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New Technology

Nerve Advancement with End-to-End Reconstruction after Partial Neurovascular Bundle Resection:A Feasibility Study

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ABSTRACT

***Background and Purpose*: It is clear that some patients with prostate cancer require a total or partial neurovascular bundle (NVB) resection for oncologic safety to be guaranteed. Nerve grafting is an alternative for these patients to maintain erectile function; however, we report on a feasible option where the NVB is released, and both terminal nerve fibers are approximated; this is the "nerve advancement technique (NAT)."**

***Patients and Methods*: Since 2005, a total of 215 men aged 48 to 70 years (mean 59 years) with a Sexual Health Inventory for Men (SHIM) score of 22 have undergone robotic radical prostatectomy for cancer. We selected prospectively seven men to have NAT performed because of clinical high-risk criteria (serum prostate specific antigen [PSA] concentration >20 mg/dL, Gleason score = 8, and stage cT_{2c} or higher), intraoperative criteria (difficulty separating the tissues around the prostate), and evidence of extracapsular extension (ECE) on magnetic resonance imaging. We performed unilateral partial resection, nerve advancement, and, finally, end-to-end anastomosis in six patients, whereas in one patient, we did a bilateral partial excision. We analyzed the results in terms of oncologic safety (positive surgical margins and PSA) and SHIM score after 18 months of follow-up.**

***Results*: Pathologic examination revealed stage T_3 disease in six patients; one had a positive surgical margin. Two patients are receiving salvage radiotherapy for PSA relapse, and five continue to have undetectable PSA concentrations after a median follow-up of 20 months. Five of the seven men recovered erectile potency with or without a phosphodiesterase inhibitor, and their median SHIM score is 18.**

***Conclusions*: We are encouraged by the initial results of NAT. The procedure may be an alternative for men who require extensive NVB dissection. However, further experience, longer follow-up, and independent trials are necessary.**

INTRODUCTION

ONE OF THE MOST IMPORTANT and still unresolved questions in the management of clinically localized prostate cancer is the optimal handling of the neurovascular bundles (NVBs) in the face of suspected invasion by the tumor. Whereas most surgeons argue that wide excision of the bundles is a prudent approach in these cases, there is no consensus about the ideal method for reconstruction of NVB tissue. There are several options already published: nerve grafting (sural or genitofemoral),[1] entubulization model of cavernosal nerve reconstruction,[2] and use of embryonic neural stem cells[3] or growth factors to enhanced neural regeneration.[4]

Radical prostatectomy (RP) is considered the standard treatment for localized prostate cancer. Since the introduction of the nerve-sparing technique by Walsh and Donker,[5] several series have been published in which patients recovered their erectile function.[6] Worse results have been reported in series in which

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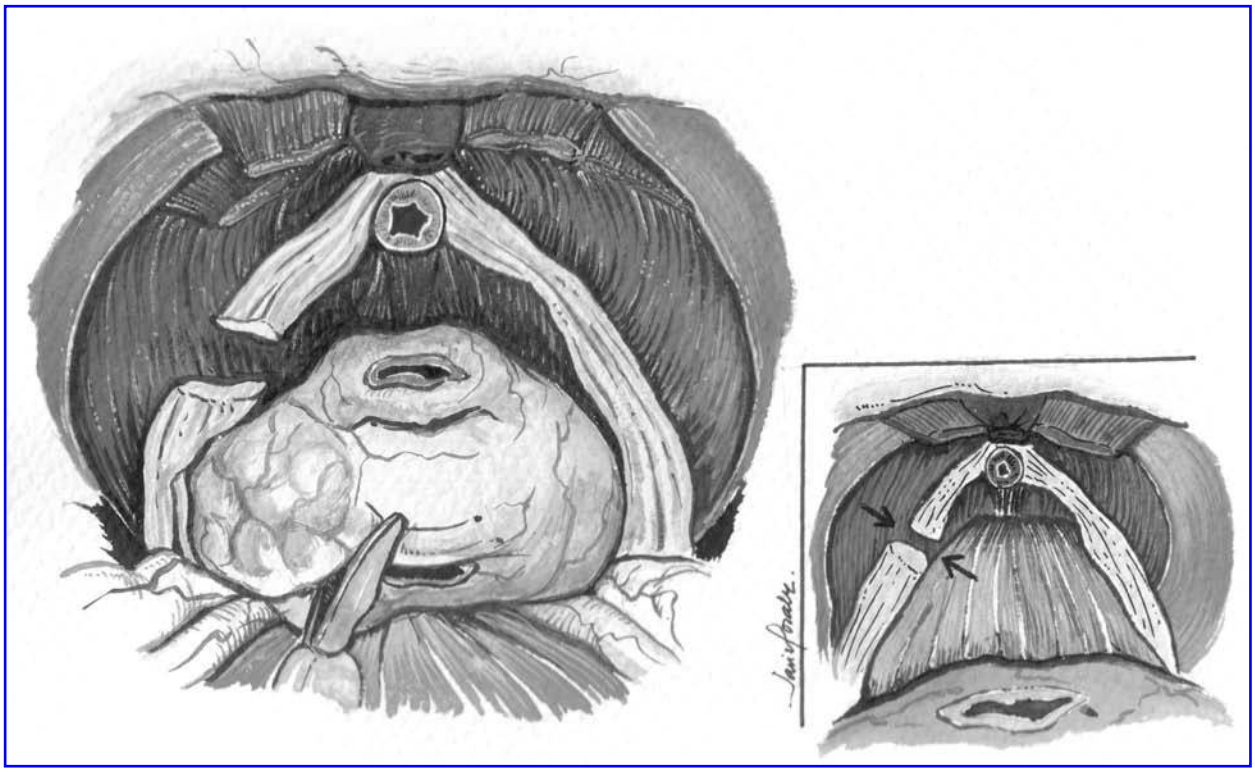

FIG. 1. Release of NVBs and NAT.

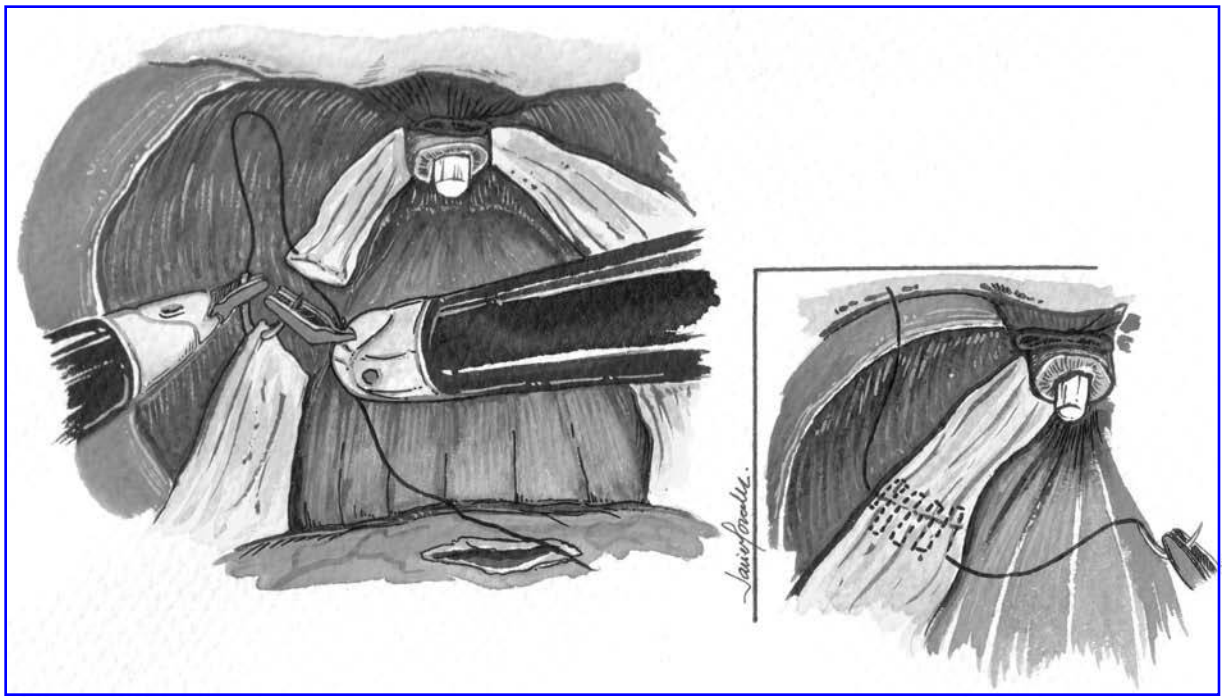

FIG. 2 End-to-end anastomosis.

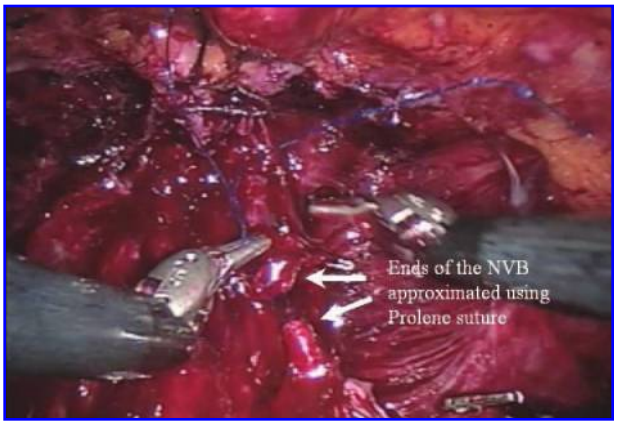

FIG. 3. Intraoperative picture, final aspect.

non-nerve-sparing techniques were used.[7] Therefore, it is clear that some patients require total or partial, bilateral or unilateral, NVB resection for oncologic safety to be guaranteed. To do an adequate NVB excision is a challenge for surgeons using robots in the absence of any tactile feedback.

Erectile dysfunction remains a common problem after RP when one or both NVBs are resected.[7,8] In a recent review of 11 series, the results of nerve grafting were modest in terms of sexual function recovery, and another incision was required, which caused some morbidity.[9]

Conceptually and on the basis of our cadaver studies,[10–12] we think that the NVB (composed of cavernous nerves and nerves fibers) is a spray-like rather than a stick-like structure. It seems likely that the bundle itself can be used to reconnect the two ends instead of using an autologous graft. We propose a novel approach for patients who are potent and have a preoperative and intraoperative high risk of extracapsular extension (ECE) (serum prostate specific antigen [PSA] concentration >20 mg/dL, Gleason score ≥8, stage cT_{2c} or higher cancer, evidence of ECE on MRI, and difficulty separating the tissue around the prostate). It is feasible to do a primary anastomosis (coaptation) of both ends of the NVB with previous mobilization using the "nerve advancement technique" (NAT). The feasibility of end-to-end and end-to-side anastomosis of the nerves and subsequent nerve regeneration has already been demonstrated in other anatomic sites.[13]

PATIENTS AND METHODS

Study design and patient eligibility

In 2005, a total of 215 consecutive patients underwent robotic radical prostatectomy (RRP) by a single surgeon (AT) in a single institution (WMC). The eligibility criteria were:

1. Preoperative (objective parameters)
   - High-risk clinical signs (PSA >20 ng/mL, Gleason score ≥8, stage cT_{2c} or higher)
   - Endorectal MRI suggests ECE
   - Palpable unilateral or bilateral at digital rectal examination under anesthesia
   - Patients previously potent (SHIM >18)

2. Intraoperative findings (surgeon's assessment/subjective parameters)
   - Difficult mechanical separation of the tissue around prostate
   - Adhesions in the extracapsular area
   - Excessive bleeding during dissection in the region of the NVB

On the basis of these criteria, we selected seven potent men on whom to perform this technique (six unilaterally and one bilaterally). All were strongly motivated to maintain sexual function. The mean age was 59 years (range 48–70 years), and the median follow-up was 21 months (range 17–22 months).

Surgical technique

Step 1: Robotic radical prostatectomy: Port placement and all the steps of RRP were performed as described previously. The procedure includes bilateral pelvic lymph-node dissection.[14]

Step 2: Partial NVB resection (unilateral or bilateral): The nerve-sparing approach to the side with suspicion of ECE was extrafascial, trying to minimize NVB resection. We do this in order to excise the entire tumor but attempt to keep as much of the bundle as possible (partial resection). This was feasible in our current series because the majority of the patients with disease classified as pT_3 had only focal ECE (<5–10 mm).

The prostate is retracted on one side, and the lateral pelvic fascia is exposed. The layers of the periprostatic fascia fuse with the anterior layer of Denonvilliers' fascia lateral to the prostate to form a potential triangular space containing the NVBs. The inner layer of the periprostatic fascia forms the medial vertical

TABLE 1. PATIENT PROFILES

			Preop.		*Final pathology*			
Pt. no.	*Age (years)*	*Follow-up (mos.)*	*PSA (ng/dL)*	*Gleason score*	*cT stage*	*Gleason score*	*pT stage*	*Most recent PSA ng/dL (mos)*
1	55	19	7.4	7 (4 + 3)	3	7 (3 + 4)	3a	<0.06 (19)
2	51	21	10.5	7 (3 + 4)	3	7 (4 + 3)	3b	0.02 (21)
3	48	18	4.2	7 (3 + 4)	3	7 (4 + 3)	3a	0.01 (17)
4	70	21	4.8	6 (3 + 3)	1c	6 (3 + 3)	3a	<0.04 (20)
5	62	22	2.7	6 (3 + 3)	1c	6 (3 + 3)	2c	<0.01 (20)
6	58	22	5.3	8 (4 + 4)	2b	8 (4 + 4)	3a	<0.1 (22)
7	70	21	4.3	7 (3 + 4)	1c	7 (3 + 4)	3b	<0.1 (21)

Table 2. Sexual Function Outcomes

Pt. no.	Baseline ($15^{th=}$)	Time postop. (mos)					Clinical status
		1 ($15^{th=}$)	3 ($15^{th=}$)	6 ($15^{th=}$)	12 ($15^{th=}$)	18 ($15^{th=}$)	
1	23 (4)	3 (1)	15 (3)	ND	9 (2)	10 (3)	Intercourse (PDE5I)
2	25 (5)	24 (5)	25 (5)	25 (5)	25 (5)	25 (5)	Unassisted intercourse
3	25 (5)	20 (4)	25 (5)	25 (5)	25 (5)	25 (5)	Unassisted intercourse
4	21 (3)	1 (1)	4 (1)	5 (1)	6 (1)	12 (3)	Partial erection (PDE5I)
5	20 (4)	1 (1)	21 (4)	24 (2)	25 (5)	25 (5)	Intercourse (PDE5I)
6	19 (5)	6 (3)	15 (4)	24 (5)	25 (5)	25 (5)	Intercourse (PDE5I)
7	12 (2)	4 (3)	1 (1)	3 (3)	4 (4)	8 (4)	Partial erection (PDE5I)

ND = no data; PDE5I = phosphodiesterase 5 inhibitor.

wall of this triangle; the outer layer or the lateral pelvic fascia forms the lateral wall, and the anterior layer of Denonvilliers' fascia forms the posterior wall. Entering the triangular space between Denonvilliers' fascia posteriorly, lateral pelvic fascia laterally, and the prostate medially best preserves the nerves. The surgeon has to reflect the lateral pelvic fascia off the prostate. It is incised in a plane superficial to the prostatic fascia from the apex to the prostate–vesical junction, always staying parallel to the NVBs and then taken off the prostate using gentle sweeping movements. This maneuver releases the NVBs and provides landmarks for later antegrade dissection. In the areas where the surgeon observes fibrotic tissue and the bundle dissection cannot be done easily, we resected a piece of the NVB outside the lateral pelvic fascia (extrafascial approach). Dissection is completely non-thermal, with clips preferred for any vascular control.

Step 3: Release of NVBs and neurovascular bundle advancement (Fig. 1): After partial excision of the bundle, it is possible to see both ends. With blunt dissection (robotic Maryland bipolar forceps), it is possible to detach the posterior and lateral aspect of the bundles from the laterorectal area. With this maneuver, we can obtain more relaxation of this tissue in order to decrease the distance before the anastomosis. In all cases, this distance was less than 2 to 3 cm (Fig. 1).

Step 4: End-to-end anastomosis: Using two robotic needle drivers and a 6–0 polypropylene suture, we performed two or three interrupted sutures between the stumps without tension (Figs. 2 and 3).

Data collection

All patients signed an Institutional Review Board-approved informed consent document in which all the details of the procedure were clarified.

All the clinical and pathologic data were obtained from the charts. All the intraoperative data related to the procedure were recorded: side of end-to-end anastomosis, estimated blood loss, and complications.

The specimen analysis was performed under a standard pathology protocol. All the specimens were reviewed by a single pathologist (JT). The presence of cancer cells at the inked margins constituted a positive surgical margin (PSM). Frozen sections were taken from suspect areas of the specimen and from the corresponding area in the patient, as well as from the two ends of the NVB before anastomosis. When the frozen-section report suggested involvement of the NVB with cancer, we excised it widely to ensure adequate surgical margins.

The erectile function assessment was performed with a series of self-administered Sexual Health Inventory for Men (SHIM) questionnaires[15] and patient interviews preoperatively and 1, 3, 6, 12, and 18 months postoperatively. The main goals during the follow-up period were monitoring PSA and erectile function. The median PSA follow-up was 20 months.

RESULTS

Preoperative data and specimen pathology information are presented in Table 1. The mean blood loss was 214 mL, and no patient required transfusion. There were no intraoperative or postoperative complications. All patients were discharged from the hospital within 24 hours.

On the side of NAT, the approaches to the bundles were extrafascial (outside the lateral pelvic fascia) in all cases. Most of our patients (85%) had stage pT_3 disease (four pT_{3a} and two pT_{3b}), and a PSM was found in one patient. Only one patient had positive intraoperative frozen biopsy. In this case, we excised more of the bundle in order to achieve negative biopsies of the ends and sides.

At last follow-up, five patients have undetectable serum PSA concentrations, and two patients (the second and third in the series) are receiving salvage radiotherapy for PSA relapse.

The mean preoperative SHIM score was 22, and the mean postoperative score was 18. Five patients (71.4%) were able to achieve intercourse with or without a phosphodiesterase-5 inhibitor. Two achieved only partial erections that are inadequate for intercourse (Table 2).

DISCUSSION

Preservation of sexual function after surgical treatment of prostate cancer without compromising oncologic results remains an important goal. Reported potency results after RRP differ widely, from 20% to 97% at 12 months.[16] Extracapsular extension of cancer is found in about 40% of RP specimens,[17] and a PSM is disturbingly common, being identified in 2% to 59% of RRP specimens.[16]

It still is difficult to determine which patients will have ECE in the NVB area. Several strategies have been implemented to predict whether a tumor is organ confined or extracapsular on the basis of digital rectal examination, the Gleason score in the preoperative biopsy, MRI, and ultrasonography or intraoperative findings such as open palpation results or endoscopic landmarks. Although useful, none of them has proved to be 100% reliable or accurate.[8,18]

In advanced cancers, unilateral or bilateral NVB excision should be considered when a substantial risk of ECE exists in the area of NVB. However, total resection of both or even one NVB results in patients losing spontaneous erection adequate for intercourse.[6,17] In this respect, Kim and associates[1] suggested in 1999 that sural nerve grafting could replace the resected cavernous nerves. After 1 and 2 years of follow-up, overall erectile activity returned in 9 of 12 patients (75%) and then in 16 of 23 patients (69%).[19] This technique was first replicated in laparoscopic surgery by Turk and colleagues[20] and then robotically by Kaouk et al,[21] both with preliminary results.

Recently, Takenaka and coworkers[10–12] described the cavernous nerves as running in spray-like fashion from the pelvic splanchinc nerves to the prostate. Accordingly, interposition nerve grafts can cover only a part on the circumferential distribution of the nerves around the prostate. Thus, the long-term results of sural nerve graft replacement of cavernous nerves await validation.

The magnified optics (10-fold) and three-dimensional view that RRP provides (combined with intraoperative surgical landmark identification) might enable a less aggressive NVB resection, thus diminishing the end-to-end gap. Frozen biopsies might be used as an additional helpful tool to confirm the absence of a PSM before anastomosis.[22] The three-dimensional magnification and robotic tools enhance dexterity and eliminate tremors and thus enable precise suturing and approximation of the NVB stumps (perineural sheaths are inside) in microsurgical coaptation.

The basic neuroscientific concept underlying the idea of repairing a peripheral nerve has been known for some time. According to Geuna and colleagues[13] and Terzis and associates,[23] if continuity is reestablished between the proximal and distal nerves stumps by end-to-end suture, the axons arising from the rich terminal sprouting immediately upstream of the point of transection will grow rapidly along the glial columns in the distal nerve stumps (bands of Büngner) and eventually reinnervate the denervated territories.

In our initial series, PSMs were found in only one specimen, which is impressive considering that 85% of the patients had disease classified as pT_3. In terms of sexual function, five of the seven previously potent men recovered erections after surgery with a median follow-up of 18 months.

We acknowledge several limitations in the current study: the small number of patients, the absence of control group (partial resection only), and lack of *a priori* computations to estimate power and significant differences. Also, so far, we cannot demonstrate regeneration between the two ends of the nerves. Now, we are working in a rat cavernous nerve model to test our hypothesis (nerve damage alone *v* autologous graft *v* NAT).

CONCLUSIONS

The NAT procedure is technically feasible and seems oncologically safe. The results with sexual function are promising. However, further experience and longer follow-up are necessary to validate the results of this pilot study.

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ABBREVIATIONS USED

ECE = extracapsular extension; MRI = magnetic resonance imaging; PSA = prostate specific antigen; PSM = positive surgical margins; NAT = nerve advancement technique; NVB = neurovascular bundle; PSA = prostate specific antigen; PSM = positive surgical margin; RP = radical prostatectomy; RRP = robotic radical prostatectomy; SHIM = Sexual Health Inventory for Men.

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