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Influence of Race on Outcomes of Patients with Localized Prostate Cancer Considered Intermediate or High Risk of Biochemical Failure Treated with High Dose Rate Brachytherapy and External Beam Radiotherapy

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Abstract

Purpose: There is a growing need to identify prognostic factors in prostate cancer (pca) to avoid excessive or inappropriate treatment of patients. It may be helpful to identify patients with poor outcomes who would be candidates for more intensive treatments.

Methods: we performed a retrospective analysis of data of the charts of all unfavorable PCA treated with the combination of High-Dose-Rate Brachytherapy (HDR-BT) and External Beam Radiotherapy (EBRT) at the department of radiation oncology (ac camargo cancer center), são paulo, brazil, between 1997 and 2010. Ethnicity definition was based on 4 categorizations: black, mulatto, white and asiatic. We included 229 patients (age range 47-83 years). The median follow-up was 70.3 months (range, 36 –155 months). There were 7.4% (17) yellow, 79.0% (181) white, 7.9% (18) black and 5.7% (13) mulatto patients.

Results: EBRT and HDR-BT doses ranged from 40 to 54 gy and 16 to 30 gy given in 4 fractions, respectively. Actuarial 5- and 10-year overall and disease free survical (DFS) rates were 87.6%, 61.3%, 90.9% and 54.2%, respectively. On univariate analysis prognostic factors related to improved DFS were white/asiatic race (p<0.001), initial clinical stage p=0.004, HDR-BT dsoe >20 gy (p<0.001) and gleason-score <7 (p<0.001). On multivariate analysis black/mulatto race (p=0.037), advanced clinical stage (p=0.038) and HDR-BT dose <20gy (p<0.001) were associated with biochemical failure.

Conclusion: The race seems to be one of the markers of prognosis for PCA. Already known predictive factors of biochemical failure were confirmed in our analysis (clinical stage, gleason score). An improved DFS was related to HDR-BT dose escalation. Further studies are still necessary to provide more information about clinical and genetic predictive factors of aggressiveness that can be used to guide a personalized dose intensification treatment.

Keywords: Race; Prostate cancer; Radiotherapy; Brachytherapy

Abbreviations: PCA: Prostate Cancer; RG: Risk Group for Biochemical Failure; IR: Intermediate Risk for Biochemical Failure; HR: High Risk for Biochemical Failure; HDR-BT: High Dose Rate Brachytherapy; EBRT: External Beam Radiotherapy; OS: Overall Survival; DFS: Disease Free Survival; BF: Biochemical Failure; NEOADJ HT: Neoadjuvant Androgen Deprivation; ADJ HT: Adjuvant Androgen Deprivation

Introduction

Prostate cancer (PCa) is reported to be a primary reason for consultation with a general practitioner amongst men with cancer. PCa is also the most common solid malignancy and the second leading cause of cancer-related death for American men. In Brazil PCa is expected to be the second most common cancer in the male population with 60,800 new diagnoses projected for 2012 and 12,778 deaths observed in 2010 [1].

There is a growing need to identify new prognostic markers and factors in PCa to avoid excessive or inappropriate treatment of patients. Furthermore, it may be helpful to identify patients with poor outcomes who would be candidates for more intensive treatments, allowing risk-based individual therapy.

A group of prognostic factors, known as markers or biomarkers, has received considerable interest from clinical trials. Few markers have achieved widespread clinical utility and there is an increasing need to develop and identify markers that provide more clinical information [2]. Based on clinical stage, initial PSA value (iPSA) and Gleason Score, PCa is classified as being at a low, intermediate (IR) or high-risk (HR) for biochemical failure (BF), as this dramatically affects outcomes. The IR group encompasses a wide variation of tumor and clinical characteristics, and both IR and HR groups are generally classified as unfavorable tumors, despite its presentation as a localized disease.

Although, the best management of the different risk groups remains controversial, surgery, external beam radiotherapy (EBRT), brachytherapy, hormonal therapy (HT), and watchful waiting can be used isolated or in combination [3].

Particularly in North America the incidence of prostate cancer in Black men is more than twice as high as that of any other race. They also they tend to be diagnosed with more advanced and aggressive disease. The reasons why Black men are at an increased risk of developing and dying from PCa are still not known [4].

In Brazil, most published studies did not demonstrate statistically significant difference in the prevalence and mortality of PCa between White and any other race patients [5-9]. Furthermore, neither evaluation of the stage of the disease nor differentiation between race and tumor characteristics, for the male Brazilian population treated with definitive radiotherapy, has been performed to date.

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The aim of this retrospective analysis is to evaluate the data of the charts of all IR and HR patients treated between March, 1997 and January, 2010 with the combination of conformal high dose rate brachytherapy (HDR-BT) and EBRT and to evaluate the influence of race and other possible predictive factors for BF for this group of patients.

Material and Methods

All patients with biopsy proven PCa adenocarcinoma, treated with EBRT and HDR-BT at the Department of Radiation Oncology, AC Camargo Cancer Center, Sao Paulo, Brazil had their charts retrospectively reviewed, after approval of the study by the Institutional Ethics' Committee. Details as race, age, Gleason score (GS), the initial PSA value (iPSA) and clinical stage (CS) using the 1992 AJCC clinical stage were collected to define the risk group for BF.

All patients were grouped according to their risk for biochemical failure. The IR group encompassed patients with either stage T2b, GS 7 or iPSA value ranging from 10–20 ng/ml. Patients who presented two or more of the characteristics of the IR or iPSA>20 ng/ml, GS > 7 or CS > T2b were grouped into the HR.

External beam treatments involved 2 or 3 dimensional plans directed to the prostate and seminal vesicles. There was no intention to treat the pelvic/obturatory lymphonodes. In the first three years of the period of analysis, conventional two dimensional external radiotherapy planning was used. The defined targets for radiotherapy were the prostate and seminal vesicles, plus a 8-10 mm margin in all directions. After 1999, all patients were treated with localized conformal radiotherapy, when the margins used to the target were in the range of 5 to 10 mm.

Technical details of HDR-BT have being already published elsewhere [10,11]. In brief, HDR-BT was performed before or after the completion of EBRT. All implants were performed in the operating room, under spinal anesthesia and with the patient in lithotomic position. Perineal template guidance and steel needles were used for all patients. The needles were uniformly placed into all the prostatic volume, but avoiding the urethra. At least 90% of the prostate volume should receive 100% of the prescribed dose and doses to the urethra should not exceed 135% of the prescribed dose.

After completion of treatment all patients were seen in follow-up 1 to 2 months after ending of the treatment and every 2-4 months for the first 24 months. Thereafter patients were seen in follow up every 6-12 months.

The ethnicity classification of the patients was based on 4 categorizations: Black, Mulatto, White or Asiatic.

Hormonal therapy was classified in adjuvant and or neo adjuvant. Patients considered having adjuvant HT should have used it at least for 12 months and neo adjuvant HT should not exceed 6 months prior to the commencement of radiation treatment. Clinical characteristics of patients are shown in Table 1.

For statistical analysis all endpoints were calculated as the interval from pathologic diagnosis of PCa to dead or failure. The BF was defined according to the RTOG-ASTRO Phoenix Consensus Conference [12]. Pearson chi-square and t tests were used to compare differences in categorical and continuous patient characteristics, respectively. Survival data were generated using the Kaplan-Meier method, with log-rank test used to compare equality of survivor functions. Statistical tests were performed using SPSS 13.0 (SPSS, Chicago, IL).

Results

The data of the charts of 229 patients considered IR or HR treated between March, 1997 and January, 2010 were evaluated. Median age of patients was 70 years (range, 47-83) and median follow-up was 70.3 months (range, 36 –155 months).

The race profile according to the risk group for BF of patients is depicted in Table 2. There were 7.4% (17) Asiatic, 79.0% (181) White, 7.9% (18) Black and 5.7% (13) Mulatto patients. One hundred seventeen patients were considered IR (51.1%) and 112 (48.9%) were considered HR. There was no statistically significant difference between risk groups and race (p=0.241).

Adjuvant HT was part of the treatment of 173 (75.5%) patients, who used it for at least one year and 53.3% (122) patients had no HT prior to the commencement of the irradiation treatment.

The dose of HDR-BT ranged from 16 to 30 Gy given in 2 to 4 fractions, twice a day, administered by one or two implants with one week interval. Median HDR-BT dose was 24 Gy.

Variable	n	%	Range	Median
Age (years)			47-83	68.7
iPSA (ng/ml)			4.1-175.0	24.2
GS			6-9	7
Follow up (Months)			24-123	62.4
Last PSA			0.01-99.7	3.4
Ethnicity				
Asiatic	17	7.4		
White	181	79.0		
Black	18	7.9		
Mulatto	13	5.7		
Clinical Stage				
T1	89	38.9		
T2a	71	31.0		
T2b	32	14.0		
T3	37	16.2		
Neo HT				
No	123	53.7		
Yes	106	46.3		
Adj HT				
No	56	24.5		
Yes	173	75.5		
Risk Group				
Intermediate	117	51.1		
High	112	48.9		
Total	229	100.0		

iPSA: Initial PSA Value; GS: Geason Score; IR: Intermediate Risk; HR: High Risk; Neo HT: Neoadjuvant Androgen Deprivation; Adj HT: Adjuvant Androgen Deprivation

Table 1: Patients characteristics.

	Risk Group		Total
Race	IR	HR	
Asiatic	7	10	17
White	91	90	181
Black	9	9	18
Mulatto	10	3	13
Total	117	112	229

IR: Intermediate Risk for Biochemical Failure; HR: High Risk for Biochemical Failure

Table 2: Race and Risk Group for Biochemical Failure distribution.

The total dose of EBRT ranged from 40 to 54 Gy (median 47 Gy) given in 15 to 30 daily fractions, with weekend rest. Time to complete the scheduled EBRT ranged from 3 to 7 weeks (median 5 weeks). The interval between EBRT and HDR-BT varied from 7 to 15 days in all patients. A hundred eight three (79.9%) patients started their treatment with EBRT. The total treatment time, including EBRT, break and HDR ranged from 5 to 9 weeks (median 7 weeks).

The crude overall survival (OS) at 10 years was 79.5%. Actuarial 5- and 10-year OS rates were 87.6% and 61.3%, respectively, as shown in Figure 1. Five- and 10-year actuarial DFS were 90.9% and 54.2%, respectively (Figure 2). Forty seven (20.5%) patients were dead at the time of this analysis, 38 (16.6%) of them died due PCa disease progression.

On univariate analysis prognostic factors related to improved DFS were race not Black/Mulatto (p<0.001), early CS (p=0.004), HDR dose>20 Gy (p<0.001) and GS<7 (p<0.001). On multivariate analysis race Black/Mulatto (p=0.037, HR 4.34, 95%CI 0.212-0.953), late CS (p=0.038, HR 4.31, 95%CI 1.036-3.331), HDR < 20 Gy (p<0.001, HR 6.58, 95% CI 0.164-0.480) were predictive factors related to BF, as shown in Table 3 and Figure 3.

Discussion

The lliterature has being also calling the attention to several risks for developing PCa since the three last decades, with race being one of them [13], but the interpretation of cancer incidence and mortality rates in a defined population requires an understanding of multiple factors that vary across time and space. These factors include changes in medical practices related to screening and treatment. Racial differences are greater for prostate cancer than for any other major cancer site and during 2003-2007, its incidence was 60% higher and the mortality was 2.4 times greater for Black men than White men in the U.S. Further more; the rates for Blacks exceeded all other racial and ethnic minorities [1].

Brazil is known for its multiracialism. The demands for recognition of multiracial identities of mulattoes (Mulatto men) in Brazil differ from North America, because of the lack of a clear color distinction and a strong cultural tradition of tolerance and miscegenation, as well as longstanding explicit laws against racial discrimination. The first European immigrants to Brazil were of Iberian origin, primarily Portuguese. There were also some Dutch immigrants to the Northeast in the sixteenth and seventeenth centuries. The Portuguese intermarried with the Amerindian population, which was decimated by conflict and

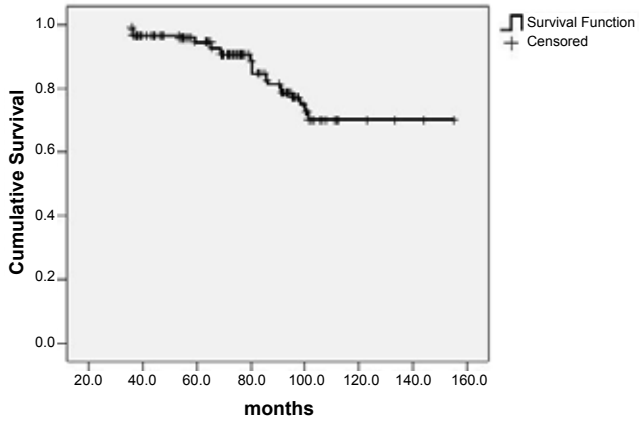

Figure 1: Overall survival.

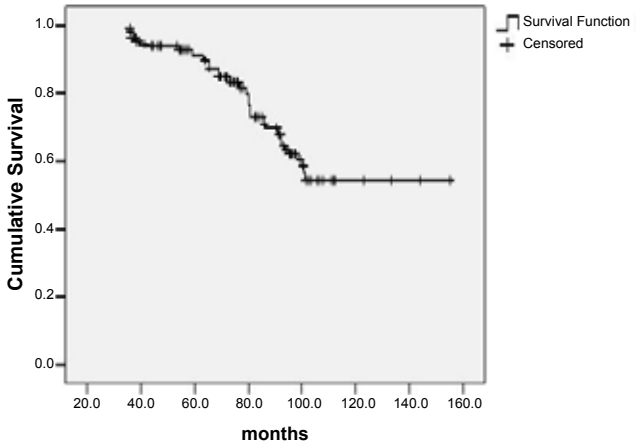

Figure 2: Disease free survival.

Variable		BF			
		Number	BF	%	p
Race	Yellow	17	1	5,9	<0.001
	White	181	49	27,1	
	Black	18	10	55,6	
	Brown	13	5	38,5	
CS	< 2b	160	35	21,9	0.004
	≥ 2b	69	30	43,5	
Neoadj HT	Yes	107	25	23,4	0.152
	No	122	40	32,8	
Adj HT	Yes	173	50	28,9	
	No	56	15	26,8	
Risk Group	Intermediate	122	25	20,5	0.055
	High	107	40	37,4	
HDR Dose (Gy)	< 20	85	45	52,9	<0.001
	20-24	144	20	13,9	
iPSA	<10	56	20	35,7	0.225
	10-20	105	25	23,8	
	>20	68	20	29,4	
GS	<7	146	36	24,7	0.001
	7	56	18	32,1	
	>7	27	11	40,7	
GS – reference 7	≤ 7	202	54	26,7	0.009
	>7	27	11	40,7	
EBRT	<50	125	39	31.2	
	≥ 50	104	26	25.0	0.060
Age	≥ 65	75	25	33.3	0.094
	>65	154	40	26.0	

iPSA: Initial PSA Value; GS: Geason Score; IR: Intermediate Risk; HR: High Risk; neoadj HT: Neoadjuvant Androgen Deprivation; adj HT: Neoadjuvant Androgen Deprivation; EBRT: External Beam Radiotherapy; HDR-BT: High Dose Rate Brachytherapy

Table 3: Univariate analysis.

disease. During the colonial period, after Indian slavery proved difficult to enforce, the colonists imported hundreds of thousands of slaves from Africa for labor on the sugar plantations, in the mines, and later on coffee plantations. At first, slaves outnumbered the white settlers in many areas, but the balance eventually changed. During the same period, settlers from Europe, primarily Germany, Italy, and Poland, established farming colonies in parts of the South. Brazil's racial mix was made more diverse with the arrival of Japanese and Middle Eastern immigrants in the early twentieth century [14]. Further more, little is known about race and race background in populations from developing

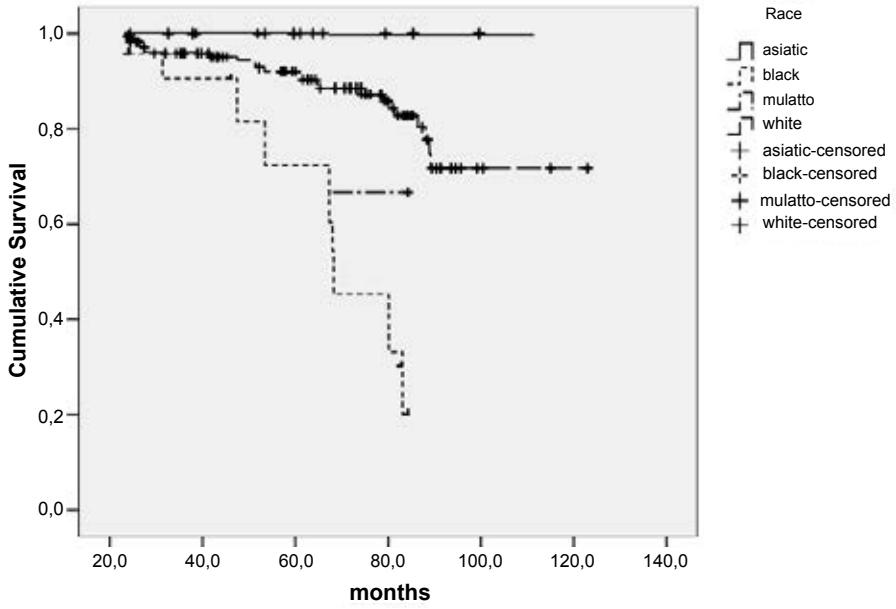

Figure 3: Disease Free Survival according to the race.

countries, which represent virtually all the projected growth for the world population by 2050 [15].

Previous researches have attempted to explain racial differences in prostate cancer incidence and mortality. In North America Black men experience greater incidence and increased burden from late-stage diagnosis, aggressive tumor biology and much higher mortality compared to other ethnicity [16]. In Brazil such distinction is more difficult and results of research in this area failed to demonstrate any difference. These results have been frequently attributed to the high race mixture index of the Brazilian population as a consequence of centuries of interethnic crosses between Europeans, Africans, and Amerindians; as well as the use of different methodology to classify individuals into racial groups and the inaccuracy in stratification of race using skin color [5,17,18].

One reason that Blacks have a worse outcome report may be due to differences in access to care and lower participation rates in preventive screening tests than White men. Another potential explanation for racial disparities observed in PCa is that Blacks may be more intensely exposed to deleterious nutritional factors, but of the few studies reporting on fiber/whole grain consumption and PCa, results have been conflicting due partly to heterogeneity in design or analysis, which include differences in case selection, race proportions and inconsistent adjustment for potential confounders [19]. The importance of accounting for social context in public health is clear and uunfortunately as a retrospective analysis we could not access this information. A few studies examined associations between cereal intake and prostate cancer mortality. In a cross-national comparison of predictive factors for PCa mortality, energy from cereal food sources were found significantly inversely associated with prostate cancer mortality [20], in contrast, Nimptsch et al. reported associations between dietary fiber and whole grain intake with LS PCa prostate cancer [21].

A recent meta-analysis performed in Brazil provided the information that the prevalence of prostate cancer in Brazil is 58% higher in Blacks, and 43% higher in Mulattoes when compared to White men, with a confidence level of 95% [22]. Barros et al. also assessed the associations between race, age and PCa in a Brazilian university hospital during the period from 1999 to 2001. They studied 580 patients with median age of 60 years, observing that 116 were Whites (20.0%), 276 Mulattoes (47.6%) and 188 Blacks (32.4%). They did not note any significant difference regarding the prevalence of PCa between Whites, Mulattoes sand Blacks (p=0.36). While studying the association between race classified in 2 groups (Whites versus Mulattos and Blacks), as we did, they observed no association in the prevalence or worse outcome, opposite to our finds [5].

Other researchers have also attempted to explain racial differences in PCa incidence and mortality, concluding that tumor grade, late stage of disease at diagnosis, and differences in access to definitive and adjuvant treatment contribute to mortality [23-26].

Tsivian at al. investigated racial differences in tumor burden in 4,157 men undergoing radical prostatectomy between1993-2010. They compared clinical and pathological data between African-American and non African-American patients, observing that black patients were younger, had higher Gleason scores, PSA levels and incidence of palpable [27]. In our analysis differences in age, iPSA or CS were not statically significant to determine BF. Conversely to our results, some published studies performed in Brazil did not demonstrate statistically significant difference in the prevalence of PCa between White and Black patients [28,9].

One can observe that the main advantage of HDR-BT is its ability to deliver a relative high dose of radiation within a well-defined volume, with a rapid fall-off of dose outside the implanted area, with some additional advantages over normal tissues sparing and on reducing miss dose to the prostate, due imprecise target localization, treatment setup uncertainties, organ motion and or deformation during the treatments, with a relative low incidence of severe acute and late side effects [10,11,29-31]. What is still not clear in the literature is that despite the higher dose escalation given with HDR-BT when compared to other techniques is enough to control the disease for determined subgroup of patients considered at higher risk of disease progression. We in this review that HDR-BT dose intensification was statistically significant (p<0.001, HR=6.8) associated with improved

DFS. In a previous publication we had noted that dose intensification is associated with improved DFS without increasing morbidity if dose three dimensional planning are used and dose constraints are respected for rectum and urethra [32]. A possible limitation of this paper is that the patient numbers are relatively low.

In conclusion, the race, despite the inaccuracy in its stratification using skin color, seems to be one of the markers of prognosis for PCa. There may be some differences in outcome for PCa in Black/Mulatto Brazilian men like in US. Our study suggest that dose intensification can superpose some unfavorable factors and can be safety used to increase the therapeutic ratio for specific subgroups of patients, despite the absence of data from prospective randomized trials comparing results of this combination with dose escalation EBRT and HDR-BT. Further studies are still necessary to confirm our findings and to provide more information about clinical and genetic predictive factors of aggressiveness that can be used to guide a personalized dose intensification treatment.

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