OPEN ACCESS

Saudi Journal of Pathology and Microbiology
Abbreviated Key Title: Saudi J Pathol Microbiol
ISSN 2518-3362 (Print) | ISSN 2518-3370 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Pattern of Testicular Atrophy in Bilateral Orchidectomy Specimens from Patients with Advanced Prostate Cancer

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DOI: 10.36348/sjpm.2024.v09i07.001 | **Received:** 19.05.2024 | **Accepted:** 27.06.2024 | **Published:** 04.07.2024

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Abstract

Introduction*:** One of the palliative treatment modalities for advanced prostate cancer (Pca) is bilateral Orchidectomy. Histopathological analysis of submitted Orchidectomy specimens may display normal to various grades of testicular atrophy. Advancing age may be related to testicular atrophy as well as pre-treatment with luteinizing hormone releasing hormone agonist [LHRH(a)], drugs and chronic illnesses. We retrospectively examined results of Orchidectomy specimens submitted for histopathological analysis. ***Materials and Methods: Bilateral orchidectomy specimen results of twenty seven (27) patients diagnosed with Pca were retrospectively studied. Their clinical information and ancillary laboratory results were retrieved. Of the 27 patients, two (7.4%) patients had no prior treatments for Pca, while twenty patients (74.1%) and five patients (18.5%) had prior exposure to anti-androgens and LHRH(a) respectively. In the histo-analysis, the specimens were graded from normal to various degrees of atrophy. Data collated were analyzed using Statistical package for social sciences (SPSS) version 20.0 software. ***Results*:** The mean age of all patients was 68.52±7.266 years, ranging from 51-87 years. Mean PSA was 59.811±38.84ng/ml, while mean Gleason score was 8.30±8.69. On the whole, 3 patients (11.1%) had normal testes, 16 patients (59.3%) and 8 patients (29.6%) respectively had mild and moderate grades of testicular atrophy. Age correlated positively with the grades of atrophy. ***Conclusion*:** Degree of testicular atrophy is widely noted to correlate with age and depends less on pre-treatment in the setting of advanced prostate cancer.

Keywords: Testicular atrophy, bilateral orchidectomy, Advanced prostate cancer.

INTRODUCTION

Prostate cancer is one of the commonest diseases that afflict men in their advancing years. Despite extensive research in prostate oncology, the cause remains unknown. However, some risk factors have been identified and include race, family history and age [1]. In the pre-PSA era about 30% of patients seen with Pca had advanced disease, but this population of men have reduced to about 5-10% in recent times in some developed countries due to widespread knowledge of Prostate specific antigen (PSA) and digital rectal examination (DRE) [2]. PSA and DRE are useful tools to screen for Pca and guarantees early diagnosis with prostate biopsy. Hormonal manipulation still remains the gold standard for palliative treatment of advanced Pca. Huggins and Hodges were the earliest researchers that demonstrated the use of bilateral orchidectomy for treatment of advanced Pca in 1941 [3]. The procedure is effective and produces castrate level of testosterone in 3 to 12 hours post-surgery [4]. This is apt especially in patients with impending spinal cord compression. In the 1980s, long acting LHRH(a) was introduced for advanced Pca patients that resolved the issues of psychological and emotional stress of an empty scrotum experienced by surgically orchidectomized men [5]. Bilateral orchidectomy is inherently cost effective and so affordable by patients alike [6].

Histology of orchidectomy specimen is of paramount importance in oncology for assessing tumour metastasis to the testes or grades of atrophy. Many researchers had assessed this topic and reported few cases of Pca metastasis to the testes and various degrees of atrophy [7, 8]. The mechanism of metastasis is likely from retrograde venous and lymphatic extension, venous or arterial embolization or endo-canalicular spread [9]. atrophic testis presents microscopically as thickening of

the basement membrane surrounding the seminiferous tubules with reduced or absent spermatogenic cells and interstitial cell hyperplasia [8]. In this study, we did not encounter testicular metastasis and we concentrated in profiling the degree of atrophy from submitted specimen results.

MATERIALS AND METHODS

Twenty seventy (27) patients with histologically diagnosed Pca who underwent bilateral orchidectomy with documented testicular histology were included in the study. It was a retrospective study between January 2023 to December 2023. Relevant data were collected from patient's case notes including biodata, laboratory results of PSA, renal function test, prostate biopsy results and histology results of orchidectomy specimens. Exclusion criteria were patients with history of mumps orchitis, testicular trauma and irradiation. Of the 27 patients, 2 patients were hormonally naïve, 20 had prior treatment with anti-androgen and 5 had LHRH(a). The indication for bilateral orchidectomy was disease progression while on medical therapy. Testicular histology was graded as normal, mild, moderate and severe based on the changes in the seminiferous tubule and its basement membrane. This system was developed by urologists and pathologists according to findings of testicular atrophy caused by medications and aging. Although not validated, it is easy to use for this purpose. In the grading system, grade 0 is defined as a grossly normal seminiferous tubules with adequate thickness of the spermatogenic cells with sperm production. Grade one as decreased thickness of the spermatogenic cell layers and decreased sperm production by the seminiferous tubules. Grade two is defined as atrophic changes of the seminiferous tubules with fewer than 2 layers of spermatogenic cells. Grade 3 is defined as marked atrophic changes in the seminiferous tubule with no visible spermatogenic cells. The results were retrieved and graded as above.

Statistical Analysis:

Data collated were analyzed using SPSS version 20.0 software. Frequency table was constructed for categorical variables while means and standard deviation were calculated for continuous variables. Students T-test was used to compare differences in means between variables.

RESULTS

Twenty seven (27) men with a mean age of 68.52± 7.266 years ranging from 51 to 87 years were studied. Mean age of men with normal testes was 61.67± 9.713 years while men with mild and moderate testicular atrophy had mean ages of 67.38±5.726 years and 73.38 ±6.989 years respectively. Mean PSA was 59.811±38. 84 ng/ml and mean Gleason score was 8.30±0.869. More than 50% of the patients were in their 8th decade of life. Pre-treatment with anti-androgen were given to 20 patients, 2 had no prior hormonal manipulation and 5 patients had LHRH(a). Histological analysis showed that 3 patients (11.1%) had normal testes, while 24 patients (88.9%) had testicular atrophy distributed as 16 (59.3%) with mild and 8 patients (29.6%) with moderate degree of atrophy. We did not encounter any case of severe atrophy or discordant changes. In 2 patients who had no prior hormonal manipulation, one had mild atrophy and the other had moderate atrophy. None in that group had normal testis. Among the 20 patients (74.1%) who received prior antiandrogen, 3 patients (11.1%) had normal testis, 12 patients (44.4%) had mild atrophy and 5 patients (18.5%) had moderate atrophy. Of the 5 patients who received LHRH(a), 3 patients (11.1%) had mild atrophy and 2 patients (7.4%) had moderate atrophy, none had normal testis. There was a statistically significant mean difference in age between men with mild and moderate atrophy ($P<0.05$). [$t=0.083$, $P=0.035$].

Table 1: Mean and standard deviation of variables

Variables	Means std	Min	Maximum
Age (Years)	68.52 ±7.266	51	87
PSA (ng/ml)	59.811±38.84	6.50	144.30
Gleason Score	8.30±0.869	7	9

Table 2: Frequency Table

Variables	Frequency(n)	Valid %	Cumulative %
(a)Age category:			
50 – 59	3	11.1	11.1
60 – 69	9	33.3	44.4
70 – 79	14	51.9	96.3
80 – 89	1	3.7	100.0
Total	**27**	**100.0**	
(b) Gleason Score Category:			
7	7	25.9	25.9
8	5	18.5	44.4

Variables	Frequency(n)	Valid %	Cumulative %
9	15	55.6	100.0
Total	**27**	**100.0**	
(c) Pretreatment Type:			
None	2	7.4	7.4
Anti-androgen	20	74.1	81.5
LHRH(a)	5	18.5	100.0
Total	**27**	**100.0**	
(d) Degree of Atrophy:			
Normal testes	3	11.1	11.1
Mild atrophy	16	59.3	70.4
Moderate atrophy	8	29.6	100.0
Total	**27**	**100.0**	

Table 3: Degree of testicular atrophy/mean Age of Patient;

Degree of atrophy	Mean age Std (Years)
No atrophy (Normal testes)	61.67±9.713
Grade 1 (mild)	67.38±5.726
Grade 2 (Moderate)	73.38±6.989

Table 4: T-test statistics between degree of atrophy/mean age t-test:

Normal testes vs Mild-atrophy:	t=1.430,	P>0.05
Normal testes vs Moderate atrophy:	t=.497,	P<0.05*
Mild atrophy vs Moderate atrophy:	t =0.83,	P=0.03*
Statistical significance set at P<0.05		

Table 5: Degree of atrophy/Pretreatments

	Medications			
	None	**Anti-androgen**	**LHRH(a)**	**Total**
Degree of atrophy				
No atrophy (n)	0	3	0	3
% within degree of atrophy	0	100.0%	0	100.0%
% within Pre-treatment	0.0%	15.0%	0.0%	11.1%
% of total	0.0%	11.1%	0.0%	11.1%
Mild atrophy(n)	1	12	3	15
% within degree of atrophy	6.2%	75%	18.8%	100.0%
% within Pre-treatment	50%	60%	60%	59.3%
% of Total	3.7%	44.4%	11.1%	59.3%
Moderate atrophy(n)	1	5	2	8
% within degree of atrophy	12.5%	62.5%	25.0%	100.0%
% within Pre-treatment	50.0%	25.0%	40.0%	29.6%
% of Total	3.7%	18.5%	7.4%	29.6%
Total(n)	2	20	5	27
% within degree of atrophy	7.4%	74.1%	18.5%	100.0%
% within Pre-treatment	100.0%	100.0%	100.0%	100.0%
% of Total	7.4%	74.1%	18.5%	100.0%

P=0.70 (>0.05). No significant statistical difference.

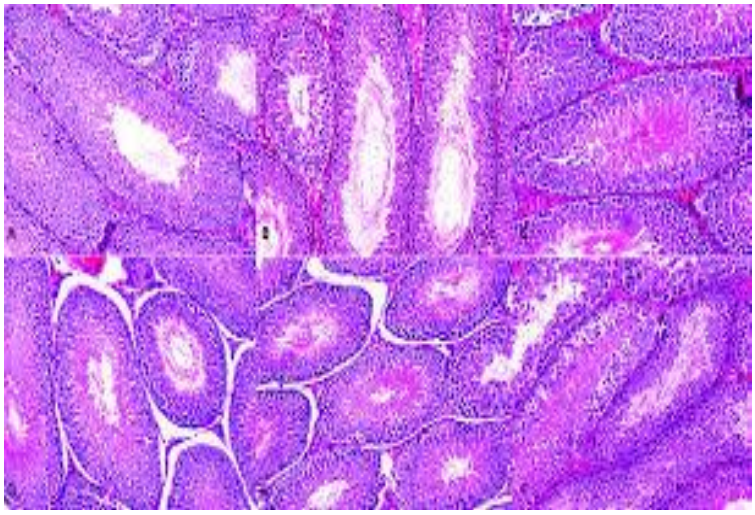

Fig. 1: Histology of Normal testis x10, H&E Stain
Normal thickness of the basement membrane of the seminiferous tubules and presence of spermatogenic cells

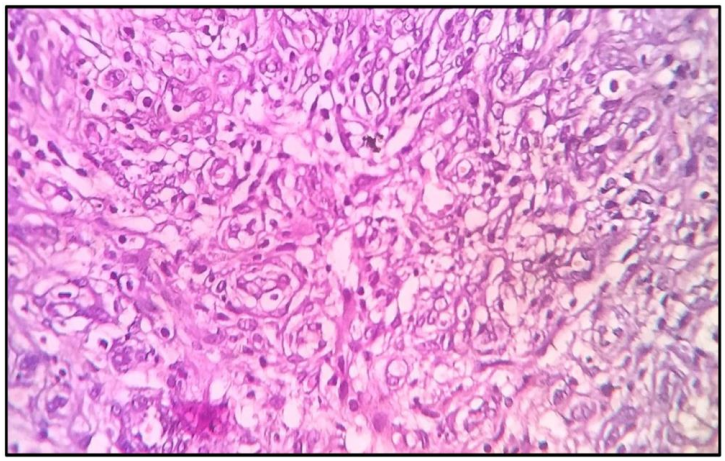

Fig. 2: Histology of atrophic testis x40 H&E Stain
Reduced population of the spermatogenic cell layer

DISCUSSION

Hormonal manipulation still remains the gold standard for palliative treatment of prostate cancer. Bilateral orchidectomy is cost effective and safe [6]. Histopathological analysis of orchidectomy specimen is usually very informative in oncology as it may reveal testicular metastasis with poorer prognosis and various grades of testicular atrophy [7, 8].

In our study of orchidectomy specimens from 27 patients; we did not encounter testicular metastasis from Pca, however, various grades of atrophy of the testes were noted. Overall mean age was 68.52±7.266 years ranging from 51 to 87 years. Similar mean age (68.22+9.18 years) was recorded in a previous study of Pca patients in this centre [10]. Mean PSA was markedly elevated (table 1) in support of peculiar PSA levels in advanced Pca disease [11]. Mean Gleason Score was in excess of 8 portraying an aggressive nature in a background of advanced disease. Similar information was also documented in this centre in a previous study [11]. Above tumour characteristics support the fact that bilateral orchidectomy with early serum castrate level of testosterone offered the best option pending the return of castrate resistant state.

Two (2) patients had no prior hormonal manipulation and this was a necessary step to forestall impending spinal collapse that was achieved by emergent surgery. More than 70% of them received prior antiandrogen and less than a quarter had prior exposure to LHRH(a). Normal testes were noted in 3 (11.1%) of the patients and 24 (89.9%) were atrophic at various grades. These findings were consistent with a similar work by saddigue *et al.*, [8]. In table 3, men with normal testes were younger than those with atrophic testes, same picture was seen between those with grade 1 (mild) atrophy and grade 2 (moderate) atrophy. We did not record severe testicular atrophy even with patients who had prior LHRH(a) exposure as expected [12]. The findings in both testes of each patient were similar and no discordant picture was recorded, again no testicular metastasis was seen. Pca metastasis was noted as incidental findings in 2(1.3%) of 154 bilateral

orchidectomy specimens submitted for histopathological analysis by Saddigue *et al.*, [8]. This may portray a widespread disease. In 1973, Weitner in his case series of testicular metastasis from Pca patients, recorded a limited survival time of less than a year for most of the patients followed up for 18 months [13]. However, in another study by McCann *et al.*, [14] which was a case report of a 74year old man with left testicular metastasis who had no other site of metastasis by imaging, underwent radical orchidectomy with resolution of biochemical markers after surgery, although the follow up time was short (6months). When this scenario of testicular metastasis is encountered, a high index of suspicion for a poorer prognosis should be entertained.

In table 4, we set out to test the mean age difference between men in their various grades of testicular atrophy. The mean age difference between men with normal testes and mild atrophic testes was not statistically significant (P>0.05). They were all in their 7^{th} decade of life. However, there was a significant statistical mean age difference between men with normal testes and men with moderate testicular atrophy (P<0.05). Men with moderate testicular atrophy were in their 8^{th} decade of life. Again, men with mild atrophy and men with moderate atrophy also had a significant mean age difference (P<0.05). Those with moderate atrophy were quite older. This is very informative and concurs with the fact that testicular morphology and even function decrease with age aside from other causes like malnutrition, drugs and chronic illnesses [15].

In table 5, no statistical significant difference was found between the degree of atrophy and pre-treatments in our cohort of patients (P>0.05). This information may be limited by the fact that no duration of pre- treatment was noted being a retrospective study. Studies had shown that pre-treatment with LHRH(a) over a prolonged period of time can cause worsening grades of testicular atrophy [12]. A second limitation is the small sample size which may not capture all the expected grades of testicular atrophy and none availability of equipment for testing prostate membrane specific antigens or the use of Choline PET CT imaging for further detection of testicular metastasis. The small sample size is accounted for by the fact that some men refuse orchidectomy on both personal and cultural inhibitions.

CONCLUSION

Bilateral orchidectomy specimens submitted for histopathological analysis from patients with advanced prostate cancer may display normal testes as well as various grades of testicular atrophy. Advancing age seems to be the strongest factor associated with testicular atrophy. This was recorded in this study and other works done by researchers in the same subject area.

Authors Contribution:

EAU: Substantial contributions to conception and design, Acquisition of data, Drafting the article, revising it critically for important intellectual content, data analysis and Final approval of the version to be published.

IUE: Substantial contributions to conception and design, revising it critically for important intellectual content and final approval of the version to be published.

AJU: Substantial contributions to conception and design, revising it critically for important intellectual content and final approval of the version to be published.

JPO: Substantial contributions to conception and design, revising it critically for important intellectual content and final approval of the version to be published.

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