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EVALUATION OF ACUTE TOXICITY IN THE TREATMENT OF PROSTATE CANCER WITH CONFORMATIONAL RADIOTHERAPY: CHOORT WITH 45 PATIENTS

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ABSTRACT

BACKGROUND: Radiatiotherapy is often associated with a wide range of significant side effects. These side effects are commonly classified as acute or delayed according to when they manifest in relation to treatment. **METHODS:** This study aimed to evaluate acute toxicity in patients with prostate cancer treated with conformational radiotherapy (3D) in an Oncology Unit in Eastern Minas Gerais. A prospective, observational, cohort study was performed through a non-probabilistic sampling of convenience, totalazing 45 patients. Patients included in the study were followed from the start of treatment to 3 months after external beam radiation therapy (EBRT). **RESULTS:** Demographic Characteristics - Of the 45 patients included, mean age was 70.6 ± 8.3 (SD) years, and predominantly white (44.0 %). The majority were married (75.6 %). Considering the risk classification, there was a homogeneous distribution between the low (33.3 %), intermediate (31.1 %) and high (35.6 %) levels. The majority of the patients (57.8 %) had a low risk (T1) classification, followed by intermediate risk classification (33.3%) and high risk (8.9 %). In the Gleason score, 44.4 % presented values below 6 (low), 40.0 % intermediate, and 15.5 % high. 62.2 % had a PSA level less than 10 $ng.mL^{-1}$, 22.2 % had an intermediate level, from 10 to 20 $ng.mL^{-1}$ and 15.6%, above 20 $ng.mL^{-1}$. Manifestation of acute toxicity - It was observed that the majority (59.1 %) of the acute effects manifested during the first consultation, prevailing the symptom of urinary frequency (64.1 %). Regarding the symptoms of acute effects most prevalent during the three consultations, we highlight the urinary frequency with 44.0 %, followed by the urinary residue (20.0 %). **CONCLUSION:** 80.0 % of the patients presented acute effects during radiotherapy, being the urinary frequency the event more frequent (44.0 %), followed by urinary residue (20.0 %). Eighteen patients (40.0 %) presented only one acute effect and 59.1 % of the effects were observed at the first visit.

1. INTRODUCTION

Prostate cancer (PC) is the most common cancer in Brazilian men, with 68,220 new cases in 2018, with an incidence of 66,82 new cases per 100,000 [1,2,3]. The incidence rates increased over the years is due to life expectancy extension associated with diagnostics methods improvement and information systems quality improvement, as well as the overdiagnosis occurrence [1].

Age is the most relevant risk factor for disease development, followed by geography, ethnicity, family history, and diet. About 85 % of the diagnosed cases are in patients over 65 years of age [4], black people has twice as risk for prostate cancer than white people. The geography and ethnicity may be due to eating habits, since it has been proven that the high unsaturated fats consumption and high body mass index increase the disease risk. In addition, low carbohydrate intake associated with high intake of omega-3s, green tea, tomatoes, and their derivatives not only shows benefits in reducing risk but also in disease progression [5].

The prostate cancer most common is adenocarcinoma. The cell characteristics is graded moderately or poorly differentiated. Nuclear content, pleomorphism, gland formation and stromal invasion are considered [6].

The current therapeutic options of prostate cancer treatment are: radical prostatectomy [7], and radiation therapy (RT) in two modalities: external (conformational or intensity modulated) and internal (also known as brachytherapy). Other treatment options are in use like low dose rate brachytherapy, high dose rate brachytherapy, cryotherapy, high intensity focused ultrasound, stereotactic body RT, Proton Therapy, Carbon Ion, Balloon/Spacer [8-12].

Between that options, the external-beam radiotherapy (EBRT) and brachytherapy (BT) are the most applied like potentially curative therapies for PC nowadays. Altogether, RT has undergone tremendous improvements in the last decades. Dose escalation in prostate EBRT leads to improved locoregional control, biochemical disease-free survival, distant metastasis-free survival, PC specific mortality, and even overall survival in intermediate- and high-risk PC [13–15]. However, dose escalation is limited by toxicity of surrounding healthy tissues, and therefore improved tumour control is expected to come at the cost of higher toxicity, greatly impacting patients' quality of life [16–18]. Still, dose escalation is possible due to advances in different RT techniques, sophisticated computer-based treatment planning, and/or development of extra devices, avoiding increased dose delivery to the surrounding healthy tissue.

Should be considered that the prostate is a mobile organ, so larger margins around the target should be added during EBRT than the margins for other non-mobile organs [19, 20]. Therefore, increasing the dose to the prostate using 3D conformal radiation therapy (3DCRT) is difficult. In recent years, image-guided radiation therapy (IGRT) and intensitymodulated radiation therapy (IMRT) have been developed to provide precise irradiation and dose escalation to the prostate without increasing the dose to normal tissues; several reports have shown good oncological outcomes for prostate cancer with IMRT [19, 21, 22]. One of the disadvantages of conventionally fractionated IMRT is the long treatment course: It usually

takes 8–9 weeks to complete treatment, which is much longer than prostatectomy and brachytherapy and is inconvenient for patients [19-21]

In locally advanced prostate cancer cases minimization of side effects is the most important factor to be evaluated. The urinary incontinence, urinary urgency, and the erectile dysfunction were the most frequent side effect after radiotherapy treatment [23]. The acute side effects are those that occur within a few days or weeks at the start of treatment up to 90 days. They are normally monitories, well tolerated and reversible. The most common, and much less presented in scientific research are in skin, such as dryness, itching, blisters or flaking and those that are related to fatigue, lack of energy that does not improve with rest [24-26].

The late events after 90 days from the start of treatment may reach 5 years. They are rarer but they can be more frequent when the dose of radiation in the tissues is exceeded. They are manifested by atrophies and fibrosis, since the genetic alterations and the formation of new tumors are very rare [24-26].

Most scientific cancer researches point to benefits of IMRT technique for prostate tumors treatment that promote a better life quality with less side effects. However, the constant increase in this technique use requires independent and individualized studies in accordance with each specificities of radiotherapy center and its socioeconomic realities to assess the feasibility of IMRT implementation. The reduction of EBRT side effects can contribute to cost reduction and to justify the public health policy financing agencies orientation on the updating of cancer procedures. Other way, knowing what and when the most common side effects are is important to prepare the service for implement alternative prevention protocol and also capacitate our multidisciplinary team for this side effect treatment. Thereby, this is a pilot study that examines the clinicopathological features and acute toxicity in 45 patients with prostate cancer treated with IMRT in an Oncology Unit of Minas Gerais over a 3-month period.

2. METHODS

2.1. Study Design and Participants

A total of 45 unselected patients participate in this study. The work was performed with a non-probabilistic sample that received definite radiotherapy for prostate cancer between September 2016 and September 2017 in a prospective, observational, and longitudinal cohort study. This research was approved by the local institutional ethics committee under the number CAAE 56573816.2.0000.5095 and conducted according to the Helsinki Declaration in its current version.

The patients were recruited during the first medical appointment at the Radiotherapy Service of the Oncology Unit of Minas Gerais. Inclusion criteria were for patients over 18 years of age with diagnosis of prostate cancer and referred to IMRT. Exclusion criteria were: disabled patients, indication of prostatectomy; severe patients whose radiation therapy was contraindicated; patient with a history of locoregional treatment prior to prostate cancer; clinical or imaging evidence of disseminated disease; recent transurethral resection and patients with neurological limitations.

The radiotherapy treatment was divided into three phases. In chronological order, they are: clinical consultation (phase 1), planning by computed tomography (CT), simulation and radiotherapy treatments (phase 2). During phase two, reports of adverse events were recorded. After three months of treatment, phase three was started, when the patient was clinically evaluated and informed of the end of the study, despite his permanence in the treatment and / or follow-up program at the Oncology Unit.

2.2. Radiotherapy treatment protocol

Each patient underwent a series of steps before the radiotherapy sections. Step one, treatment simulation that aims to determine the patient best position, to guarantee a better daily reproducibility and to optimize the target volume irradiation. Step two; tomography was performed according to treatment simulation. Step three, physicians set limits by choosing the treatment area and which organs should be protected. Step four, physicists determine the best way to irradiate so as to homogenize the dose in the target tissue by minimizing the dose in adjacent healthy tissues. Step five, another physicist recalculates the exposure time to check. Step six, the treatment plan is evaluated jointly by the physician and the physicist to finally authorize the patient for radiotherapy sessions.

To describe a treatment with ionizing radiation, at least three parameters were required: treated volume, radiation dose, and technique used. These parameters are applied in a uniform way, and according to the protocols that each institution adopts. Treatment volumes were defined according to the Internacional Commision on Radiation Units and Measurements (ICRU) [16]. Palpable tumor mass was defined as visible tumor volume, GTV (gross tumor volume). The volume that contains GTV plus malignant microscopic disease was called the clinical target volume, CTV (clinical target volume). However, the volume that takes into account the effects of all geometric variations such as: organ movements or uncertainly of its position, in order to ensure that the due dose be delivered to the CTV is called planning target volume, PTV. In order to better control the irradiation in healthy volumes, the delimitation of organs that could be at risk is also carried out in order to know and control the irradiated dose, preventing them from exceeding the tolerated dose. This last volume is called planning organ risk (PORV), considering not only the physical contour but also the possibilities of movement within the patient. Finally, it is also defined as treated volume (TV) that effectively received the prescribed dose and irradiated volume (IV) as a dose that is important to be reported for the type of patient in question [28].

In figure 1 [28], the volumes diagram presentation can be visualized.

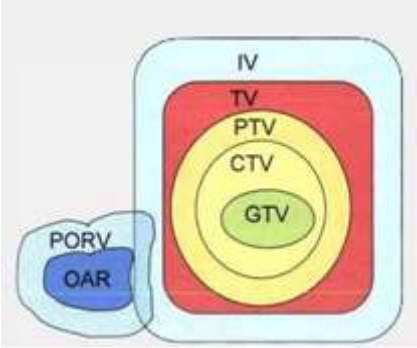

Figure 1: Definition of target volumes and risk organs [28].

In this study, patients were initially submitted to simulation using Acuity device (Varian Medical Systems, Palo Alto, CA, USA). They remained in the supine position, with the ankles fixed and the hands on the chest. The VT isocenter was 10 x 10 cm field with center in the patient's midline and lower border in the inferior border of the pubis, and lateral radiography with anterior limit field with 1 to 1.5 cm posterior to the border of the pubis. Such points were marked externally on the patient's skin. These same positioning conditions were applied to the linear accelerator Clinac® IX, (Varian Medical Systems, Palo Alto, CA, USA). CT images were processed in the Eclipse computerized planning system (Varian Medical Systems, Palo Alto, CA, USA). Subsequently, the CTV and PTV, CTV with a margin of 10 mm were defined, except for the posterior portion, which was 7 mm.

The patients received 72 Gy of dose distributed in 36 portions. Four to six treatments sites were used in the patients. The delimited limit for positioning displacement was 2.5 mm, established as the standard error (EP = 2.5 mm). The linear accelerator correction was established for variations greater than 2.5 mm.

2.3. Outcomes

These symptoms were considered acute adverse effects: pollakiuria (benign idiopathic urinary frequency), urinary residue (the bladder doesn't completely empties and a residual urine remains in the bladder), dysuria (a symptom of pain, discomfort, or burning when urinating), urinary incontinence (involuntary leakage of urine), haematuria (resence of red blood cells in the urine), diarrhea (unusually loose or watery stools), fatigue / asthenia (state of weariness or exhaustion resulting from physical or mental exertion), pain in defecation, colic pain, and nausea or vomiting. All those involved in data collection in this project underwent prior training in order to ensure the quality of the data collected and the ethical conduct.

2.4. Statistical analysis

Data were submitted to descriptive and frequency analysis. Qualitative variables were expressed in numbers and percentages, clinical and technical parameters were categorized. The arithmetic mean was used as a measure of central tendency and standard deviation for data dispersion. For the adverse events incidence used the number of consultations per patient at the numerator and the number of events occurred considering the patients number (45) times visits number for each patient (3), totaling 135 events. Odds ratio (OR) were used for assess the association between age, ethnicity, and education level with toxicity. In all statistical analyzes was adopted a significance level of 5 %. The software Prisma 6 (version 6.01) was used for calculations.

3. RESULTS AND DISCUSSION

The average age was 70 years old, with white ethnicity and Incomplete and Complete Middle School predominance. About occupation, it is notorious that there is a balance between retirees and workers and the prevailing marital status was married (Table 1).

Table 1: Demographic data of patients (n=45)

Age (years)	**N**	**%**
50-60	5	11.1 %
61-70	18	40.0 %
71-80	15	33.3 %
>80	7	15.6 %
Average age (years (DP); MIN-MAX)	70.2 (±15.1)	(54.6-86.8)
Ethnicity		
White	20	44.0 %
Yellow	3	7.0 %
Brown	17	38.0 %
Black	5	11.0 %
Indigenous	0	0.0 %
Degree of education		
Not informed	3	6.7 %
Middle School Inc.	18	40.0 %
Middle School Comp.	15	33.3 %
High School Inc.	2	4.4 %
High School Comp.	7	15.6 %
College School Inc.	0	0.0 %
College School Comp.	0	0.0 %
Graduate School	0	0.0 %
Occupation		
Retired	24	53.3 %
Working	21	46.7 %
Marital Status		
Single	3	6.7 %
Married	34	75.6 %
Stable Union	5	11.1 %
Divorced	1	2.2 %
Widow	2	4.4 %

At table 2, the risk classification assessment presented a homogeneous distribution between low, intermediate and high risks. Most patients (57.8 %) had low risk (T1) initial stage tumor classification, followed by intermediate risk (33.3 %) and high risk (8.9 %). Based on Gleasson Score, 44.0 % presented value below 6 (low), 40.0 % intermediate and 15.5 % high. Analyzing the PSA level, 62.2 % presented under 10 ng.ml, 22.2 % intermediate level (10 - 20 ng.ml) and 15.6 % above 20 ng.ml.

Table 2: Patients risk classification (n=45)

Risk Classification	**N**	**%**
Low	15	33.3 %
Intermediate	14	31.1 %
High	16	35.6 %
Tumor Initial Stage		
Low Risk (T1)	26	57.8 %
Intermediate Risk (T2)	15	33.3 %
High Risk (T3)	4	8.9 %
Gleason Score		
Low (< 6)	20	44.4 %
Intermediate (7)	18	40.0 %
High (8 – 10)	7	15.5 %
PSA (ng/mL)		
< 10	28	62.2 %
10-20	10	22.2 %
> 20	7	15.6 %

It was not possible to identify a significant association between the variables age, ethnicity and education level with manifestation of adverse effects (Table 3). However, there is a tendency for brown or black individuals to be greater chance of acute toxicity incidence than white patients. Recent research has support the presence of genetic risk factors for wound repair and toxicities of radiation. It seems that the wound repair genes can vary significantly among different ethnic groups. Increased frequency of a long GT repeat in the HMOX1 promoter was associated with late effects in both African-American and Caucasian populations. The single nucleotide polymorphisms (SNP) rs1800469 in the TGFβ1 promoter and the rs6721961 SNP in the NFE2L2 promoter were also found to significantly associate with late effects in African-Americans but not Caucasians [29]. Moreover, there is a research that matched-paired analysis and explore disparities in health-related quality of life and common toxicities between 1536 African-American and white patients with clinically localized prostate cancer treated with proton therapy. After 2 years follow-up here were no disparities in health-related quality of life, physician-reported Common Terminology Criteria for Adverse Events gastrointestinal (GI) toxicity, or biochemical relapse. No difference in Expanded Prostate Index Composite 26-question sexual summary, urinary incontinence, urinary obstruction, or bowel summary scores was detected between the 2 groups, nor was there a difference in grade 2 or higher GI toxicity (P=0.45). African-Americans had a statistically nonsignificant higher absolute incidence of late grade 3 genitourinary toxicity (4.4% vs. 0%; P=0.12) [30]. Worth mentioning that a research comparing in a prospectively collected toxicity data on 394 patients with prostate cancer who received treatment with contemporary IMRT and proton beam therapy techniques and similar dose-fractionation schedules, the risks of acute and late GI/GU (genitourinary) toxicities did not differ significantly after adjustment for confounders and predictive factors [31]. Indeed, future studies should account for the possibility in toxicities of radiation have discrepancy between the races.

Table 3: Relationship between demographical characteristics and acute toxicity manifestation

Demographical Characteristics	Acute toxicity		ODDS ratio	P value
	absent	present	(95 % CI)	
	N	N		
Age (years)				
≤ 70	5	28	0.8 (0.2 - 3.4)	0.77
> 70	4	18		
Ethnicity				
White	6	14	4.3 (0.8 - 24.4)	0.10
Brown and Black	2	20		
Degree of Education				
Middle School Inc./Comp.	9	24	7.4 (0.4 - 139.5)	0.18
High School Inc./Comp.	0	9		

Most of patients (80.0 %) presented some toxicity in this study, but the toxicity was also not more prevalent according to the clinical characteristics assessed as risk classification, tumor initial stage, Gleason score and PSA level (Table 4). In contrast, a pilot study of highly hypofractionated IMRT over 3 weeks for localized prostate cancer with a nominal dose of 54 Gy in 15 fractions (3.6 Gy per fraction) presented 24.0 % of acute toxicity. Other way, this study have two important limitation yet: it was a pilot study with 25 pacientes and .the median follow-up period was 31 months, which is too short to draw conclusions about late toxicities and tumor control outcomes [19].

Table 4: Relationship between clinical features and acute toxicity manifestations (n=45)

Clinical Features	No toxicity		With toxicity	
Risk Classification	**N**	**%**	**N**	**%**
Low	2	22.2 %	13	36.1 %
Intermediate	4	44.4 %	10	27.8 %
High	3	33.3 %	13	36.1 %
Total	9	20,0%	36	80,0%
Tumor Initial Stage				
Low Risk (T1)	4	44.4 %	22	61.1 %
Intermediate Risk (T2)	5	55.6 %	10	27.8 %
High Risk (T3)	0	0.0 %	4	11.1 %
Gleason Score				
Low (< 6)	6	66.7 %	14	38.9 %
Intermediate (7)	2	22.2 %	16	44.4 %
High (8 – 10)	1	11.1 %	6	16.7 %
PSA (ng/mL)				
< 10	5	55.6 %	23	63.9 %
10-20	3	33.3 %	7	19.4 %
> 20	1	11.1 %	6	16.7 %

Most acute effects (59.1 %) manifested during the first medical consultation, prevailing pollakiuria (64.1 %). Regarding most prevalent acute effects symptoms during all the 3 consultations, pollakiuria is highlighted with 44.0 %, followed by urinary residue (20.0 %), dysuria (9.0 %), urinary incontinence (8.0 %) and haematuria (8.0 %). There was no report of colic pain, nausea or vomiting. Symptoms like pain to defecation, fatigue and diarrhea were poorly reported (12.0 %) (Table 5).

Table 5: Acute toxicity manifestation during consultation (n=45)

Acute Effects	**Clinical Consultation**			**Total (n)**	**Freq. (%)**
	1ª	**2ª**	**3ª**		
Pollakiuria	25 (64.1 %)	1 (6.7 %)	3 (25.0 %)	29	44.0 %
Urinary residue	4 (10.3 %)	6 (40.0 %)	3 (25.0 %)	13	20.0 %
Dysuria	2 (5.1 %)	3 (20.0 %)	1 (8.3 %)	6	9.0 %
Urinary incontinence	3 (7.7 %)	1 (6.7 %)	1 (8.3 %)	5	8.0 %
Haematuria	2 (5.1 %)	0 (0.0 %)	3 (25.0 %)	5	8.0 %
Diarrhea	0 (0.0 %)	3 (20.0 %)	1 (8.3 %)	4	6.0 %
Fatigue / asthenia	2 (5.1 %)	0 (0.0 %)	0 (0.0 %)	2	3.0 %
Pain to defecation	1 (2.6 %)	1(6.7 %)	0 (0.0 %)	2	3.0 %
Colic pain	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0	0.0 %
Nausea or vomiting	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0	0.0 %
Total	39 (59.1 %)	15 (22.7 %)	12 (18.2 %)	66	100.0%

Most patients (64.4 %) had one or two adverse events, 20.0 % of patients didn't have any toxicity to radiotherapy and only 15.5 % had 3 or 4 adverse events (Table 6).

Table 6: Adverse events frequency per patient

Adverse Events	**Number of Patients**	**Frequency (%)**
0	9	20.0 %
1	18	40.0 %
2	11	24.4 %
3	6	13.3 %
4	1	2.2 %
TOTAL	**45**	**100.0 %**

4. CONCLUSIONS AND FUTURE PERSPECTIVES

An increasing number of people survive cancer but a significant proportion have gastrointestinal side effects as a result of RT, which impairs their quality of life. A Cochrane methodology using the random-effects statistical model for all meta-analyses, and the GRADE system to rate the certainty of the evidence shows that conformal radiotherapy techniques are an improvement on older radiotherapy techniques. IMRT may be better than

3D conformal RT in terms of GI toxicity, but the evidence to support this is uncertain. There is no high-quality evidence to support the use of any other prophylactic intervention evaluated. However, evidence on some potential interventions shows that they probably have no role to play in reducing RT-related GI toxicity. More RCTs are needed for interventions with limited evidence suggesting potential benefits [32].

Besides, a recent meta-analysis present the probiotics use for prophylactic intervention for side effects in radiotherapy. Their capability of preserving gut homeostasis, are currently tested to help to fight dysbiosis in cancer patients subjected to chemotherapy and RT. This work showed three independent studies with specific gut resident species that may potentiate the positive outcome of anti-cancer immunotherapy. It was reported the role of the *Lactobacillus rhamnosus* GG (LGG), as the most studied probiotic model in cancer. Overall, according to their findings, novel strategies integrating probiotics, such as LGG, with conventional anti-cancer therapies are strongly encouraged and may be indicated for prevent our minimize the side effects of RT [33].

RT for prostate cancer (PC) has steadily evolved over the last decades, with improving biochemical disease-free survival. Examples of improved RT techniques are image-guided RT, intensity-modulated RT, volumetric modulated arc therapy, and stereotactic ablative body RT, which could facilitate further dose escalation. Brachytherapy is an internal form of RT that also developed substantially. New devices such as rectum spacers and balloons have been developed to spare rectal structures. Newer techniques like protons and carbon ions have the intrinsic characteristics maximizing the dose on the tumour while minimising the effect on the surrounding healthy tissue, but clinical data are needed for confirmation in randomised phase III trials. Furthermore, it provides an overview of an important discussion issue in PC treatment between urologists and radiation oncologists: the comparison between radical prostatectomy and RT. Current literature reveals that all possible treatment modalities have the same cure rate, but a different toxicity pattern. It is recommended proposing the possible different treatment modalities with their own advantages and side-effects to the individual patient, to specificities of radiotherapy center, and to its socioeconomic realities. Clinicians and patients should make treatment decisions together (shared decision-making) while using patient decision aids [12].

This study has some limitations. First it was a pilot study with 45 patients. Second, we didn´t show the dose constraints for targets and organs at risk. Third the acute toxicities weren´t evaluated in based on the Common Terminology Criteria for Adverse Events version 4.0 or Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer (RTOG/EORTC) Acute Radiation Morbidity Scoring Schema.

In conclusion, we could show that the radiotherapy treatment of prostate cancer in our institution was associated with a wide potential for acute side effects. The acute effects incidence was of 3 toxicity event for every 10 patients consultations. Most patients (80.0 %) of this study presented acute effects. Pollakiuria was the most frequent (44.0 %). The acute adverse effects were more frequent at the first consultation (59.1 %) and the tendency of manifestations declined at the second and third ones (22.7 % and 18.2 %, respectively). The most usual was the manifestation of just one acute adverse effect on each patient (40.0 %) and the less usual was the manifestation of four acute adverse effects at once (2.2 %). There was no patient with more than four acute adverse effects.

Declaration of interests
We declare no competing interests.

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