Functional Outcomes Following Nerve Sparing Prostatectomy Augmented with Seminal Vesicle Sparing Compared to Standard Nerve Sparing Prostatectomy: Results from a Randomized Controlled Trial

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Abbreviations and Acronyms

EPIC-26 = Expanded Prostate Cancer Index Composite Short Form

IIEF = International Index of Erectile Function

NSP = nerve sparing prostatectomy

PSA = prostate specific antigen

SVS = seminal vesicle sparing

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Purpose: Seminal vesicle sparing may reduce the risk of neurovascular bundle injury and improve functional outcomes after prostatectomy. While several observational studies have shown better functional outcomes following seminal vesicle sparing approaches, evidence from randomized trials is lacking. We performed a randomized controlled trial comparing functional and cancer control outcomes between nerve sparing prostatectomy augmented with seminal vesicle sparing and standard nerve sparing prostatectomy.

Materials and Methods: A total of 140 men with early stage prostate cancer were enrolled in a randomized phase II trial comparing nerve sparing prostatectomy augmented with seminal vesicle sparing to standard nerve sparing prostatectomy. Patient reported sexual and urinary functional scores were assessed prior to surgery, and 6 and 12 months postoperatively. Surgical margin status and prostate specific antigen recurrence were evaluated as secondary outcomes.

Results: There were no differences in sexual or urinary function scores after surgery between the study groups. The median urinary incontinence domain score was 92 in the nerve sparing group and 87.5 in the nerve plus seminal vesicle sparing group at 12 months ($p = 0.77$). Median sexual function domain scores were 73.7 in the nerve sparing group and 77.1 in the nerve sparing plus seminal vesicle sparing group at 12 months ($p = 0.29$). Margin status and 12-month biochemical recurrence were similar in the groups.

Conclusions: Recovery of continence and sexual function was similar between the groups in this randomized controlled trial. Seminal vesicle sparing did not negatively affect margin status or 12-month biochemical (prostate specific antigen) recurrence. These results suggest limited usefulness of seminal vesicle sparing prostatectomy.

Key Words: prostatic neoplasms, prostatectomy, seminal vesicles, dissection, treatment outcome

Early stage prostate cancer is associated with favorable cancer outcomes in part due to the availability and use of highly effective local therapies such as surgery and radiation therapy as well as to the protracted

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clinical course of nonmetastatic disease.[1,2] However, treatment can be associated with long-term functional complications, including urinary incontinence and erectile dysfunction.[3,4] Incontinence may affect up to 10% of men after prostatectomy and greater than 40% experience some form of erectile dysfunction after surgery.[5–7] While nerve sparing prostatectomy reduces these risks, the quality of nerve sparing varies among surgeons and across cases.[8,9]

Traction and thermal related injury to the inferior hypogastric pelvic plexus and proximal neurovascular tissue may contribute to the functional complications observed after prostatectomy even when nerve sparing is performed. Several cadaveric studies have described the close proximity of these structures to the seminal vesicles and posterior bladder neck, implicating dissection in these areas in neurovascular injury.[10,11] This in combination with favorable results reported in several early observational studies of seminal vesicle sparing prostatectomy has led some surgeons to propose seminal vesicle sparing prostatectomy.[12,13] However, this approach has not yet been compared to standard nerve sparing prostatectomy in randomized trials, resulting in clinical uncertainty regarding the merits of seminal vesicle sparing or whether it should be used in practice more broadly.[14]

Given this uncertainty, we performed a phase II, randomized, controlled clinical trial comparing standard NSP to NSP augmented with SVS. The primary objective was to evaluate the effect of the surgical approach (seminal vesicle sparing with nerve sparing vs nerve sparing alone) on patient reported functional outcomes, including urinary continence and sexual function.[15] We also examined cancer control measures as secondary outcomes, including surgical margin status and biochemical (PSA) recurrence.

PATIENTS AND METHODS

Patient Population

Study participants were identified and recruited from prostate cancer clinics at University of Michigan. To be eligible for study participation subjects were required to have biopsy proven prostate cancer with a low risk of seminal vesicle invasion and elect prostatectomy for treatment. Study recruitment was independent of patient decisions regarding the type of treatment used to treat prostate cancer. A low risk of seminal vesicle invasion was defined as a 5% or less risk of seminal vesicle invasion based on pretreatment clinical parameters using established and validated prediction tables (fig. 1).[16] Patients were screened for erectile dysfunction prior to study participation. For this purpose intact baseline sexual function was defined as an IIEF score of 21 or greater before randomization and surgery.[17] Other study inclusion criteria included competence in reading and writing English, candidacy for bilateral nerve sparing and willingness to be followed and complete study surveys during the 12-month postoperative followup.

Study Design

A phase II, randomized, controlled trial design was used for this study. Randomized phase II trials include a control group and overcome outcome-trial effect confounding (the inability to separate the trial effect from the treatment effect) associated with traditional single arm phase II trials. They also lend efficiency to identifying and testing potentially promising interventions without moving to full-scale phase III, randomized, controlled clinical trials, primarily through adjustments in α, β and Δ assumptions. Some statisticians have argued that 0.20 probabilities for α and β, and a 20% target difference in outcome should be used in randomized phase II trial settings to decrease the likelihood of a negative phase III trial, prematurely ending testing of promising interventions or incorrectly rejecting a beneficial treatment.[18–20]

A sample of 64 subjects per arm for a total study population of 128 was estimated to detect a 0.5 SD difference in mean EPIC-26 sexual domain scores as the primary study outcome based on a power of 0.80 ($1 - \beta$) and a 2-sided significance level of 0.05 (α). Half of the SD is a commonly used and empirically supported measure of clinical significance for comparing differences in quality of life scores (ie the distribution based minimally important difference).[21,22] To account for an estimated 10% attrition a target of 70 subjects per treatment arm for a total study population of 140 was set for study accrual.

Randomization and Study Procedures

Randomization was performed using a randomized block design and random computer number allocation stratified by operative approach (open vs robot assisted laparoscopic prostatectomy) to prevent unbalance in surgical approach between the study groups. Assignment to the intervention and control arms was performed on the day of surgery following induction of anesthesia but prior to initiation of the operation (incision) to ensure that subjects would be blinded to randomization.

Surgical procedures were performed in a standard manner and they were similar in the 2 groups other than seminal vesicle sparing in the intervention group. The intent of nerve sparing was uniform across patients. Seminal vesicle sparing was standardized by division 1 to 2 cm below the prostate-seminal vesicle junction without dissection or mobilization of the distal seminal vesicles. The extent and quality of nerve sparing was rated by surgeon appraisal using a standardized reporting form which was completed immediately following surgery. Surgeons participating in the study were trained in urological oncology and robotic surgery, and maintained high volume prostatectomy practices.

Postoperatively patients in both study arms were treated according to standard clinical protocols. Patients in both groups were given instructions regarding erectile rehabilitation and a prescription for a phosphodiesterase type 5 inhibitor at hospital discharge.[23]