Seminal Vesicle Invasion by Prostate Cancer: Prognostic Significance and Therapeutic Implications

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When the pathologist’s report following radical prostatectomy describes seminal vesicle invasion (SVI), generally the outlook for the patient is poor. But are we all on the same page of the same book when we talk about SVI? Does it mean muscular wall invasion? Does it include the ejaculatory duct? Getting a clear definition can have far-reaching clinical implications for patient prognosis and treatment. [Rev Urol. 2000;2(3):190-195]

Key words: Cancer, prostate • Cancer, staging • Prostatectomy • Seminal vesicles

Invasion of the muscular wall of the seminal vesicles by prostate cancer is generally regarded as a marker of poor prognosis at the time of pathologic staging after radical prostatectomy. Explication of the definition and significance of seminal vesicle invasion (SVI), however, has been a relatively recent event and continues to engender controversy. This review examines the anatomic and histologic basis of SVI, the prognostic implications of a diagnosis of SVI on pathologic staging, and the therapeutic implications of this finding.

Definition of SVI
The work of Jewett and associates1 forms one of the first attempts to characterize SVI. Jewett defined SVI as the presence of prostate cancer in the areolar connective tissue around the seminal vesicles and outside the prostate. A more anatomically sound definition, proposed by Partin and associates,2 requires invasion of the muscular wall of the seminal vesicle for the diagnosis of SVI. Figure 1 shows a typical moderately differentiated prostatic adenocarcinoma invading the muscular wall of the seminal vesicle.

Villers and associates3 reported SVI in 47 of 243 patients undergoing radical prostatectomy between 1985 and 1989. Careful pathologic examination was used to elucidate the extent and route of cancer growth into the seminal vesicles. The majority of these tumors invaded via the ejaculatory duct sheath, penetrating the muscular wall of the ejaculatory duct and then extending into the seminal vesicle wall. These data refuted the contention of Jewett and associates that most SVI occurred by growth of prostate cancer into the connective tissue outside the prostatic capsule followed by invasion into the seminal vesicle.

Ohori and associates4 and Wheeler5 at the Baylor College of Medicine studied
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SVI by rigorously examining step-sectioned, whole-mount surgical specimens. They classified SVI into subtypes based on the route of invasion of the seminal vesicle by prostate cancer (Figure 2). The Baylor group defined type I SVI as the direct spread of prostate cancer along the ejaculatory duct complex into the seminal vesicle. This “internal” spread occurred in a plane around the ejaculatory duct and not in the actual duct lumen. The Baylor group defined type II SVI as invasion occurring through the prostatic capsule and into the seminal vesicle. This path of invasion was further divided into type IIA (occurring with the direct spread of prostate cancer between the base of the prostate and the seminal vesicle) and type IIB (defined by the retrograde growth of prostate cancer into the seminal vesicle from periprostatic nerve involvement). The least common form of SVI, designated as type III by Ohori and associates, is defined as prostate cancer metastases in the seminal vesicle remote from the primary intraprostatic cancer focus. In evaluating the surgical specimens of 64 men with SVI at pathologic staging, this group classified 17 men as having type I, 21 men as having type II, and 8 men as having type III SVI. An additional 18 men had features of both types I and II SVI.

Some investigators believe that the seminal vesicle extends through the prostatic capsule such that the proximal portion of the seminal vesicle and associated ejaculatory ducts are intraprostatic.6 For those adhering to this histologically based definition, a critical distinction must be made between the intraprostatic and extraprostatic seminal vesicle, as will be discussed in the next section.

**Prognostic Significance of SVI**

The finding of SVI at the time of radical prostatectomy is an adverse pathologic finding that confers a decrease in long-term freedom from biochemical (prostate-specific antigen [PSA]) recurrence exceeded in magnitude only by the finding of lymph node metastases.7–11 The natural history of prostate cancer with SVI was noted almost 30 years ago by Byar and Mostofi,12 who evaluated 208 radical prostatectomy specimens by step-sectioning and correlated their findings with long-term patient follow-up. They found that SVI conferred a 32% 7-year survival rate, while men without SVI had a 67% 7-year survival rate. In contemporary series utilizing elevated postoperative serum PSA lev-
els to determine progression, 5-year progression-free rates range from 5% to 60% (median value, 36%) (Table 1).

There are several reasons for the disparity in long-term cancer control outcomes in men with isolated (lymph node negative) SVI found on final staging after surgery for clinically localized prostate cancer. Multiple pathologic parameters impact the prognosis of patients with SVI. Differences in patient populations may produce differences in Gleason score, tumor volume, preoperative tumor stage, extent of SVI, and amount of extraprostatic extension. Differences in surgical technique may account for some of the observed prognostic variation, primarily through differences in positive surgical margin rates. Variations in the pathologic definition of SVI are likely a less recognized explanation for the observed variability in prostate cancer recurrence rates in men with the finding of isolated SVI. Some institutions have reported men having SVI as also having organ-confined prostate cancer.13-15 Some of the tumors staged as having invasion of the intraprostatic portion of the seminal vesicle should be regarded as merely demonstrating ejaculatory duct invasion.16 The diagnosis of SVI should be restricted to tumors demonstrating invasion of extraprostatic structures.

Differences in the definition of SVI have dramatic effects on apparent prostate cancer recurrence rates. Soh and associates15 described men whose tumors demonstrated invasion only of the intraprostatic portion of the seminal vesicle and ejaculatory duct complex, which they termed “level 2 prostatic capsular infiltration.” They found an actuarial 5-year biochemical (PSA) progression-free likelihood of 74% when men with level 2 prostatic capsular infiltration were classified as having SVI. Men with isolated level 2 prostate capsular infiltration had similar actuarial biochemical progression-free likelihoods as men without SVI. In contrast, men in the same series with tumors found to have established extraprostatic extension and SVI had a biochemical progression-free likelihood of less than 20% at 5-year follow-up. Although an argument can be made on histologic and anatomic grounds that a portion of the seminal vesicle is intraprostatic, invasion of these structures apparently does not impart a worse prognosis than tumors that do not show this invasion. Therefore, the argument can be made for a functional definition that excludes isolated involvement of the intraprostatic seminal vesicle from classification as SVI on the final pathologic staging.16

**Stratification of SVI by Prognostic Significance**

There have been relatively few studies attempting to stratify tumors demonstrating SVI through the correlation of histologic factors with clinical prognosis. The route of SVI has served as an obvious source of potential differentiation of tumors with SVI into prognostic groups. Villers and colleagues1 reported that the majority of SVI occurred at the ejaculatory duct sheath, either penetrating the muscular wall of the ejaculatory duct or extending up the ejaculatory duct and into muscle of the seminal vesicle wall. They found that a minority of tumors penetrated the prostatic capsule and invaded the seminal vesicle either directly or by extension into periprostatic soft tissue and then into the seminal vesicle. Villers and associates reported only 1 tumor demonstrating apparently discontinuous metastasis to the seminal vesicle remote from the primary focus of cancer in the prostate. In addition to developing a cogent anatomic classification of the routes of SVI (Figure 2), Ohori and coworkers examined the prognostic significance of these routes of invasion. They found that tumors demonstrating type I invasion were associated with a worse prognosis than were tumors revealing type III invasion. The 8 tumors (13%) demonstrating type III invasion and the relatively short follow-up for these men, however, precluded definitive conclusions. Ohori and colleagues found that when men with SVI who
also had lymph node metastasis were excluded, the better prognosis of tumors with type III SVI was not statistically significant.

Epstein and associates evaluated the surgical series of Walsh, identifying 60 men who underwent radical retropubic prostatectomy between January 1984 and December 1994 and who had isolated SVI on final pathologic analysis. The seminal vesicles in each case were serially sectioned and examined for evidence of invasion by prostate cancer. Diagnosis of SVI required involvement of the extraprostatic portion of the seminal vesicle and invasion of the muscular wall of the seminal vesicle. Multivariate analysis revealed that Gleason score, surgical margin status, and the presence of vascular invasion provided the best prediction of prognosis. This analysis stratified patients into 2 roughly equal-sized groups of good and poor prognosis using only routine pathologic variables. The seminal vesicles and ejaculatory ducts have, at times, been considered one large complex from an anatomic and functional standpoint. Consequently, if tumor extends via the ejaculatory duct into the seminal vesicles but not into the periprostatic soft tissue, some investigators would report an absence of capsular penetration. To regard these tumors as not showing extraprostatic extension ignores the clear difference in prognosis between these lesions and truly organ-confined lesions. Rather, these cases should be designated as demonstrating extraprostatic extension with SVI via the ejaculatory ducts.

Table 1

Prognosis Conferred by Seminal Vesicle Invasion (SVI) in Several Major Series as Measured by 5-Year Biochemical (PSA) Recurrence-Free Survival*

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Institution</th>
<th>Inclusive years</th>
<th>Tumors with SVI</th>
<th>5-year NED</th>
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</thead>
<tbody>
<tr>
<td>D’Amico</td>
<td>University of Pennsylvania</td>
<td>1989 - 1993</td>
<td>36</td>
<td>5%</td>
</tr>
<tr>
<td>Van Den Oudenaar</td>
<td>Erasmus University</td>
<td>1977 - 1994</td>
<td>78</td>
<td>11%</td>
</tr>
<tr>
<td>Catalona</td>
<td>Washington University</td>
<td>1983 - 1993</td>
<td>86</td>
<td>32%</td>
</tr>
<tr>
<td>Trapasso</td>
<td>UCLA</td>
<td>1972 - 1992</td>
<td>93</td>
<td>60%</td>
</tr>
<tr>
<td>Epstein</td>
<td>The Johns Hopkins Hospital</td>
<td>1982 - 1990</td>
<td>47</td>
<td>40%</td>
</tr>
<tr>
<td>Debras</td>
<td>Université Pierre et Marie Curie</td>
<td>1989 - 1994</td>
<td>52</td>
<td>17%</td>
</tr>
<tr>
<td>Tefilli</td>
<td>Wayne State University</td>
<td>1991 - 1995</td>
<td>93</td>
<td>43%</td>
</tr>
<tr>
<td>Ohori</td>
<td>Baylor College of Medicine</td>
<td>1983 - 1993</td>
<td>46</td>
<td>43%</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen; NED, no evidence of disease (undetectable PSA [less than 0.2 ng/mL], no evidence of local recurrence, no clinical or radiographic evidence of metastatic prostate cancer).

*Includes only studies that separately analyzed patients with isolated SVI, excluding those who had concomitant lymph node metastases. The only exception is the study by Van den Oudenaar and coworkers in which lymph node status is ambiguous.
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not analyzed separately, however, and 25 of the 81 tumors with SVI had lymph node metastases. Debras and associates evaluated 52 consecutive patients with positive SVI and no evidence of lymphatic metastases after radical prostatectomy, dividing tumors with SVI into limited and extensive categories based on the extent of cancer involvement. Five-year biochemical (PSA) progression-free likelihood was 45.5% for the 18 patients with limited SVI but only 4.2% for the 34 patients with extensive SVI. This marked difference in biochemical recurrence rates is likely exaggerated by classifying a large number of these patients (52%) as having both SVI and organ-confined prostate cancer. If the diagnosis of SVI is made only in tumors with prostate cancer involving the extraprostatic portion of the seminal vesicle, cases of true SVI cannot, by definition, be organ-confined lesions. The only other variable that achieved significance in the series of Debras and associates was tumor volume, although it was measured imprecisely, using the equation for an ellipse and measuring the transverse, anterior, posterior, and vertical diameters. In univariate analysis, Gleason score, extraprostatic extension, surgical margins, and bilaterality did not correlate with progression. In multivariate analysis, however, the extent of SVI and Gleason score were predictive of progression.

Tefilli and colleagues analyzed a series of 93 men found to have isolated SVI after radical prostatectomy. Multivariate analysis demonstrated that surgical margin status, Gleason score (less than 7 vs 7 or greater) and PSA (less than 10 ng/mL or 10 ng/mL or more) independently predicted prostate cancer progression. At a mean follow-up time of 3.6 years, men whose tumors demonstrated negative surgical margins or a final Gleason score less than 7 had biochemical recurrence-free likelihoods of 65% and 49%, respectively. In contrast, men whose tumors demonstrated positive surgical margins or a final Gleason score of 7 or higher had biochemical recurrence-free likelihoods of 30% and 37%, respectively. The risk of progression in men with final Gleason scores less than 7 and positive margins or negative surgical margins and final Gleason scores of 7 or higher were not reported.

While Gleason score and surgical margin status are well-recognized prognostic parameters, data regarding the role of vascular invasion in independently determining prognosis are preliminary and open to interpretation. It is possible that the presence of vascular invasion may signal an increased risk of occult lymph node metastases that confound the apparent

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Table 2

<table>
<thead>
<tr>
<th>Definition of seminal vesicle invasion</th>
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<tr>
<td>Prostate cancer penetrating the muscular wall of the seminal vesicle (SV)</td>
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<tr>
<td>Prostate cancer must involve the extraprostatic portion of the SV</td>
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<tr>
<td>Cancer in the prostate and seminal vesicle is usually directly contiguous</td>
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<td>Minority of tumors have noncontiguous metastases to the SV</td>
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<tr>
<th>Prognostic significance of seminal vesicle invasion (SVI)</th>
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<tr>
<td>SVI is an adverse pathologic factor conferring a high rate of prostate cancer recurrence</td>
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<tr>
<td>Most men with SVI fail with distant metastases, not local recurrence</td>
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<tr>
<td>Five-year progression-free rates range from 5% to 60% in major series</td>
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<tr>
<th>Stratification of men with SVI</th>
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<tr>
<td>Relatively little information is available to allow stratification by prognosis of men with SVI</td>
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<tr>
<td>Men with discontinuous metastasis to the SV may have a better prognosis than those with direct extension into the SV</td>
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<tr>
<td>In men with SVI, Gleason score, surgical margin status, and presence of vascular invasion provide the most prognostic information</td>
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<tr>
<td>Men with SVI at the time of radical prostatectomy do not seem to benefit from external beam radiotherapy administered at the time of biochemical (prostate-specific antigen) cancer recurrence</td>
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Main Points

- Invasion of the muscular wall of the seminal vesicle is required for a diagnosis of seminal vesicle invasion (SVI).
- If pathologic analysis at the time of radical prostatectomy reveals SVI, patients are not likely to have long-term freedom from biochemical prostate cancer recurrence.
- Invasion of extraprostatic structures should be documented before the diagnosis of SVI is made.
- External beam radiotherapy, used postprostatectomy at the time of prostate-specific antigen signalling cancer recurrence, may not benefit patients with a history of SVI.
- Using pathologic variables to stratify men with SVI found postprostatectomy may be critical to clinical decision making.
prognosis of men thought to have isolated SVI and that may be detectable using more sensitive histologic or molecular techniques.\textsuperscript{16} We recently evaluated the lymph node specimens of 109 men found to have isolated SVI at radical prostatectomy.\textsuperscript{23} Careful examination using routine histologic methods, immunohistochemistry for PSA, prostatic acid phosphatase, and cytokeratin; and reverse transcriptase-polymerase chain reaction for PSA and prostate-specific membrane antigen found cases of previously occult lymph node metastasis. The examination was unable, however, to demonstrate that the poor prognosis of some men with apparently isolated SVI is due to occult pelvic nodal metastases.

As discussed above, men with SVI on final pathologic analysis after radical prostatectomy have a low likelihood of durable freedom from biochemical prostate cancer recurrence. While select men with biochemical recurrence after radical prostatectomy and variable periods with undetectable PSA levels may experience long-term benefit from external beam radiotherapy initiated at the time of PSA recurrence, those with a history of SVI do not appear to derive any benefit from this therapy.\textsuperscript{23}

Conclusions
Invasion of the muscular wall of the seminal vesicle found at pathologic staging after radical prostatectomy is generally regarded as a marker of poor prognosis. Careful anatomic studies have been the basis for standardized evaluation and reporting of these lesions. Despite this, much of the extant data on SVI are based on widely divergent pathologic definitions of SVI that are likely a major source of the disparate reported prostate cancer recurrence rates in these patients. Evidence is emerging that routine pathologic variables can be used to stratify men with SVI found after radical prostatectomy into prognostic groups (Table 2). This stratification will become critical to clinical decision making as more effective adjuvant therapies are developed for postoperative use in poor-risk patients. Currently, it is clear that men with SVI are unlikely to experience long-term biochemical (PSA) freedom from cancer recurrence. While external beam radiotherapy initiated at PSA recurrence after radical prostatectomy has demonstrated benefit in select patients, this therapy appears to have no role in men with SVI at pathologic staging after radical prostatectomy who subsequently suffer a PSA recurrence.

References