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Impact of obesity on Gleason Score in elderly and elderly patients with Prostate Cancer with indication for radical radiotherapy

Crossref doi 10.56238/rcsv14n3-014

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ABSTRACT
Prostate cancer is an important public health concern in Brazil, especially among elderly men, with a significant mortality rate. In addition to advanced age, obesity emerges as a relevant risk factor, associated with a worse prognosis of the disease. Objective: To investigate the relationship between body mass index (BMI) and Gleason score in elderly and elderly patients with prostate cancer indicated for radiotherapy. Methodology: Prospective, descriptive and longitudinal study with 35 patients with prostate cancer, evaluating age, initial PSA, BMI, race and Gleason score. Results: The findings revealed an association between a higher BMI and a more aggressive degree of the disease, as indicated by higher Gleason scores. Conclusion: Overweight and obese patients have a higher and more evident Gleason score in elderly patients compared to the elderly, being more notable in the elderly. This study is one of the few studies to examine the link between BMI and a poor prognosis in patients with prostate cancer.

Keywords: Prostate Neoplasms, Body Mass Index, Radiotherapy.

INTRODUCTION

Prostate cancer is the second most prevalent among Brazilian men, with a mortality rate of 15.25 per 100,000 men (INCA, 2019). Advanced age is a risk factor for the development of the pathology, being considered a cancer of the elderly, as its incidence is common in men over the age of 65, and about 62% of the world's cases occur in individuals over the age of 65. (GONTIJO, 2015)

The aging process is inherent to human nature, according to estimates by the Brazilian Institute of Geography and Statistics (IBGE), the projection for the year 2050 suggests that the portion of the population over the age of 60 will reach the milestone of 66.5 million. Among the morbidities, about 70% of deaths in the world are attributed to chronic non-communicable diseases (NCDs), in this context, cancer emerges as one of the main NCDs that most affect men. (KRÜGER, 2018)

Some authors address that with the increase in life expectancy, the incidence of diseases related to senescence, such as prostate cancer, increases. Regarding epidemiology, it is predominant among the elderly, although screening has increased in the young population. (MORI, 2020)

In addition to the aforementioned risk factors associated with prostate cancer, obesity is recognized as a condition that increases the probability of the disease occurring, and is also related to a worse prognosis (GOLEMIS, 2018). The literature shows an association between obesity and prostate cancer, such as the progression of the pathology, aggressiveness, advanced character, biochemical recurrence and mortality from the neoplasm. (ARCHER, 2020)

Obesity generates chronic systemic inflammation that is related to prostate carcinogenesis. Consequently, there is a greater circulation of inflammatory cytokines, such as IL-6, and the prostate tissues of overweight patients have a higher expression of IL-6 when compared to patients with a BMI of less than 25 kg/m². It is important to note that IL-6 is also produced by prostate tumor cells,

and that it promotes tumor proliferation by acting on regulatory pathways, positively influencing the expression of Myc and anti-apoptotic genes, promoting tumor survival (ARCHER, 2020). In addition, in many types of cancer, patients with elevated IL-6 levels have a worse prognosis, a higher risk of metastasis, and lower survival (Ishii, 2018).

The objective of the research is to evaluate the BMI of patients and to verify whether it is associated with a worse Gleason score in elderly and elderly patients with prostate cancer indicated for radiotherapy treatment.

METHOD

This is a prospective, descriptive and longitudinal study with patients with prostate cancer. The participants in this study were treated by radiotherapy with radical intent (70 Gy in 28 fractions). Radiotherapy Treatment Planning: Clinical Target Volume (CTV) is defined as the prostate and seminal vesicles outlined by the radiation oncologist.

The Planning Target Volume (PTV) will provide a margin around the CTV to account for variability in treatment positioning and internal organ movement. A minimum of 4 mm around the CTV is required to set the PTV. The top and bottom margins should be 4 to 10 mm, depending on the thickness and spacing of the planning CT. Care should be taken when setting the margin of 4-10 mm in three dimensions. Treatment was delivered to PTV only using three-dimensional conformational fields shaped to exclude as much of the bladder and rectum as possible. The field arrangements will be determined by 3D planning to produce the optimal conformational plan according to the volume definitions.

The treatment plan used for each patient will be based on a volumetric dose analysis, including analysis of the dose-volume histogram (DVH) of PTV and critical normal structures. The prescribed dose is the minimum dose for PTV - No variation (full coverage): The prescribed isodose surface covers ≥ 98% of the PTV and the prescribed isodose surface covers 100% of the CTV. Mild variation (marginal coverage): The prescribed isodose surface covers between ≥ 95% to < 98% of the PTV and the prescribed isodose area covers 100% of the CTV. The maximum dose for PTV should not exceed the prescribed dose by more than 7% (inhomogeneity ≤ 7%) and will be classified as follows: no variation: ≤ 7%; slight variation: > 7 to ≤ 10%; Significant variation: > 10%. Slight variations, as described, are acceptable.

A total of 35 patients were selected from March/23 to August/23. Age, initial prostate-specific antigen (PSA), BMI, race, and Gleason score were evaluated. The age division was defined into elderly patients (60 to 74 years) and elderly patients (75 to 89 years). Gleason score was categorized into Group 1 with Gleason score 6 and 7 (3+4); in Group 2 with Gleason 7 (4+3), 8 and 9. There

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were no participants with Gleason 10. Body Mass Index (BMI) is defined as weight in kilograms divided by height in meters squared; kg/m².

The diagnosis of prostate cancer by histopathological study was used as an inclusion criterion, and the diagnosis of metastatic cancer was used as an exclusion criterion. BMI measurements, as well as age and PSA level at diagnosis were analyzed as continuous variables. Categorical variables included were race, Gleason score category. The correlation between BMI and age was quantified using Pearson's correlation coefficient. Clinical variables were compared between groups of Gleason score, age, and BMI using analysis of variance, Student's t-test, or Pearson's correlation coefficient for continuous variables, and chi-square test or Fisher's exact test for categorical variables. This study was approved by the Research Ethics Committee of the Faculty of Medicine of the Fluminense Federal University - CAEE 58121422.1.0000.5243.

RESULTS

A total of 35 patients were evaluated, 20 elderly patients (60-74 years old) and 15 elderly patients (75 years or older). In addition, 24 (68.6%) were brown/black and 11 (31.4%) were white. The Gleason score 6 was found in 13 patients (37.1%), Gleason 7 (3+4) in 7 patients (20%), Gleason 7 (4+3) in 3 patients (8.6%), Gleason 8 in 8 patients (22.9%) and Gleason 9 in 4 patients (11.4%). The mean BMI found was 27.3 (19.1-35.6 / 95%CI 25.8-28.7 / SD ± 4.2). Table 1 shows the characteristics of the patients.

Table 1 – Patient characteristics

	Average	Minimum	Maximum	95%CI	DP
Age	72	60	83	69 - 74	± 7.3
PSA	14,8	4,8	45	11,3 – 18,2	± 10.0
IMC	27,3	19,1	35,6	25,8 – 28,7	± 4.2
Race	N (%)				
Brown / Black	25 (68,6%)				
White	11 (31,4%)				
Escore de Gleason					
6	13 (37,1%)				
7 (3+4)	7 (20%)				
7 (4+3)	3 (8,6%)				
8	8 (22,9%)				
9	4 (11,4%)				
Gleason's Grade					
Group 1	23 (57,1%)				
Group 2	12 (42,9%)				

PSA- Prostate-specific antigen; BMI - Body mass index; 95%CI - 95% confidence interval; DP- Standard deviation

Table 2 correlates the mean BMI and the Gleason Category between the elderly and the elderly ($p<0.001$).

Table 2 – Correlation

Categoria Gleason	Age Group	N (%)	Average BMI	Sig
Group 1	Elderly	9 (45%)	25,1	0,001
	Elders	11 (55%)	24,5	
Group 2	Elderly	11 (73%)	31,4	
	Elders	4 (27%)	28,4	

N- Number of patients; BMI - Body mass index; Sig- Statistical significance.

Statistical significance ($p < 0.001$) strongly suggests that the observed differences in BMI between the groups may reflect real differences in the populations being studied. Notably, there is an association between a higher BMI and a more aggressive degree of the disease, as indicated by higher Gleason scores, in elderly and elderly patients. Interestingly, even with a lower BMI in the elderly group, in the Gleason Group 2 category, there is a trend toward greater disease severity, as expressed by higher Gleason scores.

DISCUSSION

The International Agency for Research on Cancer corroborates the importance of the cancer-obesity relationship, as it estimates that 4% of all new cancer cases in adults were attributed to high BMI levels (IARC, 2021). Directing to prostate cancer. Cao, 2016, points out that obesity is a relatively consistent association with a higher risk of aggressive prostate cancer, either due to an advanced stage or a worse prognosis. Some mechanisms may explain this association, such as: Late detection in obese men, worse response to treatment, and direct biological mechanisms (hyperinsulinemia)

The same article presents the results of a meta-analysis that addressed scientific productions up to 2010, in summary, it suggested that, among the healthy population, an increase of 5 kg m2 in BMI was associated with a 15% risk (RR 1.15; 95% CI 1.06–1.25) higher rate of dying from prostate cancer. It also pointed out that obese men have higher rates of cancer-specific mortality after diagnosis. A BMI 5 kg m2 higher was associated with a 20% increased risk (RR 1.20; 95% CI 0.99–1.46) of prostate cancer-specific mortality. (CAO, 2016)

Pati, 2023, in her research, presented a systematic review and meta-analysis of 59 studies involving 280,199 patients, and showed that obesity increases the risk of prostate cancer-specific mortality by 19% and all-cause mortality by 9%. A 5 kg/m2 increase in BMI resulted in a 9%

increase in prostate cancer-specific mortality. The study published by Sung, 2019, listed that each 5-unit increase in BMI was associated with an 8% increased risk of advanced stage prostate cancer.

The study published by Cedeño Yera, 2021, points out that the value resulting from the Gleason sum increased with the Body Mass Index (BMI), while the mean in eutrophic patients (BMI between 18.5 – 24.9 Kg/m2) was 5.8, overweight patients (25 – 29.9 Kg/m2) was 7.0 and obese patients (≥ 30 Kg/m2) had an average of 8.0 in the Gleason score.

The results of the research show an analysis of a patient with prostate cancer, where the Gleason score, a measure of the aggressiveness of the tumor, was compared with the body mass index (BMI) and the age of the patients. As shown in Table 2, patients belonging to Gleason category 2 (Gleason 7 (4+3), 8 and 9) are those with a higher BMI value when compared to Gleason category 1.

Table 2 shows that the mean BMI between the group of elderly people in Gleason category 1 and 2 had a difference of 3.9 units. It is possible to infer that among the elderly, small changes in BMI are relevant enough to interfere with the Gleason score, and consequently with the aggressiveness of the pathology.

Mori, 2020, shows that prostate cancer appears to have unfavorable characteristics when diagnosed in older men, showing that men aged 70 years or older had worse survival when compared to younger men.

On the other hand, when comparing elderly people and elderly people in table 2, it is possible to see similar values in the quantity in the category of least aggressiveness, the Gleason group 1 category. On the other hand, in the most aggressive category, the Gleason group 2 category, there was a higher value in the number of elderly people compared to the elderly. An association between higher Gleason scores and higher BMI is noted, especially among the elderly.

The present research suggests that patients with higher BMI may have more aggressive prostate tumors. In addition, the data indicate that this association is more pronounced among the elderly compared to the elderly.

CONCLUSION

Overweight and obese patients have a higher and more evident Gleason score in elderly patients compared to the elderly, and may demonstrate greater tumor aggressiveness in overweight and obese elderly patients, and greater clinical attention should be paid to the global public health problem of weight gain.

Many studies have shown a positive relationship between BMI and prostate cancer risk, and this study is one of the few to evaluate the relationship between BMI and worse prognosis in patients

with prostate cancer, where a higher Gleason score was demonstrated in patients with higher BMI and more evident in elderly patients compared to the elderly.

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