UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE

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ŞCOALA DOCTORALĂ

UROLOGIE

PENILE REHABILITATION AFTER RADICAL PROSTATECTOMY, MULTIPLE BENEFICIAL EFFECTS

PhD Thesis Summary

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Prostate cancer is the second most common cancer in men. In 2020, according to data from the World Health Organization (WHO) for Romania, out of the total of 53881 cancers diagnosed in men, prostate cancer accounted for 14.9% (8055 cases). As a result of the widespread use of prostate-specific antigen (PSA) and the improvement of diagnostic methods, the proportion of tumors detected at the early stage with intraprostatic localization increased. In the case of localized tumor, the chosen therapy depends not only on the stage of the disease and the risk group, but also on the patient's decision informed in advance on the advantages and disadvantages of various therapeutic methods. Therapeutic possibilities in this situation are external radiation therapy, with or without associated brachytherapy, brachytherapy as the only therapeutic method, radical prostatectomy or active surveillance. Radical prostatectomy has a number of advantages: it offers effective control of cancer in the long term, the prediction of the patient's prognosis is much more accurate because it is based on the result of the histopathological examination, in the same intervention can be performed and lymphodysection of the pelvic nodules when necessary, the biochemical recurrence after radical prostatectomy is easy to identify.

However, radical prostatectomy has an increased risk of erectile dysfunction, a risk of morbidity correlated with surgery, and there is also a risk of long-term urinary incontinence.

In the modern era of early diagnosis of prostate cancer, which allows the use of radical prostatectomy as a treatment with curative intent, postoperative erectile dysfunction has become a very important topic. Because the harmony of sexual life is one of the guarantees of a couple's stability. The patient's quality of life, the deterioration of couple relationships, divorce, adultery/cohabitation, leaving the family are social consequences of a deficient sexuality. According to the SHOW (Sexual Health and Overall Wellness) study conducted in Europe and the Middle East by administering a questionnaire to 3780 people, of which 1893 men (average age 44.6 years) and 1887 women (average age 44.2 years) aspects of sexual life are considered essential / very important both by men and women. Moreover, both partners believe that sexual satisfaction impacts balance in life, relationships and good living in general. The recovery of erectile function is therefore becoming an important and very actual topic.

Penile rehabilitation is defined as the use of any drug or device at the time or after radical prostatectomy with the aim of maximizing the recovery of erectile function. It aims

to prevent structural changes in the smooth muscle of the corpus cavernosum not only to increase the chance of recovery of postoperative erectile function, but also to try to return to the functional level from the preoperative, from the point of view of sexual life.

Studies conducted on both men and animals support the idea that the use of phosphodiesterase 5 inhibitors (PDE5), as well as an early return to sexual activity, can be a strategy for recovering erectile function. In addition to PDE 5 inhibitors, penile rehabilitation therapy includes intracavernous injections, vacuum devices, administration of topical/intraurethral alprostadil, vibration stimulation of the penile nerve, treatment with low-intensity shock waves (LiESWT) or combinations of these treatments. The magnitude of this recovery is not yet very clear.

Unfortunately, penile rehabilitation is in 2022 a topic as new, important and current as in 2015, when I started my PhD thesis. Radical prostatectomy is the treatment of choice of clinically localized prostate cancer with excellent oncological results. Although great progress has been made both in understanding the local anatomy and in the surgical approach (laparoscopic surgery is no longer the only minimally invasive option because robotic surgery is becoming increasingly available in our country as well), the rate of postoperative erectile dysfunction severely impacts the quality of life of patients. Current studies report a rate of postoperative erectile dysfunction between 19 and 78%. This large range of results is linked to different ways in defining postoperative erectile dysfunction (AE) as well as large differences in the characteristics of the patients included in the studies. Thanks to these things together with Professor Dan Mischianu, we thought of the design of our study as having the starting point of the erectile function of the patient from the preoperative. We are not interested in how good or how bad it is, but we are interested in how many of the patients who have undergone penile rehabilitation treatment will return to preoperative erectile function, regardless of its quality.

Both the European Association of Urology (UAE) and the American Association of Urology (AUA) and the European Society of Sexuality Medicine (ESSM) do not have clear recommendations on penile rehabilitation treatment, so the choice of treatment in the studies that are the subject of the thesis was based on data from the literature, but also on personal experience. Together with Professor Dan Mischianu, PhD, we decided that a group of patients should undergo treatment with tadalafil 5 mg daily, and the other group should be treated as a combination therapy. So the next question was what our choice for combination

therapy would be. At the beginning of 2014, Vitaros, alprostadil cream, appeared in Romania for the treatment of erectile dysfunction. Although the literature included several studies related to the effectiveness of alprostadil treatment in intraurethral administration for erectile dysfunction in general, the number of studies in which this type of treatment was used to treat erectile dysfunction occurring after radical prostatectomy was and still is extremely small (two studies, one with Vitaros administered after robotic prostatectomy without preservation of neurovascular bands and another using alprostadil gel with intraurethral administration versus sildenafil citrate daily, for 9 months). On the other hand, the mechanism of action locally, independent of the state of the erector nerves and the lack of systemic side effects seemed to make it a good choice for this type of patients. So, one group of patients followed tadalafil treatment 5 mg daily, and the other batch of tadalafil treatment 5 mg daily to which we added Vitaros when needed, 5-10 minutes before sexual intercourse, no more than once a day and a maximum of 3 times a week. The frequency limitations of sexual contact imposed by this association were not a problem from the point of view of the average age of the group of patients (66 years).

Penile rehabilitation treatment remains a current theme because damage to neurovascular bands (responsible for postoperative DE) cannot be avoided completely even if we use the best preservation techniques.

The doctoral thesis is divided into two chapters, the general part and the special part (personal contribution).

The general part comprises 6 subchapters: surgical anatomy of the prostate, erection physiology, epidemiology and etiology of prostate cancer, epidemiology and risk factors of erectile dysfunction, diagnosis and investigations into erectile dysfunction, and therapeutic options in penile rehabilitation.

From the epidemiological data presented in the general part, we noted that in Romania prostate cancer was the 4th malignancy diagnosed in 2020, with 8055 cases diagnosed at national level (representing 8.1% of cancer cases), and in men it is the 2nd type of cancer diagnosed, after lung cancer, representing 14.9% of cases. The average age of diagnosis is 41.5 years, and the mortality rate from prostate cancer was, also in 2020, 4.5%. Over the years, although the incidence of prostate cancer in Romania has been lower than in Western European countries, it has been possible to notice an increase in the mortality rate

through this form of neoplasia. This can be explained by the ratio between the rate of screening for prostate cancer and the therapeutic solutions adapted to each diagnosed tumor stage as well as by the predisposing factors for this type of cancer.

Regarding the etiological factors, it is considered that the carcinogenic process that determines the appearance of prostate cancer is based on three documented risk factors: aging, ethnic origin and heredity. But besides these, there are a multitude of factors whose role is secondary or partially understood in the pathogenesis of prostate cancer: obesity, smoking, alcohol consumption, environmental factors and dietary factors, androgen hormone levels and sexual activity.

Almost 45% of patients diagnosed with prostate cancer will be treated surgically. The use of techniques for the preservation of neurovascular strips has led to a decrease in the rate of postoperative erectile dysfunction as well as a better recovery of erectile function following penile rehabilitation treatment. Erectile dysfunction after radical prostatectomy is due to nerve lesions produced during surgery. This is due to the fact that any surgical technique, including the one that preserves the neurovascular strips, involves the manipulation and traction of the nerves that can cause varying degrees of erectile dysfunction.

Several ways to achieve penile rehabilitation are described. The basis of treatment is the use of phosphodiesterase 5 (iPDE5) inhibitors alone or in combination with other therapeutic options. These methods are represented by alprostadil therapy administered as intracavernous injections (alone or in combination with phentolamine) or gel / cream, vacuum devices, penile vibration stimulators.

A newer method is LiESWT (low intensity shock wave therapy). This is considered a possible option of penile rehabilitation treatment. The mechanism of action seems to be the stimulation of Schwann cells that form the Schwann sheath of the axon [5]. The importance of the pelvic floor in the sexual function of men is also known, that’s why it can be considered that pelvic floor rehabilitation exercises could help in the recovery of sexual function after radical prostatectomy [6]. Other ways of penile rehabilitation after radical prostatectomy may include hyperbaric oxygen therapy, aerobic exercise, and psychotherapy. Penile prosthesis can be used as a last resort to treat erectile dysfunction, including in patients with radical prostatectomy.

Regarding the use of phosphodiesterase 5 inhibitors for the treatment of penile rehabilitation, to date, clinical studies have reached a number of conclusions. Comparing the results of daily tadalafil treatment with on-demand tadalafil treatment, statistically significant differences were found. From the data we have so far we cannot support the inferiority of daily tadalafil treatment versus tadalafil on demand. Vardenafil treatment as needed had good results, and daily use did not prove superior in vardenafil either. Sildenafil used daily showed a positive effect on erectile function and in one study a shorter return time to spontaneous erections. All PDE5 inhibitors have shown beneficial effects on sexual satisfaction and especially tadalafil in daily use has increased the quality of sexual intercourse.

Intraurethral alprostadil appears to have similar beneficial effects to daily administration of sildenafil, but the evidence needs to be improved. There are few studies in the literature on the use of alprostadil cream / intraurethral, either alone or in combination treatment.

Penile rehabilitation is a necessity for sexually active patients who want to continue their sexual life after surgery for prostate cancer. In the ProtecT (Prostate Testing for Cancer and Treatment) study, 1643 men aged 50 to 69 diagnosed with prostate cancer were randomized to radical prostatectomy, active surveillance and radiation therapy. In the prostatectomy group, the rate of normal erectile function decreased from 67% preoperatively to 12% at 6 months postoperatively. Thus at 6 months postoperatively only 12% of patients could get an erection sufficient to have sexual contact, this being the definition of erectile function accepted in the study. Moreover, erectile function did not subsequently improve in patients in the radical prostatectomy group. This study highlights once again the importance of penile rehabilitation, in an attempt to improve the quality of life of patients and their partners.

Knowing the pathophysiological mechanism of the installation of erectile dysfunction in this kind of patients, we understood that the rehabilitation treatment must be started as early as possible. Some authors are even recommending that it should start immediately post surgical intervention. In open surgery patients, we suppressed the urethrovesical catheter after 21 days, and in laparoscopically operated patients after 14 days. We wanted treatment to be started in all patients at the same time, regardless of the type of intervention, and we also wanted a time interval that was not very long, but long enough that the patient can try to have some sexual contact attempts in the postoperative period, until the rehabilitation treatment begins. For this reason, I established together with Professor Dr. Dan

Mischianu the design of the study, so that the second visit will be one month postoperatively, this being the moment from which the patient will begin the penile rehabilitation treatment. Visit III was scheduled after 3 months of treatment and visit IV, the final one, after 6 months of treatment.

We included 111 patients in our study, 56 in treatment with tadalafil 5 mg daily and 55 in combination treatment, tadalafil 5mg daily combined with Vitaros cream as needed.

Visit I, which was done before surgical intervention, was the most complex. Patient's age, disease stage, risk group, associated comorbidities, life quality, and preoperative PSA value were quantified (if patients had multiple PSA determinations, the highest value was considered). The type of surgery was proposed to the patient, and erectile function was assessed using the IIEF5 questionnaire (the first 5 questions in the International Index for Erectile Function) / SHIM (Sexual Health Inventory for Men, questionnaire, has the same content as IIEF5). Visit II, one month after surgery, assessed the value of postoperative PSA as well as the presence and degree of postoperative erectile dysfunction. Also, during this visit the treatment to be followed and the route of administration was established together with the patient. Treatment began with this visit. The third visit, after 3 months of treatment, assessed the value of PSA, the degree of erectile dysfunction by completing the SHIM questionnaire and established the continuation of the same treatment for up to 6 months. Visit IV, after 6 months of treatment, was the final evaluation of the study and included the determination of the PSA value and the completion of the SHIM questionnaire in order to assess erectile function at the end of the study period.

The objectives established in the doctoral thesis were pursued by performing 4 studies:

- Study I: Identifying current therapeutic strategies for penile rehabilitation treatment - extensive literature evaluation and meta-analysis
- Study II: Efficacy of monotherapy (tadalafil 5 mg daily) versus combination therapy (tadalafil 5 mg daily plus Vitaros cream as needed) in penile rehabilitation treatment. It is the most important study of the doctoral thesis and it evaluates the recovery of sexual function in surgically treated patients with prostate cancer by using the combined treatment (tadalafil 5 mg daily combined with Vitaros cream), as needed. It also compares the effectiveness of combination therapy versus tadalafil 5 mg monotherapy daily.
- Study III: Impact of the type of surgery (open vs. laparoscopic, with or without preservation of uni / bilateral neurovascular strips) on sexual life.
- Study IV: The impact of comorbidities, stage and risk group on penile rehabilitation.

Study no. I: IDENTIFYING CURRENT THERAPEUTIC STRATEGIES FOR PENILE REHABILITATION- EXTENSIVE LITERATURE EVALUATION AND METANALYSIS

The evaluation involved the systematic literature review and collection of randomized clinical trial data that included patients with prostate cancer and who reported erectile dysfunction after radical prostatectomy. Studies published in the last five years have been selected. The PubMed and ScienceDirect international databases were used to identify them.

The first aspect considered for meta-analysis was the identification of placebo-controlled randomized clinical trials or retrospective trials that included patients with localized prostate cancer and who benefited from radical prostatectomy with preservation of neurovascular bundles but who developed postoperative erectile dysfunction. The key aspect of the research was represented by the penile rehabilitation strategy including the therapeutic measures used to recover sexual function. Also, the duration of the treatment that was used was taken into account. Other followed aspects were the evaluation methods of erectile dysfunction, the surgical techniques used and their degree of invasiveness as well as the therapeutic success rate related to the severity of ED.

The evaluation was conducted over a period of 5 years, between January 2014 and December 2018. Publications obtained byb searching both abovementioned databases led to the identification and revision of a number of six hundred and thirty-one articles published on this topic. In order to be more efficient from the point of view of the initial working time, only the title and the abstract of each article were evaluated and thus, only the articles that met the initially imposed criteria were selected. Review articles, meta-analyzes, and those discussing erectile dysfunction unrelated to prostatectomy for prostate cancer were excluded. The number of publications was thus reduced from 631 to 194. The next selection sought to exclude trials withdrawn from databases due to various causes or articles that did not discuss the therapeutic methods used to improve ED. This reduced the number to 15 items that met the proposed criteria. Of these, seven were randomized clinical trials, two of which were double-blind and placebo-controlled. Two others were non-randomized prospective clinical trials and the remaining six articles included retrospective evaluations. Although some of the identified studies looked at both erectile dysfunction and urinary incontinence issues, the focus of this research as well as the data collected were strictly on ED issues.

Although we identified a rather small heterogeneity in the design of the included studies, we were able to find important data related to the recovery of sexual function. All these data allowed the inclusion of the respective studies in subgroups in order to analyze them.

In order to perform the statistical analysis we used the ReviewManager 5.3 programs and the Microsoft Excel software.

The fifteen selected clinical trials for analysis enrolled a significant number of 11,831 patients. The average age was 61.91 years with limits between 54 and 67.9 years. Despite the fact that not all studies specifically mentioned the most common comorbidities encountered, data could still be selected. Thus, on the first place was the cardiovascular disease (with a variation between 37.5 and 100%) followed on the second place by diabetes (with a variation between 6.2 and 16.07%).

All included patieents underwent various forms of radical prostatectomy: open surgery (n = 4460), conventional laparoscopy (n = 1371) or robotic-assisted laparoscopic prostatectomy (n = 4929). In most patients, representing 63.68% of the total, radical prostatectomy was performed with the preservation of bilateral neurovascular bundles (n = 6852) by known technical procedures (interfascial or intrafascial). When the patient's condition did not require dissection of the neurovascular bundles, unilateral preservation techniques were used. This fact was identified in 3209 patients representing approximately 29.82% of operated patients. In the remaining 6.5% of patients, either the strip preservation procedure was not performed or information on its status was not mentioned. It has to be mentioned thet whether or not to perform the procedure with the preservation of neurovascular bundles is crucial because this aspect provides the premises for the rehabilitation of postoperative erectile dysfunction even if most patients will experience postoperative neuropraxia.

The IIEF questionnaire (The International Index of Erectile Function Questionnaire) was the most chosen in order to evaluate the erectile function pre and postoperatively. Different forms of it were used, the classic one with fifteen IIEF-EF questions or the shorter version IIEF-5 / IIEF-6. Due to the acquired credibility as well as the quick way to determine the status of the erectile function, most authors preferred the variant of the five-question IIEF-5 questionnaire. This is equivalent to the SHIM questionnaire, which we used in our study. Most studies that used IIEFs set a limit value of 22 points for men considered potent

preoperatively, and the rest of the studies used close limit values. Only two of the identified studies used other ways to assess erectile dysfunction.

The most common method for penile rehabilitation was the administration of a phosphodiesterase 5 inhibitor. Various ways of administration were used such as several doses which were compared in the control arm with either placebo or the complete absence of any treatment. The most commonly found drug in the clinical trials that were included in this study was Tadalafil, followed by Sildenafil and Vardenafil. PDE5 inhibitors have been used alone or in combination with PGE1 (intracavernous or intraurethral/topical administration), vacuum devices, vibration penile stimulation devices (PVS). There are no comparative studies between the action of two PDE5 inhibitors.

It should be mentioned that, although the articles introduced in our meta-analysis had criteria for inclusion and design of different studies, we were able to identify similarities between some of them, which allowed me to organize them into trial subgroups. In the multivariate analysis we included trials in which the PDE5 inhibitor was administered once daily and on-demand administration (PRN) was compared with the placebo group. The variables included in the analysis were the mean IIEF scores recorded at the end of the study for each group (once daily administration, on request and the control group). As can be seen in Figure 1, the highest rehabilitation rates were in favor of the group in which the PDI5 inhibitor was administered once daily compared to the control group (95% CI, $p < 0.0001$). On a smaller scale, the same result could be observed when daily PDE5i treatment was compared with on-demand administration - it should be noted, however, that only two of the identified studies had sufficient data to be included (95% CI, $P = 0.48$). Studies in which only the percentage of patients presenting with rehabilitation after iPDE5 administration was reported were compared by a univariate analysis.

Penile rehabilitation is a combination of therapeutic measures that include medication, medical devices, or medical activities, used separately or together in various combinations. Phosphodiesterase 5 (iPDE5) inhibitors are the most widely used therapeutic class in current clinical practice for penile rehabilitation and are currently the most studied therapeutic method administered to patients with erectile dysfunction. The main advantage of this therapy is that it is administered easily and quickly, however it should be noted that in order to be effective it requires the integrity of at least one cavernous nerve branch. Also, the cost of treatment as well as the possible side effects (headache, hot flashes, palpitations,

risk of acute coronary syndrome, hypotension) are not aspects that can be neglected. Regarding the choice of the PDE5 inhibitor type, there are currently no specific clinical trials comparing the efficacy of the various products available in patients with postoperative erectile dysfunction. In an open, randomized clinical trial conducted in 2005, Eardley et al. showed that tadalafil is the preferred phosphodiesterase 5 inhibitor for the treatment of erectile dysfunction due to its prolonged effect compared to sildenafil. This seems to be associated with less concern for patients regarding the spontaneity of the erection.

Intracavernous injections of prostaglandin E1 (PGE1 ICI), introduced and studied by Professor Montorsi et al. were the first type of therapy used to recover postoperative erectile function. The most important advantage of PGE1 ICI treatment is that it is very effective in any type of surgical approach, even if preservation of the nerve bundles has not been indicated. On the other hand, the cost, the need to refrigerate the product, the degree of invasiveness of the approach, the relative difficulty of administration as well as the possible side effects, are major factors that counterbalance the choice of such an approach.

Vacuum or vibration technology medical devices are non-invasive and highly effective options for the rehabilitation of erectile function especially when combined with phosphodiesterase inhibitors5.

Regarding the time of initiation of treatment, it has been shown that initiating penile rehabilitation as early as possible after surgery, even immediately after removal of the bladder catheter, has better recovery results than delayed initiation of postoperative treatment.

Study no. II: EFFECTIVENESS OF MONOTHERAPY (TADALAFIL 5 MG, DAILY) VERSUS COMBINED THERAPY (TADALAFIL 5 MG DAILY ASSOCIATED WITH VITAROS CREAM AS NEEDED) IN PENINE REHABILITATION TREATMENT

Between December 2015 and January 2020, we performed a prospective, non-randomized, interventional study in which we enrolled a number of 111 patients diagnosed with prostate cancer who subsequently benefited from radical prostatectomy. Patients were evaluated and stadialisation was performed by using the D'Amico score based on PSA values, MRI imaging results, and the Gleason score obtained from prostate biopsy puncture.

All patients received surgical treatment. Of these, 52 (46.8%) benefited from radical prostatectomy by open retropubic approach (PRR) and 59 patients (53.2%), respectively, benefited from laparoscopic radical prostatectomy (PRL). The surgical approach as well as the decision to preserve the neurovascular bundles were decided taking into account individual cancer stage, surgical risk and oncological safety. Preservation of neurovascular bundles was performed in 80 patients, respectively 72.1% of the group. The other 31 patients, respectively 27.9% of the patients did not benefit from the preservation of the neurovascular bundles. Bilateral preservation of neurovascular bundles was possible for 30 patients (27.9%), the other 50 (45%), respectively, benefited from unilateral preservation. All procedures were performed during surgery and followed the basic principles of preserving the neurovascular bundles by using as little electrocautery as possible for both dissection and hemostasis.

In order to analyse sexual function of the patients, we used throughout the study the questionnaire SHIM (Sexual Health Inventory for Men) translated into Romanian. Testing the integrity of the SHIM questionnaire, responses provided a Cronbach Alpha value of 0.87, 0.875, 0.945 and 0.959 for the preoperative, postoperative DE assessment at 3 months and 6 months, respectively. (over 0.7 is considered a good value) - ie there are no discrepancies in the answers given by patients to the questionnaire questions. For this study we used 4 SHIM evaluations, ie during each visit: preoperative, postoperative, at 3 and 6 months of treatment, respectively. Using these data we evaluated the difference between the preoperative and the postoperative result, thus obtaining the evaluation of the postoperative erectile dysfunction. Two treatment options were recommended to patients included in our study: Tadalafil 5 mg /day and Tadalafil 5 mg/day combined with Alprostadil cream. Patients were randomized according to the order of enrollment in the study. The first patient received Tadalfil 5 mg daily and the next received the combination of the 2 substances and so on. Follow-up assessed the recovery of preoperative erectile function after 3 and 6 months of treatment, respectively.

Data obtained during the 6-month study period were analyzed using SPSS V25 (IBM SPSS, Chicago IL, USA) and Analyze-it V5.4 (Analyze-it Software, Leeds, UK). Unevenly distributed data were analyzed as medians and differences in quantitative parameters were assessed using non-parametric tests. The differences between the semiquantitative variables were evaluated using the Mann-Whitney U test. The risk factors of the primary and secondary variables (favorable evolution at 6 months) were evaluated using logical

regression models, the results being expressed in relative risk (OR) with confidence intervals. of 95%. If the p value was below 0.05 in the univariate analysis the predictor was included in the multivariable logical regression model.

To see the evolution of sexual function after treatment (monotherapy or combination therapy) 2 evaluations were performed, one at 3 months and another at 6 months after starting treatment with Tadalafil 5 mg daily or with Tadalafil 5 mg daily + Alprostadil cream as needed.

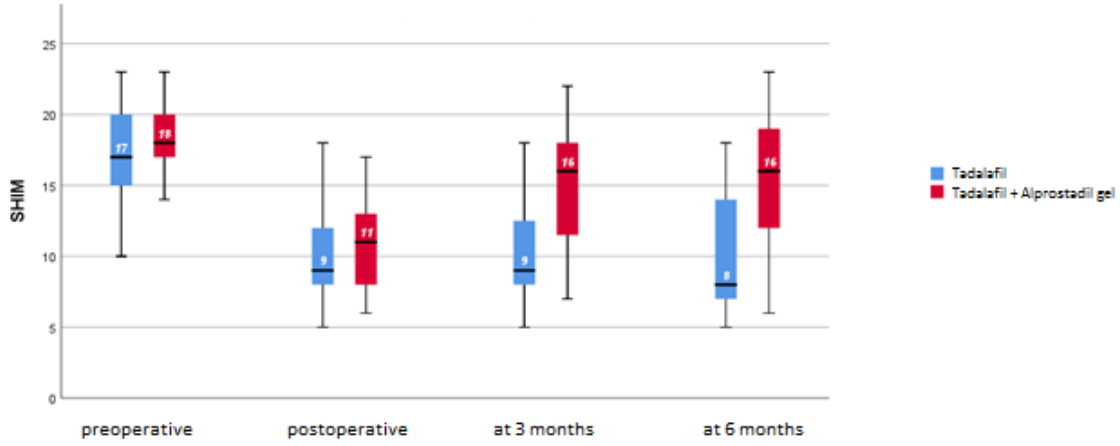
The results at 3 months were promising for patients in the Tadalafil + Aprostadil combination group. These patients obtained a SHIM score of 16 points increasing from 11 compared to the group treated with Tadalafil alone where the value remained at 9 points. This value was similar to the postoperative evaluation ($p < 0.001$, Mann-Whitney U test).

One patient in the Tadalafil and Alprostadil group reported normal erectile function at 3 months. We also found an overall improvement in erectile function with an increase in the percentage of patients with mild and moderate-mild forms compared to postoperative evaluation.

At 6 months we found an improvement in the SHIM score in the whole group (13 compared to 12 every 3 months and 10 postoperatively). Surprising results were obtained in the batch analysis. The mean SHIM score of patients treated with Tadalfil 5mg monotherapy decreased to 8 points compared with 9 points at 3 months. The mean SHIM score of patients treated with Tadalafil and Alprostadil remained constant at 16 points ($p < 0.001$, Mann-Whitney U test). The percentage of mild to moderate ED decreased in the Tadalafil group compared to the 3-month assessment (17.86% vs 25%; 35.72% vs 48.22%) but there was also an increase in mild ED. The percentage of severe erectile dysfunction also increased from 19.64% to 33.92% despite treatment with 5 phosphodiesterase inhibitors.

At the end of the 6-month study period, we found that a number of 37 patients representing 33.3% of the total recovered erectile function at the preoperative level. Of these, 31 patients were part of the group treated with the combination of Tadalafil + Alprostadil, while in the group treated only with Tadalafil only 6 patients recovered erectile function compared to its preoperative level ($p < 0.001$, Mann-Whitney U test).

The figure below shows the evolution of the SHIM score for the two treatment groups.



Given the results of the study we can say that the combination of Tadalafil 5 mg daily with Alprostadil cream when needed can increase the chance of recovering erectile function up to 10 times. The functional results are also influenced by the technique of preserving the neurovascular bundles, atherosclerosis, obesity, depression, smoking, etc.

We observed that there was a selection bias, patients selected for treatment with Tadalafil and Alprostadil had fewer comorbidities, had a lower risk score and were more likely to benefit from laparoscopic surgery compared to the group of patients treated with Tadalafil. Also, the preservation of uni- or bilateral neurovascular bundles was more frequently performed in the combined treatment group.

The results obtained at 6 months were processed in a multivariable analysis in which we included other parameters with probable impact on sexual function such as: comorbidities, local stage of the disease, risk classification, chosen surgical technique and the status of preservation of neurovascular bundles.

Following the multivariable analysis, we found that the combined treatment with Tadalafil 5mg daily plus with Alprostadil gel, if necessary, after radical prostatectomy increases the chance of recovery of erectile function at levels similar to preoperative. (OR: 3.55; 95% CI: 1,465-8.63).

Study No. III: IMPACT OF THE TYPE OF SURGERY (OPEN VS. LAPAROSCOPIC, WITH / WITHOUT PRESERVATION OF UNI / BILATERAL NEUROVASCULAR BANDS) ON SEXUAL LIFE

All 111 patients who completed our study (out of the 130 initially included) were surgically treated. 52 (46.8%) of them had retropubic radical prostatectomy while for the remaining 59 patients (53.2%) laparoscopic treatment by properitoneal approach (LARP) was performed.

Our group of patients is divided into 2 groups, namely the group of classically operated patients and that of laparoscopically operated patients. Each category is described by several factors, namely age, local tumor stage, risk group, type of preservation of neurovascular strips, Gleason score, preoperative PSA and score obtained by completing the SHIM questionnaire.

The type of surgery and the decision to preserve or not the neurovascular bandages (NVB) were chosen according to the risk group of each patient, respecting the oncological limits. Preservation of neurovascular bundles was performed in 80 patients (72.1%), while for the remaining 31 patients (27.9%) this was not possible due to oncological reasons, so, radical prostatectomy was performed without preserving them.

Bilateral preservation of NVB was performed in 30 patients (27.9%), for 7 cases (13.5%) this was done by open surgery (RRP), and for 23 cases (39%) it was performed by using laparoscopic surgery. For 50 patients (45%) the preservation of NVB was done unilaterally. In 22 of the cases (42.3%) the intervention was RRP and in 28 cases (47.5%) the intervention was performed laparoscopically. All NVB preservation maneuvers were performed intraoperatively respecting the specific preservation principles and trying to perform dissection and hemostasis without using the cauter.

Regarding the characteristics of the two groups, the one of the patients who underwent open surgery, RRP and the other of patients who underwent laparoscopic intervention (LARP), we would also mention that mean age of RRP group is 68 years while for LARP group is 64. The local tumor stage in the RRP group is T2a in 2 patients (3.8%), T2b in 8 patients (15.4%) and T2c in 42 patients (80.8%). In the LARP group, the distribution of patients according to the stage of the disease is different, 13 patients with T2a (22%), 23 patients (39%) with T2b and 23 patients (39%) with T2c.

Analyzing the distribution of patients according to the tumoral risk group, we found out that for the patients who underwent RRP, two of them, representing 3.8%, are in the low risk group, 8 (15.4%) in the medium risk group and 42 patients (80.8 %) in the high risk

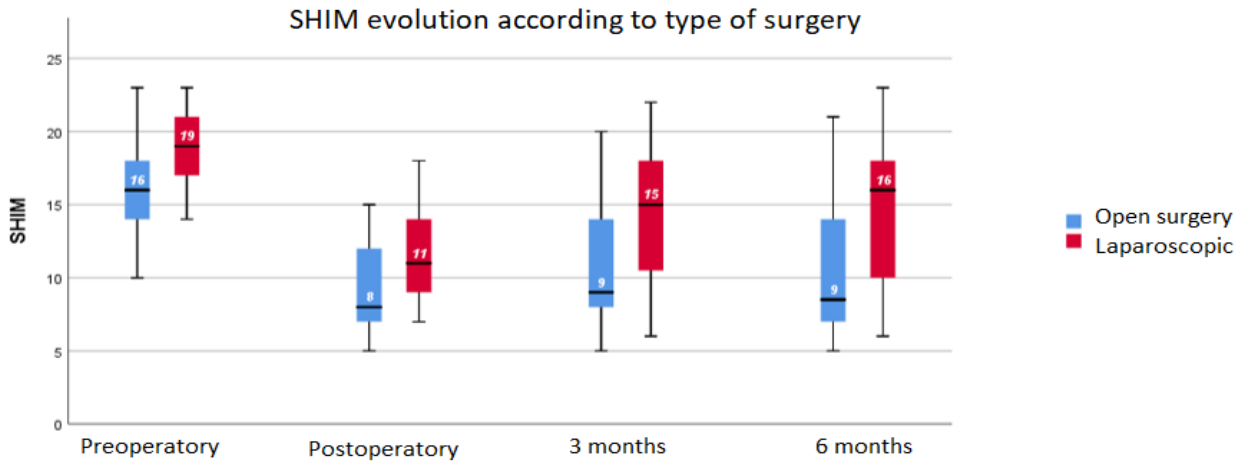
group. In the LARP group there are 12 patients (20.3%) in the low risk group, 24 patients (40.7%) in the medium risk group and 23 patients (39%) in the high risk group.

Analyzing the Gleason score of our patients according to type of surgery, we found out that for the group of patients who underwent open-classic intervention, 3 patients had the Gleason score 6 (5.8%), 22 patients had the Gleason score 7 (42.3%) and 27 patients (51.9%) Gleason score 8. In the group of patients who underwent laparoscopic surgery 12 (20.3%) had a Gleason score of 6, 39 (66.1%) had a Gleason score of 7 and 8 patients (13.6%) had a Gleason score of 8.

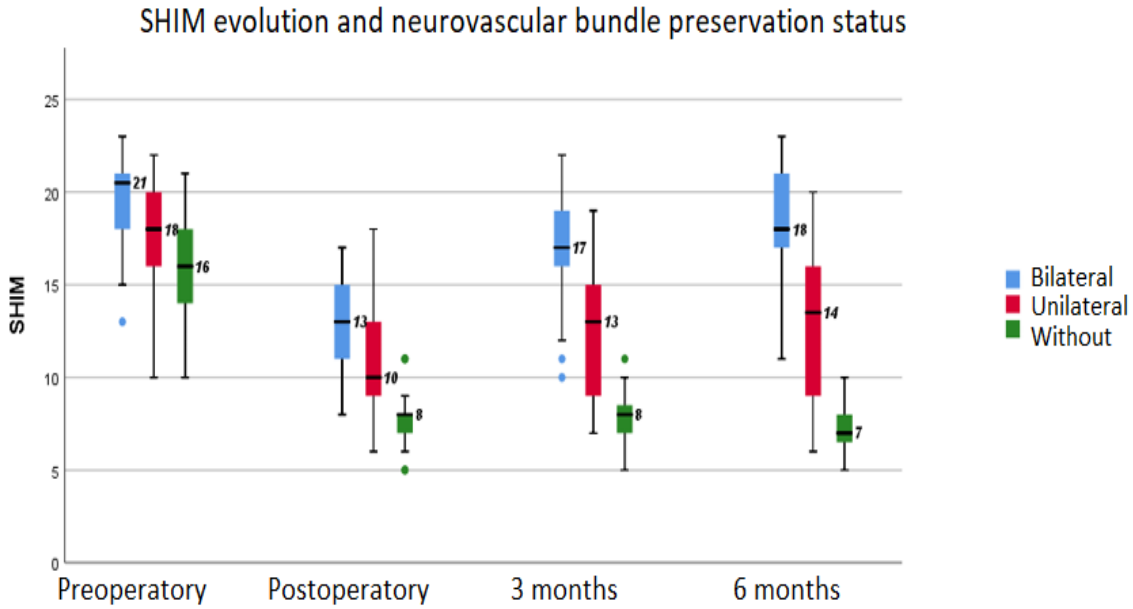
Comparing the preoperative SHIM value with the postoperative value, a marked decrease value is observed for both groups of patients. Thus, in the group of classically operated patients the value of postoperative SHIM was halved (from 16 to 8), and in the group of laparoscopically operated patients it decreased from 19 to 11. This results were as expected since it is well known that this intervention affects sexual activity.

Analyzing the distribution of patients in the two treatment groups, a selection bias of laparoscopy patients is observed - younger, lower stage, lower icicle, less at high risk, with better preoperative score, no diabetes, no consumption of alcohol, without stroke / TIA. But this selection bias of laparoscopy treated patients has no statistical significance in the multivariable logistic regression model.

The figure below shows that although the SHIM score of laparoscopically operated patients is higher since preoperatively During the study the differences between the two groups are accentuated, so that at the end of the analysis period of the 2 groups the SHIM value in the group of laparoscopically operated patients is larger than that of the group of patients classically operated, but without statistical significance.



Given the physiological relationship of the nerve sparing technique on ED, the impact on preoperative ED preservation was expected (OR 3.23, 95% CI: 1.82-5.737) – uni or bilateral bundle preservation is associated with 3.23 fold more recovery chance.



Study IV: IMPACT OF COMORBIDITIES, DISEASE STAGE AND RISK GROUP ON PENILE REHABILITATION

Analysis of the obtained rezults performed by completing the SHIM questionnaire, shows that in the preoperative moment, the situation of patients in our group was as follows: no patient had severe erectile dysfunction, 3 patients (2.7) had moderate erectile dysfunction, 36 (32.4%) had moderate erectile dysfunction- mild, 62 (55.9%) had mild erectile dysfunction and 10 patients (9%) had normal erectile function.

At the postoperative moment the situation was as follows: 16 patients (14.4%) had severe erectile dysfunction, 37 patients (33.3%) had moderate erectile dysfunction, 36 (32.4%) had moderate-mild erectile dysfunction, 4 (3.6%) had mild erectile dysfunction and no patient had normal erectile function.

At 3 months: 15 patients (13.5%) had severe erectile dysfunction, 55 patients (49.5%) had moderate erectile dysfunction, 35 (31.5%) had moderate-mild erectile dysfunction, 23 (20.7%) had mild erectile dysfunction and no patients he no longer had normal erectile function.

At 6 months of treatment: 24 patients (21.6%) had severe erectile dysfunction, 27 patients (24.3%) had moderate erectile dysfunction, 26 (23.4%) had moderate-mild erectile dysfunction, 30 (27%) had mild erectile dysfunction and 4 patients (3.6%) had normal erectile function.

From the above we can follow the evolution of the erectile dysfunction degree starting from preoperative and continuing with the key moments of our study, respectively postoperative, after 3 months of treatment and finally, after 6 months of treatment.

Associated pathologies or patient characteristics in our study group are listed in the table below.

	DISTRIBUTION
Age	66 [63; 68,8]
Arteriel hypertension	74 (66,7%)
Diabetes melitus	28 (25,2%)
Atherosclerosis	48 (43,2%)
Depression	8 (7,2%)
Obesity	39 (35,1%)
Smoking	45 (40,5%)
Alcool intake	34 (30,6%)
AIT	19 (17,1%)

The most common associated pathology is hypertension, present in 66.7% of patients, followed by atherosclerosis and chronic smoking. Each of these conditions, along

with age, is a risk factor for erectile dysfunction, with the combination of two or more factors increasing the risk.

Regarding the risk group and the stage of the disease, our study group includes 14 low-risk patients (12.6%), 32 medium-risk patients (28.8%) and 65 high-risk patients (58.6%). In terms of the stage of the disease, 15 patients (13.5%) are in the T2a stage, 31 (27.9%) in T2b and 65 (58.6%) in T2c.

The characteristics of patients by risk groups and stage according to the medical treatment administered (monotherapy vs. combination therapy) are highlighted in the table below.

Risk group		Tadalafil (n=56)	Tadalafil + Vitaros (n=55)
	Low	9 (16,1%)	5 (9,1%)
	Medium	15 (26,8%)	17 (30,9%)
	High	32 (57,1%)	33 (60%)
Stage			
	T2a	10 (17,9%)	5 (9,1%)
	T2b	14 (25%)	17 (30,9%)
	T2c	32 (57,1%)	33 (60%)

By analysing the table above it is observed that there is a high homogenicity in between, without significant differences. Of statistical significance are the preservation of neurovascular bundles and the type of treatment followed (monotherapy versus combination therapy). The statistical analysis showed in the first instance that among the diseases associated with atherosclerosis and smoking seem to influence the final outcome of treatment. The quality of the couple would also play an important role. Next, we used multivariate testing using IBM SPSS Statistic as a statistical software platform, to see which of the analyzed variables really has statistical significance.

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
time	Pillai's Trace	.639	60.858[b]	3.000	103.000	<.001	.639
	Wilks' Lambda	.361	60.858[b]	3.000	103.000	<.001	.639
	Hotelling's Trace	1.773	60.858[b]	3.000	103.000	<.001	.639
	Roy's Largest Root	1.773	60.858[b]	3.000	103.000	<.001	.639
time * faraNS	Pillai's Trace	.335	17.304[b]	3.000	103.000	<.001	.335
	Wilks' Lambda	.665	17.304[b]	3.000	103.000	<.001	.335
	Hotelling's Trace	.504	17.304[b]	3.000	103.000	<.001	.335
	Roy's Largest Root	.504	17.304[b]	3.000	103.000	<.001	.335
time * Fumat	Pillai's Trace	.021	.736[b]	3.000	103.000	.533	.021
	Wilks' Lambda	.979	.736[b]	3.000	103.000	.533	.021
	Hotelling's Trace	.021	.736[b]	3.000	103.000	.533	.021
	Roy's Largest Root	.021	.736[b]	3.000	103.000	.533	.021
time * Ateroscleroza	Pillai's Trace	.005	.174[b]	3.000	103.000	.914	.005
	Wilks' Lambda	.995	.174[b]	3.000	103.000	.914	.005
	Hotelling's Trace	.005	.174[b]	3.000	103.000	.914	.005
	Roy's Largest Root	.005	.174[b]	3.000	103.000	.914	.005
time * Cuplubun	Pillai's Trace	.040	1.428[b]	3.000	103.000	.239	.040
	Wilks' Lambda	.960	1.428[b]	3.000	103.000	.239	.040
	Hotelling's Trace	.042	1.428[b]	3.000	103.000	.239	.040
	Roy's Largest Root	.042	1.428[b]	3.000	103.000	.239	.040
time * Tratament	Pillai's Trace	.448	27.901[b]	3.000	103.000	<.001	.448
	Wilks' Lambda	.552	27.901[b]	3.000	103.000	<.001	.448
	Hotelling's Trace	.813	27.901[b]	3.000	103.000	<.001	.448
	Roy's Largest Root	.813	27.901[b]	3.000	103.000	<.001	.448

a. Design: Intercept + faraNS + Fumat + Ateroscleroza + Cuplubun + Tratament
Within Subjects Design: time
b. Exact statistic

Multivariate testing has shown that only the type of treatment and the type of preservation of neurovascular bundle had statistical significance for included patients.

The conclusion is that none of the associated comorbidities ultimately influence the outcome of penile rehabilitation. This result is somehow logical because we follow the results of penile rehabilitation treatment in a group with certain comorbidities that are present from the beginning. Thus, the SHIM score that shows the degree of erectile dysfunction is clearly correlated with the associated pathology. This correlation is found in the value of the score from the first, preoperative visit. But the change in SHIM score and implicitly the degree of erectile dysfunction in the postoperative period, ie at visit two, compared to visit one, no longer correlates with the associated patholog. Nevertheless it is due to surgical excision of prostate and seminal vesicles, which is the only factor that

deteriorates sexual life in the interval between first and second visit. The goal of penile rehabilitation treatment is to bring the SHIM value as close as possible to the initial, preoperative value. Therefore, the presence of comorbidities will not influence during the six months of treatment the degree of penile reabhilitation. This is due to the fact that we want to restore sexual function at the preoperative level and not the normalization of sexual function.

From the statistical analysis in which stage T2a, T2b and T2c are 1,2 and 3 respectively and the low, medium and high risk groups are numbered with 1, 2 and 3 respectively it results that both the disease stage and the risk group have no statistical value. in obtaining the final result. (Table 9)

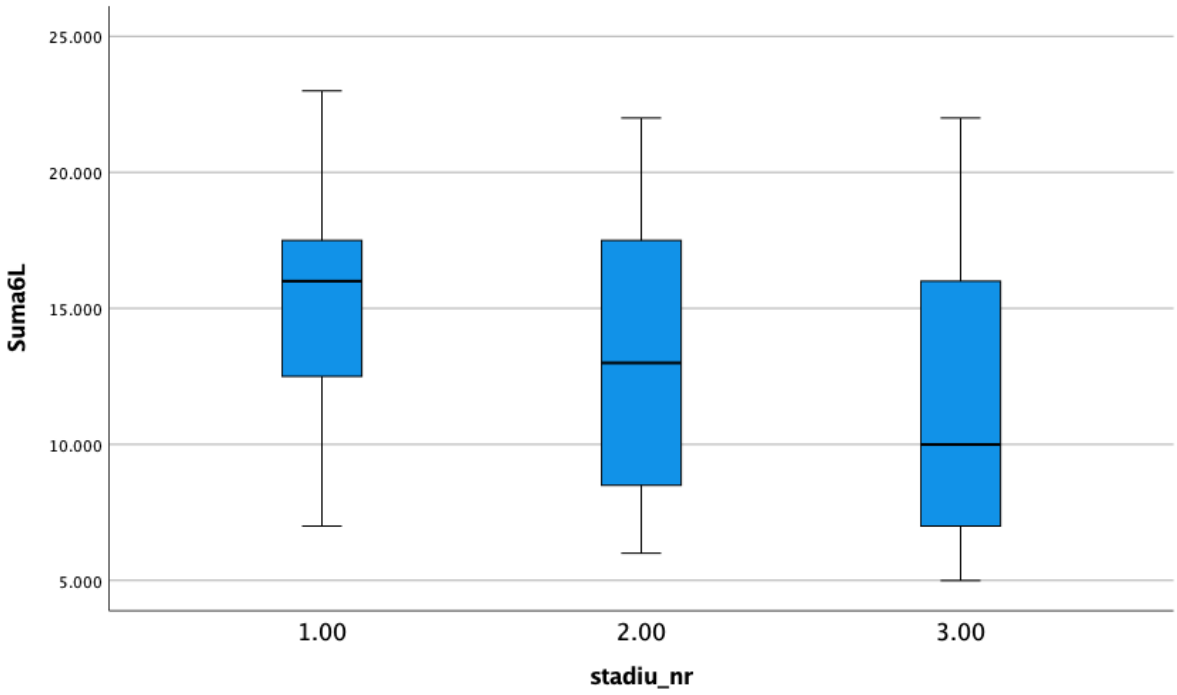
Multivariate Testsa

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
time	Pillai's Trace	.502	34.907b	3.000	104.000	<.001	.502
	Wilks' Lambda	.498	34.907b	3.000	104.000	<.001	.502
	Hotelling's Trace	1.007	34.907b	3.000	104.000	<.001	.502
	Roy's Largest Root	1.007	34.907b	3.000	104.000	<.001	.502
time * faraNS	Pillai's Trace	.307	15.364b	3.000	104.000	<.001	.307
	Wilks' Lambda	.693	15.364b	3.000	104.000	<.001	.307
	Hotelling's Trace	.443	15.364b	3.000	104.000	<.001	.307
	Roy's Largest Root	.443	15.364b	3.000	104.000	<.001	.307
time * stadiu_nr	Pillai's Trace	.015	.512b	3.000	104.000	.675	.015
	Wilks' Lambda	.985	.512b	3.000	104.000	.675	.015
	Hotelling's Trace	.015	.512b	3.000	104.000	.675	.015
	Roy's Largest Root	.015	.512b	3.000	104.000	.675	.015
time * risc_nr	Pillai's Trace	.016	.564b	3.000	104.000	.640	.016
	Wilks' Lambda	.984	.564b	3.000	104.000	.640	.016
	Hotelling's Trace	.016	.564b	3.000	104.000	.640	.016
	Roy's Largest Root	.016	.564b	3.000	104.000	.640	.016
time * Tratament	Pillai's Trace	.470	30.694b	3.000	104.000	<.001	.470
	Wilks' Lambda	.530	30.694b	3.000	104.000	<.001	.470
	Hotelling's Trace	.885	30.694b	3.000	104.000	<.001	.470
	Roy's Largest Root	.885	30.694b	3.000	104.000	<.001	.470

a Design: Intercept + faraNS + stadiu_nr + risc_nr + Tratament
Within Subjects Design: time
b Exact statistic

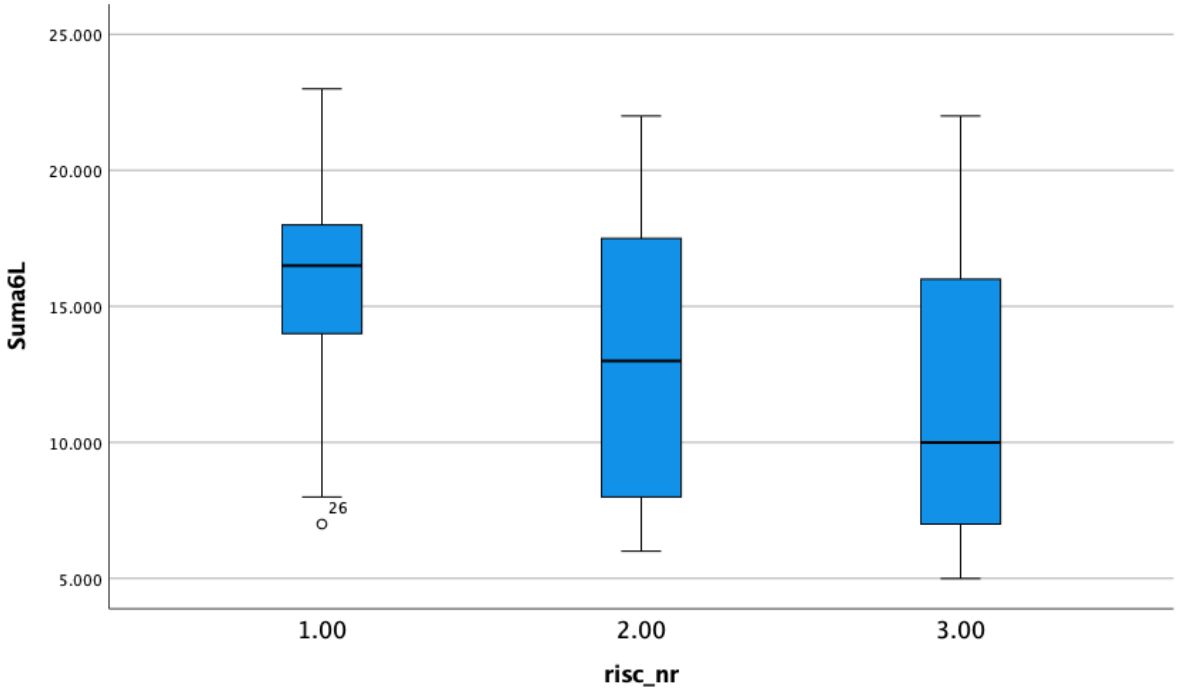
DeAlthough it does not statistically influence the result, we notice that the higher the stage, the worst results at 6 months were found.

Fig.1: Evolution of SHIM after 6 months of treatment depending on the stage of the disease (1 = T2a, 2 = T2b, 3 = T2c)



The same is observed for the risk groups: the higher the risk, the worse the results at 6 months of treatment for the whole group.

Fig 2: Evolution of SHIM after 6 months of treatment according to risk group (1 = low risk, 2 = intermediate, 3 = high)



This can be explained by the fact that for patients at higher risk and more advanced stage of the disease we did not preserve the neurovascular bundles during surgergery. The

risk of patient not obtaining the "tumor free" status is higher for those in advanced stages and high risk group, so the surgical intervention had oncological objective.

In conclusion, the main objective of the study was achieved: the combination of Tadalafil 5 mg daily with Vitaros cream as needed, before each sexual contact, increases the recovery of ED from the preoperative by 3.55 times more compared to monotherapy.

Regarding the type of operation, we notice that the SHIM value in the group of laparoscopically operated patients is higher than in the group of open-operated patients, but the difference is not statistically significant. Therefore, the type of surgery does not affect the recovery of sexual function.

Another important conclusion, besides the one regarding the superiority of the combined therapy versus monotherapy, is that the SHIM score, both the one obtained after 3 months of treatment and the one at the end of the study (after 6 months of treatment) is better for the patients at that had the prezervation of neurovascular bundles. As compared with the other group the difference is statistically significant. Given the physiological relationship of the nerve sparing technique on ED, the impact on preoperative ED preservation was expected (OR 3.23, 95% CI: 1.82-5.737) - the more I preserve the recovery of 3.23 Regarding the influence of comorbidities on penile rehabilitation, the multivariable testing performed later led us to the conclusion that none of the associated comorbidities ultimately influence the outcome of penile rehabilitation. Also, neither the stage of the disease nor the risk group is of statistical significance for penile rehabilitation.

In the literature we found only one study on treatment with Vitaros (topical alprostadil) for penile rehabilitation after radical prostatectomy (study performed on a group of 74 patients with robotically assisted radical prostatectomy, without preservation of neurovascular strips) and none with the combination of tadalafil plus alprostadil topic. Our study is the first to propose this combination for penile rehabilitation treatment and compares it with tadalafil 5 mg daily treatment (monotherapy).

There are a number of limitations of our study, including the duration of treatment of only 6 months, given that we know that an ideal duration would have been 18-24 months, but it would have been economically impossible to support such a study for such a long period. Unfortunately in our country the health insurance system does not support even partially the compensation the treatment of penile rehabilitation. On the other hand, the

duration of penile rehabilitation treatment in various studies starts from 3 months, so 6 months is a scientifically correct period.

Another thing we wanted, but failed to achieve, was the involvement of psychotherapy in the treatment of penile rehabilitation. I think the results would have been better if we combined psychotherapy with basic treatment, because our study included patients who were affected by both cancer-related trauma and major surgery.

We did not introduce the washout period in the study design because the results from the literature show that the penile rehabilitation treatment with PDE 5 inhibitors loses its effectiveness after the washout period, which is why we set the design and objectives of the study differently. Also, at the end of the study period, most patients with good treatment results wanted to continue the treatment, not accepting the idea of washout. The introduction of the washout period would have meant their exit from the study, as well as other patients who did not want to continue for other reasons, which would have affected the size of the group of patients and thus the statistical quality of the results obtained.

The results of our study were quite convincing, although the guidelines of the most important urological societies do not mention the superiority of a treatment. We are also interested in future results, from this point of view, of the robot-assisted radical prostatectomy, a method at the beginning of the road in our country. We remain anchored in this field of sexuality medicine and although we know that, at present, the guidelines of the most important uro-andrological societies (European Association of Urology, American Urological Association and European Society for Sexual Medicine) do not highlight the superiority of any treatment or a specific molecule on others, we want to investigate new treatment possibilities for penile rehabilitation.

Speaking about future treatment options, it must be said that the first treatment used in penile rehabilitation was intra-cavernous injections with alprostadil. It seems that the future is linked to intracavernous injections. Currently there are several clinical studies evaluating the efficacy of intracavernous injections with bone marrow mononuclear cells (BM-MNCs, bone marrow-mononuclear cells). This is a heterogeneous population of cells that includes mesenchymal stem cells, progenitor endothelial cells and hematopoietic stem cells. The first results look promising.

Another way of treatment could use low-intensity extracorporeal shock wave therapy (Li-ESWT). This therapy facilitates the appearance of cellular microtraumas that stimulate

the release of angiogenic factors and possibly the appearance of neo-vascularization in the treated tissue.

The third possibility of future treatment, less investigated so far uses intracavernous injections with platelet-rich plasma (PRP, Platelet-Rich Plasma). It is assumed that the angiogenic, vasculogenic and regenerative effect of PRP may be useful in the treatment of ED. We intend to study this third variant, namely intracavernous injections with PRP, which could be one of the treatments of the future, including for the penile rehabilitation of patients with radical prostatectomy.