Journal of Cell and Molecular Biology 3: 45-50, 2004.
Haliç University, Printed in Turkey.

Prostatic intraepithelial neoplasm: Retrospective results of clinical, histopathological approaches

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Received 12 December 2003; Accepted 24 December 2003

Abstract

Prostate cancer is the main problem in advanced aged population and it is the major reason causing death in western countries. Frequently the tumor metastasis or locally invades tissues when it is diagnosed. The main target should be the early diagnosis of the tumor. Today, the most important precursor lesion of prostate cancer is prostate intraepithelial neoplasm (PIN) in pathological analysis. This study aims to discuss PIN diagnostic value. This study comprimised on retrospectical determination of prostate specific antigen (PSA) levels and/or digital rectal examination (DRE) and sextant biopsies with the guide of transrectal ultrasonography (TRUS). Between April 2001 and September 2003, 166 patients were included in the study. Follow- up period was 31 months. Pathological results of prostate cancer, high grade PIN (hgPIN), low grade PIN (lgPIN) BPH and age, average serum PSA levels, DRE findings, Gleason Score and Gleason Grade results for prostate cancer patients were compared. In conclusion, the patients who had hgPIN lesions with BPH adviced for periodic follow up for prostate specific antigen (PSA) and digital rectal examination (DRE) and in necessary conditions, rebiopsy.

Key words: PIN, prostate cancer, BPH, Gleason score, PSA

Prostat intraepitel neoplazi: Klinik ve histopatolojik retrospektif sonuçlar

Özet

Prostat kanseri ileri yaş grubu erkeklerde en sık görülen ve en önemli ölüm sebeplerinden biridir. Prostat kanserinin tanısı konduğunda, genellikle kanser ya lokal invazyon göstermiş ya da metastatik hale gelmiştir. Günümüzde prostat kanseri için prekürsor lezyon kavramına uyan en önemli antite Prostatik Intraepitelyal Neoplazi'dir (PIN). Çalışma, prostat kanserinin erken tanısı amacıyla değerlendirme kapsamına alınan, serum PSA (Prostatik Spesifik Antijen) ve/veya PRM (Parmakla Rektal Muayene) sonucu TRUS (Transrektal Ultrasonografi) eşliğinde sextant prostat biyopsileri yapılan hastaların, klinik ve histopatolojik kayıtlarının retrospektif olarak incelenmesini içermektedir. Nisan 2001 - Eylül 2003 tarihleri arasındaki 31 aylık sürede, polikliniğimize başvuran ve prostat kanseri şüphesiyle TRUS eşliğinde prostat biyopsisi uygulanan 166 hastanın biyopsi materyallerinin histopatolojik bulguları retrospektif olarak incelendi. Prostat kanseri, yüksek grade (yg) PIN, düşük grade (dg) PIN ve BPH patolojik sonuçları; yaş, ortalama serum PSA değerleri, PRM bulguları ve prostat kanserli hastalann Gleason grade ve Gleason skor değerleriyle karşılaştırıldı. Bu nedenle YG PIN bulguları saptanan BPH'li olguların periyodik PSA ölçümleri ve PRM ile takip edilmesini, klinik değişkenlerin varlığı durumunda biyopsi tekrarı için yeniden değerlendirilmesini tavsiye ediyoruz.

Anahtar sözcükler: PIN, prostat kanseri, BPH, Gleason skoru, PSA

Introduction

Prostate cancer is the first reason of men deaths from cancer in advanced age. The incidence of prostate cancer is directly increased with age. Another reason for increased incidence of illness is early diagnosis and advanced techniques in diagnosis. This cancer is silently develops and its beginning and processing in the body can not be easy detectable. Because signs of prostate cancer appears in the late phase. Therefore, generally diagnosis can be done in cancer phase or locally invasive with metastatic lesions. Today, local cancer type of prostate can be cured, but late phase of neoplasms can not be cured easily. The early diagnosis of prostate cancer has been facilitated by the development of serum prostate-specific antigen (PSA) testing and evolution in transrectal ultrasound-guided biopsy of the prostate. Over a decade has passed since the initial recommendations for systematic sextant sampling of the prostate to increase the accuracy of cancer detection (Montironi and Schulman, 1986). Subsequently, variations in the number and location of biopsies have been proposed to maximize prostate cancer detection and obtain more complete information regarding tumor grade, tumor volume, and local stage (Mc Neal and Bostwick, 1986; Epstein et al., 1995; Wiley et al., 1997; Bostwick, 1996). Although current biopsy strategies provide a wide sampling of the prostate gland, biopsy histology may not be conclusive for either the presence or absence of adenocarcinoma. Prostatic intraepithelial neoplasia (PIN) is found in a significant fraction of patients undergoing transrectal prostate biopsies. In this article, we discuss the significance of prostatic intraepithelial neoplasia and other abnormal histology findings and current evidence addressing the presence of cancer and need for additional prostate biopsies.

PIN is characterized by architecturally benign prostatic acini lined by atypical cells, as defined by cytologic criteria (Kellokumpu-Lehtinen, 1980; Babanian et al., 1991). Nuclear changes are similar to those seen in prostate cancer, with nuclear enlargement and atypia, and prominent nucleoli. Accompanying architectural findings may include flat, tufting, papillary, and cribiform patterns. High-grade prostatic intraepithelial neoplasia (hgPIN) encompasses both grade 2 and grade 3 dysplasia with increasing hyperchromatism and size of nucleoli. Low-grade PIN (lgPIN), formerly grade 1 PIN, also exhibits crowding and irregularity of the secretory epithelial layer with less marked cytologic atypia; elongated hyperchromatic nuclei and small nucleoli are present yet not prominent. Table 1 summarizes features of lgPIN and hgPIN. This study comprised on patients group who have sextant biopsies with clinical history and indications. All specimens investigated pathologically and compared in eachother. We aim to show the importance of PIN findings in prostate cancer early diagnosis.

Material and methods

Between April 2001 and September 2003 total 166 patients in 31 months were investigated in our clinics for suspicious indicators for prostate cancer. Biopsy tissues were obtained with transurethral ultrasonography (TRUS) and all specimens were investigated histopathologically. Especially study group was chosen from lower urinary track syndrome patients and suspicious for prostate cancer whose PSA levels were over 4 ng per ml.

The average age of study group was 67.5 (range 45-92). All specimens were investigated by one

Table 1: Low grade and high grade PIN comparison.

	Low-grade PIN	High-grade PIN
Cytology		
Nuclei	Enlarged, pleiomorphic	Enlarged, pleiomorphic
Chromatin	Normal	Increased density, clumping
Nucleoli	Rarely prominent	Frequently large, prominent, and multiple
Architecture	Epithelial cell crowding and stratification Irregular spacing	More crowding and stratification 4 patterns: tufting, cribiform, micropapillary, flat
Basal cell layer	Intact	May show disruption
Basement membrane	Intact	Intact

Table 2: The Study group specimens histopathological characteristics.

	PCA				BPH			
	PCa+hg PIN	PCa+lg PIN	PCa+BPH	PCa	BPH+hg PIN	BPH+lg PIN	BPH	Total
Case number	34	4	5	8	21	28	66	166
Total	51				115			

Table 3: Comparison of clinical and histopathological results of BPH cases.

	BPH+hgPIN		BPH+lgPIN		BPH	
Case number	21		28		66	
Average age (year)	66.30±8.50 (49-84)		67.17±10.01 (51-86)		63.80±8.65 (45-82)	
Average PSA ng/ml	12.27±8.68		11.32±6.71		7.77±3.49	
DRE (%)	n	%	n	%	n	%
(-)	8	44	9	33	34	51
(+)	10	56	19	67	32	49

pathologist according to TNM classification and WHO system. In this study, prostate cancer, hgPIN, lgPIN and BPH pathological results were compared with serum PSA levels, DRE results. Only prostate cancer patient specimens were compared with Gleason grade to Gleason scores. PSA levels of study group were also determined before biopsy application. DRE results were evaluated as positive and negative for all patients. TRUS with 6.5 MHz probe was done transrectal (Shinokara et al., 1989). All biopsy materials were obtained with disposable 18G TRUCUT needle biopsy with automatic biopsy gun. The presence of basal cells was apparent by haematoxyline and eosin staining and was confirmed by immunohistochemistry. The intraductal and invasive signet ring cells were mucin negative and were immunoreactive for PSA.

All specimens were kept in 10% formaline solution for fixation. Prostate cancer diagnosis was obtained from Gleason grade and score system. PIN diagnosis was done according to McNeal and Bostwick (1986). Pathological isolated hgPIN and lgPIN determined in tissues followed up with DRE and PSA levels and if needed again biopsy treatment adviced to patients.

Clinically and histopathological results were investigated with SPSS statistical software version 11.0 and Kruskal-Wallis one way ANOVA and Chi-Square variability methods were applied. Smaller than 0.05 value is accepted significant for probability analysis.

Results

All patients characteristics were showed on Table 1. In this study, 51 patients (% 31.3) were prostate cancer, 115 patients (% 33.3) were BPH. 38 of 51 prostate cancer patients had also PIN lesions (74.5 %). 34 of 51 prostate cancer patients (66.6%) were also hgPIN and 4 of them (7.8%). 5 of the prostate cancer patients had also BPH focal points (9.8%) (Figure 1). In another investigation it was obtained that 8 of prostate cancer patients had only cancer findings histopathologically.

46 of 115 non cancer patients was BPH (40%) and also PIN. Isolated PIN which was not seen with cancer findings were also investigated pathological. 21 hgPIN (18.3%), 28 lgPIN (24.3%) was investigated in 46 patients (Figure 2). 66 of patients (57.4%) had no PIN and cancer findings histopathologically (Table2). Biopsy again treated for 6 of 21 (28.6%) isolated hgPIN patients and results gave neoplastic cells in this followups. Table 2 represents prostate cancer PCa, PCa+BPH, PCa+hgPIN and PCa+lgPIN histopathological results with average PSA levels and DRE findings besides Gleason grade and Gleason scores.

115 non cancer patients' characteristics such as PSA levels, DRE and percentages were described on Table 2. PSA levels of 46 isolated PIN patients was 12.2 ng per mg and their BPH findings and PSA levels correlation was highly meaningful ($p<0.05$).

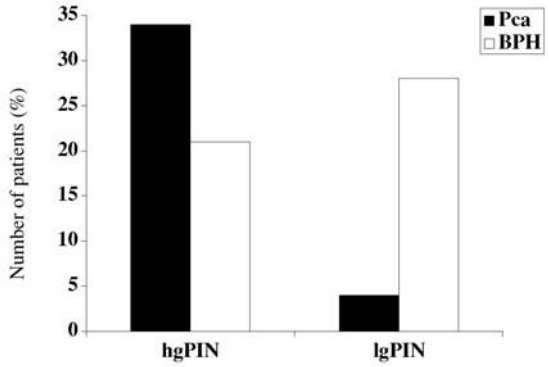


Figure 1: Prostate cancer and BPH cases according to PIN Grade.

87 of of study group (52.6%) had PIN findings and 34 of 55 hgPIN findings (61.8%) had neoplastic focal areas at the same time. 21 of the same group (38.2%) was determined as isolated PIN. 32 lgPIN specimens were investigated pathologically and 4 of them (12.5%) had also cancer lesions, 28 of them (87.5%) determined as isolated type PIN. PIN grade classification, prostate cancer and BPH results represented in Table 3.

7 different histopathological classifications when compare to ages of the patients were not statistically meaningful. Comparisons of PSA levels and DRE results with 7 different classified groups were not meaningful. Histopathologic results of patients indicated that PSA levels and DRE were important prostate cancer, but not significant within the age and age groups. When isolated PIN patients investigated in both hgPIN and ldPIN groups were not statistically significant for age, PSA levels and DRE results.

Subgroups with cancer diagnosis in biopsied patterns compared in each other for Gleason grade and Gleason score and prostate cancer isolated group with prostate cancer + hgPIN and lgPIN + prostate cancer was statistically significant. Isolated prostate cancer and hgPIN + prostate cancer subgroups had higher statistical meaning for their Gleason scores ($p<0.05$).

Benign group which consisted BPH, BPH+hgPIN, BPH+lgPIN groups and 91.3% of these groups PSA level was under 20 ng per ml. Statistically PSA and DRE results were not meaningful for these subgroups.

Discussion

PIN causes damages in basal cell layer and it thought as the one of the responsible PSA increment. However, there are different approaches about this subject. There are some reports about PSA increment and PIN relation histopathologically (Cooner et al., 1980). It is well known that PSA increment is the major clue for prostate cancer diagnosis with DRE and TRUS biopsy results. In this study, PSA, DRE and biopsy materials findings of 166 patients can diagnose 31.3% prostate cancer.

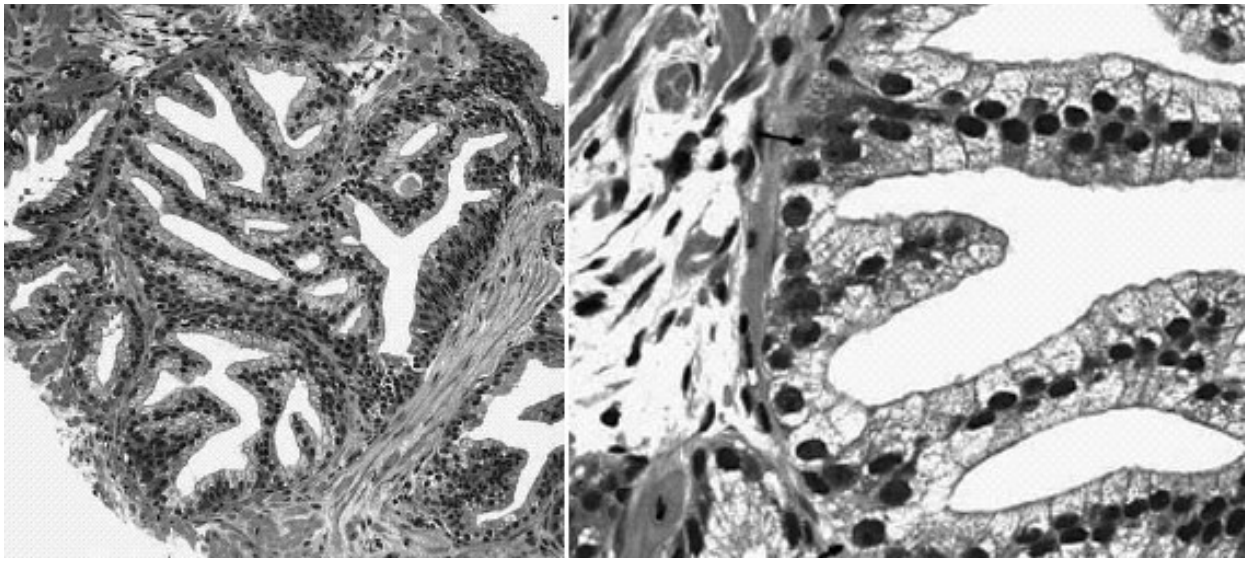


Figure 2: Prostate needle biopsy specimen with high-grade PIN. Haematoxylene-eosine stained. Left: 100x, right: 400x magnifications.

Prostate cancer diagnosis rate is increased last years. Clinical studies are able to show early precursors of illness successfully (Cooner et al., 1990). Dispersed basal layer and PIN grade has a multiple relation. 56% and 0.7% damaged basal layer showed for hgPIN and lgPIN. McNeal and Bostwick (1986) established that PIN rate for BPH was 43% and prostate cancer cases were 82%. In this study PIN grade was 42.6% for BPH and 74.5% for prostate cancer patients.

When isolated hgPIN cases followed up, their rebiopsy material showed 33-100% prostate cancer diagnosis. Therefore PIN histopathological results can be predictive factor for cancer occurence. 21 of hgPIN patient adviced for re-biopsy and 18 of them accepted. 6 of 18 re biopsied material (33.3%) investigated by one pathologist and diagnosed with prostate cancer. Keetch et al. (1995) established that PSA levels of lgPIN patients who diagnosed with prostate cancer was similar in each other. Our study group who has isolated lgPIN followed up for PSA levels and DRE results. 10 of the cases had higher PSA level, so adviced re biopsy. However 8 of them accepted our suggestion and 2 of them (7.2%). Rest of them had lgPIN pathological results. Trancoso et al. (1989) compared PIN grade and PIN with prostate cancer cases and they found that 21% of lgPIN cases and 54% hgPIN cases were showing cancer indications. This study results were 7.9% for lgPIN and 66.7% for hgPIN results.

PIN and PSA relation in literature is well studied and reports showed that average PSA levels of patients who have PIN between BPH and prostate cancer indicator values (Davidson et al., 1995; Brawer, 1989). Our results were higher than BPH patients. However these data were not statistically significant.

PIN with prostate cancer when investigated for Gleason Grade and Gleason Score, findings indicate that isolated PIN lesions in biopsy material will gain more clinical importance in the following years. Troncoso et al. (1989) explained this situation in prostatectomy materials for PIN localization, diversion, PIN grade and Gleason Grade and Gleason Scores of prostate cancer cases histopathologically. They also showed different results for DNA ploidy in these cases. PIN and cancer grades are correlated in each other and when PIN grade increment directly correlated with prostate volume. However this correlation could not be established between PIN volume and cancer volume. 11 patients who are classified as isolated prostate cancer had higher Gleason Grade and Gleason Score values than prostate cancer with hgPIN and prostate cancer with lgPIN. However prostate cancer with hgPIN had more Gleason Grade and Gleason Score, the differences were not significant ($p>0.05$).

More expanded studies with prostate cancer patients and prostatectomy materials will be useful to understand PIN and prostate cancer biological relation. Nowadays, localized prostate cancer treatments chosen and patient survival rates are depends on histopathological grade and scoring systems. If lgPIN described low grade and scored cancer, follow up procedure of lgPIN patients will be under discussion. Deprivation of androgens, PIN and other diplastic evaluations established that hormone dependency. If antiandrogen treatments and effects on PIN explained more detailed, how prophylactic or contraceptive therapies can be continued with chemotherapeutic agents will be clear. Neither patient age, PSA levels or nor DRE are not enough for detemination of BPH, hgPIN with prostate cancer and lgPIN for prostate cancer.

Conclusion

This study comprised for discuss the PIN outcome with what kind of prostatic illness. Tha data obtained from this study established that hgPIN comes with prostate cancer more than lg PIN. However, lgPIN generally seen with BPH. Therefore, hgPIN with BPH cases have to follow up with periodical PSA level determination and DRE results. If the clinical parameter have indicated changes, re biopsy should be adviced to patients.

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