

Predictors of Complications following 3D Conformational Radiotherapy in Patients with Prostate Adenocarcinoma

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Fatores Preditores de Complicações após Radioterapia Conformacional 3D em Pacientes com Adenocarcinoma de Próstata
Factores Predictores de Complicaciones después de la Radioterapia Conformacional 3D en Pacientes con Adenocarcinoma de Próstata

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Abstract

Introduction: Prostate cancer is considered the most common malignancy that affects men in all regions of the country, except for non-melanoma skin cancer. If diagnosed and treated early, prostate cancer has a high cure rate; however, therapies such as radiotherapy can generate acute complications that can impact daily activities. Despite post-treatment complications, radiotherapy has been a widely practiced method and has shown positive results, leading to improved disease-free survival. **Objective:** To evaluate the main predictive factors for acute complications that affect patients undergoing radiotherapy for prostate cancer. **Method:** To identify predictive factors for acute post-radiotherapy complications, 208 patients diagnosed with prostate adenocarcinoma treated with 3D conformational radiotherapy were consecutively and prospectively evaluated at a referral center linked to SUS between the years 2016 and 2017. It was carried out retrospective evaluation of medical records to collect additional data. Statistical analysis was performed using the chi-square test, Fisher's exact, Anova and ordinal logistic regression. **Results:** After analyzing the sample, it was evidenced that among the acute complications, those with the highest incidence were radiodermatitis, cystitis, enteritis/rectitis, so that these complications had associated predictive factors as irradiated volume, previous treatment and symptoms. **Conclusion:** The study suggests that despite the existence of complications at the end of the treatment, the vast majority are of low complexity and that the patients submitted to previous surgical procedures can evolve with the presence of more severe complications.

Key words: Prostatic Neoplasms; Prognosis; Radiotherapy; Acute Toxicity.

Resumo

Introdução: O câncer de próstata é considerado a neoplasia maligna mais comum que acomete homens em todas as Regiões do país, à exceção do câncer de pele não melanoma. Se diagnosticado e tratado precocemente, o câncer de próstata tem alta taxa de cura; contudo, terapêuticas como a radioterapia podem gerar complicações agudas que podem impactar as atividades cotidianas. Apesar das complicações no pós-tratamento, a radioterapia tem sido um método bastante praticado e que apresenta resultados positivos, ocasionando melhoria da sobrevida livre de doença. **Objetivo:** Avaliar os principais fatores preditores de complicações agudas que acometem pacientes em tratamento radioterápico para câncer de próstata. **Método:** Para identificação de fatores preditores de complicações agudas pós-radioterapia, avaliaram-se, consecutiva e prospectivamente, 208 pacientes diagnosticados com adenocarcinoma de próstata tratados com radioterapia conformacional 3D em um centro referência vinculado ao SUS entre os anos 2016 e 2017. Realizou-se ainda avaliação retrospectiva de prontuários para coleta de dados adicionais. A análise estatística foi realizada por meio dos testes qui-quadrado, exato de Fisher, Anova e regressão logística ordinal. **Resultados:** Após análise da amostra, evidenciou-se que, entre as complicações agudas, as de maior incidência foram radiodermite, cistite e enterite/retite, de forma que tais complicações tiveram como fatores associados volume irradiado, tratamento prévio e sintomas prévios ao tratamento. **Conclusão:** O estudo sugere que, apesar da existência de complicações ao final do tratamento, a grande maioria é de baixa complexidade e que pacientes submetidos a procedimentos cirúrgicos prévios podem evoluir com presença de complicações mais graves.

Palavras-chave: Neoplasias da Próstata; Prognóstico; Radioterapia; Toxicidade Aguda.

Resumen

Introducción: El cáncer de próstata se considera la neoplasia maligna más común que afecta a los hombres en todas las regiones del país, con la excepción del cáncer de piel no melanoma. Si se diagnostica y trata temprano, el cáncer de próstata tiene una alta tasa de curación; sin embargo, las terapias como la radioterapia pueden generar complicaciones agudas que pueden afectar las actividades diarias. A pesar de las complicaciones posteriores al tratamiento, la radioterapia ha sido un método ampliamente practicado y ha mostrado resultados positivos, lo que lleva a una mejor supervivencia libre de enfermedad. **Objetivo:** Evaluar los principales predictores de complicaciones agudas que afectan a los pacientes sometidos a radioterapia para el cáncer de próstata. **Método:** Para identificar los factores predictivos de complicaciones agudas posteriores a la radioterapia, 208 pacientes diagnosticados con adenocarcinoma de próstata tratados con radioterapia conformacional 3D fueron evaluados consecutiva y prospectivamente en un centro de referencia vinculado al SUS entre los años 2016 y 2017. Se realizó evaluación retrospectiva de registros médicos para recopilar datos adicionales. El análisis estadístico se realizó utilizando la prueba de chi-cuadrado, exacta de Fisher, de Anova y la regresión logística ordinal. **Resultados:** Después de analizar la muestra, se evidenció que, entre las complicaciones agudas, las de mayor incidencia fueron radiodermatitis, cistitis, enteritis/retitis y síntomas obstructivos, por lo que estas complicaciones tenían factores predictivos asociados, como el volumen irradiado, el tratamiento previo y los síntomas. **Conclusión:** El estudio sugiere que a pesar de la existencia de complicaciones al final del tratamiento, la gran mayoría son de baja complejidad. Como factores predictivos encontrados, se puede mencionar el volumen irradiado, la existencia de tratamiento previo y los síntomas en la consulta inicial.

Palabra clave: Neoplasias de la Próstata; Pronóstico; Radioterapia; Toxicidad Aguda.

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INTRODUCTION

Prostate cancer is considered the malignant neoplasm most common affecting males across all the country's regions, with exception of non-melanoma skin cancer^{1,2}. For each year of the triennium 2020-2022, it was estimated the appearance of 65,840 new cases in Brazil¹. The high incidence is associated to factors as advanced age, hypercaloric diet, hereditariness and ethnicity². The treatment can be done with surgery approach, external radiotherapy, hormone therapy, cryotherapy or active surveillance². If early diagnosed and treated, prostate cancer has high rate of cure; however, therapies as radiotherapy can create acute complications that can impact the daily activities. Acute complications are reactions that appear during the treatment or in the next three months³. The choice of the treatment should be contingent upon the wish of the patient and of the characteristics of the disease; but, many times, will depend on what kind of professional made the first approach – urologist, oncologist or radiotherapist³.

Despite post-treatment complications, radiotherapy has been a quite practiced method presenting positive results, bringing improvement of disease-free survival, mainly in patients with less than 70 years^{2,3}. In the three dimensional conformal radiotherapy (RT3D), high technology is used to allow better location of the target, ensuring more protection of the adjacent organs. When compared to the conventional method, it is observed that high doses released with RT3D generate low toxicity^{4,5}. However, complications resulting from the treatment as radiodermatitis, cystitis, proctitis among other are still verified^{6,7}.

Based in the explanation, the study aims to discover the main predictive factors of acute toxicity in the radiotherapy treatment in patients with prostate cancer. Therefore, after the analysis, it is possible to list the significant factors that may contribute for more effective medical management to ensure less complications.

METHOD

Retrospective, descriptive and unicentric study conducted between January 2016 and December 2017 at the Treatment Center Oncoradium. It consisted in the evaluation of 208 consecutive charts of only one institution associated to the National Health System (SUS) corresponding to patients with prostate adenocarcinoma diagnosed by transrectal biopsy. It was excluded from the analysis the patients who died, had metastasis or the charts were incomplete.

Data collection was performed through the analysis of the medical charts with the identification

of the patient, age, comorbidity, family cancer history, previous treatment, symptoms in the first visit with the radiotherapist, staging according to the System TNM of Classification of Malignant Tumors, Gleason, total prostatic specific antigen (PSA), card with technical data about radiotherapy, finality of the treatment and presence of acute complications. The identification of charts occurred through the Code C61 of the International Classification of Diseases and Health Related Problems – 10th, edition (ICD-10), present in every chart and the patients were staged according to the System TNM of the American Joint Committee of Cancer (AJCC), 7th, edition. For the purposes of the study, the patients were re-staged according to the updated AJCC 8th, edition. The Institutional Review Board of the College of Imperatriz approved the study, number 09422017.

The PTV – Planning Target Volume of the treatment was calculated by the department of medical physics of the facility utilizing the system Eclipse Planning (version 10.0, Varian Medical Systems, Palo Alto, CA[®]), of the program External Beam Planning, through computer tomography with additional margins of 10mm across all directions, except in the rectum with 6mm as exposed in Figure 1. All the patients of the present study were submitted to RT3D, a method that emits beams of linear photons with energy of 6MV, utilizing usually four fields of irradiation through the Lineal Accelerator Clinac 6EX[®] of the manufacturer Varian Medical Systems Brasil Ltda[®], in supine position and support under the feet, the irradiation was 1.8 to 2 Gy per day, five days a week, with dose of radiation determined at the discretion of the radiotherapist. The irradiations were divided in two phases, the first with irradiation over the prostate/prostatic bed and seminal vesicles (SV) corresponding to PTV1 and the second phase over the prostate/prostatic bed corresponding to PTV2 always respecting the limit of the dose of acceptable irradiation that do not cause specific damages; these dose restrictions are related, according to the Quantitative

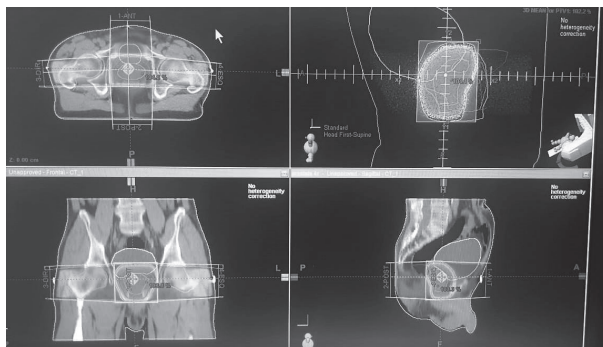


Figure 1. Print screen showing the calculation of the planning target volume of the prostate utilizing the system Eclipse Planning

Analysis of Normal Tissue Effects in Clinic (Quantec)⁹ to bladder: 80 Gy<15%, 75 Gy<25%, 70 Gy<35% and 65 Gy<50%; to the rectum: 75 Gy<15%, 70 Gy<20%, 65 Gy<25%, 60 Gy<35% and 50 Gy<50% and to the femoral heads, 50 Gy<5%.

During the treatment, the patients attended week visits where occasional urinary related complaints were investigated and possible acute gastrointestinal complications resulting from the therapy. The complications were classified pursuant to the Common Terminology Criteria for Adverse Events (CTCAE)¹⁰v5.0, according to the complaints presented by the patients (Plan 1). Other criteria evaluated are described in Tables 1 and 2.

After the identification of the patients, the data were recorded and, next, tabulated in an electronic spreadsheet elaborated with the software Excel (Microsoft Office Excel 11.0/2007 – Microsoft Corporation®) and further processed with the support of the software Minitab 18

-SPSS. The analysis was divided in exploratory with tabulation and chart of all the variables and tests of hypothesis applied via Minitab 18 – SPSS, the associations among the variables were verified by the chi-square test and by the exact Fisher test and analysis of variance Anova. Jointly, it was used the model of ordinal logistic regression, widely utilized in medicine, that aims to indicate the probability of the predictive variables to influence the occurrence of the response variable with levels of ordination. The function utilized to adjust the equations was the model Logito (logit). The level of significance attributed to the tests is 5% with confidence interval of 95% and sampling error calculated of 5%.

RESULTS

It was evaluated 208 patients with mean age of 72 years. In the analysis of habits and presence of comorbidities ($p=0.156$), it was evidenced that 131

Plan 1. Urinary and gastrointestinal complications (CTCAE v5.0)

Complications	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Radiodermatitis	Frank erythema with drying or desquamation	Erythema with moderate edema, moist desquamation, mainly in cutaneous folds	Moist desquamation in areas other than the cutaneous folds, bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration affecting the dermis. Spontaneous bleeding of the site involved with life risk. Indication of skin graft	Death
Cystitis	Microscopic hematuria, increase of frequency and urinary urgency, mild dysuria or nocturia	Moderate hematuria, dysuria and nocturia. Moderate increase of the frequency, incontinence and urinary urgency. Catheter placement or bladder irrigation indicated	Gross hematuria transfusion IV medications, or hospitalization, elective invasive intervention indicated	Life-threatening consequence, urgent invasive intervention indicate	Death
Dysuria	Present	-	-	-	-
Proctitis	Rectal discomfort without indication of intervention	Rectal discomfort, presence of blood or mucus during evacuation, indicate medical intervention	Severe symptoms with urgency or fecal incontinence needing diapers	Perforation, bleeding or necrosis with risk of death that needs surgical intervention	Death

Caption: CTCAE=Common Terminology Criteria for Adverse Event.

patients (6.35%) claimed they were ex-tobacco addicted, 53 patients (25%), ex-alcohol users, 109 patients (52%) had systemic arterial hypertension, 18 patients (9%) *diabetes mellitus* and 87 patients (41.8%), affirmed history of cancer in the family. It was observed that 126 patients (56%) reported symptoms in the initial consultation with radiotherapy pre-treatment ($p=0.026$), and, of these, the most common were moderate/severe urinary urge incontinence, present in 41 patients (20%), followed by mild urge incontinence in 30 patients (14%), terminal dripping in 26 patients (13%) and mild dysuria in 22 patients (11%). After the analysis, it was shown that 114 patients (54.8%) submitted to previous treatment and 63 patients (30.3%) to two treatments, the most frequent were neoadjuvant hormone therapy in 129 patients (62%), followed by radical prostatectomy in 76 patients (37%) as exposed in Table 1.

Most of the acute complications encountered in the sample was classified as low risk according to the Common Terminology Criteria for Adverse Event (CTCAE) v5.0, the most prevalent were radiodermatitis, cystitis, enteritis/proctitis and obstructive symptoms as verified in Table 2.

It was observed that 131 patients (62.98%) underwent radiotherapy of radical/curative characteristic ($p=0.979$) so the finality of the radiotherapy treatment applied does not influence directly in the existence of post-treatment complications. Also, it was verified that 22 patients (11%) presented biochemical relapse, but there was no direct influence in the appearance of post-radiotherapy complications ($p=0.195$).

In regard to the dose of irradiation received during the treatment, nearly 170 patients (81.73%) received the average initial dose of 54 Gy in PTV1 and 112 patients (53.85%), doses above 70 Gy as complementation dose in PTV2.

For the evaluation of the complications related to the average volume irradiated in each structure (PTV), the comparison resulting from test Anova demonstrated that the patients that were irradiated above 300 cm³ in the bladder ($p=0.059$) presented greater grade of complication, 19.7% evolved with cystitis grade 1 and 14.4% with cystitis grade 2. For those who were irradiated above 50 cm³ in the rectum ($p=0.573$), 44.2% evolved with enteritis/proctitis grade 1 and 2.4% with enteritis/proctitis grade 2 and 38% of the patients who were irradiated between 100 and 200 cm³ in the prostate + SV ($p=0.001$) presented cystitis grade 1 and 26.4%, cystitis grade 2. In 23.56% of the patients that were irradiated between 100 to 200 cm³ in prostatic bed + SV ($p<0.001$) presented cystitis grade 1 and 44.7% of the patients who were irradiated in the prostate ($p=0.019$) presented cystitis grade 2.

DISCUSSION

As observed in the results, the mean age was 72 years (43-87), which corroborates the literature, since the mean age for the occurrence of prostate cancer is above the sixth decade of life^{5,11}. The literature considers arterial hypertension, *diabetes mellitus* and vasculitis as predisposing factors for toxicity of extended radiotherapy¹¹. However, in the present study, the comorbidities did not influence the appearance of acute complications ($p=0.156$).

Nakamura et al.⁵ noticed greater incidence of prostate adenocarcinoma in more initial stages ($\leq T2a$); however, in the present analysis, stage T2b-T2c was the most prevalent. Probably the situation occurred by the difference of the population investigated, since the present study was conducted in a region where the rate of underdevelopment is significant and, possibly, for having less formal education, the patients seek for medical care late¹². In the present sample, cancer stage did not influence directly the existence of acute complications after the treatment ($p=0.522$). In the present analysis, the values of Gleason and PSA were not significant for the appearance of complications, consistent with the study conducted by Afonso-João et al.⁷.

According to the risk staging, D'Amico, James et al.¹³ evidenced higher prevalence of intermediate risk (48%) followed by high risk (32%). In the present series, the most prevalent group was high risk (60%), followed by intermediate risk (27%), being observed a slight discrepancy in relation to the current literature, which corroborates the suggestion that the patients investigated initiated the treatment later when compared to the other. It was verified also that 48.5% of the patients presented, at least, one complaint during the initial visit with the radiotherapist ($p=0.026$) and that the existence of previous treatment can influence in the appearance of acute complications after radiotherapy ($p=0.006$), so the surgical procedures as radical prostatectomy jointly with TURP – transurethral resection of the prostate and orchiectomy presented more negative effect in relation to the appearance of complications when compared with other previous therapies as hormone therapy where less than half of the patients (42.3%) evolved with mild complications as radiodermatitis grade 1 ($p=0.997$), according to Table 3.

According to Bedini et al.¹⁴, patients submitted to pre-treatment abdominal surgery present different response to radiotherapy with more acute complications because of the radiosensitivity present in the cells, added to the complications that can occur during surgery. In this study, 15% of the patients submitted to radical prostatectomy

Table 1. Characteristics of the patient and treatment RT3D

Variable	Category	Number of patients	%
Age	Until 50 years	2	1
	Between 50-70	104	43
	Between 70-80	108	52
	>80	8	4
Comorbidities	Yes	186	89
	No	22	11
Gleason	≤6	77	37
	7	90	43
	≥8	39	19
Total PSA	<4	65	31
	4<10	47	23
	10<20	38	18
	>20	57	26
Staging T	≤T2a	56	26.91
	T2b-T2c	95	45.6
	≥T3	57	27.33
Risk	Low	11	5
	Intermediate	56	27
	High	124	60
	Very High	10	5
Symptoms in the first consultation	None	92	44
	Between 1-3	101	48.5
	≥ 4	15	7.5
Type of previous treatment	Neoadjuvant hormone therapy	129	62
	Radical prostatectomy	76	37
	Orchiectomy	13	6
	Transurethral resection	20	10
Biochemical relapse	Yes	22	11
	No	18	88
Characteristic of the radiotherapy	Radical/curative	131	62.98
	Rescue/adjunct	75	36.06
Number of sessions	36-38	101	49
	39	83	40
Time of radiotherapy	1-2 months	19	9
	2-3 months	187	90
Pelvis irradiation	Yes	28	12.97
	No	180	87.03
Irradiation SV/SV bed	Yes	200	96.15
	No	8	3.85
Irradiation prostate/Prostatic bed	Yes	208	100
Dose (Gy)	Initial between 50-60	170	81.73
	Initial ≥60	30	14.42
	boost between 10-20	74	35.78
	boost>20	112	53.85
Main symptoms	Mild dysuria	105	50
	Constipation	49	24
	Obstructive Symptoms	30	14
	Polyuria	25	1

Captions: PSA=Prostatic specific antigen; RT3D= three-dimensional conformal radiotherapy; SV=seminal vesicles; Gy=gray.

Table 2. Acute complications post-radiotherapy (CTCAE v5.0)

Complications	Number of patients	%
Radiodermatitis grade 1	121	58.2
Radiodermatitis grades 2-3	14	6.7
Cystitis grades 1-2	135	64.9
Enteritis/Proctitis grades 1-2	123	59.2
Enteritis/Proctitis grade 3	7	3.4
Obstructive symptoms	12	5.7
No complications	40	19.2

Caption: CTCAE=Common Terminology Criteria for Adverse Events.

Table 3. Distribution of the patients according to the previous treatment with the complication presented after the treatment

Orchiectomy			
Cystitis	Grade 1	36.5	0.463
	Grade 2	24.5	
Dysuria	Grade 1	0.5	0.062
	Grade 2	0.5	
Enteritis	Grade 1	2.4	0.720
	Grade 2	7.7	
	Grade 3	3.4	
Radiodermatitis	Grade 1	2.4	0.233
	Grade 2	1.0	
Prostatectomia			
Cystitis	Grade 1	12.5	0.487
	Grade 2	11.5	
Enteritis	Grau 1	14.4	0.046
	Grau 2	5.8	
	Grau 3	1.0	
Radiodermatitis	Grau 1	23.6	0.565
	Grau 2	1.4	
	Grau 3	0.5	
Ressecção transuretral			
Cystitis	Grade 1	3.4	0.005
	Grade 2	5.3	
Enteritis	Grau 1	3.8	0.003
	Grau 2	1.9	
	Grau 3	1.4	
Radiodermatitis	Grade 1	7.2	0.418
	Grade 2	0.5	

Caption: P-value: <0.05 considered significant.

presented acute rectal toxicity grade 2 and 56.3% showed values of multiple toxicity (>3 complications). In the study *Protect Trial*¹⁵, the main post-operative complication encountered was urinary incontinence by 1% in the beginning of the study and 46% at six months. It is possible to infer that the data found are consistent with what is presented in the literature.

The duration time of the radiotherapy treatment was between two and three months. According to the statistical analysis performed, it is inferred that the time of treatment influences the existence of complications, indicating that as high the number of sessions and the time of treatment, better is the accumulation of irradiation the patient will receive and, consequently, will be more inclined to develop great number of adverse effects ($p=0.016$). The duration of the radiotherapy encountered contradicts the current data of the literature¹⁵. Nakamura et al.⁵ reported in their study mean time of treatment of 71 days (2, 3 months).

Regarding the complications, it was observed that the majority followed a less complexity course according to Table 2. In the study it was evaluated only the complications resulting from acute toxicity defined as adverse events occurred during radiotherapy or in the next three months^{16,17}. Dias¹⁷ found that 35.9% of the patients presented acute rectal toxicity grade 1, while 22.2% of the patients presented grade ≥ 2 . Gill et al.¹⁶ verified that the urinary toxicity grade 1 was present in 35% of the patients; grade 2 in 38% and grade 3 in 23%. About gastrointestinal affection, toxicity grade 1 was present in 35% and grade 2, in 19%. According to the study conducted by Dias¹⁷, 40.3% of the patients presented urinary complication grade 1 and 36.7%, \geq grade 2. Still in this same study, gastrointestinal complications grade 1 occurred in 17.4% of the patients and \geq grade 2 in 11.9%. It is possible to affirm that the data of the current study corroborate the existing literature because is related to the technique of treatment adopted that pursues more accurate irradiation of the target-organ. Studies indicate that the presence of acute complications \geq grade 2 constitute prognostic factor for the appearance of late complications¹⁸ so as, among patients who develop acute symptoms during the treatment, the incidence of late toxicity was 35% in ten years¹⁹.

When there are complications related to the volume of target, the study revealed that as high the average volume irradiated, bigger is the number of complications that the patient is inclined to present. It was evidenced that the average volume in prostatic bed + SV was bigger for individuals who presented four complications after the treatment in relation to those who presented three or less complications. Patients with irradiation in the bladder >300 cm³ evolved with more acute complications. This analysis is consistent with the literature, according to Monti et al.²⁰, doses >70 Gy in 30% of the volume of the bladder imply in more acute toxicity.

CONCLUSION

Despite the existence of complications in the end of the treatment, it is observed that the majority is of low

complexity, that is, acute complications grades 1-2, which reinforces the practice of the radiotherapy method as a modality that presents satisfactory results. It was possible to verify that as bigger the volume irradiated in the areas observed associated to the existence of previous treatment and symptoms in the initial consultation, high is the probability of a patient to present acute complications after the treatment. At the end of the study, it is possible to suggest that patients submitted to previous surgical procedures, many times unnecessary, can evolve with the presence of more severe complications and this reflects in the increase of the morbidity of the method.

CONTRIBUTIONS

All the authors contributed substantially for the conception and planning of the study, gathering, analysis and/or interpretation of the data, as well as in the wording and/or critical review and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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