

The association between tumour density and prostate cancer recurrence following radical prostatectomy

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See related article on page 402.

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Abstract

Purpose: Tumour density (TD) may be an independent prognostic factor in men with prostate cancer. The purpose of this study was to evaluate the association between prostate cancer TD and recurrence following radical prostatectomy.

Materials and Methods: Between 1995 and 2007, 645 patients from The Ottawa Hospital or Memorial Sloan-Kettering Cancer Center who had cancer and prostate volumes measured from radical prostatectomy specimens. Tumour density was defined as the relative tumour to prostate volume (tumour volume/prostate volume) and recurrence was defined as a prostate-specific antigen (PSA) >0.2 ng/mL and rising, or postoperative use of radiation or hormonal therapy. Associations between TD and recurrence are adjusted for preoperative PSA, prostatectomy Gleason sum, tumour stage and margin status.

Results: Median follow-up was 40.8 months. Tumour density was associated with preoperative PSA, Gleason sum, tumour stage and surgical margin status (all $p < 0.0001$). As a continuous variable, TD predicted recurrence-free survival (adjusted HR 1.34 per 10% increase in TD; $p = 0.04$). As a categorical variable, the group of patients with a TD of >10% had a 2.7 times greater hazard of recurrence compared to patients with a TD <5% (95%CI 1.41, 5.19; $p = 0.003$). Despite the independent association between TD and recurrence, the clinical value of TD remains in question as the discriminative performance (area under the curve) of predictive models only improved from 0.865 to 0.876.

Conclusions: Prostate cancer TD is associated with known prognostic factors and is also independently predictive of recurrence following radical prostatectomy.

Introduction

Prostate cancer is the most common non-cutaneous malignancy in men.¹ Radical prostatectomy (RP) is considered

the gold standard for treating clinically localized cancer.² Despite this, disease recurs in about 24% of men following RP for localized disease.³ Determining markers that predict recurrence is critical for patient counselling and treatment recommendations. Well-established prognostic factors following RP are pathologic stage, Gleason score (grade), preoperative prostate-specific antigen (PSA) and surgical margin (SM) status.⁴ These factors are used to determine prognosis, assess potential benefit of adjuvant therapy, and stratify patients in clinical trials. Other factors postulated as potential prognostic markers include: high-grade tumour volume, maximal tumour diameter, perineural invasion, DNA ploidy and molecular markers (E-cadherin, Ki-67, p53 expression).^{4,5} While many of these factors are associated with prognosis, they are not highly predictive of outcome after adjusting for stage, grade, PSA and SM status.

Tumour volume/size is independently associated with outcome in many malignancies, such as renal cell carcinoma. However, the prognostic value of tumour volume in prostate cancer is unclear since previous studies have inconsistent results.^{4,6-8} Prostate volume as a prognostic marker of prostate cancer following RP has also had variable outcomes, and thus neither tumour nor prostate volumes are routinely used for outcome prediction.

Tumour density (TD) is the tumour volume relative to the prostate volume (TV/PV), and can be thought of as the relative amount/percentage of an organ involved with cancer. Tumour density is grossly incorporated into the TNM staging system for prostate cancer in the form of pT2 substaging. The purpose of our study was to evaluate the association between TD and prostate cancer recurrence.

Methods

We obtained ethics review board approval at both research sites (The Ottawa Hospital and the Memorial Sloan-Kettering Cancer Center [MSKCC]), each of which is a tertiary care centre offering dedicated urologic oncology services. Data

from patients treated with RP were pooled from institutional databases. Available baseline information included age, pre-treatment PSA, RP Gleason sum, pathologic stage and SM status. Given the unknown significance of tumour and prostate volumes, these data were only reported by certain pathologists during certain years.

Study sample

Between 1995 and 2007, 444 patients were treated with RP by a uro-oncologist at The Ottawa Hospital. Of these, 213 had tumour and prostate volume measurements. At MSKCC, tumour volume was recorded sporadically between 2001 and 2004. Of the 2200 patients who underwent RP during this time period, 432 had tumour and prostate volume measurements. There were no known factors that influenced the decision to report tumour volume as it was reported at the discretion of the reviewing pathologist. Patients with lymph node metastases were excluded from the analysis.

Pathologic analysis

At The Ottawa Hospital and MSKCC, RP specimens were harvested in the operating room, inked to evaluate margin status and fixed in formaldehyde as per routine pathologic processing procedures. Prostate volume was measured by a water displacement method. Complete sampling using 3-mm slices on tissue slides were used to calculate the tumour volume by one of two previously validated methods in which our dedicated genitourinary pathologists had been trained, namely (1) constructed tumour maps or (2) by using the tumour dimensions and a correction factor derived from the equation for an ellipsoid structure.⁹⁻¹² All tumour foci and all cancer grades were included in the calculation of tumour volume. RP Gleason sum, SM status, seminal vesicle invasion (SVI) and extraprostatic extension (EPE) were derived using standard pathological techniques.

Statistical analysis

Data were summarized and the associations between TD and potential confounding baseline variables were performed using linear or logistic regression as appropriate. Multivariable Cox proportional hazards analyses incorporating pre-treatment PSA, RP Gleason sum, stage and SM status were conducted to assess the association between TD and recurrence (primary endpoint). Recurrence was defined as a PSA >0.2 ng/mL and rising or at the initiation of postoperative radiation or hormonal therapy. Patients were censored at the time of non-prostate cancer death or at last follow-up. Tumour volume was also analyzed for its associations with pathologic and recurrence endpoints in an identical fashion to TD.

Results

The mean age of men at the time of RP was 63.0 (standard deviation = 6.7) years with a median PSA value of 5.5 (inter-quartile range [IQR] 4.2-7.8). Median follow-up was 3.43 years (IQR 2.0-4.9). Demographic and tumour pathologic characteristics were stratified by TD (Table 1). To assess for selection bias, we compared baseline characteristics of patients with volume measurements to those who did not have these measurements performed (Table 1).

Tumour density was associated with known prognostic factors in univariate analysis (Table 2). In multivariable analysis, as a continuous variable, TD was modestly associated with cancer recurrence (HR 1.34 per 10% increase in TD; $p = 0.04$). To potentially improve clinical application, TD was modeled as a categorical variable: low TD (0-5%), intermediate TD (5.1-10%), and high TD ($\geq 10.1\%$). Patients with high TD were at significantly increased risk of recurrence compared to patients with low TD (HR 2.7; 95%CI 1.41, 5.19); $p = 0.003$) (Table 3).

Tumour volume was also assessed for its association with pathologic outcomes and prostate cancer recurrence. In multivariate analysis, tumour volume was not found to be statistically significantly associated with the prostate cancer recurrence following RP (HR 1.43 95% CI 0.71, 2.87; $p = 0.34$). Complete results of this analysis are not presented for brevity and clarity.

The ability of TD to improve current methods of predicting recurrence in patients with organ-confined prostate cancer was assessed using a receiver operator characteristic (ROC) curve and an AUC analysis. Two curves were constructed (1) a base model using EPE, SVI, SM, and RP Gleason sum (AUC = 0.865) and (2) an enhanced model including all the variables of the base model and the addition of TD (AUC = 0.876).

Discussion

Disease outcome prediction allows for proper stratification of patients in clinical trials and allows for a more informed approach to patient care.¹³ Currently, pre-treatment PSA, Gleason score, stage and SM status are accepted and used prognostic markers.^{5,7,14} In this analysis, we observed that TD was independently associated with prostate cancer recurrence, however, adding this characteristic to predictive models did not significantly improve discriminative accuracy (AUC 0.876 with TD vs. 0.865 without TD).

In previous studies, tumour volume and prostate volume have been inconsistently associated with prognosis when evaluated independently. Therefore, the prognostic role of these independent volumes has not been established. Studies focused on prostate cancer tumour volume have found larger tumours are associated with progression, however the rela-

Table 1. Demographics and tumour characteristics of men treated with radical prostatectomy at The Ottawa Hospital or Memorial Sloan-Kettering Cancer Center who had tumour and prostate volume measurements

Demographics	Tumour and prostate volume data available			Tumour or prostate volume not available	
	<5%	5-10%	>10%	Overall	Overall
Sample (n)	409	136	100	645	1999
Age					
Mean (SD)	63.5 (6.6)	61.5 (6.9)	62.7 (6.8)	63.0 (6.7)	63.4 (7.3)
Median [IQR]	63.5 [59.4, 68.1]	61.7 [56, 66]	61.8 [58, 68]	63 [58.9, 67.8]	
Tumour density					
Median [IQR]	1.5 (0.5-2.9)	7.3 (6.0 – 8.5)	12.9 (11.3 – 17.4)	3.3 [1.1, 7.6]	–
PSA					
Mean (SD)	5.79 (3.69)	7.21 (4.2)	10.1 (11.6)	6.8 (6.0)	6.3 (4.8)
Median (IQR)	5.1 [3.93, 6.9]	6.1 [4.68, 8.71]	7.4 [5.2, 11.3]	5.5 [4.2, 7.8]	–
<10	372 (91.0%)	110 (80.9%)	71 (71.0%)	553 (85.7%)	–
10-20	33 (8.1%)	22 (16.2%)	20 (20.0%)	75 (11.6%)	–
>20	4 (1%)	4 (2.9%)	9 (9%)	17 (2.6%)	–
RP Gleason sum					
2-6	207 (51%)	46 (33.8%)	21 (21.2%)	274 (42.8%)	850 (45.7%)
7	180 (44.3%)	84 (61.8%)	58 (58.6%)	322 (50.2%)	909 (48.8%)
8-10	19 (4.7%)	6 (4.4%)	20 (20.2%)	45 (7.0%)	103 (5.5%)
SM					
Positive	34 (8.3%)	27 (19.9%)	31 (31%)	92 (14.3%)	265 (13.9%)
Negative	375 (91.7%)	109 (80.2%)	69 (69%)	553 (85.7%)	1637 (86.1%)
EPE					
Positive	34 (8.3%)	41 (30.9%)	50 (50%)	166 (25.7%)	443 (23.4%)
Negative	335 (81.9%)	94 (69.1%)	50 (50%)	479 (74.3%)	1447 (76.6%)
SVI					
Positive	6 (1.5%)	6 (4.4%)	20 (20%)	32 (5.0%)	101 (5.3%)
Negative	403 (98.5%)	130 (95.6%)	80 (80%)	613 (95.0%)	1791 (94.7%)

Patient characteristics are categorized based on tumour density. Column 6 represents a comparison group of patients from the pooled database that did not have TV measurements. IQR: interquartile range; SD: standard deviation; PSA: prostate-specific antigen; SM: surgical margin; EPE: extraprostatic extension; SVI: seminal vesicle invasion.

tionship is often explained by differences in other prognostic characteristics.^{5,14-17} More recently, prostate volume has been studied to determine the association with outcome. It has been found that large prostates are more likely to be associated with organ confined tumours. However, similar to tumour size, the independent association between prostate size and prognosis has not been definitively established.^{6,18,19}

In the current study, we define density as the proportional tumour to prostate volume. Our hypothesis was that the proportion of the prostate containing tumour may be more informative than either variable alone. For example a 2-cm³ tumour in a 20-gram prostate may be more significant than the same volume of tumour inside a 60-gram prostate. Previous authors have examined tumour density under the terms *Percent Tumour Involvement*, *Percent Carcinoma*, and *Relative Tumour volume*, and although the results have been promising, it has not been incorporated into predictive nomograms.^{4,9,10,20,21} Previous studies have reported that percent tumour involvement was associated with positive SMs, EPE, SVI and biochemical progression in multivariate analysis after adjusting for other variables including year of

surgery, PSA, race, clinical stage, Gleason sum, SM, extracapsular extension and SVI.²⁰ These findings were consistent with a similar study of over 1800 patients with organ confined (pT2) disease.⁹ Some have suggested evaluating TD as a categorical variable.^{9,20} One study found that every 5% increase in the percentage of carcinoma was associated with an 11% increase in recurrence.¹⁰ Unfortunately, all studies have not confirmed these findings as some have found that density is not independent of other prognostic variables.^{21,22} Currently, there is no consensus as to the importance of reporting tumour or prostate volume in RP specimens and this uncertainty was highlighted in a recent publication by the International Society of Urological Pathology (ISUP) Consensus Conference.²²

Our study found TD to be independently associated with cancer recurrence adjusting for other currently accepted prognostic variables (pre-treatment PSA, Gleason score, tumour stage and SM status). When TD was evaluated as a categorical variable using the categories 0-5%, 5.1-10%, >10%, patients in the highest density category (>10%) demonstrated a greater than two-fold increase in the risk of recur-

Table 2. Tumour density analyzed for association with known predictors of prostate cancer disease-free interval*

	Univariate analysis	
	OR (95% CI)	p-value
Tumour density	1	0
High-grade Gleason sum	1.11 (1.07, 1.16)	<0.0001
Pre-treatment PSA*	0.26 (0.04)	<0.0001
Surgical margin	1.10 (1.07, 1.14)	<0.0001
Extraprostatic extension	1.13 (1.09, 1.17)	<0.0001
Seminal vesicle invasion	1.14 (1.09, 1.20)	<0.0001

†This includes pre-treatment PSA, surgical margin, extraprostatic extension, seminal vesicle invasion and high-grade Gleason score 7-10, using unadjusted univariate analysis.

*Note the association of TV and TD with PSA is demonstrated using a parameter estimate and standard error per 1 unit increase in PSA.

OR: odds ratio; CI: confidence interval; PSA: prostate-specific antigen.

rence when compared to the 0-5% group in multivariate analysis.

The purpose of a prognostic marker is to improve patient counselling, assist in decision-making regarding the use of adjuvant therapy and improve stratification of trial participants. Although TD is statistically significantly associated with recurrence independent of current prognostic variables, we are unsure if it adds clinical value as the discriminative performance (AUC) improvement is minimal. The accuracy in calibration of predictive models is difficult to assess. Therefore, at this time, we believe tumour and prostate volume should be routinely collected by pathologists at academic research centres to allow further long-term assessment of important outcomes, such as metastases and death. However, pending further study, we currently do not use TD for patient counselling.

Limitations of our study include a relatively short follow-up time of 40.8 months, the retrospective nature of our data, and the large number of patients for whom complete data was not available. The potential selection bias was partially assessed by comparing the characteristics of patients with volume data available to those who did not have this information available (Table 1). Based on this assessment, selection bias is unlikely to have had a large effect on the results.

Conclusions

Tumour density is associated with known prostate cancer prognostic factors. In addition, TD is independently predictive of cancer recurrence. Despite this, the discriminative accuracy of prediction models is not significantly improved by the addition of TD. Further study evaluating the association between TD and long-term prostate cancer outcomes is warranted.

Competing interests: None declared.

Table 3. Tumour density as a continuous and categorical variable predicting for recurrence-free survival while controlling for other known predictors using multivariate analysis*

Recurrence-free survival multivariate analysis		
	HR (95% CI)	p-value
Tumour density		
Continuous		
Per 1 unit	1.03 (1, 1.06)	0.04
Per 10 units	1.34 (1.01, 1.78)	0.04
Categorical		
0-5%	1	1
5-10%	1.34 (0.64, 2.81)	0.44
10%	2.7 (1.41, 5.19)	0.003
Adjusted variables		
PSA	1.02 (1, 1.04)	0.03
High-grade Gleason sum	3.18 (2.23, 4.53)	<0.0001
Surgical margin	2.52 (1.38, 4.57)	0.003
Extraprostatic extension	2.08 (1.12, 3.88)	0.02
Seminal vesicle invasion	1.4 (0.64, 3.04)	0.4

*Includes surgical margin status, extraprostatic extension, seminal vesicle invasion, PSA, and high grade Gleason sum. Categorical variable hazard ratios are compared to the lowest group (0-5%).

HR: hazard ratio; CI: confidence interval; PSA: prostate-specific antigen.

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