

Tumor Volume Associated with Recurrence in Prostate Cancer Patients with Seminal Vesicle Invasion

Paul H. Johnston^{1*}, Timothy A. Masterson¹, Liang Cheng², Michael O. Koch¹

¹Department of Urology, Indiana University Medical Center, Indianapolis, USA

²Department of Pathology and Laboratory Medicine, Indiana University Medical Center, Indianapolis, USA

Email: *phjohnston@hotmail.com

Received July 14, 2012; revised August 31, 2012; accepted September 12, 2012

ABSTRACT

Objectives: To examine predictors of progression-free survival in men with seminal vesicle invasion (SVI) following radical prostatectomy (RP) for clinically localized prostate cancer. **Methods and Materials:** Between 1999 and 2009, 1383 men underwent RP at Indiana University. Among them, 115 men were identified with SVI. Disease progression was defined by a rise in PSA ≥ 0.2 ng/ml, receipt of salvage therapy, progression to metastatic disease, or death. After excluding 13 patients for receiving adjuvant therapy, 102 were stratified according to surgical margin (SM) and lymph node (LN) status for Kaplan-Meier analysis of disease progression. Cox proportional hazards analyses of biochemical progression-free survival were undertaken with respect to margin status, pre-operative prostate specific antigen (PSA), tumor volume, age, and post-operative Gleason sum. Stem and leaf plot was undertaken for tumor volume by biochemical PFS. **Results:** Mean age was 61 years, median Gleason sum was 7, mean tumor volume was 9.7 ml, and mean pre-operative PSA was 13.6 ng/ml. Mean time to disease progression was 17 months. Mean follow-up was 37 months. Kaplan-Meier analysis revealed statistically insignificant differences in progression-free survival stratified by SM and LN status ($p = 0.12$). Cox univariate analyses revealed tumor volume to be a statistically significant predictor of progression free survival ($p = 0.02$). Stem and Leaf plot revealed tumor volume to be statistically significantly larger in patients who experienced biochemical recurrence, compared to those who did not. **Conclusion:** Tumor volume was associated progression-free survival in this cohort of SVI patients, while pathologic Gleason sum, PSA, margin and nodal status were not.

Keywords: Prostate; Neoplasm; Prostatectomy; Seminal Vesicle Invasion; Recurrence

1. Introduction

Seminal vesicle invasion (SVI) is identified in approximately 3% of prostatectomy specimens in the contemporary prostate-specific antigen (PSA) era [1]. While increased tumor volume has not been shown to be an independent predictor of survival on multivariate analysis of robust radical prostatectomy (RP) data sets, these data sets were largely comprised of patients without SVI, and these data sets did not examine the prognostic significance of tumor volume with specific reference to SVI patients [2,3]. Other studies have sought clarification of the pathologic factors predictive of survival in patients with seminal vesicle invasion specifically, yet overlooked the prognostic value of tumor volume [1,4-8]. While tumor volume has been shown to be associated with SVI in general [9], Epstein showed tumor volume as not predictive of survival in SVI patients [10]. Conversely, Sofer *et al.* demonstrated tumor volume greater than 20% to be

predictive of PSA failure in 106 prostatectomy patients with SVI and negative lymph nodes [11]. Overall, there remains equipoise with respect to tumor volume's prognostic role in SVI patients, and with respect to which clinico-pathologic parameters carry prognostic significance for SVI patients in general [7]. This paper seeks to further explore the clinico-pathologic parameters predictive of progression-free survival (PFS) in patients with SVI, with specific reference to tumor volume.

2. Materials and Methods

Between 1999 and 2009, 1383 men underwent RP, either open or robotic, at Indiana University Hospital. After obtaining IRB approval, age at prostatectomy, pathologic Gleason sum, pre-operative PSA, tumor volume, seminal vesicle invasion, surgical margin status (SM+/-), and lymph node status (LN+/-) were analysed retrospectively. Where nodal dissection was performed, all nodal tissue bordered by the pelvic sidewall, Cooper's ligament, the external iliac vein, and the hypogastric vessels was re-

*Corresponding author.

moved. Patients were excluded from analysis for receipt of adjuvant treatment.

Specimen processing occurred using the whole mount method for pathological evaluation, as described previously [12,13]. After surgical extirpation, each prostate was weighed (g), measured, inked and fixed in formalin. After fixation, the apex and the base of the prostate were amputated and sectioned in the vertical, parasagittal plane at 3 - 5 mm intervals, assessing for tumor involvement. The seminal vesicles were amputated parallel to the base of the prostate, sectioned parallel to the junction of the prostate at 3 mm intervals, and embedded entirely for histologic examination. The prostate was then sectioned perpendicularly in 5 mm increments along its long axis from the apex to the base of the gland. All slides were reviewed by a single pathologist (LC). Pathological staging of each specimen was undertaken using the 2010 TNM staging system. Tumor grade was assigned according to 2005 ISUP classification system [14]. Tumor volume was estimated using the grid method [15], and maximum tumor diameter was recorded using the greatest cross-sectional dimension (cm) of the dominant tumor.

Using analysis of variance, all 102 SVI patients were stratified into SM+ and SM- groups, and LN+ and LN- groups, and analyzed for differences in age at RP, pathologic Gleason sum (trichotomous variable), pre-operative PSA, tumor volume, and prostate weight. This same grouping was then used for Kaplan-Meier survival analysis, with respect to PFS. Additionally, Cox proportional hazards analyses of PFS were undertaken for the 83 patients with respect to margin status, pre-operative PSA, tumor volume, age, and pathologic Gleason sum. Finally, stem and leaf plot was undertaken for tumor volume by biochemical PFS. Disease progression was defined by a rise in the PSA ≥ 0.2 ng/mL, receipt of salvage therapy, development of distant metastases, or death from prostate cancer. Statistical calculations were performed using STATA statistical software (College Station, Texas), and a p-value of less than 0.05 was chosen as significant.

3. Results

From the original cohort of 1383 patients, 115 (8.3%) were identified with SVI. After exclusion of 13 SVI patients for receipt of adjuvant therapy (7 received adjuvant androgen deprivation and adjuvant chemotherapy, 3 received adjuvant androgen deprivation only, and 3 received adjuvant radiation), the remaining 102 SVI patients were analysed, and their clinico-pathologic characteristics are seen in **Table 1**. Mean age was 61 years, median Gleason sum was 7, mean tumor volume was 9.7 mL, and mean pre-operative PSA was 13.6 ng/mL. Mean time to disease progression was 17 months. Mean follow-up was 37 months, 81.3% had a pelvic lymph node dissection at time of prostatectomy, and the margin-positive rate was 43%. 56 (54.9%) patients experienced biochemical recurrence, 43 (42.2%) patients were without evidence of biochemical recurrence at last follow-up, and 3 (2.9%) patients received salvage radiation and were deemed to have recurred.

Of the 102 patients analysed, 54 (52.9%) had isolated SVI without positive surgical margins (SM-) or pathologically confirmed lymph node involvement (LN-). Of the remaining 48 (47.1%) patients with SVI, 38 (37.3%) patients had specimen-confined disease with positive surgical margins (SM+), and 10 (9.8%) patients had pathologically confirmed lymph node involvement (LN+). Following patient stratification into these three subgroups, Kaplan-Meier analysis with respect to recurrence-free survival revealed non-statistically significant differences in recurrence-free survival ($p = 0.12$). When assessing for predictors of biochemical failure in all patients, univariate and multivariate analyses were performed (**Table 2**). Tumor volume proved significant on univariate analysis. Stem and leaf plot revealed tumor volume to be statistically significantly larger in patients who experienced biochemical recurrence (BCR), compared to those who did not ($p < 0.001$).

Table 1. Clinico-pathologic characteristics of 102 patients with SVI.

Parameter	All Patients (n = 102)	SM-/LN- (n = 54)	SM+/LN- (n = 38)	LN+ (n = 10)	p value
Mean Age at Prostatectomy	61 (44 - 74)	61 (44 - 74)	62 (45 - 73)	63 (53 - 74)	0.75
Gleason Sum (%)					
≤ 6	3 (3) 67 (66)	2 (4)	1 (3)	0 (0)	
7	30 (31)	42 (78)	19 (50)	6 (60)	0.009
≥ 8		10 (18)	18 (47)	4 (40)	
Mean Tumor Volume (mL)	9.7 (0.2 - 38.0)	5.7 (0.2 - 32)	14.2 (1.2 - 38)	14.4 (3.6 - 29.3)	<0.0001
Mean Pre-op PSA	13.6	9.8 (2.9 - 39.9)	18.5 (3.8 - 150)	14.8 (6.5 - 31.6)	0.06
Mean Prostate Weight (g)	44.5 (20 - 100)	43 (25 - 95)	44.4 (20 - 76)	52 (26 - 100)	0.21

Table 2. Cox proportional hazards analyses of clinico-pathologic 83 patients with SVI.

Analysis	Parameter	Hazard Ratio	95% CI	p Value
Univariate	Age	1.04	0.99, 1.1	0.13
	PSA	1.00	0.99, 1.0	0.44
	Tumor Volume	1.04	1.0, 1.1	0.02
	Gleason Sum (<7 vs. 7 vs. 8 or more)	2.1	0.99, 4.5	0.05
	SM	1.19	0.55, 2.6	0.65
Multivariate	Age	1.03	0.97, 1.1	0.39
	PSA	1.0	0.98, 1.0	0.73
	Tumor Volume	1.08	0.99, 1.2	0.07
	Gleason Sum (>7 vs. 7 vs. 8 or more)	2.42	0.95, 6.1	0.06
	SM	0.63	0.21, 1.9	0.40

4. Comment

In this retrospective cohort of SVI patients, tumor volume was associated with PFS on univariate analysis, while margin status, age, pathologic Gleason sum and pre-operative PSA were not. Stem and leaf plot confirms smaller tumor volume to be associated with longer biochemical progression-free survival in SVI patients. Additionally, Kaplan-Meier analysis failed to demonstrate survival differences for SVI patients according to margin and node status.

Epstein *et al.* [16] defined SVI as penetration of the muscular wall of the SVI as opposed to peri-vesicle involvement of tumor, based upon differential survival for these two pathologic findings. Furthermore, they suggested that the staging definition of SVI need specify involvement of the distal, free end of the vesicle, once again on the basis of differential survival. This suggestion was supported by Debras *et al.* [17], who confirmed a worse prognosis for such patients. SVI has been further subclassified, although this subclassification does not affect prognosis in a statistically significant manner [18].

This study reveals an association between tumor volume and recurrence for SVI patients. This association can help clinicians prognosticate biochemical recurrence post-prostatectomy, but further research need be done before a pre-operative MRI revealing a large tumor volume in a patient known to harbour SVI would cancel surgery.

In addition to contributing to the relatively sparse literature on the predictive role of tumor volume in patients with SVI, this study sought to further clarify the predictive role of Gleason sum for such patients. Gleason sum is a crucial prognostic indicator of biochemical recurrence for RP patients in general [19], and for SVI patients this has largely been the case [1,4-6,10]. In reveal-

ing differences in Gleason sum on Analysis of Variance of 102 SVI patients stratified by node and margin status, despite no evidence of survival differences upon Kaplan-Meier analysis of these same strata, our study fails to add further credence to Gleason sum as a predictor of survival in SVI patients, but does not necessarily support the small body of work which suggests Gleason sum is not predictive of survival in SVI patients [8,11].

Our study offers no clarification with respect to the predictive role of positive surgical margins for SVI patients. Generally speaking, a positive surgical margin at the time of RP is a negative prognostic indicator [20]. Several papers focusing on PFS in patients with SVI and negative lymph nodes have demonstrated a prognostic value to margin status under these circumstances [1,5,6,8,10], while others have shown no such value [4,11]. Our work further confuses the issue, as a predictive role for margin status was not demonstrated on Cox multivariate analysis of all RP patients, nor was a survival difference demonstrated in the Kaplan-Meier analysis of SVI patients in particular.

In much the same manner, this study does not improve upon the controversy surrounding pre-operative PSA's predictive role for SVI patients. PSA is a well-known prognostic indicator of biochemical recurrence for prostatectomy patients in general [19] and several publications have shown a predictive value to pre-operative PSA where SVI patients have negative lymph nodes [4,6,11]. Conversely, others demonstrate no predictive value for such patients [1,5,8,10]. In failing to demonstrate differential PSA values for SVI patients stratified by node and margins status, we are unable to comment on PSA's role in the lack of survival difference seen on Kaplan-Meier analysis of these same strata of SVI patients. It's worth noting the p-value for in this case was close to significance, and it may be that our study size was simply

underpowered to reveal statistical significance.

The authors acknowledge this study's retrospective nature is subject to the selection bias inherent in its design. Furthermore, pelvic lymph node dissection was not undertaken in 18.6% patients. While nodal dissections in all patients would be advantageous from a statistical analysis point-of-view, the finding of pathologic SVI was not routinely anticipated pre-operatively, thus the decision to forgo nodal dissection in a subset of the cohort is reflective of real-world oncologic decision-making. It must also be noted that a mean follow-up of 37 months is relatively short for prostate cancer, although a mean time to progression of 17 months suggests that the vast majority of patients who were going to progress biochemically had done so by the time mean follow-up was reached. Furthermore, given the high-risk nature of SVI patients as a whole, follow-up as observed in this study is likely adequate for the endpoint of biochemical recurrence. Finally, it is worth acknowledging that a more robust data set of SVI patients would be helpful in further delineating the role of tumor volume as a prognostic pathologic parameter [1].

5. Conclusion

This data set fails to demonstrate progression-free survival differences for men with SVI, according to surgical margin and lymph node status. While there remains equipoise in this patient population with respect to which clinico-pathologic parameters confer survival advantage, this paper suggests lower tumor volume is advantageous to patients with SVI at the time of RP.

REFERENCES

- [1] P. M. Pierorazio, A. E. Ross, E. M. Schaeffer, *et al.*, "A Contemporary Analysis of Outcomes of Adenocarcinoma of the Prostate With Seminal Vesicle Invasion (pT3b) after Radical Prostatectomy," *Journal of Urology*, Vol. 185, No. 5, 2011, pp. 1691-1697. [doi:10.1016/j.juro.2010.12.059](https://doi.org/10.1016/j.juro.2010.12.059)
- [2] S. P. Porten, M. R. Cooperberg and P. R. Carroll, "The Independent Value of Tumour Volume in a Contemporary Cohort of Men Treated with Radical Prostatectomy for Clinically Localized Disease," *British Journal of Urology International*, Vol. 105, No. 4, 2010, pp. 472-475.
- [3] E. Kikuchi, P. T. Scardino, T. M. Wheeler, K. M. Slawin and M. Otori, "Is Tumor Volume an Independent Prognostic Factor in Clinically Localized Prostate Cancer?" *Journal of Urology*, Vol. 172, No. 2, 2004, pp. 508-511. [doi:10.1097/01.ju.0000130481.04082.1a](https://doi.org/10.1097/01.ju.0000130481.04082.1a)
- [4] L. Salomon, A. G. Anastasiadis, C. W. Johnson, *et al.*, "Seminal Vesicle Involvement after Radical Prostatectomy: Predicting Risk Factors for Progression," *Urology*, Vol. 62, No. 2, 2003, pp. 304-309. [doi:10.1016/S0090-4295\(03\)00373-X](https://doi.org/10.1016/S0090-4295(03)00373-X)
- [5] S. J. Freedland, W. J. Aronson, J. C. Presti Jr., *et al.*, "Predictors of Prostate-Specific Antigen Progression among Men with Seminal Vesicle Invasion at the Time of Radical Prostatectomy," *Cancer*, Vol. 100, No. 8, 2004, pp. 1633-1638. [doi:10.1002/cncr.20122](https://doi.org/10.1002/cncr.20122)
- [6] M. V. Tefilli, E. L. Gheiler, R. Tiguert, *et al.*, "Prognostic Indicators in Patients with Seminal Vesicle Involvement Following Radical Prostatectomy for Clinically Localized Prostate Cancer," *Journal of Urology*, Vol. 160, No. 3, 1998, pp. 802-806. [doi:10.1016/S0022-5347\(01\)62791-5](https://doi.org/10.1016/S0022-5347(01)62791-5)
- [7] T. A. Masterson, J. A. Pettus, R. G. Middleton and R. A. Stephenson, "Isolated Seminal Vesicle Invasion Imparts Better Outcomes after Radical Retropubic Prostatectomy for Clinically Localized Prostate Cancer: Prognostic Stratification of pt3b Disease by Nodal and Margin Status," *Urology*, Vol. 66, No. 1, 2005, pp. 152-155. [doi:10.1016/j.urology.2005.01.014](https://doi.org/10.1016/j.urology.2005.01.014)
- [8] A. R. Ramsden and G. Chodak, "An Analysis of Risk Factors for Biochemical Progression in Patients with Seminal Vesicle Invasion: Validation of Kattan's Nomogram in a Pathological Subgroup," *British Journal of Urology International*, Vol. 93, No. 7, 2004, pp. 961-964. [doi:10.1111/j.1464-410X.2003.04760.x](https://doi.org/10.1111/j.1464-410X.2003.04760.x)
- [9] A. W. Partin, J. I. Epstein, K. R. Cho, A. M. Gittelsohn and P. C. Walsh, "Morphometric Measurement of Tumor Volume and Percent of Gland Involvement as Predictors of Pathological Stage in Clinical Stage B Prostate Cancer," *Journal of Urology*, Vol. 141, No. 2, 1989, pp. 341-345.
- [10] J. I. Epstein, A. W. Partin, S. R. Potter and P. C. Walsh, "Adenocarcinoma of the Prostate Invading the Seminal Vesicle: Prognostic Stratification Based on Pathologic Parameters," *Urology*, Vol. 56, No. 2, 2000, pp. 283-288. [doi:10.1016/S0090-4295\(00\)00640-3](https://doi.org/10.1016/S0090-4295(00)00640-3)
- [11] M. Sofer, M. Savoie, S. S. Kim, F. Civantos and M. S. Soloway, "Biochemical and Pathological Predictors of the Recurrence of Prostatic Adenocarcinoma with Seminal Vesicle Invasion," *Journal of Urology*, Vol. 169, No. 1, 2003, pp. 153-156. [doi:10.1016/S0022-5347\(05\)64057-8](https://doi.org/10.1016/S0022-5347(05)64057-8)
- [12] L. Cheng, J. Slezak, E. J. Bergstralh, R. P. Myers, H. Zincke and D. G. Bostwick, "Preoperative Prediction of Surgical Margin Status in Patients with Prostate Cancer Treated by Radical Prostatectomy," *Journal of Clinical Oncology*, Vol. 18, No. 15, 2000, pp. 2862-2868.
- [13] R. E. Emerson, M. O. Koch, J. K. Daggy and L. Cheng, "Closest Distance between Tumor and Resection Margin in Radical Prostatectomy Specimens: Lack of Prognostic Significance," *The American Journal of Surgical Pathology*, Vol. 29, No. 2, 2005, pp. 225-229. [doi:10.1097/01.pas.0000146008.47191.76](https://doi.org/10.1097/01.pas.0000146008.47191.76)
- [14] J. I. Epstein, W. C. Allsbrook Jr., M. B. Amin and L. L. Egevad, "The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma," *The American Journal of Surgical Pathology*, Vol. 29, No. 9, 2005, pp. 1228-1242. [doi:10.1097/01.pas.0000173646.99337.b1](https://doi.org/10.1097/01.pas.0000173646.99337.b1)
- [15] P. A. Humphrey and R. T. Vollmer, "Intraglandular Tumor Extent and Prognosis in Prostatic Carcinoma: Application of a Grid Method to Prostatectomy Specimens,"

- Human Pathology*, Vol. 21, No. 8, 1990, pp. 799-804.
[doi:10.1016/0046-8177\(90\)90048-A](https://doi.org/10.1016/0046-8177(90)90048-A)
- [16] J. I. Epstein, M. Carmichael and P. C. Walsh, "Adenocarcinoma of the Prostate Invading the Seminal Vesicle: Definition and Relation of Tumor Volume, Grade and Margins of Resection to Prognosis," *Journal of Urology*, Vol. 149, No. 5, 1993, pp. 1040-1045.
- [17] B. Debras, B. Guillonneau, J. Bougaran, E. Chambon and G. Vallancien, "Prognostic Significance of Seminal Vesicle Invasion on the Radical Prostatectomy Specimen. Rationale for Seminal Vesicle Biopsies," *European Urology*, Vol. 33, No. 3, 1998, pp. 271-277.
[doi:10.1159/000019579](https://doi.org/10.1159/000019579)
- [18] M. Ohori, P. T. Scardino, S. L. Lapin, C. Seale-Hawkins, J. Link and T. M. Wheeler, "The Mechanisms and Prognostic Significance of Seminal Vesicle Involvement by Prostate Cancer," *The American Journal of Surgical Pathology*, Vol. 17, No. 12, 1993, pp. 1252-1261.
[doi:10.1097/00000478-199312000-00006](https://doi.org/10.1097/00000478-199312000-00006)
- [19] A. V. D'Amico, R. Whittington, S. B. Malkowicz, et al., "Biochemical Outcome after Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer," *The Journal of the American Medical Association*, Vol. 280, No. 1, 1998, pp. 969-974. [doi:10.1001/jama.280.11.969](https://doi.org/10.1001/jama.280.11.969)
- [20] P. Swindle, J. A. Eastham, M. Ohori, et al., "Do Margins Matter? The Prognostic Significance of Positive Surgical Margins in Radical Prostatectomy Specimens," *Journal of Urology*, Vol. 179, No. 5, 2008, pp. S47-S51.
[doi:10.1016/j.juro.2008.03.137](https://doi.org/10.1016/j.juro.2008.03.137)