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## **After Radical Prostatectomy: Erectile Dysfunction Diagnosis and Its Treatment – A Literature Review**

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**Abstract****Introduction and purpose of work:**

In the last 10 years, prostate cancer has become the most common cancer in the Polish population of men with the high growth dynamics. Despite the fact that we are getting better with mortality and new surgery techniques, complications in the form of urinary incontinence and erectile dysfunctions after radical prostatectomy are a common problem. This study deals with the second problem, often underestimated by the society, but equally important in maintaining high -quality life. Our goal is to present aetiology, diagnostics and treating patients with erectile dysfunction after radical prostatectomy due to prostate cancer. It can help doctors who usually do not have contact with such patients, understand the problem and manage effective treatment in their daily practice.

**Method:**

We searched for studies and articles via PubMed using the keywords prostate cancer, radical prostatectomy, erectile dysfunction. From screened documents identified from literature search, 52 articles were included in our review.

**Summary:**

Erection dysfunction is a complex problem, in which the basis is the interaction of the vascular and nervous systems. To diagnose the patient, you need to conduct a thorough interview, generally about medical history and chronic diseases, but also about sex life. After the diagnosis, there are many treatment options to choose from, pharmacological and non-pharmacological. An important aspect of treatment that you cannot forget is psychological support which should start from the moment of diagnosis of prostate cancer. Each method has pros and cons, but effective cooperation with the patient will give the desired results.

**Keywords:** Prostate cancer, Radical prostatectomy, Erectile dysfunction

**INTRODUCTION**

Prostate cancer is one of the most common malignancy in the men. Worldwide, an estimated over 1,4 million people is diagnosed with prostate cancer. In Poland, in data from 2021, the percentage share of prostate cancer in men is 21.2% - the highest of all cancers. It is the second leading cause of cancer death in men [1].

Prostate cancers characterized by the highest growth dynamics, especially in the last decade. At the same time, there has been a stabilization of mortality and a significant improvement in survival rates in the last decade [1].

The first-line treatment for clinically localized intermediate to high-risk prostate cancer is represented by radical prostatectomy [2]. The treatment allows for survival improvement with low risk of cancer recurrence in the majority of cases. It is also considered as a procedure with low risk of serious complications in comparison to the other major oncologic surgical operations.

Unfortunately, like any intervention, it has its drawbacks - urinary and sexual side-effects are common, which can reduce the patient's quality of life. According to the sources - erectile dysfunction (ED) is recognized as the one of the most common side effect even with nerve-sparing techniques [3]. Rates of erectile dysfunction ranging from 26-90% at 1 year after radical prostatectomy and from 47-94% after 2 years [4]. The study from 2019 showed that despite progress in surgical and postoperative care, erectile function outcomes after radical prostatectomy have remained stagnant over the past decade [5]. Thanks to these numbers we can

see a magnitude of this problem. Erectile dysfunction can be treated with highly successful results, but first we have to understand the issue and diagnose it properly.

The purpose of this review is to examine the literature as to aethiology, diagnosis and treatment of erectile dysfunction following radical prostatectomy.

## **AETHIOLOGY**

Fourth International Consultation on Sexual Medicine defines erectile dysfunction as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction [6]. In 2019 an epidemiology article about ED was published, which showed data from 8 countries around the world (Brazil, China, France, Germany, Italy, Spain, the United Kingdom, and the United States) [7]. The total prevalence of self-reported ED in adult men was 40.5%. The overall prevalence of erectile dysfunction among the European Union nations was 42.3%, which means around 53.9 million men on the continent. This is a higher result than assumed in previous studies, so patients with ED will arrive more and more.

Physiologically functioning erection is a complex interaction of the vascular and nervous systems. The cavernosal branches of the internal pudendal artery predominantly deliver blood to the penis, while venous drainage happens via a system of venules that can be readily compressed. An arousal activates sacral segments of the spinal cords by the parasympathetic system and it initiates a cascade of events that results in the release of nitric oxide and increases intracellular cyclic guanosine monophosphate. This induces vascular smooth muscle relaxation and an increase in blood flow into the corpora cavernosa. This quick inflow of blood participates in the compression of the venule network and decreases venous outflow, in this way, it raises intracavernosal pressure and results in an erection.

The most important predictor of ED following radical prostatectomy is pre-existing erectile dysfunction. This is related to the age of the diagnosis of prostate cancer - between the sixth and eighth decade of life. Ageing men are more likely to develop conditions such as cardiovascular disease and diabetes, which can cause erectile problems [7-11].

Table No. 1 contains the most common risk factors for erectile dysfunction.

Tobacco use	Hypothyroidism
Obesity	Hyperthyroidism
Sedentary lifestyle	Dyslipidemia
Chronic alcohol use	Depression
Hypertension	Medication side effect

**Tab 1. The most Common Risk Factors For Erectile Dysfunction. [7-12].**

The next aspect is the type of performed operation. Radical prostatectomy can be performed as open radical prostatectomy (ORP), laparoscopic radical prostatectomy (LRP) or robot-assisted laparoscopic radical prostatectomy (RARP). Studies show that the RARP is a superior surgical approach to LRP in terms of faster recovery of erectile function. After surgery, scores of The International Index of Erectile Function (IIEF-5) were higher in the RARP group as compared with the LRP at the postoperative visits, respectively [13]. Thanks to the increasing number of medical centres using robotic surgery, we have greater control over these side effects.

Knowledge of „prostate anatomy” has deeply improved over the years, with a consequent refinement of the surgical technique aimed at lowering the risk of injury to the neurovascular bundles (NVB) [14]. The possibility of carrying out a „nerve-sparing procedure” (NS) is determined by the stage of the tumor, the experience of the urological surgeon and hospital possibilities. Patient age, preoperative potency status and extent of NS are the important predictors of postoperative functional outcomes [15]. Bilateral NVB preservation is crucial for achieving better post- operative continence and potency outcomes, while maintaining oncological effectiveness. Future advancements and innovations in NS techniques are expected to further enhance the functional outcomes of RARP [15].

## **DIAGNOSIS**

In the previous paragraph, we presented that erection problems can have many causes. To holistically approach the patient, it is good to start diagnosing before the procedure is performed. The full package consists of a precise urological interview, adequate surveys, physical examination, and specialist additional research.

The first and most important is a comprehensive conversation with the patient. As we mentioned earlier, erection problems may occur before surgery and may not be related to

prostate cancer. The goal is to conduct a precise, focused urological interview about erectile function. The urologist must take a careful history to determine the extent of symptoms as well as the contribution to symptoms by associated chronic diseases, earlier operations, medication use, or psychosocial issues. An important aspect of the Doctor-Patient relationship is trust. Without it, we are not sure if the medical interview we collected is reliable. Problems with erection or other aspects of sex life for many patients is a shameful topic, which can affect their answers and determine the importance of the problem.

To diagnose ED we use a validated survey - The International Index of Erectile Function (IIEF-5) questionnaire to measure pre- and post-prostatectomy erectile function. IIEF-5 has a high degree of sensitivity to detect changes in sexual function in response to treatment. The survey contains 5 questions scored from 0 to 5 - the lower the number of points, the greater the symptoms. The possible drawback of the IIEF-5 is that it fails to distinguish between surgical, psychological, or organic aetiologies. Assessment of erectile dysfunction by this survey may be insufficient because an important element of sexual life with prostate cancer is the psychological aspect [16]. Oncological diagnosis can have negative effects on well-being and even cause depressive disorders. A bad emotional state can have a negative influence on men's sex life diagnosed with prostate cancer. Tab. 2 shows the IIEF-5 questionnaire.

	Over the past 6 months				
Points	1	2	3	4	5
1. How do you rate your confidence that you could get and keep an erection?	Very Low	Low	Moderate	High	Very high
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/always
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/always
22-25: No erectile dysfunction 17-21: Mild erectile dysfunction 12-16: Mild to moderate erectile dysfunction 8-11: Moderate erectile dysfunction 5-7: Severe erectile dysfunction					

**Tab. 2 - The International Index of Erectile Function Questionnaire [17].**

The next step is a physical examination. It aims primarily to evaluate the anatomy of the genitourinary system, as well as the endocrine, vascular and nervous systems. It may allow us to diagnose the concomitant diseases that may cause erectile dysfunction. First of all urologist should examine external genital organs and make a genitourinary ultrasound. Waist circumference measurement is helpful in counselling the patient about the risks related to obesity and the possibility of metabolic syndrome [18-19]. Particular attention should be paid to factors that can promote the occurrence of cardiovascular diseases - one of the most common



factors of erectile dysfunction. Measure blood pressure and pulse especially if they have not been assessed thoroughly in the previous 3–6 months [20].

There is also a specialist diagnostic examination involving an intracavernous injection of a vasodilating agent - prostaglandin E1 (PGE1). We call it the ICI Test. The test allows us to predict the adequacy of penile circulation by PSV parameter (peak systolic velocity) during Colour Doppler Ultrasound (PCDU) measured 5–20 minutes after PGE1 injection [21]. PCDU is nowadays considered the gold standard for the diagnosis of arteriogenic erectile dysfunction [21]. It has to be performed by an experienced ultrasonographer, in conditions suitable for the patient. The penis is examined in two projections - longitudinal and transverse, assessing the homogeneity of cavernous bodies, the presence of lumps, fibriums, calcifications and echogenicity. Measure the inner diameter of the right and left deep penile artery and the PSV. Dynamic PSV below 25 cm/s is associated with a relevant increase in cardiovascular risk [22]. During PCDU we can also measure end-diastolic velocity (EDV) and resistive index (RI) which can give information about venous system leaks.

## **TREATMENT**

As we have proven in the previous paragraphs, many factors influence pre- and post-operative erectile dysfunction. The recovery of postoperative erectile function can take several years and does not uniformly occur in all cases. Clinicians should discuss the occurrence of postsurgical erectile dysfunction with every candidate for radical prostatectomy. These do not always have to be permanent disorders, but patients must be prepared for every eventuality. Critical and realistic discussion about the timing of eventual erectile function recovery during which the patient receives information about real expectations of recovery, appears relevant to lower the risk of false expectations [5, 23]. High expectations for immediate and full success with spontaneous erectile function recovery and/or with their first erectile dysfunction treatment can cause resentment when they fail and may make the patient not want to look for other methods of treatment [24-25]. It is clinically important to provide the patient and his partner, with sufficient knowledge to understand the role of rehabilitating erectile function after radical prostatectomy.

The most common in clinical practice are rehabilitation programs using phosphodiesterase Type 5 Inhibitors (PDE5Is), intracavernosal injections (ICIs), intraurethral alprostadil, vacuum erectile device (VED) therapy, or a combination of these methods.

## Phosphodiesterase Type 5 Inhibitors

PDE5Is (sildenafil, tadalafil, vardenafil, avanafil) as the first line of treatment, are used in the early phase of post-operative recovery, regardless of the surgical technique used. In practice, tadalafil is often preferred due to the extended plasma elimination half-time that allows better patient compliance and a longer period of activity [26]. We have preclinical animal data showing that PDE5Is could prevent the degeneration of nerves, decrease erectile tissue fibrosis, and stimulate neuroregeneration [27-28]. On humans, the effect of tadalafil throughout the post-radical prostatectomy rehabilitative period was tested in a large RCT by Montorsi et al. [29]. The aim of the study was to compare the efficacy of tadalafil 5 mg once a day and tadalafil 20 mg on demand versus placebo in improving unassisted erectile function following nerve-sparing radical prostatectomy. At the end of a 9-month treatment course, the rate of an IIEF-EF5 questionnaire achievement of at least 22 points was significantly higher in patients treated with tadalafil once a day than in the placebo group. Clinical trial proved that the tadalafil once daily treatment could be used to maintain cavernosal tissue integrity. More trials confirm that state [30-31]. Moreover, one of these studies proved that stretched penile length was significantly more retained after tadalafil once a day than after a placebo [31]. These data indicate a beneficial impact of PDE5Is in drug-assisted postoperative erectile function recovery.

As proved, a once-daily regimen with tadalafil 5 mg at approximately the same time each day is the most suitable form of treatment for most patients. It provides opportunities for couples who prefer spontaneous activities and anticipate frequent sexual activity. Also, it is well-tolerated, effective and may improve the erectile function group of men who have a partial response to on-demand therapy [32]. On the other hand, tadalafil in higher doses (10 or 20 mg) on-demand may be a better solution for those, whose sexual intercourses are scheduled. Brock et al. in 2016 showed that none of the treatment schemes prevail over the other, all clinical populations of patients with erectile dysfunction made similar benefits [31]. The choice should be based on the knowledge of the doctor and the patient's preferences.

Do all patients return to baseline with PDE5Is treatment? A study published in 2013 by Nelson et al. reported on patient return to preoperative erectile function as assessed by the IIEF-5 questionnaire [32]. 180 men completed the Erectile Function Domain (EFD) of the International Index of Erectile Function and one question on PDE5is use pre-radical prostatectomy and 24 months after. Men using a PDE5is at baseline were excluded. Achieving the baseline EFD score (within 1 point or higher) 24 months after surgery was accepted as „back to baseline“. The results are presented in Tab. 3.

		<b>With/without PDE5Is at 24 months</b>	<b>95% CI</b>	<b>Not using PDE5Is at 24 months</b>	<b>95% CI</b>
Total sample	N = 180	43%	36-51%	22%	16-24%
Baseline EFD $\geq$ 24	N = 123	36%	28-44%	16%	11-23%

**Tab. 3 Percent achieving back to baseline erectile function recovery by Nelson et al. [32].**

As Tab. 3 shows - patients who use PDE5Is are more likely to achieve the baseline than those who do not use PDE5Is, but it is not 100% efficient. „Back to baseline” rehabilitation affects a lot of factors mentioned before, so all men undergoing prostate cancer treatment should be educated on the meaning of erectile function recovery.

Almost every pharmacological treatment carries the risk of side effects. When collecting a medical interview, urologists should pay attention to chronic diseases and permanent medications, because PDE5Is may interact with some of them. According to The European Association of Urology (EAU) Sexual and Reproductive Health Guidelines - no studies have shown that PDE5Is increase myocardial infarction rates in patients receiving them. It has also been emphasized that the use of PDE5Is with organic nitrates and nicorandil is contraindicated [33]. Special attention should be paid to patients taking antihypertensive drugs or  $\alpha$ -blockers - there may occur interaction between drugs such as hypotension.

### **Intracavernous injection therapy (ICIs)**

Intracavernous injections can be used as a second-line therapy when oral PDE5Is are not adequately effective or not suitable for patients after radical prostatectomy. It is the oldest method of erectile dysfunction treatment. It might be effective for men who have tried oral drugs without response, but doctors can offer ICIs at every stage of treatment. In injections, we use alprostadil as monotherapy or combined preparations.

Alprostadil is the only drug approved for intracavernous treatment as monotherapy. At the beginning, patients must learn the injection technique under the supervision of their doctor. The dosage is also determined, which is most often between 5 and 40  $\mu$ g. We expect an erection effect after 5 to 15 minutes, but the duration depends on the dose and varies between patients. Studies have shown positive results for penile rehabilitation [34-35]. In a general group of patients with erectile dysfunction, alprostadil accomplished >70% efficacy. Unfortunately, local

side effects such as penile pain, fibrosis, prolonged and unwanted erections or priapism are relatively common. Other vasoactive intracavernous treatments like combined preparations can handle some of them.

Invicorp<sup>TM</sup> is a combination of vasoactive intestinal peptide and phentolamine mesylate. Studies have shown that the drug has not only excellent effectiveness but also a reduced number of side effects such as penile pain and priapism [36-37]. This is a big advantage of this solution, but it must be noted that 5-10% of patients do not respond to combination therapy with ICIs.

### **Intraurethral alprostadil**

We have already mentioned alprostadil, but in this paragraph, we will deal with its different forms. This vasoactive agent can be used topical or by intraurethral insertion. The first method uses a cream consisting of a cutaneous permeation enhancer to facilitate the absorption of alprostadil through the urethral meatus. Local side effects in the form of penile erythema, penile burning, and pain are noticeable. The cream offers another non-invasive treatment method, but there is still not enough clinical data to confirm the applicability of topical alprostadil in patients after radical prostatectomy. Della Camera PA et al. showed promising study that topical alprostadil Vitaros<sup>®</sup> may become as a viable alternative to standard injectable therapies in carefully chosen patients after RARP [38].

The second method - intraurethral insertion. In a prospective study of 91 sexually active men after radical prostatectomy with the nerve-sparing technique, the group that started using this method early after surgery managed to achieve a shorter recovery time to regain erectile function [39]. Insertion of alprostadil into the urethra simplifies spontaneous, unassisted erections suitable for vaginal penetration in 40% of patients after 9 months, compared to the control group with only 11% of men achieving it. This method also has side effects such as local pain, dizziness with possible hypotension, urethral bleeding and urinary tract infections. The intraurethral alprostadil is not a common choice in the treatment of erectile dysfunction, but it gives us another possible method of treatment.

This type of treatment may seem not often used, but there is evidence that it is effective. Work from 2018 showed that numbers of studies proved the beneficial effect of combination therapy of PDE5Is and alprostadil (intracavernosal, intraurethral, topical cream) in patients who have previously failed either treatment as monotherapy [40]. Despite the possibility of side effects and some disadvantages of this solution, alprostadil may surprise you with the additional benefit of synergistic smooth-muscle relaxant effect.

## **Vacuum erectile device (VED) therapy**

A vacuum erectile device is used to help men with erectile dysfunction get and maintain an erection. It consists of a plastic tube and mechanical, battery-operated, or electric pump. In short - the tube is placed over the penis, and the pump is used to create negative pressure to distend the corporal sinusoids, thereby increasing the infusion of blood to the penis. An adequate erection is usually achieved in 30 seconds to 7 minutes (on average 2-3 minutes), but this does demand manual dexterity by the patient or partner.

It has been proven in preclinical trials that VED therapy is in charge of the preservation of endothelial and smooth muscle integrity due to the transient increase in arterial flow and oxygenation to the corpora cavernosa [41]. Still, over the years, there have been many studies that question the effectiveness of this modern method in the post-RP setting [41-42]. In 2011 Engel et al. showed that treatment VED + tadalafil is more efficient than only post-prostatectomy tadalafil [43]. The combined treatment group had significantly higher IIEF-5 scores, greater penile hardness scores and higher compliance than the monotherapy group. Later, with a larger number of patients, Basal et al. confirmed that state and observed less loss of penile length [42]. Studies show that the best therapy is a combination of VED and PDE5Is, satisfactory results did not apply to patients using VED as the only treatment [42-43].

Based on this, it is believed that VED may support penile rehabilitation after surgery, but there is no prescribed protocol as to how it should be used - research and discussions are still ongoing as to which schedule will be the most effective and satisfactory for the patient and his doctor [44-45].

Advantages	Disadvantages
Non-invasive	Instability at the base of the penis causing pivoting
Easy to use	
Solid	Might be messy with lubricant
Quick to use - A positive effect on spontaneity	Skin lesions, blue/cyanotic tones, petechiae, hematoma, painful venous engorgement
Can be part of the foreplay	
Purchased once, long use of the device (even more than 5 years)	Cool erection Inability to ejaculate due to urethral constriction
Few contraindications (priapism, significant bleeding disorders)	Discomfort, pain or numbness through suction or constriction

The device is solid, comparatively easy to use, and has not many contraindications. VED may be expensive, but devices are durable and can serve many years. The other advantages and disadvantages of the VED are shown in Tab. 4.

Tab 4. Advantages and disadvantages of VED [46-48].

VED can be the preferred treatment option for well-informed older patients with infrequent sexual intercourse and with a medical situation requiring the selection of non-pharmacological solutions for erectile dysfunction. It is currently the only non-pharmacological, non-invasive strategy for erectile dysfunction.

### **Penile prostheses**

The penile implant can be considered as another non-pharmacological method for patients who do not respond to other ways of treatment or pharmacological methods are not suitable for them. Non-pharmacological, but invasive and, like any operation, has its complications. Despite this fact, the surgical implantation of a penile prosthesis has very high satisfaction rates among patients dealing with erectile dysfunction for various reasons [49]. It is worth considering this option, but unfortunately, it is not available for everyone.

### **Psychosocial intervention and therapy**

As we mentioned earlier, psychological aspects can have a significant impact on erectile disorders of patients with prostate cancer diagnosis. For this reason, sexual counselling should

play an important role in penile rehabilitation. It is recommended to undertake psychological interventions and Cognitive and Behavioural Therapy [50]. Study data shows that up to 49% of patients who were highly motivated before surgery to maintain their erectile function, decided not to begin any treatment after, because of inadequate consulting throughout an 18-month post-operative period [51]. Doctors, and patients as well as us in this article, mainly focus on restoring erection, and important factors such as decreased libido, anejaculation and penile size changes are often underestimated.

The patient should discuss many topics, starting with the patients' awareness of being diagnosed with cancer, factors related to the relationship and family context. It is essential to take into account the patient's clinical and sexual history before surgery, the starting time of treatment, the patient's compliance with the therapy, any adjuvant treatment, and the follow-up term. Real expectations for recovery, as well as all therapeutic options with their defects and advantages, should be presented. These questions and observations will allow us to a holistic approach to the patient's problems - we will learn his fears and expectations and the patient will be aware of the possible consequences of sexual difficulties and recovery, informed about all therapy options, and maybe even encouraged to start earlier rehabilitation.

There are recommended different modalities like sexual skills training, marital therapy, and psychosexual education. Probable consequences of operations such as possible sexual discomfort (libido, ejaculation, orgasm) should be considered. It is reported that sexual counselling (alone or with a partner) at 3 months follow-up reduces male distress, and improves male and female global sexual function with a return to baseline observed at the 6-month assessment [52]. The number of patients who decided to treat erectile dysfunction also increased in this study (from 31% to 49%). From the beginning of therapy, it's important to encourage both the patient and, if present, the partner to explore a wider range of sexual activities, including those not reliant on erections, and to maintain sexual intimacy despite erectile dysfunction and, at times, reduced libido [25].

## **SUMMARY**

Erectile dysfunction after radical prostatectomy is one of the most common complications that can reduce the quality of patients' lives in the long run. Due to the spread of prostate cancer in the population, the problem has become very important. Research is still being conducted on how to best deal with penile rehabilitation. Understanding the aetiology and the approach to the problem on many levels plays an important role.

It has been proven that erection problems are a complex interaction of the vascular and nervous systems. Attention should be paid to chronic diseases that can affect these two systems and can cause dysfunctions not associated with prostate cancer. To minimize the risk of this complication, urologists can perform surgery using a nerve-spare technique that gives better results in later treatment.

To diagnose we conduct comprehensive conversation with The International Index of Erectile Function questionnaire, physical examination and Colour Doppler Ultrasound. These methods will allow us to better understand the matter and choose the right treatment.

There are many treatment methods, pharmacological, non-pharmacological or invasive. The doctor's task is to present all options and choose the right method taking into account the medical aspects and the patient's opinion. Treatment starts early to achieve the best results. Most often, PDE5is is chosen as the first treatment line, but also intracavernous injections, vacuum erectile device therapy or penile prosthesis are available. Sexual counselling plays a big role, so the therapy should not be omitted in the long-term treatment plan.

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