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The Clinical Impact of Unilateral Versus Bilateral Invasion Into the Seminal Vesicle in Patients With Prostate Cancer Undergoing Radical Prostatectomy

Numbereye Numbere, MD; Yuki Teramoto, MD; Pratik M. S. Gurung, MD, PhD; Ying Wang, MD, PhD; Zhiming Yang, MD, PhD; Hiroshi Miyamoto, MD, PhD

• Context.—Seminal vesicle involvement by prostate cancer has generally been considered as a key prognosticator.

Objective.—To assess the clinical significance of unilateral (Uni) versus bilateral (Bil) seminal vesicle invasion (SVI).

Design.—We compared radical prostatectomy findings and long-term oncologic outcomes in 248 patients showing Uni-SVI (n = 139) versus Bil-SVI (n = 109).

Results.—Tumor grade was significantly higher in Bil-SVI cases than in Uni-SVI cases. Additionally, Bil-SVI was significantly associated with a higher incidence of lymphovascular invasion, lymph node metastasis, or positive surgical margin, and larger estimated tumor volume. When the histopathologic features at SVI foci were compared, Grade Group (GG) 3-5/4-5/5 and cribriform morphology were significantly more often seen in Bil-SVI. Outcome analysis revealed that patients with Bil-SVI had a significantly higher risk of disease progression (P < .001) than patients with Uni-SVI. Significantly worse progression-free survival in patients with Bil-SVI was also observed in all subgroups examined, including those with no immediate adjuvant therapy (IAT) (n = 139; P = .01), IAT (n = 109; P = .001), pN0 disease (n = 153; P = .002), or pN1 disease (n = 93; P = .006). In multivariate analysis, Bil-SVI (versus Uni-SVI) showed significance for progression in the entire (hazard ratio [HR] = 1.83, P = .01), IAT (HR = 2.90, P = .006), and pN0 (HR = 2.05, P = .01) cohorts. Meanwhile, tumor grade at SVI (eg, GG4, GG5), as an independent predictor, was significantly associated with patient outcomes.

Conclusions.—Bil-SVI was found to be strongly associated with worse histopathologic features on radical prostatectomy and poorer prognosis. Pathologists may thus need to report Uni-SVI versus Bil-SVI, along with other histopathologic findings, such as Gleason score, at SVI in prostatectomy specimens.

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Prostate cancer has been one of the most commonly diagnosed malignancies among men, and cancer-related deaths worldwide have risen from an estimated 307,500 in 20121 to 358,989 in 2018.2 Although radical prostatectomy, as a definitive form of treatment, often offers excellent oncologic outcomes in those with localized disease, a considerable number of these patients develop recurrent disease following the surgery.3,4 In this context, adequate risk stratification is evidently crucial for optimal patient care with respect to not only selecting the most suitable treatment option but also managing any recurrence following such therapy.

Stage pT3b prostate cancer exhibiting seminal vesicle invasion (SVI) has long been considered as a critical prognostic factor for predicting the postoperative risk of disease recurrence and disease-specific mortality. Remarkably, however, pT3b disease does not uniformly indicate an unfavorable outcome. Indeed, several studies have attempted to identify “low-risk” pT3b prostate cancer by assessing the tumor extent of SVI and/or its volume in radical prostatectomy specimens.5–8 Particularly, in two of these studies,5,8 bilateral SVI (Bil-SVI) has been suggested to be associated with worse prognosis than unilateral SVI (Uni-SVI). Nonetheless, the cohorts of patients with pT3b disease in these studies were relatively small (eg, N = 27–93).5–8 Moreover, based on currently available evidence in the literature, the prognostic value of other histopathologic characteristics in SVI remains poorly understood. Thus, there is ample scope for more clarity in delineating the importance of histopathology for improved prognostic stratification in pT3b prostate cancer. The present study aims to compare radical prostatectomy findings and long-term oncologic outcomes in a larger cohort showing Uni-SVI versus Bil-SVI in various clinicopathologic settings, such

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From the Department of Pathology & Laboratory Medicine (Numbere, Teramoto, Wang, Yang, Miyamoto), James P. Wilmot Cancer Institute (Teramoto, Miyamoto), and the Department of Urology (Gurung, Miyamoto), University of Rochester Medical Center, Rochester, New York.

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Corresponding author: Hiroshi Miyamoto, MD, PhD, Department of Pathology & Laboratory Medicine, University of Rochester Medical Center, 601 Elmwood Avenue, Box 626, Rochester, NY 14642 (email: hiroshi_miyamoto@urmc.rochester.edu).
as patients undergoing or not undergoing adjuvant therapy immediately after prostatectomy and those with pN0 or pN1 disease.

**MATERIALS AND METHODS**

Upon approval by the institutional review board, including the request to waive patient consent documentation, we assessed consecutive patients who had undergone robot-assisted radical prostatectomy for prostatic adenocarcinoma at our institution between 2009 and 2018. Within our surgical pathology database (ie, 2993 radical prostatectomy cases), we identified a total of 252 consecutive patients who had undergone robot-assisted radical prostatectomy for prostatic adenocarcinoma at our institution. We first analyzed the entire cohort of patients with Uni-SVI or Bil-SVI was found in 139 (56.0%) or 109 (44.0%) cases, respectively.

We retrieved clinicopathologic findings, such as age at surgery, preoperative prostate-specific antigen (PSA) value, the laterality of SVI, the status of lymphovascular invasion, pN, and surgical margin, and estimated cancer volume, as well as follow-up data. In our recent study using the same cohort of patients, Gleason score/

**Table 1. Clinicopathologic Features of 248 Patients**

| Feature                                      | Uni-SVI (N = 139) | Bil-SVI (N = 109) | P     |
|----------------------------------------------|-------------------|------------------|-------|
| Age, mean (median), y                        | 64.7              | 63.9             | .28   |
| Preoperative PSA value, ng/mL                | 10.4              | 14.6             | .06   |
| Grade Groups 3-5                             | 80.6%             | 89.9%            | .04   |
| Grade Groups 4-5                             | 33.1%             | 55.0%            | <.001 |
| Grade Group 5                                | 27.3%             | 46.8%            | .002  |
| Lymphovascular invasion                      | 20.9%             | 37.6%            | .004  |
| pN1                                          | 29.5%             | 47.7%            | .003  |
| Positive surgical margin                     | 25.9%             | 51.4%            | <.001 |
| Tumor volume, mean, cm³                      | 13.3              | 24.3             | <.001 |
| Adjuvant therapy before recurrence           | 40.3%             | 48.6%            | .19   |

Abbreviation: PSA, prostate-specific antigen.

Grade Group (GG) (primarily in “dominant” nodule[s] in each case) had been reevaluated from recommendations by the International Society of Urological Pathology as well as the Genitourinary Pathology Society. In cases with GG2 or GG3 cancer, less than 5% of a minor tertiary pattern 5 was ignored for analysis. We then histologically evaluated SVI region(s) (eg, GG, cribriform morphology, total tumor size in each side) in available cases (N = 222). Seminal vesicle invasion was confirmed as tumor invasion into the muscular wall of the extraprostatic seminal vesicle, as currently defined. Biochemical recurrence after prostatectomy in patients with no adjuvant therapy was defined as a single PSA level of 0.2 ng/mL or higher, while PSA failure in those undergoing adjuvant treatments such as hormonal therapy (N = 31), radiotherapy (N = 47), or their combination (N = 31), immediately after prostatectomy (ie, prior to disease progression), was defined as an increase in PSA value of 2 ng/mL or higher, or at least 50% over nadir, or the introduction of salvage therapy. 

Prostate-specific antigen recurrence in those both with and without adjuvant therapy was considered as disease progression.

Data were analyzed by using the Student t test for continuous variables and the χ² test or Fisher exact test for noncontinuous variables. The survival rate was calculated by the Kaplan-Meier method, and comparison was made by the log-rank test. In addition, the Cox proportional hazards model was used to determine the statistical significance of prognostic factors in a multivariate setting. All statistical analyses were performed with GraphPad Prism version 5 (GraphPad Software) and EZR software, a graphic user interface for R version 4.0.2 (The R Foundation for Statistical Computing). P values less than .05 were considered to be statistically significant.

**RESULTS**

In a retrospective, blinded manner, we examined a total of 248 radical prostatectomy cases with pT3b disease. Table 1 summarizes the clinicopathologic features of these patients. Overall, Uni-SVI or Bil-SVI was found in 139 (56.0%) or 109 (44.0%) cases, respectively.

We first analyzed the entire cohort of patients with Uni-SVI versus Bil-SVI (Table 2). When compared with Uni-SVI, Bil-SVI was significantly associated with higher tumor grade, higher incidence of lymphovascular invasion, lymph node metastasis, or positive surgical margin, and larger tumor volume. In patients with Bil-SVI, preoperative PSA value was also marginally higher, but there were no significant differences in age and the need for adjuvant therapy immediately after prostatectomy (before disease recurrence).

In these patients, we then compared the histopathologic features of the tumors at the foci of SVI (Table 3; also see
Table 3. Histopathologic Findings at Seminal Vesicle Invasion

|                | Unilateral (N = 127) | Bilateral (N = 95) | P     |
|----------------|----------------------|--------------------|-------|
| Grade Groups 3-5 | 65.3%                | 92.6%              | <.001 |
| Grade Groups 4-5 | 46.5%                | 73.7%              | <.001 |
| Grade Group 5    | 13.4%                | 31.6%              | .002  |
| Cribriform morphology | 32.3%              | 46.3%              | .03   |
| Total tumor size, cm | 0.67                | 1.57               | <.001 |
| Mean tumor size, cm | 0.67                | 0.78               | .03   |

Table 1). We confirmed the original diagnosis of Uni-SVI or Bil-SVI in all available cases. In Bil-SVI cases, tumor grade (ie, the highest when there were multiple foci) was significantly higher, and cribriform morphology, a Gleason grade 4 subtype recognized as being more aggressive than other pattern 4 morphologies, 16 was significantly more often seen. In addition, even the mean of Bil-SVI sizes was significantly greater than for Uni-SVI. Ductal features, an aggressive subtype of prostatic adenocarcinoma to which Gleason grade 4 could be assigned, 17 were seen in 6 of 222 patients (2.7%), including 3 of 127 Uni-SVI (2.4%) and 3 of 95 Bil-SVI (3.2%) cases, and the difference was not statistically significant (P > .99).

Kaplan-Meier analysis coupled with log-rank test was performed to assess the impact of Uni-SVI versus Bil-SVI on the prognosis following radical prostatectomy, with mean and median follow-up of 60.2 and 50.5 months, respectively. We first compared survival in the entire cohort of patients and found that Bil-SVI, compared with Uni-SVI, was significantly associated with a higher risk of disease progression (P < .001; Figure 1, A), but not that of cancer-specific mortality (P = .31; Figure 1, B). As expected, in these patients, GG on prostatectomy was associated with the risks of disease progression (Supplemental Figure 1, A; see supplemental digital content containing 2 supplemental figures) and cancer-specific mortality (Supplemental Figure 1, B). Specifically, there were significant differences in progression (P = .02; Supplemental Figure 1, C) and mortality (P = .04; Supplemental Figure 1, D) between GG2 and GG3-5 cases, a significant difference in progression (P = .04; Supplemental Figure 1, E) and no significant difference in mortality (P = .17; Supplemental Figure 1, F) between GG2-3 and GG4-5 cases, and a significant difference in progression (P = .02; Supplemental Figure 1, G) and a nonsignificant difference in mortality (P = .06; Supplemental Figure 1, H) between GG2-4 and GG5 cases. Progression-free survival was also separately assessed in subgroups of patients. In those without (N = 139, P = .01; Figure 2, A) and with (N = 109, P = .001; Figure 2, B) adjuvant therapy before disease recurrence, Bil-SVI was associated with significantly worse outcomes than for Uni-SVI. Similarly, the risks of progression were significantly higher in Bil-SVI cases with either pN0 (N = 153, P = .002; Figure 2, C) or pN1 (N = 92, P = .006; Figure 2, D) disease than in respective Uni-SVI cases.

Associations between the highest GG in the area(s) of SVI and disease progression were then assessed (Figure 3, A). There were significant differences in progression-free survival between GG1-2 versus GG3-5 (P = .03; Figure 3, B) or GG1-3 versus GG4-5 (P = .005; Figure 3, C), but not between GG1-4 versus GG5 (P = .22; Supplemental Figure 2, A). In addition, there were no strong associations of the presence of cribriform morphology at SVI (P = .83; Supplemental Figure 2, B) or the total SVI size (dichotomized at median: P = .25; Supplemental Figure 2, C) with the progression. For the latter, no significant differences were obtained by using various cutoff values (eg, 0.5 cm [median of Uni-SVI; P = .29], 0.67 cm [median of Uni-SVI; P = .16], 1.06 cm [median in all cases; P = .40], 1.4 cm [median of Bil-SVI; P = .07; Supplemental Figure 2, D], and 1.57 cm [median of Bil-SVI; P = .09]).

To further determine if the laterality of SVI was an independent predictor of disease progression following radical prostatectomy, multivariate analysis was performed by using the Cox model. In the entire cohort (Table 4), Bil-SVI (versus Uni-SVI) showed significance for the progression (hazard ratio [HR] = 1.83, 95% CI = 1.14–2.93, P = .01). Moreover, there was an association between Bil-SVI and progression-free survival rates in patients with adjuvant therapy immediately after prostatectomy (HR = 2.90, 95% CI = 1.36–6.20, P = .006) or pN0 disease (HR = 2.05, 95% CI = 1.17–3.58, P = .01), but not in those with no adjuvant therapy or pN1 disease (Table 5). Additionally, of

Figure 1. Kaplan-Meier curves for progression-free survival (A) or cancer-specific survival (B) in all pT3b patients. Uni-SVI (n = 139) versus Bil-SVI (n = 109) were compared using the log-rank test. Abbreviations: Bil, bilateral; SVI, seminal vesicle invasion; Uni, unilateral.

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the histopathologic features examined in the area(s) of SVI, tumor grade (eg, GG4, GG5) was an independent predictor for progression, while cribriform morphology and total tumor size were not associated with prognosis (Table 6).

**DISCUSSION**

Contemporary, relatively large studies have identified SVI by prostate cancer in 3.9% to 7.6% of radical prostatectomy specimens, while SVI is still considered to be one of key prognosticators. Nonetheless, a subset of patients with SVI
show favorable outcomes after radical prostatectomy even without adjuvant therapy.\textsuperscript{5–8,20} As such, the prognosis of pT3b disease needs to be further stratified, taking into account other histopathologic data that may be relevant. Indeed, to this end, we recently demonstrated that the presence of concurrent pT3a lesions, including extraprostatic extension (other than SVI) and microscopic bladder neck invasion, in patients with pT3b disease who had undergone radical prostatectomy was associated with significantly worse clinical outcomes as independent predictors.\textsuperscript{8} In the present study, we have compared radical prostatectomy findings and long-term oncologic outcomes in a total of 248 patients with prostate cancer showing Uni-SVI versus Bil-SVI. The prognosis was also assessed in a few studies with some attendant limitations.\textsuperscript{5} In 2 studies involving 60 patients\textsuperscript{5} and 93 patients,\textsuperscript{6} Bil-SVI was associated with significantly higher risks of biochemical recurrence/progression, while 2 other studies with 27 patients\textsuperscript{6} and 60 patients\textsuperscript{7} failed to show the prognostic value of Bil-SVI (versus Uni-SVI). Additionally, in the largest of these studies, Bil-SVI was found to be an independent prognostic factor in the entire cohort of patients with pT3b (N = 93; HR = 1.75, P = .048) or pT3bN0 (N = 69; HR = 1.76, P = .046) disease.\textsuperscript{8} In line with these findings, the extent of SVI (eg, invasion limited to the proximal portion versus extension to the distal portion,\textsuperscript{21} focal versus moderate or extensive,\textsuperscript{2} base versus mid-portions versus tip of the seminal vesicle,\textsuperscript{5} invasion into the muscular wall versus with without mucosal involvement\textsuperscript{2}), as well as the volume of SVI (eg, \leq 1.63 versus >1.63 cm\textsuperscript{3}),\textsuperscript{6} has been significantly associated with patient outcomes. In some of these studies, however, there were no associations of the extent (eg, limited versus extended)\textsuperscript{6} or route (eg, extraprostatic extension ± ejaculatory duct involvement, metastasis)\textsuperscript{k} of SVI, as well as tumor grade at SVI,\textsuperscript{2} with the prognosis. Meanwhile, the prognosis of Uni-SVI versus Bil-SVI has never been compared in specific subgroups of patients, such as those with pN1 disease or adjuvant therapy.

| Table 4. Multivariate Analysis for Disease Progression in the Entire Cohort of Patients |
|-------------------------------------------------|---|---|---|
| All Cases (N = 248)                              | HR | 95% CI | P   |
| Grade Group                                    |    |        |     |
| 2                                              | Reference |
| 3                                              | 2.76 | 1.30–5.83 | .008 |
| 4                                              | 1.88 | 0.66–5.38 | .24  |
| 5                                              | 2.72 | 1.24–5.96 | .01  |
| Seminal vesicle invasion (unilateral versus bilateral) | 1.83 | 1.14–2.93 | .01  |
| pN (0 versus 1)                                 | 0.61 | 0.36–1.02 | .06  |
| Surgical margin (negative versus positive)      | 0.98 | 0.61–1.59 | .95  |
| Tumor volume (\leq median versus > median)      | 1.87 | 1.15–3.07 | .01  |
| Adjuvant therapy (no versus yes)                | 0.73 | 0.45–1.19 | .21  |

Abbreviation: HR, hazard ratio.

| Table 5. Multivariate Analysis for Disease Progression in Subgroups of Patients |
|-------------------------------------------------|---|---|---|
| Cases with no adjuvant therapy (N = 139)        |    |        |     |
| Grade Group                                    |    |        |     |
| 2                                              | Reference |
| 3                                              | 2.09 | 0.89–4.92 | .09  |
| 4                                              | 1.35 | 0.39–4.63 | .64  |
| 5                                              | 3.07 | 1.19–7.94 | .02  |
| Seminal vesicle invasion (unilateral versus bilateral) | 1.39 | 0.74–2.59 | .31  |
| pN (0 versus 1)                                 | 1.14 | 0.57–2.31 | .71  |
| Surgical margin (negative versus positive)      | 1.00 | 0.53–1.89 | .99  |
| Tumor volume (\leq median versus > median)      | 1.65 | 0.89–3.05 | .11  |
| Cases with adjuvant therapy (N = 109)           |    |        |     |
| Grade Group                                    |    |        |     |
| 2                                              | Reference |
| 3                                              | 6.47 | 0.85–49.2 | .07  |
| 4                                              | 5.94 | 0.53–67.2 | .15  |
| 5                                              | 4.06 | 0.54–30.8 | .18  |
| Seminal vesicle invasion (unilateral versus bilateral) | 2.90 | 1.36–6.20 | .006 |
| pN (0 versus 1)                                 | 0.38 | 0.19–0.76 | .006 |
| Surgical margin (negative versus positive)      | 1.03 | 0.45–2.32 | .95  |
| Tumor volume (\leq median versus > median)      | 2.28 | 1.01–5.13 | .046 |
| Cases with pN0 (N = 153)                        |    |        |     |
| Grade Group                                    |    |        |     |
| 2                                              | Reference |
| 3                                              | 3.19 | 1.34–7.59 | .009 |
| 4                                              | 1.38 | 0.35–5.47 | .65  |
| 5                                              | 2.53 | 0.96–6.69 | .06  |
| Seminal vesicle invasion (unilateral versus bilateral) | 2.05 | 1.17–3.58 | .01  |
| Surgical margin (negative versus positive)      | 0.78 | 0.43–1.40 | .40  |
| Tumor volume (\leq median versus > median)      | 2.37 | 1.31–4.29 | .004 |
| Adjuvant therapy (no versus yes)                | 1.21 | 0.67–2.19 | .52  |
| Cases with pN1 (N = 93)                         |    |        |     |
| Grade Group                                    |    |        |     |
| 2                                              | Reference |
| 3                                              | 1.24 | 0.23–6.23 | .79  |
| 4                                              | 2.13 | 0.33–13.9 | .43  |
| 5                                              | 2.05 | 0.43–9.69 | .37  |
| Seminal vesicle invasion (unilateral versus bilateral) | 1.31 | 0.50–3.44 | .59  |
| Surgical margin (negative versus positive)      | 2.29 | 0.92–5.68 | .07  |
| Tumor volume (\leq median versus > median)      | 0.94 | 0.42–2.09 | .88  |
| Adjuvant therapy (no versus yes)                | 0.32 | 0.15–0.71 | .005 |

Abbreviation: HR, hazard ratio.
immediately after radical prostatectomy. In the present study, using a larger cohort of patients, we demonstrated that Bil-SVI, as an independent predictor, was associated with a significantly higher risk of disease progression than Uni-SVI, although there was no significant difference in cancer-specific mortality. Notably, the prognostic significance of Bil-SVI was found in all of the subgroups examined, including patients with or without undergoing adjuvant therapy as well as those with or without lymph node metastasis. In subgroups of patients with adjuvant therapy or pN0 disease, Uni-SVI versus Bil-SVI was still an independent factor. Additionally, in contrast to the findings in a previous study, our data indicate that tumor grade at SVI (eg, GG1-2 versus GG3-5, GG1-3 versus GG4-5) is useful for predicting disease progression after radical prostatectomy. However, other SVI features, including cribriform morphology and total tumor size, were not significantly associated with risk of progression.

Radical prostatectomy findings have also been compared between Uni-SVI and Bil-SVI, in relation to the features of SVI. One study showed significantly higher tumor grade (eg, Gleason score 8–10: 60.0% versus 34.5%), significantly higher incidence of lymph node metastasis (45.7% versus 13.8%), and significantly larger tumor volume (median: 60% versus 37%) in Bil-SVI cases than in Uni-SVI cases, while there were no significant differences in preoperative PSA level and surgical margin status. The other demonstrated that SVI volume greater than 1.63 cm³ was associated with a significantly higher level of PSA (median: 33.5 versus 11.0 ng/mL), marginally (P = .09) higher tumor grade (eg, Gleason score 8–10: 66.7% versus 36.8%), significantly higher incidence of positive surgical margin (75.0% versus 26.3%), and significantly larger maximal tumor dimension (median: 30.5 versus 18.0 mm). In our current cohort, Bil-SVI was found to be strongly associated with a higher incidence of high-grade tumors (eg, GG3-5, GG4-5, GG5), lymphovascular invasion, lymph node metastasis, and positive surgical margin, and larger tumor volume. Bil-SVI was also strongly associated with worse histopathologic features at the SVI region(s), including higher tumor grade, cribriform morphology, and tumor size.

There are several limitations in our investigation. First, the present study is subject to potential selection bias due to the retrospective design, while we have analyzed consecutive patients who met the inclusion criteria. Second, we compared only radical prostatectomy cases, and the clinical impact of Uni-SVI versus Bil-SVI in patients undergoing other treatment options, such as hormonal therapy and upfront radical radiotherapy, was not evaluated. Third, the clinical significance of PSA progression in those who had not received adjuvant therapy immediately after prostatectomy might be different, although we additionally performed outcome analysis in each subgroup. Finally, the route of SVI, as classified previously (eg, direct spread through the ejaculatory duct, direct spread through extraprostatic extension, isolated tumor), was not assessed in the present study. As such, further studies in larger patient cohorts with pT3b prostate cancer, ideally prospectively designed, are warranted to validate our results.

In conclusion, compared with Uni-SVI, Bil-SVI was found to be strongly associated with worse histopathologic features in radical prostatectomy specimens and, more strikingly, poorer survival outcomes as an independent prognosticator in the entire cohort or subgroups of patients. Interestingly, no prognostic significance of total tumor size at SVI was identified even in a univariate setting. These data underscore the important clinical necessity of adequately clarifying the significant histopathologic metrics relevant to Uni-SVI versus Bil-SVI in patients with pT3b disease who undergo radical prostatectomy. Particularly, in addition to Uni-SVI/Bil-SVI, inclusion of other histopathologic findings, such as Gleason score at SVI, in the pathology reports may be useful for more accurately predicting the prognosis.

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| Table 6. Multivariate Analysis of the Histopathologic Features at SVI for Disease Progression |
|-------------------------------------------------|-------------------------------------------------|
| Highest Grade Group at SVI | HR | 95% CI | P |
|------------------------------------------|------|------------|------|
| 1-2 | Reference | | |
| 3 | 1.28 | 0.57–2.88 | .55 |
| 4 | 2.35 | 1.17–4.74 | .02 |
| 5 | 2.21 | 1.03–4.74 | .04 |
| Cribriform morphology at SVI (no versus yes) | 0.83 | 0.51–1.33 | .43 |
| Total tumor size at SVI (≤0.8 versus >0.8 cm) | 1.07 | 0.67–1.73 | .78 |

Abbreviations: HR, hazard ratio; SVI, seminal vesicle invasion.
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