Is There any Relationship between Age of Patients and Prostate Cancer Aggressiveness?

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ABSTRACT

Introduction: Prostate Cancer (Pca) is a disease mostly associated with an aging male population. It is also relatively found in young men less than 50 years. Autopsy studies actually confirm some reasonable percentage of young men harboring Pca. In the pre-prostate specific antigen (PSA) era, it was found that younger men harbored more aggressive disease with associated worse prognosis. But in recent literatures, conflicting reports have been documented. This study was aimed at finding the relationship between patient's age and prostate cancer aggressiveness in light of their pathological characteristics.

Material and methods: This was a retrospective study of one hundred and twenty eight (128) men diagnosed with Pca by needle biopsy of their prostates between January 2014 and December 2016. Relevant information from their case notes were retrieved. Data collated were analyzed using statistical package for social sciences (SPSS) version 20.0 and results used for discussion.

Results: The mean age of the patients was 68.03 ± 9.01 years ranging from 48 to 93 years. Men older than 65 years formed the majority (55.5%). Patients who had WHO grade group 5 were more in number (44.53%). Proportion of tumours with aggressive pathological characteristics by age stratification were 72.7% in young men, 73.9% in the middle age group and 59.2% in the elderly men.

Conclusion: Significant percentage of young and middle age men harbor tumours with aggressive pathological characteristics even more than their older counterparts. Most researchers publish indolent cancers in the young and more aggressive ones in the older men. Our study showed that tumours with aggressive pathological characteristics are commoner in the young and middle age men than their older counterparts.

Keywords: Age, Prostate Cancer, Relationship, Aggressiveness.

INTRODUCTION

Prostate cancer is a disease associated with an aging population of men with about 80% of them diagnosed at age >65 years.[1] It has also been demonstrated that Pca is not uncommon in men <50 years.[2] Age at diagnosis of Pca has been well recognized as an independent prognostic factor. Three autopsy series in Greek[3], Hungary[4] and United States of America[5] reported varying prevalence of latent Pca in younger men respectively of 2.6%, 27% and 34%. The age cut-off to define young age Pca is still uncertain, but many researchers recommend age < 55 years. Young age Pca is defined as Pca regardless of tumor extent or clinical manifestation in men aged <55 years.[6] In the pre-PSA era, it was speculated that younger men were likely to harbor more aggressive disease with worse prognosis.[7] However, more recent studies found predominantly indolent cancers associated with young men than their older counterparts in radical prostatectomy specimens which also portrays a better prognosis for them.[8,9] Association of age and timing of prostate cancer detection is quite critical when choice of treatment is at stake vis-a-viz its aggressiveness.

The Gleason grading system proposed by DF Gleason in 1966 defines the levels of pathological grading of Pca cells which also corresponds with the level of aggressiveness of the tumours. The Gleason scores generated by adding the most predominant grade to the next predominant grade is of great prognostic significance for patient's evaluation. High grade tumour is defined as a tumour with Gleason score of ≥7 and by extension an aggressive tumour.[9] The 2016 World Health Organization (WHO) Pca reporting guidelines incorporated a new grading system developed in 2014 by the international society of Urological pathology (ISUP) Conference. In this grading system, pathological characteristics of prostate biopsy specimen is classified into 5 distinct grade groups as follows; WHO grade group 1 is Gleason Score (GS) ≤ 6, WHO grade group 2 is GS 3+4 = 7, WHO grade group 3 is GS 4 + 3 = 7, WHO grade group 4 is GS 4 + 4 = 8 while WHO grade group 5 is GS 9 and 10. Here, clinically significant Pca is defined as WHO grade groups 3–5 which also signify aggressive tumours. This is an improvement in the clinico-pathological evaluation of patients with GS 7 (3+4, 4+3) which was grouped altogether as high grade even when grade 4 was not the predominant grade. It therefore specifies grade 4+3 as high grade in light of 4 being the predominant grade. The WHO grade group redefines pure high grade tumours to guide appropriate management protocols of prostate cancer, the grading system being an independent prognostic factor.

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In this study, we set out to answer this question: Is there any relationship between patient's age and prostate cancer aggressiveness in light of their pathological characteristics?

MATERIAL AND METHODS

This was a retrospective study of 128 men who were evaluated for Pca between January 2014 and December 2016. All patients had trans-rectal ultrasound (TRUS) guided systematic 10 – 12 cores prostate biopsy for diagnosis. Bowel preparation was done with lukewarm saline enema a night before and also in the morning of the procedure by all patients. Prophylactic antibiotic with a quinolone (i.v Ciprofloxacin 500mg stat) was given and informed consents taken. Above number of core needle biopsies were taken mostly from hypoechoic lesions into formalin containing bottles and transported to the laboratory for examination. Patients with confirmed Pca were included. Exclusion criteria included patients with incomplete information in their case notes, patients with history of Finesteride ingestion, and those with other lower urinary tract cancers. Information from their case notes were retrieved including bio-data, history, physical examination, findings on digital rectal examination (DRE) of the prostates. Relevant laboratory test results included pre-biopsy serum PSA, renal function test, full blood count and urine cultures. Others were TRUS examination findings of the prostate and abdominopelvic ultrasound scan results. Age of the patients were grouped in intervals of 10. Histology reports of patients were classified according to WHO grade group into 5 as follows; WHO grade group 1 as Gleason Score (GS) ≤ 6, WHO grade group 2 as GS 3+4 = 7, WHO grade group 3 as GS 4 + 3 = 7, WHO grade group 4 as GS 4 + 4 = 8 while WHO grade group 5 as GS 9 and 10. All data were summarized and entered into spread sheet for analysis using SPSS version 20.00 software.

Frequency of categorized variables was performed. Description statistics was used to analysis continuous variables. Age was stratified into 3 groups namely; Group 1 (young age) ≤ 55 years, group 2 (middle age) 56 – 65 years and group 3 (elderly) > 65 years.[10] WHO grade group for prostate histology was used to categorize Gleason score into 5 groups. Cross tabulations were done between age and the most predominant grade (P_1), between age and WHO grade groups.

RESULTS

Total number of patients included were 128 men aged 48 and 93 years with a mean age of 68.03 ± 9.0 years. Mean PSA was 54.07 ± 37.50ng/ml ranging from 4.80 to 185.70 ng/ml while mean Gleason score was 7.83 ± 1.23 ranging from 5 to 10. Elderly men (> 65 years) formed the majority (55.5%), followed by middle age men (35.9%) and young men (≤ 55 years) were the least in number (8.6%) (table-1i,ii). For the WHO grade grouping of Pca patients: Group 5 (GS 9 and 10) were more than the other groups (44.53%). Grade group 3 (4 + 3) were the least in number (10.20%) (table-1iii). Clinically significant Pca was observed in about two-third of the population (Table 2). Within age stratification, clinically significant Pca by WHO grade grouping was found more in the middle age men (73.9%), followed by young men (72.7%) and then the elderly (69.2%) Table 3. In table 4, the most predominant grade (P_1) of 5, representing anaplastic tumour, was found more in young men (8/11 = 72.7%) followed by the middle age group (22/46 = 47.8%) and the elderly men with 33.8% (24/71). In table 5, WHO grade group was cross tabulated with age stratified table into 3 groups. In the young men group, grade group 5 formed the majority (6/11 = 54.5%), this was followed by the middle age men (23/46 = 50%) and the elderly with 42.3% (30/71). Figs. 1 and 2 show bar charts for age and PSA categories. 60 – 69 years old were more in number. Most men had PSA in excess of 50ng/ml.

DISCUSSION

Prostate cancer is a disease of the elderly men population and as many as 80% of them are diagnosed at 65 years and beyond. It is a relatively common disease in men younger than 50 years.[2] Hussein S et al[6] reported an incidence of 20 – 30% of Pca in men between the ages of 40 and 50 years. This shows that the disease is not a completely rare phenomenon

	Min	Max	Mean	Standard deviation
Age	48	93	68.03	±9.01
PSA	4.80	185.70	54.07	±37.50
Gleason score	5	10	7.83	±1.23

Table-1(i): Age, PSA and Gleason score:

	Frequency (n)	Valid percent (%)	Cumulative percent (%)
≤55 years	11	8.6	8.6
56 – 65 years	46	35.9	44.5
>65 Years	71	55.5	100.0
Total	128	100.0	

Table-1(ii): Age stratification:

	Frequency (n)	Valid percent (%)	Cumulative percent (%)
Grade group 1 (GS ≤6)	21	16.37	14.8
Grade group 2 (3 + 4)	23	18.00	32.8
Grade group 3 (4 + 3)	13	10.20	43.0
Grade group 4 (4 + 4)	14	10.90	53.9
Grade group 5 (GS 9 and 10)	57	44.53	100.0
Total	128	100.0	

Table-1(iii): WHO Grade Group according to ISUP:

at this age range implying that early screening should be offered to them especially those with a positive family history. Autopsy studies have shown a reasonable percentage of latent disease in younger men.[3-5] Li J et al[2] compared the proportion of men younger than 50 years that harbored Pca in the pre-PSA era and PSA era and found an increase from 1% to 5%. PSA therefore, being the best circulating tumour marker in oncology[11] is an indispensable tool in evaluating Pca patients.

Gleason system used in grading Pca histology is based on the degree of glandular differentiation and the growth pattern of the tumour in relation to the stroma using a low-power microscope.[12] It is graded from 1 to 5 depending on the degree of differentiation from well differentiated to anaplastic tumour. The score is reached by adding the most predominant grade to the second most predominant grade. A score of 2 to 6 is regarded as well differentiated tumours with favourable prognosis while high grade tumours are scored ≥ 7 and are said to be associated with a high mortality rate.[13] A new grading system pioneered by the international society

Age stratification	Groups 1 & 2	Groups 3 – 5	Total
≤55 years			
Count	3	8	11
% of total	2.3%	6.30%	8.6%
56 – 65 years			
Count	12	34	46
% of total	9.3%	26.60%	35.9%
> 65 years			
Count	29	42	71
% of total	22.7%	32.8%	55.5%
Total(%)	44(34.3%)	84(65.7%)	128(100%)
Groups 1 & 2 = Non aggressive Tumours, Groups 3 – 5 = Aggressive Tumours			

Table-2: Tumour classification within WHO grade grouping

	WHO Grade level of aggressiveness		
Age stratification	**Non-aggressive**	**Aggressive**	**Total**
≤55 years			
Count	3	8	11
Percent	27.3%	72.7%	100%
56 – 65 years			
Count	12	34	46
Percent	26.1%	73.9%	100%
> 65 years			
Count	29	42	71
Percent	40.8%	59.2%	100%
Total			
Count	44	84	128(100%)
Percent	34.4%	65.6%	

Table-3: Tumour classification within Age stratification.

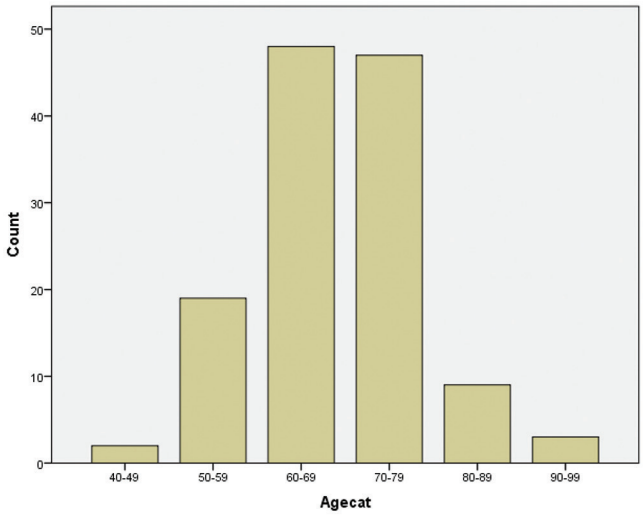

Figure-1: Bar Chart for Age Category.

	Predominant Tumour Grade (P1)					
Age Stratification	**1**	**2**	**3**	**4**	**5**	**Total**
<55 years						
Count	0	0	3	0	5	11
Percent	0.0%	0.0%	27.3%	0.0%	72.8%	100.0%
56 – 65 years						
Count	0	0	15	9	22	46
Percent	0.0%	0.0%	32.6%	19.6%	47.8%	100.0%
> 65 years						
Count	1	3	27	16	24	71
Percent	1.4%	4.2%	38.0%	22.5%	33.8%	100.0%
Total						
Count	1	3	45	25	54	128
Percent	0.8%	2.3%	35.2%	19.5%	42.2%	100.0%

Table-4: Cross tabulation between age stratification and the predominant tumour grade (P1)

	WHO Grade Group					
Age Stratification	**GG1 (GS<6)**	**GG2 (3 + 4)**	**GG3 (4 + 3)**	**GG4 (4 + 4)**	**GG5(GS9&10)**	**TOTAL**
<55 years						
Count	0	3	0	2	6	11
Percent	0.0%	27.3%	0.0%	18.2%	54.5%	100.0%
56 – 65 years						
Count	2	9	6	6	23	46
Percent	4.3%	19.6%	13.0%	13.0%	50.0%	100.0%
> 65 years						
Count	17	11	7	6	30	71
Percent	23.9%	15.50%	9.9%	8.5%	42.3%	100.0%
Total						
Count	19	23	13	14	59	128
Percent	14.8%	18.0%	10.2%	10.9%	46.1%	100.0%
GG = Grade group; GS = Gleason score						

Table-5: cross tabulation between age stratification and WHO grade groups (1 – 5).

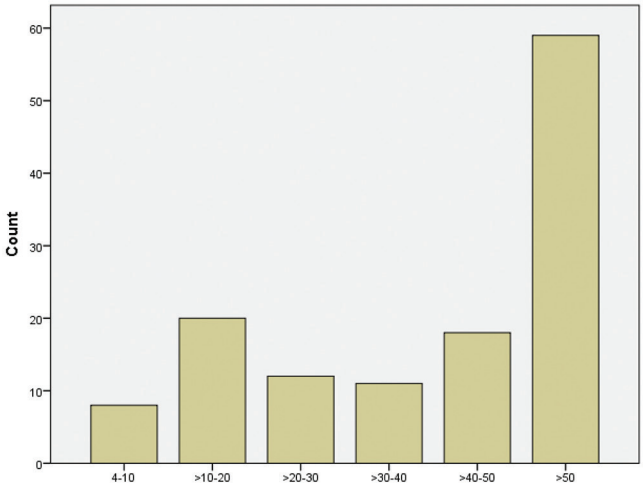

Figure-2: Bar Chart for PSA Category.

of urological pathology (ISUP) and incorporated in the new 2016 WHO Pca reporting guidelines recommend grade groups 1 and 2 and grade groups 3 to 5 as non-aggressive and aggressive tumour characteristics respectively.

The mean age of the patients was 68.03 + 9.01 years. Several studies on Pca patients have recorded similar mean age across Asia, Africa and North America (Jamaica).[10,14-16] More than half of the patients were aged >65 years. A higher proportion (80%) of men who were >65 years were also diagnosed with Pca in a study done by Jemal et al.[1] Men aged ≤55 years were less than 10% in our study with a rapid increase after 55 years (35.9%). Similar report was also made by Gronberg H.[17] Currently, over 10% of new cases of Pca occur in patients ≤ 55 years in the United States.[18] This might be due to widespread screening of young men with PSA which increases the proportion of incidental diagnosis. The prevalence per age stratification showed that young men ≤55 years, although few in this study, majority of them (72.7%) had clinically significant WHO grade groups 3 to 5 (table 3). This signifies aggressive pattern of the tumours with worse prognosis. Again in the middle age class and the elderly, similar finding was noted. This indicates that our men with Pca mostly display aggressive pathological characteristics on needle biopsy of their prostates. Conflicting reports have been documented in the literature across the globe. In two well researched articles during the pre-PSA era, they reported that younger men were likely to harbor a more aggressive disease with worse prognosis.[19,20] However, more recent studies suggest higher rates of indolent Pca in younger men with favourable outcomes.[8,9] Other authors also reported same findings.[9,21] Comparing the frequency of Gleason grade 5 tumours (anaplastic) across the 3 groups per age stratification, the young age group had the highest proportion. This was followed by the middle aged and then the elderly (table 4). Similar finding was observed when age stratification was compared with WHO grade groups. From the above, we can infer that younger men diagnosed with Pca are most likely to harbor tumours with aggressive behaviour even more than their older counterparts. A similar study in China documented same findings.[22]

Aggressive pathological tumour characteristic in the elderly is expected due to natural progression of undiagnosed tumours or changes in serum hormones with advancing age.[23] Other tested variables such as pre-diagnosis PSA velocity, which is a marker for more aggressive Pca[24], positive surgical margin, tumour upgrading and pathological stage in radical prostatectomy (RP) specimen were also known to be significantly higher in older men.[25] The cancer of the prostate risk assessment (CAPRA) score which predicts biochemical recurrence and survival after RP captures age < 50 years as one of the independent favourable risk factors. Most of these studies were done on Caucasians and we tend to predict the influence of genetic, environmental and racial factors on the biology of Pca development in this population as opposed to men in our locality. We also suspect the development of early onset Pca in our patients which is a subset of young age Pca, although, we did not evaluate the patients beyond pathological tumour characteristics to include Pca-related deaths, study being retrospective. Early onset Pca is defined as Pca detected in men aged < 55 years with at least one clinical sign of Pca, such as a positive DRE or a visible tumour at time of imaging (at least T_2 Pca) rather than a Pca incidentally detected because of PSA prompted prostate needy biopsy.[26] Our young men in this study qualify

for early onset Pca because all patients had suspicious prostates on DRE prior to biopsy irrespective of serum PSA levels.

Age at diagnosis of malignancy is a well recognized prognostic factor. This also raises concerns as to its aggressiveness and modalities of treatments. This study reveals that in our locality, significant proportion of men harbor aggressive tumours especially in the young age. It follows that widespread screening with PSA should commence with men before 50 years of age especially those with a family history of Pca. This should be complemented with a well structured modality of treatment to reduce Pca-related mortality rate in this population.

Limitation of this study was that it was retrospective and so subject to retrieval bias. Again, there was no information as to follow up of these patients to document Pca-related deaths as a means to justify the aggressive behaviour of these tumours. On the whole, we can speculate based on this study, that Pca in men in our locality especially in the young may show aggressive pathological behaviour but will require a longitudinal study to confirm.

CONCLUSION

Prostate cancer in young men display more aggressive pathological characteristics than their older counterparts although they were fewer in number. Other studies across the globe also support this finding. Different opinions are also documented especially in the western world. These differences may be related to diversities in the genetic make-up, racial and environmental factors as they influence the biology and development of prostate cancer. The way forward is to elucidate possible underlying mechanisms.

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