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ARTICLE

Biopsy core length in white versus African descendant prostate cancer patients

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ABSTRACT

Objective: To explore whether distinct prostate cancer (PCa) prognoses between ethnicities could be explained by diverse characteristics in the prostate biopsy.

Methods: Clinical, prostate biopsy and surgical single-institution data of whites and African descendants with similar access to the health system who underwent radical prostatectomy whole gland histopathology within 60 days after biopsy from 2010 to 2011 and followed for 5 years minimum were compared.

Results: Among 203 included patients, 153 (75.4%) were whites and 50 (24.6%) were African descendants. The mean patients' age was 63.7 (± 6.8) years. Digital rectal examination (DRE) was suspected of cancer in 45.2% of the patients. The prostate biopsy core length was smaller in African descendants than in whites, overall 11.0 ± 3.2 vs 12.0 ± 2.9 mm, $p = 0.037$, and without neoplasia, 10.4 ± 3.8 vs 11.7 ± 3.1 mm, $p = 0.038$, respectively. Also, suspicious DRE showed smaller biopsy core length, overall 11.1 ± 3.2 mm vs 12.4 ± 2.6, $p = 0.003$, cancer positive 12.0 ± 4.8 mm vs 13.3 ± 3.7, $p = 0.022$ and negative 10.6 ± 3.6 mm vs 12.2 ± 3.0, $p = 0.002$. On 81 months median follow-up, more African descendants were lost to follow-up (10%, $n = 5$ vs 3.9%, $n = 6$) and the biochemical recurrence rate was the same between the groups (33.3%).

Conclusion: In a PCa population with similar access to the health system, prostate biopsy core length in African descendant men is significantly smaller than in whites. This finding is new and may add to the controversial argument of PCa having a worse prognosis in African descendant patients.

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Introduction

African-American men tend to have a higher incidence and more aggressive prostate cancer (PCa) disease at diagnosis and a higher mortality rate when compared to white men [1–3]. Thus, the main guidelines suggest that the screening should be started earlier in this group of men, and it is already discussed whether the treatment should also be proposed differently according to the patient's ethnicity [4]. The American Urological Association (AUA) recommends consultations for early detection beginning at the age of 40 for African descendants (and at 55 for whites) [5] and the European Association of Urology (EAU) at the age of 45 [6].

It is not clear, however, whether such disparities stem from ethnicity itself or coexisting factors. Different cancer suppression genes, higher levels of circulating androgens, disparities in hormone metabolism and numerous environment-related variables are blamed [7,8]. In 2016, Moses et al. [9] stated that African-Americans are less likely to receive immediate treatment when compared to whites, with a particularly lower rate of radical prostatectomy.

The decision that leads to the treatment of the patient depends on the disease staging, besides factors such as patient's desire and life expectancy. Some recent studies have shown that the optimization of the preprocessed prostate biopsy core is considered the best strategy to obtain a good quality standard biopsy [10]. In practice, however, a significant percentage of pathologists do not report such data in the examination reports [11].

There are few studies in the literature focusing on biopsy quality between the ethnicities, underestimating the hypothesis that distinct prognoses in the evolution of the PCa between whites and African Americans can be better elucidated when analyzing the different characteristics of the prostate biopsies of the patients of each subgroup.

Methods

After local Ethics Committee approval, clinical records and an anatomopathological single-institution database of prostate biopsies extracted by transrectal ultrasound from consecutive white and African descendant patients with similar health system characteristics and access between 2010 and 2011, whose biopsy indication was digital rectal examination (DRE) and/or PSA (prostatic specific antigen) suspicious for cancer, and who underwent open radical prostatectomy (RP) within 60 days after the biopsy were studied.

The preoperative variables analyzed were: age, digital rectal examination (DRE, suspected or not for cancer), PSA

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value, prostate volume (according to the transrectal ultrasound), PSA density (PSA/prostate volume), biopsy information histology – Gleason and extension of the core.

In the preoperative oncological evaluation, in the case of disease classified as Damico's intermediate or high risk for biochemical recurrence [12], a bone scan was performed for complete staging and men who underwent previous prostate biopsy or those with metastatic disease were excluded. Patient follow-up was performed for a minimum of 5 years (60–96 months) to detect biochemical recurrence, with serum PSA dosages every 3 months in the first postoperative year and every 6 months thereafter. The biochemical recurrence of the disease was defined as PSA $>$ 0.2 ng/ml [13].

The physicians performing prostate biopsies were supervised senior radiology residents of a tertiary-level public institution. A 6.5 Hz transrectal ultrasound transducer (Logiq 100, GE Medical Systems, Milwaukee, WI) was used. The patient was placed in the left lateral decubitus position after rectal enema and under local anesthesia (bilateral neurovascular bundle block with 5 ml lidocaine 2%), followed by double sextant puncture with the extraction of 12 fragments with automatic pistol and lateral cutting 19 mm needle.

The specimens were placed in individual flasks containing 10% formalin solution and suitably identified (right/left; medial/lateral; apex/medium/base). They were measured in millimeters, using a ruler, and included in paraffin and stained with hematoxylin and eosin, and referred for anatomopathological evaluation. In the case of more than one fragment per sample, the total length was considered as the sum of the fragments [14]. The cores without prostatic tissue were excluded from the analysis (about 2% in this cohort).

All analyses were performed by a single expert uro-pathologist, who classified them according to the International Society of Urological Pathology (ISUP) [15]. High-grade prostatic intraepithelial neoplasm (NIP) and atypical small acinar proliferation (ASAP) were classified as negative for cancer, since their clinical impacts are limited [16].

The postoperative variables analyzed were: surgical site information (histological grade, surgical margins, extra-prostatic extension, the involvement of seminal vesicles), concordance between the biopsy and surgical specimen Gleason scores, and the occurrence of biochemical recurrence.

The whole radical prostatectomy specimen of each patient divided into 32 paraffin blocks were processed without having the results of the initial biopsy in hand so that there was no comparison bias. Extraprostatic extension was considered when the tumor reached peri-prostatic adipose tissue [17].

The ethnicity was self-reported and white and African descendant groups were compared using the Mann-Whitney, Chi-Square and Fisher's exact tests. The biopsy cores length correlation with clinically significant variables was assessed and, for the categorical variables, the Mann-Whitney or Kruskal-Wallis test was used. The significance level for the statistical tests was 95%, $p < 0.05$ using the Statistical Analysis System (SAS) for Windows version 9.4 (SaS Institute Inc., Cary, NC).

Results

The total number of included patients was 203, of which 153 (75.4%) were whites and 50 (24.6%) African descendants. The median and mean patients' age was 65 and 63.7 (± 6.8) years, respectively. Digital rectal examination (DRE) was suspected of cancer in 45.2% of the patients. The mean values of PSA and prostate volume were 10.1 (± 8.5) ng/ml and 42.2 (± 23.4) cm^3, respectively, with no difference between white and African descendant patients.

On biopsy, 37% of all patients were classified as Damico's intermediate or high-risk, with a trend to a higher percentage in African descendants (46.9% vs 33.3%) and a lower percentage of low-risk (53.1% African descendants vs 66.7% Whites). African descendant's biopsy core length was smaller than those of whites, overall 11.0 ± 3.2 mm vs 12.0 ± 2.9, $p = 0.037$, resulting mainly from the difference between cores without cancer, 10.4 ± 3.8 mm vs 11.7 ± 3.1, $p = 0.038$, while there was no significance between the cancer positive biopsy cores length, 12.2 ± 4.8 mm vs 12.8 ± 4.1, $p = 0.147$ (Table 1).

Suspicious DRE also showed a smaller biopsy core length, overall 11.1 ± 3.2 mm vs 12.4 ± 2.6, $p = 0.003$, cancer positive 12.0 ± 4.8 mm vs 13.3 ± 3.7, $p = 0.022$, and cancer negative 10.6 ± 3.6 mm vs 12.2 ± 3.0, $p = 0.002$ (Table 2).

Concordance between the Gleason biopsies versus the whole gland RP showed a trend to under-staging among African descendants with RP surgical specimens in the higher Gleason grade ISUP prognostic group $>$ 1 (67.3% vs 56.6%), ISUP prognostic group $>$ 3 (12.3% vs 6.5%) and seminal vesicle involvement (14% vs 6%) in African descendants compared to whites (Table 3). On 81 months median follow-up, more African descendants were lost to follow-up (10%, $n = 5$ vs 3.9%, $n = 6$) and the 5-year biochemical recurrence rate was the same between the groups (33.3%).

Discussion

To our knowledge, the current study is unique in correlating the extent of the prostate biopsy cores with ethnicity and interestingly a significant difference was observed in the quality of the core biopsy of the African descendants, with smaller mean size of the fragment (11.0 ± 3.2 mm vs 12.0 ± 2.9, $p = 0.037$), secondary to the significance of the core length without cancer (10.4 ± 3.8 mm vs 11.7 ± 3.1, $p = 0.038$) compared to white patients.

In addition to the disparity in the core biopsy length between the ethnicities, we have observed that the positive and negative fragments for cancer are significantly smaller in patients with DRE suspected for PCa. While DRE is somehow subjective and examiner dependent [18], it is considered a strong prognostic tool, classifying patients as a non-low risk when suspected in the widely used Damico's prognostic system [12]. The herein described shorter biopsy cores might suggest under-sampling, corroborating to the worse prognosis previously described in suspect DRE.

Several authors have shown the importance of these aspects, without specifying, however, the ethnicity of the patients. Fiset et al. [19] studied 197 Canadian patients,

Table 1. Comparison of preoperative variables between whites and African descendants.

	White ($n = 153$)	African descendants ($n = 50$)	Total	p
Age, years				
Mean ± SD)	63.5 ± 6.7	64.3 ± 7.1	63.7 ± 6.8	0.3764
Median (min–max)	65.0 (42.0–76.0)	65.5 (45.0–76.0)	65.0 (42.0–76.0)	
Digital Rectal Exam				
Not suspicious	84 (55.6%)	25 (52.1%)	109 (54.8%)	0.6672
Suspicious	67 (44.4%)	23 (47.9%)	90 (45.2%)	
PSA, ng/ml				
Mean ± SD)	9.5 ± 7.0	12.1 ± 11.7	10.1 ± 8.5	0.0618
Median (min–max)	7.8 (0.6–51.0)	10.0 (1.0–78.0)	8.0 (0.6–78.0)	
Volume, mm^3				
Mean ± SD)	41.4 ± 21.6	44.9 ± 28.6	42.2 ± 23.4	0.8227
Median (min–max)	36.5 (15.0–185.0)	35.0 (10.0–150.0)	36.0 (10.0–185.0)	
PSA density				
Mean ± SD)	0.3 ± 0.2	0.3 ± 0.4	0.3 ± 0.3	0.0881
Median (min–max)	0.2 (0.01–1.5)	0.2 (0.01–2.6)	0.2 (0.01–2.6)	
Core average, mm				
Mean ± SD)	12.0 ± 2.9	11.0 ± 3.2	11.8 ± 3.0	0.0376*
Median (min–max)	12.0 (4.3–19.0)	10.4 (4.0–18.5)	11.9 (4.0–19.0)	
Core pos, mm				
Mean ± SD)	12.8 ± 4.1	12.2 ± 4.8	12.7 ± 4.3	0.1471
Median (min–max)	12.8 (4.0–19.0)	12.0 (4.0–19.0)	12.6 (4.0–19.0)	
Core neg, mm				
Mean ± SD)	11.7 ± 3.1	10.4 ± 3.8	11.4 ± 3.4	0.0381*
Median (min–max)	11.6 (5.0–19.0)	10.4 (4.0–18.3)	11.3 (4.0–19.0)	
Gleason Biopsy				
6	102 (66.7%)	26 (53.1%)	128 (63.4%)	0.2122
7	38 (24.8%)	18 (36.7%)	56 (27.7%)	
8–10	13 (8.5%)	5 (10.2%)	18 (8.9%)	

SD, standard deviation; min, minimum; max, maximum; pos, positive; neg, negative; mm, millimeters.
*Statistically significant.

observing that the length of the biopsy fragments with cancer was significantly greater than the benign ones and Öbek et al. [20] evaluated 245 biopsies and reached the same conclusion. This corroborates our study, in which cores with cancer are larger than those without cancer (12.7 ± 4.3 vs 11.4 ± 3.4 mm, on average).

Studies published by our group showed that, in a multivariate analysis including patient age, prostate size, PSA and PSA density, for every extra millimeter in the length of the extracted prostate biopsy core, the upgrading risk in radical prostatectomy decreases by 89.9% [21]. However, such an impact will not occur before 13 mm core length is reached [22].

The main hypothesis to justify that even a small increase in fragment length would lead to a significant improvement in PCa diagnosis and staging accuracy would be a more complete sampling of the anterior portion of the gland, in addition to explaining why some studies showed that a greater number [23] or increase in the diameter of the fragments [24] do not necessarily increase the accuracy in the detection of significant PCa.

In none of the previous articles, nor the general literature, were the characteristics of the prostate biopsy evaluated considering the ethnicity of the patients. Our study proposed a comparison of the results of the biopsies, in addition to the postoperative data of African descendant and white men with similar access to the health system, exploring for the first-time data that might help to explain the black ethnicity potential worse PCa prognosis.

While in a population with the same access to the health system the African descendant might not be an independent predictor of disease recurrence after surgery [25,26] and in our series there was also no significance in the biochemical recurrence at 5 years (33.3% in each subgroup), a clear trend for more aggressive disease was observed among African descendants and also it is well known that longer follow-up is necessary for a meaningful comparison in terms of recurrence and survival post-RP.

Thus, considering that a smaller fragment on transrectal prostate biopsy means less actual sampling of the prostate, especially in more anterior regions, we can consider two consequences: the first is that African descendant men would be exposed to a lower positivity in early random biopsies and would be submitted to a late diagnosis, another factor to justify a more aggressive disease in this subgroup at diagnosis. Besides, if we consider that the diagnosis of PCa has been confirmed, such a finding of poor biopsy quality in these patients may result in disease under-staging.

This can lead to multiple scenarios. The first would be to choose to remain under active surveillance. For example, in a biopsy with two Gleason 6 fragments with less than 50% cancer involvement, and other small but tumor-free specimens, only one core with any percentage of disease would mean immediate treatment (according to the largest part of the protocols). Thus, in this case, only a subsequent biopsy would make a more accurate staging, leading to actual treatment. And so, in such cases, late therapy would be the outcome, again with the risk of worsening the prognosis.

In the second scenario, this hypothetical under-staging would involve treatment with focal therapy, brachytherapy, or external radiation therapy. Thus, in any of these alternatives, the biopsy is the only anatomopathological data to decide the therapy to be followed (since if the radical prostatectomy had been performed, the surgical specimen would

Table 2. Biopsy core length versus clinical and histopathological relevant variables.

	Mean	SD	Minimum	Median	Maximum	p
Digital rectal exam						
Not suspicious						
Overall core	12.4	2.6	6.7	12.2	19.0	0.0039*
Positive core	13.3	3.7	7.0	13.0	19.0	0.0227*
Negative core	12.2	3.0	5.0	12.2	19.0	0.0021*
Suspicious						
Overall core	11.1	3.2	4.0	11.0	18.7	
Positive core	12.0	4.8	4.0	12.0	19.0	
Negative core	10.6	3.6	4.0	10.8	19.0	
Gleason Biopsy						
6						
Overall core	11.9	3.1	2.5	11.9	18.7	0.1660
Positive core	13.0	4.8	1.0	12.6	19.0	0.4452
Negative core	11.5	3.5	1.0	11.6	19.0	0.1056
7						
Overall core	11.2	2.9	5.3	11.8	19.0	
Positive core	12.0	3.4	4.0	12.4	19.0	
Negative core	10.8	3.2	4.5	11.0	19.0	
8–10						
Overall core	12.4	2.2	9.1	12.4	16.0	
Positive core	12.9	2.1	9.0	12.9	17.0	
Negative core	12.3	3.0	7.0	12.5	17.0	
Gleason RP						
6						
Overall core	11.8	3.0	4.3	11.8	18.7	0.5606
Positive core	12.8	4.8	4.0	12.5	19.0	0.7259
Negative core	11.3	3.1	5.0	11.3	18.3	0.4927
7						
Overall core	11.6	2.9	2.5	11.8	18.6	
Positive core	12.5	3.9	2.0	12.5	19.0	
Negative core	11.3	3.5	4.0	11.4	19.0	
8–10						
Overall core	12.6	3.4	7.4	13.1	19.0	
Positive core	13.3	4.7	5.8	13.5	19.0	
Negative core	12.8	3.6	6.8	11.6	19.0	
Margin						
Negative						
Overall core	11.7	3.0	2.5	11.9	18.7	0.6635
Positive core	12.6	4.3	2.0	12.3	19.0	0.6849
Negative core	11.4	3.3	4.0	11.4	19.0	0.8736
Positive						
Overall core	11.9	3.0	4.1	11.9	19.0	
Positive core	12.7	4.3	4.0	12.7	19.0	
Negative core	11.4	3.4	3.6	11.3	19.0	
EPE						
Negative						
Overall core	11.8	3.1	2.5	11.9	19.0	0.7517
Positive core	12.7	4.3	4.0	12.5	19.0	0.6322
Negative core	11.4	3.3	3.0	11.4	19.0	0.9215
Positive						
Overall core	11.6	2.8	5.7	11.8	16.6	
Positive core	12.4	4.1	5.0	12.8	19.0	
Negative core	11.2	3.6	4.0	11.4	16.8	
SV						
Negative						
Overall core	11.8	3.0	2.5	11.9	19.0	0.4942
Positive core	12.8	4.4	4.0	12.7	19.0	0.3436
Negative core	11.4	3.3	3.0	11.4	19.0	0.5141
Positive						
Overall core	11.3	3.2	5.7	11.3	16.5	
Positive core	11.6	3.3	5.0	11.9	17.1	
Negative core	10.4	4.5	4.0	11.0	17.0	

SD, standard deviation; RP, whole radical prostatectomy specimen histopathology; EPE, extra-prostatic extension; SV, seminal vesicles.
*Statistically significant.

be used for a more complete staging). And this can result in a milder treatment than the ideal.

Two doctors are responsible for the central event of prostate cancer diagnosis and staging: the biopsy performer and the pathologist. Publications have shown that the learning curve to perform it is short and takes about 12 procedures [21,27]. In our research, the performers were supervised senior residents, which are far beyond the plateau of the learning curve. Also, the systematic real-time assessment of the biopsy core quality gives the opportunity to immediately repeat the tissue extraction if necessary.

Additionally, the pathologist should inform the length of the analyzed fragment and emphasize if it is considered insufficient with potential under-sampling. However, relevant studies show that 36% of European pathologists never report the biopsy core length that is not even considered in some publications [28], adding biases related to the lack of information on core quality.

The Committee of the European Randomized Study of Screening for Prostate Cancer in 2013 arbitrarily considered as 10 mm the smallest acceptable fragment of the biopsy [11]. Bostwick et al. [29] described a great variety in the length of the mean biopsy core length extracted around the world from 9.4 to 15.1 mm, adding to confounding related to heterogeneous pathological review due to inter- and intra-pathologist variabilities.

There are limitations to our research. The first is that it is a retrospective analysis and, thus, not all the variables were complete and after 5 years for evaluation of biochemical recurrence, for example, there was a loss of 11 (5.4%) patients. Also, though data represent the 'real life' result of prostate biopsies, with no margin for more 'careful' examination in one or other ethnicity, the present study is limited to patients with positive biopsy and does not consider any false negative that might have been wrongly considered cancer-free.

On the other hand, our study brings new data, which needs to be better studied to be confirmed and to the understanding of whether it is unique to the local population or the ethnicity in general. North American or European blacks with different heredities from African Brazilians might behave differently and should be explored in future studies. In fact, while white and Afro ethnicity can be distinguished, the miscegenation is significant in South America.

Although there is no universally accepted definition of clinically significant PCa, either at biopsy or after prostatectomy [30] and both sensitivity and specificity shows smaller differences of 0–3% when analyzing four different definitions of significant PCa [31], beyond the 5-year biochemical recurrence rate and extensive whole radical prostatectomy specimen histopathological evaluation, we have described two previously established definitions of clinically significant PCa for both groups: RP Gleason grade ISUP prognostic group $>$ 1, that means Gleason $\geq$ 7 and ISUP prognostic group $>$ 3 that means Gleason $\geq$ 8 [30].

Last, but not least, it is essential to establish a quality standard for the prostate biopsy, aiming for greater accuracy of the examination, since this influences the correct diagnosis and staging of PCa and therefore interferes in the treatment and prognosis of this disease. A prostate biopsy is still the main basis for PCa diagnosis and staging and the quality of the examination itself could be the reason for different outcomes between the ethnicities and whether we should

Table 3. Comparison of postoperative variables between whites and African descendants.

	White ($n = 153$)	African descendants ($n = 50$)	Total	p
Gleason RP 3				
6	66 (43.4%)	16 (32.7%)	82 (40.8%)	0.2546
7	76 (50.0%)	27 (55.1%)	103 (51.2%)	
8–10	10 (6.6%)	6 (12.2%)	16 (8.0%)	
Gleason RP 5				
1 ($\leq$ 6)	66 (43.4%)	16 (32.7%)	82 (40.8%)	0.4428
2 (3 + 4 = 7)	60 (39.5%)	23 (46.9%)	83 (41.3%)	
3 (4 + 3 = 7)	16 (10.5%)	4 (8.2%)	20 (10.0%)	
4 (8)	4 (2.6%)	2 (4.1%)	6 (3.0%)	
5 (9 or 10)	6 (3.9%)	4 (8.2%)	10 (5.0%)	
Changed Gleason				
No	105 (69.1%)	32 (66.7%)	137 (68.5%)	0.7538
Yes	47 (30.9%)	16 (33.3%)	63 (31.5%)	
Margin				
Negative	91 (59.5%)	30 (60.0%)	121 (59.6%)	0.9478
Positive	62 (40.5%)	20 (40.0%)	82 (40.4%)	
EPE				
Negative	116 (75.8%)	35 (71.4%)	151 (74.8%)	0.5383
Positive	37 (24.2%)	14 (28.6%)	51 (25.2%)	
SV				
Negative	141 (94.0%)	43 (86.0%)	184 (92.0%)	0.1271
Positive	9 (6.0%)	7 (14.0%)	16 (8.0%)	
BR (5 years)				
Negative	98 (66.7%)	30 (66.7%)	128 (66.7%)	0.9999
Positive	49 (33.3%)	15 (33.3%)	64 (33.3%)	
Total	147	45	192	

Gleason RP 3, Gleason of whole radical prostatectomy specimen according to D'Amico's classification (three groups); Gleason RP 5, Gleason of whole radical prostatectomy specimen according to ISUP classification (five groups); EPE, extra-prostatic extension; SV, seminal vesicles; BR, biochemical recurrence.

consider prostate biopsy in a peculiar way for African descendent men is an open question and field for further studies.

In conclusion, in a PCa population with similar access to health system, prostate biopsy core length in African descendant men is significantly smaller than in whites. This finding is new and may add to the controversial argument of PCa worse prognosis in African descendant patients.

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Ethical approval

Research involving Human Participants and/or Animals: The local research ethics committee approved the protocol.

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