Pathological Grading of Prostate Cancer in Sudanese Patients Attended Soba Teaching Hospital (2007---2009)

By

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Dedication

To my supportive family, to my father who believes on me, and to all those who suffer from prostate cancer.
Acknowledgment

First of all I would like to thank my supervisor Dr. Mohammed M. Osman for his great help, also my thanks are for the staff of histopathology lab in Soba Teaching Hospital and to the Urology department. I would like also to thank my Friends Elsadig and Shankel along with my little sister Zainb for her great contribution in typing of this research. and lastly my deep thanks are for Fadia who did the Analysis.
List of abbreviations:

UTS: Urinary tract symptoms.

PIN: Prostatic intraepithelial neoplasia.

PSA: Prostate specific antigen.

PAP: Prostate acid phosphatase.

TUR: Transurethral prostatectomy.

BPH: Benign prostatic hyperplasia.

EMA: Epithelial membrane antigen.

PTH: Para thyroid hormone.
Abstract

Background:
Prostate cancer is regarded the second cause of death in men in developed countries, in Sudan it comes in the sixth place following lung, liver, stomach, colorectal and oesophageal cancer.

Design:
This study is a cross-sectional retrospective archival study

Setting:
The study was conducted on 376 prostate cases seen in Soba teaching Hospital in the period from 2007 to 2009 from these cases 76 were cancer positive.

Objectives:
The cases studied with regard to age of presentation, pathological grading using Gleason score, association of PIN, perineural invasion, PSA level and the presence of lower UTS. The relationship between the Gleason score and age of presentation, PSA level, presence of PIN, presence of crystalloid secretions and perineural invasion were studied.

Methods:
The patient’s files, reports and slides were revised. Data was collected using tables, all information about patient’s names, age, clinical findings, their file and identification numbers, the diagnosis, Gleason score, presence of PIN, crystalloid secretions and perineural
invasion was collected. The data was analyzed using SPSS version 12. and the results were presented in tables and charts.

Results:

Prostate cancer is more common among patients older than 70 years which constitute about 60% of the patients and they usually present with high grade disease, in about quarter of the cases we found associated PIN, PSA level was high in some of the cases and is mostly associated with high grade cancer. Twenty five percent of the cases were associated with perineural invasion most of it was of high grade.

Conclusion:

The results of the study go well with the findings in the world literature, but we had a lot of missed data regarding history and prognosis.

We recommend that more studies are done specially in the area of prognosis and clinical progression of the disease.
المستخلص

هذة الدراسة دراسة وصفية استعدادية أجريت في 376 حالة بروستات في مستشفى سوبا التعليمي في الفترة من 2007 ل 2009 من هذه الحالات 76 كانت إيجابية لسرطان البروستات. دراسة الحالات فيما يتعلق بعمر المريض، درجة جليسون، وانتشار الخلايا المريضة حول الأعصاب، معدل بي إس أي ووجود أعراض في الفترة الأولية.

إنتشر الخلايا المريضة حول الأعصاب، معمل بي إس أي ووجود أعراض في الفترة الأولية، ووجود PIN ووجود الخلايا المريضة حول الأعصاب.

تمت مراجعة ملفات وتفاير وشرائحة المرضى، ومن ثم تم تجميع البيانات في جداول تحتوي كل المعلومات حول أسماء المرضى، اعصارهم، نتائج الفحوصات السريرية، التشخيص، درجة جليسون، وجود PIN ووجود إفرازات كرستالية ووجود خلايا مريضة حول الأعصاب.

البيانات خلقت باستعمال برنامج 12 SPSS. والنتائج قمت في جداول ومخططات. وجد أن سرطان البروستات أكثر شيوعًا بين المريض كان السن البالغة أعمارهم أكثر من سبعين سنة ومتولون حوالي ستين في المائة من الدراسة، والتي يتضمنهم من مرحلة متقدمة من المرض، حوالي زوج الحالات وجد، مستوي بي إس أي كان أعلى في البعض من الحالات، ومعارضا كانت من النتيجة المتقدمة، خاصة وجزء من الحالات كانت تحتوي على خلايا مريضة حول الأعصاب بغضون كلاً من الدرجة المتقدمة.

نتائج الدراسة تتوافق مع النتائج في العالم، لكن كان علينا الكثير من البيانات المقدورة بخصوص التاريخ والتشخيص. نوصي بإجراء المزيد من الدراسات بشكل خاص في مرتبط بحالة المريض على المدى الطويل ومراحل تطور المرض.
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Chapter 1
Introduction:

Prostate cancer is one of the leading causes of cancer death in men in developed countries. In the United States it is the second killing cancer among men headed only by lung cancer. Statistical studies estimate that one out of six men will be diagnosed with prostate cancer during his life, and that one out of 35 men will die with prostate cancer. Prostate cancer accounts for 10% of cancer related deaths in men.

The survival rate of patients with prostate cancer is very high reaching 100% for 5 years, 91% for 10 years and 76% for 15 years.

The prognosis in prostate cancer depend on the time of the diagnosis and the degree of differentiation along with the extent of the tumor.

With the new modalities of diagnosis and treatment the survival is far better.

In Sudan most of the patients are diagnosed late and sometimes at an extensive metastatic stage. Data regarding patients survival in Sudan is not available since most of them are diagnosed and treated at different places.
Literature Review

The prostate is a pear-shaped glandular organ that weighs up to 20 g in the normal adult male and that depends for its differentiation and subsequent growth on androgenic hormones synthesized in the testis, acting through a poorly understood mesenchymal-epithelial interaction. Traditionally, it has been divided into anterior, middle, posterior and two lateral lobes by drawing divergent lines from the centrally located urethra. A division that correlates better with the physiologic and pathologic features of the organ is to divide it into an inner (periurethral) and outer (cortical) zones. The inner zone is the primary site for nodular hyperplasia (and the rare carcinomas arising from large ducts), whereas the outer zone is the primary site for adenocarcinoma. The secretary cells, which are located in the luminal side of the gland, contribute to a wide variety of products of the seminal fluid. They produce prostatic acid phosphatase (PAP) and prostate-specific antigen (PSA) both of which can be readily identified immunohistochemically and have been proved to be of great diagnostic utility because of their organ-related specificity. PSA is a glycoprotein that has been identified as a kallikerin-like protease. Secretory cells also coexpress various keratins and vimentin. The keratins do not include high-molecular-weight types such as 34 β F12, a fact of diagnostic significance. (1)

The normal prostatic secretion is a neutral mucosubstance (a feature of some diagnostic significance because most adenocarcinomas secrete a mixture of acidic and neutral mucins. However, on occasion one encounters scattered columnar mucin-secreting cells in nonneoplastic prostatic epithelium, particularly in areas of atrophy.
The basal cells form a thin continuous layer that separates the luminal secretary cells from the basement membrane. They characteristically contain keratins 34 β E12 and 312 C8-1 and stain strongly for antikeratin antibody.

The neuroendocrine cells express chromogranin A and B secretogranin II, and various peptide hormones such as somatostatin, calcitonin and bombestin, they coexpress PSA, suggesting a common origin with the secretory cells. However, they are negative for androgen receptors.

The large prostatic ducts are lined by transitional epithelium that is continuous and indistinguishable from that lining the prostatic urethra. In contrast to bladder epithelium, its surface does not display umbrella cells but rather a single layer of columnar cells that are immunoreactive for PSA and PAP. On occasion, this epithelium undergoes squamous metaplastic changes, these were very common at the time that estrogen therapy was widely employed for prostatic carcinoma (1,2).

The prostatic stroma is notable because of its large content of smooth muscle fibers, whose function is to squeeze out the prostatic secretion when properly stimulated; it has been pointed out that the presence of this muscular stroma duplicates the function of myoepithelial cells in the other organs, such as breast. Prostatic stroma cells have been found to contain androgen receptors.

Peripheral nerves are evenly distributed in the apex, midgland, and base; they are of importance to pathologists because of the high frequency with which the loose connective space that surrounds them (formerly thought to represent perineural lymph vessels) is involved by adenocarcinomas of this organ.
The prostatic lymph vessels drain into the pelvic lymph nodes and from there into retroperitoneal chain.

Diseases affecting prostate gland:

The prostate gland is subjected to different pathologies including both benign and malignant conditions. The gland can be affected by inflammatory conditions both acute and chronic ones. It's also affected by benign neoplasms the most common is benign prostatic hyperplasia that commonly occur in men older than 40 years and it's incidence increase with age reaching 85% with age 80. The gland also is a site of leomyoma which arise from the stroma of the gland.

**Carcinoma**

**General features:**

Carcinoma of the prostate is the most common internal malignancy among men in the united states and is responsible for 10% of cancer death in this population. Each year in new York state more than 11,000 men are diagnosed with prostatic cancer, and more than 2300 die from it. Prostate cancer is the leading cause of new cancer in men and is second only to lung cancer as a leading cause of cancer-related deaths in men. Rates among black males are one and a half those of white males. The age adjusted incidence is on the increase in most countries. Hormonal factors appear to play a role in the development of prostatic carcinoma. The disease do not occur in men castrated before puberty, and its incidence is low in patients with hyperestrongensim resulting from liver cirrhosis. It has been estimated that 5% to 10% of prostatic carcinomas have genetic link. If a man's brother or father had prostatic carcinoma his own risk of developing the disease is two to three times greater than average. There is no
demonstrable correlation with diet, venereal disease, sexual habits, smoking or occupational exposure. There is no convincing evidence that patients with nodular hyperplasia (or those who have had a transurethral resection for it) are at an increased risk for the development of prostatic carcinoma, although the two conditions often coexist.

Almost 75% of the men diagnosed with prostatic cancer are age 65 or older, but the tumors can be seen in younger adults and even in the children and adolescents. Their frequency increases with age, a fact well substantiated by careful observations at autopsy. The frequency with which incidental carcinoma is found at post mortem examination varies between 15% and 70% and is directly related to the age of the patient and the thoroughness of the sampling.(3)

Every year about 600 Sudanese men are diagnosed with prostate cancer. And prostate cancer is ranked the sixth common cancer in male population preceded by lung, stomach, liver, esophageal and colorectal cancers.(30,31)

**Clinical features:**

Skillful rectal examination remains a practical and efficient method for the detection of prostatic carcinoma; however, pathologic confirmation is always necessary because early lesions cannot be distinguished with assurance from foci of nodular hyperplasia, granulomatous prostatitis, tuberculosis infarct, or lithiasis. Transrectal ultrasonography can detect carcinomas (which appear as hypoechoic lesions) as small as 5 mm in diameter; however, it will miss up to 30% of the prostatic tumors that are isoechoic and has not proved an efficient tool for screening.(4,32)
PSA is secreted by all but the most undifferentiated prostatic tumors. Gram for gram, the average prostatic carcinoma produces ten times or more the amount of PSA produced by normal tissue, and this is reflected in the circulatory levels of this marker. Serum determination of PSA has all but replaced the time-honored determination of PAP. The test has a high sensitivity and specificity to prostatic disease, is rapid and inexpensive, and is minimally invasive. Mild serum elevations of PSA can be seen with nodular hyperplasia, but levels above 4 mg/ml call for serial determination, with the performance of a biopsy if they continue to rise. Almost half of patients with prostatic carcinoma have levels over 10 mg/ml. Elevations of serum PSA also occur in prostatitis, prostatic infarct, and major trauma to the prostate, such as needle biopsy or TUR, but these elevations should be transitory and resolve with proper treatment.

The combination of digital rectal examination, transrectal ultrasonography, and serum PSA represents a powerful diagnostic triad for the detection of early prostatic carcinoma. It is not clear whether measurement of the PSA density (PSA level as a function of prostatic volume) will provide a more specific test for carcinoma. (5, 25, 21)

**Pathologic features:**

Prostatic carcinoma can be divided into two major categories;

(1) adenocarcinoma of peripheral ("secondary") ducts and acini, and

(2) carcinoma of large ("primary") ducts.

This morphologic distinction has traditionally been based on the belief of a different site of origin for the two tumors. However (and as in the breast before), this histogenetic approach has been challenged by the observation that the two patterns are
often seen together, and the alternative proposal has been advanced that it is the site of the growth rather than the origin that governs the tumors architecture. The majority of the tumors belong to the first category, and most studies dealing with grading, staging, prognosis, and therapy of the prostatic carcinoma refer exclusively to them.

These two major tumor types may coexist in the same prostate, and that these are rare tumors with combined features in the same neoplasm.

**Adenocarcinoma of peripheral ducts and acini:**

Most prostatic carcinomas arise in the posterior lobe. More important than this is the fact that most prostatic carcinoma arise in the peripheral zone, whether posteriorly, laterally, or anteriorly, with sparing of the periurethral region except for the late stages of the disease.\(^5\)

Grossly, the tumors may be difficult to see but usually can be identified as a gray or yellowish, poorly delineated, firm area. Early detection efforts are resulting in the identification of increasingly smaller tumors. As a matter of a fact, residual carcinoma may be unidentifiable grossly or even microscopically in a radical prostatectomy specimen preformed because of a positive biopsy (so-called "vanishing cancer phenomenon" or "minimal residual cancer"). The frequency of this finding has increased in recent years, probably due to earlier diagnosis and therefore smaller size of the original tumors.\(^5,6\)

Microscopically, prostatic adenocarcinoma exhibit a wide spectrum of appearances, ranging from anaplastic tumors to highly differentiated neoplasms that are distinguished from the non-neoplastic gland only with great difficulty. Four major
cytoarchitectural patterns occur. medium-sized glands, small glands, diffuse individual cell infiltration, and cribriform.

Carcinomas composed of a medium-sized glands are detected on low-power examination by virtue of the closely spaced arrangement of those glands, irregular outline, smooth inner surface, and scanty intervening stroma. Tumors made up of small glands appear as expansive nodules on low power, the individual glands having a regular round configuration and small size. Both of these architectural patterns (but particularly the latter) are accompanied by cytologic abnormalities in the form of nuclear enlargement, irregularity of contour, hyperchromasia, and most important prominent nucleoli ("macronucleoli", defined as a measuring >1 micron in diameter). These nucleoli tend to be marginated and often multiple. Mitoses are also of significance, but they are rarely found in well-differentiated tumors composed of either medium-sized or small glands. The pattern of diffuse cell infiltration resembles somewhat that of invasive lobular carcinoma of the breast, whether the cribriform pattern has high resemblance to comparable type of breast carcinoma. It has been stated that the cribriform pattern represents intraductal carcinoma, as evidence by the preservation of the epithelial basal layer. This pattern is accompanied by clearcut invasive carcinoma in the majority of cases; therefore the use of the term "intraductal carcinoma" under these circumstances may be misleading. An additional pattern of growth that has been referred to as glomeruloid is characterized by the presence of intraluminal ball-like clusters of tumors cells. (7,8)

Two opposing morphologic variations of prostatic adenocarcinoma are one in which the tumors simulates an atrophic process, and another in which it mimics a benign hyperplastic change. The first, described as prostatic adenocarcinoma with atrophic
features, is formed by tumors cells with an attenuated cytoplasm, such that the nuclei occupy almost the entire cell height. These cells are identifiable as malignant because of their infiltrative pattern of growth, nuclear enlargement. The architectural features include papillary infoldings, branching, and corpora amylacea. Features identifying the lesions as malignant are nuclear enlargement, macronucleoli, mitoses, intraluminal crystalloids, and sometimes the presence of adjacent PIN(9).

The patterns just mentioned are often seen in combination. Either synchronously or metachronously, also, a patterns of diffuse cell infiltration can be seen after the partial removal of a better differentiated neoplasm. These patterns and their admixture, as seen on low-power examination form the basis of Gleason grading scheme.

Multiple tumors foci have been demonstrated in 75% to 85% of radical prostatectomy specimens studies by step-section or whole-mount techniques. They are probably an expression of true multicentricity rather than intraglandular tumors spread, as supported by their frequent genetic heterogeneity. Multicentricity is less common in the centrally located tumors.

The presence of prostatic glands within perineural spaces is common in these tumors. This finding is a strong indicator of malignancy but is not pathognomonic. It does not represent permeation of perineural lymphatic vessels, but rather spread of glandular tissue along planes of lesser resistance. Its presence in needle biopsy specimen is a good predictor of capsular invasion by tumor(10).

The stroma surrounding the neoplastic glands may show a combination of hypercellularity and deposition of a basophilic ground substance ("mucinous fibroplasias or "collagenous micronodules"). Both intraluminal and stromal
Calcification may be seen in association with prostatic cancer, but the incidence of the latter is much lower than in benign prostate.\textsuperscript{(11,12)}

Protein crystalloid structures morphologically and immunocytochemically similar to Bence Jones crystals are seen in the glandular lumina of 10% to 23% of prostatic carcinoma and are particularly common in tumors composed of medium-sized glands. Their presence usually indicates malignancy, but their occasional occurrence in benign glands has been documented. When the latter is the case, their presence should not be viewed as indicating a significant risk factor for the subsequent development of cancer.\textsuperscript{(12)}

Electron probe x-ray microanalytic studies have shown that they are predominantly composed of inorganic sulfur. Exceptionally, these crystalloids are also found in metastatic foci. The presence of corpora amylacea in the glandular lumen is not necessarily a sign of benignancy; these formations can also be found in association with malignant glands, particularly in examples of extensive, moderately differentiated tumor.

The cytoplasm of the carcinoma cells usually has a nondescript finely granular appearance, but on occasion it is clear or foamy because of the massive accumulation of lipids ("foamy gland carcinoma"). When this feature is widespread, the tumor grossly acquires a bright yellow color and a soft consistency, making it difficult to detect on rectal palpation even when it is extensive. Its microscopic recognition can also be difficult, particularly at metastatic sites. The behavior of these tumors is often aggressive despite the deceptively innocuous microscopic features.
"Minimal adenocarcinoma" and atypical small acinar proliferation (ASAP) :

These are tumors in which you cannot say whether they are benign or malignant. For the cases in which the recommended threshold is not reached, terms such as "atypical gland suspicious of malignancy" and "atypical small acinar proliferation (ASAP) suspicious of malignancy" have been proposed. Also, these terms are mired in controversy, the main objection being that they do not represent morphologic entities. Semantics aside, the fact remains that certain number of prostatic biopsies (about 4% to 6%) cannot be confidently placed into a benign or malignant category (with or without 34BE immunostainings), and it seems to us wholly appropriate to express this uncertainty in the pathology report, whether using the ASAP acronym or with a descriptive "canned" text, as frustrating as this may be for the urologist and the patient. One thing is certain: a patient with such a diagnosis warrants a second biopsy.(13)

Carcinoma of large ("primary") ducts :

The other major (but numerically less significant) category of prostatic carcinoma originates from the large (primary) ducts that are normally found in a periurethral location. Cystoscopic examination often shows a polypoid villous or an infiltrative urethral component. Microscopically, the following types have been recognized .(14)

1. Large (prostatic) duct adenocarcinoma. This tumor is characterized by malignant changes in large dilated ducts, often shows by papillary foci and occasionally by a clear cell (mesonephroid) component. Sometimes the tumor is accompanied by pagetoid spread in the prostatic urethra. Some cases of this entity have been reported in the past as Paget's disease and Bowen's disease . Positivity for PSA
and PAP is the rule. The tumor tends to have a more advanced stage at presentation and a higher short-term survival rate than peripheral duct-acinar carcinomas.\textsuperscript{(15)}

Endometrial-type (endometrioid) adenocarcinoma was originally described as arising from the prostatic utricle (a mullerian remnant thought to represent the male homolog of the female uterus and vagina) but is currently regarded as a variant of large duct prostatic adenocarcinoma. Microscopically, glands and papillae are seen, lined by tall, pseudostratified columnar epithelium. Microscopic studies, immunocytochemical determinations (positivity for PAP and PSA), and the response to orchiectomy indicate that his tumor is truly of prostatic origin\textsuperscript{(15,18)}

2. Primary transitional cell (urothelial) carcinoma of the prostate. The existence of this tumor type is explained by the fact that the outer portion of the prostatic (periurethral) ducts emptying into the urethra are lined by transitional epithelium. This variant comprises less than 2\% of all prostatic carcinomas. The microscopic appearance of this neoplasm is identical to that of the homonymous bladder tumor. The diagnosis can be made in prostatic needle biopsies and in TUR specimens. Before a diagnosis of primary transitional cell carcinoma of prostate is made, the possibility of prostatic extension from a bladder or urethral carcinoma should be excluded\textsuperscript{(16,17,18)}

3. Mixed adenocarcinoma-transitional cell carcinoma, exhibiting a combination of types 1 and 2. Sometimes tumors having any of the appearances listed previously are seen associated with an ordinary prostatic adenocarcinoma or with an independent transitional cell tumor of the bladder. The mode of presentation,
initial stage, and response to hormone therapy for the carcinoma arising from large ducts (with the possible exception of pure transitional cell carcinoma) are similar to those of the conventional prostatic adenocarcinoma. Atypical hyperplasia and carcinoma in situ of periurethral glands, presumably representing the precursors of large duct carcinomas, have been observed.\(^{(19,20)}\)

4. Other microscopic types include:

1- Carcinoma with neuroendocrine features.

2- Mucinous secreting adenocarcinoma, they secrete large amounts of intracellular and extracellular mucin.

3- Signet ring carcinoma, it's highly malignant neoplasm which may grow in solid, acinar or Indian file pattern.

4- Adenosquamous carcinoma, may arise denovo or after radiation.

5- Squamous cell carcinoma, is a rare neoplasm.

6- Adenoid basal cell tumor, resembles adenoid cystic carcinoma of the salivary gland.

7- Basaloid carcinoma.

8- Lymphoepithelioma like carcinoma.

9- Tubulocystic clear cell adenocarcinoma, resembling mullerian-type adenocarcinoma of the female genital tract.

10- Sarcomatoid carcinoma.
**Intraepithelial proliferative lesions:**

Prostatic intraepithelial neoplasia (PIN) is the currently preferred term for a process involving prostatic ducts and acini, which has also been described as intraductal or ductal-acinar dysplasia, it is often multicentric. (~28,29~)

PIN is divided into three grades, depending on the severity of the following alterations: cell crowding and stratification; nuclear enlargement, pleomorphism, and chromatin pattern; and nuclear appearance. These three grades are currently grouped into two categories: low-grade PIN (I,II) and high-grade PIN (III) (~9~)

Several studies have shown a statistical association between high-grade PIN and prostatic carcinoma, in the sense that PIN has been found in 59% to 100% of step-sectioned radical prostatectomy specimens. It has also been shown that in prostates containing both PIN and adenocarcinoma, there is a good degree of concordance in the DNA ploidy pattern of both lesions.

These findings have led to the suggestion that PIN may have a high predictive value as a marker for carcinoma and to the recommendation to follow closely patients in whom PIN is identified in a prostatic biopsy.

**Microscopic differential diagnosis:**

1- Radiation changes.

2- Basal cell hyperplasia.

3- Transitional cell hyperplasia.

4- Squamus metaplasia.
5- Cribriform hyperplasia.

6- Sclerosing adenosis.

7- Florid hyperplasia of mesonephric remnants.

**Grading and staging:**

Several grading systems have been described, of which the Gleason system is the best known. According to the Gleason system, prostate cancers are stratified into five grades on the basis of glandular patterns and degree of differentiation as seen under low magnification.

**Gleason system**

1- Single, separate, uniform glands in closely packed masses with a definite, usually rounded, edge limiting the area of tumor.

2- Single, separate, slightly less uniform glands, loosely packed (separated by small amounts of stroma), with less sharp edge.

3a- Single-separate, much more variable glands, may be closely packed but usually irregularly separated; ragged, poorly defined edge.

3b- Like 3a, but very small glands or tiny cell clusters.

3c- Sharply and smoothly circumscribed rounded masses of papillary or loose cribriform tumor ("papillary intraductal tumor").

4a- Raggedly outlined raggedly infiltrating, fused glandular tumor.
4b- Like 4a, with large pale cells ("hypernephoid")

5a- Sharply circumscribed, rounded masses of almost solid cribriform tumor, usually with central necrosis ("comedocarcinoma").

5b- Ragged masses of anaplastic carcinoma with only enough gland formation or vacuoles to identify it as adenocarcinoma.

The Gleason score is the sum of the grade of the most dominant pattern with the least dominant one and start from 2 to 10 and accordingly divided into 3 grades 2-4 well differentiated, 5-7 moderately differentiated and 8-10 poorly differentiated cancers.

Staging of prostatic cancer is also important in the selection of the appropriate form of therapy. The most common staging system is the TNM system. stage T1 refers to cancer found incidentally either on trans-urethral resection done for BPH symptoms (T1 and T1b depending on the extent and grade) or on needle biopsy, typically preformed for elevated serum PSA levels (stage T1c). stage T2 is organ confined cancer.

Stage T3a and T3b tumors show extraprostatic extension, with and without seminal vesicle invasion, respectively. Stage T4 reflects direct invasion of contiguous organs. Any spread of tumor to the lymph nodes, regardless of extent, is eventually associated with a fatal outcome, such that the staging system merely records the presence or absence of this finding (N0/N1)

**Histochemical and immunohistochemical features:**

Prostatic adenocarcinomas produce acid mucins which stain positive for Alcian blue or colloidal iron, they are also positive for PAP and PSA\(^\text{21,22}\)
They also produce the membrane bound glycoprotein prostate specific membrane antigen and it's expressed with increased frequency with high grade cancer.

Prostatic carcinoma cells are often immunoreactive for androgen and progestron receptors but much less than estrogen and this is related to the Gleason score.\textsuperscript{(23,26)}

Her-2-neu is over expressed in androgen-independent prostatic carcinoma.

Prostatic carcinoma cells are reactive for low molecular weight keratin, they also stain positive for leu7, EMA, carcinoembryonic antigen, B72.3, cathepsin D and PTH-related protein.\textsuperscript{(24,25)}
Chapter 2
Research Methodology:

Type of study:

Retrospective archival study.

Objectives:

Major: to study prostatic cancer in Sudanese patients seen in Soba Teaching Hospital in the period from January 2007 to December 2009.

Minor:

1- To study the most common variants of prostate cancer in Sudanese patients.
2- To study the finding in histological sections.
3- To stratify the patients according to the degree of differentiation.
4- To identify the presence or absence of perinural invasion as a prognostic feature.
5- To specify the relation between Gleason score and perinural invasion, presence of crystalloid secretions, PSA level and PIN.

Research area:

Soba teaching hospital.

Research population:

All patients who underwent prostate biopsies either whole, transurethral or true cut biopsies and their specimens were sent to the lab.

Inclusion criteria:

Patient presented to Soba teaching hospital who are having clinical reports and available slides or blocks.
Exclusion criteria:
Patients with deficient data or missed slides or blocks.

Materials:
1- H&E stained sections prepared from formalin embedded blocks
2- Patients repots and files.
3- Light microscopy of the slides.

Data collection:
Data was collected by filling tables that contain informations about the following.
1- Lab no.
2- Patient age.
3- Histological diagnosis.
4- Gleason score.
5- Presence of perineural invasion.
6- The presence of PIN.
7- The presence of crystalloid secretions.
8- The PSA level.
9- The presence of lower urinary tract symptoms.
10- The PR findings.
11- The specimen type.

Data analysis using SPSS program.
Chapter 3
Results:

Table 1: Age distribution among the study group

<table>
<thead>
<tr>
<th>Age (Yrs)</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>5</td>
<td>6.6</td>
</tr>
<tr>
<td>60-69</td>
<td>26</td>
<td>34.2</td>
</tr>
<tr>
<td>70-79</td>
<td>42</td>
<td>55.3</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>3</td>
<td>3.9</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>100.0</td>
</tr>
</tbody>
</table>
**Table 2: Gleason score distribution among the study group**

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>5</td>
<td>6.6</td>
</tr>
<tr>
<td>5-7</td>
<td>21</td>
<td>27.6</td>
</tr>
<tr>
<td>8-10</td>
<td>44</td>
<td>57.9</td>
</tr>
<tr>
<td>BPH with PIN</td>
<td>6</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>76</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 3: Perineural invasion distribution among the study group

<table>
<thead>
<tr>
<th>Perineural invasion</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>19</td>
<td>25.0</td>
</tr>
<tr>
<td>No</td>
<td>55</td>
<td>72.4</td>
</tr>
<tr>
<td>Small biopsy, unable to detect</td>
<td>2</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>76</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 4: Associated PIN distribution among the study group

<table>
<thead>
<tr>
<th>Associated PIN</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>8</td>
<td>10.5</td>
</tr>
<tr>
<td>No</td>
<td>68</td>
<td>89.5</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 5: Presence of crystalloid secretions distribution among the study group

<table>
<thead>
<tr>
<th>Crystalloid secretions</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>17</td>
<td>22.4</td>
</tr>
<tr>
<td>No</td>
<td>59</td>
<td>77.6</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 6: PSA level distribution among the study group

<table>
<thead>
<tr>
<th>PSA level</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>6.6</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>2.6</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>3.9</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>3.9</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>2.6</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Missing information</td>
<td>59</td>
<td>77.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>76</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 7: Lower urinary tract symptoms distribution among the study group

<table>
<thead>
<tr>
<th>Lower urinary tract symptoms</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>43</td>
<td>56.6</td>
</tr>
<tr>
<td>No</td>
<td>33</td>
<td>43.4</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 8: PR findings distribution among the study group

<table>
<thead>
<tr>
<th>PR findings</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firm</td>
<td>17</td>
<td>22.4</td>
</tr>
<tr>
<td>Hard</td>
<td>14</td>
<td>18.4</td>
</tr>
<tr>
<td>Not mentioned</td>
<td>45</td>
<td>59.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>76</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Fig. 1: Gleason score versus associated PIN

P value = .051

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2--4</td>
<td>Yes: 50%</td>
</tr>
<tr>
<td></td>
<td>No: 5.9%</td>
</tr>
<tr>
<td>5--7</td>
<td>Yes: 0%</td>
</tr>
<tr>
<td></td>
<td>No: 30.9%</td>
</tr>
<tr>
<td>8--10</td>
<td>Yes: 50%</td>
</tr>
<tr>
<td></td>
<td>No: 63.7%</td>
</tr>
</tbody>
</table>

Legend:
- Yes
- No
Figure 2: Gleason score versus age
P value .053
Figure 3: Gleason score versus PSA level

P value = .051
Figure 4: Gleason score versus invasion

P value .291

Percentage

Perinuclear invasion

2--4
5--7
8--10

Yes

No

0
5 (9.8%)
5 (26.3%)
16 (31.4%)
14 (73.7%)
3 (56.8%)
Figure 5: Gleason score versus presence of crystalloid secretions
P value = .000
Figure (6a)  High grade prostatic adenocarcinoma Gleason grade (4+5) in a 60 years old patient & E Stain × 10
Figure (6b) high grade prostatic adenocarcinoma with perineural invasion. H&E Stain ×40
Figure (7) poorly differentiated prostatic adenocarcinoma Gleason grade (5+5) H&E stain × 10
Figure (8) low grade prostatic adenocarcinoma Gleason grade (1+4). H&E ×10
Figure (9) Prostatic adenocarcinoma Gleason grade (5+2) H&E Stain × 20
Figure (10) High grade prostatic adenocarcinoma Gleason grade (5+4) with perineural invasion H&E stain × 20
Figure (11a) Low grade prostatic adenocarcinoma Gleason grade (2+3) showing intraluminal secretions H&E Stain × 20
Figure (11b) PAS stain for intraluminal secretions in a low grade prostatic adenocarcinoma
Gleason grade (2+3) × 20
This study was conducted on cases seen in Soba University Teaching hospital in the period from 2007 to 2009. Of the 412 prostate cases presented to the histopathology department 36 cases were excluded because of missed slides or blokes. Of the remaining 376 cases, 76 cases where found to be prostate cancer.

The cases were studied in relation to age, Gleason score, perineural invasion, presence of crystalloid secretions, PSA level, the presence of lower urinary tract symptoms and the PR examination findings.

Table 1 shows the age distribution of the study group which was divided into four categories, 5 cases were found in the age 50-59 which represent 6.6%, 26 cases belong to age group of 60-69 which represent 34.2%, 42 cases were in those aging 70-79 and represent 55.3%, and 3 cases were found in patients aging more than 80 years and this represent 3.9% of the cases.

As we can see in table 2 of the 76 studied cases 5 were of low grade which account for 6.6%, 21 cases proved to be of intermediate grade and represent 27.6%, and 44 cases diagnosed as high grade forming 57.9% of the cases.

Of the studied cases 19 were associated with perineural invasion forming 25.7% of the cases as we can see in table 3. Of the 76 cases studied 8 were found to have accompanying PIN which represents 10.5% of the cases of these 5 cases have high grade PIN and 3 have Low grade PIN as presented in table 4.

Table 5 shows that 17 cases of this collection show crystalloid secretions within the glands giving 22.4% of the cases.

The information about the PSA level was incomplete because most of the patients files do not contain such information but in 17 cases the PSA level where above 4
micro gram/ml and of these 9 cases have a PSA level above 10micro gram/ml as shown in table 6.

Of the total 76 cases 43 have experienced lower urinary tract symptoms representing 56.6% in the remaining 33 cases the information was missing in the files as presented in table 7.

Table 8 presenting the PR findings of the study group which were mentioned only in the files of 31 cases, in the remaining the information was missed. Of these 17 cases have firm prostates in PR examinations and 14 have hard prostates.

5 cases of benign nodular hyperplasia have associated PIN 2 of them were high grad PIN and 3 of them are of low grade. One case of high grade prostate cancer was associated with high grade PIN, and 2 cases of low grade prostatic cancer were associated with high grade PIN. the Chi-square of this test was .051 which is significant.(see figure 1)

Of the five cases representing low grade cancer three cases were in the age group of 60-69 years one case in each age group of 70-79 years and more than 80 years while no cases found in the age group of 50-59 years. The 21 intermediate grade cases distributed as follows, three in the age group of 50-59years, six cases in the patients of 60-69years, twelve cases found in the age group of 70-79 years and no cases in the older age group. In the 44 cases that were of high grade one case found in the age group 50-59 years, 14 cases belong to 60-69 years old patients, 28 cases among age group of 70-79 years and one case in the older age, the chi-square test for this correlation was .05 which is considered statistically significant.(see figure 2).
Most of the elevations in the PSA level were associated with high grade prostatic carcinoma, followed by intermediate grade and low grade respectively and the chi-square test for this correlation was 0.051 which is statically significant.(see figure 3).

Of the 19 cases associated with perineural invasion 14 cases were of high grade prostatic cancer, 5 cases of intermediate grade and no cases of low grade cancer was associated with perineural invasion the chi-square test for this correlation was 0.291 which is statistically insignificant.(see figure 4).

Of the 17 cases having crystalloid secretions in the glands; 11 cases were of intermediate grade, 4 of high grade and 2 of low grade cancer. And the crystalloid secretions were associated mainly with cases containing Gleason grade 2 cancer. The chi-square test for this correlation was statistically significant.(see figure 5)
Chapter 4
Conclusion and recommendations:

From the results we had we concluded that prostatic cancer in Sudan is a disease of old age which goes with the general trend in the world, but it differs in the fact that more than 50% of the cases we found to be of high grade where as in the world most of the cases are well differentiated. This difference may be a true difference in the type of cancer and might be resulting from the fact that Sudanese patient seek clinical advice late in the disease.\textsuperscript{(33)}

Also in our study most of the affected patients were above 70 years of age and these have more poorly differentiated tumors, which goes well with the world literature.\textsuperscript{(34)}

In our study only 10% of the cases contained associated PIN lesion where as the literature mentioned 80% the cases contain a precursor lesion, this difference might result because of the cases we studied were true cut biopsy and the amount of the tissue screened was small.\textsuperscript{(26,29)}

The information about PSA level were incomplete but most of the elevations were associated with high grade cancer which is the case in other countries.\textsuperscript{(22)}

The presence of crystalloid secretions in the glands which is mostly associated with low grade cancer detected in 22% of the cases which is slightly lower than the 27% mentioned in the literature.\textsuperscript{(11,12)}

While conducting this study we were trying to find out some information about the risk factors and the prognosis in Sudanese patients but the clinical informations were missing although the urology department at Soba teaching hospital has designed a good card which cover all the aspects of clinical presentation, lab results, radiology
findings and follow up aspects but the cards were not filled properly in most of the cases.

The study of prostate cancer in Sudan needs more effort in all aspects specially in the fields of risk factors and the response to treatment. Also we need to start a good screening program because most of the cases present with high grade cancer.

In this study we did not include the clinical extent of the disease due to incomplete data, so further studies regarding the extent of the disease at presentation are needed with use of radiological and intra operative data.
References:


30-prostate cancer in Sudan . pcafrica.word press.com/site-map/sudan/overview.


