

Prostatic diseases under focus in a university hospital in Eastern Saudi Arabia

A 15-year experience

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ABSTRACT

الأهداف: معرفة مختلف أمراض البروستاتا التي تشخص في الخزعات الجراحية للبروستاتا من الرجال السعوديين في مختلف الفئات العمرية، واختبار ما إذا كان معدل السرطانات قد تغير على مدى السنوات الـ 15 الماضية، وتقييم العلاقة بين الالتهاب المزمن (CI) مع كل من تضخم البروستاتا الحميد (BPH) والسرطان (PCa)، والتحقق من النتائج النسيجية للحالات التي عرضت مع احتباس البول الحاد (AUR).

الطريقة: هذه دراسة استيعادية تشمل جميع خزعات البروستاتا المتوفرة في ملفات مختبر علم الأمراض الجراحي في مستشفى الملك فهد الجامعي بالخبر، المملكة العربية السعودية خلال 15 عاماً (1999-2013) للرجال السعوديين. تمت مراجعة العمر، سبب الخزعة والتشخيص النهائي، وجرى استعراض الشرائح.

النتائج: شملت الدراسة 360 حالة، متوسط عمر المرضى بلغ 65 عاماً. ألف BPH الغالبية العظمى (64.7%)، في حين شكلت السرطانات 89 حالة، 13.5% منها كانت عرضية. تم تشخيص معظم الحالات سواءاً حميدة BPH أو خبيثة في العقد السابع. لم يظهر سرطان البروستاتا تغيراً متواتراً من ارتفاع أو سقوط في معدل التشخيص على مر الزمن. الالتهاب المزمن يتعلق بالتضخم الحميد BPH أكثر من الخبيث. أظهر فقط CI علاقة ذات دلالة إحصائية مع AUR.

الخلاصة: يظهر سرطان البروستاتا معدل مستقر مع مرور الوقت. في حين CI هو قاسم مشترك لكلا BPH وPCa، إلا أنه يرتبط أكثر مع BPH. بين جميع النتائج النسيجية، فقط CI له علاقة إحصائية وثيقة مع AUR.

Objectives: To explore the spectrum of pathologies diagnosed in prostatic biopsies of Saudi men, and test whether the frequency of diagnosing the malignant fraction has been changed over the last 15 years, and assess the association between chronic inflammation

(CI) with both benign prostatic hyperplasia (BPH) and cancer (PCa), and investigate the histological findings of cases presented with acute urinary retention (AUR) clinically.

Methods: This is a retrospective cohort study including all prostatic biopsies accessed in the files in the Surgical Pathology Laboratory of King Fahd University Hospital, Alkhobar, Kingdom of Saudi Arabia over 15 years (1999-2013) for Saudi men. Age, procedure indication, and final diagnoses were retrieved and slides were reviewed.

Results: There were 360 cases included in this study with a median age of 65 year-old. The BPH comprised the most (64.7%), while PCa accounted for 89 cases, 13.5% of which were incidental. Most cases of both BPH and PCa were diagnosed in the seventh decade. The frequency of diagnosing PCa did not show a solid rise or fall over time. Chronic inflammation is more related to BPH than to PCa. Only CI showed a significant statistical association with AUR.

Conclusion: Prostatic diseases show a stable trend over time. While CI is a common dominator for both BPH and PCa, it is associated more with BPH. Among all histological findings, only CI is related to the clinical presentation of AUR.

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The spectrum of prostatic diseases is a common health concern all over the world. While benign prostatic hyperplasia (BPH) is the most frequent urologic diagnosis in elderly males worldwide, affecting approximately one third of males in their 60's,^{1,2} prostatic carcinoma (PCa) is the second most common cause of cancer-related death in males after lung cancer.³ The disease represents clear racial and national differences, with its highest incidence in blacks in the West, and lowest in Asian males.⁴ Recently, there has been a rising trend for PCa in populations that are thought to be of low risk.⁵ Furthermore, the relationship between chronic inflammation (CI) and presence and progression of both BPH and PCa is controversial.⁶⁻⁹ On the other hand, acute urinary retention (AUR), which is the most frequent emergency in urology, is mostly developed in a background of BPH.¹⁰ Whether other pathologies, such as CI and infarction increase the risk of this complication is debated.¹¹⁻¹³ In this work, we retrospectively reviewed the whole spectrum of prostatic pathologies diagnosed in our center during the last 15 years, including prostatic intraepithelial neoplasia (PIN) and atypical small acinar proliferation (ASAP), and study various diseases in relation to age of diagnosis, explore the change in trend of diagnosing PCa over a period witness an increase in screening and gradual westernization of lifestyle, test the relationship between CI and both BPH and PCa, and also, we investigate the role of different biopsy findings in relation to the clinical presentation with AUR.

Methods. This is a retrospective laboratory based study. After institutional review board approval, all prostatic biopsies routinely submitted and archived as a part of diagnostic histopathology service for Saudi citizens in the Surgical Pathology Laboratory of King Fahd Hospital of the University, Alkhobar, Kingdom of Saudi Arabia from January 1999 to December 2013 were included. The types of biopsies were trans-rectal ultrasound guided (TRUS), trans-urethral resection of the prostate (TURP), and resection. Patient's age, indications for the procedure, and final diagnoses were retrieved from pathology reports. Patients with more than one specimen were counted only once, even if not excised at the same time to avoid duplication. If different procedures were carried out, TRUS were the one counted due to the higher expected yield. Slides

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for selected cases were reviewed. Different pathological diagnoses were stratified according to the year of procedure, as well as age clustered in 8 groups starting at age of 30 years, each is 10-year interval. Chronic inflammation (defined by the presence of localized aggregates of mononuclear inflammatory cells including lymphocytes, plasma cells and histiocytes) was tested for possible association with both benign hyperplasia and cancer categories. Also, histological findings were evaluated for correlation with the clinical presentation with AUR.¹¹⁻¹³

All data were tabulated and analyzed using Microsoft Excel 2010 and GraphPad Prism 6 software 2014. Results were considered to be significant if $p < 0.05$.

Results. A total of 360 out of 767 cases met the inclusion criteria. The patients' age range between 32 and 121 (median - 65 years). The breakdown of biopsy types is shown in Table 1. The indication for TRUS biopsy was prostatic specific antigen (PSA) elevated above 4 ng/ml in 97 cases (45.5%), abnormal rectal examination in 74 (34.7%), and both reasons in 39 (18.3%), and missing in 3 cases. Among other findings, the PCa were confirmed in 77 cases accounting for 36.2% out of TRUS biopsies. Metastatic B cell lymphoma was identified in one patient, a 59-year-old man with known primary nodal lymphoma. Urothelial carcinoma extending from the urinary bladder was seen in a single case, a 55 year-old male who also has concurrent prostatic carcinoma. For specimens removed with clinical impression of benign disease including TURP and simple prostatectomy, PCa was seen in 12 cases accounting for 8.2% of these cases, and 13.5% of the total number of PCa's. The various diagnoses of prostatic biopsies irrespective of its type are listed in Table 2 with corresponding age group distribution. The table demonstrates the high frequency of cases in the age of 60's, followed by 70's, and 50's, with the highest proportion of PCa in those subjects older than 100, followed by men in their 80's, while the absolute number of PCa cases is predominantly seen in the 60's. Benign prostatic hyperplasia is the most common diagnosis in all age groups apart from men younger than 40, where uncommon pathologies usually attribute to their symptoms. An element of CI, whether pure or mixed with acute inflammation (AI) was seen in 137 out of 233 BPH cases (58.8%), while only 10 out of 89 PCa's were positive for CI. Thus, in our series, CI is significantly more associated with BPH rather than with PCa ($p < 0.0001$). A total of 24 out of 123 TURP cases presented with AUR. Histologic analysis of these groups showed pure BPH in 4, BPH with CI in 16, GI in one, and malignancy were incidentally seen in the

remaining 3 cases. Hence, only CI showed significant statistical association with the presentation of AUR in our subjects. Over the 15 year-study period, the proportion of malignant cases were always maintained between 17.5 and 33.3% (mean 25%) **Figure 1**.

Discussion. Prostatic carcinoma is the most common cancer diagnosed in men today in the West,¹⁴ and BPH is the most common urologic diagnosis worldwide, especially in older men.⁹ In an effort to explore the prostatic diseases in Saudi population, this study was conducted in the Eastern Province, which is known to have the highest prevalence of PCa in the country^{15,16} over a period witnessed increment in screening and Westernization of lifestyle. However, the hypothesis of potential increase in the malignant component overtime due to the aforementioned reasons was not supported by our results. (**Figure 1**). This is in contradiction to the situation in both Far East Asia⁵ and Africa,¹⁷ both show a solid increment trend. The local literature data in this regard showed a steady increase¹⁶ and decrease¹⁸ in different studies. A collaborative multicentric study might clear this ambiguity. If it turned that there is real resistance to PCa increment, the next step would be to investigate the reason behind it, such as possibly protective genetic factors. In this

study, most of the cases that turned out to be PCa were detected in patients in their 60's, the same age group as BPH. This finding is similar to the trend worldwide.¹⁹⁻²²

The frequency of obtaining PCa in TRUS biopsies was higher (36.2%) than previously reported in the Western province of Saudi Arabia by Tayib et al²³ (28.8%), but still lower than the one published in Nigeria (43.2%).¹⁹ On the other hand, the incidence of clinical T1, or incidental PCa diagnosed by TURP/ simple resection for clinically benign disease remained very similar (13.5%) to the one stated by Mosli et al (15%).²¹ Apart from a few cases younger than 40, BPH has the lead, accounting for 64.7% of all cases. This figure is very close to the one reported by Mosli et al²¹ in Jeddah (63.6%). Chronic inflammation was a common dominator in both PCa and BPH. Nevertheless, it is much more frequent with the latter. Our results is in

Table 1 - Type of prostatic specimens and respective age distribution in 360 Saudi males included in a study in Eastern Saudi Arabia.

Type of biopsy	n (%)	Mean age, years	Age range, years
TRUS	213 (59.2)	65	32 - 121
TURP	123 (34.1)	66	32 - 102
Simple excision	24 (6.7)	65	51 - 80

TRUS- trans-rectal ultrasound guided needle biopsy,
TURP- trans-urethral resection of prostate

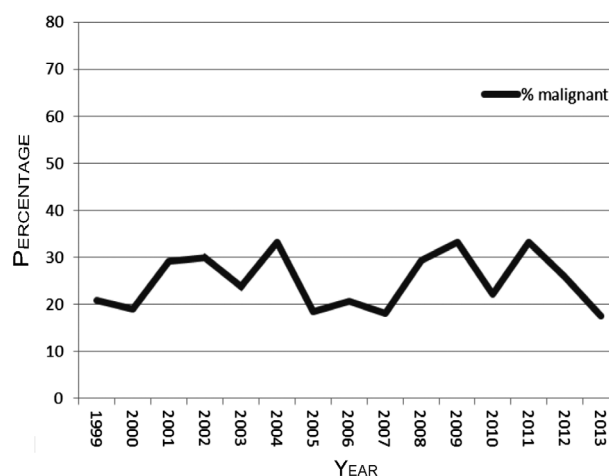


Figure 1 - Non-linear trend of prostatic carcinoma over a 15-year study period of prostatic biopsies diagnosed in Eastern Saudi Arabia.

Table 2 - Pathological findings and corresponding age group, excluding 7 inadequate biopsies included in a study in Eastern Saudi Arabia.

Age group, year	n (%)	PCa			AI	CI	GI	Infarction	PIN	ASAP	Met
		n (%)	BPH	n (%)							
30-39	3 (0.8)	1 (33.0)	0 (0.0)	0	0	1	1	0	0	0	
40-49	9 (2.5)	3 (33.0)	5 (55.6)	1	0	0	0	0	0	0	
50-59	81 (22.9)	13 (16.0)	55 (67.9)	0	2	2	5	1	2	2*	
60-69	139 (39.4)	39 (28.0)	93 (66.9)	0	0	0	3	1	3	0	
70-79	91 (25.8)	22 (24.0)	63 (69.0)	0	0	1	1	2	2	0	
80-89	25 (7.1)	9 (36.0)	14 (56.0)	0	0	0	2	0	0	0	
90-99	3 (0.8)	1 (33.0)	2 (66.7)	0	0	0	0	0	0	0	
≥100	2 (0.6)	1 (50.0)	1 (50.0)	0	0	0	0	0	0	0	

PCa - prostatic carcinoma, BPH - benign prostatic hyperplasia, PIN - prostatic intraepithelial neoplasia, ASAP - atypical small acinar proliferation, Met- metastasis, AI - acute inflammation, CI - chronic inflammation, GI - granulomatous inflammation. *2 cases of metastasis including one with concurrent primary prostatic carcinoma

agreement with one reported by Delongchamps et al⁷ after they evaluated this association in 167 autopsied prostates. On the contrary, a previous study⁶ carried out in the west of the Kingdom revealed the opposite outcome. Further studies on a larger scale is needed in this regard to reach a solid conclusion. The etiological role of finding CI in prostatic biopsy harboring PCa or BPH is yet to be established, as targeted therapy with anti-inflammatory agents has not lowered the incidence, or the progress rate of either disease.⁹

Less frequently, inflammation was the only pathological finding observed in the biopsy. Granulomatous inflammation (GI) was the main type. The presence of a granuloma in the prostate can be seen as an immune reaction to secretions released from obstructed ducts, or iatrogenic caused by TURP/TRUS procedures, or Bacillus Calmette-Guérin (BCG)-therapy, or due to certain infections.²⁴ The pitfall with GI is that the accompanying destruction of the prostatic acini can be mistaken as high grade PCa by a non-expert pathologist.²⁵ Prostatic infarcts were seen in 12 cases (3% of the total), 5 of them are in the age of 50's. This is younger than the mean age of 71 reported by Milord et al.²⁶ Infarction of the prostate is usually ischemic, and caused by either mechanical trauma such catheterization, or resulting after inflammation whether cystitis, or prostatitis. Histologically, it can be worrisome, especially if the biopsies were small, and showed extensive squamous metaplasia. However in contradictory with malignancy, the squamous epithelium is devoid of anaplasia, and confined to the vicinity of the necrotic focus. The diagnosis of ASAP was seen in 1.9% of our biopsies. Although ASAP is not a biological entity by itself, this diagnosis is made up in approximately 5%²⁴ of prostatic biopsies in cases where there is a focus composed of 2-3 small glands suspicious of cancer but does not fulfill the criteria to be labeled as such. The routine recommendation of having this diagnosis is to repeat biopsy in order to rule out missed cancer. In our series, however, none of the 7 cases showed PCa in the follow-up biopsy. On the other hand, high-grade intra-epithelial neoplasia (PIN) is a well-known pre-malignant condition defined by the growth of neoplastic cells within the pre-existing benign glands. This is purely histologic diagnosis, as PIN does not form a mass, or cause clinical symptoms. In our series, PIN was seen as an isolated lesion in 4 biopsies, and in association with PCa in 11 cases (12.4% of PCa). None of the former showed PCa in repeat biopsy. This is probably due to the small number of cases. In the revised literature, the chance of getting PCa in the repetition varies from 2.3 to 100%, with Herawi et al²⁷

reported 18% in 2006 after following up 791 cases. Therefore, the diagnosis of PIN is an indication for close monitoring with repeat biopsy whenever clinically indicated.

The presentation of AUR is the most common emergency in urology.^{11,12} It is often related to BPH in 53%.²⁸ Nevertheless, what makes the progression to AUR with a pre-existing BPH was the subject of study in the literature with contradictory outcomes.¹¹⁻¹³ There is no local data testing this matter on Saudi population. Our results is in agreement with the literature,¹¹⁻¹³ depicting that histologic evidence of chronic prostatitis is commonly seen with AUR, and hence, it might play an etiologic role by its associated edema. On the other hand, in our series, infarction was not a risk factor to develop AUR. This conclusion is similar to the previously published one by Tuncel et al,¹¹ and contradictory to the results reported by Bao et al.¹² Further study on a larger scale is needed to consolidate our conclusion, as knowing the etiology might help in predicting, and consequently preventing this adverse complications.

This retrospective study carries an inherent selection bias for biopsied cases, while many cases of BPH are medically managed without surgical intervention. Thus, the prevalence of BPH can be underestimated in such a case. Another limitation is that the sample size is not large enough. This can be attributed to the low frequency of prostatic cancers in our Saudi population in comparison to its frequency worldwide, and to other more common cancers, such as female breast cancers, and lymphomas. Also, most patients who were eligible for biopsy were biopsied more than once. We only counted them once to avoid duplication and misleading results. However, this work contributes to understand the pathology of prostatic diseases in a Saudi population. A meta-analysis for all similar studies previously conducted locally is needed to clarify the national picture of prostatic disorders in KSA.

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