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IMPACT OF FUNCTIONAL REHABILITATION FOR ERECTILE FUNCTION RECOVERY OF PROSTATE CANCER PATIENTS UNDERWENT ROBOTIC RADICAL PROSTATECTOMY WITH NERVE-SPARING APPROACH FROM A BIO-PSYCHO-SOCIAL PERSPECTIVE

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Impact of functional rehabilitation for erectile function recovery of prostate cancer patients underwent robotic radical prostatectomy with nerve-sparing approach from a bio-psycho-social perspective

ABSTRACT

Introduction: Prostate cancer is the most common malignancy among men, often detected at a localized stage in younger, healthier patients. Although robot-assisted radical prostatectomy (RARP) with nerve-sparing (NS) techniques aims to optimize recovery of erectile function (EF), outcomes remain variable, impacting quality of life. Rehabilitation protocols combining pharmacologic and psychosexual interventions may enhance EF recovery.

Materials and Methods: This retrospective cohort study included 640 patients who underwent RARP with NS techniques from 2020 to 2024. Patients with severe pre-existing erectile dysfunction (IIEF-5 score <17) or short follow-up (<24 months) were excluded. Surgical approaches were stratified into categories (bilateral intrafascial, bilateral interfascial, interfascial/extrafascial) based on nerve preservation. Postoperative rehabilitation involved tadalafil (20 mg, thrice weekly), vacuum erection devices (VED), intracavernosal injections (ICI), and optional psychosexual counseling for relational health assessment (Dyadic Adjustment Scale, PCS-12, MCS-12). EF recovery was measured using IIEF-5 scores at intervals over 24 months. Multimodal logistic estimates, Kaplan Meier curves and Cox's promotional hazard models were used to investigate the functional recovery.

Results: At 12 months, patients with bilateral intrafascial NS and combined PDE5i + VED therapy showed the highest EF recovery, particularly in younger patients (<65 years), with median IIEF-5 scores significantly improved. Psychosexual counseling positively correlated with relational and EF recovery. Kaplan-Meier curves demonstrated quicker EF recovery for younger patients and those with bilateral NS, with 86% achieving baseline EF by 24 months.

Conclusions: Robot-assisted RARP, combined with structured PDE5i + VED therapy, significantly enhances EF recovery, particularly for younger individuals with bilateral intrafascial NS. Psychosexual support further aids recovery, highlighting the importance of a biopsychosocial approach in post-RARP rehabilitation. Future multicenter studies are recommended to standardize penile rehabilitation protocols.

INTRODUCTION

Prostate cancer is nowadays the most prevalent cancer in men; a large amount of the new cases is being detected in younger and healthier patients, often in clinically localized stage (1). Radical prostatectomy (RP) or radiotherapy remain the treatment of choice for clinically localized disease (2), providing survival rates as high as 95% at 5 years after treatment, with estimates that suggest most survivors can expect 10 to 12 post-treatment life-years.

In most developed countries, more than 85% of prostatectomies are being performed robotically. Although new surgical strategies as nerve-sparing surgery (NSS) and preservation of accessory pudendal artery have been introduced to preserve erectile function (3) (4), a rate of post-operative erectile dysfunction (ED) ranging between 25% and 75% has been reported in the literature (5). While several studies reported satisfactory urinary continence recovery rates after surgery (6) (7), the postoperative recovery of erectile function (EF) still represents a great challenge for patients and clinicians.

Although surgeons should try a careful dissection in attempt to preserve the neurovascular bundle during prostatectomy, there is evidence that neuropraxia, ischemic and hypoxic nerve insults and apoptosis of cavernous smooth muscle contribute to erectile disfunction (8). The neurovascular bundle will be affected by mechanical manipulation, heating, ischemic effects, and local inflammation (9).

Considering these premises, while long-term oncological outcomes for clinically localized prostate cancer allow for a proper treatment of the disease, patients may still need to deal with these side effects years after the initial surgery (10). Chronic erectile disfunction reduces blood flow to the corporeal bodies, which leads to fibrosis and transformation of trabecular smooth muscle through collagen, which itself leads to the loss of the veno-occlusive mechanism required to maintain erections. Furthermore, ligation of accessory internal pudendal arteries during prostatectomy decreases arterial inflow which intensifies hypoxia and ultimately leads to apoptosis (11) (12).

Several perioperative factors contribute to post-prostatectomy EF: age, pre-existing ED, medical comorbidities, surgeon techniques, equipment and experience (13). First, preoperative patient characteristics play an important role on the probability of recovering EF after surgery: healthier and younger patients have substantially higher recovery rates as compared to their older and sicker counterparts (14). Second, preoperative EF represents a significant predictor of the subsequent probability of ED after surgery (15) (16). Finally, the surgical technique and surgeon experience have a significant impact on the risk of ED after surgery (17). The reported incidence rates of ED after RP range from 6% to 68% (17).

Unfortunately, sexual dysfunction after PCa treatment is often marginalized due to patient's variability. Many health care practitioners spend little or no time discussing sexual health concerns with their patients because of the discomfort in talking about sex or feeling inadequately trained to do so (18) (19).

Couples report experiencing grief over the loss of their previous sex lives, struggling with adaptation and acceptance of changes in sexual activity, and describe decreases in overall relationship intimacy (20).

Penile rehabilitation consists of understanding the mechanisms that affect EF and utilizing pharmacologic agents, devices or interventions to promote male sexual function before and after any insult to the penile erectile physiologic axis (21). The purpose of penile rehabilitation is to preserve health and minimize damage to erectile tissue during the neural recovery by delivering adequate oxygenation to the cavernous tissues (22). While several preventive and treatment strategies for the preservation and recovery of sexual function are available, there is limited consensus regarding the optimal rehabilitation or treatment protocol for men with sexual dysfunction following salvage therapy (23).

Sexual rehabilitation after PCa focused almost entirely on erectile functioning: with the of phosphodiesterase type 5 inhibitors (PDE5is) in the late 1990s, erection-focused treatment for patients after PCa treatment proliferated (24). Rehabilitating EF after RP is indeed an important first aspect

in the postoperative phase; however, other domains of sexual function must be kept in mind. These include orgasmic function, alternatives for penile penetration, penile shortening, mental state, and the impact of urinary incontinence (UI) (10). Encouragingly, sexual rehabilitation in PCa is shifted to a biopsychosocial model of care (25).

Survival, Continence and Potency (SCP) classification has been proposed by Ficarra et al in 2012 with the aim not only to offer a realistic interpretation of the results in patients undergone radical prostatectomy, but also to create a classification more applicable in the real life scenario; this new system provide a much more accurate sub-group classification of the results after RP, even in those patients who do not represent the "best" group category (26)

Classic treatment options for erectile function recovery after RP

Penile rehabilitation was first introduced by Montorsi et al in 1997 (27). There are five main categories for penile rehabilitation: phosphodiesterase type 5 inhibitors (PDE5Is), intracavernosal injections (ICIs), intraurethral and topical alprostadil, vacuum erectile device (VED) therapy, and testosterone therapy (28). It is widely accepted that penile rehabilitation should be started in the early postoperative phase (29). The Fourth International Consultation for Sexual Medicine (ICSM; 2015) provided 9 recommendations for sexual rehabilitation after RP (30):

1. Clinicians should discuss the occurrence of post-surgical erectile dysfunction (ED; temporary or permanent) with every candidate for radical prostatectomy.
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 availableto monitor EF recovery after RP.
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.

4. Recognized predictors of EF recovery include, but are not limited to, younger age, preoperative EF, and bilat- eral nerve-sparing (BNS) surgery.

5. Patients should be informed about key elements of the pathophysiology of postoperative ED, such as nerve injury and cavernous venous leak.

6. The recovery of postoperative EF can take several years.

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

8. The data are inadequate to support any specific regimenas optimal for penile rehabilitation.

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.

PDE5Is entered the market in 1998, revolutionizing the treatment of ED. PDE5 inhibitors inhibit PDE5, which metabolises cGMP, and this results in an increase in cGMP levels. This increase in the amount of cGMP coupled with nitric oxide induces corporal smooth muscle relaxation, and this leads to subsequent erection by allowing blood flow to the penis. This mechanism is boosted by nitric oxide production that is stimulated by cavernous nerves (31), requiring an adequate nerve preservation, in order to maintain a proper availability of cGMP for PDE5 to metabolise (32). The use of PDE5Is is well documented and it has a positive effect on drug-assisted erections, but less on spontaneous erections (33). To date, PDE5Is remain the standard of care although overall discontinuation rates are high, reported between 49 and 72% (34) (35). Taken together, the results of these preclinical studies raised the hypothesis that early administration of PDE5-Is might improve EF recovery after RP.

A study by Montorsi *et al.* aimed to compare the efficacy of tadalafil daily and on demand versus placebo in improving unassisted EF and reducing loss of penile length following nerve-sparing RP. Four hundred twenty-three patients were randomized: at 9 months, they found a significant difference in reaching target IIEF-EF ≥ 22 in the tadalafil once daily group compared to placebo. Regarding

penile length, there was significant protection from penile length loss in the daily tadalafil group (2.2 mm) compared to other groups. These data suggest that PDE5Is may have a role in preserving cavernosal integrity by protecting against structural changes after nerve-sparing RP (36). In order to reduce patients dropout, potential PDE5i adverse effects, such as headache, flushing, hypotension, nasal congestion, dyspepsia, and hearing or vision loss, must be thoroughly discussed (37). Safety data from the major trials suggests that the incidence of the most frequent adverse events (headache, dyspepsia and flushing) is generally mild; all the included RCTs indicated that no clinically significant changes in laboratory tests, electrocardiograms or blood pressure were observed in the PDE5 inhibitors groups (38).

IntraCavernosal Injection (ICI) and intraurethral therapy use alprostadil's vasodilation to improve erectile function. Alprostadil provides prostaglandin E1 (PGE1) that increases the levels of 3',5'-cyclic adenosine monophosphate (cAMP) within the erectile tissue and results cavernosal smooth muscle relaxation. Its intraurethral form generally does not cause systemic side-effects, but locally it can elicit urethral burning and penile pain (39). ICIs with alprostadil or prostaglandin E1, papaverine, and phentolamine have been described and are an option for men with insufficient effect of PDE5Is (40). Alprostadil can also be used as an intraurethral treatment or a topical cream in order to help erections (41). One of the pioneers in penile rehabilitation strategies were Montorsi *et al.*: they published one of the first clinical trial that assess ICI in 1997, randomizing 33 patients who underwent bilateral nerve-sparing RP to undergo alprostadil injections 3 times per week for 12 weeks versus no treatment. After six months, 67% of men in the treatment group achieved spontaneous erections sufficient for penetration when compared to 20% in the control group.

In case of PDE5i failure, the most widespread therapeutic option is PGE1 intracavernous injection (around 67.9%) in monotherapy (1–2 times/week), followed by the association of PDE5i and VED or by the combination of PDE5i, VED and PGE1 injections (intraurethral or intracavernous) (42).

VED therapy is a mechanical treatment option that takes advantage of negative pressure to distend the corporal bodies to increase the blood inflow to the penis (43). Unlike PDE5Is, VED does not

require intact corporal nerves and nitric oxide pathways for proper function; the VED device includes a constriction ring used at the base of the penis that helps maintaining erections for intercourse (44). Raina *et al.* reported VED use in patients undergoing RP. In their clinical trial, they randomized 109 patients into using daily VED versus observation: in the VED group, 80% had erections adequate for intercourse at 9 months and only 23% reported penile shrinkage (45). The low complication rates, the lack of side effects and its cost-effectiveness make VED a good addition to be taken into consideration during penile rehabilitation counseling (13).

Lastly, testosterone therapy might be a beneficial option for hypogonadal men after RP, but concerns have been raised about adverse events such as potential development of biochemical recurrence (46). There is a positive influence between physical exercise and sexual functioning, including men after RP, because it has been proven that PDE5I plus physical activity is more effective than PDE5I alone for men with Erectile disfunction (47). In addition, Pelvic Floor Muscle Training (PFMT), which is also used in the treatment of urinary incontinence, has been proven to be beneficial for sexual function in general (48).

It has been noted that a holistic approach, including the partner and a clinical sexologist, is better than isolated penile rehabilitation to improve the ability to have penetrative sex after surgery. Couples counseling has been demonstrated to improve sex life and should be started within 3 months of radical prostatectomy, according to couples itself (49). Interestingly, Rubilotta et al stated the type of surgical approach and, above all, nerve sparing surgery did not influence the choice of the ER protocol. They reported that PDE5i in monotherapy is the most prescribed medication regardless of sparing the neurovascular bundle, while in non-NSS, it was likely a significantly higher use of PGE1 as a first-line treatment since a successful effect of the PDE5i monotherapy is less expected (42). Regarding treatment with PDE5i, there is still no consensus in protocols in terms of the type of medication in mono- or combination therapy and in the dosage (50): literature showed a somewhat higher benefit in the long-term use of PDE5i than on demand (51). VED is a non-invasive and not expensive

treatment that is not commonly prescribed as monotherapy in a first line setting, but around 25% of clinicians prescribed VED in association with PDE5i or PGE1 as first-line therapy (52).

Regarding second-line treatment, there is a high difference among patients: PGE1 monotherapy is the most prescribed therapy, since it allows successful erections in most cases after RP. The use of VED, in mono- or combination therapy with PDE5i, was common among patients after first-line therapy failure. The duration of rehabilitation differed among patients: interestingly, more than 50% reported to receive treatment for less than one year, while there is clear evidence that a longer period is beneficial (51).

Since 2015, our Center established a specialist outpatient clinic for functional rehabilitation after pelvic surgery, where trained residents, under the supervision of urologists with an advanced knowledge in sexual medicine, have been taking care of the patient undergone RARP after their discharge from the hospital. From 2021 a group of psycho-sexologists joined our service to improve the follow up and the standard of care of these patients.

The aim of this study is to evaluate the impact of our rehabilitation protocol in patients who underwent RARP for prostate cancer, and investigate pattern and factors impacting on erectile function recovery.

MATERIALS AND METHODS

Study Population

The current study relied on an institutional review board-approved, prospectively maintained database. It included 1914 consecutive patients treated with prostate surgery at IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico di Sant'Orsola, between 2020 and 2024. Demographic characteristics at baseline, perioperative data, nerve-sparing techniques, and postoperative erectile function outcomes were collected for all patients. Of the 1914 patients, 197 were lost to follow-up, and 537 did not receive nerve-sparing techniques. Patients with a IIEF-5 score <17 were excluded from the analysis, due to pre-existing moderate or severe erectile disfunction. Additionally, patients with a follow-up shorter than 24 months were excluded from the analysis. This yielded a final population of 640 patients. This study was conducted in accordance with good clinical practice guidelines and the ethical principles outlined in the Declaration of Helsinki.

Data Collection

Baseline demographic and clinical variables, including age, body mass index (BMI), diabetes status, and cardiac comorbidities, were collected preoperatively. Prostate-specific antigen (PSA) levels, clinical staging (cT), and prostate volume were also recorded. Additionally, the patients' preoperative erectile function was assessed using the International Index of Erectile Function-5 (IIEF-5) score, categorized into severity groups (mild, moderate, severe erectile dysfunction). Surgical details, including the nerve-sparing approach used during prostatectomy, were documented. Postoperative data included follow-up assessments of erectile function at various intervals (3, 6, 12, and 24 months postoperatively) using the IIEF-5 score. Rehabilitation strategies, such as the use of phosphodiesterase type 5 inhibitors (PDE5i), vacuum erection devices (VED), and intracavernous injections (ICI) with aprostadil 10 mcg, were recorded at each time point.
Every patient started the assumption of tadalafil 20 mg 3 times/week immediately after catheter removal; the medication cost was entirely covered by the regional health care, which provide coverage for PDE5i to the patient undergone to pelvic surgery. During each visit the use of VED was proposed to every patient, encouraging the combined use of VED without constrictive ring to perform multi-erection cycles within a given period (eight to ten erections in 15-20 minutes). ICI was proposed in case of patient dissatisfaction or concern about the rigidity of the erection and in interested patient a training ICI was provided. A subset of 74 patients underwent an additional, structured psychosexual rehabilitation program under the guidance of a certified psycho-sexologist. This program was designed to address both the physical and emotional aspects of postoperative recovery and involved tailored interventions to improve sexual and relational health. These patients underwent an interview, designed as a semi-structured dialogue to explore the patient's emotional and relational state, the

presence of a partner, and the communicative-relational climate within the couple, if applicable. It also delves into sexual life and expectations prior to the surgery and current expectations regarding health and sexuality. Finally, it assesses the patient's compliance with the andrological rehabilitation program.

The interview is structured as follows:

a. **Collection of Anamnestic Data**: As per a structured interview format.

b. **Space for Unstructured Narration**: Employing active and empathetic listening to allow the individual to express themselves and share their experiences.

c. **Psycho-Educational Suggestions/Tasks**: Related to the sexual sphere.

d. **Quantitative Data Collection**: Through the administration of three questionnaires, which will be re-administered during follow-up control visits, sometimes incorporating psycho-educational content.

To analyze the semi-structured interviews, four areas of investigation were identified:

1. **Patient's Health**: Mood, individual resources, retirement, any personal or familial pathologies, and family bereavements.

2. **Couple Relationship**: Presence of a partner, support within the couple, extramarital relationships, and the resumption or not of sexual activity.

3. **Post-Surgery Factors**: Erectile function, perception of one's virility, and incontinence.
4. **Treatment Adherence**: Compliance with andrological rehabilitation

Psychosexual assessments were performed using the Dyadic Adjustment Scale (**DAS**) chosen to measure an individual's perception of their relationship with their partner, Physical Component Summary (**PCS-12**) Mental Component Summary (**MCS-12**) scores at the beginning of rehabilitation and again after 12 months to evaluate the general physical and psychological health of the patient. These assessments were used to track changes in psychosexual health and quality of life.

Nerve-Sparing Techniques

Patients were stratified based on the type of nerve-sparing technique employed during surgery, categorized as Bilateral Interfascial, Bilateral Intrafascial, Interfascial/Extrafascial,

Intrafascial/Extrafascial, or Intrafascial/Interfascial (Table 2). Each approach was evaluated in terms of its impact on postoperative erectile function recovery and time to return to baseline IIEF-5 scores. The nerve-sparing techniques were performed according to standardized protocols, and the decision to use a specific technique was based on tumor location, surgeon experience, and intraoperative findings.

Erectile Function Outcomes

The primary outcome of interest was the recovery of erectile function, measured by the time to return to baseline IIEF-5 scores. Baseline erectile function was defined as the patient's preoperative IIEF-5 score, and recovery was considered when the postoperative IIEF-5 score returned to or exceeded the baseline value. Erectile function recovery was assessed at 3, 6, 12, and 24 months postoperatively.

Statistical Analysis

Statistical analyses, reporting, and interpretation of the results were conducted according to established guidelines. Descriptive statistics were used to summarize demographic and baseline clinical characteristics of the study population. Continuous variables were reported as medians with interquartile ranges (IQR), while categorical variables were presented as frequencies and percentages. Comparative analyses between nerve-sparing techniques and treatment groups were performed using Kruskal-Wallis rank sum tests for continuous variables and Pearson’s chi-squared tests for categorical variables (Tables 1-3).

Seven sets of analyses were performed. First, to account for the repeated measurements of erectile function over time, a multilevel (mixed-effects) model was used to assess the impact of nerve-sparing techniques and postoperative rehabilitation therapies on erectile function recovery over time. This model included fixed effects for nerve-sparing techniques and rehabilitation therapies and random intercepts to account for patient-level variability over time (Table 4). Time was modeled as a continuous variable, and a restricted maximum likelihood approach was used to estimate the coefficients. The model's coefficients were estimated using restricted maximum

likelihood estimation, and p-values <0.05 were considered statistically significant. Second, visualization of erectile function recovery over time was performed using plots stratified by nerve-sparing technique (Figure 1 and 2) and by rehabilitation therapy (VED, PDE5i, PDE5i + VED, Figure 3 and 4), after stratifying patients below and above the median value of age at surgery. These plots provided a longitudinal depiction of the recovery trajectories over time, allowing for a clear comparison of the recovery profiles across the different interventions. Line plots were used to offer an intuitive understanding of how different strategies impacted erectile function recovery over the follow-up period.

Fourth, a Cox proportional hazards model was used to evaluate the time to return to baseline erectile function (defined as the preoperative IIEF-5 score). The model was adjusted for potential confounders, including age, comorbidities, and preoperative IIEF-5 scores. Hazard ratios (HR) with 95% CI were reported, and the proportional hazards assumption was tested using Schoenfeld residuals. Fifth, Kaplan-Meier survival curves, stratified according to the median age at surgery, were generated to visualize recovery patterns, providing insights into the time to return to baseline IIEF-5 scores (Figure 7). Sixth, a plot of the predicted probability of no longer needing rehabilitative therapy (phosphodiesterase type 5 inhibitors [PDE5i], vacuum erection devices [VED], or PDE5i + VED) due to successful recovery of erectile function was generated. This was modeled using a logistic regression framework to account for the discontinuation of rehabilitation due to sufficient recovery. Finally, for the subset of patients (n=74) who underwent psychosexual rehabilitation with a psychosexuologist, changes in Dyadic Adjustment Scale (DAS), Physical Component Summary (PCS-12), Mental Component Summary (MCS-12), and IIEF-15 scores were analyzed. Wilcoxon rank sum tests were used to compare median scores at the initiation of rehabilitation and at the 12-month follow-up.All statistical analyses were conducted using R software version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). Graphical representations and survival curves were generated using the 'ggplot2' and 'survminer' packages in R.

RESULTS

The demographic and clinical characteristics of the study population are summarized in **Table 1**. The final cohort consisted of 640 patients with a median age at surgery of 65 years (IQR: 59-69) and a median BMI of 25.0 kg/m^2 (IQR: 23.9-27.3). Overall, 33% of patients had a history of cardiac disease, and 6.1% had diabetes. The median iPSA value was 6.5 ng/ml (IQR: 5.0-8.5), and the median prostate volume was 45.0 mL (IQR: 39.0-56.0). Clinical staging of prostate cancer revealed that 59% of patients were cT1c, while 22% were cT2a, and smaller proportions were cT2b, cT2c, and cT3a. The majority of patients (71%) did not use any preoperative prostatic drugs, while 27% used alpha-blockers, and a small percentage used 5-ARI or combination therapies. Baseline erectile function, as assessed by preoperative IIEF-5 scores, revealed that 59% of patients had normal erectile function and 41% had mild erectile dysfunction. The distribution of nerve-sparing techniques is detailed in **Table 2**. Among the cohort, 15% underwent bilateral interfascial nerve sparing, 22% underwent bilateral intrafascial nerve sparing, and the remaining patients received various combinations of interfascial, extrafascial, and intrafascial approaches.

Table 1. Demographics and characteristics of the population

Variable	**N = 640**[1]
BMI (kg/m^2)	25.00 (23.92, 27.31)
Age at surgery (years)	65.00 (59.00, 69.00)
Diabetes	
Yes	39 (6.1%)
Cardiac diseases	
Yes	208 (33%)
iPSA (ng/ml)	6.50 (5.00, 8.50)
Prostatic volume (ml)	45.00 (39.00, 56.00)
Clinical Stage	
cT1c	372 (59%)
cT2a	140 (22%)
cT2b	45 (7.1%)
cT2c	71 (11%)
cT3a	12 (1.5%)
Preoperative prostatic drugs	
None	453 (71%)
5ARi	6 (1.0%)
Alpha-blockers	173 (27%)
5ARi+Alpha-blockers	8 (1.0%)
Categorized preoperative IIEF-5	
22-25	378 (59%)
17-21	262 (41%)

Table 2. Nerve sparing degrees strategies in the population

Variable	N = 640[1]
Nerve sparing degrees	
Bilateral Interfascial	95 (15%)
Bilateral Intrafascial	144 (22%)
Interfascial/Extrafascial	111 (17%)
Intrafascial/Extrafascial	137 (21%)
Intrafascial/Interfascial	153 (24%)

Rehabilitation strategies are summarized in Table 3. The early use of PDE5i was highest among the Bilateral Interfascial group (90%) and lowest in the Intrafascial/Extrafascial group (65%, p<0.001). The use of ICI at 3 months was significantly higher in the Interfascial/Extrafascial group (49%) compared to other groups (p=0.04).

Table 3. Rehabilitative strategies and follow-up questionnaires of the population stratified by nerve sparing approach

Variable	**2+2** N =95	**1+1** N =144	**2+3** N=111	**1+3** N=137	**1+2** N=153	**p-value**[2]
Preop IIEF-5	20 (19-22)	21 (19-24)	20 (16-23)	22 (19- 24)	20(19-23)	0.06
Early PDE5I Use	78 (83)	108(75)	72(65)	82(60)	124(81)	**<0.001**
IIEF-5 3 Months	12(5-19)	15(10-16)	10 (5-20)	12(5-19)	5 (3-14)	**<0.001**
Therapy 3 Mo						
No	0 (0%)	16 (9.1%)	2 (2%)	0 (0%)	0 (0%)	
PDE5i	84 (90%)	112(68%)	82 (74%)	111 (81%)	130 (85%)	**0.09**
VED	0 (0%)	0 (0%)	0 (0%)	4 (3%)	0 (0%)	
PDE5i + VED	11 (10%)	32 (22%)	27 (24%)	22 (16 %)	23 (15%)	
ICI 3 months	16 (17)	26 (18)	54 (49)	16 (12)	27 (18)	**0.04**
IIEF-5 6 Months	17(9-20)	15(5-19)	15(8-19)	15(5-19)	17(12-19)	0.3
Therapy 6 Mo						
None	0 (0%)	16 (9.1%)	0 (0%)	8 (4.8%)	0 (0%)	
PDE5i	69 (72.9%)	90 (64%)	69 (61.8%)	87 (64%)	114 (74%)	0.1
VED	7 (6.9%)	6 (4.5%)	10 (8.8%)	16 (11.9%)	10 (6.4%)	
PDE5i + VED	19 (21%)	32 (22.3%)	32 (28.9%)	26 (19%)	29 (19%)	
ICI 6 months	7 (6.9)	16 (11.4)	42 (38.2)	13 (9.5)	18 (11.6)	**0.03**
IIEF-5 12 Mo	19(14-22)	21(10-22)	15(8-19)	16(10-20)	16(10-20)	**0.025**

Therapy 12 Mo						
None	0 (0%)	10 (6.8%)	13 (12%)	19 (14%)	10 (6.4%)	
PDE5i	66 (69%)	72 (50.3%)	59 (52.9%)	78 (56.8%)	104 (68%)	**0.04**
VED	7 (6.9%)	10 (6.8%)	3 (2.9%)	3 (2.4%)	7 (4.3%)	
PDE5i + VED	23 (24.4%)	53 (36.8%)	35 (31.9%)	36 (26%)	32 (21%)	
Coital VED 12m	16 (17)	39 (27)	20 (18)	13 (9.5)	20 (13)	**<0.001**
ICI 12 months	3 (3.4)	13 (9.1)	38 (34)	7 (4.8)	18 (11.8)	**<0.001**
IIEF-5 24 Mo	19(15-20)	21 (15-22)	18(15-22)	19(12-22)	19(17-22)	0.11
Therapy 24 Mo						
None	0 (0)	13(9.1)	13 (12)	9 (6.5)	5 (3.2)	
PDE5i	64 (67)	76 (52.5)	40 (36)	66 (48.5)	98 (64)	**0.03**
VED	12 (13)	23 (16)	27 (24)	40 (29)	29 (19)	
PDE5i + VED	19 (20)	31 (21.3)	32 (29)	21 (15)	21 (14)	
ICI 24 months	0 (0)	10 (6.8)	38 (34)	3 (2.4)	0 (0)	**<0.001**
Coital VED 24m	25 (26)	43 (30)	44 (40)	58 (42)	43 (28)	**0.004**
Return to Baseline IIEF-5	27 (28)	88 (61)	52 (47)	58 (42)	90 (59)	**<0.001**
Time to Baseline IIEF-5 (Months)	11(4-12)	7 (4-11)	9 (5-12)	12 (5-15)	9.00 (5-12)	**<0.001**

[1] Median (IQR); n / N (%). [2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test. 1+1: Bilateral Intrafascial Nerve Sparing; 1+2: Monolateral Intrafascial and Monolateral Interfascial Nerve Sparing; 1+3: Monolateral Intrafascial and Monolateral Extrafascial Nerve Sparing; 2+2: Bilateral Interfascial Nerve Sparing; 2+3: Monolateral Interfascial and Monolateral Extrafascial Nerve Sparing.

The results of the multilevel mixed-effects model evaluating the impact of different treatments on erectile function recovery over time are presented in **Table 4**. Time resulted as a significant factor in erectile function recovery (Beta = 0.39; 95% CI: 0.29-0.49; $p < 0.001$), indicating a positive association between longer time from surgery and improved IIEF-5 scores. Nerve-sparing approach had a mixed impact on erectile function recovery, with bilateral interfascial procedure showing a positive effect (Beta = 1.11; 95% CI: 0.48, 1.5; $p = 0.9$), although not statistically significant; conversely bilateral intrafascial procedures had a significantly positive effect on recovery (Beta = 2.0; 95% CI: 1.48, 3.5; $p = 0.01$). Intrafascial/Extrafascial and Intrafascial/Interfascial approaches showed positive but non-significant effects (Beta = 1.39; 95% CI: 0.9, 1.3; $p = 0.5$ and Beta = 1.43; 95% CI: 0.8, 1.92; $p = 0.8$), . PDE5i + Vacuum therapy at 3 months showed a significant positive effect on recovery (Beta = 2.1; 95% CI: 1.23, 3.9; $p = 0.027$), while neither PDE5i only nor Vacuum only therapies were statistically significant at this time point ($p = 0.2$ and $p = 0.3$, respectively). At 6 months, the only statistically significant therapy was PDE5i + Vacuum, showing a positive effect on erectile function recovery (Beta = 3.0; 95% CI: 1.48, 5.5; $p = 0.019$). Finally, at 12 months, combination therapy (PDE5i + Vacuum) showed a significant positive impact on erectile function recovery (Beta = 5.8; 95% CI: 3.8, 7.8; $p < 0.001$) , while PDE5i only therapy showed a borderline significant positive effect (Beta = 3.1; 95% CI: 0.91, 5.2; $p = 0.05$).

Table 4. Multilevel (mixed-effects) model to evaluate the impact of different treatments on erectile function recovery over time

Variables	Beta	95% CI[1]	p-value
Time	0.39	0.29, 0.49	**<0.001**
Nerve Sparing Approach			
Interfascial/Extrafascial	—	—	
Bilateral Interfascial	1.11	0.48, 1.5	0.9
Bilateral Intrafascial	2.0	1.48, 3.5	**0.01**
Intrafascial/Extrafascial	1.39	0.9, 1.3	0.5
Intrafascial/Interfascial	1.43	0.8, 1.92	0.8
DE Therapy at 3 months			
None	—	—	
PDE5i only	1.85	0.56, 2.3	0.2
Vacuum only	3.0	0.31, 9.1	0.3
PDE5i + Vacuum	2.1	1.23, 3.9	**0.027**
DE Therapy at 6 months			
None	—	—	
PDE5i only	1.0	0.2, 3.2	0.4
Vacuum only	1.0	0.5, 3.5	0.4
PDE5i + Vacuum	3.0	1.48, 5.5	**0.019**
DE Therapy at 12 months			
None	—	—	
PDE5i only	3.1	0.91, 5.2	**0.05**
Vacuum only	-1.9	-4.4, 0.63	0.14
PDE5i + Vacuum	5.8	3.8, 7.8	**<0.001**

Erectile function recovery, as assessed by changes in IIEF-5 scores over time, is presented, stratified by nerve sparing technique in **Figure 1** for patients <65 years and **Figure 2** for patients ≥65 years. At 3 months postoperatively, the median IIEF-5 score was significantly higher in

patients who underwent Bilateral Intrafascial nerve sparing (15, IQR: 10-16) compared to those who received different nerve sparing techniques. By 12 months, erectile function recovery continued to improve across all groups, with a median IIEF-5 score of 21 (IQR: 10-22) in the Bilateral Intrafascial group, while the lowest recovery was observed in the Interfascial/Extrafascial group (15, IQR: 8-19, p=0.025). At 24 months, the majority of patients across all groups achieved significant recovery, with no statistically significant differences in IIEF-5 scores between groups (p=0.11). We observed a tendency, despite non-significant, to a better recovery of IIEF-5 in the Bilateral interfascial cases in the population >65 years.

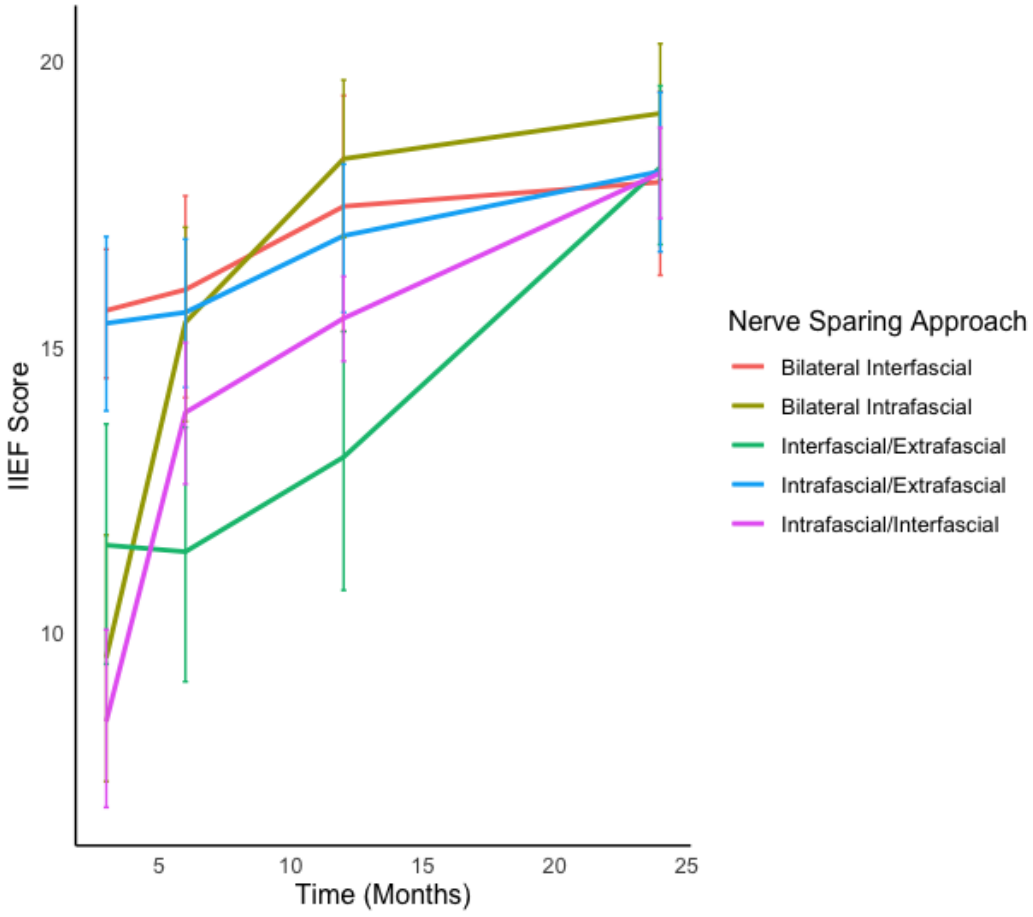

Figure 1. Line plot depicting the IIEF-5 changes over time stratified by nerve sparing technique for patients < 65 years.

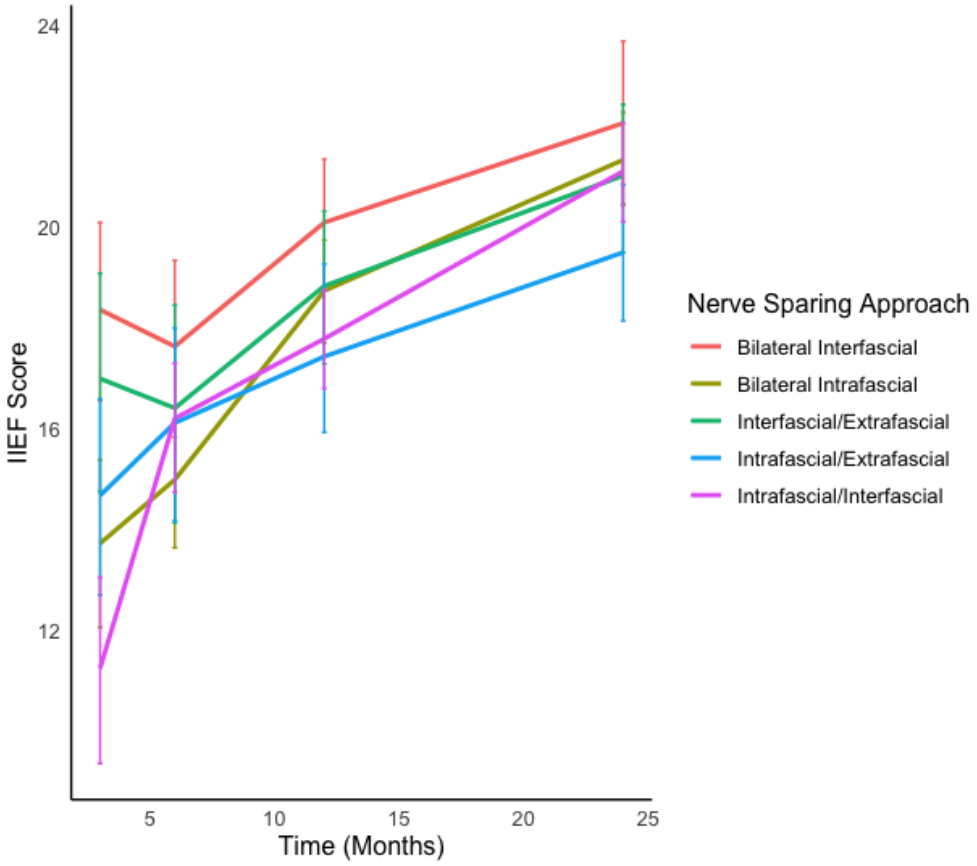

Figure 2. Line plot depicting the IIEF-5 changes over time stratified by nerve sparing technique for patients < 65 years.

Recovery of erectile function stratified by rehabilitation therapy is shown in **Figure 3** for patients <65 years and **Figure 4** for patients >65 years. Patients receiving combined PDE5i and VED therapy demonstrated the highest rates of IIEF-5 score recovery over time compared to those receiving PDE5i alone or VED alone, in both groups below and above 65 years. By 12 months, patients receiving PDE5i + VED achieved a median IIEF-5 score of 21 (IQR: 19-23), while those on PDE5i alone had a median score of 19 (IQR: 15-20, $p<0.001$). A similar trend was observed at 24 months, with patients on combined therapy continuing to show superior recovery ($p=0.03$). The use of ICI, while more frequent in certain nerve-sparing groups at 3 months, showed no significant impact on long-term recovery rates ($p=0.4$).

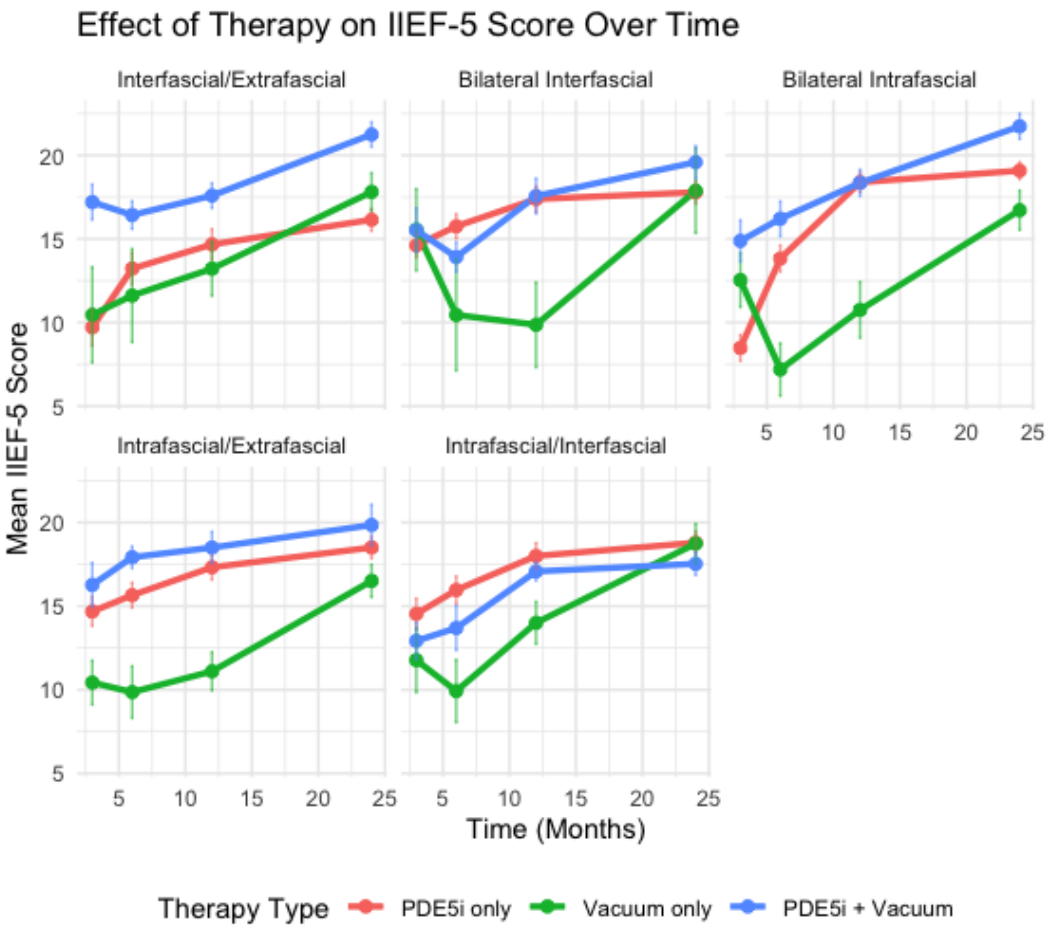

Figure 3. Line plot depicting the Impact of rehabilitative strategies on IIEF-5 over time, according to nerve sparing technique for patients <65 years

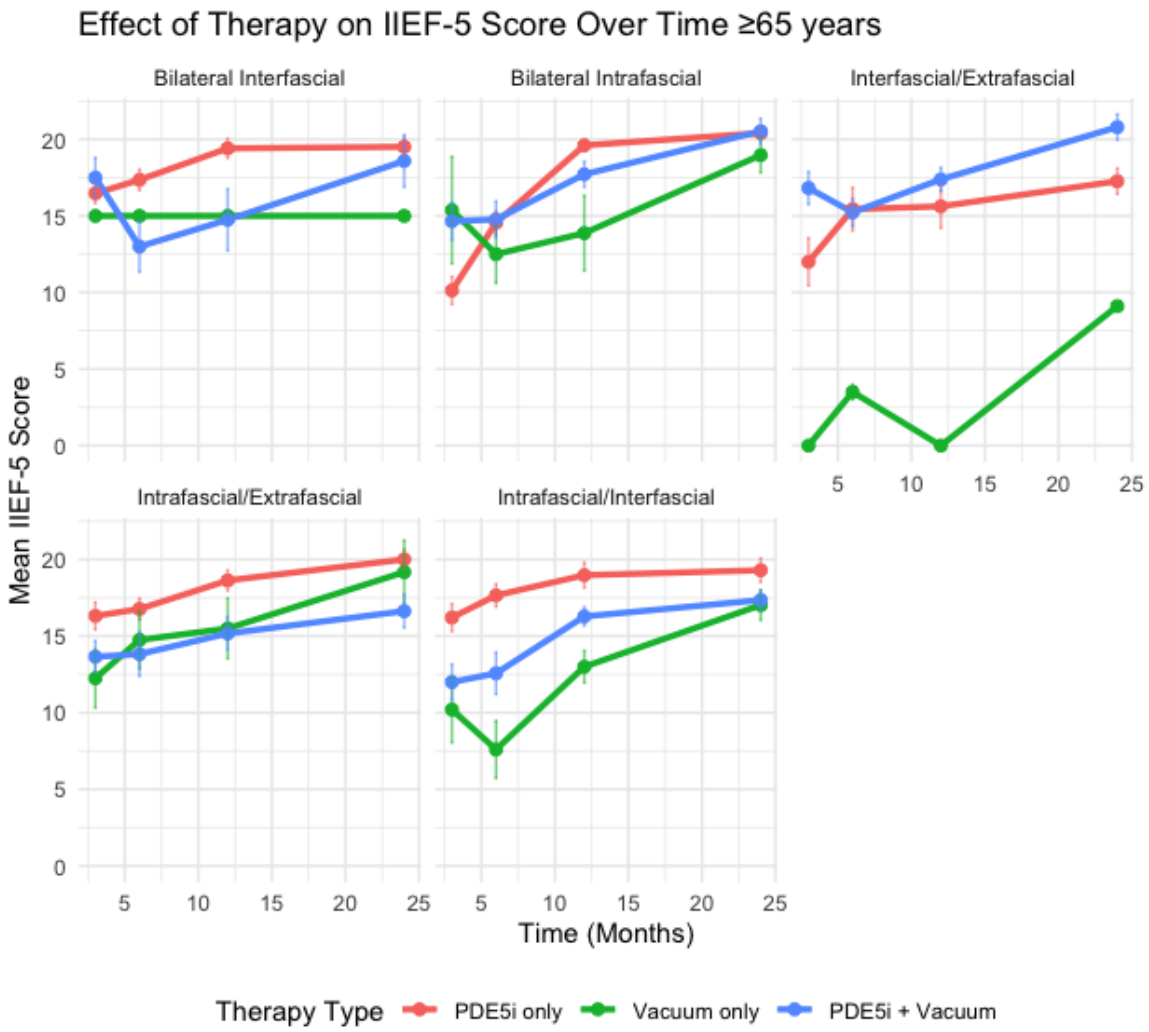

Figure 4. Line plot depicting the Impact of rehabilitative strategies on IIEF-5 over time, according to nerve sparing technique for patients ≥65 years

The results of the Cox proportional hazards model evaluating the time to return to baseline IIEF-5 scores are summarized in **Table 5**. Bilateral intrafascial nerve-sparing techniques were associated with a significantly shorter time to recovery compared to other techniques (HR 3.15, 95% CI: 2.11-4.71, p<0.001). Patients undergoing bilateral interfascial nerve sparing also demonstrated significantly faster recovery compared to patients receiving interfascial/extrafascial or intrafascial/extrafascial techniques (HR 1.49, 95% CI: 0.98-2.24, p=0.059; HR 1.52, 95% CI: 0.99-2.34, p=0.055, respectively). The type of rehabilitation therapy also significantly impacted recovery time. Patients receiving PDE5i + VED had a faster return to baseline erectile function compared to

those receiving no therapy or PDE5i alone (HR 1.56, 95% CI: 1.42-1.76, p<0.001), while the use of VED alone showed no significant effect (p=0.9).

Table 5. Cox proportional hazards model evaluating the impact of different nerve-sparing techniques and rehabilitation therapies on the time to return to baseline IIEF-5

Variables	HR[1]	95% CI[1]	p-value
Nerve sparing technique			
Bilateral Interfascial	—	—	
Bilateral Intrafascial	3.15	2.11, 4.71	**<0.001**
Interfascial/Extrafascial	1.49	0.98, 2.24	0.059
Intrafascial/Extrafascial	1.52	0.99, 2.34	0.055
Intrafascial/Interfascial	2.39	1.57, 3.65	**<0.001**
Therapy at 12 months			
None	—	—	
PDE5i only	1.48	1.37, 1.62	**0.03**
Vacuum only	0.36	0.18, 0.79	0.9
PDE5i + Vacuum	1.56	1.42, 1.76	**<0.001**

[1] HR = Hazard Ratio, CI = Confidence Interval

Kaplan-Meier survival analysis estimating the time for achieving the status of back to baseline IIEF-5 is depicted in **Figure 5**.

For the above 65 group, at 12 months, 37.1% of patients had returned to baseline erectile function, while for the below 65 group 44.1% patients had returned to baseline. At 18 months, 86.1% of older patients had returned to baseline, while all patients <65 had returned to baseline. The median time to recovery across the entire cohort was 11 months (IQR: 4-12). The survival curves indicate a steady recovery over time, with no significant plateau observed within the first 24 months. The log-rank test confirmed statistically significant differences in recovery rates between rehabilitation groups (p<0.001).

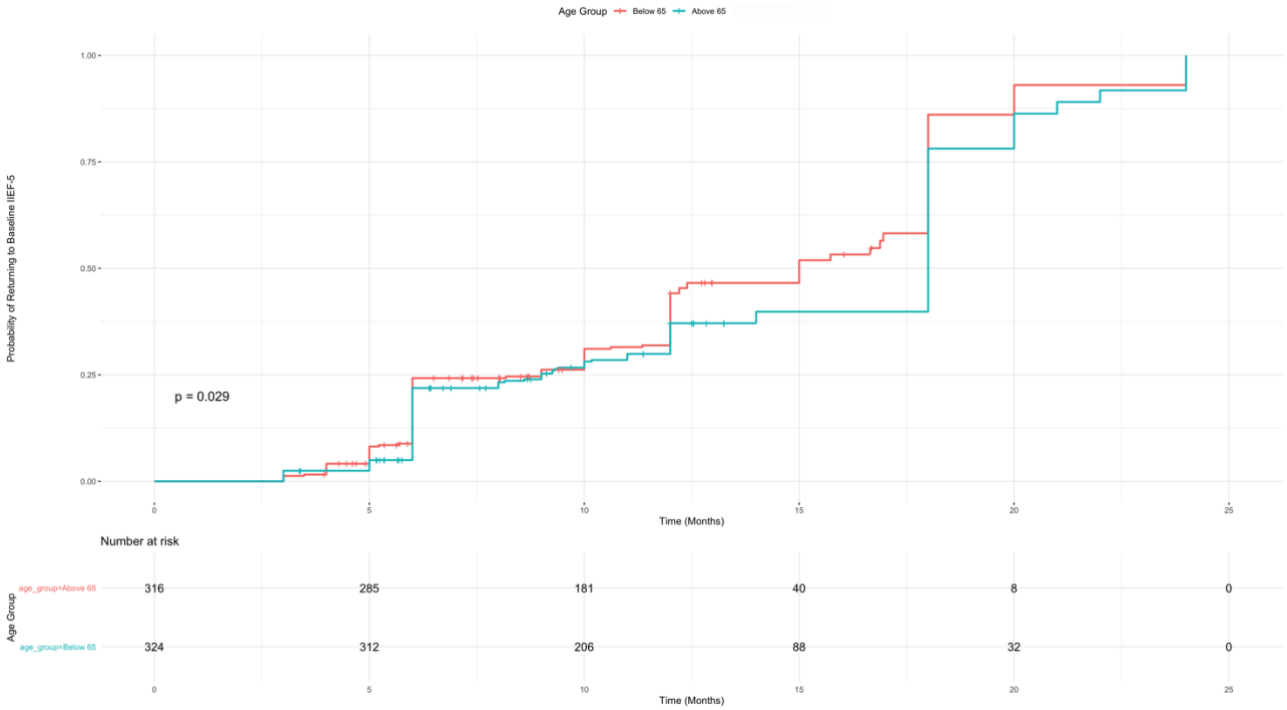

Figure 5. Kaplan-Meier survival curves to visualize recovery patterns of time to return to baseline IIEF-5 scores

A plot of the predicted probability of discontinuation of rehabilitation therapy due to sufficient recovery of erectile function is presented in **Figure 6** for patients <65 years and **Figure 7** for patients ≥65 years. Patients receiving Bilateral intrafascial nerve sparing and PDE5i + VED showed a significantly higher probability of discontinuing therapy due to no longer requiring rehabilitation to achieve sexual intercourse in both groups. The predicted probability of discontinuation at 12 months was 45.1% for the patients <65 years and 38% for patients ≥65 years in the PDE5i + VED group, compared to 30 and 40% in the PDE5i group, respectively (p<0.001). By 24 months, the probability of discontinuation increased further, with 73% of patients <65 in the PDE5i + VED group no longer needing therapy, compared to 59% in the PDE5i-only group (p=0.001).

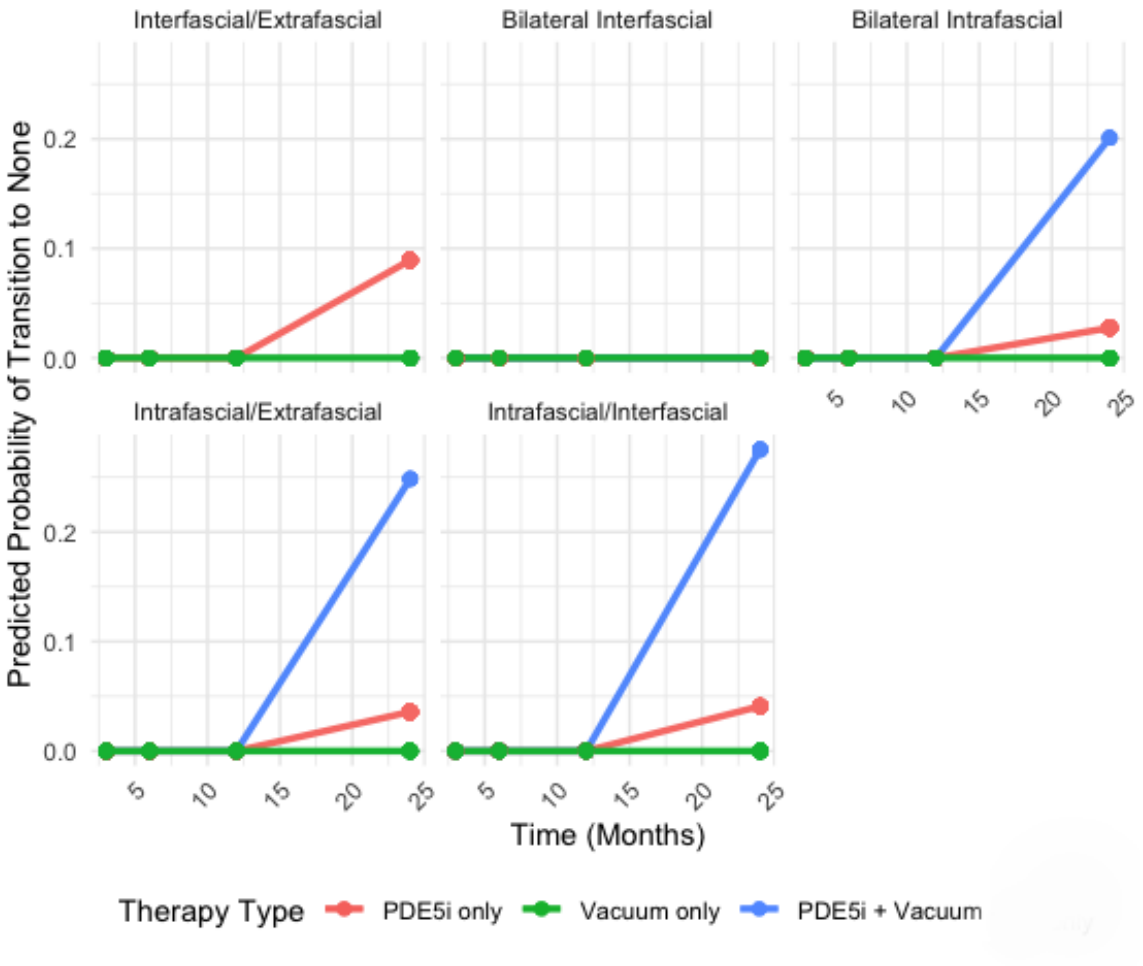

Figure 6. Line plots for predicted probability of no longer needing rehabilitative therapy (phosphodiesterase type 5 inhibitors [PDE5i], vacuum erection devices [VED], or PDE5i + VED) due to successful recovery of erectile function, stratified by nerve sparing technique for patients <65 years

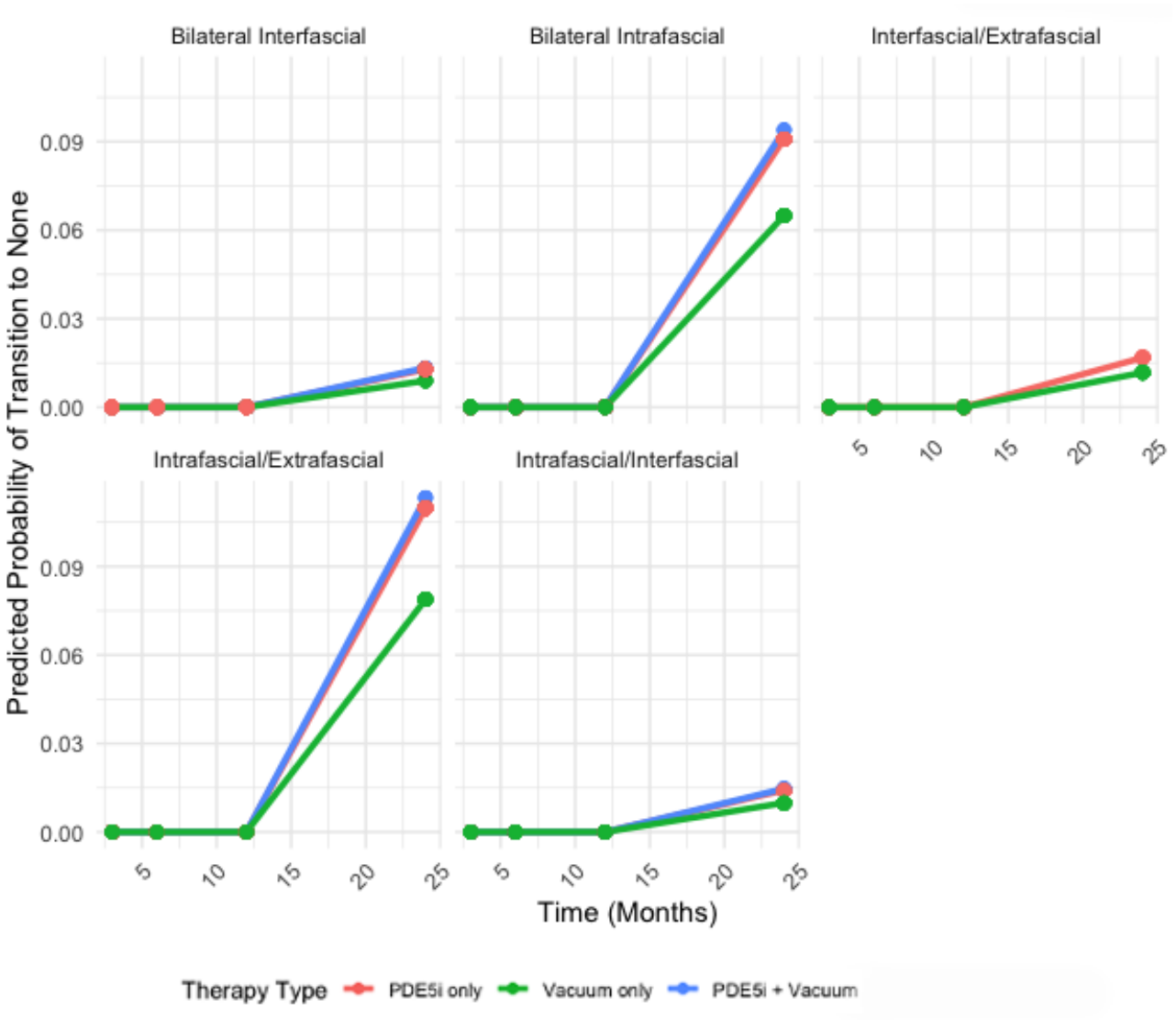

Figure 7. Line plots for predicted probability of no longer needing rehabilitative therapy (phosphodiesterase type 5 inhibitors [PDE5i], vacuum erection devices [VED], or PDE5i + VED) due to successful recovery of erectile function, stratified by nerve sparing technique for patients ≥65 years

For the subset of patients (n=74) who underwent additional psychosexual rehabilitation with a psychosexuologist, improvements in DAS, PCS-12, and MCS-12 scores were observed. At the beginning of rehabilitation, the median DAS score was 112 (IQR: 106-116), and improved significantly to 117 (IQR: 110-121, p<0.001) after 12 months (**Table 6**). Similarly, PCS-12 scores improved from 52 (IQR: 49-54) to 55 (IQR: 49-56, p=0.037), IIEF-15 scores improved from 52 (IQR:37-58) to a median score ore 57 (IQR:48-61, p=0.04), while MCS-12 scores showed no significant change (p=0.5).

Table 6. Changes in Dyadic Adjustment Scale (DAS), Physical Component Summary (PCS-12), and Mental Component Summary (MCS-12) scores before and after psychosexual rehabilitation

Variables	**Time 1**	**Time 2**	**p-value**[2]
DAS	112 (106-116)	117 (110-121)	**<0.001**
PCS-12	52 (49-54)	55 (49-56)	**0.037**
MCS-12	52 (49-54)	53 (48-56)	0.5
IIEF-15	52 (37-58)	57 (48-61)	**0.04**

[1] Median (IQR)
[2] Wilcoxon rank sum test

Regarding mood perception, it emerged that 69.6% of the total patients reported having a good or high mood. Among these patients, 90.6% regained erectile function, and 87.5% resumed post-surgery sexual activity (penetrative or non-penetrative).
Focusing on the recovery of erectile function, 67.4% of the total sample regained erection. Of these patients, 87.1% resumed sexual activity, and 100% demonstrated good compliance with treatments and expressed satisfaction with the rehabilitation process.
Analyzing the couple relationship area, 84.8% of the total patients felt they were in a relationship with a supportive partner. Among these patients, 71.8% resumed sexual activity (penetrative or otherwise).

DISCUSSION

Despite the advances in nerve sparing and minimally invasive radical prostatectomy, ED remains an important adverse event after RARP. To date, guidelines or recommendations from any national urologic organization are lacking, and the best penile rehabilitation strategy remain unclear (52) (53) (54).

Regardless the lack of conclusive data, many authors believe that rehabilitation should be started in the early post-operative phases, based on data suggesting that patients could benefit from a rehabilitative treatment, when compared with the untreated population; indeed, penile rehabilitation could lead to a faster and improved natural erection, preserve sexual activity in those unable to reach an adequate rigidity to complete an intercourse and improve the quality of life of the patient and their psychological recovery after surgery (28).

PDE5is remain the first-choice treatment in EF rehabilitation after pelvic surgery (7) (8) (10) (28), due to its non-invasive nature and due to the proven efficacy in improving the chances to achieve penile rigidity and potential successful sexual intercourse (55); furthermore, preclinical findings suggest that PDE5is could have an important role in endothelial and smooth muscle preservation, neuromodulation and reduction of corporal fibrosis (28). Due to its pharmakocinetic profile and prolonged half-life, tadalafil appear to be the best molecule for rehabilitation (56), especially when administered with higher dosages (57), despite the lack of common agreement on the topic. For these aforementioned reasons, our rehabilitative protocol included tadalafil 20 mg 3 times/week to the patient, ensuring high blood concentration of the molecule and providing the patient with ongoing coverage. Our study provided several noteworthy observations.

First, a frequent issue encountered in rehabilitation after radical prostatectomy is the adherence of the patient to the rehabilitation program, due to treatment effect below expectation, cost of the therapies, cumbersome treatments, psychological factors (10) (58); in our cohort the drop out was about 10%. The low rates of drop-out could be addressed to our dedicated setting and the financial coverage of therapies (PDE5i or Aprostadil), providing an accessible and sustainable supportive care to the

patient, who is competently followed in his sexual recovery. The elevate usage of VED in our cohort may represent another indicator of the high adherence to our rehabilitation protocols. These data suggest that an adequate cost-coverage and the constant referral to andrologists, may encourage patients to continue the rehabilitative course.

Second, as potency rates and erection recovery after RARP can range dramatically depending on the patients pre operative characteristics (16), in our study we considerate only patients with a pre operative normal erectile function or a mild erectile dysfunction, with oncological findings suitable for a nerve sparing surgery.

In our population several factors seem to had a significant influence in erection recovery: nerve sparing technique (bilateral vs unilateral nerve sparing prostatectomy – intrafascial vs interfascial approach), age of the patients at surgery time, rehabilitative therapies employed.

Consistently with data widely available in literature (16) patients who undergone intrafascial bilateral nerve sparing prostatectomy (BNSP) and intrafascial-interfascial BNSP showed a faster and better recovery of IIEF score over the 24 months follow up with a positive association between longer time from surgery and improved IIEF-5 scores, addressing the known issue of post-operative neurapraxia (11) ; as Menon et al reported a 94% potency rate recover in a cohort of young patients with a mean age of 55 years and normal pre operative EF (59), also in our cohort all patients below the median age of 65 yo showed a complete return to the preoperative IIEF score, while older patients reached the baseline only in the 86% of cases despite the use of erection aids. Of note, while the nerve sparing strategy significantly impacted the recovery of younger patients, in the older population we failed to find a significant correlation between nerve sparing strategy and functional recovery indicating no clear advantage of these techniques over others in this cohort; a possible explanation of this results may reside in the presence of other biological factors limiting or impacting the optimal recuperation of these patients, such as unhinged vascularization, weight, body mass index, type 2 diabetes and psychological factors, as suggested by Salonia et al. (60) Also the time of recovery during the follow up resulted significantly faster in the younger group with a

nearly complete return to the baseline ad 12 month follow up. Third, in terms of timing of recovery appears to be a significant correlation between the rehabilitation therapies and the rapidity of return to the baseline. In every step of the short term follow up (at 3, 6 and 12 month) combination therapy PDE5i + Vacuum showed a significant positive effect on recovery appearing beneficial both at the early stage and intermediate follow-up period and keeping a lasting and strong influence on the return to baseline erectile function; conversely neither PDE5i only nor Vacuum only therapies were statistically significant in early stages of follow up and PDE5i only therapy showed a borderline significant positive effect at 24 months follow up. As Rubillotta et al. denoted in a recent survey PDE5i is more used first line treatment in penile rehabilitations among (42), nevertheless combination therapies with PDE5i + VED frequently shown benefits in terms of IIEF score recovery as Qin underlined in his metanalysis associated (61) with other advantages which are not considered in our study such as prevention of penile shrinkage and preservation of penile length. Fourth, the pattern of IIEF score recovery was different in our population according to the age of the patients: in younger patient (<65 yo) the association of PDEi + VED led to faster recovery confirming what suggested by Marchioni et Al. (62), despite the grade of nerve sparing surgery performed; contrarywise in older patients the correlation between association therapy and timing of IIEF score recovery was not significant such as the long term recovery in comparison with other therapies. Combination therapy obviously represent a more aggressive approach in penile rehabilitation, as suggested by Clavel-hernandez and Wang (13) (57) forced oxygenation of corpora cavernosa and penile stretching could somehow increase the role played by PDE5i in the preservation of cavernosa integrity by protecting against structural changes after nerve sparing prostatectomy: probably younger patients with a better preoperative erectile function could benefit more from this kind of therapy since age and better pre operative EF represent independent predictors of postoperative erection recovery [60]. On the other hand, the more common use of ICI in older population may represent the worst response to first line treatments to restore erection function and the higher requirement of drug induced forced erection to achieve an intercourse. Under this standpoint combination therapy may

represent an inadequate forceful approach in certain older patient, requiring an individualized rehabilitation therapy based on preoperative EF, extent of neurovascular bundle (NVB) preservation, and erectile haemodynamic changes after surgery; to reduce the intensity of rehabilitation programs in older patient, as Salonia et al. suggested , should not be seen as a kind of discrimination against some patients but rather a strong awareness by the clinician and the most respectful, and appropriate, form of aid that the patient can receive.

Patient's age appears to represent a discriminant factor in the predicted probability of discontinuation of rehabilitation therapy due to sufficient recovery of erectile function, but in this case there is a strong association also with the surgical technique, as intrafascial NSRP (bilateral and unilateral) showed an higher prediction of natural erection restoration compared to the other groups, Bilateral NSRP showed the best prediction in both younger and older patients; confirming the superiority of potency recovery of this technique as recently highlighted by Weng et al. in their metanalysis (63). If we take in account the rehabilitative therapy received, patients receiving Bilateral intrafascial nerve sparing and PDE5i + VED showed a significantly higher probability of discontinuing therapy in both groups. The predicted probability of discontinuation at 12 months for the patients <65 years and for patients ≥65 years was 45.1% vs 38% in the PDE5i + VED group, compared to 30 vs 40% in the PDE5i group, respectively. By 24 months, the probability of discontinuation increased further only in the patients <65 yo, with 73% in the PDE5i + VED group no longer needing therapy, compared to 59% in the PDE5i-only group. The prediction of natural erection restoration in our series was slightly higher compared the data published By Capogrosso et al. in 2019, that referred a 34% in EF recovery after 24 month follow up in a population of patients undergone BNSRP (lacking pre operative IIEF score) treated with on demand PDE5i as rehabilitation therapy (64). Only in younger patients undergone intrafascial BNSP the potency recovery is approximately comparable to the results reported by Raina and Briganti, which referred respectively a 71% and 72% of potency recovery after a longer period of follow up of 36 months in heterogeneous patients in terms of age and pre operative IIEF score, and undergone nerve sparing prostatectomy treated only with PDE5i in their rehabilitation protocols (32)

(65). Futhermore in our population combination therapy appears to have a strong influence on the outcome of potency restoration over the population treated only with PDEi, especially in younger patients; these findings could be a confirmation of the beneficial effect of association therapy between PDE5i and VED already described by Wang (8) and Basal (66)

For the psycho-sexological evaluation we began by comparing findings from the DAS questionnaire with qualitative data. The couple relationship area, investigated through interviews, confirms the significant increase in overall scores observed in the DAS questionnaire. This suggests, as reported by Noseda in a recent study, that the presence of psychosexual counseling, which also involves the partner, enhances the relational and sexual well-being of the couple (67).

Quantitative data from the PCS-12 scale reveal an improvement in patients' perception of physical health. This lead to the belief that the restoration of erectile function post-surgery and compliance with treatment, bolstered by psychosexual counseling, as suggested by Toccafondi et al. positively influence physical progress and increase the perception of physical well-being (68).

Observing the MCS-12 scale, dedicated to assessing the patient's mental and psychological state, quantitative data did not reveal a significant change. This finding diverges from the authors' expectations that counseling would enhance mental well-being, as proposed by other authors (67) (69). Consequently, the quantitative results were compared with the patient health area, revealing that in the analyzed age group, numerous psycho-social and familial changes may impact the individual's psycho-physical domain.

Specifically, life cycle changes such as caregiving for elderly parents or a partner, bereavement, retirement, caregiving for grandchildren, and supporting children are aspects not captured by the semi-structured interview. These factors are believed to have a strong impact on the individual's

perception of psychological and mental health. Therefore, it would be appropriate to include them in future research.

Despite its noteworthy findings, our study is not devoid of limitations. First, its retrospective design and the inherent related biases. Second, surgeries were performed by several surgeons with different surgical experience, although reflecting the real-life scenario of a high volume Center. As a single-center series, these results may not be generalized to a larger population depending on surgical techniques and management employed. studies involving different institutions are certainly needed to validate our findings.

Third, the financial coverage of the PDE5i provided by our regional health care to the people undergone pelvic surgery, probably lead patients to continue on demand tadalafil assumption even when not needed. Fourth, we did not investigate on other sexual difficulties (impairments of sexual desire, anejaculation, orgasmic troubles, cosmetic alterations) that could impact negatively on patients' intimacy (28) (64). All these issues deserve to be further investigated.

Finally, while we presented a reasonable follow-up period of 2 years after-surgery, it is possible that further improvements in EF could have occurred at later time points, as has been observed by Lee et Al. (70)

CONCLUSIONS

Nowadays, sexual rehabilitation remains a debated topic among urologists and andrologists, with significant heterogeneity in outcomes concerning erectile function (EF) recovery after surgery and inconsistent rehabilitation strategies, reflecting a substantial lack of standardized protocols and guidelines.

Our knowledge is based on reviews that mostly consider research from the last decade, which likely does not fully account for advances in surgical techniques and postoperative management.

To the best of our knowledge, none of the available randomized controlled trials have definitively demonstrated the superiority of a specific PDE5i over others, or the preferability of daily administration of PDE5i compared to on-demand dosing. Furthermore, there is no evidence that combination therapies are more effective than monotherapy in penile rehabilitation. Some authors have suggested that PDE5i therapy after radical prostatectomy might be more beneficial for patients with an intermediate risk of ED after surgery than for younger, healthier patients, who may experience more favorable outcomes in erection restoration regardless of the rehabilitation therapy. However, even in this case, the data are inconclusive (7) (56) (65).

In other words, everything we know about penile rehabilitation after radical prostatectomy is experiential, and the results of various studies are highly heterogeneous and poorly reproducible.

In our experience, gathered over almost 10 years of dedicated clinical practice in an outpatient clinic for functional rehabilitation after pelvic surgery at an academic high-volume center for RARP, which we have synthesized in this paper, combination therapy of tadalafil 20 mg and VED, administered with the aforementioned modalities, demonstrated superiority over tadalafil monotherapy in restoring preoperative IIEF scores and reducing the time required for score restoration.

Since rehabilitation therapy has the secondary goal of preserving sexual activity, and this combination therapy showed the best results not only in restoring natural erections in the long term but also in quickly allowing erectogenic aid-assisted erections in the first months after surgery, every patient could benefit from this therapy, regardless of their risk of postoperative ED, provided the therapy is

effective. For this reason, combination therapy might be considered stressful overtreatment for older or comorbid patients, who are less responsive in terms of erection restoration and may require individualized therapy protocols, including ICI or surgical solutions.

Further prospective studies could help improve patient selection and better define potential outcomes and optimal rehabilitation strategies. Additionally, as other authors have suggested, erectile recovery should not solely emphasize penile function; it should also strive to create a fulfilling and healthy sexual life for both the patient and their partner, irrespective of whether full restoration of spontaneous erection occurs. A biopsychosocial approach that includes clinical sexologists may prove advantageous (13).

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