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End-to-side Somatic-to-autonomic Nerve Grafting to Restore Erectile Function and Improve Quality of Life After Radical Prostatectomy

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Abstract

Background: Radical prostatectomy (RP) is recommended for the treatment of men with clinically localised prostate cancer. However, RP is associated with a high incidence of erectile dysfunction (ED), which can impact the quality of life (QoL) significantly.

Objective: To evaluate the effectiveness of end-to-side nerve grafting surgery to restore erectile function and improve sexual QoL in men with ED after RP.

Design, setting, and participants: A retrospective review of a single-centre experience of nerve grafting in men with ED following RP was performed. Seventeen men had surgery between March 2015 and October 2017 in Melbourne, Australia, which fulfilled study inclusion and exclusion criteria.

Intervention: Microsurgical bilateral end-to-side nerve grafts from a selective fascicular neurotomy of the femoral nerve to the penile corpora cavernosa.

Outcome measurements and statistical analysis: Results were serially measured utilising the International Index of Erectile Function (IIEF-5) and the sexual domain of Expanded Prostate Cancer Index Composite (EPIC-26). The proportion and 95% confidence interval (CI) of men recovering sexual function following nerve grafting were determined.

Results and limitations: All patients had ED following their RP. Median age at nerve grafting was 64 yr (interquartile range [IQR] 60–66 yr). Median time between nerve- and non-nerve-sparing RP, and nerve grafting was 2.4 (IQR 2.1–3.1) and 2.2 (IQR 1.7–5.1) yr, respectively. Median follow-up was 18 (IQR 15–24) mo. At 12 mo after nerve grafting, 71% (95% CI 44–90%) of patients had erectile function recovery sufficient for satisfactory sexual intercourse, and 94% (95% CI 71–99%) and 82% (95% CI 57–96%) had clinically significant improvements in sexual function and reduced bother, respectively. There were two minor wound infections. Limitations include the retrospective study design.

Conclusions: End-to-side nerve grafting restored erectile function in 71% of men with ED following RP, supporting previous findings. Of the men, 94% had clinically relevant improvements in sexual QoL. We recommend multicentre implementation of post-RP nerve grafting into clinical practice with appropriate data collection to confirm its efficacy and feasibility.

Patient summary: We provide confirmatory evidence that end-to-side nerve grafting surgery restored erectile function and improved sexual quality of life in, respectively, 71% and 94% of men with erectile dysfunction following radical prostatectomy.

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1. Introduction

Prostate cancer is the most frequently diagnosed cancer in men in the developed world, with around 1.3 million new diagnoses expected worldwide in 2018 [1]. Radical prostatectomy (RP) is recommended as a frontline treatment for men with clinically localised prostate cancer [2]. However, RP is associated with a high incidence of erectile dysfunction (ED) [3–5]. ED can impact a man's quality of life (QoL) significantly [3,5–7].

Erectile dysfunction is defined as “the inability to achieve, and/or maintain an erection sufficient for satisfactory sexual performance” [8]. The predominant cause of ED following RP is injury to cavernous nerve bundles [9,10]. Despite nerve-sparing techniques [11], around 70% of men will be burdened with ED following RP, regardless of the surgical technique [3]. Non-nerve-sparing post-RP ED rates approach 100% [4]. Phosphodiesterase type 5 inhibitors (PDE5i's) have slightly improved erectile function outcomes after RP [9,12]. Nonsurgical treatment modalities for ED refractory to PDE5i's are restricted to vacuum pumps and intracavernous injections, which are often associated with high dropout rates [13]. Penile prostheses are associated with up to 17% adverse complications [14].

End-to-end nerve grafts to repair severed cavernous nerves have had limited success [15]. While end-to-end nerve grafting is considered the “gold standard” for the repair of nerve gaps [16], resulting poor rates of erectile function following this procedure were likely to be attributable to the “web-like” nature of the cavernous nerve bundles [10], which makes accurate nerve graft coaption difficult [15].

The unsatisfactory outcomes of previous nerve graft surgery required the development of a new technique to restore erectile function in these men. End-to-side nerve grafts are based on the principle of creating new nerve pathways from a donor nerve to denervated end organs when end-to-end nerve grafting is not suitable [16]. Souza Trindade et al. [17] introduced a new end-to-side nerve grafting procedure, which we have modified. Our procedure utilises end-to-side nerve grafts from the femoral nerve motor fascicles only to directly reinnervate the corpora cavernosa. A partial judicious neurotomy of the femoral nerve motor fascicles is used to enhance axonal regeneration and maximise penile reinnervation without diminution of

femoral nerve function. The nerve grafts replace the function of injured cavernous nerves. Approximately 12 mo after nerve grafting, new nerve connections are anticipated to have formed in the corpora cavernosa, which help restore erectile function. The potential of our end-to-side nerve grafting technique to restore erectile function and improve sexual QoL in men with ED following RP was evaluated by a chart review.

2. Patients and methods

2.1. Patients

The study protocol was approved by the hospital ethics board (HREC #227). Men with post-RP ED who had end-to-side nerve grafting between March 2015 and October 2017 were included in this retrospective analysis if they fulfilled the inclusion criteria: (1) prostate-specific antigen levels (<0.01 ng/ml), (2) urinary continence at the time of nerve grafting, and (3) no pre-RP ED. Exclusion criteria were (1) age >70 yr, (2) no sexual partner, (3) collected outcomes <12 mo after nerve grafting, and (4) comorbidities (eg, insulin-dependent diabetes) or conditions that compromised the ability to achieve erections.

Data, including visit date, clinical observations, and penile rehabilitation therapy used, were collected from before nerve grafting until the last clinical visit, and any adverse events were recorded.

2.2. Surgical procedure

Nerve grafting was performed >3 mo after non-nerve-sparing RP and >1.8 yr after nerve-sparing RP.

All patients had nerve grafting using both sural nerves (Fig. 1). Under nonrelaxant general anaesthesia, sural nerve grafts were harvested (Fig. 2). Following exposure of the femoral nerves (Fig. 3) and the corpora cavernosa bilaterally, the nerve grafts were microsurgically coapted to appropriately selected and partially neurotomed motor fascicles of the femoral nerve (Fig. 4) with 8/0 or 9/0 nylon. Six centimetres of the distal grafts were passed along the length of each corporal body, via a small (1 cm) corporotomy incised on the lateral aspect of the proximal penile shaft to maximise the area of neurotisation within each corpus cavernosum (Fig. 5). The corporotomies were closed in a watertight fashion with 3/0 polyester sutures. All skin incisions were closed in layers with 3/0 polyglycaprone 25.

To allow nerve grafts to heal, patients abstain from sexual activities and do not overmanipulate their penis (milking urine or excessive shaking) for the first 3 mo postoperatively. At 3–6 mo after operation, all patients commenced PDE5i treatment (100 mg sildenafil or 20 mg tadalafil) three times weekly.

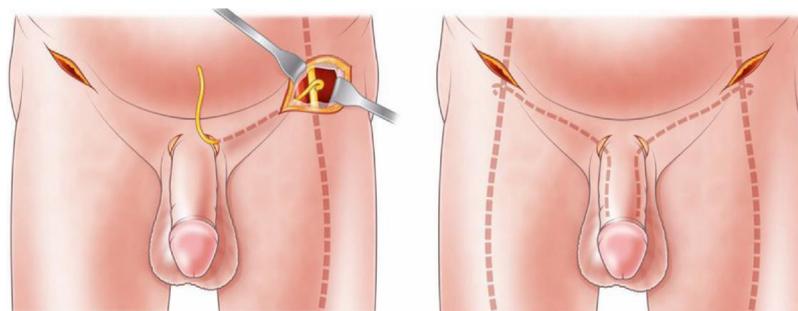


Fig. 1 – Schematic representations of the sural nerve graft procedure to restore erectile function after radical prostatectomy. The procedure involves bilateral end-to-side sural nerve grafts from the femoral nerve to the corpora cavernosa of the penis.



Fig. 2 – Sural nerve harvesting utilising two incisions and a nerve stripper.

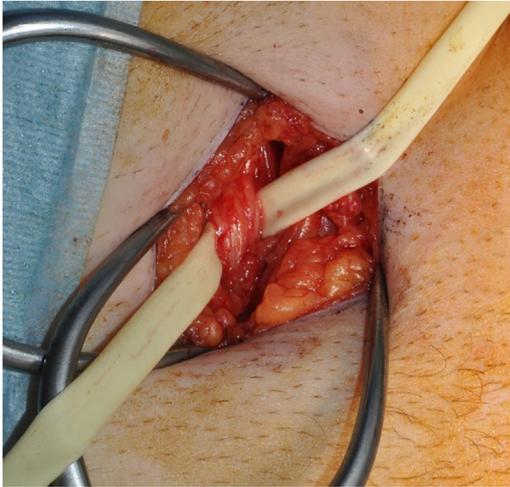


Fig. 3 – Exposure of the femoral nerve.

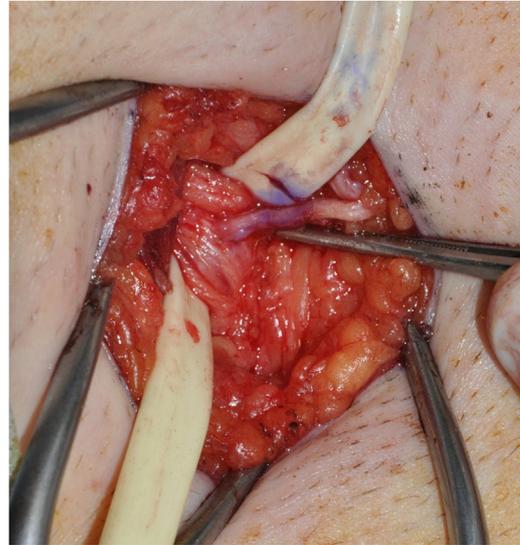


Fig. 4 – End-to-side neurorrhaphy of sural nerve to femoral nerve.

2.3. Patient-reported outcomes

As part of routine care, patients completed validated questionnaires used to evaluate erectile function and sexual QoL outcomes. Questionnaires were completed at 1 mo prior to nerve grafting and at every 3–6 mo after nerve grafting. Prior to nerve grafting, patients were asked to recall pre-PP measures. Questionnaire evaluation was performed independently of the treating surgeons.

Patient-reported erectile function was measured using the International Index of Erectile Function (IIEF-5) [18], where patients were requested to recall their erectile function over the past 4 wk. Successful restoration of erectile function was defined as post-nerve grafting IIEF-5 scores ≥ 17 [9], either spontaneously or with the use of PDE5i's where these were ineffectual after RP. Additionally, patients had to “achieve and/or maintain erection sufficient for satisfactory performance” to provide practical relevance to patient clinical care [8]. That is, the combined IIEF-5 score for question 2 (“When you had erections with sexual stimulation, how often were your erections hard enough for penetration?”) and question 3 (“During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?”) had to be ≥ 8 [19]. Sexual QoL outcomes were measured using the sexual domain of the Expanded Prostate Cancer Index Composite (EPIC-26), which comprises *function subscale* and *bother subscales* within the total *summary score* [20]. Changes in EPIC-26 scores of ≥ 10 represent minimally important differences of clinical significance [5].

Patient-reported outcomes were analysed at 12 mo after nerve grafting. The 95% confidence intervals (CIs) were determined as a

predictor of outcomes if this procedure was performed in a larger population; 95% CIs were calculated using the exact method of Clopper and Pearson [21], as implemented by the function “binom test” in R version 3.4.1.

3. Results

A retrospective chart review identified 21 patients fulfilling the study inclusion criteria who had nerve grafting between March 2015 and October 2017. Of these, four patients were excluded due to insulin-dependent diabetes (one patient), follow-up outcomes <12 mo after nerve grafting (one patient), >70 yr of age (one patient), and no sexual partner (one patient). Retrospective analysis was performed on data from 17 patients with 100% follow-up of 3–6-monthly questionnaires.

Summary and individual patient clinical data are provided (Table 1 and Supplementary Table 1). The average operative time was 3 h. All patients were discharged the day following surgery. The median time between RP and nerve grafting was 2.3 (interquartile range [IQR] 2.1–3.1) yr. Median patient age at nerve grafting was 64 (IQR 60–66) yr.

All patients had pre-PP erectile function (IIEF-5 score ≥ 17 ; Supplementary Figs. 1A–3A). After RP, all patients had

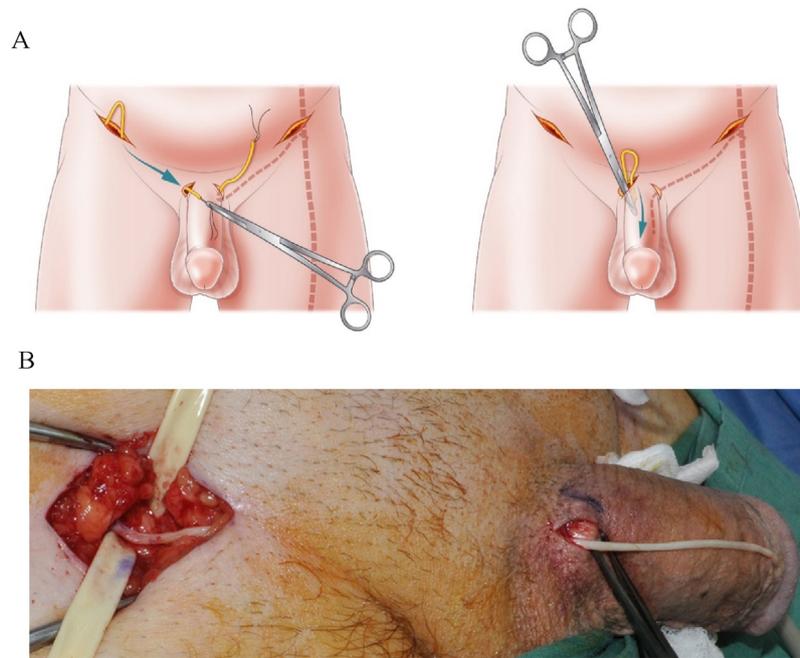


Fig. 5 – Nerve graft from inguinal to penile incision. (A) Schematic diagram showing passage of reversed nerve graft from inguinal to penile incisions. (B) Passage of reversed nerve graft from inguinal to penile incisions in the patient.

Table 1 – Summary of patient clinical details

Before RP	Before nerve grafting		After nerve grafting
Median age at RP, yr (IQR)	Median time between RP and penile reinnervation, yr (IQR)	Median age at penile reinnervation, yr (IQR)	Median post-penile reinnervation follow-up, mo (IQR)
61 (56–64)	2.3 (2.1–3.1)	64 (60–66)	18 (15–24)

IQR = interquartile range; RP = radical prostatectomy.

severe or moderate ED (IIEF-5 score ≤ 11), refractory to regular PDE5i use. Postoperative complications included two minor wound infections. Transient quadriceps weakness was observed in three patients for the 1st postoperative week. All patients had predictable sural nerve paraesthesia.

3.1. Erectile function outcomes

Summary pre- and post-nerve grafting IIEF-5 outcomes are presented in Fig. 6 (individual data—Supplementary Figs. 1A–3A). Successful erectile function recovery sufficient for satisfactory sexual intercourse (IIEF-5 score ≥ 17 and combined scores of ≥ 8 for questions 2 and 3) was achieved in 12 out of 17 men (71%; 95% CI 44–90%) at 12 mo after nerve grafting.

Following nerve grafting, three patients (P2, P6, and P10) had intermittent erections sufficient for satisfactory intercourse after intracavernous injections, but were unable to achieve erections without injections or with PDE5i's alone (Supplementary Figs. 1–3). Despite fulfilling the IIEF-5 criteria for erectile function restoration, these patients were

not classified as those having successful erectile function (Fig. 6A).

3.2. Sexual QoL outcomes

Median and IQRs of EPIC-26 summary, function, and bother subscale scores are presented in Fig. 7 (individual data—Supplementary Figs. 1B–3B). All patients, except for P2, had clinically relevant improvements in sexual QoL summary and function scores (≥ 10 ; Supplementary Table 2) [5]. Median improvements in function and bother scores at 12 mo after nerve grafting compared with those prior to nerve grafting were 44 (IQR 34–55) and 31 (IQR 19–63), respectively. The proportion and 95% CI of clinically relevant outcomes at 12 mo after nerve grafting compared with those before nerve grafting are provided in Table 2.

4. Discussion

We report the effect of this simplified end-to-side nerve grafting procedure on erectile function recovery in men

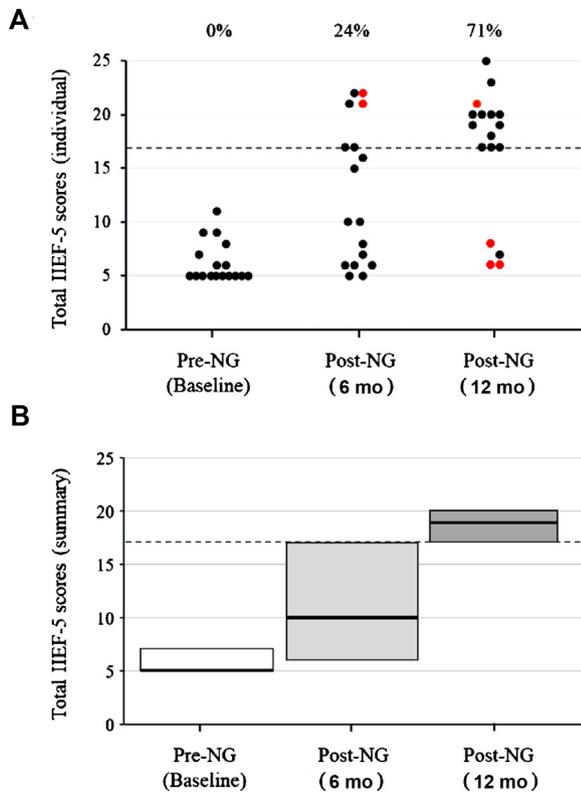


Fig. 6 – Patient-reported International Index of Erectile Function (IIEF-5) outcomes. Total IIEF-5 scores at baseline and at 6 and 12 mo after nerve grafting. Scoring of the IIEF-5 questions is based on a five-point ordinal scale from 1 to 5, with total IIEF-5 scores corresponding to the sum of scores for each question (minimum score is 5, maximum score is 25). Lower values represent poorer sexual function. Restored erectile function IIEF-5 score of ≥ 17 and a combined score of ≥ 8 for questions 2 and 3 (dotted line). (A) Scatterplot of all patients' total IIEF-5 scores, with the proportion of men with restored erectile function presented at the top of each time interval. Patients on intracavernous injections are presented in red and considered to have continuing erectile dysfunction. (B) Medians and corresponding IQRs of total IIEF-5 scores. The median marking the midpoint of the data is shown by a line and the box spans the IQR (the middle 50% of scores), with the ends of the box representing the lower (25%) and upper (75%) quartiles. IQR = interquartile range; NG = nerve grafting.

with ED following RP. Erectile function sufficient to achieve and maintain satisfactory sexual intercourse was selected as the principal endpoint to provide a concrete metric of practical relevance to patient clinical care [8]. Successful erectile function recovery was achieved in 71% (95% CI 44–90%) of men with ED following nerve grafting. In men with restored erectile function, 58% did not require pharmacological assistance.

Given the excellent oncological outcomes following RP [22], but a high incidence of postoperative ED [3–5], treatment modalities to improve post-RP sexual function have become increasingly important. Compounding this problem is the significant impact that ED has on a man's QoL [3,5,7], with emotional domains often being more profoundly affected than physical domains [6]. In our cohort, we observed clinically significant improvements in sexual function and reduced bother, respectively, in 94% (95% CI 71–99%) and 82% (95% CI 57–96%) of men at 12 mo after nerve grafting.

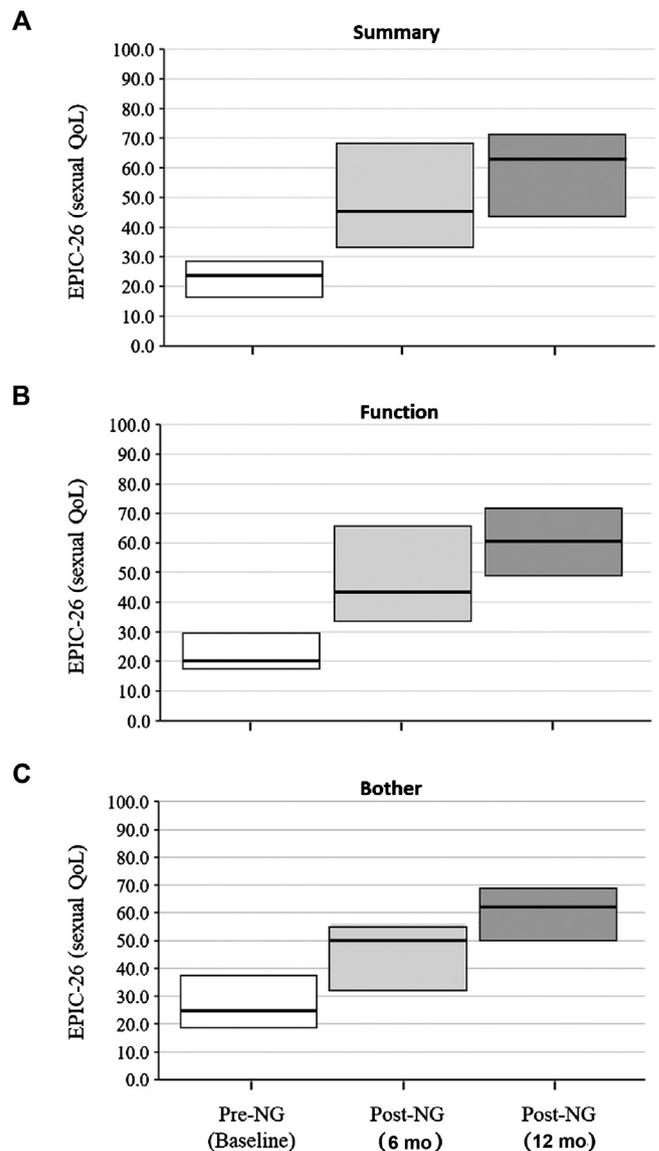


Fig. 7 – Patient-reported Expanded Prostate Cancer Index Composite-26 (EPIC-26) sexual QoL outcomes. EPIC-26 sexual domain scale scores for (A) summary, (B) function, and (C) bother presented as medians and corresponding IQRs for 17 patients at baseline and at 6 and 12 mo after nerve grafting. Scores are scaled from 0 to 100, with higher scores indicating better function and less bother. The median marking the midpoint of the data is shown by a line and the box spans the IQR (the middle 50% of scores), with the ends of the box representing the lower (25%) and upper (75%) quartiles. IQR = interquartile range; NG = nerve grafting; QoL = quality of life.

The importance of assessing sexual QoL outcomes is further exemplified as QoL outcomes have the potential to influence a patient's selected treatment regime for localised prostate cancer. Singer et al. [23] found that 32% of men without prostate cancer valued sexual potency more than survival when asked to select a treatment regime if they had prostate cancer. Sanda et al. [7] also found that distinct patterns of changes in sexual QoL EPIC-26 scores directly influenced patients' levels of satisfaction following their treatment for T1 or T2 prostate cancer. In this context, our nerve grafting procedure could influence the first-line treatment chosen by men for localised prostate cancer if

Table 2 – Proportions of clinically relevant outcomes at 12 mo after nerve grafting

Sexual function measure	Threshold cut-off	Proportion (95% CI) ^a
<i>International Index of Erectile Function-5</i>		
Sum of questions 1–5 (range, 5–25)	≥17, with Q2 and Q3 combined score ≥8	71% (44–90%)
<i>Sexual domain of Expanded Prostate Cancer Index Composite-26</i>		
Summary	Scale improvements ≥10	94% (71–99%)
Function	Scale improvements ≥10	94% (71–99%)
Bother	Scale improvements ≥10	82% (57–96%)

CI = confidence interval.
^a Proportions and corresponding 95% confidence intervals were calculated using the exact method of Clopper and Pearson [21].

they were aware that a procedure was available that could restore ED following RP.

This study indicates that end-to-side nerve grafting is a feasible and safe procedure for restoration of erectile function after RP. End-to-side nerve grafting was first reported in 1903 for the treatment of facial palsy and brachial plexus with promising, yet inconsistent, outcomes [24]. Currently, end-to-side nerve grafting is an accepted adjunct technique for peripheral nerve injury repair in the fields of facial reanimation, brachial plexus injury, and muscle neurotisation [25].

Two studies recently highlighted the potential of end-to-side nerve repair and grafting to restore erectile function [17,26]. Dong et al. [26] applied end-to-side nerve repair to rats with transected spinal nerves and successfully restored erectile function in 42% of rats compared with 0% in the nonsurgical group. More recently, Souza Trindade et al. [17] introduced end-to-side nerve grafting from the femoral nerve to the corpus cavernosum and also to the dorsal nerve of the penis in men with ED after RP, and successfully restored erectile function in six out of 10 men on average 13 mo after nerve grafting.

Functional outcome studies following end-to-side nerve grafting suggest that the degree of donor motor nerve injury incurred through the epineurium and perineurium is directly related to the degree of donor nerve regeneration [27]. To initiate reinnervation of the recipient nerve, both Dong et al. [26] and Souza Trindade et al. [17] utilised an “epineurial window” at the neurorrhaphy site. We increased the nerve regeneration potential by performing a judicious fascicular neurotomy of the selected motor fascicles. Incorporation of a partial neurotomy of the donor nerve fascicles leads to enhanced axonal sprouting from the donor nerve, increased reinnervation of muscles, and improved functional outcomes [27]. We also simplified the procedure of Souza Trindade et al. [17] by removing the sensory nerve grafts, as all our patients had normal sensation.

Our modified end-to-side nerve grafting technique with selective partial neurotomy of the motor fascicles of the femoral nerve will result in increased motor axonal sprouting to maximise penile reinnervation without diminution of femoral nerve function. As complete harvest of the rectus femoris muscle for reconstructive purposes is not associated with a reduction in quadriceps function [28], we feel that a judicious partial neurotomy of the femoral nerve motor fascicles should not change quadriceps function. As

our cohort had normal sensation, bilateral sural nerve grafts from each femoral nerve to the corpora cavernosa restored erectile function without the need for additional sensory nerve grafts to the dorsal nerve of the penis [17]. However, it should be emphasised that our nerve grafting procedure should be reserved only to an experienced surgical team comprising a microsurgeon working alongside a urologist.

The mechanisms behind how erectile function is restored after nerve grafting can only be theorised. Current understanding of penile erectile function is only partially elucidated, and complex factors including neurovascular physiology, emotional factor, sensory pathways, olfactory function, visual processes, and intact libido all play a role in normal erectile function [10]. The process of erection is mediated by a spinal reflex, which requires a variety of central and peripheral neural inputs with an overlay of humoral mechanisms. The end result of these interactions is the release of prostaglandins and neurotransmitters such as acetylcholine and nitric oxide from the cavernous nerves that lead to erection [12]. While the central somatic interplay of how these factors result in erections in this cohort of men who have had somatic-to-autonomic nerve grafting is unknown, we anticipate that the provision and release of neurotransmitters from the regenerated femoral nerve axons into the corpus cavernosum of the penis are responsible for the occurrence of penile erections [13].

Why erectile function recovery sufficient for sexual intercourse following nerve grafting was not achieved in five of the 17 patients is uncertain. Causes other than cavernous nerve damage may be responsible for ED in these patients [13]. Likewise, cavernous nerve damage is thought to result in penile smooth muscle hypoxia leading to cavernosal fibrosis and venous leakage, as demonstrated by animal and human studies [13]. Interestingly, the presence of sleep-related erections was reported by three men without restored erectile function after nerve grafting, which were absent before nerve grafting (Supplementary Fig. 4), suggesting a potential psychogenic aetiology of ED in these men [29].

Our study includes comprehensive measures of a patient’s recent sexual function status using two well-validated instruments (IIEF-5 and EPIC-26 sexual domains) to avoid patient recall bias and an independent assessment of outcomes to avoid the potential for any overestimation of outcomes. Well-defined and strict criteria were used to

classify clinically relevant erectile function recovery [9,19] and sexual QoL outcomes [5]. While our study included a range of patient follow-up times after nerve grafting, this was unavoidable due to staggered presentation of patients for the procedure. As this is a retrospective analysis, we used predefined stringent exclusion and inclusion criteria for data abstraction to avoid a potential selection bias. Pre-RP data may also have resulted in a patient recall bias, but this was unavoidable due to patients presenting only after RP.

5. Conclusions

This technique of end-to-side nerve grafting successfully restored erectile function in 71% of men with post-RP ED. Our results support those of a previous study by Souza Trindade et al. [17]. In combination with the improved clinically relevant sexual QoL outcomes observed, we recommend end-to-side nerve grafting in clinical practice. Larger studies to determine erectile function recovery rates utilising end-to-side nerve grafting to restore erectile function in men with post-RP ED are advised.

Author contributions: Christopher J. Coombs had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Reece, Dangerfield, Coombs.

Acquisition of data: Reece, Dangerfield.

Analysis and interpretation of data: Reece, Dangerfield, Coombs.

Drafting of the manuscript: Reece, Dangerfield, Coombs.

Critical revision of the manuscript for important intellectual content: Reece, Dangerfield, Coombs.

Statistical analysis: Reece.

Obtaining funding: None.

Administrative, technical, or material support: Reece.

Supervision: Reece, Dangerfield, Coombs.

Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.eururo.2019.03.036>.

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