

Prevention and management of post prostatectomy erectile dysfunction

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Abstract: Sexual dysfunction is common in patients with prostate cancer (PC) following radical prostatectomy (RP). Review the available literature concerning prevention and management strategies for post-RP erectile function (EF) impairment in terms of preoperative patient characteristics, intra and postoperative factors that may influence EF recovery, and postoperative treatments for erectile dysfunction (ED). A literature search was performed using Google and PubMed database for English-language original and review articles, either published or e-published up to July 2013. The literature still demonstrates a great inconsistency in the definition of what is considered normal EF both before and after RP. Thus, using validated psychometric instruments with recognized cut-offs for normalcy and severity during the pre- and post-operative evaluation should be routinely considered. Therefore, a comprehensive discussion with the patient about the true prevalence of postoperative ED, the concept of spontaneous or pharmacologically-assisted erections, and the difference between “back to baseline” EF and “erections adequate enough to have successful intercourse” clearly emerge as key issues in the eventual understanding of post-RP ED prevention and promotion of satisfactory EF recovery. Patient factors (including age, baseline EF, comorbid conditions status), cancer selection (non- *vs.* uni- *vs.* bilateral nerve-sparing), type of surgery (i.e., intra *vs.* inter *vs.* extrafascial surgeries), surgical techniques (i.e., open, laparoscopic and robotically-assisted RP), and surgeon factors (i.e., surgical volume and surgical skill) represent the key significant contributors to EF recovery. A number of preclinical and clinical data show that rehabilitation and treatment in due time are undoubtedly better than leaving the erectile tissue to its unassisted postoperative fate. The role of postoperative ED treatment for those patients who received a non-nerve-sparing RP was also extensively discussed. Optimal outcomes are achieved mainly by the careful choice of the correct patient for the correct type of surgery. Despite a plethora of potential rehabilitative approaches, they should be only considered as “strategies”, since incontrovertible evidence of their effectiveness for improving natural EF recovery is limited. Conversely, numerous effective therapeutic options are available for treating post-RP ED.

Keywords: Prostate cancer (PCa); radical prostatectomy (RP); erectile function (EF); erectile dysfunction (ED)

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Introduction

Radical prostatectomy (RP) is the recommended cure for patients diagnosed with low and intermediate-risk localized prostate cancer (PCa) and a life expectancy of at least 10 years (1). European Urology Association (EAU) guidelines report that, in all men characterized by a normal preoperative erectile function (EF) and an organ-confined disease, either bilateral (BNSRP) or unilateral (UNSRP) nerve sparing RP represent the recommended approach of choice (1). Conversely, EAU guidelines suggest a non-nerve sparing (NNS) surgical approach for selected patients with a low-volume high-risk localized PCa and highly selected patients with very high-risk localized PCa, in the context of multimodality treatment (1).

Hence, there is a large amount of patients who may benefit from RP; however, due to several reasons, such as cancer-related, anatomical and technical factors, a reduced surgical and technical skill, or a low surgical volume, many patients undergo RP without NS intent. It is implicit that even many of these men would like to continue to have a satisfactory sexual activity. Moreover, PCa diagnosis is becoming more and more frequent in younger patients, who are particularly interested in maintaining an excellent postoperative health-related quality of life (HRQoL) (2-4). These are just some of the reasons why clinicians should be interested and updated in terms of prevention and management of postoperative erectile dysfunction (ED) in PCa patients, who mostly wish to continue to be sexually active even after surgery. Likewise, it would be of great importance to support those who, conversely, may not or dislike having sex after PCa diagnosis and treatments.

Evidence acquisition

A literature search for English-language original and review articles either published or e-published up to July 2013 was performed using Google and the National Library of Medicine's PubMed database. Keywords included: *radical prostatectomy, nerve sparing, sexual function, sexual dysfunction, erectile function, erectile dysfunction, phosphodiesterase-5 inhibitors, intracavernosal injection, and penile prosthesis*. Of all manuscripts potentially available, we have considered articles with the highest level of evidence (from 1b to 3b). The retrieved articles were gathered and examined. Reference lists of retrieved articles as well as relevant review articles were also studied.

Prevention of post-RP erectile dysfunction (ED)

As correctly stated by the International Consultation on Sexual Medicine (ICSM) committee (5), the first concept in terms of post-RP ED prevention is that, well before RP, the patient and, whenever possible his partner (6), has the inalienable right to be given realistic expectations regarding his postoperative erectile and sexual functioning (7). This will help anyone (i.e., physicians and patients) understanding how to start with the prevention of damage and the subsequent EF recovery, thus reducing the plausible false expectations and subsequent frustrations.

Most of the historical data refer to open RP; overall, the incidence of post-RP ED varies between 14% and 90% (8,9). As a whole, the incidence of reported postoperative ED is extremely discrepant among series, because of a great variation in the nature of the populations studied and the modality for data collection and reporting; the great inconsistency in the definition of what is considered a normal EF before surgery and what one may consider a normal erection after RP emerged as the key problem in almost all these studies (8-11). The results of the meta-analysis conducted by Tal *et al.* (10) clearly stated that most of the published literature does not meet strict criteria for reporting post-EF recovery. The same meta-analysis found as many as 22 different definitions of favorable EF outcome. In this context, the overall fixed effects EF recovery rate was 58% (95% CI: 56-60%), with significant heterogeneity among effect impacts (10). Similar results were also discussed by Burnett *et al.* (8) as a side analysis of outcomes assessed as part of an update of the American Urological Association (AUA) PCa guidelines. They reported how, in many instances, only qualitative and subjective determinations were used, thus interpretable at best as erectile ability insufficient, somewhat functional, or regularly sufficient for sexual intercourse. Moreover, it has been well-observed that EF data from the largest series often refer only to a small fraction of the total RP population since the evaluable number of patients often had represented only a fraction of the total exposed to surgery (10). Therefore, these are some of the most significant obstacles to the accurate interpretation of the incidence and prevalence of post-RP ED, mainly when considering all study types and all technical approaches available (5,8-10).

Laparoscopic and, even more, many large series of robotic-assisted approaches are mature enough and have demonstrated that EF outcomes are at least equivalent to

those obtained with open RP (12-20). Still, a number of limitations for a correct and objective interpretation of results are also discernible in the literature that deals with this type of surgery.

The literature clearly highlights that preoperative EF is an important predictor of EF recovery after RP (7,21-29). To this specific purpose, it is mandatory to verify how the definition of baseline EF was done; indeed, numerous assessment modalities have been reported in the literature, thus including patients subjective self-reports, partner-corroborated function and validated psychometric instruments. Overall, we consider of critical importance the analysis made by Mulhall (9), who reported that a clear mention of baseline EF was only given in only 16 (66%) of 24 studies considered as representative of the experience of large volume worldwide centers. In this context, it was a further recommendation of the ICSM committee that clinicians should use a validated psychometric instrument, with recognized cut-offs for normalcy and severity, during the pre and postoperative evaluation of their patients (5). Either the International Index of Erectile Function (IIEF) (30) or the Sexual Health Inventory for Men (SHIM) (31)—with cut-off scores for ‘normal’ EF of 26 and 21, respectively (30-32)—keep their clinical usefulness to define EF.

Baseline EF assessment is still problematic and the most reliable timing of this assessment is even more poorly defined (5): on the one hand, some patients might overestimate their previous EF; on the other hand, proximity to the surgery may reduce the sexual activity/desire of either the patient, his partner or the couple as a whole (7,22,24). PCa diagnosis, cancer-related or treatment-associated psychological distress may also significantly impair the real-time assessment of EF immediately prior to RP; therefore, this “late” real-time evaluation might not be fully representative of the patient’s true sexual functioning (7,33). Kim *et al.*, for instance, reported that in order to accurately assess the pre-diagnostic baseline EF in candidates for RP, the psychometric tools should be administered before prostate biopsy rather than before robot-assisted laparoscopic radical prostatectomy (RARP) since cancer diagnosis-related symptoms and depression can ultimately affect sexual function and index scores (34).

Overall, the definition of ED of the National Institutes of Health (NIH) was not designed to be applied to a specific population, and even less for a complex population such as the patients undergoing RP (35); this is of particular importance today because such a widely-used definition does not include any mention of the role or use of erectogenic

aids or other assistance, which are hugely suggested in PCa patients after surgery (36-38). Adequate knowledge of the potential use of any preoperative or post-RP erectogenic aid and what proportion of data in any given series was collected from patients using these agents are of relevant importance to allow an accurate interpretation of the findings. These further aspects make giving a proper definition of postoperative EF extremely difficult (5,7,9,10).

A further crucial aspect is the definition of what the patient can actually expect after surgery, that is the concept of regaining EF “back to baseline” (5); indeed, a significantly small proportion of preoperative potent men may spontaneously return to baseline EF after RP (7-10,39-42). Having in mind the clear intention of limiting patient false expectations, clinicians have to comprehensively discuss the objective of regaining an erection equivalent to that prior to RP, especially using data from their own RP population. If we start from the NIH definition of ED, the focal point would become the fact that adequate postoperative erections may be “at least” sufficient for satisfactory sexual performance (35). Mulhall (9) reported that adequate EF was defined as the “ability to have successful intercourse by patient self-report” in 42% out of the series taking into consideration in his own meta-analysis. Unfortunately, overall 37% of the series did not even report how the authors define adequate erections (9). More recently, Nelson *et al.* (42) considered 24-mo follow-up data from 180 men submitted to RP; of them, when including men who were using a PDE5I at 24 months, 43% got back to their baseline EF, while 22% of the whole cohort returned to the baseline EF without the use of any PDE5I. For this group, there was a significant difference by age, which remained a significant predictor (OR =6.25, $P < 0.001$) at multivariable analysis.

In an attempt to combine the two concepts of getting EF “back to baseline” and being able to achieve erections sufficient for satisfactory sexual intercourses, as originally suggested by the NIH, it becomes important to consider the potential misinterpretation of the *established cutoffs for normalcy as well as the grading of ED severity* (mild, moderate and severe) of both the IIEF-EF domain and SHIM. Indeed, using the usual cutoffs for normal function—which are generally considered for the broad-spectrum ED population—might be overly stringent for post-RP populations; indeed, there are patients that still consider themselves to be fully functional while having lower scores (7,8,43,44). In order to try and define a cut-off value as close as possible to the real-life setting, Briganti *et al.* (44) considered a relatively small cohort of preoperatively fully

potent patients (IIEF-EF ≥ 26) treated with retropubic BNSRP at a single institution and suggested that a cut-off of IIEF-EF ≥ 22 may represent a reliable score for defining EF recovery after BNSRP (44).

Another crucial aspect that has to be discussed with the patient is the issue of the *chronology of events of recovery* and the post-operation period. Burnett *et al.* (8) rightly commented that in the modern era of RP the majority of men usually achieve resumption of all physical activities, recovery of urinary control and normalization of bowel function within a few months after surgery. In contrast, postoperative EF continues to improve over time, at least up to 24 months and in some series up to 48 months post-RP (8,9,21,45-48). Overall, although the data are not entirely unambiguous (49,50), RARP seems to promote a faster EF recovery as compared to open RP (19,51).

Time of erection recovery does not uniformly occur in all cases and a number of predictors of EF recovery have been identified, including patients' age at surgery (i.e., the younger the better), better preoperative EF, extent of neurovascular bundle preservation and erectile hemodynamic changes after surgery (5). In this context, surgery (i.e., type, quality, surgical volume and the actual NS approach) probably emerges as the most compelling aspect (7,52). In this context, Tal *et al.* reported that BNSRP was certainly associated with higher EF recovery ($P=0.01$) as compared with UNSRP (10). When dealing with preservation of the neurovascular bundles (NVB), most patients—and, unfortunately, a number of clinicians—do not have an adequate understanding of the concept of NS; indeed, they think that NS always leads to complete preservation of the nerves and, consequently, to the absence of any transient postoperative ED. This is not correct; even when surgeons believe that they have achieved complete BNS (5,7,53), there is inevitably some trauma to the nerves so, in order to prevent false and unrealistic expectations, clinicians have to provide patients with a realistic time frame for EF recovery. Experts suggest that a potential period of 6-36 months would be necessary, although most men have a functional recovery within 12 and 24 months since RP (5). Katz *et al.* showed that the recovery of functional erections in the early postoperative phase, especially without the need for PDE5Is, is a good prognostic indicator for EF at 12-mo assessment (54). Thus, it should be stated with the patients that the ability to have either a spontaneous or a pharmacologically-assisted functional erection (namely PDE5I-sustained) within three months of RP is an excellent prognostic indicator (9). No less important, the fact that it

can take a long time until the first spontaneous erections occurs should not lead the physician to wait inactively: indeed, the patient should start with supportive medication therapy for EF recovery as early as possible (5,7,37,55,56).

As a further major aspect, the clinician should also debate issues concerning the *quality of erection*. In this context, one of the parameters which have to be taken into account is the *hardness of erection*, mostly defined using a 4-point scale such as the Erectile Hardness Score (EHS) (57). Indeed, although a patient may postoperatively have functional erections, which allow him to have sexual intercourse, a more or less severe loss of erection hardness may lead to erection dissatisfaction for the same man. Consequently, he might deserve erectogenic compounds for greater erection hardness, or even a second or third line treatment, if that gentleman was already using an erectogenic medication (5,9,38). A second parameter is the *consistency of functional erections*, which means how consistently a functional erection can be obtained (9). Data regarding RP populations are still lacking.

Prevention and management of EF in patients treated with RP is necessarily heavily predicated upon a careful choice of the correct patient for the correct type of surgery: clinicians should comprehensively discuss the recognized predictors of EF recovery with any candidate for RP (5,7,33,38), and all patients with PCa who might benefit from RP as a curative treatment should also receive an appropriate counseling regarding (I) the possibility of being subjected to a RP [see, in this context, the most updated EAU guidelines (1)]; and, (II) the possibility of being subjected to a NSRP or, conversely, the need to be treated with NNSRP, according to the baseline oncological condition (1). Imbimbo *et al.* (58) investigated factors related to patients' desire to preserve post-RP sexual activity and those determinants for surgeons' final decision to eventually perform a NSRP. Overall, 69% of the patients were preoperatively interested in preserving their sexual activity. Of the entire cohort, 13% were not interested but suitable for a BNSRP, 18% were neither interested nor suitable, 39% were both interested and suitable, but up to 31% were interested but not suitable. Age and normal preoperative sexual function parameters emerged as independent determinants of patients' desire to preserve postoperative sexual functioning. Overall, 13% underwent an UNSRP and 36% a BNSRP. Along with oncological indications, age and patients' desire to preserve sexual activity were among the main independent determinants of surgeon's final decision for a NSRP. Overall, findings from this study

underlined the existence of discrepancies among patient's desire to preserve postoperative sexual function, guideline indications to NSRP, and surgeons' final decision for a NS approach (58).

Therefore, once established that the patient can eventually receive a NSRP, counseling should focus on the patient's baseline functional situation along with the potential predictors of post-operative EF recovery. Preoperatively, these factors necessarily include age at surgery, baseline EF, body mass index and comorbidities (7,38). Likewise, type of surgery, coupled with surgical volume and surgical skill, and NS status achieve the role of significant contributors to EF recovery (5). Briganti *et al.* (55) developed a preoperative risk stratification tool aimed at assessing the probability of EF recovery after open BNSRP. They used routinely-available baseline data, such as patient age and preoperative EF, as psychometrically objectified with the IIEF; moreover, as a proxy for general health status, the authors scored health-significant comorbidities using the Charlson Comorbidity Index (CCI) (59). For the specific purpose of the analysis, CCI was categorized as a score of 0, 1, or ≥ 2 . The resulting tool was able to stratify patients into three groups according to the relative preoperative risk of post-RP ED: low (age ≤ 65 years, IIEF-EF ≥ 26 , CCI ≤ 1), intermediate (age 66-69 years or IIEF-EF 11-25, CCI ≤ 1), and high risk (age ≥ 70 years or IIEF-EF ≤ 10 or CCI ≥ 2). More recently, Novara *et al.* (28) applied the same risk stratification categories to a relatively small cohort of patients treated with BNS RARP who were assessed at a minimum 12-mo follow-up; according to the risk-group stratification proposed by Briganti *et al.*, the 12-mo EF recovery rate was 82%, 57% and 29% in the low-risk, in the intermediate-risk, and in the high-risk group, respectively ($P < 0.001$) (28).

Overall, prevention and management of postoperative EF necessarily pass through rigorous selection of the patients who may benefit from RP: the clinician must clearly inform the patients that the NS approach does not invariably ensure the recovery of erections at all; moreover, since this type of surgery may be potentially subjected to a number of sequelae, a NS approach should be reserved for young patients without significant comorbidities and an adequate preoperative EF (5,7,21,27,28,55).

Functional and topographic anatomy of the prostate—key aspect of intraoperative preservation of erectile functioning

Since NSRP was introduced long time ago, it was

continuously accompanied by the discussion about the right indication for this type of surgical modification (1). Indeed, NS approaches should not compromise the effectiveness of RP by producing artificial surgical margins, whenever a non-NS approach would have been chosen as a better indication in some specific cases. Therefore, in order to carefully preserve the oncological aspect, an estimation of organ confinement of the cancer becomes crucial; thus tailoring the NSRP approach according to the cancer extension of each individual is important in order to save as many neurovascular bundles as possible thus improving the sexual function outcomes (60-62).

Once the right candidate for NSRP has been clearly defined, controversies still exist about the surgical approach to the NVBs that may provide the best EF outcomes. A growing body of evidence concerning the potential consequences of cavernous nerve injury from any type of surgical procedure (thus including pinch, compression, percussion, traction, cautery, and even transection) (7,52,60,63), the importance of the accessory pudendal arteries (64,65), and the eventual subsequent impact on cavernous smooth muscle, have stimulated a large amount of preclinical and clinical research aimed at evaluating different strategies to promote the preservation and the fastest recovery of post-RP EF (5,38). In order to improve cancer control and concurrently to prevent and, where necessary, to treat post-RP sexual disorders (therefore not only ED), it clearly emerged that having an adequate idea of the anatomy and of the topography of pelvic organs—i.e., prostate and adjacent tissues—as well as having some familiarity with aspects of functional anatomy of erection and ejaculation are of major importance (7,60). The fascia on the outer surface of the prostate—mostly termed periprostatic fascia (PPF) after Walz *et al.* (60)—is the key to better develop a correct surgical approach; indeed, these fasciae represent important surgical planes, since numerous technical variations are possible according to the dissection plane chosen by the surgeon during the procedure. Regardless of the technology (i.e., laparoscopic or robotic-assisted RP) and the type of intervention chosen (open, laparoscopic, and robotic RP), the possibility of recognition of three surgical approaches, which ultimately refer to the relationship between the NVB and the PPF (52,60,63), is compulsory for the functional outcomes: (I) *intrafascial dissection* of the NVB, that is considered the surgical approach allowing a whole-thickness preservation of the lateral prostatic fascia, which is completely lateralized altogether with a virtually intact NVB; (II) *interfascial dissection* of the NVB, where the

dissection might not necessarily allow the preservation of all the nerve fibers dispersed on the anterolateral surface of the prostate (64); and, (III) *extrafascial dissection* of the NVB, where the dissection is carried lateral to the levator ani fascia and the Denonvilliers' fascia, thus completely resecting the NVBs (60).

The scientific literature still largely lacks studies that rigorously compare the currently-available different surgical techniques (i.e., open, laparoscopic and robotically-assisted RP) (66,67); the number of prospective, randomized studies of the type of surgical aggression (i.e., intra- to interfascial) according to the different surgical techniques is even more limited. In this context, we shall attempt to briefly summarize a number of key points.

- (I) *Open NSRP*—mainly retropubic RP—is still a common surgical approach for operable PCa (1); to this we must add that the whole wealth of literature on the topic of the last 20 years specifically refers to open surgery (7,38). Budäus *et al.* reported the most updated description of the open intrafascial NSRP coupled with the 12-mo postoperative functional outcome, using the abridged five-item version of the IIEF to assess EF (68). The analyses excluded those men with a preoperative IIEF score below 19, indicating some degree of ED, and the patients who stated not having had sexual stimulation within the last six months. Defining as potent those men who reported erection sufficient for penetration after sexual stimulation, EF recovery rates varied between 84% and 92% in men who underwent a BNSRP, being between 58% and 70% in those submitted to UNSRP. The authors also reported that the use of PDE5Is was left to the patient's discretion, and 80% of men who completed the questionnaire did not use such medications—thus ultimately meaning spontaneous recovery of postoperative EF (68). When a “strict” definition of EF was applied (namely, a postoperative IIEF score >19), the corresponding potency rates were 25-59% (68).
- (II) *Laparoscopic/endoscopic NSRP*—The results reported in the literature for this technique are objectively very heterogeneous, and among other reasons, the possibility of an approach either extraperitoneal or transperitoneal surgery is responsible for an even more complex objective assessment of the functional outcomes (69,70). Greco *et al.* (69) reported the results of a retrospective, parallel-arms study

comparing the 12-mo follow-up functional outcomes in patients undergoing intrafascial retropubic and laparoscopic NSRPs, both performed by high volume surgeons. At that time assessment, 66% of patients in the laparoscopic and 51% in the open group reported being able to engage in sexual intercourse, respectively ($P<0.05$). A comparison between intra- and interfascial laparoscopic extraperitoneal BNSRPs in preoperative potent patients was recently reported by Stolzenburg *et al.* (70). At 12-mo follow-up assessment, the authors concluded that intrafascial laparoscopic BNSRP overall provides significantly better EF recovery rates than interfascial surgery, according to the same age stratification. Using the dichotomous definition of erections satisfactory or unsatisfactory for intercourse, Stewart *et al.* confirmed this significant difference between the two types of dissections, also highlighting that men younger than 60 years of age may certainly achieve the highest functional results with the intrafascial laparoscopic approach (71,72). Conversely, Neill *et al.* (73) did not find a significant difference in terms of both continence and EF recovery rate after an intrafascial versus an interfascial extraperitoneal laparoscopic NSRP. As a major constraint, the rates of men who actually had spontaneous erections were not even considered in almost all the previous studies; this does not allow to provide any clear-cut conclusion both concerning the type of surgery (namely, laparoscopic RP) and the appropriateness of the selected anatomical dissection.

- (III) The outcomes of intrafascial versus interfascial BNSRP techniques have been more recently considered also for RARP (74-78). Beyond the oncological considerations, Potdevin *et al.* (74) defined EF as being able to achieve erection adequate enough for penetration more than half the time with or without PDE5Is, according to the Expanded Prostate Cancer Index Composite (EPIC) (79); EF recovery rates at three, six and nine months in the intrafascial group were 24%, 82%, and 91%, respectively, whereas in the interfascial group were 17%, 44%, and 67% at the same follow-up time-points. Xylinas *et al.* supported the idea that a formal robotically-assisted intrafascial approach provided early (namely, 1-mo assessment) satisfactory functional results with

respect to postoperative continence and potency (75). Of their cohort of patients, 60% exhibited erection sufficient for intercourse, with 50% of these latter not requiring the use of any PDE5I. Asimakopoulos *et al.* (80) reported the results of a prospective, randomized study aimed at comparing the functional results of 128 consecutive patients treated by a single experienced surgeon with either laparoscopic RP or RARP with intrafascial intent in all cases. At 12-month postop RARP scored significantly better ($P<0.0001$) than laparoscopy in terms of EF, defined as capability for sexual intercourse. Men in the RARP group did also show a faster time to capability for intercourse ($P=0.0001$) and a higher rate of return to baseline IIEF-EF domain scores ($P=0.0002$) than those operated with a laparoscopic RP (80). Conversely, a similar rate of patients with functional erections did use PDE5Is within the two groups.

Despite the belief that there are not sufficient prospective, randomized and rigorously-conducted clinical trials to confirm this unequivocally—especially with external validation of the data already published—there is an increasing school of thought that RARP may be the most potency-protective surgical approach (14,17,80). In this context, the circumferential extent of fascia preservation—otherwise known as intrafascial surgery—and patient age (81), as well as preoperative EF and patient comorbidity (7), emerged as the best independent predictors of postoperative EF even for RARP.

Accumulating evidence suggests that a certain amount of men have vascular abnormalities after RP (82) that may be generally traced to two main forms, arterial insufficiency and venous leakage (7,82,83). Mulhall *et al.* clearly showed that in a cohort of men who underwent open BNSRP, had ED and never received any pharmacotherapy, up to 75% had some form of vascular alterations; overall, 59% of the patients had arterial insufficiency and 26% had venous leakage (82). In this context, *arterial insufficiency* has been attributed to the trauma to one of two types of accessory pudendal arteries (84). Between 4% and 75% of all men have accessory or aberrant pudendal arteries (APAs), that may originate from the internal or external iliac or obturator arteries (7,60,84). The importance of preserving accessory pudendal arteries comes from a number of observations that support the concept that they could be solely responsible for arterial blood supply to the corpora cavernosa (65); if this was the case (85), preservation of these arteries during any surgical approach (i.e., open,

laparoscopic or robot-assisted) would be compulsory to avoid ED secondary to penile arterial insufficiency (83,86). Overall, published data support the concept that accessory pudendal arteries may have a role in preserving post-RP EF and in promoting postoperative recovery of EF, as well (83). Surgical approaches with a clear intrafascial goal have been postulated to eventually allow a more stringent preservation of any accessory pudendal artery (87). Failure to recover EF after RP may also result from *venous leakage* as sequelae of neuropraxia-induced, and possibly absence of cavernosal oxygenation associated to erectile tissue damage (65). Overall, data seems to suggest a clinical correlation between postoperative time/interval of EF recovery and the incidence of venous leakage. As a whole, these reports suggest that venous leakage portends poor EF recovery prognosis, with a high probability of never recovering preoperative EF, to poor response to PDE5Is, and even an unsatisfactory outcome with intracavernosal injection therapy (ICI) (65,88). All these observations outline the importance of performing NS surgery whenever possible; therefore, not only considering those men who might either preserve or recover spontaneous, pharmacologically-unassisted postoperative erections, but also all those individuals who are destined to need second line erectogenic pharmacotherapy, which still deserve preservation of the best cavernous tissue to ensure continued excellent response to ICI (11,65).

Management of postoperative EF impairment

Regardless of the surgical technique, the removal of the prostate may ultimately result in an almost-obligatory period of dormancy of the nerves which govern the functional aspects of erection. This may lead to a loss of daily and nocturnal erections, with a consequent persistent failure of cavernous oxygenation and a secondary erectile tissue damage as a result of the production of pro-apoptotic factors (i.e., loss of smooth muscle) and pro-fibrotic factors (i.e., an increase in collagen) within the corpora cavernosa (5,37,89). As outlined above, these changes may be dangerously coupled with postoperative ED of varying degrees and the development of venous leakage, which portends a poor prognosis for EF recovery (5,37,65). In this context, the importance of promoting erectile tissue preservation becomes compelling and the practice of suggesting and applying any form of rehabilitative strategy in post-RP patients has been widely reported in the everyday clinical scenario. Using a web-based survey, Teloken *et al.* assessed

the reality of such an approach among members of the International Society for Sexual Medicine (ISSM) and/or its affiliated societies (90). The survey showed that 87% of the 301 physicians (of them, 82% were urologists) who completed the questionnaire performed some form of rehabilitation. As part of the primary rehabilitation strategy, 95% used PDE5Is, 75% used ICI, 30% used vacuum device, and 9.9% used intraurethral prostaglandin. Among the primary reasons for avoiding EF rehabilitation, the authors found excessive cost (50% of the times); even more important, up to 25% of the physicians replay outlined that the explanation not to perform any EF rehabilitation was the fact that there were no supportive clinical evidence-based data (90). It is of paramount importance to consider that the vast majority or almost all of those data referred to a historical epoch dominated by open surgery, and to centers mainly devoted to this type of surgery. In return, it is not possible to say that the reality would be different if this type of investigation were performed today.

Overall, it is unfortunately true that sufficient clinical evidence supporting such rehabilitation is still lacking (18,39,91-95). In fact, almost all of the available data refers to *in vitro* or in animals studies (38), and concerns exist regarding the translatability of those data to humans. An increasing amount of experimental data, for instance, support the concept of cavernosal damage and suggest a protective role for prolonged dosage of a PDE5I (96-103); however, similar data have not yet been clearly and uniquely replicated in humans (38).

It is certainly true that penile rehabilitation programs using PDE5Is are common in clinical practice, but there is no definitive evidence to support their use or the best treatment strategy (5,18,38,39,91-95,104-106). In this context, the ICSM committee recommended that clinicians should instruct the patients with the essential elements of the pathophysiology of postoperative ED (5). Moreover, the ICSM committee listed very precisely five different types of rehabilitative approaches, including (I) PDE5Is; (II) intracavernosal injections; (III) intra-urethral alprostadil; (IV) vacuum therapy; and, (V) neuromodulatory agents (5). A sort of rigorous road-map to rehabilitation success was then postulated by other authors, taking into account the wealth of potential predictors of as favorable as unfavorable functional (reading, EF) outcome (38).

First, it is essential that *rehabilitation and treatment are undoubtedly better than leaving the erectile tissue to its unassisted, unfavorable fate* (38,55,93,104). This resolute attitude is supported by a plethora of preclinical data,

showing that structural alterations may lead to veno-occlusive dysfunction (96-101), whose incidence ultimately increases in a time-dependent fashion after surgery. These observations may provide robust clinical rationale for early penile rehabilitation prior to penile fibrosis development (37,38,92,107). Overall, the idea that *treating is at least better than doing nothing* certainly derives from the historical studies of Montorsi *et al.* (108) and, subsequently, Mulhall *et al.* (107) concerning the use of relatively-early postoperative ICI. As far today, the concept can be more easily applied learning from the experiences with PDE5Is. Indeed, it has been demonstrated that sildenafil, tadalafil, vardenafil (37,38,92) and, more recently avanafil (109), taken when needed, may be successfully used out of the scope of rehabilitation in those men who underwent a RP with a clear BNS intent. Likewise, no little controversial and non-unique data suggested that bedtime sildenafil [i.e., 25 (104) or 50 to 100 mg (103) daily] led to a significant improvement of EF recovery. In this context, Bannowsky *et al.* (104) specified that sildenafil was significantly active in those men who had early postoperative nocturnal erections. More recently, Montorsi *et al.* (91) reported that nightly dosing of vardenafil for nine consecutive months did not have any effect beyond that of a flexible-dose on-demand vardenafil dose (starting at 10 mg with the option to titrate to 5 or 20 mg) in patients submitted to a BNSRP. Of clinical relevance, this study confirmed that vardenafil taken when needed during the double-blind treatment period was associated with significantly better results as compared with placebo (91). Overall, those results further support the idea that *treating patients early postoperatively is of major importance and may certainly lead to better long-term results in terms of either EF recovery or ED treatment possibilities* (38). In this context, translating this concept to the everyday clinical practice setting, Briganti *et al.* (55), in a large contemporary series of patients treated by high volume surgeons, showed that the 3-year EF recovery rates were significantly higher in patients who did as compared with those who did not use any postoperative PDE5Is (namely, 73% *vs.* 37%, respectively; $P < 0.001$), regardless of the class of risk to which patients belonged according to their own preoperative characteristics. Even more impressive, EF recovery rates were not significantly different according to PDE5Is treatment schedule (chronic *vs.* on-demand) after BNSRP (55). More recently, Gallina *et al.* (56) also showed that after a mean follow-up of more than 2 years, only 35.8% of patients left untreated after open BNSRP recovered ED after surgery, reaching an IIEF-EF domain

score ≥ 22 . However, these authors also demonstrated that, in patients younger than 55 years, and with a pre-operative IIEF-EF ≥ 22 , the rate of EF recovery at 1-year assessment was as high as 69%; this rate increased up to 88% ($P=0.11$) for those receiving PDE5Is of any type and with any posology. Even though such difference did not reach a statistical significance, a higher EF was associated with the use of PDE5Is also among patients with such excellent pre-operative characteristics. Taken together, all this data could suggest that although younger patients with a good preoperative EF may experience good EF recovery rates even without any treatment, using PDE5Is after BNSRP they further improved their functional outcomes (56).

Timing of rehabilitation and treatment is a major clinical matter (5,38,109). Giuliano *et al.* (110) clearly reported that overall 9% of all urologists recommended that ED treatment—of any type—was initiated within the first few days after surgery, whereas 79% (92% of routine prescribers) within 3 months after surgery. This led to have a third of the patients under treatment at 1-2 months postoperatively, and a half between 3 and 4 months after the RP. However, at 8 months or more, still 46% of patients were not being treated at all (109). Given what we now know from animal studies—i.e., treating is of great importance for endothelial and smooth muscle protection, neuromodulation, and reduction of corporal fibrosis (96-103)—*the literature is today almost unique in trying to stress how any form of rehabilitation or treatment should begin as early as possible, and certainly as close to the surgery as possible* (5,38,92,95,106). This is certainly easily applicable for PDE5Is, which have a relatively low probability of side effects; this means that PDE5Is could be initiated as early as the removal of the catheter or during the very first month after surgery (38,95). In a sort of “multimodal massive attack” program for EF preservation, for instance, Moskovic *et al.* instructed their patients to take sildenafil 25 mg nightly as well as to use alprostadil 250 μg urethral suppositories 3 times per week, even beginning 1 week prior to surgery (111). Of interest, preoperative female partner sexual functioning significantly correlated with greater patient compliance with the localized component of the EF rehabilitation program (111). Similarly, McCullough reported the results of a prospective, randomized, open-label, multicenter study comparing nightly intra-urethral alprostadil and oral sildenafil in men with preoperative fully-normal EF (IIEF-EF ≥ 26) who underwent BNSRP (either open or robotic) (112). Interestingly, both nightly treatments were started within 1 month since surgery, at the catheter removal visit, to

be continued for 9 consecutive months. Their findings suggested that there were no statistically significant differences between the two groups in terms of IIEF-EF domain scores and intercourse success rates, both at the end of the treatment period and the completion of the study itself. Similarly, patients started with both treatments as early as 1 month post-RP, without significant treatment-emergent side effects (112).

Conversely, when ICI is the treatment of choice—mainly in those patients with relative ineffectiveness of PDE5Is (5,38,96,107)—*timing for starting ICI should be accurately defined* (5,38,95,113-115). Indeed, ICI often causes penile pain (5,114), which may ultimately lead to a high treatment discontinuation rate (116,117). Yiou *et al.* reported the results of a prospective study aimed at assessing safety and efficacy of intracavernosal alprostadil in a cohort of men who underwent laparoscopic NSRP by high volume surgeons and started self-injection treatment 1 month after surgery (116). Patients were advised to start with alprostadil 2.5- μg twice a week, which was then uptitrated till they were able to reach an erection hard enough to allow vaginal penetration; at the same time, patients were also suggested to attempt intercourses as often as possible. Both pain during injections and pain during erections were assessed using two different Lickert scales; interestingly, 15 (11%) of the 142 originally-enrolled men discontinued due to painful erection since the beginning, and were offered different treatment modalities. Among those who continued the treatment, pain intensity during erection significantly decreased over time (i.e., between 6 and 12 months after RP). Likewise, at the 6-month assessment pain scores correlated negatively with the IIEF-EF, intercourse satisfaction (IS), overall satisfaction (OS) and erection hardness. Conversely, none of the two pain scales correlated significantly with any of the sexual scores at 12-month, thus suggesting that the adverse impact of pain diminished over time. Of importance, patients with greater pain scores at 12-month did also report the lowest SD score. Interestingly, the authors did not find any significant dose-correlation between alprostadil and pain intensity after ICI or during erection (116). Mulhall *et al.* (107) evaluated the postoperative outcome of men with functional preoperative erections who underwent either BNS, or UNS or NNSRP and were challenged early postoperatively with oral sildenafil. Non-responders were switched to ICI and were instructed to either self-inject three times a week, as for rehabilitative purposes, or to use on demand ICI. Trimix (papaverine, phentolamine, and PGE1) was

the medication of choice as a starting agent for the penile injection program; on average, self-injection was started four months postoperatively, with a range of 1-10 months. At 18-month post-RP, all of those patients who had used trimix did report neither pain nor prolonged erections (107). These results seem to support the concept that *injectable erectogenic preparations other than alprostadil may ultimately lead to a less frequent pain complaint, both after injection and during erection*. Of importance, caution should be paid to this issue since, (I) the pathophysiology of penile pain after ICI is still controversial; (II) alprostadil is still the only drug widely approved as an ICI agent for ED; and (III) all the studies dealing with ICI in post-NSRPs did not yet comprehensively assess the potential fluctuation of the painful-penile symptomatology on a time-by-time basis, thus not allowing to clearly make a final suggestion upon the best timing for beginning postoperative early ICI in men who received either an inter- or an intrafascial RP. It is certainly important to specify that early postoperative treatment should not only occur in patients who have undergone surgery with NVBs bilateral preservation: those numerous patients for whom RP was intentionally done with an extrafascial approach may also benefit from early therapy for the treatment of ED. In men who received a NNSRP, Gontero *et al.* showed a trend towards a progressively decreasing erectile response with time from the operation (114); Gontero *et al.* outlined that as many as 70% of the patients who received ICI within the first 3 months after RP did also achieve an erection sufficient for sexual intercourse; conversely, after that period of time the chances of an acceptable response to alprostadil decreased to 40% (114), with a sort of age-related responsiveness. The study of Gontero *et al.* acquires even greater importance when one considers the temporal aspect in terms of adherence to and rate of tolerability to the same treatment. Indeed, despite reporting the highest response rate to alprostadil, patients scheduled for an injection as early as 1-month postoperatively did also more frequently experience complications in terms of (I) prolonged painful erections, and (II) ICI-related discomfort (114). The authors suggested three months after surgery as a reasonable compromise in terms of effectiveness and patient compliance (114).

Psychological and sexual counseling is of major importance to improve any source of rehabilitation and treatment of postoperative EF impairment. Many studies have shown that sexual counseling would eventually contribute to a better treatment efficacy and patient acceptance and compliance, which is generally quite poor (118). In this context, Salonia

et al. analyzed acceptance of and discontinuation data of 100 consecutive, age-comparable, pre-open BNSRP self-reported potent patients who at discharge from the hospital received a PDE5I prescription (119). Thereafter, patients did not receive any further specific counseling throughout an 18-month follow-up period, being completely free to use or not use any ED therapy. Surprisingly, the results indicated that up to 49% of the patients—preoperatively self-reporting to be fully potent and strongly motivated to maintain postoperative EF—actually decided not to even begin any ED treatment after hospital discharge. In addition, an increasing number of men did not even attempt sexual intercourse over the course of the follow-up period; up to 72.5% of those who freely decided to begin PDE5Is, but who did not receive a formal and adequate counseling over time, eventually discontinued the therapy (119). The authors thus concluded that specific counseling on ED treatment modalities, coupled with re-education of the patients, could represent key points in promoting a higher initial acceptance rate and a reduction of the postoperative discontinuation rate from PDE5Is (119). The same concept applies to patients who underwent a NNSRP, for whom ICI alprostadil may be of great benefit. To this aim, Titta *et al.* reported that patients who received sexual counseling coupled with ICI therapy did also report the best quality in all IIEF domains, the lowest discontinuation rate, and the highest degree of couple's satisfaction as compared with those who did not receive any proper counseling (120). In this context, sexual counseling allowed to reduce patients' feeling of lack of sexual spontaneity, dissatisfaction, and fear of needles (120). Hence, an *effective psycho-sexual counseling* up from the preoperative period is strongly recommended to make patients aware of the possible sequelae in terms of sexual difficulties and sexual recovery and of the existence of appropriate therapies that have to be started as soon as possible after RP.

Patients with ED after any type of RP may benefit from penile prosthesis implantation after failure of less invasive treatments (6,38,121-123). Likewise, as previously outlined, many patients received an operation with non-NS intent and they will continue to desire a satisfactory sexual activity, therein including adequate erections. Penile implant surgery is a well-recognized ED treatment even for these latest cancer survivors who wish to remain sexually active and in whom nonsurgical treatments are ineffective, unpalatable or even unacceptable (121,122,124). In this context, penile prostheses are indicated as a 3rd line treatment (121). Tal *et al.* published the results of a crucial analysis aimed at describing the actual use of penile implants after RP or radiation

therapy (RT) for PCa, using data from the Surveillance Epidemiology and End Results cancer registry data linked with Medicare claims (SEER-Medicare Database) (122). The analysis considered 68,558 men aged 66 years or older, of whom 52,747 (77%) had RT and 15,811 (23%) had RP as their initial PCa treatment between 1998 and 2005. Moreover, the study cohort also considered 17% [2,722] of patients who had RP and subsequently received adjuvant RT and men who were treated with androgen deprivation therapies for metastatic diseases. Overall, 533 men had a claim for penile implant surgery, yielding an overall penile implant utilization rate of 0.78% (95% CI: 0.71-0.85%). Patients who underwent RP did also receive penile implant earlier after PCa initial treatment as compared with those who were submitted to RT (median interval, 18.3 *vs.* 24.3 mos, $P < 0.0001$). At multivariate analysis, predictors of penile implant surgery were younger age, being unmarried, and a greater number of comorbidities (121). Men who had undergone RP were more likely than those who underwent RT to receive a penile implant, after adjusting for other variables (OR: 5.4, $P < 0.0001$), and the same was also found for men who received adjuvant RT as compared with patients who had RT as primary treatment (OR: 5.5, $P < 0.0001$). More important, penile implant utilization rate was dramatically low, being 0.31% (95% CI: 0.26-0.36%) in the RT group and 2.3% (95% CI: 2.1-2.6%) in the RP group. Patient's age, being unmarried, and RT emerged as independent predictors of a reduced utilization rate among patients (all $P < 0.001$) (121). Overall, the results of these analyses clearly highlight that penile prostheses are scarcely requested after PCa treatment in the everyday clinical scenario. Although the analyses could be limited by the entry criteria (i.e., age ≥ 66 years, potential use of androgen deprivation therapy with its consequent reduction of SD, etc.), the manuscript clearly raises the question that prostheses are uncommonly implanted after both RP and RT because of a poor outcome; this is not the case according to most of the published literature that demonstrates technical feasibility of placing a penile implant in men who have had RP (121,123,125), safety with a low morbidity rate (123), highly effective ED treatment with higher treatment satisfaction compared with PDE5Is or ICI in both patients (121-123,126) and partners (121,127) (although data in post-RP women populations are almost absent), and excellent long-term mechanical reliability of contemporary penile implant models (122). Overall, Akin-Olugbade *et al.* (128) reported that having a history of RP was predictive of lower patient satisfaction with penile implant surgery compared to

non-RP patients. This ulteriorly outlines the importance of giving the candidates to RP and, subsequently, the patients who had undergone surgery for PCa, a multimodal support both in terms of "organic treatment" and psychological and sexual counseling, without forgetting patient's expectations and his actual needs/desires, as well.

Conclusions

The literature offers a great inconsistency in the definition of what is considered a normal EF before surgery and what a man may consider a normal erection after RP. Validated psychometric instruments with recognized cut-offs for normalcy and severity during the pre- and postoperative evaluation have to be routinely considered. Therefore, a comprehensive discussion with the patient about the true prevalence of postoperative ED, the concept of back to baseline, the meaning of either spontaneous or pharmacologically-assisted erections clearly emerge as key issues to eventually understanding how to prevent and to promote recovery of satisfactory post-RP EF.

In this context, patients should be given individualized outcomes based on a tailored surgical technique, and on patient and surgeon factors. Even if the literature lacks comprehensive data, type of surgery (i.e., intra *vs.* inter *vs.* extrafascial surgeries) and surgical techniques (i.e., open, laparoscopic and robotically-assisted RP) achieve the role of significant contributors to EF recovery. The complexity of the issues discussed throughout this manuscript precisely outlines that prevention and possible management of EF of patients treated with RP necessarily passes once more through a careful choice of the right patient at the right time for the correct type of surgery.

Several preventive and therapeutic "strategies" for the preservation and recovery of post-RP EF are available in the everyday clinical setting. Conversely, no specific recommendation emerges regarding the structure of the optimal rehabilitation or treatment regimen. It is of major importance to stress that "postoperative EF rehabilitation" could mean interventions designed to achieve faster and better natural EF recovery, but it could also mean interventions actually able to preserve sexual continuity without necessitating natural EF. In this context, rehabilitation and treatment, set as early as possible, are undoubtedly better than leaving the erectile tissue to its unassisted, unfavorable fate. Likewise, the role of postoperative ED treatment for those patients who received a non-NS surgical approach (i.e., ICI and penile prosthesis

implantation) also deserves the highest attention of the clinicians.

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Footnote

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