

# Is it Necessary to Remove the Seminal Vesicles Completely at Radical Prostatectomy? Decision Curve Analysis of European Society of Urologic Oncology Criteria

Fernando P. Secin, Fernando J. Bianco, Angel Cronin, James A. Eastham, Peter T. Scardino, Bertrand Guillonneau and Andrew J. Vickers\*

From the Department of Urology, Sidney Kimmel Center for Prostate and Urologic Cancers and Department of Epidemiology and Biostatistics (AC, AJV), Memorial Sloan-Kettering Cancer Center, New York, New York

**Purpose:** A publication on behalf of the European Society of Urological Oncology questioned the need for removing the seminal vesicles during radical prostatectomy in patients with prostate specific antigen less than 10 ng/ml except when biopsy Gleason score is greater than 6 or there are greater than 50% positive biopsy cores. We applied the European Society of Urological Oncology algorithm to an independent data set to determine its predictive value.

**Materials and Methods:** Data on 1,406 men who underwent radical prostatectomy and seminal vesicle removal between 1998 and 2004 were analyzed. Patients with and without seminal vesicle invasion were classified as positive or negative according to the European Society of Urological Oncology algorithm.

**Results:** Of 90 cases with seminal vesicle invasion 81 (6.4%) were positive for 90% sensitivity, while 656 of 1,316 without seminal vesicle invasion were negative for 50% specificity. The negative predictive value was 98.6%. In decision analytic terms if the loss in health when seminal vesicles are invaded and not completely removed is considered at least 75 times greater than when removing them unnecessarily, the algorithm proposed by the European Society of Urological Oncology should not be used.

**Conclusions:** Whether to use the European Society of Urological Oncology algorithm depends not only on its accuracy, but also on the relative clinical consequences of false-positive and false-negative results. Our threshold of 75 is an intermediate value that is difficult to interpret, given uncertainties about the benefit of seminal vesicle sparing and harm associated with untreated seminal vesicle invasion. We recommend more formal decision analysis to determine the clinical value of the European Society of Urological Oncology algorithm.

**Key Words:** prostate, prostatic neoplasms, prostatectomy, seminal vesicles, algorithms

A recent communication by Zlotta et al from ESUO questioned the routine practice of complete resection of the SVs during RP.<sup>1</sup> This was based on a retrospective analysis of the records of 1,283 patients, of whom 137 (10.6%) had SVI. The investigators first noted that PSA, biopsy Gleason

grade and the number of biopsy cores positive for cancer were predictive for SVI. They went on to propose a prediction rule, that is patients with PSA 10 ng/ml or greater, biopsy Gleason grade greater than 6 or greater than 50% biopsy cores positive were at high risk for SVI and should undergo SV

## Abbreviations and Acronyms

ESUO = European Society of Urologic Oncology

PSA = prostate specific antigen

RP = radical prostatectomy

SV = seminal vesicle

SVI = SV invasion

Submitted for publication June 25, 2008.

Study received institutional board approval.

Supported by National Cancer Institute SPORE in Prostate Cancer Grant P50-CA92629, the Koch Foundation, Prostate Cancer Foundation, Leon Lowenstein Foundation, American Foundation for Urologic Disease (FJB) and National Institutes of Health Training Grant T32-82088 (FJB).

\* Correspondence: Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, New York 10021 (telephone: 646-735-8023; FAX: 646-735-0011; e-mail: vickersa@mskcc.org).

removal, while patients with PSA less than 10 ng/ml, biopsy Gleason grade less than 7 and 50% or fewer biopsy cores positive were unlikely to have SVI and might be spared complete SV resection. The recommendation was that this strategy be applied in a prospective study comparing "SV-sparing surgery . . . to standard retropubic prostatectomy in selected individuals [ie those negative on the algorithm] analyzing potential benefits on erectile function and urinary continence."<sup>1</sup>

The rationale for SV preservation is that the tip of the SV is close to the arterial supply of the bladder base and the proximal neurovascular bundles. Therefore, complete dissection of the SV might damage these structures, raising the likelihood of postoperative urinary incontinence and erectile dysfunction. Thus, if resection of the tip of the SV is not oncologically necessary, it would seem prudent to preserve this structure.

We applied the ESUO algorithm to data from our institution to determine its predictive validity (external validation). We also used a decision analytic method to explore the effects of implementing the algorithm in clinical practice. We believe that a prospective trial, as recommended by the ESUO investigators, is likely to be infeasible. For example, a trial planning to show that SV sparing improved function but did not increase the recurrence rate by more than 2% might well require more than 10,000 patients. Accordingly decision analysis remains the most feasible method for assessing the clinical impact of a SV sparing strategy in select patients.

## MATERIALS AND METHODS

### Study Cohort

The study cohort consisted of 2,959 consecutive men with localized prostate cancer who underwent RP between January 1998 and August 2004. We chose January 1998 as the start of the cohort because few men treated before 1998 had data available on the number of biopsy cores positive. The 228 men who received neoadjuvant hormonal therapy, chemotherapy or radiation therapy before surgery were excluded from study. Of the remaining 2,731 patients 1,406 had complete information available on preoperative serum PSA, biopsy Gleason score and the percent of biopsies with prostate cancer involvement, defined as the number of cores with any amount of prostate cancer divided by the total number of prostate biopsies. There were no exclusions from study for type of surgery or pathological findings.

Data on the cohort were treated according to the United States Health Insurance Portability and Accountability Act. The data set was obtained after receiving institutional board approval and it was de-identified before analysis.

### Surgical Treatment and Pathological Findings

All patients underwent transrectal ultrasound guided prostate biopsy with a minimum of 6 cores. Pathological slides of patients in whom biopsy was performed elsewhere were reviewed by a specialized urology pathologist at our institution. The Gleason system was scored on all biopsies as the sum of the primary and secondary patterns.

All RPs included complete removal of the SVs and pelvic lymph nodes. Procedures were performed by experienced surgeons using the standard, previously described technique.<sup>2</sup> All RP specimens were sectioned with the whole mount technique by specialized urological pathologists. Tumor invasion of the SVs (SVI) was recorded when malignant cells invaded the muscular layer of the SV wall.

### Statistical Analysis

Patients with PSA 10 ng/ml or greater, biopsy Gleason grade greater than 6 or greater than 50% biopsy cores positive were classified as ESUO positive and the remainder was classified as ESUO negative. Patients were classified as SVI positive or negative regardless of lymph node status, eg a patient with positive lymph nodes but no SVI was classified as disease negative. We calculated the sensitivity, specificity, and positive and negative predictive values of the ESUO prediction rule.

Although they are no doubt informative, measures of diagnostic accuracy such as sensitivity have limited value for clinical decision making. For example, how high must sensitivity and specificity be to justify clinical use of the ESUO prediction rule? Our answer to this question depends on the clinical consequences of our results. A false-negative result, that is failing to completely remove a cancerous SV, has more serious consequences than a false-positive result, that is unnecessarily radical resection of an SV free of cancer. Therefore, we used a decision analytic technique (decision curve analysis<sup>3</sup>) to evaluate the clinical value of the ESUO rule. Decision curve analysis incorporates the clinical consequences of using a prediction rule by applying a different weight to positive and false-positive results. This weighting can be varied to reflect different patient preferences or differences in opinion about the risks of a procedure. These preferences are expressed in terms of a threshold probability for action. A man has a threshold probability of X% if he chooses complete SV removal when his risk of SVI is X% or greater, but he chooses SV preservation if his risk of SVI is less than X%. Decision curve analysis provides a net benefit for each treatment strategy at each threshold probability, calculated at positive and false-positive results with the latter weighted by the odds at the threshold probability (ie  $p/[1 - p]$ ). The optimal strategy is the one with the highest net benefit. All statistical analysis was done using Stata® 9.2.

## RESULTS

Table 1 lists preoperative and pathological patient characteristics. A total of 303 cases of biopsy Gleason 6 were upgraded on pathological analysis of the RP specimen, including 296, 5 and 2 to Gleason 7, 8 and 9, respectively. Four of these cases, which were

**Table 1.** Patient characteristics

No. pts	1,406	
Median preop PSA (ng/ml)	5.53	(4.32, 7.68)
Median % pos biopsy cores (IQR)	33	(17, 50)
No. clinical stage T2 or greater/total No. (%)	518/1,315	(39)
No. biopsy Gleason grade (%):		
6 or Less	887	(63)
7	422	(30)
8 or Greater	97	(7)
No. pathological Gleason grade (%):	1,394	
6 or Less	641	(46)
7	665	(47)
8 or Greater	88	(6)
No. extracapsular extension/total No. (%)	353/1,399	(25)
No. seminal vesicle invasion (%)	90	(6)
No. pos surgical margins/total No. (%)	220/1,403	(16)
No. lymph node involvement/total No. (%)	50/1,264	(4)

Gleason 7, were classed as ESUO negative but showed SVI. Of the 1,406 patients 90 (6.4%) had SVI. Table 2 shows the ESUO classification. Of the patients 741 (53%) were classified as ESUO positive, primarily due to a biopsy Gleason grade of greater than 6. Table 3 lists principal study results. Of the 90 patients with SVI 81 were ESUO positive for 90% sensitivity and 656 of 1,316 without SVI were ESUO negative for 50% specificity. The negative predictive value was 98.6%. None of the 9 patients with SVI who were negative by ESUO criteria had positive lymph nodes.

Part A of the figure shows the decision curve. The x axis is the threshold for action, that is the probability of SVI at which a man would elect complete SV resection. The y axis represents the clinical net benefit in terms of the probability of positive results, ie removing a cancerous SV, minus the probability of false-positive results, ie unnecessarily resecting an SV without cancer, with the latter weighted by the odds at the threshold.

**Table 2.** ESUO classification with PSA, biopsy Gleason grade and percent of biopsy cores positive

	No. Pts (%)
ESUO classification:	
Neg	665 (47)
Pos	741 (53)
Criteria met for ESUO pos:	
Only preop PSA 10 ng/ml or greater	66 (5)
Only biopsy Gleason grade greater than 6	287 (20)
Only greater than 50% biopsy cores pos	133 (9)
Preop PSA 10 ng/ml or greater + biopsy Gleason grade 6 or greater	54 (4)
Preop PSA 10 ng/ml or greater + greater than 50% biopsy cores pos	23 (2)
Biopsy Gleason grade 6 or greater + greater than 50% biopsy cores pos	146 (10)
Preop PSA 10 ng/ml or greater, biopsy Gleason grade greater than 6 + greater than 50% biopsy cores pos	32 (2)

**Table 3.** Diagnostic findings in patients with true SVI by ESUO algorithm results

ESUO Criteria	No. Current Series SVI		Totals
	Pos	Neg	
Pos	81	660	741
Neg	9	656	665
Total No.	90	1,316	1,406

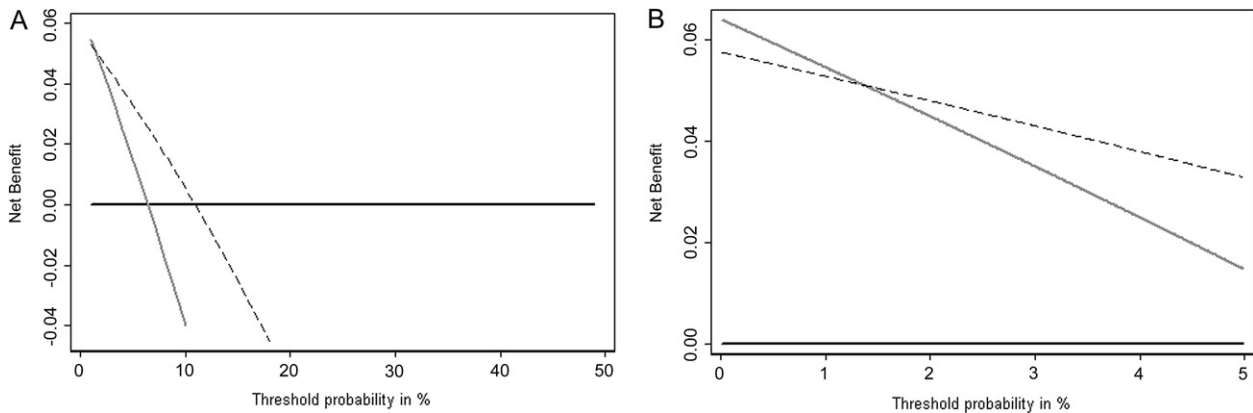
Sensitivity 90.0% (81 of 90 patients), specificity 49.9% (656 of 1,316), positive predictive value 10.9% (81 of 741) and negative predictive value 98.6% (656 of 665).

To interpret part A of the figure we considered what a reasonable range of thresholds might be in the community. Clearly any man who is told that he has a 50% chance of SVI would elect SV removal. Similarly a man who is told that he had only a 1 in a million chance of SVI would elect SV preservation. We thought that few if any men would ever have a threshold much above 10%. However, given that the benefits of SV preservation are unclear, some men might elect complete SV resection even if the probability of SVI was 1% or less. Part A of the figure shows that, although the net benefit of the ESUO prediction rule is higher than the curve for the strategy of SV resection in all men for a threshold of 2% or higher, it is actually lower at a threshold of approximately 1% or lower. Part B of the figure shows this more clearly.

The net benefit of the prediction rule is lower than that of treating all men when the threshold probability for resection is 1.35% or less, which is simply 1 minus the negative predictive value. Because the odds at 1.35% probability were close to 1/75 (0.0135/[1 - 0.0135]), this result may be phrased in certain terms. If the loss in health when SVs are invaded and not completely removed is considered at least 75 times greater than unnecessarily radical resection, the algorithm proposed by the ESUO should not be used. We consider 75 to be an intermediate value that is difficult to interpret, given uncertainty about the value of SV sparing and the harm associated with untreated SVI.

## DISCUSSION

SV sparing surgery is just one of a number of technical options meant to decrease the surgical trauma of RP. However, whether considering the original nerve sparing technique of Walsh and Mostwin<sup>4</sup> or the fascia sparing techniques piloted at the Vattikuti Urology Institute<sup>5</sup> any technique must weigh any benefits in terms of functional preservation against possible risks in terms of decreased oncological control. SV involvement has historically been associated with poor prognosis in patients undergoing RP.<sup>6</sup> However, the cumulative probability of



A, ESUO algorithm decision curve. B, ESUO algorithm decision curve showing key 0% to 5% range. Dashed line indicates net benefit of SV dissection only in cases classified as ESUO positive. Gray line indicates net benefit of SV dissection in all cases. Black line indicates net benefit of SV preservation for all men.

freedom from biochemical recurrence in patients with SVI and no nodal metastasis treated with RP alone was 36% and 32% at 10 and 15 years, respectively, in our contemporary series of 4,441 men.<sup>7</sup> The cumulative 10 and 15-year cancer specific survival probability in those patients was 89% and 81%, respectively, although men remain at risk for many more years. Other studies have shown similar findings.<sup>8</sup>

To our knowledge there are no compelling data to estimate recurrence and survival in men with SVI who do not undergo complete SV removal. It may be that surgery may still be adequate because the tumor usually extends only into the proximal portions of the SV and rarely involves the tip. Hence, a man with SVI undergoing tip preservation may still receive cancer appropriate surgery but in about 20% of patients with SVI the pattern of spread is diffuse, similar to satellite metastasis, and often involves the tip of the SV.<sup>9</sup> However, patients who have cancer in preserved tissue may not experience a PSA nadir postoperatively and they will undoubtedly require adjuvant therapy that will worsen quality of life.<sup>10</sup> In comparison, adjuvant therapy for SVI in a patient with completely resected SVs is a matter of surgeon choice and by no means mandated in all men.

The ESUO investigators argued that the benefit of SV preservation is to lower the probability of damage to the pelvic plexus and the blood supply to the cavernous bodies.<sup>1</sup> There are isolated, small, nonrandomized series of patients who underwent SV sparing and investigators have typically reported better than expected outcomes for urinary and erectile function.<sup>11–14</sup> However, more recently Albers et al reported the results of a trial of an SV sparing strategy.<sup>15</sup> Patients were deemed eligible for SV sparing using more liberal criteria than those

of the ESUO, including PSA 10 ng/ml or less, biopsy Gleason score 7 or less and a total prostate volume of 50 ml or less. Urinary function was superior in the 146 patients randomized to SV sparing RP compared to that in the 171 who underwent total SV resection with 96% vs 86% continence at 1 year ( $p = 0.005$ ). Potency rates were similar. Unfortunately however, oncological control was poorly reported. The group mentioned a recurrence proportion without providing followup, a survival curve or the CI for the difference between groups. Moreover, all patients in the main comparison underwent perineal prostatectomy, which is less common than the retropubic approach.

The benefits and the risks of SV tip preservation are subject to considerable uncertainty. We have no good estimates as to the degree to which SV preservation improves function and similarly we have no good estimates as to the degree to which SV preservation in a man with SVI increases the risk of recurrence. The latter estimate is likely to remain uncertain. The key number in our analysis is that SV preservation is harmful below a 1.35% probability threshold for SV removal, equivalent to the loss of health caused by preserving the affected SV being considered 75 times worse than that of SV removal. Had this number been much lower, ie 0.25%, or higher, such as 10%, our conclusions would be clear, that is use or avoid the ESUO algorithm, respectively. However, the actual value that we derived is indeterminate. As such, we recommend more formal decision analysis to explore the value of the ESUO algorithm. Such analysis would involve entering a range of specific values for the risk of SV preservation (HR for recurrence) and the harm of SV resection (RR for poor erectile or urinary function), and then exploring the conditions under which the ESUO algorithm would provide a better expected

outcome than the current strategy of resection in all patients.

Regardless of the results of this planned decision analysis, the algorithm proposed by the ESUO could be helpful in patients who undergo external beam radiation therapy. This is because the threshold probability of SVI at which a radiotherapist would choose to irradiate the SV likely differs from the threshold probability of SVI at which a surgeon would completely excise the SV. The volume of normal surrounding tissue irradiated is larger when the SVs are included in the radiation field.<sup>16</sup> Thus, decreasing the target volume may decrease normal tissue reactions, particularly those of the bladder and the rectum, facilitate dose escalation and increase local control.<sup>17,18</sup> Accordingly the balance between the benefit of avoiding unnecessary treatment and the harm of under treatment differs between radiotherapy and surgery. We believe that a reasonable range of threshold probabilities of SVI that would indicate a wider field irradiation would be 2.5% to 15%. Even for the conservative clinician who

would irradiate the SV if the risk of SVI was 2.5% or more but not if the risk was less than 2.5%, the ESUO algorithm should be used to select patients for SV irradiation because the net benefit of the algorithm is superior to the strategy of irradiating all men for all values within this range (part *B* of figure). Hence, decision curve analysis supports the application of the ESUO algorithm for radiotherapy planning.

## CONCLUSIONS

Whether to use the ESUO algorithm depends not only on its accuracy, but also on the cost of false-positive and false-negative results. We recommend further decision analysis to characterize the uncertainty associated with the health effects of SV resection or preservation.

## ACKNOWLEDGMENTS

Jason Stasi assisted with data retrieval.

## REFERENCES

- Zlotta AR, Roumeguere T, Ravery V, Hoffmann P, Montorsi F, Turkeri L et al: Is seminal vesicle ablation mandatory for all patients undergoing radical prostatectomy? A multivariate analysis on 1283 patients. *Eur Urol* 2004; **46**: 42.
- Ohuri M and Scardino PT: Localized prostate cancer. *Curr Probl Surg* 2002; **39**: 833.
- Vickers AJ and Elkin EB: Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006; **26**: 565.
- Walsh PC and Mostwin JL: Radical prostatectomy and cystoprostatectomy with preservation of potency. Results using a new nerve-sparing technique. *Br J Urol* 1984; **56**: 694.
- Savera AT, Kaul S, Badani K, Stark AT, Shah NL and Menon M: Robotic radical prostatectomy with the "Veil of Aphrodite" technique: histologic evidence of enhanced nerve sparing. *Eur Urol* 2006; **49**: 1065.
- Jewett HJ, Bridge RW, Gray GF Jr and Shelley WM: The palpable nodule of prostatic cancer. Results 15 years after radical excision. *JAMA* 1968; **203**: 403.
- Secin FP, Bianco FJ Jr, Vickers AJ, Reuter V, Wheeler T, Fearn PA et al: Cancer-specific survival and predictors of prostate-specific antigen recurrence and survival in patients with seminal vesicle invasion after radical prostatectomy. *Cancer* 2006; **106**: 2369.
- Baccala AA, Reuther AM, Bianco FJ Jr, Scardino PT and Klein EA: Complete resection of the seminal vesicles at radical prostatectomy results in substantial long-term disease-free survival: a multi-institutional study in 6,740 patients. *J Urol, suppl.*, 2005; **173**: 189, abstract 692.
- Ohuri M, Scardino PT, Lapin SL, Seale-Hawkins C, Link J and Wheeler TM: The mechanisms and prognostic significance of seminal vesicle involvement by prostate cancer. *Am J Surg Pathol* 1993; **17**: 1252.
- Miller DC, Sanda MG, Hollingsworth JM 3rd, Dunn RL, Montie JE, Sandler HM et al: Salvage therapy adversely affects long-term HRQOL among localized prostate cancer treatment survivors. *J Urol, suppl.*, 2005; **173**: 224, abstract 827.
- Shidham VB, Lindholm PF, Kajdacsy-Balla A, Basir Z, George V and Garcia FU: Prostate-specific antigen expression and lipochrome pigment granules in the differential diagnosis of prostatic adenocarcinoma versus seminal vesicle-ejaculatory duct epithelium. *Arch Pathol Lab Med* 1999; **123**: 1093.
- Bellina M, Mari M, Ambu A, Guercio S, Rolle L and Tampellini M: Seminal monolateral nerve-sparing radical prostatectomy in selected patients. *Urol Int* 2005; **75**: 175.
- John H and Hauri D: Seminal vesicle-sparing radical prostatectomy: a novel concept to restore early urinary continence. *Urology* 2000; **55**: 820.
- Sanda M, Dunn R, Wei J, Resh J and Montie J: Seminal vesicle sparing technique is associated with improved sexual HRQOL outcome after radical prostatectomy. *J Urol, suppl.*, 2002; **167**: 151, abstract 606.
- Albers P, Schäfers S, Löhmer H and de Geeter P: Seminal vesicle-sparing perineal radical prostatectomy improves early functional results in patients with low-risk prostate cancer. *BJU Int* 2007; **100**: 1050.
- Jacob R, Hanlon AL, Horwitz EM, Movsas B, Uzzo RG and Pollack A: Role of prostate dose escalation in patients with greater than 15% risk of pelvic lymph node involvement. *Int J Radiat Oncol Biol Phys* 2005; **61**: 695.
- Pollack A, Hanlon AL, Horwitz EM, Feigenberg SJ, Uzzo RG and Hanks GE: Prostate cancer radiotherapy dose response: an update of the fox chase experience. *J Urol* 2004; **171**: 1132.
- Peeters ST, Hoogeman MS, Heemsbergen WD, Slot A, Tabak H, Koper PC et al: Volume and hormonal effects for acute side effects of rectum and bladder during conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1142.

## EDITORIAL COMMENT

SVI at RP is generally considered an ominous sign. However, its decreasing incidence in the PSA era may obviate the need for complete excision for an oncologically safe operation, given its potential benefits of improved continence and/or erectile function. Therefore, the issue of defining the most suitable candidates who can be safely spared SV excision is important.

The results of the current study clearly validate the findings in the original ESOU series (reference 1 in article). Although these authors considered 90%

sensitivity and a 98.6% negative predictive value as indeterminate, their analysis indicated a low 1.3% risk of missed SVI when ESOU criteria were used. The most important issue that will keep the debate warm is the current uncertainty surrounding the degree of harm associated with unresected disease in the SVs as well as the benefit(s) of sparing them.

---

**Levent Türkeri**

*Department of Urology  
Marmara University School of Medicine  
Istanbul, Turkey*