ORIGINAL PROF-1573

PROSTATE CANCER;

CORRELATION OF GLEASON'S SCORE AND PRETREATMENT PROSTATE SPECIFIC ANTIGEN IN PATIENTS

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Article Citation:
Mawakyoma H A, Mabandi J L. Prostate cancer; Correlation of gleason's score and pretreatment prostate specific antigen in patients. Professional Med J Jun 2010;17(2): 235-240.

ABSTRACT... Objectives: To correlate histopathological grades of prostate cancer by Gleason's scoring system and pretreatment PSA levels in patients with prostate cancer. **Study Design:** A prospective longitudinal study. **Setting:** Muhimbili National Hospital in the Departments of Histopathology and Morbid anatomy, Surgery and Biochemistry. **Study Period:** 15 months (from November 2006 to March 2008). **Patients and Methods:** Tissues were obtained from 131 cases of Transurethral Trucut biopsy and were formalin fixed and paraffin-embedded for diagnosis. The prostatic tumours were diagnosed and assigned Gleason's histopathological grades and scores using Haematoxylin and Eosin (H&E) stained sections. Blood for PSA assay was analyzed by a method based on the immunoradiometric principle in which two monoclonal antibodies are directed against two different epitopes of PSA molecule. **Results:** During the period of study, 113 patients were diagnosed to have carcinoma of the prostate. The mean age at diagnosis was 68 years. The predominant histological type was adenocarcinoma (99.1%). The majority (45.1%) had moderately differentiated adenocarcinoma. Sixty one percent (61%) of patients had Gleason's score of 5-7 and 81.5% of patients had significant elevation of pretreatment PSA of > 20.0 ng/ml. There was a positive correlation between Gleason's score and pretreatment PSA levels in patients with Prostate cancer (r = +0.6) and was statistically significant (P< 0.05). **Conclusions:** It is known that the intermediate (5-7) Gleason's score prostatic cancers are highly unpredictable in their clinical aggressiveness. This limitation is of particular importance as the majority of the tumours (76%) in our study fell into this intermediate category. Thus, predicting the biological potential of the majority of prostatic cancers in asymptomatic patients based upon histology alone is problematic. The combination of pretreatment PSA levels which correlated well with Gleason's score in our study will be helpful in planning the choice of therapy in most patients with prostatic cancer in order to improve the prognosis.

Key words: Prostate cancer, Gleason's score, PSA, Correlation.

INTRODUCTION

Prostate cancer is an important growing health problem, presenting a challenge to urologists, radiologists and oncologists[1,2]. Prostate cancer is the most common non dermatologic cancer, yet despite this frequent occurrence, the clinical course is often unpredictable[3]. Many men are found to have had incidental microscopic foci of prostate cancer at postmortem examination, and most cancers are slow growing and do not manifest during the man's life time[3]. Thus, many men die with prostate cancer rather than die from prostate cancer, however, some cancers are aggressive with a rapidly worsening course.

Currently, many men are identified as having early prostate cancer through the use of prostate specific antigen (PAS) screening[4,5,6,7] but few indicators currently distinguish progressive prostate tumours from indolent cancers[8,9,10]. Expression of PSA is controlled by androgens and is considered an indicator of differentiation of prostate cells into functional luminal

Article received on: 06/10/2009
Accepted for Publication: 15/12/2009
Received after proof reading: 12/04/2010
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phenotype. PSA which is produced only by the prostate gland, is normally secreted in small amounts into the blood stream, but, larger amounts of PSA are released in benign prostatic hyperplasia (BPH), prostatitis, or carcinoma of the prostate (CP). Because PSA is produced by the body and can be used to detect malignancy, it is sometimes referred to as biological marker or tumour marker[7]. Many clinics are now using the following ranges with some variations: 0 to 2.5ng/ml is low, 2.6 to 10ng/ml is slightly to moderately elevated, 10 to 19.9ng/ml is moderately elevated and 20ng/ml or more is significantly elevated.

Prostatic intraepithelial neoplasia (PIN), which is a dysplasia of the epithelium lining prostate glands, is a probable precursor of prostatic carcinoma. The appearance of PIN may precede carcinoma by 10 or more years[11,12]. It can be divided into low grade and high grade PIN. Low grade PIN may be found even in men in middle age. PIN does not routinely increase the serum prostate specific antigen (PSA)[12].

Approximately 95 – 98% of prostate cancers are adenocarcinomas developing in acini of prostatic ducts[10]. Other rare histopathologic types of carcinoma prostate occur in approximately 5% of patients; these include small cell carcinoma, mucinous carcinoma, adenoidcystic carcinoma, signet-ring carcinoma and neuroendocrine cancer. Other none carcinomatous histopathological types include primary prostatic lymphoma, rhabdomyosarcoma and leiomyomas. Prostate cancer is frequently multifocal within the prostate, 70% of cancers occur in the peripheral zone (PZ) and approximately 20% are found in the transitional zone (TZ)[13].

Disturbances of architecture, invasion, and anaplasia are the important histopathologic criteria for the diagnosis of prostate cancer. Various grading systems have been proposed; the Gleason system is one of the most widely used internationally. It recognizes a primary and secondary patterns and in each 5 sub-patterns.

The sum of the two patterns contributes the Gleason's score. The score are of prognostic significance, independent of tumour grade[14,15]. In Gleason's system, grading is based upon the degree of glandular differentiation and growth pattern of the tumour as it relates to the prostatic stroma[5]. The pattern may vary from very well differentiated (grade 1) to very poorly differentiated (grade 5). This system takes into account tumour heterogeneity by scoring both the primary and secondary tumour growth patterns. For example, if the majority of the tumour is very well differentiated (grade 1) and the secondary growth pattern is very poorly differentiated (grade 5), the combined Gleason sum would be a 6. Low (i.e. < 5) Gleason score prostate cancers predictably have minimal aggressive behaviour whereas very high (8 – 10) Gleason score tumours are usually highly aggressive[3,14]. Unfortunately, the intermediate (5-7) Gleason score tumours are highly unpredictable in their clinical aggressiveness[3]. This limitation is of particular importance as the majority of tumours (76%) fall into this intermediate category[13]. Thus predicting the biological potential of the majority of prostate cancer based upon histology alone is problematic. However, grading in the form of Gleason's scoring system is an important factor in determining the prognosis. Patients with low Gleason's score live longer and few die of prostate cancer[3,14].

Similarly, like most other tumour markers, PSA has been shown to be valuable as a prognostic marker for monitoring disease recurrence and treatment response and that lower the pretreatment PAS the longer the survival[6]. It is the intention of this study to correlate the Gleason's score and the pretreatment PSA so as to predict who among patients with prostate cancer stand a better chance of long survival when both parameters are considered together, so that effective treatment modalities may be planned accordingly.

BROAD OBJECTIVES

To correlate histological grades of prostate cancer by Gleason's scoring system and pretreatment PAS levels in patients with prostate cancer at Muhimbili National Hospital(MNH), TANZANIA.

SPECIFIC OBJECTIVES

- To determine the age distribution of patients with prostate cancer
- To determine the histological types of prostate cancer
- To determine the histological grades by Gleason's scoring system in patients with prostate cancer.
- To determine levels of Pretreatment PSA in patients with prostate cancer
- To correlate Gleason's scores and pretreatment PAS levels in patients with prostate cancer.

MATERIALS AND METHODS

STUDY DESIGN

A prospective longitudinal study (hospital series) was carried among all patients with prostate cancer diagnosed by tissue biopsy and PAS levels at Muhimbili National hospital surgical clinics and wards and Histopathology laboratory for 15 months from November 2006 to March 2008.

TISSUES

Routinely fixed and processed paraffin-embedded tissues were obtained from 131 cases of Transperineal Trucut needle biopsy for diagnosis of prostate cancer.

The tumours were diagnosed and assigned Gleason histopathological grades and scores using haematoxylin and eosin (H&E) stained sections.

BLOOD FOR PSA ASSAY

5ml of venous blood was collected in a sterile non-heparinized tube at urology clinic or in the ward at MNH. Separation of serum was done at Muhimbili University College of Health Sciences (MUCHS) in the department of Biochemistry and stored at 2-8^{0}C and performed within 24 hours. The method is based on the immuno-radiometric principle in which two monoclonal antibodies are directed against two different epitopes of PSA molecule. The samples were incubated in monoclonal-coated tubes with the second ^{125}I-labelled antibody. After incubation, the liquid content of the tubes were aspirated and washed. This removed the unbound signal antibody, and the bound radioactivity was measured by gamma counter details of the assay procedures as per PAS total IRMA Kit supplied by the reagent from Immunotech A Beckman Counter Company. The PSA results were compared and correlated with the Gleason's grades and scores obtained from histopathological results of tissue biopsy.

STATISTICAL DATA

The correlation between Gleason's score and pretreatment PAS was done using spearman's Rank correlation (r) and the correlation coefficient was related to t-distribution since the sample size was small (< 500) and thus we used the expression $t = r\sqrt{\{(n-2)/(1-r^2)\}}$, where n was the sample size.

RESULTS

During the period of 15 months, from November 2006 to March 2008 a total of 131 biopsies were done and among these 114 patients were found to have prostate cancer and 17 had Benign Prostatic Hyperplasia (BPH). The age range of patients with prostatic cancer ranged from 48 to 100 years with a mean age of 68 years (table-I).

Table-I. Age distribution of 114 patients with prostate cancer.

Age in years	No. of Pts.	%age
< 50	1	0.8
50 - 59	19	16.7
60 - 69	45	39.5
70 - 79	36	31.6
≥ 80	13	14.5
Total	114	100.0
Mean: *68.12*	***Median:*** *68*	

Two histological types of prostatic cancer were found in 114 patients, namely adenocarcinoma 113(99.1%) and embryonal rhabdomysarcoma 1(0.9%). Among the adenocarcinomas, 4(3.5%) were very well differentiated (VWD), 6(5.3%) well differentiated (WD), 51(45.1%) moderately differentiated (MD), 36(31.9%) poorly differentiated (PD) and 16(14.2%) very poorly

differentiated (VPD) (table-II).

Of the 114 patients with prostate cancer, 113 had adenocarcinoma and were scored using Gleason's scoring system. Only 6(5.3%) had a score of 2-4, and the majority of the patients, 69(61.1%) had Gleason's score of 5-7 while 38(33.6%) had Gleason's score of 8-10 (table-III, figures 1,2,3,4&5). One case was of embryonal rhambdomyosarcoma.

Correlation between Gleason's score and average pretreatment PSA levels showed that the Gleason's score in patients with adenocarcinoma were as follows: (2-4),- 30.8ng/ml, (5-7) – 53.9ng/ml, and (8-10)- 103.0ng/ml (Table-IV). The highest PSA level was in Gleason's score of 8-10. The PSA average level correlated well with Gleason's scores (Pearson's correlation coefficient (r) = 0.6, t =0.74 degree of freedom (df) =4) and was statistically significant (P< 0.05).

Table-II. Frequency distribution of adenocarcinoma of prostate with respect to histological differentiation and Gleason's grades.

Histological differentiation & grades	No. of Pts.	%age
VWD (Grade 1)	4	3.5
WD (Grade 2)	6	5.3
MD (Grade 3)	51	45.1
PD (Grade 4)	36	31.9
VPD (Grade 5)	16	14.2
Total	113	100.0

VWD: Very well Differentiated, WD: Well Differentiated, MD: Moderately differentiated, PD: Poorly Differentiated, VPD: Very Poorly Differentiated.
NB: 1 additional case was of embryonal rhabdomyosarcoma (114).

DISCUSSION

The incidence of prostate cancer increases with age. The mean age in this study was 68 years and the youngest patient was 48 years old. These figures are comparable with findings from other studies which report the mean

Table-III. Frequency distribution of Gleason's score at presentation.

Gleason's score	No. of Pts	%age
2 - 4	6	5.3
5 - 7	69	61.1
8 - 10	38	33.6
Total	113	100.0

Table-IV. Distribution of pretreatment PAS levels in patients with prostate cancer.

PSA levels in ng/ml	No. of Pts.	%age
0 - 2.5	0	0
2.6 - 10	6	5.3
10 - 19.9	15	13.2
≥ 20	93	81.5
Total	114	100.0

Table-V. Correlation between Gleason's score and pretreatment PSA levels.

Gleason's score	No. of Pts.	Average PSA level (ng/ml)
2 - 4	6	30.8
5 - 7	69	53.9
8 - 10	38	103.0

age of 69 years[8] and a slightly low mean age of 65 years has also been reported[6]. These findings confirm that prostate cancer is a disease of elderly men although young men are not excluded.

Adenocarcinoma was the predominant histological type in this study as it represented 99.1% of histological types. This finding is in very close agreement with previously reported figures[8]. Embryonal rhabdomyosarcoma was encountered in one patient who presented with a six months history of a progressive pelvic mass.

Prostatic intraepithelial neoplasia (PIN) was not encountered during the study period. The reasons for the absence of this histological type could be due to the fact that PIN does not appear to elevate serum PSA[15] and more over patients with PIN are unlikely to come to hospital as they probably have no symptoms. Digital rectal examination (DRE) findings need to be used in conjunction with serum PSA level to enhance early detection of prostate cancer[13]. The need of having screening facilities for metastatic lesions is highly emphasized at this hospital where only X-ray and ultrasound are availalbe.

Regarding Gleason's score, 61.1% of our patients were found to have Gleason's score of 5-7 and 33.6% presented with high Gleason's score (8-10). Comparing these findings with those of others,[9] the histological findings indicated that their patients had more aggressive disease than patients in our region. In their study, 60% of patients showed cancer of high histological grade (Gleason's score 8-10) compared to 33.6% in our patients, and there was no patients with low grade (Gleason's score 2-4) adenocarcinoma in their series[9]. It is the authors' speculation that genetic, environmental, racial and dietary factors are possible explanations for this difference.

Most tumours in our study were of intermediate scores (Gleason's 5-7). These are known to have heterogenous biological aggressiveness[5]. Our study revealed that the correlation between Gleason's score and pretreatment PSA levels was statistically significant ($P < 0.05$). This is contrally to one study,[9] where they found that PSA level was not closely related to both clinical and pathological stage ($P = 0.07$) but is in close agreement with others[5]. The prognosis and choice of therapy for most patients with prostate cancer depend on clinical stage, serum prostatic specific antigen (PSA), and histological grade (Gleason score) of the tumour[10]. In addition, the strongest predictive factors for distant metastasis and lymph node positive disease have been found in some studies to be serum level of PSA of more than 20ng/ml and a Gleason score of more than 8[10]. The finding of 81.1% of our patients in the study having serum PSA levels of at least 20ng/ml and 33.6% of them with Gleason score 8-10, suggests the possibility of distant metastasis and positive lymph node disease to be a highly likely event in our cases.

CONCLUSION

The intermediate (5-7) Gleason's score prostatic cancers (PC) are highly unpredictable in their clinical aggressiveness as inferred from other previous studies. This limitation is of particular importance as the majority of tumours (76%) in our study fell into this intermediate category. Thus, predicting the biological potential of the majority of carcinoma prostate in asymptomatic patients based upon histology alone is problematic. Therefore, the combination of pretreatment PSA levels which correlated well with Gleason's score will be helpful in planning the choice of therapy in patients with PC in order to improve the prognosis.

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PREVIOUS RELATED STUDIES

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