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Incidence of Carcinoma of the Prostate in Patients with Normal Prostatic Specific Antigen Following Prostatectomy

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Objective: To detect patients with prostate cancer, in prostatectomy specimens, with normal preoperative PSA levels. To try to suggest a base line level of PSA above which prostatectomy should not be performed unless having a histological tissue diagnosis.

Materials and methods: This is descriptive, prospective cross sectional, hospital based study, conducted at Soba University Hospital, Omdurman Military Hospital, IbnSina specialized Hospital in the period from September 2012 to August 2013All patients above 40 years of age undergoing prostectomy with normal PSA levels in the above mentioned hospitals were enrolled in this study, their surgical specimens was sent for histology.

Results: The PSA level was below 4ng/ml in all cases, with a mean of 1.85ng/dl (total), and 0.36ng/dl free PSA. The histology of the prostatectomy specimens showed adenocarcinoma in 14 Pts (13.1%) and BPH in 93 pts (86.7%).

Conclusion: There was a detection rate of (13.1%) among patients with PSA below ng/ml, with high grade Gleason scores. Suspicious DRE in low PSA patients enhances the cancer detection rate.

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I. Introduction

The fourth most common male malignant neoplasm worldwide is prostatic cancer, 18% of American men were affected with causing death in 3% in2005. (1)In Japan death from prostatic cancer was one- fifth to one-half the rate in United States and Europe in the 1990s. (2) It has gained increased attention from Sudanese urologists owing to its rapidly increasing incidence as recent reports have indicated.(3)

Prostatic cancers vary widely across the world, with the south and west Asia detecting less frequently than in Europe, and especially in United states. Prostatic cancer tend to develop in men over the age of fifty, and it's the second leading cause of cancer related death in men in the United States. (4) However many men with prostatic cancer never have symptoms, undergo no therapy, and eventually die of other unrelated causes .Many factors including genetic diets, have been implicated in the development of prostatic cancer .The presence of the prostatic cancer may be indicated by symptoms, physical examination, prostatic specific antigen(PSA) and biopsy. Prostatic-specific antigen increases the cancer detection but does not decrease mortality. (5) The American cancer Society position regarding early detection is research has not yet proven that the potential benefits of testing outweigh the harms of testing and treatment. The American cancer society believes that men should not be tested without learning about we know and don't know about the risks and possible benefit of testing and treatment Starting at age 50, if African American or brother or father suffered from condition before age of 65 he would know pros and cons of testing so you can decide if testing is the choice for you.(6) The only test that can fully confirm the diagnosis of prostatic cancer is biopsy, the removal of small pieces of the prostate for microscopic examination.There are also several other tests that can be used together for more information about prostate and urinary tract. Cystoscopy shows the urinary tracts from the inside the bladder, using a thin flexible camera tube inserted down the urethra. Transurethral ultrasanography creates a picture of the prostate using sound waves from the probe in the rectum. Prostatic specific antigen (PSA) testing, PSA is Kallikrein111seminin, semenorgelase, gama-seminoprotein and P-30 antigen is a 34KD glycoprotein. While PSA testing may help 1 in 1000 avoid death due to prostatic cancer, 4 to 5 in 1000 would die from prostatic cancer after 10 years even with screening.

PSA levels between 4 and 10 ng\ml are considered to be suspicious and consideration should be given to confirming the abnormal PSA with repeat test.If indicated prostatic biopsy is performed to obtain tissue sample for histopathology analysis. In the United Kingdom the National Health Service (2005) doesn't mandate, nor advice for PSA tests, but allows patients to decide based on their advice (7) PAS is normally present in the blood at very low levels. The reference rate of less than 4ng\ml for the first commercial PAS test, the Hybritech tandem-PSA test released in

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February 1986, was based on study that found 99% of 472 apparently healthy men had a total PSA level below 4ng\ml, the upper limit of normal is much less than 4ng\ml (6) Increase level of PSA may suggest the presence of prostatic cancer .However prostatic cancer can be present in the complete absence of an elevated PSA level, in which case the result would be false negative.(8)

Large series have shown that 21-43% cancers will occur in patients with PSA in the normal range (0-4 ng/ml)(9) in this study none of the cancer patients has abnormal PSA. The choice of a PSA threshold or cut point above which one would recommend further evaluation to rule out prostate cancer (prostate biopsy) is controversial (Carter, 2000; Catalona et al, 2000b, 2000c.(10) Although the PSA threshold of 4 ng/mL has been most commonly used, the PSA threshold that most efficiently balances the dual goal of reducing cancer mortality and reducing unnecessary testing (PSA measurements and biopsies) is not known. Many studies have made an effort to evaluate other thresholds to maximize the positive biopsy rate of PSA-based screening.

In the Sudan there was study titled Prostatic Specific Antigen versus Digital rectal examination as screening for prostatic cancer in Sudanese patients. A prospective study carried out in Elgezira Hospital for Renal Diseases and Surgery in the period June 2003-May 2005. An elevated PSA and DRE pointedto the diagnosis of prostate cancer in 100% and 88.9% respectively. The rate of prostate cancer detection showed to be 26% for combination of the positive DRE and PSA > 4 ng/ml, while it was only 4.1% in BPH patients. (11)

In a study carried out in the Urology Clinic of Soba University Hospital from August 2008 and January 2010 titled significance of serum total prostatic antigen and DRE in the diagnosis of prostatic cancer. The outcome was that combining DRE and tPSA test increase the sensitivity, specificity of prostatic cancer detection. (12)Prostate cancer is diagnosed in about 1% of men aged 50, rises abruptly in the sixth and seventh decade of life, the highest incidence being recorded in the seventh and eighth decade of life NAZ KR.(13)

II. Results

A total of 107 patients were included in the study, their ages ranged between 50-95 years, with a mean age of 67 years (table1).

The PSA level was below 4ng/ml in all cases, with a mean of 1.85ng/dl (total), and 0.36ng/dl free PSA. FPSA/tPSA ratio was is 1.4-50% with a mean of 18.4%, PSA density was o.02-2.2 with a mean of o.27 in 107 patients. From the 14 pts with prostate cancer 5 pts(35.7%) presented with acute urine retention,7 pts(50%) had haematuria and irritative symptoms of (frequency, urgency, dysuria, nocturia) in(12 pts(85%),13 pts(92%),11 pts(78.5%), 6 pts (42.8%) respectively. Obstructive symptoms as weak stream and dribbling were found in 7pts(50%),9(64.2%) respectively. 4pts (28.5%) complained of back pain, 2 pts (14.2%) were smokers,consuming more than 10 cigarette per day. Positive family history of prostatic cancer was found in 2pts (14.2%). The histology of the prostatectomy specimens showed adenocarcinoma in 14 Pts (13.1%) and BPH in 93 pts (86.7%) chart (2). The mean age of the patients with prostatic cancer was 72.7 years, ranging from (57-87) years table (2), with PSA ranging from (0.02 -3.4ng/ml) with a mean of 1.7ng/ml, the free PSA was between 0.00-0.8ng/ml with a mean of 0.33ng/ml. The Gleason score was ranged from 3-7 with a mean of 4.6, 3pts(21.4%) had a score of 7, in 4 pts(28.5%) a Gleason score of 5 was found and 5 pts(35.7%) had a Gleason score of 5 table (21). In this study when correlating tPSA to the Gleason score we found that pts who had cancer with tPSA level ranging from 0.02-1.02/ml had Gleason score of <4,tPSA ranging from 1.02-2.05ng/ml had Gleason score of 4-6 and Gleason score of more than 6 the tPSA was more than 2.05.ng/ml.

Table 1 : Age distribution in 107 pts

Age	40-50 yrs	51-60yrs	61-70ys	71-80yrs	>80	
	1	29	38	27	12	Total
	0.93%	17.1%	36.5%	25.2%	11.2%	107

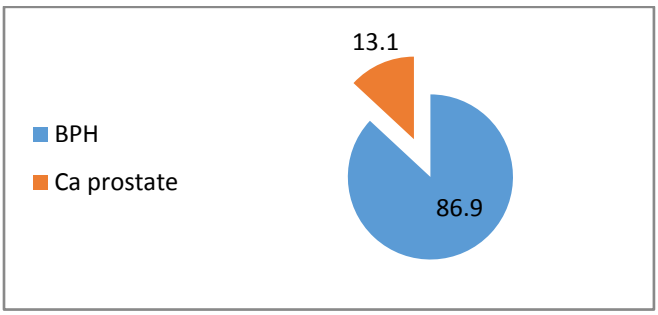
Table 2 : Age distribution in 14 patients

Age	Number	Percentage	Total
50-60 year	1	7.1%	14
61-70 year	5	35.7%	
71-80 year	6	42.4%	100%
81-90 year	2		

*Table (21).*The Gleason score in 14 pts and their tPSA ranges

Gleason score	>4	4-6	>6	Total 14 100%
	5	5	4	
	35.7%	35.7%	42.8%	
tPSA ranges	0.02-1.02ng/ml	1.03-2.05ng/ml	>2.05ng/ml	

Chart no (2). The frequency of Ca prostate in 107 pts



III. Discussion

In this study group the patients ages were between 50 and 95 years of age, the commonest age for cancer was between 70-79 years, their tPSA range was between 0.3- 3.2, this is in contrast to a study conducted in Austria that showed that prostate cancer with a PSA value of 2 - 3.9 ng/ml occurs in younger patients.(13) It has been noticed that African males have in general higher tPSA values than European men.(14) In African men the cut off points for ages 50-59 years were (6.5 ng/ml), 60-69 years was (11.3ng/ml), 70-90 years was (12.5 ng/ml) .(15) A Sudanese study showed that age specific reference ranges in Sudanese men were even lower, cut off points for ages 50-59 years are (0 – 3.02 ng/ml), 60-69 years (0 – 3.8 ng/ml), 70-90 years (0 – 8.7 ng/ml). (16)

Literature reported that most of prostate cancer patients present with no symptoms initially because of the peripheral location of the tumour in the prostate gland. (17) The lower urinary tract symptoms present after invasion of the urethra and the prostate. (18) In this study the most common presenting symptoms were urgency, frequency and dysuria (80 - 92%) of patients; these symptoms are collectively known as LUTS. Most of our patients presented late after the establishment of their symptoms and were included in the study with symptoms and signs that warranted surgical intervention. In a study by Willam Hamilton, Deborah J Slap, they reported that most cases presented with urinary symptoms that uncovered their disease; these symptoms were urinary retention, frequency, hesitancy and nocturia which most probably represent enlargement of the prostate gland.(17)

Haematuria was present in 50% of patients in this study; a Belgian study (19) reported haematuria as the presenting symptom in 10.3% of all urologic cancer and recognized it as a risk for urologic cancer. Hamilton and Deborah reported haematuria as having a PPV of 1% in prostate cancer patients which accords with the figure in the Belgian study, as bladder and renal cancer will account for the majority of malignant causes of haematuria. (17)

Urine retention in this study was present in 35% of patients, in the same study by Hamilton, retention had the strongest association with prostate cancer.(20) They concluded that cancer should be clearly considered as a possibility when the PPV for retention is 3.1%. They argued that the risk for prostatic cancer is higher in symptomatic older men, and the results supported diagnostic testing in these circumstances, since some cases reported symptoms over 6 months before diagnosis. They concluded that diagnostic testing by such time period may not improve mortality but should at least allow for early remission of symptoms.(17)

In our study group regarding the risk factors for prostate cancer, positive family history was found in three patients (14.2%) of whom two had prostate cancer. The international reference studies show that positive family history of prostate cancer in 1st degree relatives (brothers) will double the risk of developing the disease. (21) Only nine patients were smokers consuming more than 10 cigarettes per day, the low exposure to risk factors in our study group may explain the relatively low incidence (13.1%) of prostate cancer among our patients compared to (15%) in international references.

Currently the suggested PSA cutoff to biopsy a male patient for screening differs between 2.6-4.0 ng/ml (22). In this study the results showed that half of the patients with prostate cancer had a PSA of (1.2 – 2.1 ng/ml), which is way below the cut-off point suggested. The group of patients in our study within the reference range of tPSA (<4 - >2.1) represented 14% of the study group. This suggests that the cut off point for screening should be lowered for our Sudanese patients. Most of

the studies are conducted in European patients with different environmental and genetic risk factors which might have an influence on the total PSA levels.

In this study DRE in patients with prostate cancer showed a soft gland in (57.1%), this shows the low rate of cancer detection on DRE in patients with low PSA. In a study by Fritz H.Schrode, ArotoBoeka et al, they concluded that use of DRE in detection of prostate cancer among patients with PSA 0-2.9 has a sensitivity of (4%-11%) while DRE detection rate was (83%) in patients with PSA 3 – 9ng/ml. (23)In a randomized study by Thomposon et al, DRE in patients with PSA less or equal to 3ng/ml with a normal DRE, after a 7 year follow up period the prostate cancer was found in 15% of pts. They concluded that men with low PSA level values less than 3ng/ml have a 15% prostate cancer detection rate with or without use of DRE.

In two Sudanese studies by El Imam et al.,Abdelkarim A. Abdrabo ,Adil I. Fadlallalmad M. Fadl-Elmula, the found that the combined use of DRE and PSA increases the cancer detection rate more than PSA or DRE alone. The rate of prostate cancer detection showed to be (25.7%) for PSA > 4ng/ml, (13.31%) for abnormal (positive) finding of DRE, and (27.8%) for combination of the positive DRE and PSA > 4 ng/ml. The rate of BPH detection showed to be (68.6%) for PSA > 4ng/ml, (28.6%) for positive finding of DRE, and (4.1%) for combination of the positive DRE and PSA >4 ng/ml.(25-25)

In studies conducted by Jewett in cancer screen, Jewett found that approximately 50% of palpable prostate nodules were diagnosed as prostate cancers on prostate biopsy.(26) However, DRE findings are only moderately reproducible, even amongst experienced urologists.(27) Further, DRE tended to diagnose prostatic cancer when they are pathologically advanced and therefore less likely to be curable by radical prostatectomy. (27) Cattolonaet al examined prostate cancer detection at low PSA levels by DRE; clinically aggressive tumours on omission of DRE at PSA levels less than 3ng/ml would have detected (14%) of Prostate cancer. (28) In contrast, Okotie OT, Roehl KA, Han they report that is that screening without DRE at low PSA levels (PSA<3.0 ng/ml) did not lead to the detection of significantly more (poorly differentiated) prostate cancer for 4 years follow up later compared to screening with the use of DRE in the ERSPC.(29)

The detection rate of cancer in the 107 postsurgical specimens was in 14 patients(13.1%) (chart 3), four of these patients (28.5 %) had a high Gleason scores of 7 and their tPSA ranged between 2.05-3.4 ng/ml, while Gleason score of < 4 and between 4 - 6 was(35.7 %) for each score.The tPSA for Gleason scores <4 ranged between 0.02 – 1.02 ng/ml, while Gleason scores between 4 – 6 their tPSAranged between 1.03 – 2.05 ng/ml (table 19). This is almost similar to the study from the Division of Urology, Department of Surgery, University of Texas Health Science Center at San Antonio about prevalence of prostate cancer among men with a low prostate-specific antigen, prostate cancer was diagnosed in 449 (15.2 %); 67 of these 449 cancer patients (14.9 %) had a Gleason score of 7 or higher. The prevalence of prostate cancer was (6.6%) among men with a PSA level of up to 0.5 ng/ml, (10.1%) among those with values of 0.6 to 1.0 ng/ml (17.0 %) among those with values of 1.1 to 2.0 n/ml, (23.9 %) among those with values of 2.1 to 3.0 ng/ml, and (26.9 %) among those with values of 3.1 to 4.0 ng/ml. (30)

In contrast to this study, and the American study, had low Gleason scores which may be due to early detection of cancers achieved by close follow up of asymptomatic patients in their study, which lead to early detection of low grade tumors' before the development of advanced high grade cancers.

IV. Conclusion

In this study we found that a significant number of patients with high grade Gleason score prostate cancer can be detected among patients with features of benign prostatic hyperplasia and a PSA less than 4 ng/ml. We suggest that the cut off point for tPSA used for screening Sudanese males for prostate cancer to be lowered to 0.2 – 2.1 ng/mland the f/t PSA of 11 – 20 %, instead of the current PSA age-specific reference range used.

AtPSA< 4 ng/ml and a negative DRE doesn't exclude the presence of prostate cancer; risk factors to be considered before excluding the possibility of malignant disease are in age groups between 70 – 79 years, significant lower urinary tract symptoms, haematuria, urine retention and positive family history. These patients should be considered for a prostatic biopsy; if negative a second biopsy preferably a TRUS biopsy should be taken to confirm absence of the disease and close follow up is recommended in this group of patients.

The combination of digital rectal examination and PSA increases the cancer detection rate more than PSA alone.

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