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OPTIMIZED MICROVESSEL DENSITY ANALYSIS IMPROVES PREDICTION OF CANCER STAGE FROM PROSTATE NEEDLE BIOPSIES

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Objectives: Clinical staging of prostate cancer is inaccurate, often with significant upstaging on final pathologic review. We previously demonstrated the ability to predict extraprostatic extension of cancer by use of the Gleason score and serum prostate-specific antigen (PSA) measurements. Herein we present an interim analysis of data from an ongoing multi-institutional study to determine the predictive power of an enhancement of microvessel density analysis in combination with Gleason score and serum PSA to predict extraprostatic extension. Methods. We evaluated a total of 186 randomly selected needle biopsy samples and matched totally embedded radical prostatectomy samples with preoperative PSA concentrations and patient demographics. Gleason score and optimized microvessel density (OMVD) were determined from the needle biopsy samples; pathologic stage was verified by independent review of the radical prostatectomy samples. An automated digital image analysis system measured microvessel morphology and calculated the OMVD in the biopsy samples (Biostage; Bard Diagnostic Sciences, Seattle, Wash). Results. Prediction of extraprostatic extension was increased significantly when OMVD analysis was added to Gleason score and serum PSA concentration ($P = 0.003$). Conclusions. Optimized microvessel density analysis significantly increases the ability to predict extraprostatic extension of cancer preoperatively when combined with Gleason score and serum PSA concentration. This method appears to be a useful tool that can assist with treatment decisions in selected patients.

Extraprostatic extension is an unfavorable prognostic finding in patients with prostate cancer. Accurate prediction of extraprostatic extension would be of great clinical value in stratifying patients for therapy. However, current methods are imprecise in predicting the presence of extraprostatic extension, resulting in a substantial level of clinical understaging) ° Previous efforts to preoperatively predict extraprostatic extension in prostate cancer have focused on Gleason score of the needle biopsy sample, serum prostate-specific antigen (PSA) concentration, extent of cancer, and clinical stage. Alone, these biomarkers are not sufficiently accurate predictors of extraprostatic extension of prostate cancer in an individual patient. In combination, such biomarkers are more accurate, but remain imprecise, with a substantial level of understaging, even in highly selected patients. Also, none of these biomarkers measure the stromal host response to cancer despite its potential importance. Additional biomarkers are needed to increase the predictive accuracy for pathologic stage, but each must be evaluable from a needle core biopsy core with cancer, recognizing that this is the only tissue specimen obtained from patients who are not treated surgically. Potential limiting factors for many biomarkers include heterogeneity of prostate cancer and sampling error in biopsy specimens. Microvessel density analysis satisfies all the criteria for a potentially

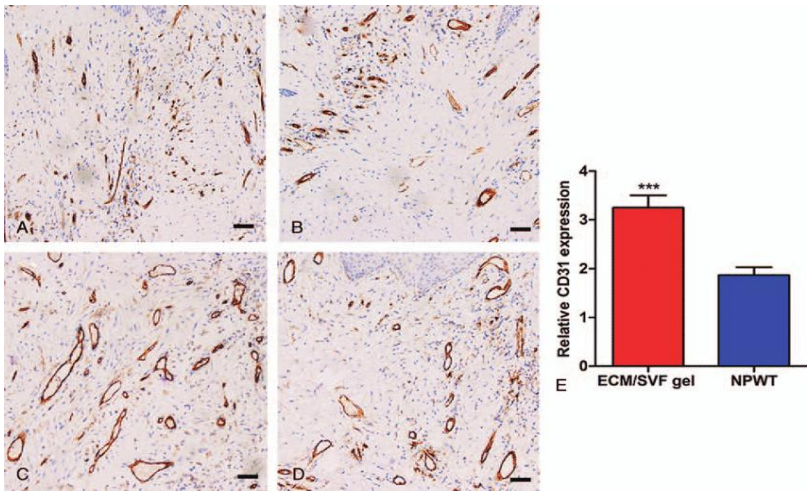
useful biomarker in prostate cancer and, in combination with other biomarkers such as Gleason score and serum PSA concentration, may heighten the predictive accuracy for pathologic stage and patient outcome. Microvessel density is higher in cancer tissue from patients with extraprostatic extension than in those without extension beyond the prostate, and appears to be a significant predictor of patient outcome. Microvessel density is also higher in the center of the cancer than at the periphery, but with significant overlap; it is significantly higher in cancer tissue than in the adjacent benign and hyperplastic tissue. Newly formed blood vessels and branches of pre-existing vessels account for the increased number of microvessels, reflecting the stromal host response to the cancer. It is likely that this biomarker is less influenced by tumor heterogeneity than other cellular prognostic factors. In the present investigation, we evaluated the predictive value of microvessel density, in combination with biopsy Gleason score and preoperative serum PSA concentration, for extraprostatic extension. This collaborative multi-institutional study included a large series of totally embedded, serially sectioned prostate tissues from previously untreated patients with clinically localized prostate cancer undergoing bilateral pelvic lymphadenectomy and radical prostatectomy. An enhancement by digital image analysis of slides stained for factor VIII-related antigen allowed calculation of the optimized microvessel density (OMVD) in needle biopsy specimens.

MATERIAL AND METHODS PATIENTS We undertook a retrospective multi-institutional study of 186 previously untreated patients with prostatic adenocarcinoma who underwent bilateral pelvic lymphadenectomy and radical retropubic prostatectomy between 2000 and 2020. No patient had clinical evidence of extraprostatic extension or immunohistochemistry for microvessels using factor related antigen Immunohistochemical staining was performed using the avidin-biotin-peroxidase complex (ABC) method. Access to tissue antigen sites for antibody attachment was enhanced by microwaving slides for 10 minutes in a low-voltage (500 W) oven. Water was added as necessary to ensure that the solution did not evaporate below tissue level during the microwaving. After cooling for 20 minutes and after each subsequent step, slides were rinsed at room temperature in phosphate-buffered saline. Enzyme digestion was performed with 0.05% pronase solution. A protein-blocking agent (PBA, Shandon Lipshaw, Pittsburgh, Pa) was applied for 15minutes. Slides were incubated with polyclonal rabbit antibody to human von Willebrand Factor (Factor VIII-related antigen) (Dako Corporation, Carpinteria, Calif) at 1:500 dilution for 15 minutes. Slides were then incubated for 15 minutes with the secondary antibody, swine anti-rabbit immunoglobulins (Dako Corporation), at 1:400 dilution for 15 minutes. ABC complex (Vectastain ABC kit, Vector Laboratories, Burlingame, Calif) was applied for 15 minutes. Sections were developed with the chromogen 3,3 '-diaminobenzidine tetrahydrochloride (Sigma Chemical, Saint Louis, Mo); an 8% solution of nickel chloride (15 L/100/.tL) was added to enhance the dark cytoplasmic reaction product within endothelial cells. Sections were lightly counterstained with eosin Y. Intense cytoplasmic immunoreactivity was observed in endothelial ceils of small, medium-sized, and large blood vessels in all study specimens.

DIGITAL IMAGE ANALYSIS AND CALCULATION OF OMVD NEEDLE BIOPSY SPECIMENS WITH CANCER The OMVD was determined from immunohistochemically stained slides of each needle biopsy core with cancer (Fig. 1). Quantitation consisted of area and perimeter measurements for each microvessel in each field. Images were captured digitally at a resolution of 512 × 480 × 8 pixels using a 0.5-in. monochrome CCD camera (Dage-MTI, Michigan City, Ind) interfaced to a 16-bit Occulus F64 image capture board. The CCD camera was attached to a Nikon Optiphot bright-field microscope, utilizing a 20 × 75-na objective and a 100-W quartz halogen focusable lamp housing (Nikon, Inc., Tokyo, Japan). To avoid error introduced by pixel-size conversion, all areas were based on raw pixel count; the conversion factor 6.13E-7 mm2/pixel converted raw pixel count to true area. We developed an automated algorithm utilizing classical image processing and mathematical morphometry that reduced the full 256 gray-level images to binary images, isolated the individual microvessels, and calculated the OMVD (Fig. 2 and 3) (BioStage, Bard Diagnostic Sciences). A serially sectioned slide stained with hematoxylin and eosin was used as a map

of the Factor VIII-stained slide to accurately target areas of cancer for analysis. For each cancer field in the Factor VIIIstained slides two images were acquired: an enhanced vessel image and a tissue image. Each image was processed digitally to exaggerate the contrast between microvessels and lumen space (Fig. 3). The processing of each image involved three steps: (1) mathematical reduction of images; (2) reconstruction and separation of vessel structures; and (3) measurement of vessel count and tissue area (Fig. 2). The summed microvessel count and total tissue area for all fields in all cores of each specimen were combined to calculate the OMVD. The OMVD algorithm focused on fields of cancer, without identifying the specific region of origin in the prostate of the field. This approach was based on the assumption that the inclusion of core identification in the feature-extraction algorithm provided no apparent useful information regarding correlation of the microvessel density analysis and the primary outcome measurements. A number of different microvessel density analyses were calculated, and the results reported here are based on the vessel count per unit area of tissue.

RADICAL PROSTATECTOMY EVALUATION Bilateral open pelvic lymphadenectomy was performed before or during radical retropubic prostatectomy in all cases, and lymph nodes were evaluated by frozen section at the time of surgery at the discretion of the surgeon. Each prostate was weighed, measured, inked, and fixed routinely for up to 3 days in 10% neutral buffered formalin. After fixation, the apex and base were amputated at a thickness of 3 to 5 mm, and each was serially sectioned at approximately 3-mm intervals in the vertical parasaggital plane. Pathologic staging of the radical prostatectomy was performed by the pathologist at each institution participating in the study. Stage was subsequently confirmed by an independent panel of two pathologists who examined all histologic tissue sections in a blinded manner. Cases with discrepant staging were excluded from this analysis, accounting for 12% of evaluable cases. In most cases, tumor maps were available, and foci of extraprostatic extension were outlined in ink. Extraprostatic extension was defined as tumor extending into extraprostatic tissue, according to the criteria of the recent Mayo Clinic consensus meeting. Seminal vesicle invasion was defined as tumor within the muscular coat, as previously described. Involvement of periseminal vesicular tissue only was considered extraprostatic extension but not seminal vesicle invasion. Surgical margins were considered positive when tumor cells were in contact with ink. Surgical margin involvement and extraprostatic extension were considered independently, as previously described, and surgical margin involvement was not included in pathologic staging. The following variables were evaluated in the cancer in the radical prostatectomy specimens: Gleason score, extraprostatic extension, seminal vesicle invasion, and lymph node metastases.



Immunohistochemistry with CD34 of tissue from the wound area. (A) Scant neovascularization before ECM/SVF gel grafting. (B) Scant neovascularization before negative pressure wound therapy. (C) The greatest extent of neovascularization was seen after ECM/SVF gel grafting. (D) Neovascularization increased after negative pressure wound therapy. (E) Relative quantification of neovascularization. P < .001. Scale bar=20 mm. ECM = extracellular matrix, SVF = stromal vascular fraction gel.

Table I.

Table I Correlation of preoperative variables and pathologic stage in 186 patients with prostate cancer			
	Pts With Pts With Organ-Extraprostatic confined Cancer* Extension * (Stage T2) n = 60 (n = 30 [50%]	Pts With Pts With Organ-Extraprostatic confined Cancer* Extension * (Stage T3) (n = 60) (n = 30[50%]	All Pts (n = 186 [100%])
Age at surgery (yr) Mean _+ SD	63.6 ±7.0	65 ±6,8	64±6,9
Range	45-75	47-76	45-76
Preoperative PSA (ng/mL)			
Mean _ SD	7.5 ± 6.4	16,6± 6.8	11 ± 14,1
Range	0.6-43.9	2,0-150,0	0,6-150,0
Gleason score (biopsy) (No. [%] of pts)			
2	0	0	0
3	1	0	1 (0,5%)
4	5	4	9(4,8%)
5	18	3	21(11,3%)
6	68	18	86(46,2%)
7	21	35	56(30,1%)
8	2	9	11(5,9%)
9	0	1	1 (0,5%)
10	0	1	1 (0,5%)
Positive surgical margins (No. [%] of pts)	10 (9%)	49 (69%)	59 (32%)

KEY: pts patients. * Pathologic stage according to results of radical prostatectomy specimen evaluation (see text).

STATISTICS. Logistic regression models for predicting the probability of extraprostatic extension of cancer included three biomarkers: preoperative serum PSA concentration (loglO scale), highest Gleason score from the needle biopsy cores, and OMVD (log10 scale). Two models were generated; one included only serum PSA concentration and Gleason score, whereas the second additionally included OMVD. Because of intrinsic right skewness, serum PSA concentration and OMVD were transformed using the log (base 10) scale. For example, the difference between 10 and 20 ng/mL of serum PSA is considered more significant than a difference of 20 and 30 ng/mL of PSA, yet both differences are 10 ng/mL.

RESULTS . Five institutions submitted 186 evaluable cases, including 68 from the Mayo Clinic, 66 from Baylor College of Medicine, 28 from Washington University, 15 from Laval University, and 9 from the University of Colorado. CLINICAL AND PATHOLOGIC FINDINGS Table I summarizes the findings in

the biopsy specimens. Mean patient age at biopsy was 64 years (range 45 to 76). Serum PSA concentration and percent of positive surgical margins were higher in patients with extraprostatic extension than in those with organ-confined cancer. Time from biopsy to surgery was variable, but was usually within a few months. The distribution of Gleason scores for the biopsy specimens (highest score) is also shown in Table I.

Table II.

Table II Needle biopsy findings in 186 patients with prostatic adenocarcinoma			
	Minimum	**Median**	**Maximum**
No. positive cores/case	1	1	5
No. microscopic fields/case	1	11	118
Total No.microvessels/case	3	120	3401
Median No. Microvessels/field/case	1,5	9	68
Maximum No. Microvessels /field/case	2	18	128

Most patients (138 [74%] of 186) had only one cancer-positive biopsy core, whereas 23 had two, 13 had three, 9 had four, and 3 had five (Table II). Four patients had cancer in one field, 9 in two fields, 9 in three fields, 14 in four fields, and 10 in five fields. Pathologic stage included 115 patients (62%) with organ-confined cancer and 71 (38%) with extraprostatic extension. Gleason score, logPSA, and logOMVD were each significant and independent predictors of extraprostatic extension (P 0.10 for both).

LOGISTIC REGRESSION MODELS Two logistic regression models were calculated for prediction of extraprostatic extension (Tables III and IV). The first used only biopsy Gleason score and logPSA as independent variables, and the second added logOMVD to the first model. Gleason Score and IogPSA Model. Gleason score and logPSA were significant predictors of extraprostatic extension, both individually and in combination (Tables III and IV); however, the interaction was not significant (P > 0.05), indicating that these were independent and additive. The odds ratio for biopsy Gleason score indicated that for a single PSA value, the odds of extraprostatic extension increased 2.45 times with every unit change in Gleason score. Also, for a single Gleason score, the odds of extraprostatic extension increased 15.76 times with every unit change in logPSA. Addition of OMVD (logOMVD) to Gleason Score and IogPSA

Table III Logistic regression models for predicting extra prostatic extension in 186 patients with prostatic adenocarcinoma			
Model and Independent variables	Beta ±SE	P Value	Odds ratio
Mosel using only Gleason score and PSA			
Intercept	-8.63±1,52	<0,0001	-
Gleason score	0.90±0,22	<0,0001	2,45
PSA	2,76±0,60	<0,0001	15,76
Final model			
Intercept	-11,54±1,94	<0,0001	-
Gleason score	0,86±0,22	<0,0001	2,37
PSA (log10)	2,75±0,61	<0,0001	15,67
OMVD (log10)	1,78±0,61	0,0036	5,97

KEY: OMVD = optimized microvessel density. * Logistic regression model: Probability ofextraprostatic extension = exp[logit(EP)]/[1 + exp[logit(EP)]], where logit(EP) = b(O) + b(1) × Gleason score + b(2)

IogPSA + b(3) IogOMVD; coefficients b(O), b(1), b(2), and b(3) are estimates from Table; based on the results, thefinal model = -11.54 + 0.86 × Gleason score + (2.75) × IogPSA + 1.78 × IogOMVD + 0.86 × Gleason score + (2.75) × IogPSA + 1.78 X IogOMVD. Regression coefficient from the logistic model; positive values of beta indicate that the probability of extraprostatic extension increases as the variable increases. * P value for test beta O.

The addition of logOMVD to the previously described model provided significant predictive value (P = 0.0036); however, the interaction of logOMVD with the other two variables was not significant (P >0.05 for both), indicating that log OMVD was independent and additive. The odds ratio for logOMVD indicated that, for a single Gleason score and PSA value, the odds of extraprostatic extension increased 5.97 times with every unit change in log OMVD. For example, a patient with a biopsy Gleason score of 7 and serum PSA of 8 ng/mL had a 53% chance of extraprostatic extension; the addition of logOMVD to the model caused this probability to vary from 37% (OMVD of 25) to 89% (OMVD of 750). No difference was found in the model results from the different institutions contributing to this study when analyzed individually (data not shown; P >0.05). The area under the receiver operating characteristic curve for this model was 0.82, indicating a high predictive power over all ranges of Gleason score, PSA concentration, and OMVD.

COMMENT In this investigation, we studied the ability of three preoperative variables (Gleason score, serum PSA concentration, and OMVD) to predict extraprostatic extension of cancer. An enhanced method of digital image analysis of microvessel density (OMVD) was used to evaluate 186 needle biopsy specimens from patients with untreated, clinically localized prostate cancer. Our results indicate that the addition of the OMVD significantly enhanced the power of the Gleason score and serum PSA concentration to predict pathologic stage. The predictive accuracy of this combination of biomarkers was sufficiently high to be useful in determining treatment for some individual patients. Our results provide probability estimates that can be used to determine the likelihood of extraprostatic extension. For example, a patient with a serum PSA of 8 ng/mL, Gleason score of 8, and OMVD of 500 in the needle biopsy specimen has an estimated 93% chance of extraprostatic extension of cancer; some urologists may choose not to operate on this patient because of such a high likelihood. The probability tables (Table IV) for preoperative prediction of extraprostatic extension presented here appear to be useful guides for patient management and may be of greatest value in planning treatment for patients under consideration for radiation therapy, nerve-sparing radical prostatectomy, expectant management, and androgen-deprivation therapy. Accurate preoperative prediction of extraprostatic extension may also avoid surgery that otherwise might be canceled intraoperatively. Extraprostatic extension is an important prognostic factor for progression and survival in prostate cancer, according to most reports. 1-9 The 1992 revision of the TNM staging system recognized the clinical importance of extraprostatic extension and pathologic staging of prostate cancer, 34 and this was recently confirmed at an international consensus conference at the Mayo Clinic sponsored by the American Cancer Society. Mukamel et al. 7 identified local recurrence rate in 17% of patients with extraprostatic extension and metastases in 37% at 8 years. Hering et al. 4 found an 83% 5-year cause-specific survival rate in patients with extraprostatic extension. Conversely, in patients with extraprostatic extension and no seminal vesicle invasion, Scardino recently found a 5- to 10-year progression-free probability of 72% (Scardino PT: Personal communication). The prognostic difference between pathologic Stages T3a/T3b and T3c are significant. Patients with seminal vesicle involvement have a very poor prognosis. Although extraprostatic extension of cancer is a significant prognostic variable, alone it does not provide enough additional information to categorically rule out surgery in patients with clinically localized prostate cancer. What may be of significant help to the clinician in counseling patients about surgery would be refinements in our ability to predict seminal vesicle invasion or lymph node status. Nonetheless, OMVD will aid in more accurately counseling patients about the final pathologic stage of their cancer and the probability of long-term cancer-free survival. There is a significant increase in microvessel density in prostatic adenocarcinoma than in normal prostatic tissue, 14-18,20-23 and this increase is also observed in prostatic intraepithelial

neoplasia. 18a9 Microvessel density is higher in cancers with than without metastases, 14,16,20 and it appears to be predictive of cancer recurrence and survival after surgery and radiation therapy. 21 Increased microvessel density in prostatic carcinoma is probably related to the production of angiogenesis-associated growth factors 35-4° or matrix-degrading enzymes, similar to other organs26'43; these mechanisms are apparently independent of cancer cell proliferation. Microvessel density is also associated with microvascular invasion by cancer cells, and both are strongly linked with extraprostatic extension and pathologic stage. Microvascular invasion, present in 53% of cases of prostatic adenocarcinoma, is uncommon in organ-confined prostate cancer (18% of cases with Stage T2a+b and 33% of those with Stage T2c), unlike cancer that is not organ confined (up to 84% of cases with pathologic Stage T3c) Microvascular invasion is also an important predictor of outcome, with a fourfold greater risk of tumor progression and death. 46 The cumulative evidence suggests that microvessel density and microvascular invasion are important indicators of extraprostatic spread of adenocarcinoma. Other biomarkers have been proposed as adjuncts to serum PSA concentration and Gleason score to preoperatively predict pathologic stage, including clinical stage,8 percent cancer in needle biopsy specimens, 12 and reverse transcriptase-polymerase chain reaction (RT-PCR) for PSA-producing cells in serum. 47 Clinical staging by digital rectal examination is an important tool for diagnosing prostate cancer but is limited by an error rate that approaches 50%. Percent cancer in needle biopsy specimens is a surrogate of cancer volume that enhances the predictive value for extraprostatic extension when combined with serum PSA concentration and Gleason score, but its utility has only recently been demonstrated and needs to be confirmed. 12 Nested RT-PCR may also be of value for preoperative staging, but the methods are not standardized, and the results are contradictory (Katz et al.47; Wheeler T: Personal communication). Accurate estimates of cancer volume cannot be obtained preoperatively.

Our study of microvessel density used several enhancements to control subjectivity and obtain accurate results. Variability in radical prostatectomy sampling was controlled by only including totally embedded specimens, and we recommend this as a quality-control measure in future studies of staging. Interobserver variability in pathologic staging was controlled by independent review of the specimens by a panel of two independent pathologists, as well as comparison of results from the five participating centers; no differences were found (data not shown). Subjectivity in the identification and interpretation of blood vessels in tissue samples was controlled by using computerbased digital image analysis. Our results are limited by the lack of an independent data set to validate the findings. Logistic models provide estimates of the probability of an event occurring, such as the presence or absence of extraprostatic extension, but the clinician needs to decide what probability cut point to use to manage patients. The 95% confidence intervals are relatively narrow, indicating a high level of precision in predicting pathologic stage for selected patients.

TABLE IV. Probability that a patient will have extraprostatic extension according to Gleason score serum PSA, and optimized microvessel density

Gleason score	PSA ng/ml	Optimized Microvessel Density									
		0	**25**	**50**	**75**	**100**	**150**	**200**	**250**	**500**	**750**
4	2	0,01	0,01	0,01	0,02	0,02	0,03	0,04	0,05	0,08	0,11
4	4	0,03	0,02	0,03	0,04	0,05	0,07	0,09	0,10	0,17	0,21
4	6	0,03	0,03	0,05	0,07	0,08	0,11	0,14	0,16	0,24	0,31
4	8	0,05	0,04	0,07	0,09	0,12	0,15	0,18	0,21	0,31	0,38
4	10	0,07	0,05	0,09	0,12	0,15	0,19	0,23	0,26	0,37	0,45
4	12	0,09	0,07	0,11	0,14	0,17	0,22	0,27	0,30	0,42	0,50
4	14	0,11	0,08	0,13	0,17	0,22	0,26	0,30	0,34	0,47	0,55

4	16	0,13	0,09	0,15	0,19	0,23	0,29	0,34	0,38	0,51	0,59
4	18	0,15	0,10	0,17	0,22	0,26	0,32	0,37	0,41	0,53	0,62
4	20	0,17	0,12	0,18	0,24	0,28	0,35	0,40	0,44	0,58	0,64
4	25	0,19	0,15	0,23	0,29	0,34	0,41	0,46	0,56	0,64	0,71
4	30	0,23	0,18	0,27	0,34	0,39	0,46	0,52	0,61	0,69	0,74
4	35	0,27	0,21	0,31	0,38	0,43	0,51	0,57	0,68	0,73	0,76
4	40	0,31	0,23	0,34	0,42	0,47	0,55	0,60	0,70	0,76	0,79
4	45	0,35	0,26	0,37	0,45	0,51	0,58	0,64	0,73	0,78	0,81
4	50	0,41	0,28	0,40	0,48	0,54	0,61	0,67	0,72	0,80	0,83
5	2	0,04	0,02	0,03	0,04	0,06	0,07	0,09	0,11	0,17	0,221
5	4	0,08	0,04	0,07	0,10	0,12	0,16	0,19	0,21	0,32	0,39
5	6	0,12	0,07	0,11	0,15	0,18	0,23	0,27	0,31	0,43	0,51
5	8	0,16	0,09	0,15	0,20	0,24	0,30	0,35	0,39	0,52	0,60
5	10	0,20	0,12	0,19	0,29	0,29	0,35	0,42	0,45	0,58	0,66
5	12	0,24	0,15	0,23	0,32	0,33	0,42	0,46	0,50	0,64	0,70
5	14	0,27	0,17	0,26	0,36	0,38	0,45	0,51	0,55	0,68	0,74
5	16	0,30	0,19	0,29	0,39	0,41	0,49	0,55	0,62	0,71	0,77
5	18	0,34	0,22	0,32	0,42	0,45	0,53	0,58	0,465	0,74	0,79
5	20	0,36	0,24	0,35	0,49	0,48	0,56	0,61	0,71	0,76	0,81
5	25	0,43	0,29	0,41	0,54	0,55	0,62	0,67	0,75	0,81	0,85
5	30	0,48	0,34	0,47	0,59	0,60	0,67	0,72	0,79	0,84	0,88
5	35	0,53	0,38	0,51	0,63	0,64	0,71	0,75	0,81	0,86	0,90
5	40	0,57	0,42	0,55	0,66	0,68	0,74	0,78	0,83	0,88	0,91
5	45	0,60	0,45	0,59	0,69	0,71	0,77	0,81	0,85	0,89	0,92
5	50	0,63	0,48	0,61	0,72	0,73	0,79	0,82	0,86	0,91	0,93
6	2	0,08	0,05	0,07	0,10	0,12	0,16	0,19	0,22	0,33	0,40
6	4	0,17	0,10	0,16	0,20	0,24	0,30	0,35	0,39	0,57	0,60
6	6	0,25	0,15	0,30	0,29	0,34	0,41	0,47	0,51	0,64	0,71
6	8	0,32	0,20	0,36	0,37	0,42	0,50	0,55	0,66	0,72	0,78
6	10	0,238	0,24	0,41	0,43	0,49	0,57	0,62	0,71	0,77	0,82
6	12	0,43	0,29	0,45	0,49	0,54	0,60	0,67	0,74	0,80	0,85
6	14	0,48	0,33	0,49	0,53	0,59	0,66	0,71	0,77	0,83	0,87
6	16	0,52	0,36	0,53	0,57	0,62	0,70	0,74	0,80	0,85	0,89
6	18	0,55	0,40	0,56	0,61	0,66	0,72	0,77	0,82	0,87	0,90
6	20	0,58	0,43	0,62	0,64	0,69	0,75	0,79	0,85	0,88	0,91

6	25	0,65	0,49	0,67	0,69	0,74	0,80	0,83	0,88	0,91	0,93
6	30	0,69	0,55	0,71	0,74	0,78	0,83	0,86	0,90	0,92	0,94
6	35	0,73	0,59	0,74	0,77	0,81	0,85	0,88	0,91	0,94	0,95
6	40	0,76	0,63	0,77	0,80	0,83	0,87	0,90	0,92	0,95	0,95
6	45	0,79	0,66	0,79	0,82	0,85	0,89	0,91	0,93	0,95	0,96
6	50	0,81	0,69	0,82	0,84	0,87	0,90	0,92	0,94	0,96	0,97
7	2	0,18	0,10	0,16	0,21	025	0,31	0,36	0,40	0,53	0,61
7	4	0,33	0,20	0,31	0,38	0,43	0,51	0,56	0,61	0,72	0,78
7	6	0,45	0,29	0,42	0,49	0,55	0,63	0,68	0,71	0,81	0,85
7	8	0,53	0,37	0,50	0,58	0,63	0,70	0,75	0,78	0,86	0,89
7	10	0,60	0,43	0,57	0,64	0,69	0,75	0,79	0,82	0,89	0,92
7	12	0,65	0,49	0,62	0,69	0,73	0,79	0,68	0,78	0,91	0,94
7	14	0,69	0,53	0,66	0,73	0,72	0,82	0,75	0,87	0,92	0,96
7	16	0,72	0,57	0,70	0,76	0,80	0,84	0,79	0,87	0,93	0,96
7	18	075	0,61	0,73	0,78	0,83	0,86	0,83	0,89	0,94	0,97
7	20	0,77	0,64	0,75	0,80	0,84	0,88	0,85	0,90	0,95	0,95
7	25	0,82	0,70	0,83	0,68	0,89	0,90	0,87	0,91	0,96	0,96
7	30	0,85	0,74	0,85	0,87	0,93	0,93	0,89	0,93	0,97	0,96
7	35	0,87	0,77	0,85	0,89	0,95	0,96	0,90	0,94	0,97	0,97
7	40	0,89	0,80	0,89	0,90	0,95	0,96	0,92	0,95	0,98	0,98
7	45	0,90	0,82	0,90	0,89	0,98	0,97	0,93	0,96	0,98	0,98
7	50	0,91	0,84	0,91	0,92	0,99	0,95	0,95	0,97	0,98	0,99
8	2	0,18	0,10	0,16	0,21	025	0,31	0,36	0,40	0,53	0,61
8	4	0,33	0,20	0,31	0,38	0,43	0,51	0,56	0,61	0,72	0,78
8	6	0,45	0,29	0,42	0,49	0,55	0,63	0,68	0,71	0,81	0,85
8	8	0,53	0,37	0,50	0,58	0,63	0,70	0,75	0,78	0,86	0,89
8	10	0,60	0,43	0,57	0,64	0,69	0,75	0,79	0,82	0,89	0,92
8	12	0,65	0,49	0,62	0,69	0,73	0,79	0,68	0,78	0,91	0,94
8	14	0,69	0,53	0,66	0,73	0,72	0,82	0,75	0,87	0,92	0,96
8	16	0,72	0,57	0,70	0,76	0,80	0,84	0,79	0,87	0,93	0,96
8	18	075	0,61	0,73	0,78	0,83	0,86	0,83	0,89	0,94	0,97
8	20	0,77	0,64	0,75	0,80	0,84	0,88	0,85	0,90	0,95	0,95
8	25	0,82	0,70	0,83	0,68	0,89	0,90	0,87	0,91	0,96	0,96
8	30	0,85	0,74	0,85	0,87	0,93	0,93	0,89	0,93	0,97	0,96
8	35	0,87	0,77	0,85	0,89	0,95	0,96	0,90	0,94	0,97	0,97
8	40	0,89	0,80	0,89	0,90	0,95	0,96	0,92	0,95	0,98	0,98

8	45	0,90	0,82	0,90	0,89	0,98	0,97	0,93	0,96	0,98	0,98
8	50	0,91	0,84	0,91	0,92	0,99	0,95	0,95	0,97	0,98	0,99
9	2	0,57	0,39	0,53	0,65	0,72	0,76	0,79	0,87	0,90	0,90
9	4	0,75	0,59	0,16	0,20	0,24	0,30	0,35	0,39	0,57	0,95
9	6	0,83	0,77	0,30	0,29	0,34	0,41	0,47	0,51	0,64	0,97
9	8	0,87	0,79	0,36	0,37	0,42	0,50	0,55	0,66	0,72	0,98
9	10	0,90	0,83	0,41	0,43	0,49	0,57	0,62	0,71	0,77	0,99
9	12	0,92	0,84	0,45	0,49	0,54	0,60	0,67	0,74	0,80	0,99
9	14	0,93	0,85	0,49	0,53	0,59	0,66	0,71	0,77	0,83	0,99
9	16	0,94	0,86	0,53	0,57	0,62	0,70	0,74	0,80	0,85	1.00
9	18	0,95	0,88	0,82	0,87	0,90	0,82	0,87	0,82	0,87	1.00
9	20	0,95	0,88	0,85	0,88	0,91	0,85	0,88	0,85	0,88	1,00
9	25	0,97	0,89	0,88	0,91	0,93	0,88	0,91	0,88	0,91	1,01
9	30	0,98	0,90	0,90	0,92	0,94	0,90	0,92	0,90	0,92	1,02
9	35	0,98	0,93	0,91	0,94	0,95	0,91	0,94	0,91	0,94	1,03
9	40	0,98	0,94	0,92	0,95	0,95	0,92	0,95	0,92	0,95	1,04
9	45	0,99	0,95	0,93	0,95	0,96	0,93	0,95	0,93	0,95	1,04
9	50	0,99	0,97	0,94	0,96	0,97	0,94	0,96	0,98	0,99	1,04

CONCLUSIONS

We found that the addition of OMVD to serum PSA concentration and Gleason score in needle biopsyspecimens provided the best preoperative prediction of extraprostatic extension. Microvesseldensity is biologically and clinically significant andis objectively measured by computer-based digital image analysis in needle biopsy specimens. By combining OMVD with serum PSA concentration and Gleason score, we created probability tables that allow more accurate therapeutic stratification of patients with prostate cancer. For example, apatient with a serum PSA concentration of 8 ng/mL, Gleason score of 8, and OMVD of 500 has an estimated 93% chance of extraprostatic extension.Determination of OMVD appears to be a useful measure of host stromal response to cancer that can assist with treatment decisions for selected patients.

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