Sexual Rehabilitation After Treatment for Prostate Cancer—Part 2: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015)

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ABSTRACT

Introduction: Sexual dysfunction is common in patients after radical prostatectomy (RP) for prostate cancer.

Aim: To provide the International Consultation for Sexual Medicine (ICSM) 2015 recommendations concerning management strategies for post-RP erectile function impairment and to analyze post-RP sexual dysfunction other than erectile dysfunction.

Methods: A literature search was performed using Google and PubMed database for English-language original and review articles published up to August 2016.

Main Outcome Measures: Levels of evidence (LEs) and grades of recommendations (GRs) are provided based on a thorough analysis of the literature and committee consensus.

Results: Nine recommendations are provided by the ICSM 2015 committee on sexual rehabilitation after RP. Recommendation 6 states that the recovery of postoperative erectile function can take several years (LE = 2, GR = C). Recommendation 7 states there are conflicting data as to whether penile rehabilitation with phosphodiesterase type 5 inhibitors improves recovery of spontaneous erections (LE = 1, GR = A). Recommendation 8 states that the data are inadequate to support any specific regimen as optimal for penile rehabilitation (LE = 3, GR = C). Recommendation 9 states that men undergoing RP (any technique) are at risk of sexual changes other than erectile dysfunction, including decreased libido, changes in orgasm, anejaculation, Peyronie-like disease, and changes in penile size (LE = 2, GR = B).

Conclusion: This article discusses Recommendations 6 to 9 of the ICSM 2015 committee on sexual rehabilitation after RP. **Salonia A, Adaikan G, Buvat J, et al. Sexual Rehabilitation After Treatment for Prostate Cancer—Part 2: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med 2017;14:297—315.**

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Key Words: Prostate Cancer; Radical Prostatectomy; Erectile Dysfunction; Rehabilitation; Phosphodiesterase Type 5 Inhibitors; Alprostadil; Intracavernosal Injections; Sexual Desire; Orgasm; Climacturia; Peyronie Disease

INTRODUCTION

Significant long-term morbidity in men's sexual health is still reported in most contemporary surgical series after RP.[1–6] In parallel, significant improvement in knowledge concerning the anatomy (topographic and surgical) of the pelvic organs[7–13] and the pathophysiologic basis of post-RP ED[1] have stimulated a large amount of preclinical research and clinical trials aimed at evaluating different strategies to promote the preservation and recovery (early or late) of postoperative EF.[2,3] Overall, to improve cancer control and to prevent and treat post-RP sexual disorders (ie, other than ED),[4,6]

RECOMMENDATIONS

1. Clinicians should discuss the occurrence of post-surgical erectile dysfunction (ED; temporary or permanent) with every candidate for radical prostatectomy (RP; expert opinion, clinical principle).

2. Validated instruments for assessing erectile function (EF) recovery such as the International Index of Erectile Function (IIEF) and Expanded Prostate Cancer Index Composite questionnaires are available to monitor EF recovery after RP (level of evidence [LE] = 1, grade of recommendation [GR] = A).

3. There is insufficient evidence that a specific surgical technique (open RP [ORP] vs laparoscopic vs robot-assisted RP [RARP]) promotes better results for postoperative EF recovery (LE = 2, GR = C).

4. Recognized predictors of EF recovery include, but are not limited to, younger age, preoperative EF, and bilateral nerve-sparing (BNS) surgery (LE = 2, GR = B).

5. Patients should be informed about key elements of the pathophysiology of postoperative ED, such as nerve injury and cavernous venous leak (expert opinion, clinical principle).

6. The recovery of postoperative EF can take several years (LE = 2, GR = C).

7. There are conflicting data as to whether penile rehabilitation with phosphodiesterase type 5 inhibitors (PDEIs) improves recovery of spontaneous erections (LE = 1, GR = A).

8. The data are inadequate to support any specific regimen as optimal for penile rehabilitation (LE = 3, GR = C).

9. Men undergoing RP (any technique) are at risk of sexual changes other than ED, including decreased libido, changes in orgasm, anejaculation, Peyronie-like disease, and changes in penile size (LE = 2, GR = B).

having some familiarity with aspects of the functional anatomy of erection and ejaculation[3,7,8] and with the possible different effects on patients' postoperative sexual health with significant changes in surgical technique in recent years[14–18] is of major importance.

This article completes the discussion on a shareable roadmap for managing sexual dysfunction in those patients who wish to continue to be sexually active after RP. The members of Committee 12 (pharmacotherapy for ED, testosterone [T] deficiency, and sexual rehabilitation after treatment for prostate cancer [PCa]) of the International Consultation for Sexual Medicine (ICSM) 2015 undertook a comprehensive review of the peer-reviewed scientific literature, with the goal of providing an unbiased integrated analysis of the most updated knowledge on the potential recovery of EF and sexual dysfunction other than ED after RP. To this aim, a literature search for English-language original and review articles published up to August 2016 was performed using Google and the National

Library of Medicine's PubMed database. Keywords included *radical prostatectomy, robotic, laparoscopic, nerve sparing, sexual function, sexual dysfunction, erectile function, erectile dysfunction, decreased libido, orgasmic dysfunction, anejaculation, penile deformities,* and *Peyronie's disease.* The retrieved articles were gathered and examined. Reference lists of retrieved articles and relevant review articles also were studied. For completion of the clinically useful roadmap provided by the committee, LEs (1–5) were used to substantiate the GR (A–D). When the only LE available was expert panel consensus, it was noted as expert opinion. The term *clinical principle* was applied when GRs could not be assigned.[19]

This article is the result of an interactive peer-reviewing process by the members of Committee 12 of the Fourth ICSM regarding Recommendations 6 to 9.

EVIDENCE SYNTHESIS—ED

Recommendation 6: The recovery of postoperative EF can take several years (LE = 2, GR = C).

The chronology of events must be accurately addressed when dealing with the numerous aspects of EF recovery with a candidate for RP and with the patient postoperatively. Indeed, the concept that patients should be given realistic expectations (in this context, see Recommendation 1)[1,20,21] appears relevant to lower the risk of false expectations through a critical and realistic discussion about the timing of eventual EF recovery; this needs be assessed according to the results of each institute and each surgeon.[1,3] Patients and partners who expect immediate and complete success with spontaneous EF recovery and/or with their first ED treatment can be demoralized when they the treatment fails, which could contribute to a reticence to explore other ED aids.[22–24] Burnett et al,[25] well before the impressive advent of RARPs, correctly highlighted that in the modern era of RP most men usually achieve resumption of all physical activities, recovery of urinary control, and normalization of bowel function within a few months after RP; conversely, postoperative EF continues to improve over time, at least up to 24 months, and in some series up to 48 months after RP.[24,26–32] Therefore, studies limiting follow-up assessment to shorter than 24 months likely underestimate EF recovery[33] (LE = 2, GR = B). Overall, RARP seems to promote more rapid EF recovery compared with ORP; the original meta-analysis of six comparative studies published by Ficarra et al[16] reported better return to sexual health after RARP than after ORP at 12 months (odds ratio [OR] = 2.84; LE = 1, GR = B). A growing amount of equivocal data are published almost daily to reinforce and better specify this type of widespread opinion.

Recovery of EF does not uniformly occur in all cases and several predictors of EF recovery have been identified, including patient age at surgery (ie, the younger, the better).[1–3,34] better preoperative EF, extent of neurovascular bundle preservation, and erectile hemodynamic changes after surgery.[3] In this context surgery (ie, type, quality, surgical volume, and actual NS approach) probably emerges as the most compelling aspect[35] (LE = 2, GR = B).

As stated by the Third ICSM,[2] when dealing with neurovascular bundle preservation, most patients—and, unfortunately, many clinicians—do not have an adequate understanding of the concept of NS per se; indeed, there is a misconception that NS always leads to complete preservation of the nerves and, hence, to the absence of any transient postoperative ED. Therefore, to prevent false and unrealistic expectations, clinicians have to provide patients with a realistic timeframe for EF recovery[24–32] (LE = 4, GR = B); as a whole, experts suggest that a period of 6 to 48 months would be necessary, although in most cases there could be functional recovery within 24 months after RP.[3,7,27–32] Toward this aim, some investigators have stated that the recovery of functional erections in the early postoperative phase, especially if spontaneous (ie, not pharmacologically assisted), is a good prognostic indicator for EF at the 12-month assessment.[24,33] Schauer et al[35] recently published the findings of a systematic analysis of 11 randomized controlled trials (RCTs) on penile rehabilitation after RP; using the rate of positive response to question 3 (EF sufficient for successful intercourse) of the Sexual Encounter Profile (SEP3) in the control arms of trials after NSRPs, the systematic analysis showed that the rate of undisturbed EF ranged from 20% to 25% in most studies, and that these rates have not substantially improved within the past two decades.[35] Of clinical relevance, some data have suggested that physicians should not wait inactively, although rates of unassisted EF recovery remain close to 25% of surgically treated patients and it can take a long time until the first spontaneous erections occur. Rather, the patient should start with supportive medication therapy for EF recovery as soon as possible.[2–4,36–38]

Recommendation 7: There are conflicting data as to whether penile rehabilitation with PDE5Is improves recovery of spontaneous erections (LE = 1, GR = A).

Recommendation 8: The data are inadequate to support any specific regimen as optimal for penile rehabilitation (LE = 3, GR = C).

Whether the type of surgery received involves open or minimally invasive techniques with a non-NS (NNS), unilateral NS, or BNS procedure, the postoperative setting represents an extremely important step toward preventing ED or eventually treating postoperative ED. Removal of the prostate can result in an almost obligatory period of dormancy of those nerves responsible for the functional aspects of erection.[3,24–34] This can lead to a loss of daily and nocturnal erections associated with the persistent failure of cavernous oxygenation[39] and secondary erectile tissue damage, resulting in veno-occlusive dysfunction.[2,4,40] Overall, these changes are coupled with postoperative ED in a broad range of severity and the development of venous leakage, which portends a poor prognosis for EF recovery.[13] In this context, the importance of promoting erectile tissue preservation is obvious; likewise, the practice of suggesting and applying any form of postoperative rehabilitative strategy has been largely discussed, with equivocal results.[2,4,18,40–44]

In the historical article by Teloken et al,[45] a web-based survey assessed the reality of EF rehabilitation among members of the International Society for Sexual Medicine and its affiliated societies. Of 301 physicians, 87% of those who completed the questionnaire performed some form of rehabilitation. Conversely, of those who did not suggest or prescribe EF rehabilitation, the primary reasons were excessive cost (50% of the time) and the lack of supportive clinical evidence-based data (up to 25% of physicians).[45] Although worrisome, it is true that insufficient clinical evidence supports the concept of postoperative rehabilitation in the clinical setting to promote a significant increase of spontaneous erections over time.[41–43,46–49] Although animal studies and some early clinical experience have demonstrated that penile rehabilitation can better preserve endothelium and cavernous smooth muscle, significant concerns remain on the translatability of those data to humans.[4,46–49] Increasing preclinical data support the concept of cavernosal damage and suggest a protective role for prolonged dosage of a PDE5I,[50–55] but similar data have not been clearly and uniquely replicated in humans.[46–49,56]

Therefore, although it is certainly true that EF rehabilitation programs using PDE5Is, intracavernosal injections (ICIs), and vacuum erectile device (VED) therapy are quite common in clinical practice, there is no definitive evidence to support their use or the best treatment strategy to promote satisfactory unassisted erections (Recommendation 8, LE = 3, GR = C).

In summary, clinicians should instruct patients about the essential elements of the pathophysiology of postoperative ED (Recommendation 5, expert opinion, clinical principle).[1] This is clinically relevant to provide the patient, and potentially his partner, with sufficient knowledge to understand the actual role of rehabilitating EF recovery after RP. To this aim, penile rehabilitation involves the use of any intervention or combination of interventions (medications, devices, or actions) with the goal of restoring EF to pretreatment levels (LE = 3, GR = C). The ICSM 2015 committee mainly paid attention to the impact that any kind of penile rehabilitation approach can have in clinical terms in the real-life setting. To this purpose, five different types of rehabilitative approaches were discussed, including (i) PDE5Is; (ii) ICIs; (iii) intraurethral and topical alprostadil; (iv) VED therapy; and (v) T therapy (TTh). We confirm the previous observations of the Third ICSM that no specific recommendation can be given regarding the structure of the optimal rehabilitation regimen (LE = 3, GR = C).[2]

PHOSPHODIESTERASE TYPE 5 INHIBITORS

The concept of penile rehabilitation with the use of early postoperative ICIs to promote spontaneous EF recovery was historically introduced by Montorsi et al[57] and then by Mulhall et al.[58] Thereafter, the advent of PDE5Is in the clinical scenario led to the development of several RCTs assessing the role of different oral compounds in possibly promoting unassisted erections in men treated with RP of any technique (Table 1). As debated previously,[1] these studies were encouraged by strong

preclinical animal data showing that PDE5Is could decrease erectile tissue fibrosis, prevent the degeneration of nerves, and stimulate neuro-regeneration.[2,36,46−53,63−66]

In their trailblazer study, Padma-Nathan et al[56] randomized 76 patients treated with ORP to receive sildenafil nightly or placebo for 36 weeks; after a 8-week drug-free period, they found that patients treated with sildenafil more frequently recovered EF, with higher mean IIEF-EF scores and an improvement of nocturnal penile erections compared with those treated with placebo. More recently, in a trial assessing the effect of nightly vs on-demand sildenafil after BNSRP, Pavlovich et al[60] failed to confirm any superiority of one therapeutic regimen over another and did not find a significant improvement in EF recovery with the two treatment protocols. Similarly, in a double-blinded RCT (Recovery of Erections: Intervention with Vardenafil Early Nightly Therapy [REINVENT]), Montorsi et al[46] presented data assessing the effect of on-demand vs nightly treatment with vardenafil 10 mg for penile rehabilitation after BNSRP; on-demand dosing was associated with significantly higher IIEF-EF scores and higher positive response rates to the SEP3 than placebo after 9 months of treatment. Of clinical relevance, results after a 2-month drug washout period showed that unassisted EF recovery rates were not significantly improved for nightly or for the on-demand vardenafil group.[46] Likewise, the effect of tadalafil throughout the post-RP rehabilitative period was tested in a large RCT (A Study of Tadalafil After Radical Prostatectomy [REACTT]) that compared tadalafil 5 mg once daily (OaD) and on-demand tadalafil 20 mg with placebo after NSRP.[47] At the end of a 9-month treatment course, the rate of an IIEF-EF score of at least 22 was significantly higher in patients treated with tadalafil OaD than in the placebo group; likewise, IIEF-EF scores significantly improved and exceeded the minimal clinical important differences criteria in the two tadalafil groups and were significantly higher only for tadalafil OaD compared with placebo. Moreover, at the end of the treatment protocol, the SEP3 positive response rate was significantly higher only for the OaD-treated group but not for the placebo arm. In contrast, data collected after a 6-week drug washout period showed no difference in men treated with the two active treatments compared with those in the placebo arm for all measured outcomes. After an open-label treatment phase, patients randomized to tadalafil OaD had a statistically higher positive response rate for the SEP3 compared with placebo group. Overall, the investigators concluded that although tadalafil could not "rehabilitate" (ie, promote the onset of drug-unassisted EF recovery after RP), the OaD treatment could be used to maintain cavernosal tissue integrity.[47] Moncada et al[61] conducted a sub-analysis of the same data showing that the administration of tadalafil OaD was associated with a shorter time to EF recovery during the 9-month treatment course compared with the other groups. Similar findings were confirmed.[48,49] In this context, Mulhall et al[48] observed that changing the definition for EF recovery from an IIEF-EF score of at least 22 to the more strict definition of "returning back to baseline IIEF-EF" had no major impact in the real-life setting. Similarly to what was reported, tadalafil OaD started soon after NSRP improved drug-assisted EF but had no effect on unassisted EF after treatment cessation at 9 months.[48] In addition, Brock et al[49] analyzed data from an RCT (randomization protocol = 1:1:1 to 9-month double-blinded treatment with tadalafil 5 mg OaD, on-demand tadalafil 20 mg, or placebo) using tadalafil after NSRP. The focus of their analyses was to report on penile integrity measures, including stretched penile length, which was significantly more retained after tadalafil OaD than after placebo. No significant effects on stretched penile length were found for on-demand tadalafil vs placebo.[49] More recently, Montorsi et al[62] published the results of another analysis on data from the same multicenter phase 4 RCT,[47] which was performed to understand predictors for EF recovery after NSRP and help clinicians and patients in preoperative counseling and expectation management of EF rehabilitation strategies. This analysis concluded that high preoperative sexual desire, confidence, and intercourse satisfaction were key predictors for EF recovery. Patients meeting these criteria might benefit the most from conserving surgery and early postoperative EF rehabilitation protocols. Of clinical relevance, for patients meeting these criteria, additional non−IIEF-related predictors included RARP, quality of NS surgery, and treatment with tadalafil OaD.[62]

On the one hand, current evidence fails to clearly demonstrate improvement in spontaneous, unassisted erections with PDE5Is; on the other, previous observations support the concept that rehabilitation and treatment are undoubtedly better than leaving the erectile tissue to its unassisted fate; therefore, treatment with on-demand PDE5Is is better than doing nothing for the patient and his partner, although the baseline condition is rarely recoverable (Recommendation 7, LE = 1, GR = A).[2−4] This consideration is supported by findings from RCTs on on-demand PDE5Is. It has been extensively demonstrated that sildenafil,[36,41,42,67,68] tadalafil,[36,41,42,67,69] vardenafil,[36,41,67,70,71] and more recently avanafil,[41,59,67,72] taken when needed, can be successfully used beyond the scope of rehabilitation in those men who underwent RP with a clear BNS intent (LE = 1, GR = A). As a whole, these data suggest a positive effect of PDE5Is in drug-assisted postoperative EF recovery, although the advantage of a specific drug compared another and—and even more clinically relevant—of a daily on-demand protocol has not been demonstrated (Recommendation 8, LE = 3, GR = C).

Similarly, the need to start the rehabilitation protocol as soon as possible after surgery has been extensively discussed, because it can lead to better long-term results for EF recovery or ED treatment possibilities; this indicates the importance of timing more in determining irreversible structural changes of the erectile tissue as a consequence of postoperative neurapraxia than in promoting the onset of unassisted erections (Recommendation 8, LE = 3, GR = C).[2,4,43] In this context, Briganti et al[37] reported

Table 1. Randomized clinical trials assessing outcomes of penile rehabilitation with PDE5Is

	Cases (n)	Study design	Patient characteristics	Rehabilitation protocol	Primary outcome
Padma-Nathan et al[56]	Sil 50 mg OaD (23), Sil 100 mg OaD (28), placebo (25)	Double-blinded RCT	Age 18—70 y, preoperatively potent, BNS	Started 4 wk after RP, EDT at 36 wk, 8-wk DFW	EF recovery* (P = .02), 27% Sil, 4% placebo
Montorsi et al[46]	Vard OaD (137), Vard PRN (141), placebo (145)	Double-blinded double-dummy RCT	Age 18—64 y, preoperatively potent, BNS	Started 14 d after RP, EDT at 9 mo, 2-mo DFW, 2-mo Vard OaD OL	IIEF-EF score ≥ 22 at EDT, 48.2% Vard PRN (P < .0001 vs placebo), 32% Vard OaD, 24.8% placebo; IIEF-EF score ≥ 22 at DFW (P > .05 all comparisons), 29.1% Vard PRN, 24.1% Vard OaD, 29.1% placebo
Mulhall et al[59]	Ava 200 mg (94), Ava 100 mg (90), placebo (87)	Double-blinded RCT	Age 18—70 y, history of ED after BNS	Started ≥6 mo after RP, EDT at 12 wk	IIEF-EF score change at EDT (P < .01 all comparisons), 5.2 Ava 200 mg, 3.6 Ava 100 mg, 0.1 placebo
Pavlovich et al[60]	Sil OaD + placebo PRN (50), Sil PRN + placebo OaD (50)	Double-blinded RCT	Age < 65 y, preoperatively potent, UNS or BNS	Started 1 d after RP, EDT at 12 mo, 1-mo DFW	Recovery of baseline IIEF-EF score at EDT (P = .4), 63% Sil PRN, 57% Sil OaD; recovery of baseline IIEF-EF score at DFW (P = .01), 65% Sil PRN, 47% Sil OaD
Montorsi et al[47]	Tad OaD (139), Tad PRN (143), placebo (141)	Double-blinded double-dummy RCT	Age < 68 y, baseline IIEF-EF score ≥ 22, BNS	Started within 6 wk after RP, EDT at 9 mo, 6-wk DFW, 3-mo OL	IIEF-EF score ≥ 22 at DFW, 20.9% Tad OaD (P = .6 vs placebo), 16.9% Tad PRN (P = .7 vs placebo), 19.1% placebo
Mulhall et al[48]	Tad OaD (139), Tad PRN (143), placebo (141)	Double-blinded double-dummy RCT	Age < 68 y, baseline IIEF-EF score ≥ 22, BNS	Started within 6 wk after RP, EDT at 9 mo, 6-wk DFW, 3-mo OL	Patients' return to baseline IIEF-EF score at EDT (P value not provided), 22.3% Tad OaD, 11.3% Tad PRN, 7.8% placebo; patients' return to baseline IIEF-EF score at DFW (P value not provided), 12.2% Tad OaD, 9.2% Tad PRN, 11.4% placebo
Moncada et al[61]	Tad OaD (139), Tad PRN (143), placebo (141)	Double-blinded double-dummy RCT	Age < 68 y, baseline IIEF-EF score ≥ 22, BNS	Started within 6 wk after RP, EDT at 9 mo, 6-wk DFW, 3-mo OL	Time to EF recovery during DBT (for 25% of patients), Tad OaD 5.8 mo (P = .03 vs placebo), Tad PRN 9 mo (P = .01 vs placebo), placebo 9.3 mo

Table 1. Continued

	Cases (n)	Study design	Patient characteristics	Rehabilitation protocol	Primary outcome
Brock et al[49]	Tad OaD (139), Tad PRN (143), placebo (141)	Double-blinded double-dummy RCT	Age < 68 y, baseline IIEF-EF score ≥ 22, BNS	Started within 6 wk after RP, EDT at 9 mo, 6-wk DFW, 3-mo OL	Stretched penile length at EDT, Tad OaD −2.2 mm ($P = .03$ vs placebo), Tad PRN −7.9 mm ($P = .3$ vs placebo), placebo −6.3 mm
Montorsi et al[62]	Tad OaD (139), Tad PRN (143), placebo (141)	Double-blinded double-dummy RCT	Age < 68 y, baseline IIEF-EF score ≥ 22, BNS	Started within 6 wk after RP, EDT at 9 mo, 6-wk DFW, 3-mo OL	Predictors for recovery of EF, high preoperative IIEF-SD score, high preoperative IIEF score on item 15, robotic surgery, NS score, Tad OaD

AVA = avanafil; BNS = bilateral nerve-sparing procedure; DBT = double-blinded treatment; DFW = drug-free washout period; ED = erectile dysfunction; EDT = end of study treatment; EF = erectile function; IIEF = International Index of Erectile Function; IIEF-EF = International Index of Erectile Function erectile function domain; IIEF-SD = International Index of Erectile Function sexual desire domain; NS = nerve-sparing; OaD = once daily; OL = open-label treatment; PDE5Is = phosphodiesterase type 5 inhibitors; PRN = on demand; RCT = randomized clinical trial; RP = radical prostatectomy; Sil = sildenafil; Tad = tadalafil; UNS = unilateral nerve-sparing procedure; Vard = vardenafil.
*Defined as a score higher than 8 on questions 3 and 4 of the IIEF and a "yes" response to the question, "Over the past 4 weeks, have your erections been good enough for satisfactory sexual activity?"

that 3-year EF recovery rates were significantly higher in patients who did compared with those who did not use any postoperative PDE5Is (73% vs 37%, respectively; $P < .001$), regardless of the patients' class of risk according to their preoperative characteristics. Of translational importance, EF recovery rates were not significantly different according to PDE5I treatment schedule (long term vs on demand) after BNSRP, thus confirming in the real-life setting what has been widely reported by several RCTs.[46−49,60−62] Gallina et al[73] also reported that after a mean 2-year follow-up, only 35.8% of patients untreated after BNSORP recovered from ED with satisfactory erections. Moreover, in patients younger than 55 years and with a preoperative IIEF-EF score of at least 22, the rate of EF recovery at 1-year assessment was as high as 69%; although not reaching statistical significance, this rate increased to 88% for those receiving PDE5Is of any type and with any posology. Taken together, these data suggest that although younger patients with a good preoperative EF can have good EF recovery rates even without any treatment, using PDE5Is after BNSRP improves their functional outcomes.[73]

INTRACAVERNOSAL INJECTIONS

In addition to PDE5Is, the effect of ICIs in the context of penile rehabilitation protocols have shown positive results for EF recovery.[2,4,43,74−76] As a whole, (i) early postoperative alprostadil ICI can be useful for penile rehabilitation (GR = B); for PDE5Is, to date no sufficient human data suggest the possibility of regaining spontaneous unassisted erections after an ICI course;

(ii) ICIs with prostaglandin E$_1$, papaverine, phentolamine, or their combinations are quite successful at achieving erections on demand for men with post-RP ED, especially in men for whom NSRP could not be achieved (GR = B); (iii) timing for starting should be accurately defined because of a relatively high probability of alprostadil-associated painful erections (GR = B); therefore, no final suggestions for the best timing to begin postoperative ICI are possible (GR = D); and (iv) overall, ICI is effective for men who have tried oral agents without response (GR = C). A comprehensive discussion on the physiology of the mechanism of action of ICIs, type of possible ICI treatments, and its possible side effects was finalized by this committee in the report by Hatzimouratidis et al.[67] Of relevance to patients after RP is the concept that successful treatment is more likely with greater patient motivation and adherence to the protocol. For instance, Yiou et al[75] reported on data of a prospective study conducted on a cohort of men treated with laparoscopic NSRP and treated twice a week with alprostadil 2.5 µg; up to 11% of treated men discontinued the therapy because of pain and pain scores were negatively correlated with the IIEF-EF score at 6-month follow-up. This aspect has major clinical relevance because although the literature would suggest starting any form of rehabilitation or treatment as soon as possible after surgery,[2,4,36,43] this is easily applicable for PDE5Is, which have a relatively modest probability of side effects,[36,67] but not for ICIs. Indeed, when ICI becomes the treatment of choice—mainly in patients with relative postoperative ineffectiveness of PDE5Is[2,4,36,58,67]—the timing for starting ICI should be accurately defined.[4,75−78] Indeed, ICI often causes penile pain,[75,76,78]

which can lead to a high treatment discontinuation rate.[75,76,79] To this aim, Gontero et al[80] suggested 3 months after surgery as a reasonable compromise for effectiveness and patient compliance to ICIs. Moreover, Mulhall et al[58] in a prospective non-randomized study evaluated the postoperative outcome of men with functional preoperative erections who underwent BNSRP, unilateral NSRP, or NNSRP and were challenged early postoperatively with oral sildenafil. Non-responders were switched to ICI and were instructed to self-inject three times a week (trimix of papaverine 30 mg/mL, phentolamine 1 mg/mL, and prostaglandin E_1 10 μg/mL) for rehabilitative purposes or to use on-demand ICIs; on average, self-injection was started 4 months after RP (range = 1−10 months). At 18 months after RP, all those patients who had used the trimix did not report pain or prolonged erections.[58] These results suggested that injectable erectogenic preparations other than alprostadil could lead to less frequent pain complaints after injection and during erection (LE = 3, GR = B). However, these results should be viewed with caution because the pathophysiology of penile pain after ICI remains controversial and alprostadil remains the only drug approved for ICI treatment of ED.

All these considerations also apply to patients who undergo NNSRP for oncologic reasons and might benefit from early therapy for the treatment of ED.[81] In this regard, the literature suggests that patients undergoing NNSRP should not expect to regain any spontaneous EF, and the lack of natural erections could produce cavernosal hypoxia that could induce fibrosis, with a possible increased risk of venous leakage[4,39,82]; as a clinical consequence, any severe impairment of the native structure of the corpora cavernosa could lead to greater difficulty even with the use of second-line treatment for ED, including ICIs.[4,43]

INTRAURETHRAL ALPROSTADIL

The intraurethral alprostadil suppository (IUA; MUSE = Medical Urethral System for Erection) continues to play a small but definite role in ED management.[67] Given its erectogenic capabilities, there has been interest in assessing its role in penile rehabilitation after RP. Raina et al[83] reported that the use of early IUA after ORP (125 μg three times per week for the first 6 weeks, following the paradigm of the ICI trial of Montorsi et al,[57] and then up-titrated to 250 μg three times per week for 4 months) promoted natural unassisted erections sufficient for vaginal penetration at 9 months in 40% of patients compared with only 11% men in the control group. Although the investigators concluded that early IUA with alprostadil (at low doses of 125/250 μg) increased the frequency of sexual activity, shortened the period of neurapraxia, increased the incidence of spontaneous erections, and increased the incidence of erections sufficient for vaginal potency, the lack of randomization and patient self-selection of therapy clearly limited the generalizability of the findings (LE = 3, GR = C).[83] McCullough et al[84] conducted a randomized trial with the goal of determining whether early nightly treatment with IUA after NSRP (RARP or ORP)

hastened the return of EF. At catheter removal, all men were randomized to nightly IUA (125 μg and then up-titrated to 250 μg after 1 month) or sildenafil (50 mg) in a 2:1 ratio and stretched penile length was measured. Doses remained stable for the remaining 8 months; at month 9, all nightly medication was discontinued, patients were given no medication for 1 month, and patients attempted sexual activity without medication. At the 10-month evaluation, patients were provided with six sildenafil (100 mg) tablets and instructed to use each tablet on an empty stomach 1 hour before initiation of sexual activity. Eleven months after surgery, all patients completed the Erectile Dysfunction Inventory of Treatment Satisfaction questionnaire, the IIEF, the Global Assessment Question, and the SEP and had their stretched penile length measured. Overall, dropout rates were 19% for sildenafil and 30% for IUA (mostly occurring at dose escalation to IUA 250 μg because of pain). As in the REINVENT trial,[46] the primary outcome was not achieved. Although IUA trended toward favoring an earlier return of function by all the metrics used by 11 months, differences in outcomes were not statistically significant. Conversely, at the 6-month visit, the percentage of patients responding "yes" to the Global Assessment Question was larger in the IUA group than in the sildenafil group. More than 75% of patients in the two groups believed their erections were not as hard as before surgery. The end-of-trial IIEF-EF scores were similar to those in the sildenafil rehabilitation study and the percentage of intercourse success was not dramatically different than that in the REINVENT trial. Despite aggressive rehabilitation, a loss of penile length that occurred almost immediately was seen in the two arms[84] (LE = 2, GR = B).

TOPICAL ALPROSTADIL

Topical alprostadil cream was introduced in the previous decade as a non-invasive treatment option to locally deliver alprostadil.[67] A novel easy-to-use formulation (Vitaros, Apricus Biosciences, San Diego, CA, USA) combines alprostadil (300 μg; 0.33%) with 2.5% of a cutaneous permeation enhancer (dodecyl-2-n,n-dimethylaminoproprinate hydrochloride).[67,85] The published results are still too sparse to give a clinically relevant opinion of the applicability of Vitaros in patients after RP for EF recovery and ED treatment (Recommendation 8, LE = 3, GR = C).

VACUUM ERECTILE DEVICE THERAPY

In addition to pharmacologic treatments, the effect of the VED has been tested for penile rehabilitation after RP.[86] Preclinical studies have shown that VED therapy is responsible for the preservation of endothelial and smooth muscle integrity because of the transient increase in arterial flow and oxygenation to the corpora cavernosa.[87] However, studies assessing the effect of VED in the post-RP setting have shown controversial results[87−90]: although the effectiveness of on-demand VEDs is

unquestionable in men with ED after RP, its role in penile rehabilitation is unclear. In men with or without NSRP, application of the VED results in a response rate higher than 92%, yet few choose to continue with the VED.[91] In a randomized trial, Basal et al[90] showed that only PDE5Is alone or the combination of the VED and PDE5Is significantly improved postoperative EF recovery, but these results did not hold true for patients receiving the VED alone. Overall, robust clinical data supporting the use of the VED for penile rehabilitation after RP are lacking, even if it might have a role in selected patients, especially in combination with oral therapy. Moreover, despite its widespread use, there is no prescribed protocol as to how it should be used. In a prospective study of 20 patients at different times after ORP, application of the VED for 10 consecutive cycles over 2 minutes resulted in a 55% increase in corporal and glandular oximetry, which lasted for as long as 60 minutes.[92] In a randomized prospective study, a relatively small cohort of patients was instructed to apply the VED daily for 9 months after NSRP or NNSRP and compared with men with no treatment.[93] The duration of VED application was not specified, although the constriction band was used only for intercourse. The results were inconclusive; 32% of the VED group reported spontaneous erections and 17% reported vaginal potency; conversely, in the "no treatment" group, 37% reported spontaneous erections and 11% reported erections satisfactory for vaginal penetration. Follow-up was done through mailed questionnaires. The VED group reported subjectively that they had less penile shrinkage but no objective measurements were done. Of all patients, 76% to 86% of men were able to have sexual intercourse with the VED irrespective of NS surgery. No long-term follow-up or PDE5I responsiveness was reported.[93] Köhler et al[88] reported on a randomized study of early intervention (6 months of treatment, starting 1 month after RP) with the VED compared with no treatment after RP. The use of PDE5Is was not allowed during the first 6 months in either group, but subsequently the groups were allowed to use PDE5Is if they desired. Patients were evaluated with the Sexual Health Inventory for Men (SHIM) questionnaire and with questions on spontaneous erections and adequacy of erections for intercourse. Stretched penile lengths also were measured. The primary end point of the study was the proportion of patients with moderate to severe ED (SHIM score ≤ 11); secondary end points considered penile size, including significant penile shortening, for which 2 cm was used as the threshold; progression of SHIM scores over time; and occurrence of spontaneous erections in the early period after RP. The results were inconclusive; at last follow-up (mean = 9.5 months), there was no significant difference between groups in SHIM scores or in the percentage of men with moderate to severe ED. Disappointingly, no spontaneous erections adequate for intercourse were reported in either group.[88] A randomized pilot study of 23 men after NSORP compared tadalafil 20 mg three times a week (group 1) with to tadalafil 20 mg three times a week combined with an unbanded VED for 10 minutes a day for 5 days a week (group 2) for 12 months.[94] At 3-month assessment, group 2 was allowed to use tadalafil with the banded VED, whereas group 1 was allowed to use tadalafil alone. Not surprisingly, group 2 fared better. PDE5I responsiveness without the VED was not compared between groups, thus limiting the conclusions derived from the study.[94]

In summary, larger prospective randomized trials are needed to validate this cost-effective modality of penile rehabilitation with the VED (LE = 3, GR = 2).

TESTOSTERONE THERAPY AFTER RP

Serum T levels below the normal range are common in men, especially after 50 years of age, but they are not associated with symptoms of T deficiency in every case. In this context, data from three large cohort studies showed that less than one third of men who had a low total T level reported at least two or three symptoms of T deficiency.[95–97] This underlines the importance of considering T deficiency a clinical and biochemical syndrome deserving defined laboratory and clinical criteria and the prevention of overdiagnosis, as supported by all major currently available guidelines and recommendations.[98–101] Although several reports have suggested that TTh might produce significant benefits for hypogonadal men, many concerns remain about the prevalence and severity of potential treatment-emergent adverse events, with much attention paid to the correlation between T administration and the eventual risk of developing PCa.[102] An association between circulating androgens and PCa has not been clearly confirmed in epidemiologic studies[102–104]; the impact of circulating androgens after RP has been even more neglected.[102,104,105] For instance, Gacci et al[106] found conditions suggestive for hypogonadism in 61 of 257 consecutive patients (23.7%) who underwent RP; those men showed a slightly significant correlation between preoperative sexual functioning and T values ($P = .05$), whereas preoperative sexual functioning parameters were significantly higher in patients with normal T compared with patients with low T levels. This led them to conclude that T was positively correlated with sexual activity (ie, EF) in eugonadal patients with PCa.[106]

Overall, these observations suggest that although the relation between T levels and improvement in EF should be well established, the role of T in postoperative ED recovery could be of even greater significance.[102,104] Animal models have shown a clear role for T in regulating nitric oxide formation, regulating PDE5 expression at the cavernosal level, maintaining innervation of penile tissue, and protecting the corpora cavernosa from veno-occlusive disease and increased collagen deposition[107]; in contrast, human data are not as robust.

Until recently, the use of TTh in men with any history of PCa was contraindicated. However, with advances in our understanding of the relation between PCa and androgens, the possible use of TTh after RP bears reconsideration.[108] According to most available recommendations and guidelines, TTh should not be started before 1 year after surgery,[102,109] when fibrotic changes are most likely irreversible. There are no current clinical data to

support the early use of T as a penile rehabilitative strategy. Well-controlled in human trials are necessary to assess the efficacy and safety of T normalization in hypogonadal men after RP.

PSYCHOLOGICAL ISSUES

The importance of sexual counseling should not be undervalued in the postoperative setting[4,110]; despite the good results of strategies to recover EF and to treat ED, the discontinuation rates of any treatment remain high. In men with ED (but without PCa), 34.6% of patients successfully treated with sildenafil eventually discontinued the treatment[111]; the main reason for this was considered "shortcomings in the partners' or patients' emotional readiness for the restoration of sexual life after long-term abstinence." We can extrapolate this for men who undergo RP and their partners and then avoid or postpone attempts to return to sexual activity because of fears from cancer-related issues and surgical complications. In this regard, it has been found that up to 49% of patients not adequately counseled throughout a 18-month postoperative period decided not to begin any ED treatment, although they were preoperatively highly motivated to preserve EF.[112] In summary, data suggest that, before RP (any type), patients must be carefully counseled on the need for a correct rehabilitation treatment to increase the possibility of regaining adequate (ie, satisfactory) sexual functioning. A patient's main goal after RP is restoring erections; however, psychological factors—such as relationship quality and depression or anxiety—are very important for the postoperative couple's sexuality.[113] Canada et al[113] reported that sexual counseling intervention (alone or together with the partner) at 3-month follow-up alleviated male overall distress ($P < .01$), improved male global sexual function ($P < .0001$), and improved female global sexual function ($P < .05$), with a return to baseline conditions at 6-month assessment. Interestingly, the use of ED treatments increased from 31% at baseline to 49% at 6-month follow-up ($P = .003$).[113] Likewise, men who underwent RP or cystectomy, after repeated sessions of sexual counseling throughout an 18-month follow-up, increased compliance and satisfaction with injection therapy, and they showed a marginally positive effect on treatment efficacy.[114] Therefore, psychological and sexual counseling is of major importance to improve any rehabilitation and treatment of postoperative EF impairment. From the outset of therapy, the patient and the partner (if present) should be encouraged to broaden their sexual repertoire, incorporate erection-independent sexual activities, and continue to be sexual despite ED and, sometimes, decreased libido.[23] Among other forms of penile rehabilitation, even masturbation has to be considered, although it is not usually viewed as a medical intervention.[23] As a whole, renegotiation of sexual activity emerges as an essential part of sexual adaptation (sometimes to a new form of sexual performance).[23]

As a whole, psychosexual counseling is an aspect of clinical relevance that deserves attention even by the most skeptical surgeon in a multimodal approach.[23,110,115–118] This implies that several factors, such as patients' awareness of being diagnosed with cancer,[110,119] patient's age and sociocultural background (among others, factors related to the relationship and family context),[20,23] clinical and sexological history before surgery, starting time of treatment, patient's compliance with the therapy, any adjuvant treatment, and follow-up term, should be considered.[110,114,120] Together these observations indicate the clinical relevance of implementing effective psychosexual counseling from the preoperative period,[4,5,121] so that patients (i) are actually aware of the possible sequelae of sexual difficulties and sexual recovery; (ii) are informed about the existence of appropriate therapies; (iii) are encouraged for early tailored ED treatment after RP[23,122]; and (iv) understand the need of an objective use of erection aids.[4] Likewise, this multimodal approach could certainly help overcome unwanted misconceptions on spontaneous recovery of overall sexual function and EF in particular.[123] To this aim, patients' education (and patients' partners, if available and possible[23,124–127]) should become an essential part of the preparations before and after RP.[4,110,119,123] Sexual counseling also should stress to men and their partners that even if EF is not restored quickly after surgery, it can be partly or fully regained after multifaceted combined approaches.[124]

Recommendation 9: Men undergoing RP (any technique) are at risk of sexual changes other than ED, including decreased libido, changes in orgasm, anejaculation, Peyronie-like disease, and changes in penile size (LE = 2, GR = B).

Although most scientific and clinical efforts are dedicated to the preservation and/or proper recovery of EF after RP, postoperative male sexuality is not just erection.[4,6] Indeed, there are many aspects of possible sexual discomfort after surgery, including decreased libido, anejaculation, orgasm changes, penile size alterations, and possibly Peyronie-like disease.[4,6,17,22,23,128]

DECREASED LIBIDO AND INTEREST

Data on male sexual desire disorders are particularly sparse, so most epidemiologic studies have defined these disorders differently, complicating an accurate estimate of the postoperative incidence and prevalence.[129,130] In addition to what is historically reported in the literature for the broad male population,[131,132] the psychological impact of PCa and its uncertain outcome can decrease male sexual desire and subjective arousability. However, the scientific literature almost completely lacks a systematic and comprehensive evaluation of issues relating to the domain of sexual desire in patients undergoing RP.[4,6,23,133,134] Overall, loss of or decrease in sexual desire has been reported to range from 60% to 80% in patients after RP.[4,135,136] As a whole, it seems that patients undergoing curative surgery for PCa are distressed not only about loss of EF but also about decreased sexual desire.[4,137] Overall, an adequate surrogate of the intensity of post-RP sexual desire can be the attitude of men toward seeking help for sexual problems.[133,138] Moreover, although the correlation between sexual desire and sexual motivation can be arbitrary, the level of sexual motivation

could be related to the request for help and the use of specific therapies for ED after RP. Therefore, the prevention and management of a poor functional outcome in sexual desire would necessarily require a comprehensive prevention and management of postoperative EF recovery and satisfactory ED treatment; as a whole, psychological and sexual counseling interventions are of major importance to improve postoperative EF and, possibly, the level of sexual desire.[4,23,112,114,120,123,139,140]

Data related to any impairment in sexual desire for individuals with a homosexual sexual orientation are very sparse.[141−143] Gay and bisexual men with PCa have been described as an "invisible diversity" in PCa research because of their lack of visibility and lack or at least total poverty of identification of their needs and expectations.[142−145] Penile-vaginal intercourse and EF have been the primary focus of sexual research and rehabilitation for men with PCa and do not adequately reflect the sexual practices of men who have sex with men. In this context, data have suggested that men who have sex with men report ED and complain of emotional distress, negative impact on gay identities, and feelings of sexual disqualification. Other sexual concerns have included loss of libido, climacturia, loss of sensitivity or pain during anal sex, non-ejaculatory orgasms, and smaller penis.[145] Moreover, research and validated instruments for sexual quality-of-life assessment based on heterosexual samples have limited applicability for men who have sex with men.[143]

Special attention must be given to the correlation between low sexual desire and T deficiency in the particular subset of patients with PCa[4,104,146]; in this context, decreased sexual interest is a well-documented symptom of low androgen levels and TTh in hypogonadal men with low desire can be used as effective treatment.[97,99,104,147,148] Some data from some small series of patients treated with TTh after RP have been published, with positive results, at least for EF recovery.[4,109,149] The impact of TTh on sexual desire recovery after RP has been even less investigated.

ORGASM AND EJACULATORY ALTERATIONS

Orgasmic function (OF) has not been fully assessed in patients who underwent RP,[4,6,17,150] and data are even more scanty for minimally invasive surgery.[17,151] The fact that the ejaculatory apparatus (prostate, seminal vesicles, and ejaculatory ducts) is removed with RP certainly can explain at least in part any eventual postoperative orgasm impairment.[4,6] In this context, orgasmic modifications, including (i) complete absence of orgasm, (ii) alterations in orgasm intensity, and (iii) orgasmic pain (ie, dysorgasmia), are not uncommon in men after RP.[4,6] Moreover, patients might complain of postoperative orgasm-associated urinary incontinence (UI; climacturia).[4,6,17,150,152−155]

Decreased intensity of orgasm, or even anorgasmia, often has been considered a psychological event after RP.[4,156] Recently, Frey et al[150] reported findings of a single-center, cross-sectional, questionnaire-based investigation on a wide range of issues with the main focus on postoperative sexual side effects in patients after RP treated at their department 3 to 36 months before study initiation. In the group of sexually active patients, anorgasmia, decreased intensity of orgasm, increased intensity of orgasm, and no change were reported by 5%, 60%, 6%, and 29% of patients, respectively.

Data on the impact of ejaculation loss after PCa treatments are scarce. Anejaculation has several implications: (i) it can interfere with a patient's self-perception of his manhood and body image; (ii) because ejaculation and orgasmic sensations are closely related at least in some men, anejaculation might be associated with lower orgasmic quality; and (iii) it renders men infertile. In this context, although PCa is usually perceived as a disease of older men to whom infertility is no longer an issue, currently men are diagnosed with PCa at a younger age and generally have excellent long-term recurrence-free survival rates. Therefore, the issue of anejaculation and its implication on future fertility should be always discussed.[157−159] In a real-life survey that assessed information on sexual function received preoperatively by patients who then underwent RP, Deveci et al[160] found that almost half the patients were unaware that they were rendered anejaculatory by their surgery. Likewise, none of the patients with RARP and only 10% of patients with ORP recalled being informed of the potential for penile length loss and none were aware of the association between RP and Peyronie disease (PD).

As a whole, adequate preoperative counseling is crucial to make the patient aware that some factors might be crucial for the recovery of his postoperative orgasm sensation (Recommendation 9, LE = 2, GR = B). For instance, Dubbelman et al[161] reported that postoperative OF showed an age-related decline, with a similar finding confirmed by Salonia et al.[162] Likewise, men who underwent NNSRP were more likely to have orgasmic dysfunction compared with those after NS surgery, with these variables emerging as independent predictors at multivariate analyses. Moreover, severe postoperative UI showed a negative effect on OF[161,162]; conversely, timing throughout the post-RP follow-up and the use of PDE5Is were associated with OF amelioration.[71,155,162−164]

The few available data seem to suggest that dysorgasmia occurs in 14% of patients.[71,156] The cause of dysorgasmia is not well understood; Barnas et al[156] postulated that the physiologic bladder neck closure that occurs during orgasm in these men might translate into postoperative spasm of the vesicourethral anastomosis or pelvic floor musculature dystonia. This hypothesis led them to experimentally use the α-blocker tamsulosin 0.4 mg/d in a relatively small cohort of patients,[165] of whom 77% reported an improvement in pain and 8% reported complete resolution of pain. In their analysis, pain during orgasm was located in the penis (63%), abdomen (9%), rectum (24%), and other areas (4%)[156]; moreover, pain was reported to occur always (with every orgasm) in 33%, frequently in 13%, occasionally in 35%, and rarely in 19%.[156] Most patients (55%) had

orgasm-associated pain for less than 1 minute, a third reported pain for 1 to 5 minutes, and pain lasting longer than 5 minutes was reported by 12%; only 2.5% of patients complained of pain lasting longer than 1 hour.[156] Frey et al[150] reported that painful orgasm was experienced by 9% of their patients at least a few times after the operation, with a median pain score of 3 (range = 1−8). A few reported that the pain persisted for longer than 1 minute.[150]

Capogrosso et al[17] recently published the findings of a study that assessed the prevalence and predictors of recovery from climacturia and painful orgasm (dysorgasmia) after RARP and ORP. Overall, painful orgasm was reported significantly more frequently after ORP than after RARP ($P = .04$). Kaplan-Meier analysis showed no differences between types of RP for postoperative recovery from painful orgasm.[17] The scientific literature completely lacks rigorous trials aimed at assessing potential treatments for orgasm-associated pain after RP, and this is even more relevant in RARP series.

Climacturia, or orgasm-associated UI, can become significantly bothersome for the patient and cause embarrassment, avoidance of sexual activity, and relationship problems between partners.[4,17,152−154,161,164] Data have suggested a prevalence ranging from 20% to 93% according to different cohorts in ORP series[152−154,161,166]; data addressing potential differences among types of surgery are scanty.[17] Choi et al[154] reported a 20% rate of climacturia in patients who underwent ORP and a 24% rate in men who underwent laparoscopic RP. Recently, Capogrosso et al[17] compared prevalence and predictors of climacturia in patients with ORP vs RARP; overall, 221 of 749 patients (29.5%) reported climacturia, without differences between RARP and ORP.

Lee et al[152] stated that 21% of patients reported climacturia only rarely after RP, 47% reported it occasionally, 11% reported it often, 16% reported it most of the time, and 5% reported it all of the time. For volume of urine leakage, 58% reported only a few drops. Interestingly, climacturia rates were higher in patients presenting within the first 12 months postoperatively compared with those presenting after year 1 (relative risk = 1.82; $P < .01$). Capogrosso et al[17] observed that of 354 men who underwent RARP, climacturia was reported as occurring at every orgasm in 25 (19.6%), in more than half time in 16 (12.6%), and fewer than 50% in 54 (42.5%). Self-reported urine leakage volume associated with orgasm was no larger than 5 mL in 85.8% of patients, with no significant differences between patients with ORP and those with RARP. Of clinical relevance, patients with RARP showed a significantly faster recovery from climacturia than patients with ORP ($P < .01$).

As a whole, most data indicated that climacturia occurrence was not associated with the presence of UI; conversely, O'Neil et al[166] recently reported that in their cohort of men treated with RP and/or radiation therapy and who were sexually active or experiencing orgasms, climacturia was reported by 22.6% of respondents, with UI and the use of erectile aids achieving independent predictor status for climacturia.

For management of climacturia, it is important to know that no differences in rate of climacturia have been found based on patient age, preoperative EF, last reported postoperative erection grade, NS status, presence or strength of nocturnal erections, libido level, and—surprisingly—daytime UI. Conversely, Lee et al[152] found a larger—although not significant—number of patients with climacturia who also had UI (11% vs 4%).

Various coping strategies and therapies have been suggested and applied with anecdotal success in men with climacturia. Usually, men complaining of urine leakage are managed behaviorally (fluid intake restriction, bladder emptying before sexual activity, the use of condoms, and the application of a penile constricting band at the base of the penis) before foreplay.[4,153,167] Anecdotally, daily use of the tricyclic antidepressant imipramine or antimuscarinic compounds has been suggested.[4] Sighinolfi et al[168] and Geraerts et al[169] reported that pelvic floor rehabilitation programs promoted significant improvement, with urine leakage very rare or absent, in men with climacturia.

The take-home message for the clinician is that alterations in OF after RP are common and frequently impactful to the patient and partner.[4] Currently, there is no specific recommendation for effective treatment to restore the nature of preoperative orgasm. This stresses the importance of counseling patients pre- and postoperatively to decrease the risk of complete sexual avoidance, which could result in serious damage to the structure of the penis and can negatively affect the psychological and emotional state of patients.

PEYRONIE DISEASE

The prevalence of PD after RP has been seldom addressed; only a few studies have investigated macroscopic signs of fibrosis or PD and available data only refer to ORP series.[13,40,170−172] For instance, Ciancio and Kim[170] analyzed outcome data of 110 men who presented with postoperative ED; of these, 45 (41%) had penile fibrotic changes, representing 11% of all men who had RP in their institute at the specified period. The clinical presentation was penile curvature in 93% and "waistband" deformity in 24%; palpable plaques were present in 69% of patients.[170] Tal et al[13] analyzed data from a large cohort of 1,011 men who had ORP; 77 developed PD after RP within 1 year, 139 within 2 years, and 161 within 3 years, yielding an overall PD incidence of 15.9% within 3 years. After an analysis of the role of cardiovascular comorbidities as possible predictors of PD, they found that patients with PD did not have a higher incidence of hypertension, hypercholesterolemia, ischemic heart disease, or peripheral vascular disease than men who did not develop postoperative PD. Of clinical relevance, NS status was a

predictor with marginal statistical significance, whereas erection quality was not. At multivariable logistic regression analysis, younger age and white race emerged as independent predictors of PD occurrence after RP.[13]

Originally ascribed to undiagnosed preoperative PD or spongio-fibrosis from urethral catheterization, catheter-related spongio-fibrosis is not likely to be a significant factor. Another explanation that has been debated is the role of ICIs after surgery, which could cause tunica fibrosis, although there are no data to support this.[13] Although the precise process of plaque formation leading to eventual clinically evident PD after RP remains ill-defined, it could be related to other post-RP penile fibrotic changes secondary to denervation and/or local ischemia.[40]

In summary, patients after RP should be routinely evaluated for the existence of penile plaques as part of their postoperative follow-up even in RARP series. Of patients presenting after ORP or RARP and who were questioned about the information on sexual function that they received preoperatively, Deveci et al[160] found none of the patients with RARP were aware of the association between RP and PD.

PENILE VOLUME ALTERATIONS

Postoperative changes in penile length have been described and seemed to vary from 0% to 55% depending on when and how estimates were obtained.[6,150,154,160,173–181] Fraiman et al[178] found significant a decrease in all penile dimensions after ORP: decreased penile length of 9% and decreased volume of 22% in the erect state, with the most substantial changes occurring up to 8 months postoperatively. Munding et al[179] found a measured decrement in penile length in 71% of men after RP, which was greater than 1 cm in 48% of cases, 3 months postoperatively. Similar findings were obtained in a study by Savoie et al,[180] with a decrease in the stretched penile length in 68% of cases and greater than 15% length loss in 19%. In contrast, Briganti et al[177] did not find changes in penile length 6 months after NSRP when exact measurements were performed. When the same patients were asked to subjectively estimate whether their penis was shortened after the operation, 14% answered affirmatively. Carlsson et al[174] analyzed self-perceived penile shortening in a cross-sectional study of 1,288 men after RP. Patients and controls were asked about their perceived penile shortening by comparing penile length at that time with penile length at 30 years of age. Moreover, patients were compared with a sample of age-matched population-based controls. Of all patients with RP, 663 reported self-perceived penile shortening (55%) compared with 85 of 350 men (26%) in the control group (risk ratio = 2.1; 95% CI = 1.8–2.6). Age, ED severity, and angina were correlated with self-perceived penile shortening in the operated and control groups. Extensive NS technique seemed to be associated with less self-perceived penile shortening compared with NNSRP.[174] In a more recent prospective study,[181] the stretched flaccid penile length was evaluated by a single evaluator in 118 men before surgery, in 76 patients at 2

months after RP, and in 63 men 6 months after RP. All men entered a rehabilitation program. They concluded that men noted early loss of mean stretched flaccid penile length (at 2 months), which mostly recovered to baseline at 6 months after surgery. The investigators concluded that a penile rehabilitation program could prevent—at least in some men—the loss of postoperative penile length. Similarly, Vasconcelos et al[175] observed that in their small cohort of men who underwent RP, the mean differences in penile length before and after RP were not significant 48 months after surgery. Of clinical relevance, the preservation of postoperative EF emerged as predictor for penile length recovery.[175] Gontero et al[173] found that penile shortening was associated with NS status and postoperative EF outcome. In their cohort of 316 men, Frey et al[150] used multivariable logistic regression analysis and found that ED (OR = 1.81) and increasing body mass index (OR = 1.11) significantly increased the risk of reporting subjective penile shortening, whereas NS surgery lowered the risk of this side effect (OR = 0.32).

The reasons for changes in penile volume can be explained by structural and functional alterations in the penis.[40] It also has been historically postulated that the long-term absence of erectile activity leads to the absence of cavernosal oxygenation.[39] In addition to the well-known anatomic changes, there are functional alterations. Indeed, even after NSRP, some degree of nerve injury, commonly neurapraxia, is likely to occur. Overall, any factors that result in decreased nitric oxide production or increased sympathetic tone, such as nerve injury after RP, can lead to decreased relaxation or distensibility of corporal smooth muscle and can lead to loss of length.

CONCLUSIONS

Overall, preventive and therapeutic "strategies" for the preservation and recovery of post-RP EF deserve comprehensive assessment for postoperative factors that could influence EF recovery. Likewise, it is of great relevance to analyze post-RP sexual dysfunctions other than ED, including decreased libido, changes in orgasm, anejaculation, PD, and changes in penile size. In this context, the ICSM 2015 Committee 12 unanimously discussed nine recommendations on sexual rehabilitation after RP. The present article analyzed Recommendations 6 to 9. Of these, Recommendation 6 (the recovery of postoperative EF can take several years) and Recommendation 8 (the data are inadequate to support any specific regimen as optimal for penile rehabilitation) confirmed previous recommendations of the Third ICSM. Conversely, Recommendation 7 (there are conflicting data as to whether penile rehabilitation with PDE5Is improves recovery of spontaneous erections) has been modified according to the current evidence, which fails to clearly demonstrate improvement in spontaneous, unassisted erections with postoperative rehabilitative approaches. Moreover, Recommendation 9 (men undergoing RP [any technique] are at risk of sexual changes other than ED, including decreased libido, changes in orgasm, anejaculation, Peyronie-like disease, and

changes in penile size) is novel and emerged as a mandatory update of previous knowledge in the field.

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