EUROPEAN JOURNAL OF CANCER 43 (2007) 536–543

available at www.sciencedirect.com

journal homepage: www.ejconline.com

Tumour volume and high grade tumour volume are the best predictors of pathologic stage and biochemical recurrence after radical prostatectomy

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ARTICLE INFO

Article history:
Received 26 August 2006
Received in revised form
12 October 2006
Accepted 17 October 2006

Keywords:
Prostate cancer
Tumour volume
Biochemical recurrence
Radical prostatectomy

ABSTRACT

Introduction: Our goal was to examine to what extent tumour volume (TV) and percentage of high grade tumour volume (%HGTV) affect the rate of positive surgical margins and the rate of biochemical recurrence after radical prostatectomy.

Materials and methods: TV and %HGTV were routinely planimetrically quantified in a cohort of 780 consecutive patients. Mean follow-up was 46.7 months. Multivariable regression models addressed two separate endpoints: positive surgical margins and biochemical recurrence. The increase in model predictive accuracy related to the addition of TV and %HGTV to radical prostatectomy stage and grade was assessed, after 200 bootstrap resamples to reduce overfit bias.

Results: In multivariable logistic regression models addressing positive surgical margins rate, predictive accuracy increased by 1.9% ($p < 0.001$) when TV was added to other covariates. No further increment was noted when %HGTV was added ($p = 0.3$). In multivariable Cox regression models addressing biochemical recurrence, accuracy increased by 0.6% ($p = 0.002$) when TV was added and an additional increase of 0.7% was recorded when %HGTV ($p < 0.001$) was added.

Conclusion: Tumour bulk reflected by TV affects local cancer control rate, which is reflected in the rate of positive surgical margins. Conversely, high grade cancer determines the rate of biochemical recurrence. These two variables represent the most powerful predictors of cancer control in men treated for localised prostate cancer. Moreover, they increase the ability of established predictors to predict the outcomes of interest. In consequence, they warrant consideration in future predictive and prognostic tools.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.10.018

1. Introduction

Radical prostatectomy (RP) offers the best chances of long-term survival for men with early stage prostate cancer.[1–6] However, approximately 20% of PCa patients experience a biochemical recurrence at 5 years and 30% may relapse at 10 years after RP.[7–10] Pathological variables such as extracapsular extension, seminal vesicle invasion, lymph node invasion and surgical margins status are able to predict the rate of biochemical recurrence.[11] However, their accuracy is not perfect, which drives the search for novel predictors.[12,13]

Stamey *et al.* introduced the importance of pathologic tumour volume (TV) and percentage of high-grade Gleason and showed that TV is statistically significantly correlated with prostate specific antigen (PSA), surgical margin status, extracapsular extension, seminal vesicle invasion and lymph nodes invasion (all $p < 0.001$).[14] Moreover, TV and percentage of high-grade Gleason were independently associated with BCR after RP. His landmark analysis represented TV as the foremost predictor of biochemical recurrence after radical prostatectomy. However, the value of measuring TV remains controversial, as subsequent studies have questioned Stamey's findings.[15,16]

We decided to address the effect of TV and percentage of high grade tumour volume (%HGTV) on two important endpoints, namely positive surgical margins and the rate of biochemical recurrence after radical prostatectomy. Our hypothesis stated that tumour bulk, defined by tumour volume, primarily affects the rate of positive surgical margins. Conversely, we hypothesised that %HGTV drives the rate of BCR. Besides testing the multivariable independent status of these two predictors, we quantified their effect by measuring the increment in predictive accuracy related to the inclusion of these two variables to established predictors of cancer control at radical prostatectomy, as important variables should not only demonstrate independent predictor status but should also increase the ability to predict the outcome of interest.

2. Materials and methods

2.1. Patient population

Between January 1996 and October 2003, specimens of 780 patients, aged from 37 to 75 years (mean and median 62) and treated with radical prostatectomy at a single institution, were subjected to meticulous pathologic assessment, which focused on detailed planimetric, computer-assisted assessment of TV and %HGTV. The 780 specimens approximately represent a 25% sample of all radical prostatectomies performed during the study period. No specific clinical or pathological criteria were used to select these 780 individuals. However, the selection was not randomised according to strict statistical criteria and no official protocol was followed. Moreover, PSA, extracapsular extension, seminal vesicle invasion, lymph node invasion, surgical margin status, radical prostatectomy primary and secondary Gleason scores, year of surgery, follow-up time, and the biochemical recurrence status were available in all men.

2.2. Pathological and clinical evaluation

Prior to the planimetric assessments of TV and %HGTV, all prostatectomy specimens were inked over their entire surface and processed according to the Stanford protocol.[17] Histological tumour grading was performed according to the Gleason grading system.[18] A +SM was defined as cancer cells in contact with the inked specimen surface. Pathological stage was defined according to the 2002 AJCC staging classification.[19] TV measurements were performed as previously described using a computerised planimetric method.[20] In brief, TV was ascertained by multiplication of the measured areas with the section thickness. Percentage of Gleason grades 4 or higher of TV were defined as %HGTV. The volume of high-grade tumour (Gleason score 4 or score 5) was determined separately with the same procedure, when distinct areas of low differentiation were present and was estimated when high-grade tumour was diffusely mixed with lower-graded tumour parts.

The Abbott Axym PSA assay (Abbott Park, IL, USA) was used, and pre-treatment PSA was measured prior to digital rectal examination and transrectal ultrasound guided biopsy. In all patients, PSA values were measured quarterly in the first year, followed by biannual measurements in the second and annual measurements in the third year after radical prostatectomy. Biochemical recurrence was defined as a postoperative PSA of 0.1 ng/ml and rising after an initial undetectable PSA. The first PSA value above or equal to 0.1 ng/ml was used to define the time of biochemical recurrence. Patients without evidence of biochemical recurrence were censored at last follow-up.

2.3. Statistical analyses

Statistical models addressed two different outcomes, namely positive surgical margins at final pathology and biochemical recurrence after radical prostatectomy. The main predictors were TV and %HGTV. Covariates consisted of PSA, extracapsular extension, seminal vesicle invasion, lymph node invasion, as well as primary and secondary pathologic Gleason patterns. In models of biochemical recurrence, surgical margin status was also included among covariates. The ability to predict positive surgical marigins was tested in logistic regression models, whereas BCR was addressed in Cox regression models. The predictive accuracy of the logistic regression models was quantified with the receiver operator characteristic area under the curve. A modification of this method for censored data, Harrell's concordance index, was used in Cox regression models. Accuracy of predictions was quantified with and without TV and/or %HGTV. This method was selected with the intent of quantifying the increment in predictive accuracy, associated with the addition of one or both variables to established predictors. Two hundred bootstrap resamples were used to reduce overfit bias. The predictive accuracy means were tested using the independent sample t-test. All statistical tests were performed using S-PLUS Professional, version 1 (MathSoft Inc., Seattle, Washington). Moreover, all tests were two-sided with a significance level at 0.05.

3. Results

Patient characteristics are shown in Table 1. Median and mean pre-treatment PSA were 7.9 and 11.5 ng/ml, respectively. Extracapsular extension, seminal vesicle invasion, lymph node invasion and positive surgical margins were recorded in 324 (41.5%), 130 (16.7%), 47 (6.0%) and 173 (22.2%). Of all patients, 147 (18.8%) demonstrated biochemical recurrence during follow-up, which ranged from 1 to 96 months (mean 46.7; median 43.4 months). Time to biochemical recurrence ranged from 1 to 84 months (mean 20.4; median 16.7 months). Median and mean TV were 4.5 and 6.6 cc, respectively (range 0.1–63.6). Median and mean %HGTV were 10.0% and 20.4%, respectively (range 0–100).

Table 2 shows a comparison of mean TV and mean %HGTV stratified according to Partin stages. In the lower panel, a comparison of rates of biochemical recurrence stratified according to quartiles of TV and %HGTV is shown. For each Partin stage (all $p < 0.001$) and for biochemical recurrence rates stratified according to quartiles, TV and %HGTV (all $p < 0.001$), comparisons were statistically significant, demonstrating higher TV and %HGTV with increasing Partin stage as well as higher rates of biochemical recurrence with either increasing TV or %HGTV quartile. Fig. 1 shows the Kaplan–Meier plots of overall biochemical recurrence (Fig. 1a) and stratified according to TV quartiles (Fig. 1b), as well as %HGTV quartiles (Fig. 1c).

Table 3 shows the uni- and multivariable logistic and Cox regression models predicting positive surgical margins and biochemical recurrence, respectively. In both univariable analyses, all variables were highly significantly associated with either positive surgical margins at final pathology ($p \leqslant 0.002$) or biochemical recurrence ($p < 0.001$). In univariable analyses predicting positive surgical margins, TV (67.1%) achieved the highest predictive accuracy. In univariable models predicting biochemical recurrence, %HGTV (79.9%) represented the most informative predictor and was closely followed by TV (75.8%). In both analyses, TV and %HGTV predicted more accurately than Gleason patterns.

In multivariable models addressing positive surgical margins where TV and %HGTV were included, extracapsular extension ($p < 0.001$) and TV ($p < 0.001$) represented the only independent predictors. Neither primary ($p = 0.6$) nor secondary ($p = 0.07$) Gleason patterns achieved independent predictor status. The addition of TV to base predictors of positive surgical margins enhanced accuracy by 1.9% ($p < 0.001$). Subsequent inclusion of %HGTV failed to exert any additional effect on predictive accuracy.

In the multivariable models predicting biochemical recurrence, where TV and %HGTV were included, only TV ($p = 0.005$), %HGTV ($p < 0.001$), extracapsular extension ($p < 0.001$), and PSA ($p = 0.013$) represented statistically significant predictors. Again, neither primary ($p = 0.6$) nor secondary ($p = 0.7$) Gleason patterns achieved independent predictor status. In multivariable BCR models, addition of TV to base predictors increased accuracy by 0.6% ($p < 0.001$). When %HGTV was added, accuracy further increased by 0.7% ($p < 0.001$) leading to a cumulative increase in predictive accuracy of 1.3% ($p < 0.001$).

Table 1 – Descriptive characteristics of 780 men treated for radical prostatectomy between January 1996 and October 2003

Variables	Number of patients
Total number of patients (%)	780 (100.0)
Age (years)	
Mean (median)	62.2 (62.0)
Range	37–75
Clinical stage (%)	
T1c	413 (52.9)
T2a	295 (37.8)
T2b	47 (6.0)
T3	25 (3.2)
PSA (ng/ml)	
Mean (median)	11.5 (7.9)
Range	0.5–125.0
Presence of ECE	324 (41.5%)
Presence of SVI	130 (16.7%)
Presence of LNI	47 (6.0%)
Surgical margin status	173 (22.2%)
Primary RP Gleason pattern	
2	10 (1.3%)
3	632 (81.0%)
4	135 (17.3%)
5	3 (0.4%)
Secondary RP Gleason pattern	
2	95 (12.2%)
3	334 (42.8%)
4	337 (43.2%)
5	14 (1.8%)
Tumour volume (cc)	
Mean (median)	6.6 (4.5)
Range	0.1–63.6
Quartiles	
Q1: 0–2.13	196 (25.1%)
Q2: >2.13–4.54	195 (25.0%)
Q3: >4.54–8.52	194 (24.9%)
Q4: >8.52	195 (25.0%)
Percent high grade tumour volume (%)	
Mean (median)	20.4 (10.0)
Range	0–100.00
Quartiles	
Q1: 0	287 (36.8%)
Q2: >0–10	174 (22.3%)
Q3: >10–30	138 (17.7%)
Q4: >30	181 (23.2%)
Follow-up time (months)	
Mean (median)	46.7 (43.4)
Range	1–96
Patients with a follow-up above 24 months	604 (77.4%)
Time to BCR recurrence (months)	
Mean (median)	20.4 (16.7)
Range	1–84
No. of patients with BCR recurrence after RP (%)	147 (18.8)

PSA, prostate specific antigen; ECE, extracapsular extension; SVI, seminal vesicle invasion; LNI, lymph node invasion; BCR, biochemical recurrence defined as PSA >0.1 ng/ml; RP, radical prostatectomy.

Table 2 – Comparison of the effect of tumour volume and percent high grade tumour volume on Partin stages and biochemical recurrence rates

Type of analyses	TV (cc)	*p*-Value (independent sample *t*-test)	% HGTV (%)	*p*-Value (χ^2 test)
Effect on Partin stages				
OC *versus* non-OC	3.8 *versus* 10.4	<0.001	9.5 *versus* 35.2	<0.001
ECE *versus* non-ECE	10.5 *versus* 3.8	<0.001	35.4 *versus* 9.7	<0.001
SVI *versus* non-SVI	13.4 *versus* 5.2	<0.001	44.4 *versus* 15.6	<0.001
LNI *versus* non-LNI	13.5 *versus* 6.1	<0.001	43.4 *versus* 18.9	<0.001
Rates of BCR	TV	*p*-Value (log rank test)	% HGTV (%)	*p*-Value (log rank test)
Total (%)	147 (100)	<0.001	147 (100)	<0.001
Q1	8 (5.4)		10 (6.8)	
Q2	18 (12.2)		22 (15.0)	
Q3	41 (28.0)		35 (23.8)	
Q4	80 (54.4)		80 (54.4)	

TV, tumour volume; %HGTV, percent high grade tumour volume; OC, organ confinement; ECE, extracapsular extension; SVI, seminal vesicle invasion; LNI, lymph node invasion; BCR, biochemical recurrence.
In the upper panel, tumour volume and percent high grade tumour volume are stratified according to Partin stages. In the lower panel, rates of biochemical recurrence after radical prostatectomy are stratified according to tumour volume quartiles and percent high grade tumour volume quartiles.

4. Discussion

Our hypothesis stated that tumour bulk, defined by TV, primarily affects the rate of positive surgical margins. We also hypothesised that the quantity of high grade tumour, defined as %HGTV, drives the rate of biochemical recurrence. Our first hypothesis was based on the fact that tumour volume might be superior to current estimators of positive surgical margins. Our second hypothesis was based on the observation that the biological aggressiveness of prostate cancer may not be most accurately defined with Gleason patterns, as the most dominant cancer patterns may not necessarily reflect the prognosis. A non-dominant Gleason pattern 5 may outweigh the effect of dominant Gleason patterns 4 and 3, but might go unnoticed if Gleason scoring is enforced.

Our analyses demonstrated that TV is indeed the most accurate univariable indicator (67.1%) of positive surgical margins (Table 3). Its contribution exceeded that of either primary (55.2%) or secondary (57.9%) Gleason patterns. Interestingly, TV was more accurate in predicting positive surgical margins than extracapsular extension (66.1%). In multivariable +SM analyses, TV remained an independent predictor ($p < 0.001$) of +SM at final pathology, whereas primary ($p = 0.4$) and secondary (0.1) Gleason patterns failed to demonstrate multivariable statistical significance. These observations confirm our hypothesis that TV represents a key determinant of positive surgical margins. Moreover, in the multivariable models, the predictive accuracy of positive surgical margins predictions increased by 1.9% ($p < 0.001$), when TV was added to all other predictors. Interestingly, no further accuracy gain was recorded when %HGTV ($p = 0.15$) was added. These findings further corroborate the importance of TV and indicate that TV represents a statistically significant predictor. More importantly, this variable improves the ability of all other predictors to discriminate between those with and those without positive surgical margins. Taken together, our analyses indicate that tumour bulk, but not its grade represents the determinant of the presence of positive surgical margins.

In biochemical recurrence analyses, %HGVT (79.9%) and TV (75.8%) represented the most accurate univariable variables and exceeded the accuracy of primary (68.1%) and secondary (57.4%) Gleason patterns, as well as that of all other predictors. In multivariable Cox regression models, %HGVT ($p < 0.001$) and TV ($p = 0.005$) demonstrated independent predictor status. Conversely, primary ($p = 0.6$) and secondary ($p = 0.7$) Gleason patterns failed to do so. These findings confirm our hypothesis and indicate that %HGTV represents the most informative and a highly significant predictor of biochemical recurrence. %HGTV demonstrates better univariable and multivariable ability to predict biochemical recurrence than either primary or secondary Gleason pattern. These characteristics are shared with TV and when both variables are combined, they increase the ability to predict biochemical recurrence by 1.3% ($p < 0.001$).

Our findings have important clinical implications. Our logistic regression analysis indicates that tumour bulk, expressed as TV, is the foremost determinant of positive surgical margins. Its effect exceeds that of extracapsular extension and Gleason patterns and, contrary to %HGTV, TV adds to the combined ability of all other variables. Thus, our findings suggest that tumour bulk represents the most important variable, which may compromise local cancer control by virtue of a positive surgical margin at radical prostatectomy. Moreover, our results indicate that %HGTV does not have the same characteristics. Extrapolation of our findings to needle biopsies suggests that the risk of positive surgical margins might not be affected by the presence of high grade tumour within biopsy specimens. Instead, it is crucial to consider the cumulative amount of cancer within biopsy cores. These findings are in direct agreement with our previous work, where we found that the cumulative percentage of cancer in all biopsy cores represented the most informative predictor of extracapsular extension (74%) and surpassed that of biopsy Gleason sum (71%).[21] Moreover, our nomogram based on the cumulative percentage of cancer in all cores was substantially more accurate (84%) than our previous tree regression model

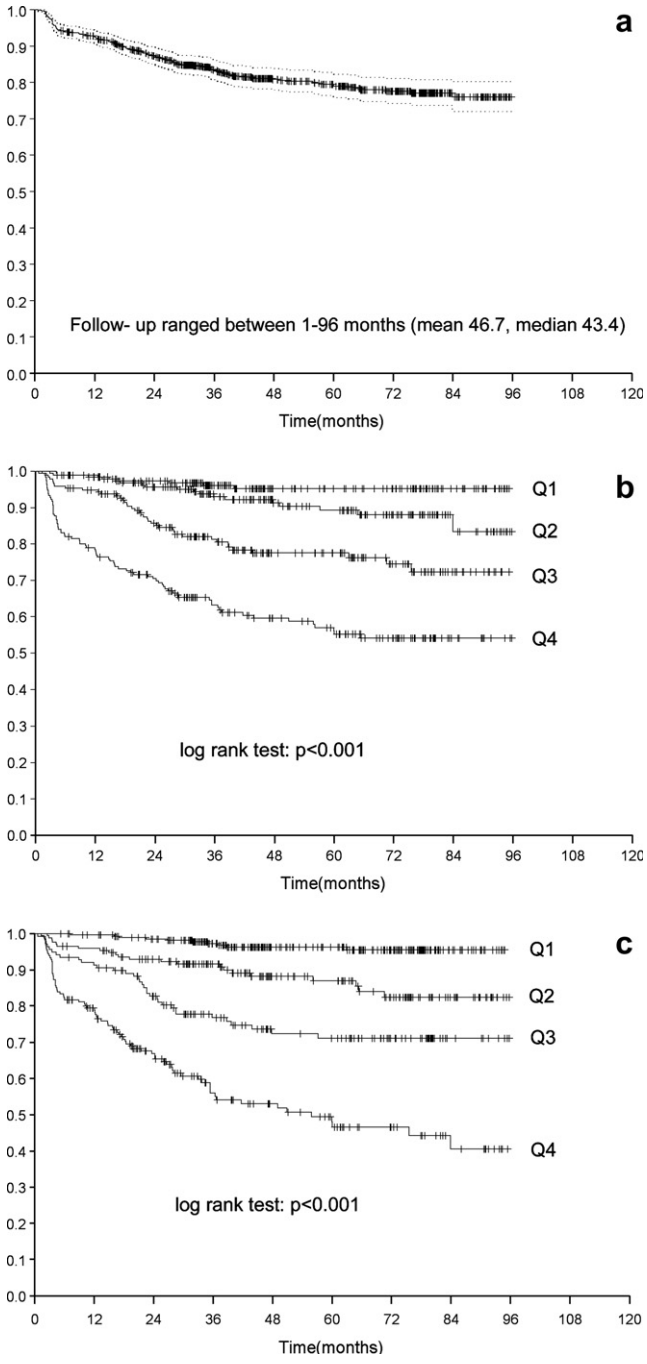

Fig. 1 – Kaplan Meier plots displaying the effect of tumor volume and percent high grade tumor volume stratified according to quartiles on estimates of biochemical recurrence (BCR)-free probability. (a) Overall Kaplan-Meier estimates of biochemical recurrence (BCR), (b) Kaplan-Meier estimates of biochemical recurrence (BCR)-free probability stratified by tumor volume quartiles, (c) Kaplan-Meier estimates of biochemical recurrence (BCR)-free probability stratified by percent high grade tumor quartiles.

(70%), where the presence of high grade prostate cancer was thought to represent the key determinant.[22] Taken together, these findings confirm that tumour bulk is the most important determinant of local prostate cancer extension and that the presence or absence of high grade components has little impact on either surgical margins or extracapsular extension.

Our observations regarding the rate of biochemical recurrence are different. Here %HGTV represents the most important variable. It is closely followed by TV, as evidenced by univariable predictive accuracy estimates, respectively, 79.9% for HGTV and 75.8% for TV. These values exceed the accuracy of radical prostatectomy primary (68.1%) and secondary (57.4%) Gleason patterns, as well as of all other predictors. The importance of %HGTV ($p < 0.001$) and of TV ($p = 0.005$) is highlighted in the multivariable analyses, where %HGTV and TV represent highly statistically significant independent predictors of biochemical recurrence. In the same model, except for PSA and extracapsular extension, Gleason patterns as well as all other predictors failed to demonstrate statistical significance. Thus, once the percentage of HGTV and TV is known, the knowledge of all other variables except for PSA and extracapsular extension becomes secondary. Although %HGTV and TV virtually eclipsed the significance of all other variables, their contribution to predictive accuracy was not stellar. Only a 1.3% increase was noted ($p < 0.001$). This relatively small increase to predictive accuracy needs to be interpreted in the light of simultaneous inclusion of seven other powerful and established predictors of biochemical recurrence, such as Gleason patterns, extracapsular extension, seminal vesicle invasion, lymph node invasion, surgical margins and PSA. When this fact is considered, an increase of 1.3% might be interpreted as non-negligible.

From a clinical perspective, the implications of our findings suggest that the prediction of the rate of biochemical recurrence can be resumed within one variable, namely %HGTV. This variable alone is 80% accurate *versus* 82.5% (Table 3) for the combined accuracy of Gleason patterns, extracapsular extension, seminal vesicle invasion, lymph node invasion, surgical margins and PSA. This finding might be interpreted as a suggestion to revise the grading of radical prostatectomy specimens. However, our intent is not to suggest an instant change in the post-operative prediction of Gleason patterns, extracapsular extension, seminal vesicle invasion, lymph node invasion, surgical margins and PSA. Instead, our objective is to indicate that prostate cancer biology is virtually exclusively driven by %HGTV, as suggested by McNeal, Stamey, Palisaar and Cheng.[14,23–25]

McNeal *et al.* assessed 209 radical prostatectomy specimens and demonstrated that %HGTV was predictive of lymph node invasion.[24] Stamey *et al.* assessed 379 radical prostatectomy specimens and found that %HGTV represented the foremost predictor of Gleason patterns, extracapsular extension, seminal vesicle invasion, lymph node invasion, surgical margins and PSA, beyond that of Gleason score.[14] Palisaar *et al.* assessed 331 stage pT2 specimens and found that %HGTV represents the most accurate predictor of Gleason patterns, extracapsular extension, seminal vesicle invasion, lymph node invasion, surgical margins and PSA (90%) *versus* Gleason sum (83%).[25] Finally, Cheng *et al.* assessed 364 radical prostatectomy specimens and identified %HGTV as an independent multivariable predictor of Gleason patterns, extracapsular extension, seminal vesicle invasion, lymph node invasion,

Table 3 – Logistic and Cox regression models predicting positive surgical margins at final pathology and rates of biochemical recurrence after radical prostatectomy

Type of analyses	Logistic regression models predicting positive surgical margins				
	Univariate analyses		Multivariate analyses		
Variables	OR; *p* value	Predictive accuracy (%)	Base model[+] OR; *p* value	Base model + TV OR; *p* value	Base model + TV, %HGTV OR; *p* value
PSA	1.03; <0.001	58.4	1.02; 0.026	1.01; 0.484	1.01; 0.418
Presence of ECE	3.41; <0.001	66.1	2.70; <0.001	2.21; < 0.001	2.19; <0.001
Presence of SVI	3.08; <0.001	59.6	1.48; 0.111	1.22; 0.428	1.23; 0.414
Presence of LNI	2.53; 0.002	53.1	1.26; 0.487	1.06; 0.877	1.08; 0.833
Primary RP Gleason (4 or 5 *versus* 2 or 3)	1.80; <0.001	55.2	0.83; 0.569	0.74; 0.366	1.39; 0.589
Secondary RP Gleason	–; <0.001		–; 0.205	–; 0.114	–; 0.069
3 *versus* 2	1.74; 0.029	57.9	1.57; 0.242	1.89; 0.105	1.85; 0.120
4 *versus* 2	2.67; <0.001		1.58; 0.212	1.91; 0.083	0.26; 0.040
5 *versus* 2	9.25; <0.001		4.31; 0.038	5.19; 0.022	5.68; 0.017
Tumour volume	1.10; <0.001	67.1	–	1.06; <0.001	1.06; <0.001
Percent high grade tumour volume	1.01; <0.001	60.4	–	–	0.99; 0.273
Predictive accuracy (%)			68.1	70.0	70.0
Increment in predictive accuracy (%)				+1.9	±0
Type of analyses	Cox regression models predicting biochemical recurrence				
	Univariate analyses		Multivariate analyses		
Variables	RR; *p* value	Predictive accuracy (%)	Base model[*] RR; *p* value	Base model + TV RR; *p* value	Base model + TV, %HGTV RR; *p* value
PSA	1.04; <0.001	71.5	1.02; <0.001	1.01; 0.023	1.01; 0.013
Presence of ECE	7.61; <0.001	73.3	2.50; <0.001	2.24; <0.001	2.43; <0.001
Presence of SVI	5.87; <0.001	64.4	1.20; 0.353	1.04; 0.851	0.97; 0.872
Presence of LNI	5.10; <0.001	57.8	1.81; 0.007	1.58; 0.042	1.49; 0.074
Positive surgical margin status	2.71; <0.001	59.6	1.40; 0.107	1.26; 0.199	1.25; 0.225
Primary RP Gleason (4 or 5 *versus* 2 or 3)	7.69; <0.001	68.1	6.36; <0.001	6.16; <0.001	0.74; 0.592
Secondary RP Gleason	–; <0.001		–; 0.002	–; <0.001	–; 0.747
3 *versus* 2	2.43; 0.008	57.4	0.70; 0.463	0.79; 0.619	0.87; 0.773
4 *versus* 2	2.69; 0.003		1.88; 0.122	2.25; 0.049	1.23; 0.634
5 *versus* 2	27.30; ⩽ 0.001		1.40; 0.558	1.61; 0.407	1.09; 0.882
Tumour volume	1.09; <0.001	75.8	–	1.03; 0.002	1.03; 0.005
Percent high grade tumour volume	1.04; <0.001	79.9	–	–	1.03; <0.001
Predictive accuracy (%)			82.5	83.1	83.8
Increment in predictive accuracy (%)				+ 0.6	+ 0.7

[+]Logistic regression base model, PSA, ECE, SVI, LNI, primary and secondary RP Gleason score. [*]Cox regression base model PSA, ECE, SVI, LNI, surgical margin status, primary and secondary RP Gleason score. OR, odds ratio; SVI, seminal vesicle invasion; RR, rate ratio; LNI, lymph node invasion; PSA, prostate specific antigen; RP, radical prostatectomy; ECE, extracapsular extension.

surgical margins and PSA, whereas ($p = 0.04$), Gleason sum failed to reach significance ($p = 0.4$).[23]

Kikuchi *et al.* also assessed the effect of TV on biochemical recurrence, without considering %HGTV.[15] The study included 1302 men with a median follow-up of 46 months and concluded that TV was not an independent, multivariable predictor ($p = 0.2$). Interestingly, despite lower TV than in our population (4.54 cc *versus* 1.6 cc, $p < 0.05$), lower rate of seminal vesicle invasion than in our population (10.9 *versus* 16.7%, $p < 0.001$) and virtually the same rate of extracapsular extension (38.9 *versus* 41.5%, $p > 0.05$) and lymph node invasion (5.6 *versus* 6.0%, $p > 0.05$), Kikuchi's reported relative risk of biochemical recurrence associated with each 1 cc TV increment was even higher than in our present analyses (relative risk [RR] = 1.28 *versus* current RR = 1.03). Despite a higher RR, TV failed to reach statistical significance in the analysis of Kikuchi. Notably, statistical significance and relative risk for seminal vesicle invasion and nodal metastasis were also

substantially different between our and Kikuchi's study, which may suggest that the two populations exhibit biological differences. This hypothesis was corroborated by Cheng's data, where TV was not significant in multivariable analyses ($p = 0.147$), despite highly significant status of %HGTV ($p = 0.04$).[23] Thus, TV may be more important in European men than in their counterparts from the United States. However, this hypothesis is still speculative at best and requires further consideration in future studies. Our findings are also in disagreement with Salomon *et al.*, who showed in a cohort of 200 men that TV did not represent an independent predictor of biochemical recurrence ($p = 0.35$).[16] The absence of positive findings might be related to power considerations. Unfortunately, power was not reported in all of the studies, where TV was deemed non-significant.[15,16,23]

Several differences may distinguish our study from others and several limitations may apply to our findings. First, the findings of our study are limited in their practical applicability, as TV cannot be known pre-operatively to identify patients at high risk of +SM. Thus, positive surgical margins analyses were meant to represent an assessment of tumour biology and not to represent a clinical predictive model.[26] Second, our median follow-up was relatively short (median 43.4 months). Therefore, the rates of observed biochemical recurrence might be lower than in a longer follow-up cohort. Nonetheless, our follow-up was similar to the follow-up of Kikuchi *et al.* [15] and to Cheng *et al.*[23] but not as long as that reported by Salomon *et al.*[16] Third, biochemical recurrence rate represents a surrogate marker and the definitive assessment of the effect of any predictor will require analyses of survival or of metastatic progression rates.[1] This limitation was shared with all other previous analyses.[14–16,23–25] However, D'Amico *et al.* showed that patients with evidence of biochemical recurrence are at increased risk to die of PCa.[27] Finally, whole-mounting of radical prostatectomy specimens may not be universally available and/or may not be feasible because of cost considerations.[1]

Despite these limitations, our study is based on the second largest cohort, which was only exceeded in size by this of Kikuchi *et al.*[15] Our findings corroborate smaller scale studies, as suggested by Cheng *et al.*[23] Moreover, we demonstrate that %HGTV represents an independent predictor of biochemical recurrence, not only in North American patients, but also in European patients. Thus, the effect of %HGTV is generalisable across two different continents.

5. Conclusion

TV determines the rate of positive surgical margins and %HGTV determines the rate of biochemical recurrence, beyond that of any other standard variable. From the perspective of prostate cancer biology, these findings suggest that tumour bulk is the determinant of local tumour extension and that percentage of high grade cancer is a key determinant of biochemical recurrence after radical prostatectomy.

Conflict of interest statement

None.

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