

Impact of advanced prostatic cancer treatment on quality of life and sexual function

Impacto do tratamento avançado do câncer de próstata na qualidade de vida e na função sexual

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ABSTRACT

Introduction: The studying the quality of life after cancer treatment has become a priority in oncology. **Objectives:** To evaluate the impact of different treatments for recurrence prostate cancer on quality of life and sexual activity. **Material and Methods:** Two hundred patients with recurrence prostate cancer after initial treatment were distributed into four groups according to the following protocol: group 1 - open prostatectomy and androgen deprivation hormone therapy; group 2 - open prostatectomy combined with radiotherapy and androgen deprivation hormone therapy; group 3 - androgen deprivation hormone therapy alone; and group 4 - radiotherapy combined with androgen deprivation hormone therapy. All patients answered two questionnaires validated for Brazil related to the quality of life, the European Quality of Life Questionnaire and the International Index of Erectile Function. The presence of urinary tract infection, hematuria, hematochezia, urinary incontinence, and urethral stricture after the treatments were also investigated. The adverse effects reported in the four groups following the treatments were statistically compared and significance was considered indicated by p -values of <0.05 . **Results:** This study revealed worse mobility and self-care, greater limitations of usual activities, and a higher incidence of urinary incontinence and erectile dysfunction in patients who underwent prostatectomy. All these adverse effects were worse when the surgical procedure was associated with radiotherapy and androgen deprivation hormone therapy. **Conclusion:** Prostatectomy is associated with complications, which are responsible for a worse quality of life due to mobility limitations, difficulty in self-care, urinary incontinence, and sexual dysfunction. All these adversities worsen when the surgery is combined with radiotherapy and androgen deprivation hormone therapy.

Keywords: Quality of life; Erectile dysfunction; Prostatectomy; Radiotherapy.

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RESUMO

Introdução: Estudar a qualidade de vida após o tratamento do câncer tornou-se uma prioridade na oncologia. **Objetivos:** Avaliar o impacto de diferentes tratamentos para recidiva do câncer de próstata na qualidade de vida e na atividade sexual. **Material e Métodos:** Duzentos pacientes com recidiva de câncer de próstata após tratamento inicial foram distribuídos em quatro grupos de acordo com o seguinte protocolo: grupo 1 - prostatectomia aberta e terapia hormonal de privação de androgênio; grupo 2 - prostatectomia aberta combinada com radioterapia e terapia hormonal de privação de androgênio; grupo 3 - terapia hormonal de privação de androgênio isoladamente; e grupo 4 - radioterapia combinada com terapia hormonal de privação de androgênio. Todos os pacientes responderam a dois questionários validados para o Brasil relacionados à qualidade de vida, o Questionário Europeu de Qualidade de Vida e o Índice Internacional de Função Erétil. Também foi investigada a presença de infecção do trato urinário, hematúria, hematoquezia, incontinência urinária e estenose uretral após os tratamentos. Os efeitos adversos relatados nos quatro grupos após os tratamentos foram comparados estatisticamente e a significância foi considerada indicada por valores de $p < 0,05$. **Resultados:** Este estudo revelou pior mobilidade e autocuidado, maiores limitações nas atividades habituais e maior incidência de incontinência urinária e disfunção erétil em pacientes submetidos à prostatectomia. Todos esses efeitos adversos foram piores quando o procedimento cirúrgico foi associado à radioterapia e à terapia hormonal de privação de androgênio. **Conclusão:** A prostatectomia está associada a complicações, responsáveis por pior qualidade de vida devido a limitações de mobilidade, dificuldade no autocuidado, incontinência urinária e disfunção sexual. Todas essas adversidades pioram quando a cirurgia é combinada com radioterapia e terapia hormonal de privação de androgênio.

Descritores: Qualidade de vida; Disfunção erétil; Prostatectomia; Radioterapia.

INTRODUCTION

Prostate cancer (PC) is the most common nonskin cancer in the United States, with an estimated 268,490 new cases associated with 34,500 deaths in 2022.^[1] When small and located only in the prostate, PC can be clinically followed up with biopsies and periodic imaging exams or treated with curative intent, through prostatectomy and radiotherapy (RT).^[2] Even after a properly treated cancer limited to the prostate, approximately 30% of PC persist.^[3] There are several criteria to define recurrence prostate cancer (RPC) after treatment, being the prostate-specific antigen (PSA) level being the most used and studied.^[4]

Quality of life is a multidimensional concept, that considers the patient's subjective regards. About themselves, considering multiple aspects of their real and desired lives. Studies on quality of life include health, social, mental, and physical characteristics.^[5] Most studies on quality of life in PC refer to the initial stage of the disease and compare various treatments, with a focus on isolated prostatectomy or combined with RT and hormone therapy. According to Chen et al. (2017),^[6] surgical procedures on prostate are frequently associated with urinary incontinence (UI)

and sexual dysfunction. Other treatments such as RT are also responsible for sexual dysfunctions, UI, urinary infections, cystitis, and severe dermatitis, as well as digestive complications, including diarrhea, hematochezia, and strictures.^[7] To prevent these adversities and maintain quality of life, the option of not treating PC has been accepted as an active follow-up approach.^[8] Most studies have not revealed any difference in quality of life after different treatments, which may be isolated or combined.^[9]

Considering RPC after different managements protocols, many new treatments are indicated to prevent PC growth and metastasis. These therapies do not cure patients, but control complications, such as bone pain, urinary disorders, infections, and digestive disorders, which worsen the quality of life. On the other hand, the various treatments for RPC are accompanied by adverse effects, which also interfere with quality of life.

MATERIAL AND METHODS

This work was approved by the Ethics Committee for Human Research - CAAE: 4149021.1.0000.5140. All patients were invited to participate in this study, and they signed their agreement to the Free and Informed Consent Terms. This study was carried

out on 200 consecutive patients with RPC after treatment at the Oncology Services of the Municipal Health Department, Belo Horizonte, Brazil. The RPC was established by persistence of PSA after radical prostatectomy or after radiotherapy any PSA increase >2ng/ml higher than the PSA nadir, regardless of the nadir value.^[10] The adenocarcinoma was confirmed by needle biopsy guided by ultrasound. The interviews with the patients occurred about symptoms before any treatment and six months after the last treatment for RPC, to avoid the immediate and transient effects of the treatment. Patients were distributed into the following four groups, according to the treatments they underwent: group 1 (N=35) – open prostatectomy and androgen deprivation hormone therapy (ADHT); group 2 (N=69): open prostatectomy combined with RT and ADHT; group 3 (N=29): only ADHT; group 4 (N=67): RT combined with ADHT.

This study assessed the quality of life outcomes in the four groups of treated patients with biochemical recurrence, comparing the results before and after each treatment. The quality of life was assessed by means of the European Quality of Life Questionnaire (EQ-5D5L), a questionnaire validated internationally and in Brazil for five dimensions (mobility, self-care, usual activities, pain, and emotional disorders).^[11] In addition to these parameters, the presence of urinary infection, hematuria, hematochezia, UI, and urethral stricture were investigated. Recurrent urinary tract infection was considered when there were more than two episodes in one year.^[12] Hematuria was confirmed by routine urinary examination. Hematochezia was confirmed by fecal occult blood test. UI was considered when there was a need to use more than one diaper per day.^[13] Urethral stricture was assessed by delayed onset of voiding, with a fine stream and multiple voiding interruptions.^[14] Each dimension and complication was classified according to intensity as follows: 1 (no complaints), 2 (few complaints), 3 (moderate complaints), 4 (intense complaints), and 5 (very intense complaint).^[15]

Erectile dysfunction (ED) was uniformly assessed in 25 randomized patients from each group by means of the International Index of Erectile Function (IIEF-5), comparing the results before and after each treatment. Erection and sexual satisfaction were classified by frequency 0 (never), 1 (rarely), 2 (moderately), 3 (frequently), 4 (almost always), and 5 (always).^[16]

Nominal variables were expressed as frequencies and percentages, and numerical variables such as age, EQ-5D5L domains and IIEF-5 assessment, which did not have a normal Gaussian distribution, were calculated using the nonparametric Kruskal-Wallis test. In comparing the medians between two independent groups, referring to age and IIEF-5 data, the nonparametric Mann-Whitney test with Bonferroni correction was used. The association of hypotheses between categorical variables from different groups was verified by applying Fisher's

exact test. All analyses were performed using SPSS 23 software (Statistical Package for the Social Sciences 23) and the significance level considered was greater than 95%, corresponding to $p < 0.05$.

RESULTS

The median age of patients in group 1 was 71 (65 to 75) years, in group 2 it was 68 (62 to 72) years, in group 3 it was 69 (63 to 76) years and in group 4 it was 72 (67 to 78) years. In the four groups, the age range was similar and the single difference between the groups was that the age was lower in group 2 than in group 4 ($p < 0.041$), but without significance for this study.

According to the EQ-5D5L, the mobility of patients after the treatments studied was worse in group 2. It should be noted that most patients in all groups had no mobility limitation and no patient suffered severe limitation (Table 1). Self-care was assessed by the ability to shower alone and get dressed. Groups 2 and 3 had the worst results, with most patients in all groups having up to moderate limitations in self-care (Table 1). There was no difference between the four groups in routine activities, although group 2 had greater difficulties (Table 1). Pain was also not different between the four groups. On the other hand, emotional disorders were less apparent in group 1 and more intense in group 3 (Table 1).

UI occurred in all four groups: in group 1 (20.0%), group 2 (30.4%), group 3 (6.9%), and group 4 (7.5%). The results of group 2 were worse than the other three groups ($p = 0.002$). Other complications were observed, including urethral stricture, urinary infection, hematuria, and hematochezia. All of them occurred in a few patients and there was no difference between groups, probably due to the reduced number of cases with complications (Table 2).

According to the responses to the IIEF-5 questionnaire, there was a worsening on sexual function in all four treatments, with no difference among them. There was erection dysfunction and sexual dissatisfaction after all treatments, and with greater severity in the groups submitted to prostatectomy. All patients had erection and sexual satisfaction, even if rarely, and no patient showed erection and sexual satisfaction always (Table 3).

DISCUSSION

This study adopted the EQ-5D5L questionnaire to assess the quality of life of patients with RPC, as it is a standardized protocol accepted in the Brazilian literature, with reliable results. Studies on quality of life in patients with RPC were not found in the literature. Considering that RPC survival, regardless of treatment, exceeds ten years in 98% of patients, quality of life becomes relevant.^[17] The treatments aim to control the disease, even if it is not cured, preserving or improving the quality of life.

Table 1. Dimensions of the European Quality of Life Questionnaire, in the four types of treatment for remaining prostate cancer, presented as number of cases (N) and their percentage in each group.

Dimension	Group 1 (N = 35)		Group 2 (N = 69)		Group 3 (N = 29)		Group 4 (N = 67)		P
	Before N (%)	After N(%)	Before N (%)	After N(%)	Before N (%)	After N(%)	Before N (%)	After N(%)	
Mobility									
1	34(97)	33(94.3)	49(71)	50(72.5)	24(83)	24(82.8)	60(89.6)	60(89.6)	0.014
2	1(3)	2(5.7)	19(27)	18(26.1)	5(17)	4(13.8)	7(10.4)	7(10.4)	0.020
3	0(0)	0(0)	1(2)	1(1.4)	0(0)	1(3.4)	0(0)	0(0)	0.299
Self-care									
1	35(100)	8(22.9)	53(77)	8(11.6)	20(69)	8(27.6)	52(78)	12 (17.9)	0.232
2	0(0)	18(51.4)	15(22)	27(39.1)	9(31)	14(48.3)	11(16)	42(62.7)	0.055
3	0(0)	9(25.7)	1(1)	24(34.8)	0(0)	6(20.7)	4(6)	12(17.9)	0.138
4	0(0)	0(0)	0(0)	8(11.6)	0(0)	1(3.4)	0(0)	1(1.5)	0.025
5	0(0)	0(0)	0(0)	2(2.9)	0(0)	0(0)	0(0)	0(0)	0.646
Activities									
1	29(82)	23(65.7)	60(87)	36(52.2)	14(48)	20(69)	52(78)	52(77.6)	0.019
2	5(14)	6(17.1)	7(10)	10(14.5)	10(34)	5(17.2)	10(15)	4(6)	0.246
3	1(4)	5(14.3)	2(3)	18(26.1)	4(14)	2(7.0)	4(6)	11(16.4)	0.116
4	0(0)	1(2.9)	0(0)	5(7.2)	1(4)	3(4)	1(1)	0(0)	0.102
5	0(0)	0(0)	0(0)	0(0)	0(0)	1(3.4)	0(0)	0(0)	0.145
Pain									
1	19(54)	14(40)	42(61)	27(39.1)	13(45)	11(37.9)	31(46)	30(44.8)	0.891
2	15(42)	17(48.5)	22(32)	25(36.2)	9(31)	9(31)	21(31)	24(35.8)	0.480
3	1(4)	3(8.6)	5(7)	10(14.5)	5(17)	2(6.9)	10(15)	8(11.9)	0.750
4	0(0)	0(0)	0(0)	3(4.3)	2(7)	3(10.4)	5(8)	3(4.5)	0.260
5	0(0)	1(2.9)	0(0)	4(5.9)	0(0)	4(13.8)	0(0)	2(3.0)	0.200
Emotional disorders									
1	34(97)	33(94.2)	65(94)	57(82.6)	25(86)	20 (69.0)	64(96)	60 (89.5)	0.022
2	1(3)	1(2.9)	3(4)	11(15.9)	5(7)	5(17.3)	2(3)	4(6.0)	0.061
3	0(0)	0(0)	1(2)	0(0)	0(0)	1(3.4)	0(0)	0(0)	0.145
4	0(0)	1(2.9)	0(0)	1(1.5)	2(7)	3(10.3)	1(1)	3(4.5)	0.215

Group 1 – prostatectomy and androgen deprivation hormone therapy (ADHT); Group 2 – prostatectomy associated with radiotherapy (RT) and ADHT; Group 3 – ADHT alone; Group 4 – RT associated with ADHT. Before and After treatment. Dimensions intensity: 1(without complaint), 2(little complaint), 3 (moderate complaint), 4 (intense complaint) e 5 (very intense complaint). P corresponding to Fisher's exact test.

According to the analysis of the EQ-5D5L domains, the results of this study revealed that all treatments interfere with mobility and are accompanied by difficulties in self-care, with restrictions on the patients' usual activities. Restrictions are moderate and many of them are result from the RPC itself associated with advanced age and metastases. Comorbidities such as fatigue due to cardiopulmonary failure, sarcopenia and osteoporosis are also responsible for greater

limitations in the quality of life.^[18] More aggressive treatments, mainly the open prostatectomy associated with RT worsen the limitations to mobility and self-care, as well as UI, which negatively interfere on the quality of life.^[19]

The results of this work contradict the publication by Downing et al. (2019),^[20] who assign the worsening in quality of life only to the advanced cancer

Table 2. Late urological and digestive manifestations after treatments for remaining prostate cancer. Results are presented as number of cases (N) and their percentage in each group.

Clinical manifestations	Group 1 (N = 35)		Group 2 (N = 69)		Group 3 (N = 29)		Group 4 (N = 67)		P
	Before	After	Before	After	Before	After	Before	After	
Urinary incontinence	0(0)	7(20,0)	0(0)	21(30,4)	0(0)	2 (6,9)	0(0)	5 (7,5)	0,002
Urethral stricture	0(0)	2(5,7)	0(0)	7 (10.1)	0(0)	4(13.8)	0(0)	7(10.4)	0.769
Urinary infection	0(0)	1(2,9)	0(0)	2(2,9)	0(0)	0(0)	0(0)	1(1,5)	1.000
Hematuria	0(0)	0(0)	0(0)	5(7,2)	0(0)	1(3,4)	0(0)	1(1,5)	0.209
Hematochezia	0(0)	0(0)	0(0)	4(5,8)	0(0)	0(0)	0(0)	2(3,0)	0.389

Group 1 – prostatectomy and androgen deprivation hormone therapy (ADHT); Group 2 – prostatectomy associated with radiotherapy (RT) and ADHT; Group 3 – ADHT alone; Group 4 – RT associated with ADHT; Before and After treatment P corresponding to Fisher's exact test.

stage. UI is the most frequent complication after prostatectomy, and it is present in 4% to 69% of the patients submitted to prostatectomy, depending on the surgical methods and experience of the surgeons.^[21] This adversity, sometimes definitive, despite not being life threatening, is harmful to the quality of life. UI is, in general, a consequence of surgical injury to the neurovascular plexus, including the pudendal nerve. This injury is more frequent in open prostatectomies performed by less skilled surgeons.^[22] On the other hand, in conservative treatments, such as RT and hormone therapy, UI is rare (1% to 5%).^[23] This complication is also associated with dysfunctions resulting vesical sphincter hypotonia due to aging.

Obesity, neurological disorders and alcoholism may curse with UI, even without cancer treatment. It is important to point out that group 1, open prostatectomy and ADHT, were formed with patients that probably suffered surgical treatment and patient didn't agree to treat with salvage radiotherapy or new exams revealed new lesions that didn't justify any radiotherapy. Moreover, group 3 formed with patients that received only ADHT differs from the others because they were on slightly more advanced stages than other groups. Notwithstanding, we observed that patients in group 3 with more advanced diseased produced any difference on the final results because the biggest loss in quality of life maintained with group 2 (prostatectomy combined with RT and ADHT).

Anxiety and depression are psychiatric manifestations often attributed to cancer treatments, but they are rarely diagnosed by psychiatrists. The real feeling is generally an emotional disorder, most often sadness, which is due to the cancer, its complications, aggressive treatment, and social limits. In this study, emotional disorders were more frequent after TAD, probably due to adverse drug effects in more advanced stages of RPC. According to the

literature, hormonal blockade for RPC has a 23% higher risk of adverse emotional manifestations and dementia states, which may be treated with testosterone.^[24] Emotional adversities occur more frequently in elderly people who live in isolation and especially in the presence of comorbidities.^[25]

In this study, the four treatments impaired the sexual performance. Prostatectomy and RT were the treatments more frequently associated with sexual dysfunction and worsening of quality of life. Sexual dysfunction occurs in 30% to 50% of patients with RPC, with an increase in prevalence with advancing age and the presence of comorbidities, such as diabetes mellitus, obesity, heart disease, and restrictive lung diseases.^[26] It should be noted in this study that more than 40% of patients undergoing prostatectomy preserved their sexual ability and more than half of patients undergoing RT reported erections with sufficient rigidity to establish satisfactory sexual performance, similar to other studies.^[27] It should be noted that the literature reports less sexual dysfunction, UI and effect on quality of life after prostatectomies performed by minimally invasive methods and with the aid of robotic equipment.^[28] However, in the series all patients underwent open prostatectomy.

Male libido is influenced by testosterone receptors, which are essential for penile smooth muscle relaxation promoting erection. RT modifies the penile architecture, with reduction of smooth muscle and its replacement by fibrous tissue, compromising erection.^[29]

CONCLUSION

Open prostatectomy is associated with complications, which are responsible for a worse quality of life due to mobility limitations, difficulty in self-care, urinary incontinence, and sexual dysfunction. All these adversities worsen when the surgery is combined with radiotherapy and androgen deprivation hormone therapy.

Table 3. Comparison between the values of the International Erectile Dysfunction Index Questionnaire from the six months prior to this study, in the four types of treatment for remaining prostate cancer, presented as number of cases (N) and their percentage in each group composed of 25 patients.

Variable	Group 1 (N = 25)		Group 2 (N = 25)		Group 3 (N = 25)		Group 4 (N = 25)		P
	Before N (%)	After N(%)	Before N (%)	After N(%)	Before N (%)	After N(%)	Before N (%)	After N(%)	
Frequency of rigid erection maintenance									0.031
1	0(0)	12(48)	0(0)	16(64)	0(0)	10(40)	1(4)	10(40)	
2	0(0)	13(52)	0(0)	9(36)	0(0)	10(40)	4(16)	0(40)	
3	1(4)	0(0)	0(0)	0(0)	5(20)	3(12)	0(0)	0(0)	
4	6(24)	0(0)	6(24)	0(0)	15(60)	2(8)	9(36)	5(20)	
5	18(72)	0(0)	19(76)	0(0)	5(20)	0(0)	11(44)	0(0)	
Degree of confidence in erections with sufficient rigidity									0.049
1	0(0)	11(44)	0(0)	16(64)	0(0)	10(40)	0(0)	10(40)	
2	0(0)	13(52)	0(0)	9(36)	0(0)	10(40)	2(8)	10(40)	
3	1(4)	0(0)	0(0)	0(0)	5(20)	3(12)	0(0)	0(0)	
4	6(24)	0(0)	6(24)	0(0)	15(60)	2(8)	11(44)	5(20)	
5	18(72)	0(0)	19(76)	0(0)	5(20)	0(0)	12(48)	0(0)	
How many erections had sufficient rigidity during intercourse									0.017
1	0(0)	10(40)	0(0)	16(64)	0(0)	11(44)	2(8)	10(40)	
2	0(0)	15(60)	0(0)	9(36)	0(0)	9(36)	3(12)	10(40)	
3	0(0)	0(0)	0(0)	0(0)	5(20)	3(12)	0(0)	0(0)	
4	6(24)	0(0)	6(24)	0(0)	15(60)	2(8)	14(56)	5(20)	
5	19(76)	0(0)	19(76)	0(0)	5(20)	0(0)	6(24)	0(0)	
Maintain an erection with sufficient rigidity during intercourse									0.017
1	10(40)		0(0)	16(64)	0(0)	11(44)	1(4)	10(40)	
2	15(60)		0(0)	9(36)	0(0)	9(36)	1(4)	10(40)	
3	0(0)	0(0)	0(0)	0(0)	4(16)	3(12)	0(0)	0(0)	
4	6(24)	0(0)	6(24)	0(0)	13(52)	2(8)	12(48)	5(20)	
5	19(76)	0(0)	19(76)	0(0)	8(32)	0(0)	11(44)	0(0)	
Patient satisfaction during sexual intercourse									0.018
1	0(0)	10(40)	0(0)	16(64)	0(0)	10(40)	2(8)	10(40)	
2	0(0)	15(60)	0(0)	9(36)	0(0)	10(40)	2(8)	10(40)	
3	0(0)	0(0)	0(0)	0(0)	4(16)	3(12)	0(0)	0(0)	
4	6(24)	0(0)	6(24)	0(0)	13(52)	2(8)	11(44)	5(20)	
5	19(76)	0(0)	19(76)	0(0)	8(32)	0(0)	10(40)	0(0)	

AUTHORS' CONTRIBUTIONS

- FPM Collection and assembly of data, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient
- AP Conception and design, Data analysis and interpretation, Final approval of manuscript

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