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Outcomes of Patients with Unfavorable Prostate Cancer Treated with High-Dose Rate Brachytherapy and External Beam Radiotherapy

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Authors' contributions

This work was carried out in collaboration between all authors. Author ACAP designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author RCF made the final review of the paper. All authors read and approved the final manuscript

Research Article

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ABSTRACT

Aims: Literature is calling the attention to several risks for developing prostate cancer (Pca), and race is one of them. We performed an analysis of data of the charts of all unfavorable PCa (uPCa) treated with the combination of high-dose-rate brachytherapy (HDR) and external beam radiotherapy (EBRT).
Study Design: Retrospective study.
Place and Duration of Study: Department of Radiation Oncology (AC Camargo Vancer Center), São Paulo, Brazil, between 1997 and 2010.
Methodology: The data of all uPCa treated between 1997 and 2010 were evaluated. Ethnicity definition was based on 3 categorizations: Black, 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) Asiatic, 79.0% (181) Whiten and 13.6% (31) Black patients.
Results: EBRT and HDR doses ranged from 40 to 54 Gy and 16 to 30 Gy given in 4

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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>20Gy (p<0.001) and Gleason-Score<7 (p<0.001). On multivariate analysis race (p=0.037), late clinical satge (p=0.038) and HDR<20Gy (p<0.001) were associated with biochemical failure.

Conclusion: An association with aggressive PCa was observed in Black when compared to White/Asiatic patients. Already known predictive factors of biochemical failure were confirmed in our analysis. Improved DFS was related to HDR 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 treatment.

Keywords: Prostate cancer; radiotherapy; brachytherapy.

ABBREVIATIONS

***Pca**: prostate cancer; **uPCa:** unfavorable prostate cancer; **RG**: risk group for biochemical failure; **IR**: intermediate risk for biochemical failure; **HR**: high risk for biochemical failure; **HDR**: high-dose-rate brachytherapy; **EBRT**: external beam radiotherapy; **OS**: overall survival; **DFS**: disease free survival; **BF**: biochemical failure.*

1. INTRODUCTION

Prostate cancer (PCa) is 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].

PCa is generally 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. Although, the best management of both favorable and unfavorable PCa (uPCa) remains controversial, surgery, external beam radiotherapy (EBRT), brachytherapy, hormonal therapy (HT), and watchful waiting can be used isolated or in combination to treat the different risk groups [2].

The incidence of prostate cancer in Black men is more than twice as high as that of any other race, particularly in North America, and the reasons why Black men are at an increased risk of developing and dying from PCa are not known [3].

In Brazil, most published studies did not demonstrate statistically significant difference in the prevalence and mortality of PCa between White and Black patients [4-8]. 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. Between March, 1997 and January, 2010 a total of 257 uPCa were treated at Hospital AC Camargo with the combination of conformal high dose rate brachytherapy (HDR) and EBRT. We performed a retrospective analysis of the data of the charts to evaluate the influence of race and other possible predictive factors for BF.

2. MATERIALS AND METHODS

All patients with biopsy proven uPCa adenocarcinoma, treated with tridimensional EBRT in combination with HDR at the Department of Radiation Oncology, Hospital AC Camargo, Sao Paulo, Brazil had their charts retrospectively reviewed. The study was approved by a review board and the institutional ethic 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 biochemical failure, according to the Fox Chase definition. Patients with either stage T2b, GS 7 or iPSA value ranging from 10–20 ng/ml were considered IR. 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.

2.1 Ethnicity Classification

Ethnicity classification was based on 3 categorizations: White, Black and Asiatic. The use of HT was classified in adjuvant and or neoadjuvant. Neoadjuvant HT lasted from 12 to 3 months (median 6 months). Patients considered having adjuvant HT (AD) should have used it at least for 12 months and maximum 36 months (median 26 months). Clinical characteristics of patients and tumors are depicted in Table 1.

Table 1. Patients and Tumor characteristics

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	31	13.6		
Clinical Stage				
T1	89	38.9		
T2a	71	31.0		
T2b	32	14.0		
T3	37	16.2		
NAAD				
No	123	53.7		
Yes	106	46.3		
AD				
No	56	24.5		
Yes	173	75.5		
Risk Group				
Intermediate	117	51.1		
High	112	48.9		
Total	229	100.0		

Legend - iPSA – initial PSA value, GS – Geason score IR- intermediate risk, HR – high isk, NAAD – neoadjuvant androgen deprivation, AD- adjuvant androgen deprivation

2.1.1 High dose rate brachytherapy

Technical details of HDRT have being already published elsewhere [9-10]. In brief, HDR 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 and corrected their position whenever necessary as already published by Huang et al. [11].

2.2 External Beam Radiotherapy

In the first three years of the period of analysis, conventional two dimensional external radiotherapy planning was used, but all patients had a pretreatment diagnostic computed tomography scan (CT), urethrogram and rectal contrast to assist in defining the prostate, seminal vesicles and normal tissue volumes at risk. No patient got treatment to the pelvic lymphatic nodes.The defined targets for radiotherapy were the prostate and seminal vesicles, plus a 10 mm margin in all directions, but posterior that ranged from 7-10 mm. After 1999, all patients were treated with localized conformal radiotherapy, when the margins used to the target were in the range of 7 to 10 mm.

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

2.3 Statistical Analysis

All endpoints were calculated as the interval from pathologic diagnosis of PCa to BF, 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).

3. RESULTS

Between March, 1997 and January, 2010 a total of 337 patients with PCa were treated with combination of EBRT and HDR at the Department of Radiation Oncology, Hospital AC Camargo, Sao Paulo, Brazil, of these, 257 patients were uPCa. Twenty eight patients were lost of follow up before two years after the completion of the treatment and 229 were eligible for study entry. Median age of patients was 70 years (range, 47-83) and median follow-up was 70.3 months (range, 36 –155 months). Race profile and risk group of patients are depicted in Table 2. There were 7.4% (17) Asiatic, 79.0% (181) White, 7.9% (18) Black and 5.7% (13) Black 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) Table 2. Of the total, 53.3% (122) patients did not use HT prior to the commencement of the irradiation treatment and 75.5% (173) had at least one year of adjuvant HT.

Table 2. Race and risk group for biochemical failure distribution

Race	Risk Group		Total
	IR	HR	
Asiatic	7	10	17
White	91	90	181
Black	19	12	31
Total	117	112	229

Legend - IR – intermediate risk for biochemical failure; HR – high risk for biochemical failure

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

The dose of HDR 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 dose was 24 Gy. The crude overall survival (OS) at 10 years was 79.5%. Table 3.

Table 3. Status of the patients

Status	Number	%
NED	164	71.6
BF	18	7.9
DOC	9	3.9
DPCa	38	16.6
Total	229	100.0

Legend – NED- no evidence of disease, BF – biochemical failure, DOC - dead due others causes, DPCa- dead due prostate cancer

Actuarial 5- and 10-year OS rates were 87.6% and 61.3%, respectively. Fig 1.

Five and 10-year actuarial DFS were 90.9% and 54.2%, respectively. Fig. 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 ($p<0.001$), early CS ($p=0.004$), HDR dose >20 Gy ($p<0.001$) and GS < 7 ($p<0.001$). Fig. 3. Table 4.

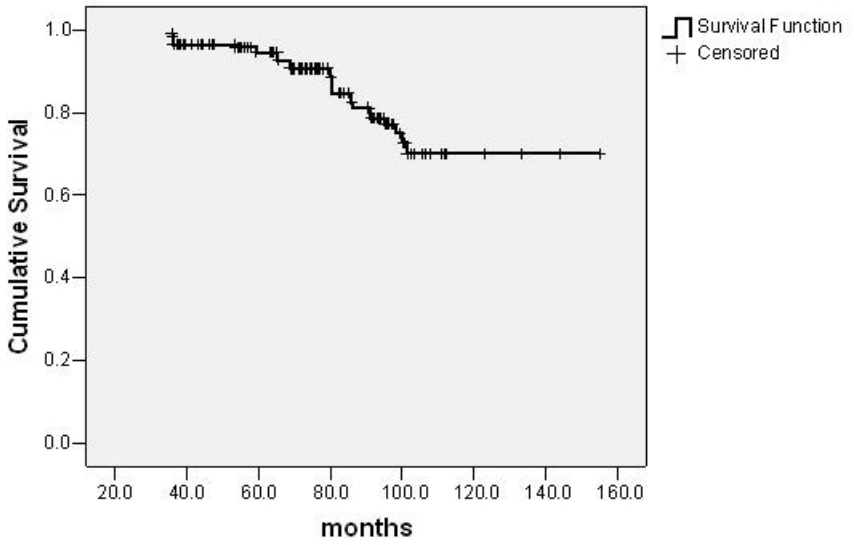

Fig. 1. Overall survival

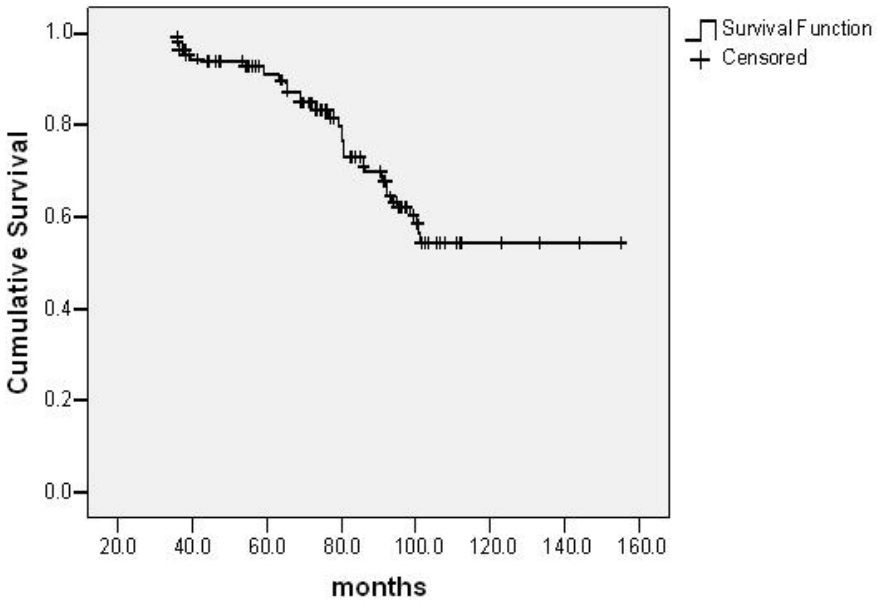

Fig. 2. Disease Specific Survival

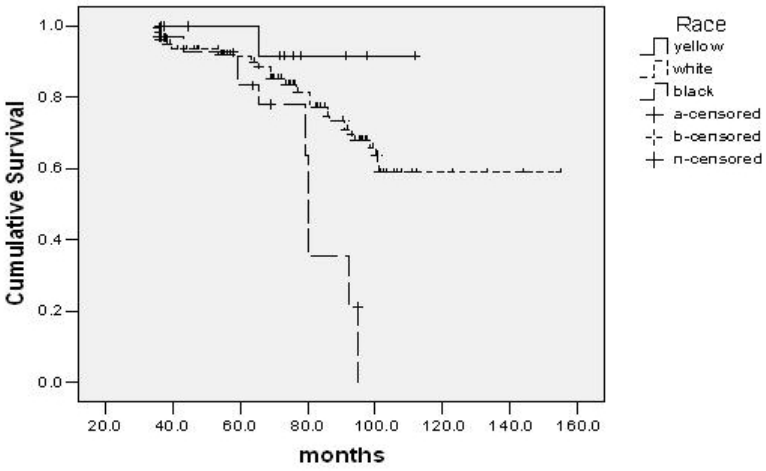

Fig. 3. Disease Specific Survival according to Race

Table 4. Univariate analysis

Variable		BF			
		Number	BF	%	p
Race	Asiatic	17	1	5.9	<0.001
	White	181	49	27.1	
	Black	31	15	48.3	
Race	White/Asiatic	198	50	25.3	<0.001
	Black	31	15	48.4	
CS	< 2b	160	35	21.9	0.004
	> = 2b	69	30	43.5	
NAAD	Yes	107	25	23.4	0.152
	No	122	40	32.8	
AD	Yes	173	50	28.9	0.772
	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	

Legend - iPSA – initial PSA value, GS – Geason score IR- intermediate risk, HR – high isk, NAAD – neoadjuvant androgen deprivation, EBRT – external beam radiotherapy, HDR-BT – high dose rate brachytherapy.

On multivariate analysis race Black (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 21.51, 95%CI 0.164-0.480) were predictive factors related to BF.

4. DISCUSSION

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. Furthermore; the rates for Blacks exceeded all other racial and ethnic minorities [13].

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 [14], 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.

HDR is a successful method for delivering higher dose of radiation to the prostate when compared to radiotherapy alone. The main advantage of HDR 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 [9]. This approach is ideal for the treatment of prostate cancer, where the gland lays very close to critical normal tissues, in particular the anterior rectal wall and bladder neck. HDR has also 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 [10,15-17].

Although HDR allow higher dose escalation when compared to other techniques , it is still not clear if the higher dose level given to the prostate is enough to control the disease for determined subgroup of patients considered at higher risk of disease progression.

When comparing treatment outcomes of PCa from different studies, it is important to know the distribution of risk groups as this dramatically affects results. The inclusion of patients presenting with two of the parameters of IR into the HR showed a significant refection on biochemical control. Although there may be some differences between institutions in classification systems, there is a consensus that standard definitions must involve CS, GS and iPSA. For patients with locally advanced disease significant clinical data are available demonstrating that dose escalation EBRT has a significantly better outcome as the dose to the prostate is increased [18-20].

Several retrospective studies with more than 5-year follow up have previously described a better outcome of patients treated with combination of EBRT and HDR [10, 15, 21,22], but data from prospective randomized trail comparing results of this combination with dose escalation 3D-RT3D or IMRT is still missing.

Brazil is known for its multiracialism. 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 [23]. Furthermore, little is known about race and race background in populations from developing countries, which represent virtually all the projected growth for the world population by 2050 [24].

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 [25]. 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 [5,26,27].

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 [28], 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 [29]. 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 [30], in contrast, Nimptsch et al. reported associations between dietary fiber and whole grain intake with LS PCa prostate cancer [31].

A recent meta-analysis performed in Brazil provided the information that the prevalence of prostate cancer in Brazil is 58% higher in Blacks when compared to White men, with a confidence level of 95% [32]. 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%), 464 Blacks (32.4%). They did not note any significant difference regarding the prevalence of PCa between Whites and Blacks ($p = 0.36$), the opposite of 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 [33-37].

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 [38]. In our analysis differences in age, iPSA or CS were not statically significant to determine BF. HDR dose up to 20 Gy was marginally significant ($p=0,059$, HR=3.6) and the only factor associated with a worse outcome on multivariate analysis was the HR group risk ($p=0.009$, HR=6.8).

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 [39,40].

A possible limitation of this paper is that the patient numbers are relatively low and over 70% remained with no evidence of disease.

5. CONCLUSION

We conclude that despite the inaccuracy in stratification of race using skin color and 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, there may be some differences in outcome for late stage prostate cancer in Black Brazilian men. Further studies are still necessary to confirm our findings.

CONSENT

All authors declare that 'written informed consent' was obtained from the patient (or other approved parties) for this publication.

ETHICAL APPROVAL

This protocol is approved by the AC Camargo Hospital Institutional Ethics Committee and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Câncer Incidence. Available: http://www2.inca.gov.br/wps/wcm/connect/tiposdecancer/site/home/prostata/definicao.
2. Ali AS, Hamdy FC. The spectrum of prostate cancer care: from curative intent to palliation. Curr Urol Rep. 2007;8:245-252.
3. Ledet EM, Hu X, Sartor O, Rayford W, Li M, Mandal D. Characterization of germline copy number variation in high-risk African American families with prostate cancer. Prostate; 2013. DOI: 10.1002/pros.22602
4. Barros MS, Silva VR, Santos GB, Hughes A, Silveira MA. Prevalence of prostate adenocarcinoma according to race in an university hospital. Int Braz J Urol. 2003;29:306-311.
5. Martins AC, Reis RB, Suaid HJ, Maciel LM, Cologna AJ, Falconi RA. Screening for carcinoma of the prostate in volunteers. Int Braz J Urol. 2000;26:516-522.
6. Antonopoulos IM, Pompeo ACL, Hayek OR, Sarkis AS, Alfer W Jr, Arap S. Results of prostate cancer screening in non-symptomatic men. Braz J Urol. 2001;27:227-34.
7. Glina S, Toscano IL Jr, Mello JF, Martins FG, Vieira VL, Damas CG. Results of screening for prostate cancer in a community hospital. Int Braz J Urol. 2001;27:235-43.
8. Dini LI, Koff WJ. Profile of prostate cancer at the general hospital of Porto Alegre. Rev Assoc Med Bras. 2006;52:28-31.

9. Pellizzon AC, Salvajoli J, Novaes P, Maia M, Fogaroli R, Gides D et al. The relationship between the biochemical control outcomes and the quality of planning of high-dose rate brachytherapy as a boost to external beam radiotherapy for locally and locally advanced prostate cancer using the RTOG-ASTRO Phoenix definition. Int J Med Sci. 2008;5(3):113-120
10. Pellizzon AC, Salvajoli JV, Maia MA, Ferrigno R, Novaes PE, Fogarolli RC et al. Late urinary morbidity with high dose prostate brachytherapy as a boost to conventional external beam radiation therapy for local and locally advanced prostate cancer. J Urol. 2004;171:1105-1108.
11. Roach III M, Hanks G, Thames Jr H, Schellhammer P, Shipley WU, Sokol GH et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006;65:965-974.
12. Huang Y, Miller B, Doemer A, Babij D, Kumar S, Frontera R ET AL. Online correction of catheter movement using CT in high-dose-rate prostate brachytherapy. Brachytherapy. 2013;12(3):260-6. doi: 10.1016/j.brachy.2012.08.008. Epub 2013 Feb 28.
13. American Cancer Society. Cancer facts and figures, 2011. Atlanta, GA. American Cancer Society; 2011. Available at: http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics
14. Morton RA Jr. Racial differences in adenocarcinoma of the prostate in North American men. Urology. 1994;44:637-645.
15. Phan TP Syed AM, Puthawala A, Sharma A, Khan F. High dose rate brachytherapy as a boost for the treatment of localized prostate cancer. J Urol. 2007;177(1):123-127.
16. Galalae RM, Kovacs G, Schultze J, Loch T, Rzehak P, Wilhelm R et al. Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. Int J Radiat Oncol Biol Phys. 2002;52:81-90.
17. Pellizzon AC, Nadalin W, Salvajoli JV, Fogaroli RC, Novaes PE, Maia MA et al. Results of high dose rate afterloading brachytherapy boost to conventional external beam radiation therapy for initial and locally advanced prostate cancer. Radiother Oncol. 2003;66(2):167-72.
18. Chism DB, Hanlon AL, Horwitz EM, Feigenberg A. Comparison of the single and double factor high-risk models for risk assignment of prostate cancer treated with 3D conformal radiotherapy. Int J Radiat Oncol Biol Phys. 2004;59(2):380-385.
19. Morgan PB, Hanlon A L, Horwitz EM, Buyyounouski MK, Uzzo RG, Pollack A: Radiation dose and late failures in prostate cancer. Int J Radiat Oncol Biol Phys. 2007;67(4):1074-1081.
20. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phy. 2008;70:67–74.
21. Martin JM, Bayley A, Bristow R, Chung P, Gospodarowicz M, Menard C et al. Image guided dose escalated prostate radiotherapy: still room to improve.Radiat Oncol. 2009;4:50.
22. Kwok Y, Yovino S: Update on radiation-based therapies for prostate cancer. Curr Opin Oncol. 2010;3:257-262.

23. Parra FC, Amado RC, Lambertucci JR, Rocha J, Antunes CM, Pena SD. Color and genomic ancestry in Brazilians. Proc Natl Acad Sci USA. 2003;100:177-182.
24. Lutz W, Samir KC: Dimensions of global population projections: what do we know about future population trends and structures? Philos Trans R Soc Lond B Biol Sci. 2010;365(1554):2779–2791.
25. Klassen AC, Curriero FC, Hong JH, Williams C, Kulldorff M, Meissner HI et al. The role of area-level influences on prostate cancer grade and stage at diagnosis. Preventive Medicine. 2004;39(l3):441–448.
26. Bouchardy C, Mirra AP, Khlat M, Parkin DM, de Souza JM, Gotlieb SL. Ethnicity and cancer risk in São Paulo, Brazil. Cancer Epidemiol Biomarkers Prev. 1991;1:21-7.
27. Paschoalin EL, Martins AC, Pastorello M, Sândis KA, Maciel LM, Silva WA Jr et al. Racial influence on the prevalence of prostate carcinoma in Brazilian volunteers. Int Braz J Urol. 2003;29:300-5.
28. Freeman VL, Leszczak J, Cooper RS. Race and the histologic grade of prostate cancer. The Prostate. 1997;30(2):79–84.
29. Lewis JE, Soler-Vilá H, Clark PE, Kresty LA, Allen GO, Hu JJ. Intake of plant foods and associated nutrients in prostate cancer risk. Nutrition and Cancer. 2009;61(2):216–224.
30. Hebert JR, Hurley TG, Olendzki BC, Teas J, Ma Y, Hampl JS. Nutritional and socioeconomic factors in relation to prostate cancer mortality: a cross-national study. Journal of the National Cancer Institute. 1998; 90(21):1637–1647.
31. Nimptsch K, Kenfield S, Jensen MK, Stampfer MJ, Franz M, Sampson L et al. Dietary glycemic index, glycemic load, insulin index, fiber and whole-grain intake in relation to risk of prostate cancer. Cancer Causes and Control. 2011;22(1):51–61.
32. Romero FR, Romero AW, de Almeida RM, Tambara Filho R. The prevalence of prostate cancer in Brazil is higher in Black men than in White men: systematic review and meta-analysis. Int Braz J Urol. 2012;38(4):440-7.
33. Xiao H, Tan F, Goovaerts P. Racial and geographic disparities in late-stage prostate cancer diagnosis in Florida. J Health Care Poor Underserved. 2011;22(4):187-99.
34. Tewari A, Horninger W, Pelzer AE, Demers R, Crawford ED, Gamito EJ et al. Factors contributing to the racial differences in prostate cancer mortality. BJU Int. 2005;96(9):1247-52.
35. Shavers VL, Brown ML. Racial and ethnic disparities in the receipt of cancer treatment. J Natl Cancer Inst. 2002;94(5):334-357.
36. Shavers VL, Brown ML, Potosky AL, Klabunde CN, Davis WW, Moul JW et al. Race/ethnicity and the receipt of watchful waiting for the initial management of prostate cancer. J Gen Intern Med. 2004;19(2):146-155.
37. Marlow NM, Halpern MT, Pavluck AL, Ward EM, Chen AY. Disparities associated with advanced prostate cancer stage at diagnosis. J Health Care Poor Underserved. 2010;21(1):112-131.
38. Tsivian M, Bañez LL, Keto CJ, Abern MR, Qi P, Gerber L et al. African-American men with low-grade prostate cancer have higher tumor burdens: Results from the Duke Prostate Center. Prostate Cancer Prostatic Dis. 2012;16(1):91-94.
39. Dini LI, Koff WJ. Profile of prostate cancer at the general hospital of Porto Alegre. Rev Assoc Med Bras. 2006;52:28-31.

40. Antonopoulos IM, Pompeo AC, Goes PM, Chade J, Sarkis AS, Arap S. Racial differences in prostate cancer prevalence. Int Braz J Urol. 2002;28:214-220.

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