Published in final edited form as:

J Urol. 2019 March ; 201(3): 535–540. doi:10.1016/j.juro.2018.09.060.

Clinical Utility of Prostate and Tumor Volume-Related Parameters Following Radical Prostatectomy for Localized Prostate Cancer

Yujiro Ito^a, Kazuma Udo^a, Emily A. Vertosick^b, Daniel D. Sjoberg^b, Andrew J. Vickers^b, Hikmat A. Al-Ahmadie^c, Ying-Bei Chen^c, Anuradha Gopalan^c, S. Joseph Sirintrapun^c, Satish K. Tickoo^c, Peter T. Scardino^a, James A. Eastham^a, Victor E. Reuter^c, Samson W. Fine^c

^aDepartment of Surgery (Urology Service), Memorial Sloan Kettering Cancer Center, NY, NY

^bDepartments of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, NY, NY

^cDepartment of Pathology, Memorial Sloan Kettering Cancer Center, NY, NY

Abstract

Purpose: To evaluate whether prediction of biochemical recurrence (BCR) after radical prostatectomy (RP) is enhanced by any of six parameters: prostate volume, total tumor volume (TV), high grade TV, ratio of high grade TV to TV, ratio of TV to prostate volume and/or ratio of high grade TV to prostate volume.

Materials and Methods: 1261 patients who underwent RP over a 3 year period had tumor maps constructed with Gleason pattern denoted as either low (3) or high (4 or 5) and volumetric data generated using commercially available software. Univariate Cox regression models were used to assess whether each volume-related parameters was associated with BCR after RP. A multivariable Cox regression “base model” (age, PSA, Gleason score/grade group, pathologic stage and margin status) was compared with 6 additional models (base model + each volume-related parameter) to evaluate enhancement in predictive accuracy. Decision curve analysis was performed to determine the clinical utility of parameters that enhanced predictive accuracy.

Results: On univariate analysis, each parameter was significantly associated with BCR except prostate volume. Predictive accuracy of multivariable base model was high (c-index=0.861). Adding volume-related parameters marginally enhanced discrimination. Decision curve analysis failed to show added benefit even for high grade TV/TV (parameter with highest discriminative improvement).

Conclusions: Tumor volume-related parameters are significantly associated with BCR, but do not add important discrimination to standard clinicopathologic variables for BCR prediction nor provide benefit across a range of clinically-relevant decision thresholds. Volume-related measurement is not warranted in routine pathologic evaluation and reporting.

Keywords

tumor volume; Gleason score; Grade group; radical prostatectomy; biochemical recurrence

Introduction

It is well known that increased total tumor volume (TV) is associated with a number of prostate cancer grading and staging parameters¹, which, in turn, portend adverse clinical outcomes, most commonly, biochemical recurrence (BCR) following radical prostatectomy (RP). The degree to which TV aids prediction of BCR in the post-RP setting is more controversial, with variable published results over the past two decades. Some studies have demonstrated statistically significant independent predictive value for BCR prediction^{2–3}, while others have argued that TV provides no additional prognostic information when taking into account Gleason score (GS) and pathologic stage^{4–5}.

A host of reports have also evaluated volume-related parameters beyond TV. For instance, percent of prostate volume (PV) involved by tumor (i.e. TV/PV) has been shown to be predictive of BCR in some studies^{6–8}, while others have shown that TV/PV offers no prognostic information for pathologic stage pT2 patients⁹. Prostate cancer grade-related volumes have been tested and similar to other parameters, volume of high grade tumor (HGTV) and percent TV composed of high grade cancer (i.e. HGTV/TV) have shown conflicting results in BCR prediction^{3, 10–13}. Despite the conflicting data, the current guidelines of the College of American Pathologists require, rather than recommend, that some estimation of tumor volume be reported¹⁴.

While a few studies^{8, 12, 15} have compared more than one volume-related parameter, to our knowledge, no one has compared a full complement of these parameters to ascertain which one, if any, best predicts BCR. Similarly, among reports showing a volume-related parameter to be of independent predictive value for BCR, none have moved beyond pure statistical significance to examine clinical significance, that is, whether knowledge of the volume parameter could influence patient management, such as adjuvant therapy post-RP. In this study, we evaluated a large cohort of whole-mounted and entirely submitted RP specimens. We investigated the effect of six volume-related parameters on prediction of BCR following RP to determine whether any parameter had utility for clinical decision making.

Materials and methods

Study Population & Outcomes Definition

After obtaining Institutional Review Board approval, we retrospectively identified 2030 patients who underwent RP at Memorial Sloan Kettering Cancer Center between January 2005 and December 2007, a period during which tumor mapping of RP specimens was conducted. A total of 1261 patients had both RP tumor maps and detailed volumetric data available for analysis and constituted the study cohort. Clinical follow-up post-RP involved serum prostate specific antigen (PSA) levels and physical examination at 3-month intervals

for the first year post-operatively, at 6-month intervals during years 2 to 5 and annually thereafter. BCR after RP was defined as a PSA level of > 0.1 ng/ml with a confirmatory rise.

Tumor Mapping & Volume Quantitation

All RP specimens were inked (separate colors for right and left), serially-sectioned, whole-mounted and entirely-submitted, as previously described¹⁶. Tumor maps were constructed with Gleason grade denoted as either low (grade 3) or high (grade 4/5). All specimen maps were evaluated for accuracy by one of two genitourinary pathologists (VER, SWF). Volume measurements were accomplished by planimetry using Photoshop CC (Adobe Systems, San Jose, CA).

Statistical Analysis

We evaluated whether a cadre of volume-related parameters – PV, TV, TV/PV, HGTV, HGTV/TV and HGTV/PV – improved the predictive accuracy for BCR following RP. We first assessed whether any of these measurements were associated with time to BCR using univariate Cox proportional hazards. To evaluate whether volume-related measurements added to our ability to predict BCR, we used the linear predictor from the MSKCC post-operative nomogram for BCR, which includes pre-operative PSA, RP grade group (GrdGrp), extraprostatic extension (yes/no), seminal vesicle invasion (yes/no), lymph node involvement (yes/no) and surgical margin status (positive v. negative). In some cases, the number of events limited the number of covariates that we could include in the models. The linear predictor was used to account for this, since it provides a way to control for the effects of these covariates in all models regardless of the number of events, using only a single covariate (the linear predictor).

Six additional Cox models, adjusted for the linear predictor and age with the addition of each tumor volume measurement, were created and c-indices were calculated to compare discrimination between these models and the base model. As a sensitivity analysis, we repeated all calculations excluding patients with GrdGrp 1 on pre-RP needle biopsy who are unlikely to undergo RP in current practice. For the volume-related parameter showing the greatest increase in predictive accuracy beyond that provided by the base model, we further constructed a decision curve analysis to determine whether there was benefit for clinical decision making. All analyses were performed using Stata 15 (StataCorp, College Station, TX).

Results

In our cohort of 1,261 patients, 197 patients experienced BCR after RP. Median follow-up time for patients who did not have BCR was 5.2 years (quartiles 3.9, 7.0). Patient and disease characteristics are presented in Table 1, with 78% of cases showing GS 3+4=7 (GrdGrp 2) at RP and 34% having non-organ-confined disease. On univariate analysis, TV, TV/PV, HGTV, HGTV/TV and HGTV/PV were all significantly associated with time to BCR ($p<0.0001$ for all), while PV ($p=0.8$) was not.

In the multivariable analysis, discrimination for the base model (age, PSA and RP GrdGrp, stage and margin status) was 0.861. We found improved discrimination beyond that provided

by the base model for HGTV, HGTV/TV and HGTV/PV (Table 2a), although the increases in discrimination were small. The largest improvement was seen when adding percent HGTV (HGTV/TV) to the base model (c-index improvement of 0.004).

In order to determine the clinical utility of these findings, a decision curve analysis was undertaken (Figure 1a). As these models may be used to determine which patients should undergo more aggressive management following RP and as the value of adjuvant therapy remains controversial in prostate cancer, we assumed that a patient would require a relatively high probability of recurrence before accepting treatment. Hence the decision curve is shown for threshold probabilities up to 50%. Decision curve analysis revealed that there is little net benefit gained by adding HGTV/TV (the parameter that added the most discrimination in multivariable analysis) to the base model.

We repeated our analyses excluding 591 patients with GrdGrp 1 on biopsy, which left a cohort of 670 patients, 171 of whom had BCR. Median follow up time for patients who did not have BCR was 5.1 years (quartiles 3.9, 7.1). Similar to the full cohort, TV, HGTV, HGTV/TV and HGTV/PV were significantly associated with time to BCR ($p < 0.0001$ for all) on univariate analysis and in multivariable analysis, HGTV/TV provided increased discrimination beyond that seen with the base model (Table 2b), with an increase in discrimination of 0.008). However, consistent with the previous analysis, the increase in discrimination was small and there was little improvement in clinical utility as assessed by decision curve analysis (Figure 1b).

Discussion

The post-operative management of prostate cancer patients who have undergone RP is controversial. While randomized trials have demonstrated that adjuvant radiation therapy in the setting of adverse pathologic features (i.e. pT3b or positive surgical margin) may delay BCR^{17–19}, their interpretation is biased by the inclusion of patients who never achieved undetectable PSA levels following radical prostatectomy. Specifically, these patients are best-considered early BCR patients who received early salvage, rather than adjuvant, radiotherapy. Given that clinical observation, followed by salvage radiotherapy when BCR occurs, has been associated with durable cancer control, and that post-operative adjuvant radiotherapy is associated with short- and long-term side effects, many centers will wait to intervene until PSA rises. As such, parameters beyond those provided in standard pathology reporting should be evaluated in the clinical context of whether or not that information provides substantive additional information to aid prediction of BCR.

In this large prostatectomy series, we have demonstrated that some tumor volume-related parameters increase the discriminative accuracy of predicting BCR in a multivariable analysis that controlled for standard clinical and pathologic variables. However, these improvements were very small and failed to add benefit across the range of clinically-relevant decision thresholds.

The prior literature examining the value of TV calculations yields conflicting results among variable cohorts which differ by era (with impact on tumor grading), stage of disease and

methods of volume calculation^{2-9, 13, 15, 20}. A common result among a large number of these studies is the claim that the given parameter does or does not show 'independent predictive value' for BCR prediction. Fewer reports have assessed whether the given tumor volume-related variable added discrimination beyond standard clinical and pathologic factors. Such an evaluation of clinical, rather than just statistical, significance would seem to be a prerequisite for any justification of routine TV calculation and reporting. Indeed, when such advanced analysis was performed for TV and percent HGTV (HGTV/TV) by the same investigators a decade apart, the more recent study found that adding percent HGTV to standard covariates did not increase predictive accuracy in a meaningful way¹³⁻¹⁴. This latter result is concordant with our findings in the present study.

A fair amount of data has been generated regarding the relationship of gland size – in the current study reflected as PV – and the incidence of high grade prostate cancer²¹⁻²⁴. Freedland et al used the Shared Equal Access Regional Cancer Hospital (SEARCH) database and reported an inverse association between prostate weight (another measure of gland size) and high grade disease, pathologic stage, margin status and BCR²¹. While the reason for these findings remains unknown, it has been postulated that men with smaller prostates may have lower levels of testosterone, which has been shown to correlate with more aggressive prostate cancer or that a tumor within a small prostate has to migrate a smaller distance to invade beyond the prostatic capsule²²⁻²³. Importantly, Liu et al have suggested that the association between prostate size and high grade cancer may be a consequence of grade-dependent performance of PSA, rather than tumor biology²⁴. In the current study which assessed the impact of PV – among other parameters – on BCR prediction, no significance was seen in uni- or multivariate analysis. As a caveat, PV was measured from a reconstructed tumor map, instead of the excised prostate weight and might have been influenced by routine processing and scanning.

The current findings are also relevant to prostate cancer reporting for pathologists in practice. It is important to recall that volume calculations in this study were accomplished by planimetry using commercial software. Volume measurement in this fashion, which may be considered more standardized, if not more objectively accurate, than the visual estimation utilized in many TV studies^{6-9, 11, 15}, is a complex and time-consuming task that could only be deemed appropriate for routine clinical practice if it importantly increased model predictiveness. It involves both constructing digital tumor maps with careful delineation of tumor grade and applying imaging software to calculate the volume-related parameters and their ratios. Even after studying RP specimens with this relatively sophisticated process, it is interesting to note that percent HGTV, the parameter which added the most discriminative accuracy to the base model in this study, failed to show added clinical benefit in decision curve analysis. This may be due to the incorporation of GS 7 as GS 3+4=7 (GrdGrp 2) and GS 4+3=7 (GrdGrp 3) which may function as surrogates for the percent HGTV and whose predictive ability for BCR is well-validated²⁵⁻²⁷.

The proceedings of the 2009 International Society of Urological Pathology consensus conference on RP reporting favored inclusion of tumor volume/quantitation in some form²⁸, yet there was no agreement on the ideal method and the crucial issue of interobserver reproducibility was acknowledged. However, current guidelines of the College of American

Pathologists require some estimation of tumor volume be reported¹⁴. Given the marginal improvements over the base model and the lack of clear benefit to clinical decision making as reflected in decision curve analysis, our results with planimetry suggest that volume-related measurement is not warranted in routine pathologic evaluation and reporting.

Some prior reports have alternatively evaluated maximum tumor diameter of the index or dominant tumor mass, as a predictor of BCR. Similar to the findings with TV, some have seen independent predictive value²⁹, while others found no added predictive accuracy when accounting for usual covariates³⁰. While we did not measure maximum tumor diameter in this study, we would suggest that, in light of our results, any tumor quantitation variable considered for inclusion in standard reporting for RP specimens be supported by evidence of its clinical utility.

Any study with a retrospective single institution design may be influenced by the selection of a particular cohort of patients. In this study, limited to those who had available RP tumor maps and volumetric data, this raises the possibility of whether the results may be extrapolated to all RP patients. Nonetheless, the current cohort of 1261 cases is comparable in number to other single institution studies of tumor volume and its association with BCR. A main strength of our study is that all RP specimens were uniformly processed and examined by dedicated urologic pathologists, minimizing variation in interpretation. Moreover, our current analysis goes beyond prior studies in attempting to show the clinical utility of volume-related parameters.

Conclusions

Tumor-volume related parameters in radical prostatectomy provide limited improvement in discrimination of multivariable models for BCR and no utility in clinical decision making beyond that provided by standard predictors. Routine reporting of tumor-volume related parameters is not warranted.

Supported by:

MSK Cancer Center Core Grant (P30 CA008748); The Sidney Kimmel Center for Prostate and Urologic Cancers [MSKCC]

References

1. McNeal JE. Cancer volume and site of origin of adenocarcinoma in the prostate: relationship to local and distant spread. *Hum Pathol* 1992;23:258–266. [PubMed: 1555836]
2. Nelson BA, Shappell SB, Chang SS, Wells N, Farnham SB, Smith JA Jr, et al. Tumor volume is an independent predictor of prostate-specific antigen recurrence in patients undergoing radical prostatectomy for clinically localized prostate cancer. *BJU Int* 2006;97:1169–1172. [PubMed: 16686706]
3. Stamey TA, McNeal JE, Yemoto CM, Sigal BM, Johnstone IM. Biological determinants of cancer progression in men with prostate cancer. *JAMA* 1999;281:1395–1400. [PubMed: 10217055]
4. Kikuchi E, Scardino PT, Wheeler TM, Slawin KM, Ohori M. Is tumor volume an independent prognostic factor in clinically localized prostate cancer? *J Urol* 2004;172:508–511. [PubMed: 15247716]

5. Salomon L, Levrel O, Anastasiadis AG, Irani J, De La Taille A, Saint F, et al. Prognostic significance of tumor volume after radical prostatectomy: a multivariate analysis of pathological prognostic factors. *Eur Urol* 2003;43:39–44. [PubMed: 12507542]
6. Ramos CG, Roehl KA, Antenor JA, Humphrey PA, Catalona WJ. Percent carcinoma in radical prostatectomy specimen is associated with risk of recurrence after radical prostatectomy in patients with pathologically organ confined prostate cancer. *J Urol* 2004;172:137–140. [PubMed: 15201754]
7. Rampersaud EN, Sun L, Moul JW, Madden J, Freedland SJ. Percent tumor involvement and risk of biochemical progression after radical prostatectomy. *J Urol* 2008;180:571–576. [PubMed: 18554662]
8. Uhlman MA, Sun L, Stackhouse DA, Caire AA, Polascik TJ, Robertson CN, et al. Tumor volume, tumor percentage involvement, or prostate volume: which is predictive of prostate-specific antigen recurrence? *Urology* 2010;75:460–466. [PubMed: 19819532]
9. Epstein JI, Carmichael M, Partin AW, Walsh PC. Is tumor volume an independent predictor of progression following radical prostatectomy? A multivariate analysis of 185 clinical stage B adenocarcinomas of the prostate with 5 years of followup. *J Urol* 1993;149:1478–1481. [PubMed: 8501792]
10. Cheng L, Davidson DD, Lin H, Koch MO. Percentage of Gleason pattern 4 and 5 predicts survival after radical prostatectomy. *Cancer* 2007;110:1967–1972. [PubMed: 17823907]
11. Cheng L, Koch MO, Juliar BE, Daggy JK, Foster RS, Bihle R, et al. The combined percentage of Gleason patterns 4 and 5 is the best predictor of cancer progression after radical prostatectomy. *J Clin Oncol* 2005;23:2911–2917. [PubMed: 15860849]
12. Chun FK, Briganti A, Jeldres C, Gallina A, Erbersdobler A, Schlomm T, et al. Tumour volume and high grade tumour volume are the best predictors of pathologic stage and biochemical recurrence after radical prostatectomy. *Eur J Cancer* 2007;43:536–543. [PubMed: 17222546]
13. Hansen J, Bianchi M, Sun M, Rink M, Castiglione F, Abdollah F, et al. Percentage of high-grade tumour volume does not meaningfully improve prediction of early biochemical recurrence after radical prostatectomy compared with Gleason score. *BJU Int* 2014;113:399–407. [PubMed: 24053339]
14. College of American Pathologists. Cancer Protocol Templates, Prostate Gland. cap.org/cancerprotocols. Accessed January 29, 2018.
15. Meyer CP, Hansen J, Boehm K, Tilki D, Abdollah F, Trinh QD, et al. Tumor volume improves the long-term prediction of biochemical recurrence-free survival after radical prostatectomy for localized prostate cancer with positive surgical margins. *World J Urol* 2017;35:199–206. [PubMed: 27260503]
16. Fine SW, Al-Ahmadie HA, Gopalan A, Tickoo SK, Scardino PT, Reuter VE. Anatomy of the anterior prostate and extraprostatic space: a contemporary surgical pathology analysis. *Adv Anat Pathol* 2007;14:401–407. [PubMed: 18049129]
17. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomized controlled trial (EORTC trial 22911). *Lancet* 2012;380:2018–2027. [PubMed: 23084481]
18. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* 2009;181:956–962. [PubMed: 19167731]
19. Weigel T, Bartkowiak D, Bottke D, Bronner C, Steiner U, Siegmann A, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96–02/AUO AP 09/95 Trial. *Eur Urol* 2014;66:243–250. [PubMed: 24680359]
20. Schroeck FR, Sun L, Freedland SJ, Jayachandran J, Robertson CN, Moul JW. Race and prostate weight as independent predictors for biochemical recurrence after radical prostatectomy. *Prostate Cancer Prostatic Dis* 2008;11:371–376. [PubMed: 18427570]
21. Freedland SJ, Isaacs WB, Platz EA, Terris MK, Aronson WJ, Amling CL, et al. Prostate size and risk of high-grade, advanced prostate cancer and biochemical progression after radical

- prostatectomy: a SEARCH database study. *J Clin Oncol* 2005;23:7546–7554. [PubMed: 16234520]
22. D'amico AV, Whittington R, Malkowicz SB, Schultz D, Tomaszewski JE, Wein A. A prostate gland of more than 75 cm³ predicts for a favorable outcome after radical prostatectomy for localized prostate cancer. *Urology* 1998;52:631–636. [PubMed: 9763083]
23. Massengill JC, Sun L, Moul JW, Wu H, McLeod DG, Amling C, et al. Pretreatment total testosterone level predicts pathologic stage in patients with localized prostate cancer treated with radical prostatectomy. *J Urol* 2003;169:1670–1675. [PubMed: 12686805]
24. Liu JJ, Brooks JD, Ferrari M, Nolley R, Presti JC Jr. Small prostate size and high grade disease – biology or artifact? *J Urol* 2011;185:2108–2111. [PubMed: 21496855]
25. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. *J Urol* 1974;111:58–64. [PubMed: 4813554]
26. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. *BJU Int* 2013;111:753–760. [PubMed: 23464824]
27. Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason system. *Eur Urol* 2016;69:428–435. [PubMed: 26166626]
28. van der Kwast TH, Amin MB, Billis A, Epstein JI, Griffiths D, Humphrey PA, et al. International Society of Urological Pathology (ISUP) consensus conference on handling and staging of radical prostatectomy specimens. Working group 2: T2 substaging and prostate cancer volume. *Mod Pathol* 2011;24:16–25. [PubMed: 20818340]
29. Fukuhara H, Kume H, Suzuki M, Fujimura T, Enomoto Y, Nishimatsu H, et al. Maximum tumor diameter: a simple independent predictor for biochemical recurrence after radical prostatectomy. *Prostate Cancer Prostatic Dis* 2010;13:244–247. [PubMed: 20567255]
30. van Oort IM, Witjes JA, Kok DE, Kiemeny LA, Hulsbergen-vandeKaa CA. Maximum tumor diameter is not an independent prognostic factor in high-risk localized prostate cancer. *World J Urol* 2008;26:237–241. [PubMed: 18265988]

Figure 1a.

Decision curve analysis comparing the added benefit of percent high grade tumor volume (HGTV/TV) (yellow line) in addition to standard clinical and pathologic characteristics (green line) for the outcome of BCR at 5 years. Treat all is represented by the blue line and treat none by the red line. Clinical net benefit for the models (y-axis) is plotted against the risk threshold (x-axis) at which a patient or clinician would opt for adjuvant treatment.

Figure 1b.

Among men with biopsy grade group 2 or higher, decision curve analysis comparing adding the percent high grade tumor volume (HGTV/TV) (yellow line) to standard covariates (green line) for the outcome of BCR at 5 years.

Table 1.

Patient and disease characteristics (n=1261). Data are presented as frequency (%) or median (quartiles).

Age at surgery	60 (55, 65)
Pre-RP PSA (ng/ml)	5.4 (3.8, 7.7)
Grade group at RP	
1	283 (23%)
2	647 (51%)
3	228 (18%)
4	35 (3%)
5	68 (5.5%)
Pathologic T stage	
pT2	836 (66%)
pT3a	358 (28%)
pT3b	65 (5.1%)
pT4	2 (0.2%)
Extraprostatic extension	
None	839 (67%)
Focal	135 (11%)
Non-focal/Established	285 (23%)
Seminal vesicle invasion	67 (5.3%)
Lymph node involvement (n=1213)	92 (7.6%)
Positive surgical margins	230 (18%)

Table 2a.

Improvement in discrimination when adding tumor volume measurements to the base model adjusted for age, pre-operative PSA, RP grade group, stage and surgical margin status, and p values for tumor volume measurement on multivariable analysis.

Model	C-index	Improvement	p-value
Base model	0.861		
+ Prostate volume (cc)	0.863	0.002	0.6
+ Tumor volume (cc)	0.860	0.000	0.2
+ Ratio of tumor volume to prostate volume	0.861	0.000	0.4
+ High grade tumor volume (cc)	0.862	0.001	0.2
+ Ratio of high grade tumor volume to tumor volume	0.864	0.004	<0.0001
+ Ratio of high grade tumor volume to prostate volume	0.862	0.001	0.2

Table 2b.

Improvement in discrimination among patients with biopsy grade group 2 or higher when adding tumor volume measurements to the base model adjusted for age, pre-operative PSA, RP Grade group, stage and surgical margin status, and p values for tumor volume measurement on multivariable analysis.

Model	C-index	Improvement	p value
Base model	0.810		
+ Prostate volume (cc)	0.811	0.001	0.14
+ Tumor volume (cc)	0.810	0.000	0.2
+ Ratio of tumor volume to prostate volume	0.811	0.001	0.3
+ High grade tumor volume (cc)	0.813	0.002	0.094
+ Ratio of high grade tumor volume to tumor volume	0.818	0.008	0.001
+ Ratio of high grade tumor volume to prostate volume	0.813	0.002	0.2