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Original Research Article

Pattern of Gleason Grade and Score in Prostate Cancer Histology- A Four (4) Year Review

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Abstract: Prostate cancer is the commonest cancer of the urogenital origin in males. It affects mostly elderly men. Definitive diagnosis is usually made by examination of prostate biopsy specimen and grading of the cellular architecture as proposed by Dr. Gleason among others. The grading system bears a strong relationship with prognosis. This was a retrospective study of 148 histology reports of prostate cancer specimens in our facility from January 2012 to December 2015 (4 year period) using biopsy needle. It was aimed at studying the pattern of histologic characteristics of prostate cancer and to find out its relationship with age. The result showed that the highest number of tumours was in the 7th decade with moderately differentiated tumours topping the list. Tumour grade 3 remains the commonest. There was no significant statistical association between histologic characteristics and age of the patients. Early diagnosis should be anticipated as high grade tumours have bad prognosis.
Keywords: Gleason Score/grade, prostate cancer, histology.

INTRODUCTION

Cancer of the prostate is the commonest malignancy of the male urogenital tract [1]. Globally, it records the second most common type of cancer and 5th leading cause of cancer-related death in men [2]. It was the most common cancer in males in 84 countries [2] seen more in the developed world and recently increasingly common in the developing countries [3]. Detection has increased in the last two to three decades due to increased prostate specific antigen (PSA) testing [2]. Although many of these tumours occur in the elderly males with progression being slow and indolent, few may however display aggressive and fatal progression [4]. Predictors of clinical course and likelihood of advanced disease in early stage tumours are host factors, clinical tumour progression and diagnostic factors. Host factors include patients' age, race, hormonal factors and environment while clinical tumour progression is usually correlated with microscopic features of the tumour and include cell motility, nuclear features, lymphatic and blood vessel invasion. The diagnostic factors importantly correlate with prognosis. Of the diagnostic factors, tumour grade correlates better than tumour volume and DNA ploidy in terms of prognosis [5]. Gleason grading system has stood the test of time as an established prognostic indicator. This system of grading was devised in the 1960's and 1970's by Dr. Donald F. Gleason who was a pathologist in Minnesota and a member of the veterans Administration Cooperative Urological Research Group (VACURG) [6]. He actually pioneered this work by enrolling 5000 patients in a prospective randomized trial. The patients were followed up for a long time with survival as the end point. It is currently the most widely used grading system [7]. There are other competing systems such as the World Health Organization (WHO) system [8]. While the Gleason grading system is based entirely on the histologic pattern and arrangement of cancer cells, the WHO system uses both gland-forming ability and nuclear anaplasia [9]. Gleason noted the heterogeneity of prostate cancer cells at different stages of differentiation and therefore categorized them into 5 basic grade patterns which are used to generate the scores ranging from 2 to 10. Grade 1 pattern resembles normal cellular component of prostate gland while grade 5 patterns contains anaplastic cells leaving grades 2 to 4 with increasing loss of normal cellular pattern and architecture. All existing grading systems just like Gleason grouped the computed scores into well differentiated (score 2-4) which is said to progress slowly to the extremes of poorly differentiated tumour (score 8-10) with fast progression. The division into moderately differentiated group is quite misleading, because score 7 has high grade invasive component (4/5) which may not predict an intermediate clinical or biological potential [10]. While the concluding facts about histological pattern of cancer of the prostate is that it correlates strongly with biological behavior of malignancy, the moderately differentiated group by reason of the above, may not altogether reflect this.

In this article, we retrospectively studied the pattern of prostate cancer histology using the Gleason system with interest on the pattern of the grade, score, degree of differentiation and their associations with the age of the patients.

MATERIALS AND METHOD

A search was made in the archives of the department of pathology for histology reports of cases of prostate cancer done between January 2012 and December 2015 using biopsy needle. Documented demographic data, clinical features and mode of diagnosis were retrieved. One hundred and forty eight (148) histology reports were retrieved. Indications for prostate biopsy were mainly a suspicious clinical history of prostate cancer, physical examination including a focused digital rectal examination (DRE) of the prostate and a raised PSA (>10ng/ml). Data collected were analyzed using the statistical package for social sciences (SPSS) version 20.0 software and presented here for discussion.

RESULTS

One hundred and forty-eight (148) histology reports of men aged between 45 and 90 years with a mean age of 67.16±9.820 were analyzed. The highest number of cases [50(33.8%)] appeared in the 7th decade of life (Table 1), closely followed by those in the 8th decade of life [43(29.1%)]. 78(52.7%) of the cases were moderately differentiated tumour followed by 65(43.9%) cases of poorly differentiated tumour (Table 2). Grade 3 pattern was the most common both in the predominant (P_1) and the second most predominant (P_2) cellular type (Tables 4,5). Score of 7 had the highest frequency 36(24.3%) also found most in the 7th decade of life. There was no statistically significant association between the age of the patients and the characteristics of the prostate cancer histology.

Table-1: Age in decades/number of cases

Years (in decades)	Frequency	Valid Percent	Cumulative Percent
41-50 (5th)	11	7.4	9.4
51-60 (6th)	31	20.9	28.4
61-70 (7th)	50	33.8	62.2
71-80 (8th)	43	29.1	91.2
81-90 (9th)	13	8.8	100.0

Table-2: Degree of differentiation

Classification	Frequency	Valid Percent	Cumulative Percent
Well differentiated	5	3.4	3.4
Moderately Differentiated	78	52.7	56.1
Poorly differentiated	65	43.9	100.0

Table-3: Frequency of diagnosis/year

Year	Frequency	Valid Percent	Cumulative Percent
2012	40	27.0	27.0
2013	41	27.7	54.7
2014	30	20.3	75.0
2015	37	25.0	100.0

Table-4: Association between age/ tumour grade (P_1):

Age (in decades)	Predominant		Grade (P_1)			Test statistic & values
	1	2	3	4	5	
41-50 (5th)	0(0.0)	1(0.7)	4(2.7)	4(2.7)	2(1.4)	X^2=12.762
51-60 (6th)	2(1.4)	7(4.7)	10(6.8)	5(3.4)	31(20.9)	DF=16
61-70 (7th)	0(0.0)	8(5.4)	18(12.3)	10(6.8)	14(9.5)	P value = 0.690*
71-80 (8th)	2(1.4)	5(3.4	13(8.8)	15(10.1)	8(5.4)	
81-90 (9th)	0(0.0)	3(2.0)	5(3.4)	4(2.7)	1(0.7)	
Total	4(2.7)	24(16.2)	50(33.8)	29(25.7)	32(21.6)	

There is no statistically significant association between age and characteristics of prostate cancer histology (p value >0.05*).

Table-5: Association between age and second most predominant tumour grade (P_2):

Age (in decades)	**Second most predominant Grade(P2)**					**Test statistic & value**
	1	**2**	**3**	**4**	**5**	
41-50 (5^{th})	0(0.0)	0(0.0)	5(3.4)	4(2.7)	2(1.4)	X^2=16.040
51-60 (6^{th})	0(0.0)	3(2.0)	12(8.1)	11(7.4)	5(3.4)	DF=16
61-70 (7^{th})	1(0.7)	6(4.1)	15(10.1)	16(10.8)	12(8.1)	P value=0.45*
71-80 (8^{th})	0(0.0)	5(3.4)	17(11.5)	6(4.1)	15(10.1)	
81-90 (9^{th})	0(0.0)	0(0.0)	4(2.7)	7(4.7)	2(1.4)	
Total	1(0.7)	14(9.5)	53(35.8)	44(29.7)	36(24.3)	

There is no statistically significant association between age and P_2. (P value >0.05*).

Table-6: Association between age and score:

Age (in decades)	Scores								
	3	4	5	6	7	8	9	10	Test statistic & values
41-50 (5^{th})	0(0.0)	0(0.0)	1(0.7)	2(1.4)	4(2.7)	1(0.7)	2(1.4)	1(0.7)	X^2=17.863
51-60 (6^{th})	1(0.7)	0(0.7)	7(4.7)	3(2.0)	8(5.4)	4(2.7)	6(4.1)	1(0.7)	DF=28
61-70 (7^{th})	0(0.0)	2(1.4)	7(4.7)	5(3.4)	13(8.8)	12(8.1)	8(5.4)	3(2.0)	Pvalue=
71-80 (8^{th})	1(0.7)	0(0.0)	7(4.7)	7(4.7)	7(4.7)	8(5.4)	12(8.1)	1(0.7)	0.930*
81-90 (9^{th})	0(0.0)	0(0.0)	3(2.0)	0(0.0)	4(2.7)	4(2.7)	2(1.4)	0(0.0)	
Total	2(1.4)	3(2.0)	25(16.9)	17(11.5)	36(24.3)	29(19.6)	30(20.3)	6(4.0)	

There is no statistically significant association between age and Gleason score (p value > 0.05*).

Table-7: Association between age and degree of differentiation:

Age(in decades)	Degree of differentiation			Test statistics and values
	Well Differentiated n(%)	Moderately Differentiated n(%)	Poorly Differentiated n(%)	
41-50 (5^{th})	0(0.0)	7(4.8)	4(2.7)	X^2=3.540
51-60 (6^{th})	2(1.4)	18(12.2)	11(7.5)	DF=8
61-70 (7^{th})	2(1.4)	24(16.3)	23(15.6)	P value=0.896*
71-80 (8^{th})	1(0.7)	21(14.3)	21(14.3)	
81-90 (9^{th})	0(0.0)	7(4.8)	6(4.1)	
Total	5(3.4)	77(52.4)	65(44.2)	

There is no statistically significant association between age and degree of differentiation
(p value > 0.05*)

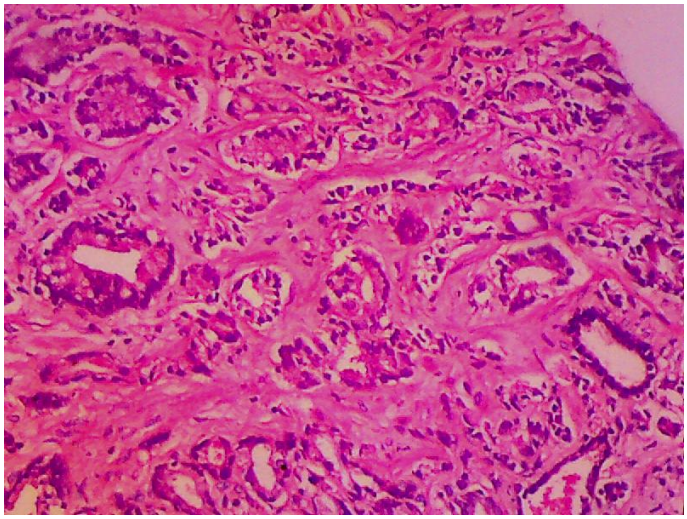

Fig-1: Photomicrograph of prostate showing adenocarcinoma, Gleason score of 3+3, H & E X 40

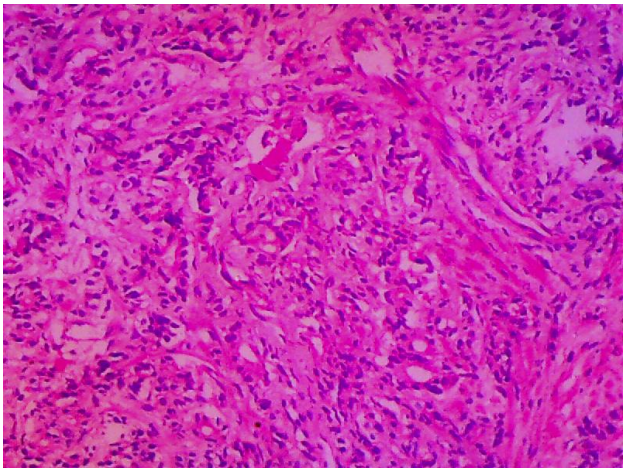

Fig-2: Photomicrograph of prostate showing adenocarcinoma, Gleason score of 3+4, H & E X 40.

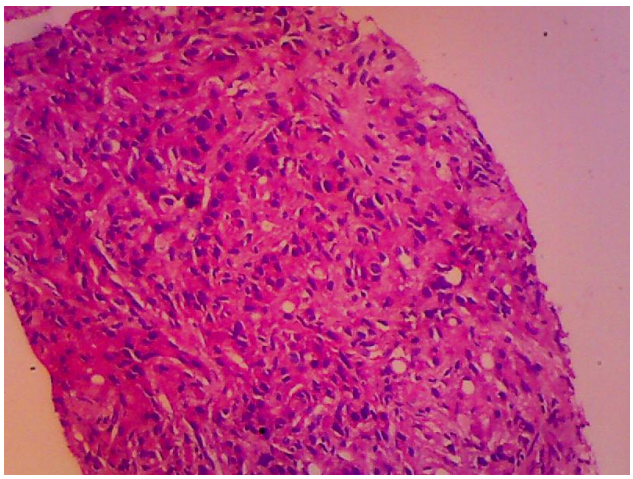

Fig-3: Photomicrograph of prostate showing adenocarcinoma, Gleason score of 5+5, H & E X 40.

DISCUSSION

Histological grade of a neoplasm is important in the management of most cancer cases including prostate cancer. Its diagnostic value can be closely linked to determination of degree of resemblance to the mononuclear cells, otherwise referred to as degree of differentiation of the neoplastic cells. Beside histological grade of cancer, tumour stage also forms the bedrock of prognostification of cancer and it entails characteristics which elucidate the extent of spread of the tumour. These characteristics include tumour size, lymph node and lymphovascular involvement as well as perineural spread and distant metastasis [9].

Prostate cancer grading system is a strong prognostic factor better than tumour volume and DNA ploidy [5]. Tumour volume is difficult to quantify and so carries low sensitivity and DNA ploidy on the other hand correlates better with prognosis yet the sensitivity is also poor [5]. Histologic patterns of prostate cancer strongly correlate with the biological behavior and the long term outcome and this is very important in the clinical scenario and quite informative in the management of these patients with regards to long term expectations [11].

Gleason grading system for prostate adenocarcinoma is widely used with many advantages including simplicity, used under standard Haematoxylin and Eosin (H&E) stained tissue sections and largely relies on architectural growth patterns of tumour cells [9].

The Gleason grading system presents a platform for assessing the level of differentiation of prostate cancer cells with regards to prognosis vis-a-vis a measure of recurrence after treatment and survival. One of the adjuncts of prostate cancer evaluation is the measurement of serum Prostate Specific Antigen (PSA), where its elevation is more likely to be associated with a higher grade tumour, larger volume and a more advanced pathological stage than cancers with normal PSA level [12]. Grade of prostate cancer may be related to its location in the prostate gland being higher grade in the peripheral zone than in the transitional zone of the prostate [13]. The common denominator adopted by the different grading systems in prostate cancer has been the recognition of the differentiation capacity, architectural growth patterns, mitotic activity and nuclear abnormalities to generate the histological grade. Five basic grades are used to form the scores ranging from 2 to 10. The primary pattern (P_1) is the most

common or predominant and the secondary pattern is the second most common pattern (P_2). Addition of these 2 patterns generates the score. Although these 2 patterns of tumour grade have been constantly used in clinical practice, the histomorphological appearance of prostate cancer is more heterogeneous than this. The number of grades however depends on the tumour sample size and size of the tumour in the whole gland where it has been shown that 28% of transurethral resection of the prostate (TURP) chips revealed more than 2 grades while 4% of needle biopsies showed more than 2 grades [14] and it has been documented that tumours >1-2cm^2 in size tend to have more than 2 grades [15]. There are limited data and analyses to establish a definitive approach to scoring when more than 2 patterns are encountered but the following points have been adopted and widely used. A recent data on radical prostatectomy specimen having a high grade tertiary component (grade 4/5) and occupying <5% of the tumour was said to influence pathological stage and progression rate[16], and so high tertiary grade pattern should be reported and incorporated in the score. With regards to needle biopsy specimen, Gleason recommended that the two highest grades be recorded [17], however where the worst grade is neither the primary nor secondary grade pattern, the primary and the highest grade should be chosen to generate a score[18].

A common practice is to summarize Gleason score 2-4 carcinoma as well differentiated, 5-7 as moderately differentiated and 8-10 as poorly differentiated. Questions always arise where score 7 is included in the moderately differentiated group that harbours an element of high-grade pattern (4/5) which is said to be an intermediate between score 5-6 and 8-10 in terms of aggressiveness [19]. They argue that score 7 should be classified as poorly differentiated, but many authors including our work was based on the former. Needle biopsy specimen is a valid sample for grading of prostate cancer. Gleason in his original series of 2911 patients, 60% was graded solely on the basis of needle biopsy [20]. However, under-grading of tumour with a higher Gleason score and over-grading of tumour with a lower Gleason score in needle biopsy specimens have been known due mostly to difficulty in appreciating an infiltrative growth pattern, tissue sampling error related to small amount of tissue. Others are grade heterogeneity, tissue distortion, and pathologist experience and observer variability. These errors in biopsy specimen are overcome in prostatectomy specimens and TURP chips where larger tissue samples are examined [9]. With a greater tissue to examine, well differentiated tumours are commoner in prostatectomy specimens and TURP chips than in needle biopsies. Secondly, biopsy needle may not reach the transitional zone of the prostate where low grade tumours are commonly found unlike in enucleated specimen where the whole gland is examined. In our study, grade 3 pattern dominated both the primary and the secondary grades. Grade 1 and 2 were few for the reason given above. High grade pattern (4/5) was 47.3% in the primary pattern and 45.0% in the secondary pattern signifying a high percentage of poorly differentiated tumour in our cohort of patients. This actually portrays a bad prognosis and demands proactive measures and need for early detection.

In our study, majority of the patients were seen in their 7th decade of life. This finding is similar to another study conducted by Imdal et al[5]. Moderately differentiated tumours were more than half of the cases in our study, also similar to the later study [5]. Moderately differentiated grade is the most common pattern of growth of prostatic adenocarcinoma; this has been recognized both in the pre-PSA and the PSA screening era [21, 22]. Also, Gleason scores of 5-7 with component of grade 3 pattern are the commonest histologic grades in prostate cancer which concurs with the findings in our study [9]. In other studies [23, 24], poorly differentiated tumours ranked highest which must have translated to poor prognosis in their cohorts in keeping with a strong relationship between tumour grade (score) and outcome.

This study did not show any statistically significant association between age of the patients and histological characteristics of their tumours (grade, score and degree of differentiation). However, whatever age is involved in prostate cancer, early diagnosis, prompt treatment and survival should be the end point.

CONCLUSION

Histological grading of prostate cancer is an important tool used to stratify and offer useful information for treatment and prognosis. Needle biopsy specimens, howbeit small is capable of giving reliable reports. Gleason system of grading among other competing systems has stood out and widely utilized. However, it does not distinguish between in-situ growths from invasive carcinoma; again majority of the low grade tumours residing in the transitional zone may not be reached by needle biopsy to complete the report. On the whole, Gleason grading of needle biopsy specimens of prostate cancer cases have been clinically proven to direct treatment modalities and also offer prognostic information to both the pathologist and the urologist.

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