SVI = seminal vesicle invasion; LNI = lymph node invasion; SM = surgical margin status.  
 BCR predicted with clinical variables. Predictors included: pPSA, clinical stage, biopsy Gleason sum.  
 BCR predicted with pPSA and pathological variables. Predictors included: pPSA, ECE, SVI, LNI, SM, pathologic Gleason sum.  
<sup>a</sup> Predictors in base model included pPSA, clinical stage, biopsy Gleason sum.

base model, independent predictor status was reached in OC status (Table 4), and in SVI and LNI (Table 5). The variable defining the number of positive cores also reached independent predictor status in preoperative models predicting BCR, as well as in postoperative models predicting BCR (Table 6). Conversely, the number of positive cores failed to reach independent predictor status in ECE analyses.

The MVA effect of the variable defined by the percentage of positive cores achieved independent predictor status in models addressing OC and ECE (Table 4), and SVI and LNI (Table 5), as well as in preoperative models predicting BCR (Table 6). Conversely, percentage of positive cores failed to reach independent predictor status in postoperative models predicting BCR.

Assessment of the effect of either the number or the percentage of positive cores on PA gains in the prediction of pathologic stage revealed that the maximum increase in PA was related to the consideration of the percentage of positive cores in the model predicting OC status (+1.4%), ECE (+0.8%), SVI (+1.5%), and LNI (+1.4%) (all  $p < 0.001$ ). Consideration of the number of positive cores resulted in lower PA gains. Finally, consideration of both variables resulted in marginal PA gains relative to the inclusion of percentage of positive cores alone (Table 7).

Assessment of the effect of either the number or the percentage of positive cores on the PA gain in the prediction of BCR revealed that the maximum increase in PA was related to the consideration of the number of positive cores in both preoperative (+1.1%,  $p < 0.001$ ) and postoperative (+0.3%,  $p = 0.006$ ) models predicting BCR. Consideration of the percentage of positive cores yielded lower PA gains. Finally, consideration of both variables resulted in either the same PA or lower PA relative to the inclusion of the number of positive cores (Table 7).

#### 4. Discussion

Accurate prediction of pathologic stage and outcome after definitive treatment for localized prostate cancer is important for patient counseling, follow-up, and treatment planning. Recently, many prognostic tools incorporating various clinical parameters have been created to increase disease staging accuracy and relapse predictions [1-4]. Many of them have also included detailed biopsy information (such as number and/or percentage of positive cores), which was complemented with established prognostic factors such as pPSA, clinical stage, and biopsy Gleason grade [6-22]. The rationale for inclusion of core-derived information relates to their

**Table 7 - Increase in predictive accuracy (PA) of multivariable models including either the number of positive cores (model 2), the percentage of positive cores (model 3), or both (model 4), compared with base model (model 1)**

Outcome	Model 2 vs. 1	Model 3 vs. 1	Model 4 vs. 1
	Increase in PA (%) p value	Increase in PA (%) p value	Increase in PA (%) p value
Organ-confined status	0.51 <0.001	1.43 <0.001	1.39 <0.001
Extracapsular extension	0.36 <0.001	0.83 <0.001	0.96 <0.001
Seminal vesicle invasion	0.63 <0.001	1.49 <0.001	1.47 <0.001
Lymph node invasion	1.14 <0.001	1.39 <0.001	1.42 <0.001
BCR predicted with clinical variables*	1.08 <0.001	0.89 <0.001	1.06 <0.001
BCR predicted with pPSA and pathologic variables†	0.36 0.006	0.06 0.6	0.24 0.07

BCR = biochemical recurrence; pPSA = pretreatment prostate-specific antigen.

Model 1: pPSA, clinical stage, and biopsy Gleason sum (base model).

Model 2: pPSA, clinical stage, biopsy Gleason sum, and number of positive cores.

Model 3: pPSA, clinical stage, biopsy Gleason sum, and percentage of positive cores.

Model 4: pPSA, clinical stage, biopsy Gleason sum, and number and percentage of positive cores.

\* Predictors in the base model included pPSA, clinical stage, and biopsy Gleason sum.

† Predictors in the base model included pPSA, pathologic Gleason sum, extracapsular extension, seminal vesicle invasion, lymph node invasion, surgical margin status.

ability to identify adverse pathologic findings and predict BCR [13,14].

Despite independent predictor status, Graefen and colleagues [15] showed that the number and/or the percentage of positive cores might not actually add to the PA. From a practical perspective, a predictor that is significant, but does not improve the discriminant ability of a MVA model, is of no practical use. We tested this dichotomy in all of the addressed outcomes, namely in prediction of pathologic stages, preoperative prediction of BCR, and postoperative prediction of BCR.

To the best of our knowledge, our report represents the first systematic and comprehensive analysis of the importance of the information contained within the variable that codes either the number or the percentage of positive cores. Moreover, our analysis represents the first systematic and comprehensive assessment of PA gains related to the consideration of either of these variables in MVA models.

Our analyses of the independent predictor status of the number and the percentage of positive cores confirmed the importance of these variables in the prediction of pathologic stage, except for ECE predictions. Interestingly, when the number and the percentage of positive cores were combined within the same model, the number of positive cores was no longer an independent predictor of either SVI or LNI. In models predicting BCR with preoperative variables, the number and the percentage of positive cores also achieved independent predictor status when only one variable was included at a time. When number and percentage were considered simultaneously, neither reached independent predictor status.

Taken together, these data indicate that either the number or the percentage of positive cores is virtually invariably independent predictors of all pathologic or biochemical outcomes. Moreover, when these variables are combined, they fail to independently contribute to the model. Lack of independent predictor status of the number and the percentage of positive cores in models that combine both variables implies that these variables quantify highly interrelated information. Consideration of this information within the same model results in detrimental effects on the model's PA. From a practical standpoint, this observation makes sense, because inclusion of one variable in absolute format (number of cores) and its simultaneous inclusion in the relative format (percentage of cores) do not add novel information to the model.

Although testing of independent predictor status is important statistically, it is somewhat secondary

from a practical standpoint. Independent predictor status does not help to identify individuals at risk of unfavourable pathologic stage or men at risk of BCR. Conversely, a variable that increases PA helps discriminate between individuals destined to fail and those at low risk of failing. Similarly, an informative variable also helps to identify those at high risk of pathologically adverse prostate cancer.

Our study attempted to measure both effects, namely the presence of independent predictor status as well as the increase in PA, when information derived from biopsy cores was considered. We addressed this issue by comparing bootstrap-corrected PA of models with and without data derived from biopsy cores. Our analysis showed that either the number or the percentage of positive cores significantly increased the PA ( $p < 0.001$ ; Table 7). This benefit was noted in both pathologic and BCR models. It is of interest that the consideration of the percentage of positive cores was invariably related to higher PA gains in models addressing pathologic stage. Conversely, the consideration of the number of positive cores led to higher PA in BCR models.

In all six examined end points, the consideration of both variables simultaneously never increased PA beyond 1% point. Specifically, in models predicting the pathologic stage, the gain related to simultaneous inclusion of both variables never improved the PA. PA actually decreased in the SVI model when both variables were considered. This implies that only information from the percentage of positive cores should be used in models predicting pathologic stage.

In models predicting BCR, the simultaneous consideration of the number and of the percentage of positive cores resulted in PA gains of 0.2% and 0.3%. Such gain is negligible from a practical perspective. This implies that, in models addressing BCR, only one way of coding should be used, and our data indicate that the number of cores provides the optimal PA gain.

Taken together, these data suggest that models predicting pathologic stage and BCR could be improved when information from biopsy cores is considered. Pathologic stage predictions seem to be better when the percentage of cores is added to standard predictors. Conversely, BCR predictions seem to be better when the number of positive cores is added. Inclusion of both variables does not appear to be recommended.

It is important to notice that some of the reported gains are small and may not be clinically relevant. For example, a gain of 0.4%, recorded with ECE predictions, was complemented with the number of positive cores. This finding implies that 4 of 1000

additional patients would be correctly classified if the number of positive cores were considered in ECE models. Such gain might be of importance in clinical trials, but might also be of no importance in daily clinical practice.

Several studies addressed the effect of either the number or the percentage of positive cores [6,7,10,11,16–19]. However, far fewer relied on the analytic approach that we used [10,15]. Egawa and colleagues [10] addressed the prediction of pathologic stage in 96 Japanese patients, and found that the number and percentage of positive cores improve PA of ECE and SVI. Increments were rather impressive and ranged from 9.3% to 12.9%. OC and LNI were not examined. Graefen and colleagues [15] examined the effect of core-derived information on the ability to predict BCR in 1152 patients, and found that the number and the percentage of cores improve PA by 1.0–1.4%, which is consistent with our findings.

Our findings have some limitations. First, our analyses did not include more detailed biopsy core information, such as the length of cancer or the percentage of cancer length relative to cumulative core length. These data may provide even more accurate predictions and may increase the PA beyond what we reported [23]. Second, the total number of cores that were obtained ranged from 2 to 36, and the median was between 6 and 7. This finding indicates that our cohort was exposed to a range of biopsy schemes (Table 1) that extended from sampling of digitally or ultrasonically suspicious areas to truly extended or even saturation biopsies. Our sample reflects an averaged yield of these different approaches and is not fully characteristic of either the sextant or the extended biopsy schemes. It is possible that the information from core material may contribute more to PA if it exclusively originates from individuals subjected to extended biopsies. Third, the included population was treated between 1992 and 2005. Therefore, a part of our cohort is very contemporary. Conversely, some patients may not reflect the effect of stage migration that swept over Europe and North America. Fourth, the definition of BCR (0.1 and rising) is stricter than that of some centers where a cut-off of 0.4 was used. Fifth, there was no central pathology, different surgical techniques were used, and not all patients were followed in the same fashion. Despite these differences, we were able to demonstrate a benefit from inclusion of core-derived information. The heterogeneity of our population adds to the strength of our findings, because variability may undermine the strength of tenuous relationships. This was not the case in our

study, which shows that the effect of positive cores is robust and significant.

## 5. Conclusions

The information derived from biopsy cores is important and can improve the ability to predict pathologic stage and BCR. It appears that the percentage of cores is most helpful in stage predictions. Conversely, the number of cores appears to improve mostly BCR predictions. Consideration of both variables might not be helpful because of the similarity of information that they encode.

## Conflicts of interest

There are no conflicts of interest.

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**Editorial Comment on: Systematic Assessment of the Ability of the Number and Percentage of Positive Biopsy Cores to Predict Pathologic Stage and Biochemical Recurrence after Radical Prostatectomy**

Kiril Trpkov

*Department of Pathology and Laboratory Medicine, Calgary Laboratory Services and University of Calgary, Calgary, AB, Canada*

[kiril.trpkov@cls.ab.ca](mailto:kiril.trpkov@cls.ab.ca)

The authors examined whether the percent of positive cores or number of positive cores, used as surrogate markers for biopsy tumor volume, predict better adverse radical prostatectomy outcomes and biochemical recurrence [1]. The tested cohort reflects real-life practice and

involves a multi-institutional effort. Univariable and multivariable models are examined in a systematic fashion with and without the tested variables for well-defined end points. A novelty of the study is a “head-to-head” comparison of the incremental gain for the predictive accuracy (PA) of the tested variables, used either individually or combined with the base predictive model, for each specific end point, as suggested by Kattan [2]. The limitations of the study include an inhomogeneous patient cohort, different biopsy strategies, prostate cancer stage shift over the study period, and lack of more accurate measurements of biopsy tumor volume.

However, the PA gains for the tested variables are negligible or minimal (0.06–1.49%) for all outcomes. This is statistically significant in the

multivariable models and maybe significant in large clinical trials, but as the authors point out, these findings may not be clinically relevant or practically useful to predict outcomes for individual patients. A possible reason for the limited PA gain is that percent core involvement and number of positive cores are imprecise measurements of biopsy tumor volume and both may overestimate biopsy cancer volume. For example, 3 positive cores in a 10-core biopsy result in 30% positive cores, although each core may contain only cancer microfoci amounting to 3% cancer in the biopsy. To optimize the performance of predictive models in guiding pretreatment planning and to achieve more robust prediction of specific prognostic outcomes, it may be necessary to investigate other pretreatment variables in combination with the

biopsy Gleason score, such as prostate-specific antigen (PSA) density, total biopsy cancer, or other emerging biologic and molecular markers.

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### Editorial Comment on: Systematic Assessment of the Ability of the Number and Percentage of Positive Biopsy Cores to Predict Pathologic Stage and Biochemical Recurrence after Radical Prostatectomy

Damian R. Greene

Sunderland Royal University Hospital,  
University of Sunderland,  
Sunderland SR4 7TP, England  
[Damien.Greene@chs.northy.nhs.uk](mailto:Damien.Greene@chs.northy.nhs.uk)

The authors present a large retrospective analysis of the predictive quality of prostatic biopsies based on six different pathologic and biochemical end points. In particular, the number and percentage of positive biopsy cores were examined with respect to their ability to predict pathologic stage and biochemical recurrence in patients undergoing radical retropubic prostatectomy [1].

The study has a number of shortcomings, some of which are identified by the authors. These include a variation in the number of biopsy cores taken, which ranged from 2 to 36. This wide range reflects the change in biopsy strategy over time as transrectal ultrasound-guided biopsy evolved from a lesion-directed protocol to a systematic sextant [2] and more recently to an extended core biopsy protocol [3–5]. Clearly, where only two cores were taken and one of these cores was involved with a tiny focus of adenocarcinoma, it would still involve 50% of the cores. If the same patient had a 10-core biopsy with only one focus then only 10% of the cores would be involved.

In all six end points used to evaluate the predictive accuracy (PA) gain using both

variables (number and percent positive cores) simultaneously, the increase in PA was small. Indeed, the PA never increased beyond 1% [1]. The authors also point out that analysis did not include more detailed biopsy core information such as the length of cancer or the percentage of cancer length relative to cumulative core length. It would certainly be interesting to have such detail in a prospective study with an extended core biopsy protocol. However, the PA of such an examination would have to be significant to justify a workable model for a busy pathologist. A less frequently identified limitation of transrectal ultrasound-guided prostate biopsy studies is the variation in the ability of the operator to sample the relevant areas of the prostate with respect to the large variation in prostate volumes encountered and the possibility of biopsy cores being adjacent to previous cores thus potentially “over sampling” some areas of cancer within the prostate.

Overall, this study offers a wealth of information on prostate biopsies and examines the effect of the number and percentage of positive cores on several simultaneous outcomes in a novel way.

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