

ORIGINAL RESEARCH—ERECTILE DYSFUNCTION

Chronology of Erectile Function in Patients with Early Functional Erections Following Radical Prostatectomy

Darren Katz, MBBS,* Nelson E. Bennett, MD,*† Jason Stasi, BSc,* James A. Eastham, MD,* Bertrand D. Guillonneau, MD,* Peter T. Scardino, MD,* and John P. Mulhall, MD*†

*Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA;

†Male Sexual and Reproductive Medicine Program, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

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ABSTRACT

Introduction. The association between erectile dysfunction (ED) and radical prostatectomy (RP) is well established. It is our clinical experience that some men who have functional erections in the days to weeks after RP go on to lose erectile function (EF) after the first 3 months postsurgery.

Aim. To assess EF over a 12-month period in patients with functional erections at 3 months following RP.

Methods. As part of a large prospective quality-of-life (QOL) study of men undergoing RP at our institution, EF is measured postoperatively at regular time intervals using serial administration of the International Index of Erectile Function (IIEF) questionnaire. For study inclusion, patients had to have functional erections (a score 4 or 5 on IIEF question 3) at the third postoperative month, and have at least 12 months of follow-up.

Main Outcome Measures. Assessment of EF and phosphodiesterase type 5 inhibitor (PDE5i) use at 3, 6, and 12 months after RP.

Results. At 3 months, 76 of 482 patients (16%) had functional erections. Between 3 to 6 months postoperatively, 20% of men deteriorated in their functional status. Of these men, 91% had functional erections at 1 year. Comparing patients who did not require PDE5i to obtain a functional erection at 3 months with those who did, the EF outcomes were superior at 6 months (80% vs. 72%, $P=0.74$) and 12 months (100% vs. 88%, $P=0.33$).

Conclusion. The recovery of functional erections in the early postoperative phase, especially without the need for PDE5i, is a good prognostic indicator for EF at 12 months. However, a distinct cohort of men lose functional erections within 6 months after surgery. It is important to inform patients of this possibility, as it has an impact on their QOL and, potentially, on their compliance with post-RP therapy for ED. **Katz D, Bennett NE, Stasi J, Eastham JA, Guillonneau BD, Scardino PT, and Mulhall JP. Chronology of erectile function in patients with early functional erections following radical prostatectomy. J Sex Med 2010;7:803–809.**

Key Words. Prostate Cancer; Erectile Function; Radical Prostatectomy; IIEF

Introduction

More cases of prostate cancer are diagnosed each year in the United States than any other solid organ cancer. The American Cancer Society predicted that in 2008, approximately 186,000 men in the United States would be diagnosed with prostate cancer and almost 30,000 would die of the disease [1]. More than 30% of patients with prostate cancer undergo radical prostatectomy (RP); therefore, a thorough

understanding of the potential complications is crucial [1,2]. The association between erectile dysfunction (ED) and RP is well established. However, reported recovery rates of erectile function (EF) vary dramatically, ranging between 20% and 90% [3–6], largely due to discrepancies in the literature regarding patient cohorts, methods of data collection, and the definitions used for evaluating postoperative EF [7]. Moreover, the etiology of ED is multifactorial, and it is likely that postoperative factors such as

perineural edema and fibrosis are also at work [8–10].

Postoperative EF has been shown to improve with time. Data demonstrate ongoing recovery up to 18–24 months postoperatively [11,12]. However, the definitive chronology of EF recovery has not been formally assessed. It has been our clinical experience that some men have recovery of functional erections within a short period of time (days to weeks) after surgery, even with a urethral catheter in situ. Conversely, it has also been our experience that a proportion of these men lose their functional erections by the third to fourth month post-RP. We prospectively followed a cohort of men who experienced functional erections early post-RP in order to evaluate the chronology of their EF over a 12-month period after surgery.

Methods

Patient Population

Data were acquired from an ongoing institutional Ethics Review Board-approved prospective quality-of-life (QOL) study of men treated for localized prostate cancer. That study included data on men treated with surgery (either open or laparoscopic RP), radiation, or active surveillance. For the purposes of the present study, we included patients who have undergone either surgical approach. No patients were on hormonal therapy during the follow-up period.

EF Assessment

The validated QOL questionnaire has 74 questions divided into seven separate domains. There is also a pretreatment version, which includes a series of questions on patient demographics and comorbidities. The post-treatment questionnaire is administered serially at 3, 6, 12, 18, 24, and 36 months post-therapy (whether surgery, radiation, or active surveillance).

In the QOL questionnaire, sexual function was assessed using the EF domain of the International Index of Erectile Function (IIEF). This domain consists of six questions, (questions 1–5 and question 15). Response to each question is scored between 1 and 5; maximum score is 30, and in a sexually active patient, the minimum score is 6 [13]. The lower the score, the poorer the erectile response is. We focused on question 3 (Q3) of the IIEF as the basis for patient selection for our study. This question asks “Over the preceding 4 weeks, how often were you able to penetrate (enter) your

partner when sexual activity was attempted?” As we wanted to select only patients who had robust EF in the early postoperative period, we included only patients with a Q3 score ≥ 4 at the 3-month time point. A score of 4 indicates that penetration was successful “most times,” and a score of 5 indicates that penetration was successful “almost always/always.” These men were classified as having functional erections. Men with a score of ≤ 3 were classified as having nonfunctional erections. All patients included in this analysis also had complete data at the 12-month time point. There were small patient numbers followed up beyond 12 months so the study is limited to the first year postsurgery.

Phosphodiesterase Inhibitor 5 (PDE5i) Utilization

Only one question assessed PDE5i use, which was categorized into three groups: “never/almost never,” “sometimes,” and “always/almost always.” Based on this question, patients were classified as either PDE5i “non-users” or “users.” Men were considered nonusers if over the preceding 4 weeks, they never or almost never used a PDE5i to aid their erections. Users took a PDE5i sometimes, always or almost always in an “on-demand” fashion to assist with their erections.

Statistical Analysis

The proportion of patients in each group (PDE5i users vs. nonusers) who had functional erections was compared using a two-tailed Fisher’s exact probability test.

Results

Patient Population

There were 482 patients enrolled in the QOL study. Seventy-six patients (16%) had a score of 4 or 5 on Q3 of the IIEF at 3 months after RP. The mean patient age was 56 ± 6 years. All had had bilateral nerve-sparing procedures. Comorbidity profile included dyslipidemia (45%), hypertension (20%), ischemic heart disease (7%), and diabetes (7%). There were no statistically significant differences between PDE5i “users” or “non-users” in terms of age or comorbidities.

EF

Figure 1 summarizes the outcomes of the group of 76 patients who had functional erections at 3 months regardless of PDE5i use. Fifteen men (20%) experienced deterioration in their functional status between 3 and 6 months; however, 69

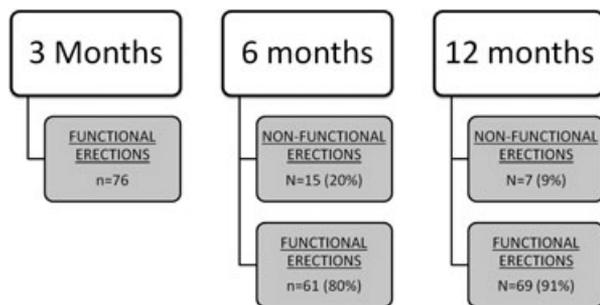


Figure 1 Outcomes of all patients with functional erections at 3 months (either phosphodiesterase type 5 inhibitor user or nonuser).

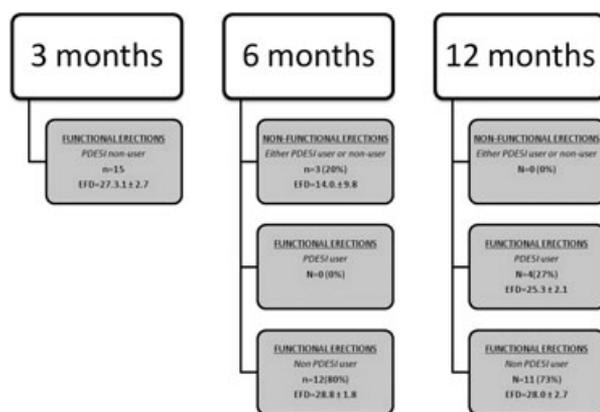


Figure 2 Outcomes of patients with functional erections at 3 months who were phosphodiesterase type 5 inhibitor (PDE5i) nonusers. EFD = Erectile Function Domain score.

(91%) had functional erections by 1 year after RP. Figure 2 details the patients who were functional at 3 months without the use of PDE5i. Functional status was maintained at 6 months in 80% of these patients, while 20% could not achieve an erection with or without a PDE5i at this time point. By 12 months, all of these patients could achieve functional erections, 27% with the use of a PDE5i and 73% without the need for any pharmacological assistance. The outcomes of the patients requiring PDE5i at 3 months to achieve a functional erection are shown in Figure 3. At 6 months, 28% of these patients had nonfunctional erections with or without PDE5i use. The rest of the men were functional either with PDE5i assistance (61%) or without (12%). At 12 months, 62% needed a PDE5i to achieve a functional erection, while 26% did not. Only 12% of patients in this latter subgroup failed to achieve a functional erection at 12 months. When comparing the PDE5i nonusers and users at 3 months, there was no statistically

significant difference between the proportion of patients who were potent at 6 months (80% vs. 72%, $P = 0.74$) and at 12 months (100% vs. 88%, $P = 0.33$).

Discussion

As age at the time of diagnosis decreases and life expectancy of prostate cancer survivors increases, the potential impact of treatment on QOL is amplified [14]. EF, along with oncological control and continence, are among the most important factors in clinical decision-making for men with localized prostate cancer [15]. Preservation of sexual function was rated as very important by 79% of men aged ≥ 75 years and by 90% of men aged ≤ 60 years, demonstrating that the potential loss of EF influences a patient’s disease-management decision [16]. However, there are a multitude of perioperative factors that can impact a patient’s sexual function post-RP, and accurate predictions of ED are difficult. Moreover, there is scant information in the literature regarding ongoing preservation of postoperative EF. A better understanding of the possible chronology of a patient’s EF is vital if he is to be optimally managed.

ED can significantly impair a patient’s QOL [17]. It can strain relationships, be a source of distress, and lower a patient’s self-esteem [12,18–21]. It is therefore important for the treating physician to be vigilant in assessing EF post-RP. Our study demonstrated that 20% of men who have functioning erections at 3 months postoperatively lose their erections by the sixth month. This effect was more pronounced if at 3 months, a patient

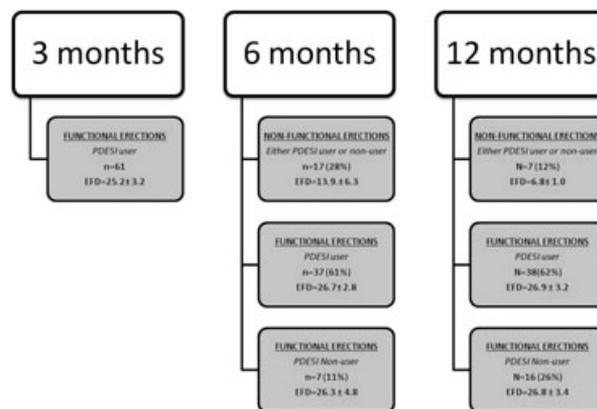


Figure 3 Outcomes of patients with functional erections at 3 months who were PDE5i users. EFD = Erectile Function Domain score.

required use of a PDE5i to achieve this functional state. Nonetheless, an important finding in our study was that more than 90% of men who are functional at 3 months will either retain or regain functional erections by 12 months. Informing patients of this potentially brief deterioration can alleviate significant anxiety for both the patient and partner.

Indeed, all men who had unassisted functional erections at 3 months were also functional at 12 months, regardless of whether they lost their functional status in the interim. This cohort of PDE5i nonusers at 3 months had a higher proportion of patients with functional erections at both 6 months and 12 months than did those who needed a PDE5i at 3 months. Because of limited patient numbers, these differences were not statistically significant, but we believe that if a patient does not require medication for EF, this logically portends a good prognosis.

Several studies have looked at the more established prognostic indicators for return of EF after RP, including degree of nerve sparing, preoperative EF, and age of the patient [9,10]. Preservation of the accessory pudendal arteries may also be of benefit [22]. However, we have shown that if a patient has functional erections soon after surgery, then the chances that he will be functional at 12 months are exceptionally high. Although the ability to have a strong erection soon after surgery is uncommon (16% in this study), we demonstrated that in those men in whom it occurs, the prognosis of 12 months is excellent regardless of any intervening deterioration. The outcome beyond the first year in this cohort of patients is still unknown, and in our study, limited follow-up to date beyond 12 months did not allow analysis beyond this date. We aim to update this study at the 24-month period.

Since it cannot be assumed that return of a functional erection early after RP will be maintained, patients who are enrolled in a post-RP rehabilitation program should be informed of this potential deterioration, because a drop in EF may encourage the treating clinician to institute other strategies. Iacono et al. demonstrated that by just 2 months after RP, when no rehabilitation program is utilized, men without any erections experience histological changes (loss of elastin and smooth muscle, collagen deposition) in the corpora [23]. In contrast, Schwartz et al. demonstrated in a small study of 21 patients, randomized to 50 mg sildenafil or 100 mg sildenafil every other night for 6 months after RP, that the early and regular use of

this agent resulted in preservation of corporal smooth muscle content [24].

However, the discontinuation rate for PDE5i responders is as high as 35% at 6 months [25]. Multiple studies have shown that lack of ongoing education, especially with respect to efficacy of the medication, is a major factor [26–28]. For a patient undergoing penile rehabilitation, the loss of EF during the first year may be the catalyst for such discontinuation of therapy. Periodic reassessment of the patient's EF, even after he has achieved functional erections, may help the urologist detect any deterioration. This could also serve as an opportunity to reinforce and champion the proposed benefits of erections in the early stages of recovery after RP.

A combination of neurological and vascular (both arterial and venous) factors are believed to underpin the pathogenesis of ED after RP. It is probable that these factors do not act in isolation, although a neurological cause is likely to be central. In a study by Bannowsky et al. [29], the investigators demonstrated that 93% of patients who had a unilateral or bilateral nerve-sparing RP had nocturnal rigidity increases of greater than 70% the night after catheter removal. In a control group without a nerve-sparing procedure, no nocturnal erections were recorded. Furthermore, the degree of neurological insult is frequently reported to be the one of the most important prognostic indicators of potency rates post-RP [4,9,30].

We have demonstrated that there is potential for functional decline in erections after the third postoperative month. We do not know the pathophysiological basis for these findings and can only hypothesize. Delayed Wallerian degeneration might explain this phenomenon. When a peripheral nerve is damaged, it undergoes antegrade and retrograde degeneration to at least the next node of Ranvier [31,32]. A gene mutation that may delay this neurodegeneration and allow the nerve to continue functioning despite trauma has recently been found in animal models [33–35]. However, there is no human evidence of this mutation, and it remains a theoretical concept.

The major strengths of our study are its prospective nature and the use of a validated self-reported questionnaire. Although there were only 76 patients included in the study, these patients were generated from a larger study of almost 500 men. Therefore, we believe that this gives a fair representation of the incidence of early postoperative functional erections in a large academic

center. Our results add to the sparse literature on the chronology of subsequent EF in patients who have recovered early EF. Other papers have reported on studies in which patients are generally censored at the time of achieving a functional erection, and therefore, their long-term outcomes are unknown. Concerning the limitations of our study, we arbitrarily chose a score of ≥ 4 on Q3 of the IIEF as indicating good EF. Although selecting a different threshold may have altered the results, this value has been used previously and is generally accepted as representing robust EF [36]. In addition, using the complete IIEF-15 item survey may have resulted in more comprehensive outcomes of EF. However, we used the abbreviated version as our QOL survey needed to be succinct and user-friendly and it already contains 74 separate questions. Another limitation is a lack of detailed knowledge regarding the precise quantity of PDE5i utilization per patient. Lastly, data on preoperative EF were unavailable for analysis. Although this is an important prognostic factor, we believe that it is unlikely that a patient with sub-optimal EF before surgery would be able to have functional erections in the early postoperative period.

Conclusion

The recovery of functional erections in the early postoperative phase is a good prognostic indicator for EF at 12 months. All the patients in our study who had erections at 3 months without the aid of medication also had functional erections at 12 months. However, there is a small percentage of men who lose functional erections by the sixth postoperative month regardless of PDE5i use. It is important to inform patients of this possibility, as it may impact both their QOL and their compliance with erectogenic pharmacotherapy. The mechanisms for such a decline in EF during this time frame after achieving early EF recovery are unknown, and more research is needed in this area.

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Corresponding Author: John P. Mulhall, MD, 353b E 68th St, NY, NY 10065. Tel: 646-422-4359.

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Statement of Authorship

Category 1

(a) Conception and Design

Darren J. Katz; Nelson E. Bennett; Jason Stasi; James A. Eastham; Bertrand D. Guillonneau; Peter T. Scardino; John P. Mulhall

(b) Acquisition of Data

Darren J. Katz; Nelson E. Bennett; Jason Stasi; James A. Eastham; Bertrand D. Guillonneau; Peter T. Scardino; John P. Mulhall

(c) Analysis and Interpretation of Data

Darren J. Katz; Nelson E. Bennett; Jason Stasi; James A. Eastham; Bertrand D. Guillonneau; Peter T. Scardino; John P. Mulhall

Category 2

(a) Drafting the Article

Darren J. Katz; Nelson E. Bennett; Jason Stasi; James A. Eastham; Bertrand D. Guillonneau; Peter T. Scardino; John P. Mulhall

(b) Revising It for Intellectual Content

Darren J. Katz; Nelson E. Bennett; Jason Stasi; James A. Eastham; Bertrand D. Guillonneau; Peter T. Scardino; John P. Mulhall

Category 3

(a) Final Approval of the Completed Article

Darren J. Katz; Nelson E. Bennett; Jason Stasi; James A. Eastham; Bertrand D. Guillonneau; Peter T. Scardino; John P. Mulhall

References

- 1 Agarwal PK, Sadetsky N, Konety BR, Resnick MI, Carroll PR. Treatment failure after primary and salvage therapy for prostate cancer: Likelihood, patterns of care, and outcomes. *Cancer* 2008;112:307–14.
- 2 Underwood W 3rd, Jackson J, Wei JT, Dunn R, Baker E, Demonner S, Wood DP. Racial treatment trends in localized/regional prostate carcinoma: 1992–1999. *Cancer* 2005;103:538–45.
- 3 Fowler FJ Jr, Barry MJ, Lu-Yao G, Roman A, Wasson J, Wennberg JE. Patient-reported complications and follow-up treatment after radical prostatectomy. The National Medicare Experience: 1988–1990 (updated June 1993). *Urology* 1993;42:622–9.
- 4 Kundu SD, Roehl KA, Eggener SE, Antenor JA, Han M, Catalona WJ. Potency, continence and complications in 3,477 consecutive radical retropubic prostatectomies. *J Urol* 2004;172:2227–31.
- 5 Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW, Albertsen PC, Harlan LC, Potosky AL. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: The Prostate Cancer Outcomes Study. *JAMA* 2000;283:354–60.

- 6 Menon M, Shrivastava A, Kaul S, Badani KK, Fumo M, Bhandari M, Peabody JO. Vattikuti Institute prostatectomy: Contemporary technique and analysis of results. *Eur Urol* 2007;51:648–57; discussion 57–8.
- 7 Mulhall JP. Defining and reporting erectile function outcomes after radical prostatectomy. *J Urol* 2009;181:462–71.
- 8 Ayyathurai R, Manoharan M, Nieder AM, Kava B, Soloway MS. Factors affecting erectile function after radical retropubic prostatectomy: Results from 1,620 consecutive patients. *BJU Int* 2008;101:833–6.
- 9 Rabbani F, Stapleton AM, Kattan MW, Wheeler TM, Scardino PT. Factors predicting recovery of erections after radical prostatectomy. *J Urol* 2000;164:1929–34.
- 10 Dubbelman YD, Dohle GR, Schroder FH. Sexual function before and after radical retropubic prostatectomy: A systematic review of prognostic indicators for a successful outcome. *Eur Urol* 2006;50:711–8; discussion 18–20.
- 11 Walsh PC, Marschke P, Ricker D, Burnett AL. Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. *Urology* 2000;55:58–61.
- 12 Matthew AG, Goldman A, Trachtenberg J, Robinson J, Horsburgh S, Currie K, Ritvo P. Sexual dysfunction after radical prostatectomy: Prevalence, treatments, restricted use of treatments and distress. *J Urol* 2005;174:2105–10.
- 13 Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49:822–30.
- 14 Greene KL, Cowan JE, Cooperberg MR, Meng MV, DuChane J, Carroll PR. Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) investigators. Who is the average patient presenting with prostate cancer? *Urology* 2005;66:76–82.
- 15 Eastham JA, Scardino PT, Kattan MW. Predicting an optimal outcome after radical prostatectomy: The trifecta nomogram. *J Urol* 2008;179:2207–10; discussion 10–1.
- 16 Crawford ED, Bennett CL, Stone NN, Knight SJ, DeAntoni E, Sharp L, Garnick MB, Porterfield HA. Comparison of perspectives on prostate cancer: Analyses of survey data. *Urology* 1997;50:366–72.
- 17 Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, Lin X, Greenfield TK, Litwin MS, Saigal CS, Mahadevan A, Klein E, Kibel A, Pisters LL, Kuban D, Kaplan I, Wood D, Ciezki J, Shah N, Wei JT. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358:1250–61.
- 18 Montorsi F, Padma-Nathan H, Glina S. Erectile function and assessments of erection hardness correlate positively with measures of emotional well-being, sexual satisfaction, and treatment satisfaction in men with erectile dysfunction treated with sildenafil citrate (Viagra). *Urology* 2006;68:26–37.
- 19 Althof SE, O’Leary MP, Cappelleri JC, Crowley AR, Tseng L-J, Collins S. Impact of erectile dysfunction on confidence, self-esteem and relationship satisfaction after 9 months of sildenafil citrate treatment. *J Urol* 2006;176:2132–7.
- 20 Rust J, Golombok S, Collier J. Marital problems and sexual dysfunction: How are they related? *Br J Psychiatry* 1988;152:629–31.
- 21 O’Leary MP, Althof SE, Cappelleri JC, Crowley A, Sherman N, Dutttagupta S. Self-esteem, confidence and relationship satisfaction of men with erectile dysfunction treated with sildenafil citrate: A multicenter, randomized, parallel group, double-blind, placebo controlled study in the United States. *J Urol* 2006;175:1058–62.
- 22 Mulhall JP, Secin FP, Guillonneau B. Artery-sparing radical prostatectomy—myth or reality? *J Urol* 2008;179:827–31.
- 23 Iacono F, Giannella R, Somma P, Manno G, Fusco F, Mirone V. Histological alterations in cavernous tissue after radical prostatectomy. *J Urol* 2005;173:1673–6.
- 24 Schwartz EJ, Wong P, Graydon RJ. Sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy. *J Urol* 2004;171:771–4.
- 25 Son H, Park K, Kim S-W, Paick J-S. Reasons for discontinuation of sildenafil citrate after successful restoration of erectile function. *Asian J Androl* 2004;6:117–20.
- 26 Salonia A, Gallina A, Zanni G, Briganti A, Dehò F, Saccà A, Suardi N, Barbieri L, Guazzoni G, Rigatti P, Montorsi F. Acceptance of and discontinuation rate from erectile dysfunction oral treatment in patients following bilateral nerve-sparing radical prostatectomy. *Eur Urol* 2008;53:564–70.
- 27 Raina R, Lakin MM, Agarwal A, Sharma R, Goyal KK, Montague DK, Klein E, Zippe CD. Long-term effect of sildenafil citrate on erectile dysfunction after radical prostatectomy: 3-year follow-up. *Urology* 2003;62:110–5.
- 28 Gruenewald I, Shenfeld O, Chen J, Raviv G, Richter S, Cohen A, Vardi Y. Positive effect of counseling and dose adjustment in patients with erectile dysfunction who failed treatment with sildenafil. *Eur Urol* 2006;50:134–40.
- 29 Bannowsky A, Schulze H, van der Horst C, Seif C, Braun PM, Junemann KP. Nocturnal tumescence: A parameter for postoperative erectile integrity after nerve sparing radical prostatectomy. *J Urol* 2006;175:2214–7.
- 30 Noldus J, Michl U, Graefen M, Haese A, Hammerer P, Huland H. Patient-reported sexual function after nerve-sparing radical retropubic prostatectomy. *Eur Urol* 2002;42:118–24.
- 31 Saxena S, Caroni P. Mechanisms of axon degeneration: From development to disease. *Prog Neurobiol* 2007;83:174–91.

- 32 Sanchez EC. Hyperbaric oxygenation in peripheral nerve repair and regeneration. *Neurol Res* 2007;29:184–98.
- 33 Mack TG, Reiner M, Beirowski B, Mi W, Emanuelli M, Wagner D, Thomson D, Gillingwater T, Court F, Conforti L, Fernando FS, Tarlton A, Andressen C, Addicks K, Magni G, Ribchester RR, Perry VH, Coleman MP. Wallerian degeneration of injured axons and synapses is delayed by a Ube4b/Nmnat chimeric gene. *Nat Neurosci* 2001;4:1199–206.
- 34 Laser H, Conforti L, Morreale G, Mack TG, Heyer M, Haley JE, Wishart TM, Beirowski B, Walker SA, Haase G, Celik A, Adalbert R, Wagner D, Grumme D, Ribchester RR, Plomann M, Coleman MP. The slow Wallerian degeneration protein, WldS, binds directly to VCP/p97 and partially redistributes it within the nucleus. *Mol Biol Cell* 2006;17:1075–84.
- 35 Coleman M. Axon degeneration mechanisms: Commonality amid diversity. *Nat Rev Neurosci* 2005;6:889–98.
- 36 Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2008;179:S97–102.