

Nerve Graft to Restore Erectile Function During Radical Prostatectomy (for Ohio Only)

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Related Policies
None

Application

This Medical Policy only applies to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using Ohio Administrative Code 5160-1-01.

Coverage Rationale

Autologous (e.g., sural) or allogenic nerve grafts to restore erectile function during or after radical prostatectomy are unproven and not medically necessary due to insufficient evidence of efficacy.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
55899	Unlisted procedure, male genital system
64999	Unlisted procedure, nervous system

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Description of Services

Erectile dysfunction (ED) is a common problem after radical prostatectomy (RP). In particular, spontaneous erections are absent in patients who have bilateral resection of the neurovascular bundles as part of the RP procedure for treatment of localized prostate cancer. A technique called nerve-sparing surgery has been developed to prevent damage to these nerves; however, this technique is not possible in some patients.

Nerve grafting to replace resected cavernous nerves during radical retropubic prostatectomy (RRP) has been proposed as a technique to increase the likelihood of restoring spontaneous erectile function (EF). During the procedure, a donor nerve (e.g., sural nerve, genitofemoral nerve) is harvested from the patient and joined to the distal and proximal ends of the resected cavernous nerve. Grafting may be performed on one or both resected cavernous nerves. The sural nerve (a nerve traveling along the short saphenous vein in the lower leg) is the most common donor nerve used in the nerve grafting procedure during RP. The nerve is considered expendable and has been used commonly in other nerve grafting procedures for repairing injured peripheral nerves. During the sural nerve grafting (SNG) procedure, a portion of the nerve is harvested from one leg of the patient and grafted to the resected cavernous nerve.

Advocates of nerve grafting believe that nerves should be preserved whenever compatible with complete resection of cancer, but that when the cavernous nerve must be resected or is damaged severely, graft replacement should be a consideration (Kim et al., 2001; Scardino et al., 2001). While the decision to spare or resect the neurovascular bundles is based on the surgeon's preference, it is influenced by clinical stage, prostate-specific antigen level, and transrectal ultrasound/biopsy results (Kim et al., 2001).

Clinical Evidence

There is insufficient quality scientific evidence in the clinical literature demonstrating that the use of nerve grafting results in improved outcomes for ED following RP. Further studies, including additional well-designed randomized controlled trials with long-term follow-up, would be needed to establish the efficacy and long-term value of nerve grafting for the prevention or treatment of ED after RP, but findings from one randomized controlled trial already suggest evidence for lack of benefit.

Harke et al. (2023) conducted a case series to investigate the safety and feasibility of spider silk grafting for erectile nerve reconstruction in patients undergoing robotic radical prostatectomy (RARP). The major-ampullate-dragline from *Nephila edulis* was used for spider silk nerve reconstruction (SSNR). After removal of the prostate with either unilateral or bilateral nerve-sparing, the spider silk was laid out on the site of the neurovascular bundles. Data analysis included inflammatory markers and patient reported outcomes. Six patients underwent RARP with SSNR. In 50% of the cases, only a unilateral nerve-sparing was performed, bilateral nerve-sparing could be performed in three patients. Placement of the spider silk conduit was uneventful, contact of the spider silk with the surrounding tissue was mostly sufficient for a stable connection with the proximal and distal ends of the dissected bundles. Inflammatory markers peaked until postoperative day 1 but stabilized until discharge without any need for antibiotic treatment throughout the hospital stay. One patient was readmitted due to a urinary tract infection. Three patients reported about erections sufficient for penetration after three months with a continuous improvement of erectile function both after bilateral and unilateral nerve-sparing with SSNR up to the last follow-up after 18 months. The authors concluded this analysis of the first RARP with SSNR, a simple intraoperative handling without major complications was demonstrated. While the series provides evidence that SSNR is safe and feasible, a prospective randomized trial with long-term follow-up is needed to identify further improvement in postoperative erectile function due to the spider silk-directed nerve regeneration. Given the nonrandomized design of this study and the retrospective nature of data collection and analysis, one cannot rule out residual confounding factors that could influence the results. Further research is needed to determine the clinical relevance of these findings.

Shauly et al. (2019) conducted a systematic review of recent articles and identified 19 articles/studies addressing relatively new interventions for ED. The review documented evidence supporting the use of two microsurgical treatments for ED - namely microvascular arterial bypass penile revascularization surgery and cavernous nerve graft reconstruction. For cavernous nerve graft reconstruction, the authors identified six publications, but they all seem limited by lack of a comparison group. Although the authors indicated that their analysis served to organize the most up-to-date data in treating ED and showed promise, they concluded that many of the studies lacked a large enough study population to make material claims and further clinical evidence is required.

Reece et al. (2019) performed a retrospective review of a single-center experience of nerve grafting in a case series of seventeen men who had erectile dysfunction (ED) following RP surgery. Microsurgical bilateral end-to-side nerve grafts from a selective fascicular neurotomy of the femoral nerve to the penile corpora cavernosa was performed. 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 months 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. The authors indicated this provided 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. The authors recognized that the limitations include the retrospective study design and concluded that larger studies to determine erectile functions recovery rates utilizing end-to-side nerve grafting to restore erectile function in men with post-RP ED are advised to confirm its efficacy and feasibility. The findings are limited by lack of comparison group.

Souza Trindade and colleagues (2017) conducted a long-term case series study on 10 patients at 6, 12, 18, and 36 months postoperatively for patients who had surgery involving bridging of the femoral nerve to the dorsal nerve of the penis and the inner part of the corpus cavernosum with sural nerve grafts and end-to-side neurographies after having undergone a radical prostatectomy at least 2 years previously. Four patients had also undergone radiotherapy after RP. All patients reported satisfactory sexual activity prior to RP. The surgery involved bridging of the femoral nerve to the dorsal nerve of the penis and the inner part of the corpus cavernosum with sural nerve grafts and end-to-side neurographies. Patients were evaluated using the IIEF questionnaire and phallo-penile Doppler ultrasonography (PPDU) pre-operatively and at 6, 12 and 18 months post-operatively, and using a Clinical Evolution of Erectile Function (CEEF) questionnaire, administered after 36 months. The IIEF scores showed improvements with regard to ED, satisfaction with intercourse and general satisfaction. Evaluation of PPDU velocities did not reveal any difference between the right and left sides or among the different time-points. The introduction of nerve grafts neither caused fibrosis of the corpus cavernosum, nor reduced penile vascular flow; CEEF results showed that sexual intercourse began after a mean of 13.7 months with frequency of sexual intercourse varying from once-daily to once-monthly. The authors concluded that a total of 60% of patients were able to achieve full penetration, on average, 13 months after re-innervation surgery. Patients previously submitted to radiotherapy had slower return of erectile function. The authors concluded that penile re-innervation surgery is a viable technique, with effective results, and could offer a new therapeutic option for ED after RP. This study was limited by the small number of cases (n = 10) and lack of comparison group.

Kung et al. (2015) performed a retrospective study on 38 consecutive patients who underwent immediate unilateral or bilateral nerve reconstruction after open prostatectomy. Additionally, 53 control patients who underwent unilateral, bilateral, or non-nerve-sparing open prostatectomy without nerve grafting were reviewed. Outcomes included rates of urinary continence, erections sufficient for sexual intercourse, and ability to have spontaneous erections. Analysis was performed by stratifying patients by D'Amico score and laterality of nerve involvement. There was no significant benefit for patients who had unilateral nerve grafting (UNG) versus unilateral nerve-sparing (UNS) prostatectomy. Patients with bilateral nerve-sparing (BNS) demonstrated superior functional outcomes compared to patients with bilateral non-nerve-sparing, whereas patients with bilateral nerve-grafting displayed a trend toward functional improvement. With increasing D'Amico score, there was a trend toward worsening urinary continence and EF regardless of nerve-grafting status. The authors concluded that immediate nerve grafting for reconstruction of the prostatic plexus after RP may be most valuable for improving postoperative morbidity in patients requiring bilateral neurovascular bundle resections. Currently, the benefit of nerve grafting is limited by the inability to accurately isolate the putative nerves, which mediate EF and urinary continence. Further investigation is needed to improve the potential of bilateral nerve grafting after non-nerve-sparing prostatectomy. Limitations to this study include small sample size, the subjective nature of the postoperative outcomes, and lack of randomization to intervention groups.

Siddiqui et al. (2014) examined the long-term outcome of SNG during RRP performed by a single surgeon. Sixty-six patients with clinically localized prostate cancer and preoperative International Index of Erectile Function (IIEF) score > 20 who underwent RRP were included. Neurovascular bundle excision was performed if the risk of side-specific extra-capsular extension was > 25% on Ohori's nomogram. SNG was harvested by a plastic surgeon, contemporaneously as the urologic surgeon was performing RRP. IIEF questionnaire was used pre- and postoperatively and at follow-up (3 years). Recovery of potency was defined as postoperative IIEF-EF domain score > 22. There were 43 (65%) unilateral SNGs and 23 (35%) bilateral SNGs. The mean preoperative IIEF score was 23.4 + 1.6. Long term assessment reflected 19 patients (28.8%) had IIEF scores > 22. The IIEF-EF scores for those who had unilateral SNG and bilateral SNG were 12.9 + 4.9 and 14.8 + 5.3, respectively. The

authors concluded that SNG can potentially improve EF recovery for potent men with higher stage prostate cancer undergoing RP; and that the contemporaneous, multidisciplinary approach provides a good quality graft while expediting the procedure without interrupting the workflow. However, the evidence is insufficient to conclude that this surgical technique is equivalent to BNS prostatectomy or that long-term outcomes are improved by nerve grafting. The findings are limited by lack of relevant comparison group.

Davis et al. (2009) evaluated whether UNS RP plus SNG would result in 50% relative improvement in potency at 2 years compared to UNS RP alone. The plan was to enroll 200 patients from October 2001–May 2006 in a RCT from a single academic center. After 107 patients were randomized in a 3:2 ratio (66 SNG, 41 controls), a protocol-planned interim analysis was performed which reflected potency rates of 18 of 41 (44%) in the SNG group and 10 of 23 (43%) in the control group. Based upon slower-than-estimated accrual (8 per month planned vs 2 per month actual) and a < 5% posterior probability that the groups would show a difference, early termination of the trial was recommended by the Data Monitoring Committee. Using data gathered from the 107 participants, the authors concluded that in this single-institution randomized study, unilateral SNG did not result in an increased potency rate at 2 years compared to UNS RP alone based upon a threshold significance level of at least a 20% (absolute) improvement. Secondary endpoints also did not show an improvement in time to potency or urinary function at 1 year. Based upon the power of this study, a smaller benefit could not be excluded. The authors believed that future study designs should anticipate inconsistent compliance with penile rehabilitation and 20–30% patient attrition.

Sugimoto et al. (2009) evaluated 24 patients who underwent UNS with contralateral cavernous nerve-grafting or bilateral nerve-grafting and 64 patients who underwent prostatectomy without nerve-sparing procedure. Patients in the nerve-grafting group who recovered potency demonstrated higher sexual function scores compared with those without nerve-sparing procedure. However, the majority of these patients were not satisfied with their sexual function.

Kuwata et al. (2007) prospectively investigated health-related quality of life, including sexual function, in 66 patients who underwent nerve grafting during a RP in comparison with those who underwent a non-nerve-sparing RP (22 patients had nerve-grafting procedures, 44 underwent non-nerve-sparing and non-nerve-grafting procedures). The observation periods ranged from 12-46 months (median: 29 months). For individuals who had nerve-sparing graft procedures (bilateral or unilateral), the sexual function score was significantly better than in the non-nerve-sparing/non-nerve-grafting patients. The sexual bother score, however, was more serious for the patients who underwent nerve-grafting surgery than for the non-nerve-sparing/non-nerve-grafting patients.

Saito et al. (2007) evaluated 64 patients who underwent a RP and intraoperative electrophysiological confirmation of cavernous nerve preservation. Twelve patients underwent a unilateral SNG for the resected neurovascular bundle. Twenty-one and 31 patients underwent BNS and UNS surgery without a nerve graft, respectively. As the age of patients was significantly younger in the SNG group than in the other groups, age-matched analysis also was conducted. In the age-matched analysis, the postoperative sexual function (SXF) score of the SNG group showed an intermediate level of recovery between those of the BNS and UNS groups at 12 months and reached the same level as the score at 12 months of the BNS group at 18 months postoperatively. The difference in the SXF score between the SNG and UNS groups began to appear after 6 months postoperatively and increased steadily with time. However, the background factors, such as the baseline SXF score, the usage rate of phosphodiesterase 5 inhibitors, and the rate of comorbidities were different between the SNG and UNS groups.

A prospective observational study by Namiki et al. (2007) evaluated 113 patients undergoing RRP for the rate of recovery of urinary continence and sexual potency. Patients were classified into 3 groups according to the degree of nerve sparing: unilateral nerve preservation with contralateral SNG interposition, BNS, and UNS. The BNS group showed the fastest recovery, although by 24 months there were no significant differences observed between the BNS group and the UNS group with SNG. The BNS group reported a better sexual function score than the UNS group throughout the postoperative period. During the first year postoperatively, the BNS group and the UNS group with SNG had better urinary function results than the UNS group. The authors concluded that the nerve graft procedure may contribute to the recovery of urinary function as well as sexual function after RRP; these findings need to be validated in a RCT.

Clinical Practice Guidelines

American Urological Association (AUA)

The 2018 American Urological Association guideline on erectile dysfunction recommends six types of treatment that could be considered for ED. Three are medications, while the others are vacuum erection devices, penile prosthesis implantation, and

penile arterial reconstruction. Treatments not recommended are venous surgery, low-intensity extracorporeal shock wave therapy, intracavernosal stem cell therapy, and platelet-rich plasma therapy (Burnett et al., 2018).

Guideline 11 specifically states men who desire preservation of erectile function after treatment for prostate cancer by radical prostatectomy (RP) or radiotherapy (RT) should be informed that early use of PDE5i post-treatment may not improve spontaneous, unassisted erectile function. (Moderate Recommendation; Evidence Level: Grade C).

National Comprehensive Cancer Network (NCCN)

According to the National Comprehensive Cancer Network (NCCN) prostate cancer guideline, recovery of erectile function following radical prostatectomy is related directly to the degree of preservation of the cavernous nerves, age at surgery, and preoperative erectile function. Improvement in urinary and sexual function has been reported with nerve-sparing techniques. Replacement of resected nerves with nerve grafts does not appear to be effective for patients undergoing wide resection of the neurovascular bundles (NCCN, 2022; updated 2023).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Sural nerve transplant is a procedure, and as such, is not regulated by the FDA.

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Policy History/Revision Information

Date	Summary of Changes
12/01/2023	<p>Application</p> <ul style="list-style-type: none">Added language to indicate any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using <i>Ohio Administrative Code 5160-1-01</i> <p>Supporting Information</p> <ul style="list-style-type: none">Updated <i>Clinical Evidence</i> and <i>References</i> sections to reflect the most current informationArchived previous policy version CS081OH.I – P

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state (Ohio Administrative Code [OAC]) or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state (OAC) or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state (OAC) or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state (OAC) or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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