Published in final edited form as:

BJU Int. 2008 May ; 101(10): 1217–1222. doi:10.1111/j.1464-410X.2008.07511.x.

MODIFICATION IN TECHNIQUE FOR NEUROVASCULAR BUNDLE PRESERVATION DURING RADICAL PROSTATECTOMY: ASSOCIATION BETWEEN TECHNIQUE AND RECOVERY OF ERECTILE FUNCTION

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Abstract

Purpose—We recently modified our radical prostatectomy (RP) technique such that the neurovascular bundle (NVB) is completely mobilized off the prostate from the apex to above the seminal vesicles, including incision of Denonvilliers' fascia, prior to urethral division and mobilization of the prostate off the rectum. We prospectively evaluated whether this modification in surgical technique was associated with an improvement in postoperative erectile function (EF) recovery.

Materials and Methods—Data from patients treated prior to technique modification was used to create a predictive model for EF at 6 months after RP using age, date of surgery, and nerve sparing (none vs unilateral vs bilateral) as predictors for patients who received the modified technique (MT) to estimate the expected outcomes had they received the standard technique (ST), and compared these with actual outcomes.

Results—Of 372 patients with evaluable data, 275 (74%) underwent the ST from January 1, 2001 through December 31, 2004 and 97 (26%) underwent the MT from January 1, 2005 through May 30, 2006. Sixty-five of the 97 patients (67%) receiving the MT had EF recovery at 6 months, whereas the expected probability of 6-month EF, had they received the ST, was 45%. The absolute improvement in EF recovery attributable to the MT was 22% (95% CI 5% to 40%; $p = 0.013$).

Conclusions—Technical modifications to NVB preservation during RP were associated with improved rates of EF recovery. Whether a causal association exists between change in technique and outcome requires further evaluation. Additionally, longer follow-up will be required to determine the effect our MT has on the quality of erections and overall EF recovery rates.

Keywords

erectile dysfunction; neurovascular bundle preservation; prostate cancer; radical prostatectomy; surgical technique

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INTRODUCTION

Since the detailed description of the anatomic relationship between the NVB and capsule of the prostate,¹ modifications in RP surgical technique have been developed to reduce the long-term morbidity of ED without compromising cancer control. Devising a surgical approach that minimizes treatment related morbidity and maximally reduces time to recovery provides patients with the optimal treatment strategy.

A commonly used approach for NVB preservation is initial incision of the lateral prostatic fascia and partial mobilization of the NVB from the apical third of the gland.^{2, 3} This is followed by urethral transection and subsequent elevation of the apex of the prostate (usually with a Foley catheter as a tractor) to allow further lateralization of the NVB and posterior dissection of the prostate. It has been demonstrated that early release of the NVB from the apex of the prostate prior to initiation of the posterior dissection reduces both the time to recovery as well as the overall likelihood of recovery of potency.⁴ Nonetheless, we hypothesize that this technique (subsequently referred to as our “standard technique” or “ST”) continues to place undo tension on the NVB resulting in traction injury and a delay in EF recovery as it fails to release attachments tethering the NVB to the mid-gland and base of the prostate, Denonvilliers’ fascia, and the seminal vesicles. We modified our technique so that, before urethral division and mobilization of the prostate off the rectum, the NVB was completely mobilized off the prostate from apex to above the level of the seminal vesicles. Additionally, Denonvilliers’ fascia is incised along the length of the prostate to further lateralize the NVB so that any manipulation of the prostate during the apical and posterior dissection results in complete protection of the NVB from traction injury. We investigated whether time to EF recovery was improved by this modified technique (MT).

MATERIALS AND METHODS

Patient Selection

Between January 2001 and May 2006, 513 consecutive men with normal preoperative EF underwent open RP with NVB preservation (visual status 1 or 2- see below) for clinically localized prostatic adenocarcinoma. All surgical procedures were performed by 1 surgeon (J.A.E.). With approval of our IRB, data was collected prospectively into our SPORE prostate cancer database. All information was treated according to the HIPAA and was de-identified before analysis. Patients who received prior radiation and/or chemotherapy (n = 1) or neoadjuvant hormonal therapy (n = 22) were excluded, leaving 490 patients in our sample for analysis.

Surgical Technique

All patients underwent a meticulous pelvic lymph node dissection followed by RP. The operative approach serving as our “ST” has been previously described (Fig. 1).²⁻⁵ Modifications in our approach to NVB preservation began immediately after ligation and division of the dorsal venous complex. Depending upon preoperative and intraoperative assessment of the extent and location of disease, we utilized either an intrafascial or interfascial plane of dissection to release the NVB off the prostatic capsule.⁶ This dissection was initiated at the apex of the prostate and continued along the posterolateral aspect to above the level of the seminal vesicles (Fig. 2). After this initial mobilization of the NVB, Denonvilliers’ fascia was incised by sharp dissection from prostatic apex to base facilitating complete mobilization and lateralization of the NVB off the prostate. This maneuver ensures that any subsequent manipulation of the prostate avoids traction and potential injury to the NVB. The division of the urethra followed by the apical and posterior dissection was then completed. Patients who

received the ST and MT were treated, respectively, from January 1, 2001 through December 31, 2004 and from January 1, 2005 through May 30, 2006.

Data Collection and Follow-up

The following data were collected prospectively: preoperative clinical characteristics (PSA, clinical stage and biopsy Gleason scores), intraoperative visual assessment of the quality of NVB preservation (1- preserved, 2- possible damage, 3- definite damage, 4- complete resection), estimated blood loss and surgical time, pathological features of the RP specimen (established extracapsular extension, seminal vesicle invasion and lymph node metastases, presence of tumor at the inked margin of resection, specimen Gleason score), administration of adjuvant radiation or hormonal therapy, and all imaging and laboratory data. Our follow-up protocol during the first postoperative year called for serum PSA measurements every 3 months. If results were under the upper limit of detection of the assay, the PSA was done semiannually during the second year and annually thereafter.

At each visit, outcomes regarding EF were evaluated by the treating physician through patient-reported questionnaires assessing for the quality and frequency of sexual activity and graded on a 5-point rigidity scale (1- normal, full erections, 2- full, but diminished erections satisfactory for sexual activity, 3- partial erections occasionally satisfactory for sexual activity, 4- partial erections unsatisfactory for sexual activity, 5- no erection). We have previously published data demonstrating good agreement between this 5-point scale and the International Index of Erectile Function (IIEF) for defining functional recovery of EF after RP.⁷ Additionally, the type and start date of medical treatment for ED was recorded. Any relevant EF information obtained through clinical protocols and patient surveys were uploaded into our database system by research assistants.

Erectile Function Endpoints

All patients were encouraged to use daily oral PDE-5 inhibitors postoperatively once the Foley catheter was removed.^{8, 9} EF recovery was recorded if a postoperative erectile rigidity score of 1 or 2 was achieved with or without the use of PDE-5 inhibitors. Patients with erectile rigidity scores of 3 to 5 or those requiring the assistance of vacuum devices or injection therapy to achieve erections suitable for sexual activity were considered to have ED. Because the development of neuropraxia and subsequent postoperative ED is transient and proportional to the degree of traction injury sustained at the time of RP, the evaluation of EF recovery was centered on short-term outcomes at the 6-month postoperative period to assess for differences in the rate of EF recovery.

Statistical Analysis

EF data are subject to interval censoring. For example, consider a patient seen in clinic at 3 months and noted to have ED, who then returns at 9 months and reports full recovery of EF. Although this man regained EF somewhere between 3 and 9 months, in a traditional Kaplan-Meier survival type analysis, such a patient would be counted as having an "event" at 9 months. To avoid interval censoring in this series, we first converted the survival-time data to binary data for the outcome of 6-month EF. For patients evaluated for EF recovery between 4.5 and 7.5 months after surgery, we used the evaluation closest to 6 months ($n = 314$). For patients not evaluated between 4.5 and 7.5 months after surgery, we included those with an evaluation less than 4.5 months following surgery and an evaluation more than 7.5 months after surgery, provided that EF status was the same on both occasions ($n = 58$); otherwise, patients were excluded from analysis ($n = 118$). Of the 118 patients excluded, all were evaluated for EF recovery on at least one occasion after surgery; 73 (62%) were not evaluated after 4.5 months; 21 (18%) were not evaluated before 7.5 months; and 24 (20%) had ED before 4.5 to 7.5 months but recovered EF after that.

Our aim was to evaluate the association between surgical technique (ST vs MT) and EF recovery after RP, controlling for age at RP and nerve sparing status (none vs unilateral vs bilateral). We first considered a “naïve” analysis, which would simply use a dummy variable for surgical technique; the p-value associated with this dummy variable would indicate whether EF rates differed before and after January 1, 2005, when the change in technique was made. However, this analysis is likely confounded by secular changes over time: improved treatment of post-prostatectomy ED, or improved surgical EF outcomes with greater experience of the treating surgeon (the “learning curve”). We then considered controlling for time by including the date of surgery in the multivariable model. However, the high correlation between surgical technique and date of surgery (that is, all patients treated after January 1, 2005 received the MT) makes this approach questionable.

We therefore decided to conduct an analysis whereby we compared the actual outcome for patients who received the MT with their expected outcome had they been treated using the ST, which was determined by a predictive model created with data from patients who received the ST. We fitted a logistic regression model using only patients who received the ST; the outcome of this model was 6-month EF recovery and the predictors were date of surgery, age at RP, and nerve sparing status. Inclusion of date of surgery in this model controlled for the surgical learning curve and secular changes in the treatment of ED. From the model, we obtained the predicted probability of 6-month EF recovery for patients who received the MT. The predicted probability was compared to the actual EF recovery status at 6 months using a statistic, denoted by S , which is the mean difference between actual EF recovery status at 6 months and the predicted probability from the model among patients who received the MT. This statistic, S , can be interpreted as the estimated improvement in EF recovery attributable to the use of the MT. To obtain a CI for S , we first define Y as indicator variable for EF recovery (1- EF recovery, 0- no EF recovery); $p^{\wedge}$ as the predicted probability of 6-month EF recovery from the logistic regression model described above; n as the number of patients receiving the MT. We can then

formally define S as $\frac{1}{n} \sum_{i=1}^n Y_i - \widehat{p}_i$. To obtain a central estimate and standard error for S we used a bootstrapping method (see **Table 1**).

As a check on our results, we used a previously developed method of comparing predictions to results.¹⁰ An analogous method was used to illustrate our results graphically: the logistic regression was run separately for ST and MT patients and the 2 lines plotted on a single graph. All analyses were conducted using Stata 9.2 (Stata Corp, College Station, Texas).

RESULTS

After exclusion of 118 patients with unknown EF recovery status at 6 months after surgery, 372 men in our cohort provided evaluable data: 275 patients (74%) underwent the ST and 97 (26%) underwent the MT (**Table 2**). Age distribution was similar in both groups: median ages were 57 and 59 years, respectively. No important differences were observed between the 2 groups regarding operative time, estimated blood loss, preoperative features of the prostate cancer, or pathological features of the RP specimen (**Table 2**). The positive surgical margin rates were 9% and 10%, respectively ($p = 0.8$, Fisher’s exact test).

In total, 176 (47%) men had functional erections 6 months after RP. The 6-month predicted probability of EF recovery, with adjustment for age and nerve sparing status, is shown in Figure 3 separately by surgical technique. As expected, the EF recovery rates improved with time, irrespective of surgical technique. Of note, improvement in EF recovery rates spiked immediately after the surgeon commenced the MT. To formally test for an improvement in EF based on surgical technique, we compared the observed outcome in men who received the MT against their expected outcome, had they received the ST. One hundred eleven of the 275

patients (40%) who received the ST and 65 of the 97 patients (67%) receiving the MT had EF recovery at 6 months. The expected probability of 6-month EF recovery in patients undergoing the modified surgery, had they received the ST, was 45%. Therefore, the absolute improvement in EF apparently attributable to the new surgical technique is 22% (95% CI 5% to 40%; $p = 0.013$). Use of the Heller method¹⁰ gave extremely similar results (absolute improvement of 22%; 95% CI 4% to 40%; $p = 0.015$).

Results for the subset of 269 men who received bilateral NVB preservation (visual status 1 bilaterally) were very similar: the expected probability of 6-month EF recovery for the 53 men who received the MT, had they received the ST, was 57%; 42 of those men (79%) had EF recovery at 6 months, resulting in an absolute improvement of 22% (95% CI 2% to 41%; $p = 0.03$).

DISCUSSION

Surgical treatment of clinically localized prostate cancer has focused on decreasing inherent morbidity. Historically, ED had been universal in patients undergoing RP. However, through anatomic studies performed by Walsh and Donker,^{1, 11} identification of the course and relationship of the NVB relative to the prostatic capsule has allowed for intraoperative modifications facilitating recovery of EF.

Increased surgeon experience and surgical modifications have been observed to improve EF outcomes.¹² In addition to preoperative EF, NVB preservation, and patient age, fine details in surgical technique have proven to be independent predictors for recovery of EF after RP.¹³ Through retrospective review of intraoperative videotapes, Walsh and colleagues were able to identify 4 modifications that appeared to correlate with recovery of EF.¹⁴ More recently, they reported improvements in 18-month EF recovery rates among 86% of selected patients with and without the use of PDE-5 inhibitors using validated QOL surveys.¹⁵ Similarly, use of video at our own institution facilitated identification of technical aspects during laparoscopic RP that contributed to reduced positive surgical margin rates through pathological and intraoperative documentation review.¹⁶

The concept of early release of the NVB from the prostate prior to the apical and posterior dissection and the prostate is not new.²⁻⁴ Chuang et al. reported their experience in early release after anterior division of the urethra prior to the posterior dissection by evaluating whether technique change and the use of loupe magnification improved EF recovery.⁴ In this study, the authors demonstrated that with both optical magnification and early release of the NVB, improved rates of overall EF recovery were seen at an average of 15.9 months. However, it remains uncertain whether traction placed on the NVB is completely circumvented when release is confined to the apical third of the prostate. Based upon surgeon experience and intraoperative observations, NVB preservation techniques were modified in the current study. In an effort to try and minimize traction on the NVB, we now completely mobilize the NVB off the prostate from apex to beyond the tips of the seminal vesicles and further lateralized the NVB by incising Denonvilliers' fascia along the entire length of the prostate prior to dividing the urethra. We hypothesized this would reduce the degree of neuropraxia encountered postoperatively that might contribute to a delayed recovery of EF after RP. Because neuropraxia is transient and proportional to the degree of traction injury, we assessed for differences in short-term outcomes for postoperative EF recovery. In our study, patients undergoing the MT experienced 6-month EF recovery rates 22% higher than what would have been expected had they received the ST. Importantly, we saw no evidence that the MT compromised cancer control as the rate of positive surgical margins was similar for the two study groups.

Although further evaluation of EF recovery rates at 12, 18, and 24 months will be required to assess the effect our change in technique has on overall EF recovery, evidence suggests that the effect of delayed EF recovery beyond 6 months results in corporal fibrosis predisposing to venous leak and secondary ED despite resolution of the postoperative neuropraxia.¹⁷ With earlier recovery of EF, longer-term recovery rates may be improved. The 6-month rate of EF recovery of 67% (79% in those undergoing bilateral neurovascular bundle preservation) is comparable to other contemporary published series. Walsh et al. reported 54% recovery rate at 6 months in 64 men undergoing anatomic (bilateral NVB preservation) RP with and without the use of PDE-5 inhibitors.¹⁵ Our 6-month results compare favorably to those of Menon et al who recently published 12- and 48-month EF recovery results in men undergoing their modified technique of robotic RP. In men in whom a bilateral preservation of the “veil of Aphrodite” was achieved (only 33% of their cohort was amenable to this technique), 70% had return of EF at 12 months postoperatively,¹⁸ similar to the results obtained at 6 months in this series of open RP. These results would argue against the notion that robotic RP was universally associated with better EF outcomes compared to open RP as suggested in 78% of 116 robotic RP websites, despite the absence of scientific data supporting their claims.¹⁹

The functional outcomes in this study are subject to those limitations inherent to retrospective studies. Variations in either patient’s perceived or actual baseline EF, individual surgeon assessment of the quality of NVB preservation, and patient compliance with and/or physician recommendations for the use of postoperative PDE-5 inhibitors all potentially influence our ability to interpret improvements in rate of EF recovery attributable only to changes in technique. Also, the rigidity assessment scale utilized to assign the degree erectile function recovery requires further validation at other centers; although, we have previously published data demonstrating good agreement between levels 1 and 2 on the 5-point scale and functional outcomes as defined by the EF domain score of the IIEF.⁷ In our previous publication, the mean EF domain score equating to a level 2 erection was 19.6 (95% CI 17, 22.5). This translates to a per question mean of 3.3 indicating the ability to have sexual intercourse between ‘half the time’ (3) and ‘most of the time’ (4). The IIEF is validated for all forms of sexual activity, thus we would contend therefore so too is the 5-point erection scale for such activity. Additionally, expected improvement in oncologic and functional outcomes related to the individual surgeon’s progression along a learning curve with increased experience and the influence of interval censoring on data interpretation during the postoperative period also potentially affect results. Nonetheless, the effect of technique modification on time to recovery after controlling for secular changes appears to remain significant. Longer follow-up will ultimately be necessary to determine whether the modifications will have any impact on the quality of erections and overall EF recovery rates.

CONCLUSION

Technical modifications made in our approach to NVB preservation during RP were associated with a shorter time to return of potency. Whether a causal association exists between change in technique and outcome requires further evaluation. Additionally, longer follow-up will be required to determine the impact our MT has on the quality of erections, overall potency rates, and oncologic outcome.

Acknowledgements

Sources of funding for this study: none

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Fig. 1.

ST: The NVB has been released from the apical-third of the prostate. The urethra has been completely divided and the anastomotic sutures have been placed. A catheter has been placed through the urethra into the bladder. Upward traction on the catheter allows the lateral vascular pedicles to be easily isolated (A), controlled with clips (B), and divided to expose the lateral aspect of the seminal vesicle (C).

Fig. 2.

MT: The entire NVB has been dissected off the lateral aspect of the prostate from just beyond the apex to above the seminal vesicle. Denonvilliers' fascia is sharply incised along the length of the prostate to further lateralize the NVB. Minimal traction is placed on the prostate/NVB during this dissection. The urethra is left intact until after both NVB's have been released from the prostate.

Fig. 3.

Predicted probability of potency at 6 months following RP by surgical technique, with adjustment for age and nerve sparing status, with 95% confidence intervals. Years 2001 to 2004: ST; years 2005 to 2006: MT. The 6-month probability of potency, adjusted for age and nerve-sparing, for each year of surgery is denoted by an "x".