



NERVE GRAFT TO RESTORE ERECTILE FUNCTION DURING RADICAL PROSTATECTOMY

Protocol: SUR044

Effective Date: April 11, 2011

Table of Contents	Page
<u>COMMERCIAL, MEDICARE & MEDICAID COVERAGE RATIONALE</u>	1
<u>BACKGROUND</u>	2
<u>CLINICAL EVIDENCE</u>	2
<u>U.S. FOOD AND DRUG ADMINISTRATION</u>	5
<u>APPLICABLE CODES</u>	6
<u>REFERENCES</u>	6
<u>PROTOCOL HISTORY/REVISION INFORMATION</u>	8

INSTRUCTIONS FOR USE

This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice.

COMMERCIAL, MEDICARE & MEDICAID COVERAGE RATIONALE

Sural or other nerve grafts to restore erectile function during radical prostatectomy are **not medically necessary.**

No comparative studies between nerve grafts and standard medical therapy (e.g., intracorporal injection, vacuum erection devices, or pharmacotherapy with sildenafil, tadalafil, or vardenafil) have been completed. The evidence for nerve grafts for restoration of erectile function is derived mainly from non-randomized studies limited by small sample sizes. Randomized controlled trials are needed to demonstrate the benefits of this technology.

Medicare does not have a National Coverage Determination or a Local Coverage Determination for Nevada for Nerve Grafts to Restore Erectile Function During Radical Prostatectomy. (Accessed May 2010)

For Medicare and Medicaid Determinations Related to States Outside of Nevada:

Please review Local Coverage Determinations that apply to other states outside of Nevada.

<http://www.cms.hhs.gov/mcd/search>

Important Note: Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare and Medicaid Services' Website.

BACKGROUND

Erectile dysfunction is a common problem after radical prostatectomy. In particular, spontaneous erections are absent in patients who have bilateral resection of the neurovascular bundles as part of the radical prostatectomy 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 has been proposed as a technique to increase the likelihood of restoring spontaneous erectile function. 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 radical prostatectomy. 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 procedure, a portion of the nerve is harvested from one leg of the patient and grafted to the resected cavernous nerve.

CLINICAL EVIDENCE

In a randomized trial, Davis et al. (2009) compared nerve-sparing retropubic radical prostatectomy with unilateral sural nerve grafting versus the same procedure without unilateral sural nerve grafting for clinically localized prostate cancer. The study planned to enroll 200 patients, but an interim analysis at 107 patients met criteria for futility and the trial was closed. For patients completing the protocol to 2 years, potency was recovered in 32 of 45 (71%) of the sural nerve graft recipients and 14 of 21 (67%) of the controls ($p=0.777$), which was not a statistically significant difference. By intent-to-treat analysis, potency was recovered in 32 of 66 (48.5%) of the sural nerve graft recipients and 14 of 41 (34%) of controls ($p=0.271$). No differences were seen in time to potency or quality-of-life scores for erectile dysfunction and urinary function. The investigators concluded that the addition of sural nerve graft to a unilateral nerve-sparing radical prostatectomy did not improve potency at 2 years following surgery.

Sugimoto et al. (2009) evaluated 24 patients who underwent unilateral nerve-sparing with contralateral cavernous nerve-grafting or bilateral nerve-grafting and 64 patients who underwent prostatectomy without nerve-sparing procedure. Patients in nerve-grafting group who recovered potency



demonstrated higher sexual function scores compared with those without nerve-sparing procedure ($P = 0.022$ and 0.001 in 25-48 and 49 months or later, respectively). However, sexual bother scores in nerve-grafting group who recovered potency were lower than those without nerve-sparing procedure throughout the observation periods ($P = 0.012$ in 49 months or later).

Kuwata et al. (2007) prospectively investigated health-related quality of life (HR-QOL), including sexual function in patients who underwent nerve grafting during a radical prostatectomy in comparison with those who underwent a non-nerve-sparing radical prostatectomy in 66 patients (22: nerve-grafting patients, 44: non-nerve-sparing and non-nerve-grafting patients). The observation periods ranged from 12-46 months (median: 29 months). The sexual function score was significantly better in the nerve-grafting (bilateral nerve graft or unilateral nerve graft with contra-lateral nerve-sparing) patients 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.

Porpiglia et al. (2005) evaluated 29 men who underwent laparoscopic radical prostatectomy with deliberate wide unilateral neurovascular bundle resection and preservation of the contralateral bundle. Fifteen men (group A) had an interposition sural nerve graft on the sectioned bundle, and 14 (group B) had laparoscopic radical prostatectomy with preservation of the unilateral bundle only. Erectile function was evaluated after surgery, and at 3, 8, 12 and 18 months, using the five-item version of the International Index of Erectile Function (IIEF-5) questionnaire. The follow-up was complete for 12 men in group A and 10 in group B. Group A had significantly higher erectile function scores on the IIEF-5 at 12 and 18 months than immediately after surgery ($P < 0.01$), whereas in group B the improvement was not statistically significant. According to the investigators, the study results suggest that laparoscopic sural nerve grafting during radical prostatectomy is feasible and safe; nevertheless it cannot be concluded that sural nerve grafting is more effective than preserving the neurovascular bundle alone in retaining sexual potency.

Saito et al. (2007) evaluated 64 patients who underwent a radical prostatectomy and intraoperative electrophysiological confirmation of cavernous nerve preservation. Twelve patients underwent a unilateral interposition sural nerve graft (UNG) for the resected neurovascular bundle. Twenty-one and 31 patients underwent bilateral nerve-sparing (BNS) and unilateral nerve-sparing (UNS) surgery without a nerve graft, respectively. As the age of patients was significantly younger in the UNG 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 UNG 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 UNG 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 UNG and UNS groups.

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, 2001a; Scardino, 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, 2001a).

A prospective study by Namiki et al. (2007) evaluated 113 patients undergoing radical retropubic prostatectomy 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 sural nerve graft interposition, bilateral nerve sparing, and unilateral nerve sparing. The bilateral nerve sparing group showed the fastest recovery, although by 24 months there were no significant differences observed between the bilateral nerve sparing group and the unilateral nerve sparing group with sural nerve grafting. The bilateral nerve sparing group reported a better sexual function score than the unilateral nerve sparing group throughout the postoperative period. During the first year postoperatively, the bilateral nerve sparing group and the unilateral nerve sparing group with sural nerve grafting had better urinary function results than the unilateral nerve sparing group. The authors concluded that the nerve graft procedure may contribute to the recovery of urinary function as well as sexual function after radical retropubic prostatectomy; however these findings need to be validated in a randomized trial.

Kim et al. presented the results for 12 potent men (mean age 57 years) with clinically localized prostate cancer who underwent radical retropubic prostatectomy with deliberate wide bilateral neurovascular bundle resection and placement of bilateral nerve grafts. Minimum follow-up was 12 months. The control group consisted of 12 potent men (mean age 61 years) who underwent bilateral nerve resections but declined nerve graft placement. A series of patient and partner erectile dysfunction questionnaires and patient interviews were administered at 3, 6, 12, and 18 months postoperatively. The mean (+ or - standard deviation) follow-up was 21 (+ or - 5) months (range 12 to 28) for the cases and 18 (+ or - 5) months for the control group. Compared with the control group, at their most recent follow-up, men who underwent nerve grafts had a significantly higher visual assessment scale score, IIEF domain I score, IIEF total score, and partner questionnaire score. Before and after surgery comparisons using all of these measures were significant, with lower values after surgery, for all but the partner questionnaire. The control group had significantly worse postoperative scores compared with preoperative scores for all questionnaires. Nerve graft patients had a greater operative time and blood loss, although no transfusions were required (Kim, 2001a; Kim, 2001b; Kim, 2001d).

A prospective phase I study by Chang et al. (2003) included 30 men who underwent non-nerve-sparing radical prostatectomy with sural nerve grafting. Eighteen patients (60%) demonstrated evidence of spontaneous erectile activity. Of these 18 men, 13 (72%) were able to have intercourse. Follow-up ranged from 13 to 33 months.

In a prospective review by Zorn et al. (2008), 27 men who underwent robotic-assisted sural nerve grafting via laparoscopic radical prostatectomy (RLRP) were reviewed. Of the 27 men who underwent sural nerve grafting, 4 men had bilateral sural nerve grafting and 23 had unilateral sural nerve grafting. Sexual function was prospectively evaluated preoperatively and at 1, 3, 6, 12, and 24 months postoperatively using validated questionnaires. Mean age was 57.2 years. Mean follow-up was 26.1 months. Results showed that 11 patients with unilateral sural nerve graft regained potency while none of the men with bilateral sural grafting regained potency. By 24 months postoperatively, rate of return of sexual function was achieved in 45% of men having unilateral sural nerve grafting compared to none in the bilateral nerve graft patients. The authors concluded that despite optimism regarding sural



nerve grafting, long-term functional outcomes have been disappointing, particularly for men having bilateral nerve interposition. Unilateral sural nerve grafting does not appear to improve outcomes when compared with men with unilateral nerve preservation. These results suggest that for patients who are candidates for sural nerve grafting, newer treatment modalities are needed to cure disease while preserving sexual function.

Secin et al. (2007) retrospectively reviewed the records of 44 consecutive patients who underwent bilateral nerve grafting from 1999 to 2004. Post-operative erectile function was defined as the achievement of erections satisfactory for intercourse with or without oral medication. They calculated cumulative erectile function recovery rates using Kaplan-Meier curves. The log rank test was used to compare variables affecting erectile function recovery. The overall 5-year cumulative recovery of erectile function permitting penetration was 34 % and the rate of consistent penetration was 11 %. None of the analyzed variables was significantly associated with recovery of post-operative erectile function, including patient age, incomplete bilateral cavernous nerve resection, sural nerve grafts compared to genito-femoral or ilio-inguinal nerves as donor sites, post-radiation salvage radical prostatectomy, neoadjuvant hormone therapy and co-morbidities, or medications affecting erectile function. The authors concluded that bilateral cavernous nerve grafts might be beneficial in select patients. A definitive answer awaits the performance of a multi-institutional, randomized, controlled trial.

Anastasiadis et al. (2003) studied 10 patients who underwent radical prostatectomy and sural nerve grafting. Mean follow-up was 16.1 months. Three patients were fully potent after surgery. Six patients had no erections. The authors conclude that randomized trials with more patients and longer follow-up are necessary to define patient selection criteria.

A randomized phase II trial is currently being conducted by the National Cancer Institute to compare radical prostatectomy and unilateral sural nerve grafting with radical prostatectomy without sural nerve grafting (NCI, 2009). The purpose of the study is to determine how well sural nerve grafting and standard therapy work compared to standard therapy alone in treating erectile dysfunction in patients undergoing nerve-sparing radical prostatectomy.

Nerve grafting during radical retropubic prostatectomy is still a relatively new procedure. Preliminary evidence suggests that nerve grafting with unilateral nerve sparing radical prostatectomy may improve rates of return of sexual and urinary function. However, the evidence is insufficient to conclude that this surgical technique is equivalent to bilateral nerve sparing prostatectomy or that long-term outcomes are improved by nerve grafting

U.S. FOOD AND DRUG ADMINISTRATION

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



APPLICABLE CODES

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

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

CPT® is a registered trademark of the American Medical Association.

ICD-9 Code	Description
185	Malignant neoplasm of prostate
233.4	Carcinoma in situ of prostate
607.84	Impotence of organic origin
V45.77	Acquired absence of organ, genital organs

REFERENCES

Anastasiadis AG, Benson MC, Rosenwasser MP, et al. Cavernous nerve graft reconstruction during radical prostatectomy or radical cystectomy: safe and technically feasible. *Prostate Cancer Prostatic Dis.* 2003;6(1):56-60.

Canto EI, Nath RK, Slawin KM. Cavermap-assisted sural nerve interposition graft during radical prostatectomy. *Urol Clin North Am.* 2001 Nov;28(4):839-48.

Chang DW, Wood CG, Kroll SS, et al. Cavernous nerve reconstruction to preserve erectile function following non-nerve-sparing radical retropubic prostatectomy: a prospective study. *Plast Reconstr Surg.* 2003 Mar;111(3):1174-81.

Davis, JW, Chang, DW, Chevray, P, et al. Randomized phase II trial evaluation of erectile function after attempted unilateral cavernous nerve-sparing retropubic radical prostatectomy with versus without unilateral sural nerve grafting for clinically localized prostate cancer. *Eur Urol.* 2009;55(5):1135-1143.

ECRI Institute. Hotline Response. Sural Nerve Grafting during Radical Prostatectomy to Maintain Erectile Function. November 2009.

Kim ED, Scardino PT, Kadmon D, et al. Interposition sural nerve grafting during radical retropubic prostatectomy. *Urology.* 2001a;57:211-216.



Kim ED, Nath R, Slawin KM, et al. Bilateral nerve grafting during radical retropubic prostatectomy: extended follow-up. *Urology*. 2001b Dec;58(6):983-7.

Kim ED, Seo JT. Minimally invasive technique for sural nerve harvesting: technical description and follow-up. *Urology*. 2001c;57:921-924.

Kim ED, Nath R, Kadmon D, et al. Bilateral nerve graft during radical retropubic prostatectomy: 1-year followup. *J Urol*. 2001d;165:1950-1956.

Kuwata, Y, Muneuchi, G, Igawa, HH, et al. Dissociation of sexual function and sexual bother following autologous sural nerve grafting during radical prostatectomy. *Int J Urol*. 2007;14(6):510-514.

Namiki S, Saito S, Nakagawa H, et al. Impact of unilateral sural nerve graft on recovery of potency and continence following radical prostatectomy: 3-year longitudinal study. *J Urol*. 2007 Jul;178(1):212-6; discussion 216.

National Cancer Institute (NCI). Clinical Trials. Nerve-sparing radical prostatectomy with or without nerve grafting followed by standard therapy for erectile dysfunction in treating patients with localized prostate cancer. Last update October 31, 2009. Available at:

<http://clinicaltrials.gov/ct2/show/NCT00080808?term=nerve+sparing+prostatectomy&rank=3>.

Accessed November 2010.

Porpiglia, F, Ragni, F, Terrone, C, et al. Is laparoscopic unilateral sural nerve grafting during radical prostatectomy effective in retaining sexual potency? *BJU Int*. 2005;95(9):1267-1271.

Rabbani F, Ramasamy R, Patel MI, et al. Predictors of recovery of erectile function after unilateral cavernous nerve graft reconstruction at radical retropubic prostatectomy. *J Sex Med*. 2010 Jan;7(1 Pt 1):166-81.

Saito, S, Namiki, S, Numahata, K, et al. Impact of unilateral interposition sural nerve graft on the recovery of sexual function after radical prostatectomy in Japanese men: a preliminary study. *Int J Urol*. 2007;14(2):133-139.

Satkunasivam R, Appu S, Al-Azab R, et al. Recovery of erectile function after unilateral and bilateral cavernous nerve interposition grafting during radical pelvic surgery. *J Urol*. 2009 Mar;181(3):1258-63.

Scardino PT, Kim ED. Rationale for and results of nerve grafting during radical prostatectomy. *Urology*. 2001;57:1016-1019.

Secin FP, Koppie TM, Scardino PT, et al. Bilateral cavernous nerve interposition grafting during radical retropubic prostatectomy: Memorial Sloan-Kettering Cancer Center experience. *J Urol*. 2007;177(2):664-668.



Sugimoto, M, Tsunemori, H, and Kakehi, Y. Health-related quality of life evaluation in patients undergoing cavernous nerve reconstruction during radical prostatectomy. Jpn J Clin Oncol. 2009;39(10):671-676.

Zorn k, Berstein A, Gofrit O, et al. Long-Term Functional and Oncological Outcomes of Patients Undergoing Sural Nerve Interposition Grafting during Robot-Assisted Laparoscopic Radical Prostatectomy. Journal of Endourology. 2008;22(5).

PROTOCOL HISTORY/REVISION INFORMATION

Date	Action/Description
02/24/2011	
06/24/2010	Corporate Medical Affairs Committee
06/26/2009	

The foregoing Health Plan of Nevada/Sierra Health & Life Healthcare Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.