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THE RELATIONSHIP BETWEEN TUMOR VOLUME AND THE NUMBER OF POSITIVE CORES IN MEN UNDERGOING MULTISITE EXTENDED BIOPSY: IMPLICATION FOR EXPECTANT MANAGEMENT

ATSUSHI OCHIAI, PATRICIA TRONCOSO, MICHAEL E. CHEN, JOSEPH LLORETA AND R. JOSEPH BABAIAN*

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas

ABSTRACT

Purpose: We assessed the relationship between the number of positive cores obtained at extended biopsy and tumor volume in radical prostatectomy specimens as a tool for predicting the biological significance of prostate cancer from biopsy data.

Materials and Methods: The study group included 207 men who were treated with radical prostatectomy without neoadjuvant therapy at our cancer center. All patients were diagnosed by systematic extended biopsy (10 or 11 cores) performed between 1997 and 2003. The variables analyzed were patient age, prostate specific antigen, clinical stage, biopsy Gleason score, maximum tumor length in a core, greatest percent of tumor in a core, total tumor length, total percent of tumor in all cores, positive core location, initial or repeat biopsy and prostate volume in subgroups based on the number of positive cores, that is group 1—1, group 2—2 and group 3—3 or more cores. Bivariate correlation analysis and multiple logistic regression analysis were used to determine the predictors of insignificant cancer.

Results: The number of positive cores was significantly related to total tumor volume ($r = 0.433$, $p < 0.001$). Insignificant prostate cancer (volume less than 0.5 cc and Gleason score 6 or less) was found in 21.7% of patients (45 of 207). The incidence of insignificant cancer was 42.5% (31 of 73 patients) in group 1, 16.4% (10 of 61) in group 2 and 5.5% (4 of 73) in group 3. There was a significant difference in the incidence of insignificant cancer among the subgroups (group 1 vs 2 $p < 0.001$, group 1 vs 3 $p < 0.0001$ and group 2 vs 3 $p < 0.05$). The best model for predicting insignificant cancer in group 1 was the combination of tumor length less than 2 mm, Gleason score 3 + 4 or less and prostate volume greater than 50 cc with 83.9% sensitivity (26 of 31 patients) and 61.9% specificity (26 of 42).

Conclusions: The probability of insignificant cancer was directly related to the number of positive cores. Tumor length in a core, Gleason score and prostate volume significantly enhanced the prediction model for insignificant cancer in men with 1 positive core who underwent extended biopsy.

KEY WORDS: prostate, prostatic neoplasms, biopsy, tumor burden

Several studies have shown that tumor volume in prostate cancer is associated with pathological stage, Gleason grade, lymph node metastasis and progression.[1–4] However, the significance of tumor volume as an independent predictor for progression is controversial. Stamey et al investigated the relationship of tumor volume to clinical significance using cystoprostatectomy specimens and proposed that tumors less than 0.5 cc in volume at diagnosis were not likely to achieve a clinically significant size.[1] Epstein et al defined insignificant cancer based on tumor volume, Gleason score and organ confined status.[5] Several investigators considered that tumor volume less than 0.5 cc, Gleason score less than 7 and organ confined disease were indicative of insignificant cancer.[6–8] The reported incidence of insignificant cancer in men who have undergone radical prostatectomy is 8.3% to 30.7%.[6,7,9] It is important to assess tumor volume as a potential predictor of the biological significance of a given prostate cancer preoperatively to determine the best treatment option, including expectant management, in any individual.

Since systematic sextant biopsy was introduced in 1989, several investigators have evaluated the relationship of biopsy core information obtained by sextant biopsy with tumor volume and with pathological outcome.[10] This information has been used to develop models to predict the significance of biopsy detected prostate cancer.[6,7,9] Recently several extended biopsy strategies showed an increasing cancer detection rate compared to systematic sextant biopsy. In our previous study we have observed a 33% increase in the cancer detection rate with a multisite extended biopsy strategy compared with sextant biopsy alone.[11] However, only a few groups have investigated the relationship between biopsy core information obtained by extended strategies and tumor volume.[12–14] In the current study we analyzed the relationship between variables obtained by extended biopsy and tumor volume in radical prostatectomy specimens to predict the potential significance of cancer from biopsy data.

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* Correspondence: Department of Urology, University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Unit 446, Houston, Texas 77030-4009 (telephone: 713-792-3250; FAX: 713-794-4824; e-mail: rbabaian@mail.mdanderson.org).

MATERIALS AND METHODS

Of 502 men diagnosed with prostate cancer by systematic extended biopsy (10 or 11 cores) from 1997 to 2003, 207 underwent radical prostatectomy without neoadjuvant therapy. All patients underwent clinical examination, including digital rectal examination, prostate specific antigen (PSA) determination and transrectal ultrasound using a 7.5 MHz

transducer. Prostate volume (PV) was measured by transrectal ultrasound using the formula for elliptical volume, $\pi/6 \times$ height $\times$ width $\times$ length. Age, preoperative PSA, digital rectal examination, clinical stage, prostate volume, PSA density (PSAD), that is PSA/prostate volume, and volume referenced PSA were determined in each patient.

Ten core biopsy for initial biopsy consists of standard sextant cores and 2 cores from each (right and left) anterior horn of the peripheral zone, while 11 core biopsy for repeat biopsy consists of standard sextant cores, including 1 core from the right and left anterior horns of the peripheral zone, 1 from the right and left anterior transition zones, and 1 from the midline peripheral zone.[11] Prostatectomy specimens were analyzed by a single pathologist (PT) according to a previously described method.[12] Total tumor volume and the tumor volume of each cancer focus (median 3.0 cancer foci) were calculated using the formula, 0.4 $\times$ length $\times$ width $\times$ cross-section thickness, ie number of cross sections $\times$ section thickness.[13] Insignificant cancer was defined as a dominant tumor volume of less than 0.5 cc, absent Gleason grade 4 or 5 cancer and absent extraprostatic extension.[6] Histopathological features of the biopsy specimens, including Gleason score, number of positive cores, maximum tumor length in a core (TL), greatest percent of tumor in a core, total tumor length, total percent of tumor in all cores and tumor location (base or not base and sextant or alternate site) were determined from the pathology reports. Men were divided into subgroups by the number of positive cores, including group 1—1, group 2—2 and group 3—3 or more positive cores.

The Mann-Whitney test was used to compare variables among the groups. The chi-square test was used to assess trends. Bivariate correlation analysis (Pearson's correlation coefficient or r) was used to test the linearity of relationships among the variables. Multiple stepwise logistic regression analysis was used to determine the significant predictors of significant cancer. These statistical analyses were performed using commercially available software with $p < 0.05$ considered statistically significant.

RESULTS

Of the 207 men 168 (81.2%) had organ confined disease. Of the 39 men with extraprostatic extension 28 (13.5%) had capsular penetration only, 5 (2.4%) had seminal vesicle invasion and 6 (2.9%) had positive lymph nodes. The median total tumor volume in men with organ confined disease was significantly lower than that in men with extraprostatic extension (0.77 vs 2.84 cc, $p < 0.001$). The incidence of organ confined disease was 100% (95% CI 94.5 to 100), 88.8% (95% CI 79.7 to 94.7), 53.5% (95% CI 37.7 to 68.8) and 47.4% (95% CI 24.5 to 71.1) when total tumor volume was less than 0.50, 0.50 to 1.99, 2.00 to 3.99 and 4.00 cc or greater, respectively. The incidence of organ confined disease was significantly higher in men with a total tumor volume of less than 2 cc than in men with a total tumor volume of 2 cc or greater (93.8% or 136 of 145 vs 51.6% or 32 of 62, $p < 0.001$).

Table 1 lists the characteristics of men undergoing radical prostatectomy in subgroups based on the number of positive cores. Median tumor volume in groups 1 to 3 was 0.27, 1.13 and 1.78 cc, respectively (group 1 vs 2 $p < 0.001$, group 1 vs 3 $p < 0.001$ and group 2 vs 3 $p < 0.05$). Total tumor volume was significantly related to the number of positive cores ($r = 0.433$, $p < 0.001$), maximum tumor length in a core ($r = 0.436$, $p < 0.001$), greatest percent of tumor in a core ($r = 0.374$, $p < 0.001$), total tumor length ($r = 0.483$, $p < 0.001$) and total percent of tumor in all cores ($r = 0.439$, $p < 0.001$).

Of the 207 men 77 (37.2%) had a dominant tumor volume of less than 0.5 cc. The incidence of dominant tumor volume less than 0.5 cc was 65.8% (48 of 73 patients) in group 1, 32.8% (20 of 61) in group 2 and 12.3% (9 of 73) in group 3 (group 1 vs 2 OR 3.9, $p < 0.001$, group 1 vs 3 OR 13.7, $p < 0.0001$ and group 2 vs 3 OR 3.5, $p < 0.01$). Insignificant prostate cancer based on dominant tumor volume and grade was found in 21.7% of patients (45 of 207). The incidence of insignificant cancer was 42.5% (31 of 73 patients, 95% CI

TABLE 1. *Characteristics of men undergoing radical prostatectomy in subgroups based on number of positive cores*

	No. Pos Cores						p Value		
	1		2		3 or More		1 vs 2	1 vs 3	2 vs 3
No. pts	73		61		73				
Median age (IQR)	60	(55–64)	61.0	(57–64)	62.0	(57–64)	Not significant	Not significant	Not significant
Median ng/ml PSA (IQR)	5.0	(4.0–8.1)	6.4	(4.9–8.7)	5.5	(4.3–7.6)	Not significant	Not significant	Not significant
Median cc prostate vol (IQR)	41.1	(32.2–50.5)	37.3	(26.6–48.5)	34.9	(26.8–43.0)	Not significant	0.05	Not significant
No. clinical T stage:									
T1c	58		42		38		Not significant	0.001	0.05
T2	15		19		34				
T3	0		0		1				
No. biopsy Gleason score:									
6 or Less	57		35		20		0.05	0.001	0.01
3+4	7		14		24				
4+3	6		7		17				
8 or Greater	3		5		12				
Median cc total tumor vol (IQR)	0.27	(0.07–0.94)	1.13	(0.57–2.37)	1.78	(0.98–2.74)	0.001	0.001	0.05
No. dominant tumor focus vol (cc):									
Less than 0.5	48		20		9		0.001	0.0001	0.01
0.5 or Greater	25		41		64				
No. pathological stage:									
pT2	68		54		46		Not significant	0.001	0.01
pT3a	4		5		19				
pT3b	1		2		2				
pTanyN1	0		0		6				
No. radical prostatectomy Gleason score:									
6 or Less	38		18		14		0.01	0.001	0.05
3+4	22		26		27				
4+3	12		11		15				
8 or Greater	1		6		17				
No. Ca:									
Insignificant	31		10		4		0.001	0.0001	0.05
Significant	42		51		69				