

# Comorbidities Associated with Erectile Dysfunction Following Radical Prostatectomy at a University Hospital

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**Abstract:** Prostate cancer is the second most common type of cancer among men. The main therapeutic approach is radical prostatectomy (RP), which exposes patients to erectile dysfunction (ED) as a postoperative risk. In the present retrospective study, records were analyzed of 431 patients submitted to RP. The prevalence of ED in the sample was 84.7%. Higher Gleason scores denote greater disease aggressivity and predispose patients to a greater use of tadalafil in the postoperative period. Older patients and those with high PSA levels used fewer medications for ED, possibly due to the lower response to the drugs. Moreover, ED following RP was correlated with anxiety and depression, predisposing patients to a greater use of medications for ED at the onset of treatment. Adjunct therapy to RP (hormone blocking and/or radiotherapy) was associated with a higher frequency of persistent ED. Thus, age, Gleason score, anxiety, depression, diabetes mellitus and adjunct therapy are variables that predispose patients to a higher incidence of erectile dysfunction following radical prostatectomy.

**Keywords:** Prostate Cancer, Prostatectomy, Erectile Dysfunction, Comorbidities, Diabetes Mellitus

## Introduction

With the exception of non-melanoma skin cancer, prostate cancer (PC) is the most common form of cancer among men and the second most common type in terms of deaths in this population.<sup>1,2</sup> The most affected age group is 60 to 69 years, accounting for 38.21% of cases, according to the Brazilian Ministry of Health.<sup>1</sup>

The suspicion of PC is based on a high level of prostate-specific antigen (PSA) or results of the rectal exam indicating the need for biopsy.<sup>3</sup> The anatomopathological analysis confirms the diagnosis of PC and determines the Gleason classification, which, along with the PSA level determines the stage of the disease. A Gleason score of 6 corresponds to a low risk of relapse, a score of 7 corresponds to intermediate risk and scores of 8 and 10 correspond to high risk.<sup>3</sup> Moreover, PSA <10 ng/ml characterizes low risk, 10 to 20 ng/ml characterizes intermediate risk and >20 ng/ml characterizes high risk. The best treatment depends on the stage and prognostic factors of the clinical evolution in each patient.<sup>3</sup>

Radical prostatectomy (RP) is the gold standard in treatable cases<sup>2,4</sup>. This procedure can be performed

through the perineal route, laparoscopy (robot-assisted or not) or the retropubic route<sup>1, 4, 5</sup>. Erectile dysfunction (ED) is common in the postoperative period and is defined as an imbalance between contraction and relaxation of the smooth musculature of the corpus cavernosum.<sup>4,6</sup> The risk of ED is greater if RP compromises the nerve cells that innervate the penis. Therefore, surgery should involve modern preservation techniques for local neurovascular bundles.<sup>2</sup> Due to the fundamental role of neurotransmitters, there is also a strong psychogenic component in ED.<sup>4,7,8</sup>

The first line of treatment for ED is the use of phosphodiesterase type 5 inhibitors (PDE5 inhibitors), which inhibit the enzyme that enables the return of the penis to the flaccid state. The second line of treatment is intracavernous self-injection and the third line is a penile prosthesis.<sup>4</sup> The health provider should actively ask the patient about the occurrence of ED, especially following RP, as patients often do not complain about the problem, but rather wait for the physician to take the initiative.<sup>9</sup>

The aim of the present study was to characterize ED in patients submitted to RP and correlate the



prevalence of this condition with different variables to furnish risk and protection factors. The variables of interest characterized epidemiology (age and marital status), comorbidities (anxiety, depression, diabetes mellitus and smoking) and stage of PC (Gleason score and preoperative total PSA). Adjunct therapies associated with RP were also studied, such as hormone blocking (HB) and/or radiotherapy (RT).

### Methods

A retrospective, descriptive, cross-sectional study was conducted involving the records of patients submitted to RP between January 3rd, 2018 and August 29th, 2022. A maximum N of 431 patients operated for PC was obtained. Epidemiological variables, comorbidities, disease stage and adjunct therapies were investigated. This study received approval from the Human Research Ethics Committee and no data enabling the identification of the patients were used or revealed.

The data were entered onto a spreadsheet and descriptive statistics were performed with the calculation of central tendency and dispersion measures as well as frequencies. Comparisons of frequencies were performed using the classic chi-square test.

Spearman's correlation coefficients ( $r$ ) were interpreted based on Dancey and Reidy,<sup>10</sup> as follows:

- $r = 0.10$  to  $0.39$  (weak correlation)
- $r = 0.40$  to  $0.69$  (moderate correlation)
- $r = 0.70$  to  $1$  (strong correlation)

A P-value  $\leq 0.05$  was considered indicative of statistical significance in all analyses. The SPSS (IBM, version 23, 2014), PRISMA (version 6.10, 2015) and GraphPad InStat (3.10, 2009) programs were used for the statistical analyses.

### Results

Mean age was 64.608 years [95% CI: 63.911 / 65.305 | standard deviation (SD):  $\pm 7.358$  years], with a maximum of 82 and minimum of 45 years. Married individuals accounted for 66.4% of the sample (286 patients).

Mean total PSA was 10.915 ng/ml (95% CI: 9.908 / 11.922 | SD:  $\pm 10.636$  ng/ml), with a minimum of 1.29 ng/ml and maximum of 86.2 ng/ml.

Recent studies found a greater frequency of Gleason score 7 (3+4), accounting for 41.2% of cases. In the present investigation, score 7 (4+3) was also found in the largest proportion (31.3%) (Table 1).<sup>11</sup>

**Table 1.** Gleason scores of patients submitted to radical prostatectomy.

Gleason	Frequency	Percentage
10 (5+5)	1	0.2%
6 (3+3)	120	27.8%
7 (3+4)	135	31.3%
7 (4+3)	75	17.4%
8 (3+5)	16	3.7%
8 (4+4)	30	7.0%
8 (5+3)	5	1.2%
9 (4+5)	42	9.7%
9 (5+4)	7	1.6%
Total	431	100.0%

The majority of patients ( $n = 298$ ; 69.1%) reported being non-smokers, whereas 62 (14.4%) were ex-smokers and 71 (16.5%) were current smokers. No significant correlations were found between smoking habit and the other variables ( $p > 0.05$  for all correlations).

The majority of patients ( $n = 371$ ; 86.1%) reported not taking medication for diabetes mellitus (DM). The other 60 patients (13.9%) used such medications and, by inference, had diabetes, with 43 of these individuals taking metformin.

With regards to anxiety and depression, 392 (91.0%) patients reported not taking psychiatric medications. The other 39 (9.0%) took such medications. It is important to consider, especially in this group, the extent to which ED could be aggravated by the psychogenic component.<sup>4,7,8,12</sup> Amitriptyline, sertraline and clonazepam were the most frequent medications for these conditions.

Adjunct treatment to RP may be radiotherapy (RT) or hormone blocking (HB).<sup>4,13</sup> A total of 59.4% of the patients in the present study only underwent RP (Table 2).

**Table 2.** Adjunct therapies employed.

	Frequency	Percentage
Disregarded/without reports	26	6.0%
Reported not taking tadalafil	40	9.3%
Yes, takes 5 mg	363	84.2%
Yes, takes 7 mg (COMPOUNDED)	2	0.5%
Total	431	100.0%

In the first three months, the prescription and/or use

of daily oral tadalafil was, by inference, to diagnose ED. Thus, most patients ( $n = 365$ ; 84.7%) had ED for up to three months following RP (Table 3). The observational nature of this study does not enable the use of the International Index of Erectile Function (IIEF)<sup>14</sup>. However, the rate was close to that found in the recent literature, which reported the prevalence of ED following RP to be 82.6%, without describing the time of the postoperative period or severity of ED<sup>15</sup>. Rates of severe dysfunction six months after the procedure were 74% and 57.3% in two studies,<sup>5,11</sup> whereas other studies reported the prevalence to be 76 to 87% at six months after the procedure, depending on the preservation of local nerves.<sup>2</sup> The daily use of tadalafil in the first three months following RP was significantly correlated with the Gleason score ( $p = 0.001$ ).

**Table 3.** Use of oral tadalafil in first three months.

	Frequency	Percentage
RP + HB	12	2.8%
RP alone	256	59.4%
RP + RT + HB	80	18.6%
RP + RT	83	19.3%
Total	431	100.0%
RP = radical prostatectomy / RT = radiotherapy / HB = hormone blocking		

A total of 431 patients used an “attack” dose (tadalafil 20 mg or sildenafil 100 mg prior to relations), with the following distribution: 39.2% reported not taking an attack dose; 34.8% took tadalafil 20mg; 3% took sildenafil 100 mg and 23% were disregarded or did not report taking such a dose.

Age was weakly and inversely proportional to the use of PDE5 in an attack dose ( $r = -0.117$ ; 95% CI: -0.225 to 0.005 /  $p = 0.033$ ). Total PSA was also weakly and inversely proportional to the use of PDE5 in an attack dose ( $r = -0.128$ ; 95% CI: -0.236 to -0.017 /  $p = 0.019$ ). A significant correlation was found between the attack dose and psychiatric comorbidities ( $p = 0.026$ ). The attack dose was also significantly associated with adjuvant therapies ( $p = 0.012$ ).

The response of the 431 patients to the medications was divided into sex groups based on clinical status and reports of the daily use of PDE5 inhibitors and/or attack doses. Groups 1 to 4 were analyzed in a weighted, graded manner, whereas Groups 5 and 6 were excluded from the analysis.

1. Persistent ED (44.5%): continued with the complaint without improvement despite medication.

Greater ED severity.

2. Partial improvement (5.3%): taking medication with improvement in erection, but still irregular and below the preoperative level.
3. Satisfactory improvement (6.7%): erections with the use of medication with consistency and regularity for sexual relations.
4. Potent (3.5%): erections with no need for medications.
5. Complained and was not treated (0.2%): only one patient, who complained of ED but had no prescription for medication in his records; excluded from the analysis.
6. Disregarded/no information (39.7%): not cases of ED or did not take medications.

5. The use of tadalafil was analyzed temporally after six and 18 months (Table 4).

DM was significantly correlated with the daily use of tadalafil at both six months ( $p = 0.017$ ) and 18 months ( $p = 0.034$ ).

**Table 4.** Temporal changes in use of tadalafil.

	Use of tadalafil 6 months after radical prostatectomy		Use of tadalafil 18 months after radical prostatectomy	
	Frequency	Percentage	Frequency	Percentage
Disregarded/no information	174	40.4%	211	49%
No	40	9.3%	48	11.1%
Yes	217	50.3%	172	39.9%
Total	431	100%	431	100%

## Discussion

The mean age of 64.608 is in the 60-to-69-year-old age range in which PC is more prevalent in Brazil.<sup>1</sup> ED was expected to increase with age, but the opposite was found: a weak, inversely proportional correlation was found between age and the use of PDE5 in an “attack” dose. Thus, by inference, older people use tadalafil less and would have less ED. However, this inverse correlation is distorted and may be the result of the resignation to impotence and the consequent less use of PDE5 inhibitors with age. Indeed, 46% of patients in previous studies who decided to forego sex one year after RP complained of a loss of interest.<sup>8,16</sup> Moreira Júnior et al.<sup>12</sup> concluded that the both the prevalence and severity of ED increase with age, which would explain the lower response to and lower use of medications. In contrast, younger patients use PDE5 inhibitors more as a result of a greater attempt to maintain their sex life as well as due to the lower incidence and severity of ED.<sup>12</sup> Thus, the diagnosis of ED tends to be more prevalent as a more active sexual life is expected of the patients, especially younger patients, whereas

ED is underestimated in older patients.

Total PSA had a weak, inversely correlation with tadalafil used as an “attack” dose. Higher total PSA in the preoperative period, which denotes more aggressive PC according to the disease stage, is associated with the lower use of tadalafil. With age, the direct influence with the lower use of PDE5 inhibitors cannot be used to infer that the prevalence of ED is lower. Patients with more aggressive PC and high PSA are more likely to resign themselves to a lack of a sex life in the occurrence of post-RP impotence due to the low effectiveness of first-line medications and, therefore, do not take PDE5 inhibitors<sup>8</sup>. This lends strength to the hypothesis of a lower response to PDE5 inhibitors with the increase in PSA and the severity of PC. Thus, there is a proximity of conclusions among ED, an advanced age and the increase in PSA: older patients with high PSA levels (hence, more aggressive PC) also use PDE5 inhibitors less, since they have a lower response to medications and, possibly, a less active sex life, which denotes an underreporting of ED.

With regards to disease stage, the Gleason score was significantly correlated with the daily use of tadalafil in the first three months following RP. For equal but distinct sum scores, the rate of the use of PDE5 inhibitors at three months was 85.18% (115 of 135 patients) for score 7 (3+4) and 93.33% (70 of 75 patients) for score 7 (4+3). For score 9, the rate of tadalafil use was 78.57% (33 of 42 patients) for score 9 (4+5) and 85.71% (6 of 7 patients) for score 9 (5+4). Thus, the increase in the Gleason score was accompanied by greater use of tadalafil and a greater occurrence of ED in the prognosis of the patients, especially in the first three months. In a study conducted in March 2023, Konstantinos et al.<sup>5</sup> also found greater ED severity following RP with the increase in the Gleason score. In the present investigation, however, this same tendency was not found for score 8, likely due to the smaller *N* as a limiting factor: tadalafil use rate of 56.66% for 8 (3+5) (9 of 16 patients), 66.66% for 8 (4+4) (20 of 30 patients) and 100% for 8 (5+3) (5 of 5 patients). A score of 10 (5+5) was only found in one patient without the use of PDE5 inhibitors in the first three months. The tadalafil use rate was 89.16% for 6 (3+3) (107 of 120 patients), which was the second highest percentage. However, this high percentage for score 6 (3+3) is relative. As more aggressive PC tends to make patients quit using medications for ED, by the same rationale, patients with less aggressive PC would use such medications more, which explains the high percentage of use in the score 6 category. This lends strength to the findings for scores 7 and 9 as well as the hypothesis that higher Gleason scores imply a higher ED index in the prognosis, as expected based on the literature.<sup>5</sup>

Smoking was not significantly correlated with any of variable of PDE5 inhibitor use. Thus, there were no relevant statistical differences among smokers, ex-smokers and non-smokers for ED following RP in this study. Smokers (not submitted to RP for the treatment of PC) have an OR of 1.1 (95% CI: 1.1-1.2) for ED.<sup>12</sup> Recent studies report smoking to be a risk factor for ED also for individuals submitted to RP.<sup>17</sup> The lack of a correlation in the present investigation underscores the need for further studies on the influence of smoking in the postoperative period of RP.

For psychiatric comorbidities, the patients were divided into those with anxiety and depression who took medication and those who did not take medication. Among the non-users, 159 took PDE5 inhibitors in an “attack” dose (144 took tadalafil 20 mg and 15 took sildenafil 100 mg) and 163 reported not taking an attack dose, corresponding to a 49.37% rate of use. Patients with anxiety and depression were divided into 17 who took an attack dose (16 took tadalafil 20 mg and one took sildenafil 100 mg) and nine who did not take an attack dose of PDE5 inhibitors, corresponding to a 65% rate of use in this group. Studies show that patients with depression generally have an OR of 2.2 (95% CI: 2.1 – 2.4) for ED.<sup>12</sup> Considering the significant correlation of the percentages described, patients with anxiety and/or depression tend to have a greater occurrence of ED in the postoperative period and a greater recurrence of the use of PDE5 inhibitors in an attack dose. This shows the negative impact of psychiatric diseases on erections in patients submitted to RP, as also occurs in the general population.<sup>7,8,12</sup>

DM was associated with ED in the long term. The patients were divided into two groups: those who took medication for DM and those who did not take medication for DM. At six months after RP, the group with diabetes was composed of 26 patients who took tadalafil daily and four who did not take medication for ED, corresponding to an 86.66% rate of use. Among non-diabetics, 207 routinely took PDE5 inhibitors and 37 did not, corresponding to an 84.48% rate of use. At 18 months, however, the pattern was reversed, 18 diabetics took tadalafil and eight did not (69.23% rate of daily use), whereas 169 non-diabetics habitually used PDE5 inhibitors and 40 did not (80.86% rate of daily use).

The lower rates of PDE5 inhibitor use between six and 18 months by individuals with diabetes is likely due to non-response to the drug. The possibility that DM is a protective factor at 18 months and patients do not take tadalafil because they are not impotent is unlikely. The literature describes that only 38% of patients having been submitted to RP are not impotent at 18 months and DM is known to be

associated with ED (OR = 2.3; 95% CI: 2.2 – 2.4) in the general population.<sup>12, 16</sup> Extrapolating the rationale of Table 4, the cessation of PDE5 inhibitor use would globally affect patients submitted to RP irrespective of their comorbidities, as persistent ED affected 44.5% to the total *N* of 431 patients. Divergent opinions are found with regards to the maintenance of ED: Recent meta-analysis showed good recovery with the use of PDE5 inhibitors, whereas other studies report that 20 to 80% of patients became potent again.<sup>16, 18</sup> Excluding those disregarded for the improvement with medication, we have 192 patients with persistent ED among 260 valid patients and the rate increases to 73.84% in this study, although the percentage was not obtained by the IIEF.<sup>14</sup> One may hypothesize that diabetic patients had a higher incidence of ED in the first six months, but ceased taking the medications over time due to the occurrence of persistent ED.

Adjunct therapy (Table 2) was significantly associated with the use of an attack dose of PDE5 inhibitors. Among the patients submitted to RP + HB + RT, 18 took attack doses of the medication and 38 did not, corresponding to a 32.14% rate of use. Among those submitted to RP alone, the attack dose rate of use was 56.25% for PDE5 inhibitors (105 took 20 mg, 12 took sildenafil 100 mg and 91 reported not taking medications). Despite the percentage, rather than drawing the conclusion that adjunct therapy predisposed patients to a lower incidence of ED based on the use of ED, the lower use of attack doses by patients submitted to trimodal therapy may be due to the cessation of use and the greater chance of developing persistent ED. The following response rates to medications for ED were found: 71.60% (116 of 162 patients) of those submitted to RP alone had persistent ED, whereas this rate was 85.71% (36 of

42 patients) among those treated with RP+HB+RT. Adjunct therapy in PC is used in cases of greater disease aggressivity and ED is one of the complications of such therapy.<sup>5,19</sup> In the literature, RT alone for the treatment of low-risk PC increased the rate of impotence by 32% in patients who previously did not have ED and by 42% one year after treatment.<sup>5,19</sup> Thus, patients having undergone trimodal treatment are expected to be more prone to impotence as well as the cessation of medications due to persistent ED and the ineffectiveness of PDE5 inhibitors in these patients.

Limitations are inherent to the interpretation of information in patient records. In cases of ambiguity or the omission of data, the patient was excluded.

Oral medicinal treatment is considered the first choice of therapy and was therefore the most studied. However, intracavernous injection (2<sup>nd</sup> line

of therapy) and penile prosthesis 3<sup>rd</sup> line),<sup>4</sup> although initially considered suitable to the objectives of the study, were not addressed because the *N* of patients did not enable inferences.

### Conclusion

ED is highly prevalent in the postoperative period of RP, with an 84.7% rate of occurrence in the first three months. High Gleason scores indicated a higher incidence of ED and greater continuous use of tadalafil in the period. Higher levels of preoperative total PSA and the increase in age were correlated with a lower use of PDE5 inhibitors in an “attack” dose. The daily use of tadalafil also diminished between six and 18 meses in the postoperative period. The cessation of sex, persistent ED and the non-adherence to treatment for ED in the long term were found, especially in patients with a high PSA level and Gleason score.

Patients with anxiety and/or depression taking psychiatric medications for these conditions had a greater occurrence of ED, inferred by the use of “attack” doses of PDE5 inhibitors. The use of tadalafil diminished significantly among patients with diabetes between six and 18 months after RP, suggesting persistent ED in this group. Patients having been submitted to trimodal therapy (RP+RT+HB) took “attack” doses of PDE5 inhibitors less and complained of persistent ED more compared to those submitted to radical prostatectomy alone. Therefore, these comorbidities and variables are predisposing factors to the greater use of PDE5 inhibitors or, in more severe cases, persistent ED.

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