RESEARCH ARTICLE

Comparative Histopathological Characterization of Prostate Cancer in Saudi Patients by Conventional and 2005 ISUP Modified Gleason Systems

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Abstract

Background: The aim of this study was to compare the characterization of prostate cancer using the conventional and 2005 ISUP modified Gleason systems. Materials and Methods: The study employed samples from 40 prostate cancer patients with resection, biopsy and RP materials. The majority of cases (95%) comprised adenocarcinoma of the prostate with a modified combined Gleason score of 7 in 20 of the cases (50%). Results: Upgrading of Gleason scores to a score of 7 occurred in more than 45% of the cases. Conclusion: The study successfully showed that by the use of the 2005 ISUP modified Gleason system, score 6 cancers decreased from 25% to 17.5% of cases, whereas score 7 cancers increased from 45% to 50%.

Keywords: Prostate cancer - conventional Gleason grading - 2005 ISUP modified Gleason - histopathology

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Introduction

Both benign prostatic hyperplasia (BPH) and prostate cancer are age-related diseases in males that develop late in life. The human prostate gland contains several different zones. BPH typically arises within the transitional zone (Tz), whereas prostate cancer predominantly occurs in the peripheral zone (Pz) (Zhao et al., 2009). The reason why both these diseases arise in different zones is unclear, but changes in stromal-epithelial signaling, receptor and enzyme expression might have a role. The activation of local estrogen receptor β (ER_β) is required to prevent BPH. In prostate cancer, however, the activation of ER_β appears to be beneficial (McPherson et al., 2010). The activation of ER promotes the development of inflammation which can stimulate the aromatase enzyme and result in the further activation of ERα (Figure 1).

The enlargement of the prostate gland is the result of benign hyperplasia (Goldstein et al., 2010). Prostate cancer is a leading cause of mortality worldwide. It is increasing significantly in the developed countries and most common cause of cancer death in the men (Ferlay et al., 2010). Environmental factors constitute a large influence on the development of human cancers. 90% of all cancers could be preventable, if no environmental carcinogenic factors existed. The host is influenced by various factors such as genetic factors, gender, age and nutritional state (Pourmand et al., 2007; Park et al., 2008).

Prostate biopsy is a procedure in which small needle-core samples are removed from a man's prostate gland to be examined microscopically for the presence of cancer (de la Taille et al., 2003). It is typically performed when the result from a PSA blood test rises to a level that is associated with the possible presence of prostate cancer (Hugosson et al., 2010; Par Kash et al., 2014). It may also be triggered by an abnormal digital rectal exam (Par Kash et al., 2014). PSA screening is controversial, and PSA levels may also be high due to presence of BPH, infection or by manipulation of the prostate gland by surgery or catheterization (Svetec and Thompson, 1998). Using histopathological procedure for prostate cancer diagnosis, pathologists obtain tissue samples from prostate biopsies and examine it after staining protocols to identify the tissue structures (Orozco et al., 1998; Verim et al., 2013). This traditional histopathological-based diagnosis has remained the standard diagnostic method for many years but with the introduction of advanced techniques like microarrays, mass spectrometry and DNA sequencing, new avenues have opened in cancer diagnosis and therapeutics.

The development and metastasis of Prostate cancer (Figure 1) involves a tumor becoming un-responsive to regulatory factors in the Prostate gland. Cancer cells differ in their morphology from normal prostate gland cells (Visvader, 2011). The degree to which they differ from the normal cell is what determines the cancer grade. The most commonly followed method of grading cancer of prostate is Gleason grading (Epstein et al., 2005). The higher the Gleason grading the more aggressive the tumor

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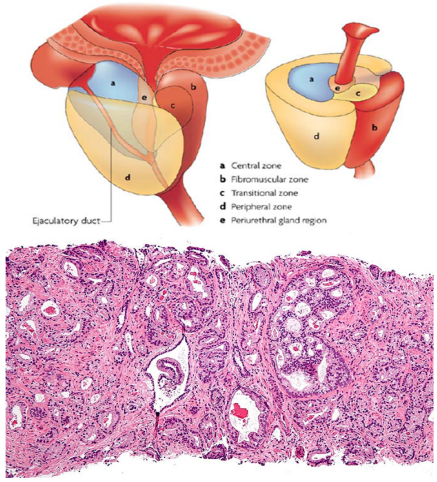

Figure 1. The Prostate Gland Containing Four Zones: the Central Zone, Fibromuscular Zone, Transitional Zone and Peripheral Zone. Prostate cancer often originates in the peripheral zone. Shown below is Gleason pattern 4 micrograph of prostate adenocarcinoma, acinar type which is the most common type of prostate cancer

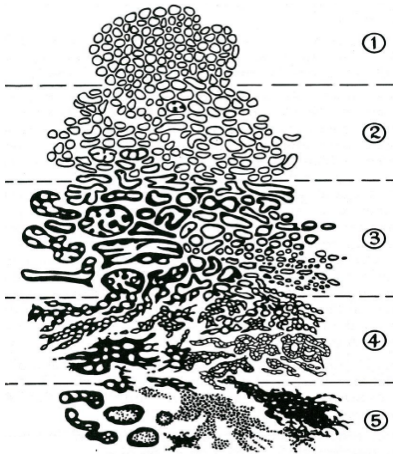

Figure 2. Shown is the Original Gleason Grading System. The figure shows patterns from 1 to 5 (1 is the most differentiated, 5 is the least differentiated) (Bayder; Epstein 2009). The Gleason score is the sum of the two most common Gleason grades in multiple biopsy samples. Prostate Cancer tumor is graded on the basis of glandular structure

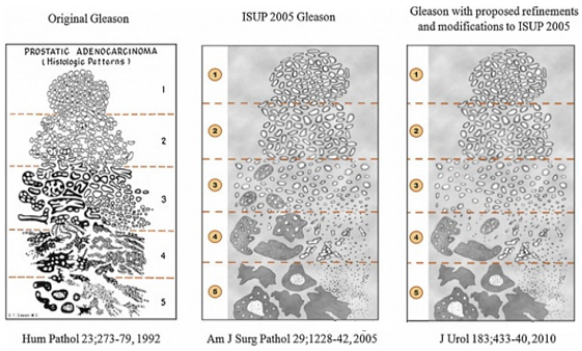

Figure 3. Schematic Representations of (a) Conventional and (b) Modified Gleason Grading Systems. The most important changes between them are in patterns 3 and 4. In the modified system, most cribriform patterns and also poorly defined glands are included in pattern 4, (c) in the 2010 system all cribriform glands are included in pattern 4 (Brimo et al., 2013)

is likely to be and also more likely to spread to other organs of the body.

The Gleason system was developed in 1966 by Dr. Donald Gleason. The score is based on the appearance of the cancer cells when viewed under a microscope (Gleason 1992). Human judgment is involved in Gleason scoring (Figure 2), which always raises suspicion of variable accuracy, but there are the objective and essentially statistical considerations associated with extrapolation from limited number of samples. This grading system is based on the degree of glandular structure and the growth pattern of the tumor. A primary (predominant) pattern is graded and assigned from (1 to 5), and a secondary (second most prevalent) if present is also graded and assigned from (1 to 5). By adding both patterns, Gleason score or combined Gleason score is obtained (Allsbrock et al., 1999) (Figure 2). Gleason scores of 6 or lower are assigned to low or well differentiated tumors, a Gleason score of 7 is given to intermediate or moderately differentiated tumors, and finally a Gleason score of 8-10 or higher is for poorly differentiated tumors and these patients need adjuvant therapy or radiation therapy (Timmerman et al., 2010).

The U.S. and Canadian Academies of Pathology convention updated the Gleason grading system in 2005 based on the data present in literature (Epstein et al., 2005). By the modification of the Gleason grading system there has been a shift in the most frequent scores from 6 (3+3) to 7 (3+4) in biopsy specimens. In the past, there also was a problem with the conventional Gleason grading system of under-grading of biopsy specimens compared with radical prostatectomy (RP) specimens which has been reported at ~45% (Egevad et al., 2001; Epstein et al., 2005). The change in the Gleason system as applied to score of 3 and 4 is to limit the definition of score 3 carcinoma and widen the scope of score 4 carcinoma (Figures 3, 4). To investigate the new developments, this study used samples from 40 prostate cancer patients to compare the characterization of prostate cancer by the conventional and 2005 ISUP modified Gleason system

Materials and Methods

The study employed 40 prostate cancer samples. These samples comprised 22 (55%) cases of transurethral resections of the prostate (TURP), 14 (35%) cases of trans-rectal ultrasound guided biopsies (TRUS) of the prostate and 4 (10%) cases of radical prostatectomy. All of them were collected from the Department of Pathology, King Abdul Aziz, University Hospital and Arar Central hospital, KSA in 24 months period from April 2011 through March 2013. The provided clinical data was received in the urologic outpatient clinic from patients complaining from lower urinary tract symptoms and difficulty in urination. Some cases were suffering from urine retention also. After examination, laboratory investigations were perfomed which included routine investigation, as well as liver and renal functions tests also investigation of prostate specific antigen (PSA) level was done that was high in some cases. Transurethral Resection (TUR-P) and Sextant Transrectal Sonographic-guided biopsies (TRUS) were acquired for the majority of cases. The obtained prostatic

samples were fixed in 10% formaldehyde and sent for preparation of Formalin-fixed paraffin-embedded blocks and tissue sections with 3 μ thickness. The specimens were processed and stained by Hematoxylin and Eosin (H&E) as well as some cases were already stained with some immunohistochemical markers for more cellular visualization, then all cases were examined and evaluated histologically for prostatic carcinomas which were graded according to Gleason grading system. Gleason scores and modified combined scores were estimated (Bayder; Epstein 2009).

Results and Discussion

Prognostic tumor characteristics like differentiation grade, growth fraction, blood or lymph vessel invasion, or extension of necrosis can only be evaluated by histopathology. A thorough histopathological evaluation is always needed to guide the clinician to the most likely primary tumor site or sites, to give reason to further specific examinations, for example endoscopy, and to deliver important information about the tumor that may have influence on the prognosis and possibly the choice of therapy and improvement of clinical outcome (Varadhachary et al., 2008).

The study characterized samples from 40 prostate cancer patients obtained via resections, biopsies and radical prostatectomy by the conventional and 2005 ISUP modified Gleason system (Table 1). Histopathological examination of all these specimens revealed 2 (5%) out of the 40 cases were small cell carcinoma (Figure 5), and 38 (95%) cases were adenocarcinoma (Figure 6). Microscopically, Gleason grading of prostatic adenocarcinoma showed 2 cases were Gleason score (2+2) and of combined Gleason score 4, as well as 8 cases were Gleason score (3+3) and of combined score 6. The cases exhibiting combined Gleason scores of 2 and 6 are of well-differentiated tumors. Eighteen cases were of moderately differentiated and were of Gleason score (4+3) and of combined Gleason score 7. Ten cases were of poorly differentiated prostatic adenocarcinoma, 6

Table 1. Histopathological Findings for 40 Cases of Prostate Cancer

Category	No. of cases	%
Specimen:		
TRUS	14	35
TURP	22	55
Prostatectomy	4	10
Histological type of tumor:		
Adenocarcinoma	38	95
Small cell carcinoma	2	5
Gleason Grade:		
Well Differentiated	10	25
Moderately Differentiated	18	45
Poorly Differentiated	10	25
Gleason Score:		
2+2	2	5
3+3	10	25
4+3	18	45
4+4	6	15
4+5	4	10
Modified Combined Gleason Score:		
4	2	5
6	7	17.5
7	20	50
8	8	20
9	3	7.5
Perineural invasion:		
Present	15	37.5
Absent	25	62.5
Seminal vesicle invasion:		
Present	One prostatectomy	
Absent	Three prostatectomies	

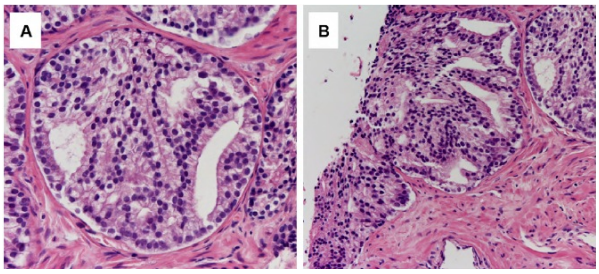

Figure 4. Adenocarcinoma of the Prostate with (A) Gleason Pattern 3 and (B) Gleason Pattern 4

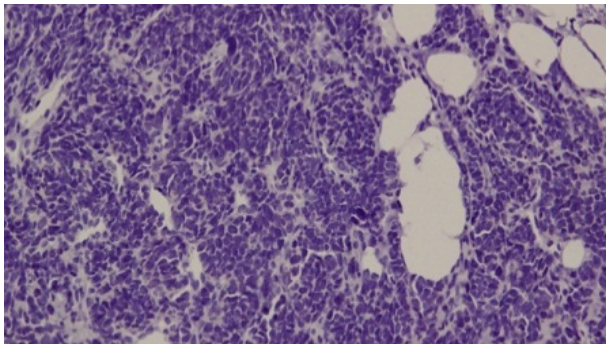

Figure 5. Small Cell Carcinoma of Prostate (DAB 200×)

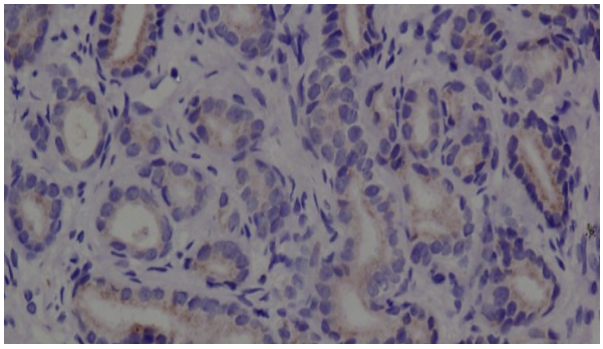

Figure 6. Well Differentiated Adenocarcinoma Gleason Score (2+2), Combined Score 4 (DAB 200×)

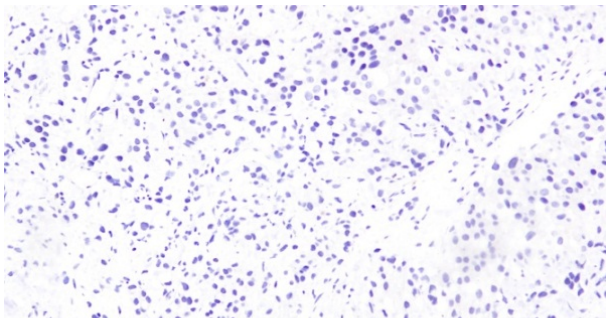

Figure 7. Poorly Differentiated Adenocarcinoma Gleason Score (5+4), Combined Score 9 (DAB 100×)

cases among them received a Gleason score of 4+4 and a combined Gleason score of 8, whereas 4 cases received a Gleason score of 4+5 and a combined Gleason score of 9 (Figure 7). A shift was also seen from the original Gleason score of 6 to 7 by the use of 2005 ISUP modified Gleason system which provided 20 cases instead of the original 18 cases. Histologically, prostatic intraepithelial neoplasia (PIN) was seen in 5 cases, perineural invasion was found in 15 cases, and 25 cases were negative. Seminal vesicle invasion was observed in one case of the prostatectomy specimens, whereas, all radical prostatectomy specimens were free from lymph node invasion (Table 1).

In conclusion, the study successfully compared the characterization of prostate cancer using the conventional and 2005 ISUP modified Gleason system. The majority of prostate cancer specimens (95%) in the study showed tumor of adenocarcinoma type. Only 5% showed small cell carcinoma. The same cell carcinoma of the prostate could not be assigned a Gleason score as chemotherapy is the mainstay of its therapy. The results suggest that there is migration or upgrading of scores to higher scores and an increase in a score of 7 in more than 45% of the cases by the use of 2005 ISUP modified Gleason system.

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