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The role of high-grade prostatic intraepithelial neoplasia for biochemical relapse of prostate carcinoma after radical prostatectomy

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Key words: *prostate cancer; high-grade prostatic intraepithelial neoplasia; radical prostatectomy; biochemical relapse after radical prostatectomy.*

Summary. *The objective of the study was to evaluate the relationship between high-grade intraepithelial neoplasia diagnosed after radical retropubic prostatectomy and the clinical and pathological characteristics of prostate cancer, and to evaluate the time to biochemical relapse of the disease within the groups of high-grade prostatic intraepithelial neoplasia (HGPIN) and non-HGPIN patients.*

Material and methods. Patients, clinically diagnosed with local prostate carcinoma at the Clinic of Urology, Kaunas University of Medicine, during 2003–2007 and treated with radical retropubic prostatectomies, were distributed into two groups according to the HGPIN detected in the postoperative material: HGPIN and non-HGPIN. The two groups were compared in terms of preoperative and postoperative characteristics. The patients who were followed up for at least 12 months were included into the study. The biochemical relapse of prostate cancer was determined if there were two consecutive rises of prostate-specific antigen (PSA) level above 0.2 ng/mL or according to the attending physician's opinion, there was a need for adjuvant treatment even with onetime rise of PSA level above 0.2 ng/mL.

Results. There was no significant difference between the HGPIN and non-HGPIN groups in terms of time to biochemical relapse and frequency of biochemical relapses, time before surgery, the timing of the HGPIN diagnosis, age, or PSA level.

After radical prostatectomy, patients in the HGPIN group were found to have significantly more often poorer cancer cell differentiation according to the Gleason score (≥7 vs. <7; P=0.001) and higher TNM stage (T3a,b vs. T2a,b,c; P=0.001). Fewer positive resection margins were diagnosed in the HGPIN group (P=0.05). The groups did not differ in terms of the degree of differentiation according to the Gleason score or perineural invasion (P=0.811 and P=0.282, respectively).

Conclusions. HGPIN was more often associated with the characteristics of the poor prognosis for relapse of prostate cancer: poorer tumor cell differentiation according to the Gleason score and more cases of higher TNM stage. HGPIN did not have any influence on biochemical relapse of the disease during the short-term follow-up.

Introduction

High-grade prostatic intraepithelial neoplasia (HGPIN) is traditionally attributed to precancerous conditions or precursors of prostate cancer (PC). The majority of patients with diagnosed HGPIN are expected to develop prostate cancer within 10 years (1). The degree of association between HGPIN and prostate cancer in different sources of literature ranges between 22% and 100% (2–5). The mean incidence of HGPIN in patients undergoing prostate biopsy is

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9% (1). Following radical prostatectomy, prostate cancer in conjunction with HGPIN is detected in 88.4% of cases (6). The majority of current studies focus on the significance of HGPIN detected during the first prostate biopsy for the prognostication of prostate cancer in subsequent biopsies. The prognostic value of HGPIN for diagnosing prostate cancer depends on the number of samples obtained during the first biopsy, the number of samples obtained during subsequent biopsies, and the time interval between the biopsies. The significance of HGPIN for follow-up, the selection of the treatment tactics, and the prognostication of the course and characteristics of PC after positive biopsy remain under discussion. In the presence of preneoplastic high-grade dysplastic changes in other sites (e.g. uterine cervix, breast, or urinary bladder), the course of the disease is associated with progression to cancer and requires invasive treatment (7, 8). In the article published in 2007, Pierorazio et al. (6) stated that prostate cancer in conjunction with HGPIN detected following radical prostatectomy was more frequently associated with perineural invasion and multifocal nature of the tumor; besides, patients with HGPIN had a 1.9-fold higher risk of biochemical relapse of prostate cancer as compared to non-HGPIN patients.

The objective of this study was to evaluate the relationship between high-grade intraepithelial neoplasia diagnosed in prostate tissues after radical retropubic prostatectomy and the clinical and pathological characteristics of prostate cancer, and to evaluate the time to the biochemical relapse of the disease within the groups of HGPIN and non-HGPIN patients.

Material and methods

We analyzed data on patients who were clinically diagnosed with local prostate carcinoma at the Clinic of Urology, Kaunas University of Medicine, during 2003–2007 and were treated with radical retropubic prostatectomies. According to the HGPIN detected in the postoperative material, the patients were divided into two groups: HGPIN and non-HGPIN. The two groups were compared in terms of preoperative (patients' age, prostate-specific antigen (PSA) levels during biopsy, Gleason score, and time to surgery) and postoperative (postoperative stage according to the TNM classification, postoperative Gleason score of PC, resection margins, and perineural invasion) characteristics. After the surgery, the patients were followed up by monitoring PSA levels at 1, 3, 6, 9, and 12 months during the first year and every 6 months later on. The study included patients who were followed up for at least 12 months. The biochemical relapse of prostate cancer was determined if there were two consecutive rises of PSA level above 0.2 ng/mL or according to the attending physician's opinion, there was a need for adjuvant treatment even with onetime rise of PSA level above 0.2 ng/mL.

Statistical data analysis was performed using the SPSS 13.1 software for Windows. The relationship between qualitative variables was evaluated using the chi-square χ^2 criterion. The Kolmogorov-Smirnov test was used to verify the distributions of quantitative variables. Data of two independent groups were compared by applying the Student's t test. Quantitative variables, which were not normally distributed, were compared using the Wilcoxon-Mann-Whitney test. Since the significance level of Student's t and Mann-Whitney tests coincided in all the analyzed quantitative variables with nonnormal distribution, the results are presented as parametric variables. Difference between the groups was considered significant when $P<0.05$.

To clarify the marginal value of the time of the diagnosis of HGPIN, the receiver operating characteristic (ROC) analysis was applied. The power of the study was 0.93; type I error was $\alpha=0.05$, $r_1=0.3$; $r_2=-0.099$.

Results

The studied group consisted of 390 male patients with a mean age of 65.1 (SD, 6.3) years (the youngest and oldest patients were 47 and 78 years old, respectively; median, 66 years). The mean time to surgery was 71.7 (SD, 88.1) days (min, 11; max, 1533; median, 57.5 days); mean time to biochemical relapse was 21.4 (SD, 12.3) months (min, 1; max, 72; median, 18.0 months); the mean number of biopsies was 1.3 (SD, 0.6) (min, 1; max, 5; median, 1). The time to diagnosis was, on the average, 27.1 (SD, 16.2) months (min, 0.4; max, 67.6; median, 24.7 months). HGPIN was diagnosed in 172 (44.1%) patients, while 218 (65.9%) patients were attributed to the non-HGPIN group. The comparative characteristics of the groups are presented in Table 1.

The evaluation of patients with and without HGPIN showed no statistically significant differences in patients' age, time to surgery, mean time to biochemical relapse, mean PSA, Gleason score before and after surgery, the stage of the disease, or the perineural invasion comparing both the groups (Table 1). Positive postoperative margins were statistically significantly less common in the HGPIN group ($P=0.001$). The frequency of relapses was also statistically significantly lower in the HGPIN group ($P=0.043$). In

Table 1. Comparison of the studied patients' characteristics with respect to the HGPIN groups

Characteristic	HGPIN group	Non-HGPIN group	*P* value
Age, mean (SD), years	65.3 (6.3) n=172	65.1 (6.2) n=218	0.753
Time to surgery, mean (SD), days	71.78 (44.9) n=162	71.7 (111.3) n=202	0.993
Time to biochemical relapse, mean (SD), months	21.2 (12.0), n=172	21.6 (12.6) n=218	0.706
PSA, mean (SD), ng/mL	7.7 (4.3) n=171	8.3 (5.7) n=218	0.282
Number of biopsies, mean (SD)	1.4 (0.7) n=162	1.2 (0.5) n=201	**0.038**
Gleason score before surgery, n (%)			
<7	148 (86.5)	175 (80.6)	χ^2=2.964;
7	20 (11.7)	39 (18.0)	*df*=2;
>7	1.8 (3)	1.4 (3)	*P*=0.227
Gleason score after surgery, n (%)			
<7	53.8 (92)	57.0 (122)	χ^2=3.161;
7	43.3 (74)	36.9 (79)	*df*=2;
>7	2.9 (5)	6.1 (13)	*P*=0.206
PSA, n (%)			
≤10 ng/mL	136 (79.5)	163 (74.8)	0.269
>10 ng/mL	35 (20.5)	55 (25.2)	
Positive resection margins, n (%)			
No	117 (70.5)	105 (53.0)	**0.001**
Yes	49 (29.5)	93 (47.0)	
Cancer stage, n (%)			
T2a,b,c	128 (74.9)	174 (80.2)	0.209
T3a,b	43 (25.1)	43 (19.8)	
Biochemical relapse, n (%)			
No	160 (93.0)	189 (86.7)	**0.043**
Yes	12 (7.0)	29 (13.3)	
Number of biopsies, n (%)			
1	120 (74.1)	166 (82.6)	**0.049**
>1	42 (25.9)	35 (17.4)	
Perineural invasion, n (%)			
No	95 (55.6)	114 (52.3)	0.522
Yes	76 (44.4)	104 (47.7)	
Time to diagnosis, mean (SD), months	24.9 (14.9)	28.9 (16.9)	**0.01**

HGPIN, high-grade prostatic intraepithelial neoplasia.

addition to that, these groups statistically significantly differed in the number of biopsies performed (1.4 [SD, 0.7] in the HGPIN group vs. 1.2 [SD, 0.5] in the non-HGPIN group; *P*=0.038). However, the evaluation of the groups concerning the timing of the diagnosis of HGPIN showed that the time to diagnosis was statistically significantly shorter in the HGPIN group, compared to that in the non-HGPIN group (24.9 [SD, 14.9] months and 28.9 [SD, 16.9] months, respectively; *P*=0.01). This means that recently the number of cases diagnosed with HGPIN has increased. This tendency is reflected in Fig. 1 that shows the frequency of the detection of HGPIN in histological samples by year. We used the ROC test to clarify the marginal value of the timing of the HGPIN diagnosis, i.e., to determine the point in time where there was no difference in the timing of diagnosis between the HGPIN and non-HGPIN groups. The analysis of the ROC curve (Fig. 2) showed that 24.5 months were the marginal value for the timing of the HGPIN diagnosis, i.e., the sensitivity and specificity for HGPIN was 0.5. Further data analysis was performed only for patients in whom the time to HGPIN diagnosis was <24.5 months (2006–2007) (n=192; 84 [43.8%] patients in the HGPIN

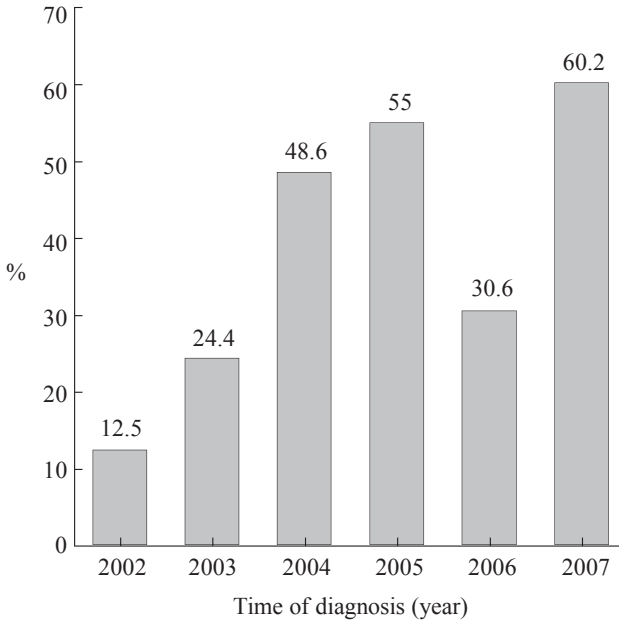

Fig. 1. The percentage distribution of diagnosis of high-grade prostatic intraepithelial neoplasia by the years of the study

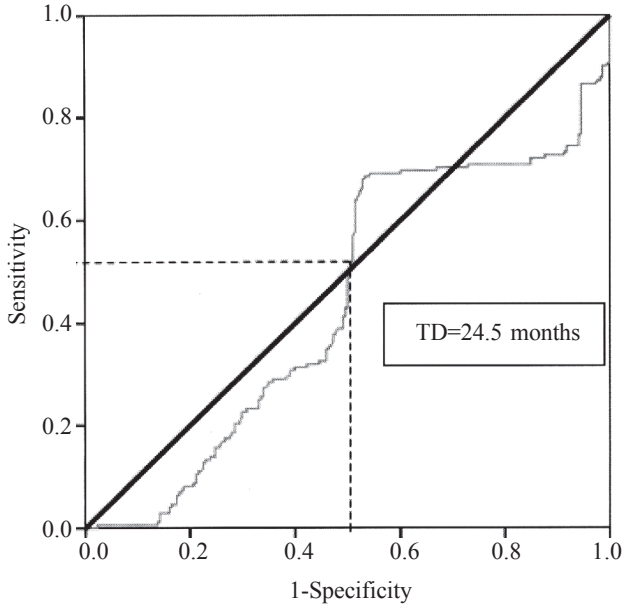

Fig. 2. Marginal value of high-grade prostatic intraepithelial neoplasia with respect to the timing of the diagnosis (TD)

group and 108 [56.2%] patients in the non-HGPIN group) (Table 2).

The comparative analysis of subjects in the HGPIN and non-HGPIN groups showed no statistically significant differences between the two groups concerning the timing of diagnosis, the patients' age, PSA, time to surgery, time to biochemical relapse, or the frequency of relapses. Patients with HGPIN after radical prostatectomy were found to have significantly more frequently poorer cancer cell differentiation according to the Gleason score (≥7 vs. <7; P=0.001) and prostate cancer of higher TNM stages (T3a,b vs. T2a,b,c; P=0.001). In addition, fewer positive resection margins were detected in this group (P=0.05). There was no difference between the groups concerning the Gleason scores in biopsy material or perineural invasion (P=0.811 and P=0.282, respectively).

Discussion

In 1986, McNeal and Bostwick differentiated prostatic intraepithelial neoplasia into low-grade, medium-grade, and high-grade (9). Recently, prostatic intraepithelial neoplasia is considered synonymous to HGPIN (grades 2 and 3) (1). In 1987, Bostwick and Braver (10) defined prostatic intraepithelial neoplasia as a precursor of prostate cancer and prostatic in situ neoplasia, which is characterized by changes similar to tumorous prostate gland cells (increased cell size, higher polymorphism of the cells, more prominent nucleoli, and atypia of the nuclei), but differing from adenocarcinomas in that basal cell layer and basement membrane are intact. These authors also found the association between high-grade prostatic intra-epithelial neoplasia and prostate cancer: higher number of HGPIN foci increased the probability of concomitant prostate cancer; besides HGPIN, similarly to prostate cancer, is more frequently localized in the peripheral area of the prostate. The majority of patients with diagnosed HGPIN are expected to develop cancer within 10 years (1). However, it remains unclear which HGPIN foci will transform into prostate cancer and which will not. The mean frequency of prostate cancer detection in repeat biopsies in HGPIN patients ranges between 4.5% and 100% of cases (5, 11–16). In more recent studies (dated 2004–2005) applying more extended biopsy schemes during the first sampling, the frequency of cancer detection during repeat biopsies ranged from 20.8% to 30.5% (5, 15, 16). Such a wide variety of results raise further discussions concerning the significance of HGPIN in the development of prostate cancer. Discussions continue concerning the frequency of serial prostate biopsies in the presence of HGPIN, how the patients should be followed up, what the significance of PSA is in the diagnosis and follow-up of patients, and how important higher number of biopsy samples with HGPIN is. Roscigno et al. (4) indicated that the multifocal nature of HGPIN is directly related to higher risk of prostate cancer, whereas Naya et al. (16) in their study found that the number of cores positive for HGPIN was not predictive for prostate cancer on repeat biopsies.

Table 2. Comparison of the characteristics of studied patients' in the HGPIN and non-HGPIN groups in whom the time to diagnosis was <24.5 months

Characteristic	HGPIN group	Non-HGPIN group	*P* value
Age, mean (SD), years	63.7 (6.3) n=84	63.8 (6.0) n=108	0.838
Time to surgery, mean (SD), days	82.8 (8) n=81	91.8 (8) n=99	0.598
Time to biochemical relapse, mean (SD), months	16.4 (6.7) n=84	17.0 (6.9) n=108	0.598
PSA, mean (SD), ng/mL	7.1 (4.4) n=83	7.9 (5.6) n=108	0.308
Number of biopsies, mean (SD)	1.24 (0.5) n=78	1.24 (0.6) n=100	0.965
Gleason score before surgery, n (%)			
<7	65 (78.3)	83 (76.9)	0.811
≥7	18 (21.7)	25 (23.1)	
Gleason score after surgery, n (%)			
<7	35 (42.2)	70 (67.3)	**0.001**
≥7	48 (57.8)	34 (32.7)	
PSA, n (%)			
<4 ng/mL	7 (8.4)	12 (11.1)	χ^2=2.79;
4–10 ng/mL	65 (78.3)	73 (67.6)	*df*=2;
>10 ng/mL	11 (13.3)	23 (21.3)	*P*=0.248
Positive resection margins, n (%)			
No	57 (73.1)	54 (58.7)	**0.05**
Yes	21 (26.9)	38 (41.3)	
Cancer stage, n (%)			
T2a,b,c	58 (69.9)	96 (89.7)	**0.001**
T3a,b	25 (30.1)	11 (10.3)	
Biochemical relapse, n (%)			
No	81 (96.4)	99 (91.7)	0.176
Yes	3 (3.6)	9 (8.3)	
Number of biopsies, n (%)			
1	62 (79.5)	83 (82.0)	0.672
>1	16 (20.5)	18 (18.0)	
Perineural invasion, n (%)			
No	35 (42.2)	54 (50.0)	0.282
Yes	48 (57.8)	54 (50.0)	

HGPIN, high-grade prostatic intraepithelial neoplasia.

After radical prostatectomy, PC in conjunction with HGPIN was found in 86.8% to 88.4% of cases (6, 17). In our study, the respective percentage was 44.1% (n=172).

Findings on the significance of HGPIN in prognosticating the relapse of prostate cancer following radical prostatectomy are controversial. Qian et al. (18) found a positive correlation between the total volume of HGPIN and the volume, stage, and differentiation degree of PC, which corroborates the theory that HGPIN is associated with poorer clinical outcomes and poorer histological characteristics of PC. Pierorazio et al. (6) in their study also found that in patients with HGPIN, histological samples following radical prostatectomy significantly more frequently showed evidence of perineural invasion (69.9% vs. 57.7%, *P*=0.003) and multifocality (63.0% vs. 38.4%, *P*<0.001). In patients without HGPIN, biochemical relapse-free survival was better (50-month follow-up, 87.3% vs. 81.0%; and 9-year follow-up, 73.6% vs. 67.0%, *P*=0.045). The risk of biochemical relapse was 1.9-fold higher in the HGPIN group (*P*=0.006). However, there also are results indicating the contrary, i.e., that HGPIN is associated with lower risk of PC. In a study by Lopez (2), prostate cancer in the HGPIN group, compared to the non-HGPIN group, was associated with older age, lower Gleason score (*P*=0.017), lower tumor volume (*P*=0.033), and lower

amount of PC cells in biopsy samples.

The results of our study – excluding the timing of the diagnosis – would also indicate that PC volume in HGPIN patients was lower because its diagnosis required statistically significantly more biopsies (1.4 [SD, 0.7] in the HGPIN group vs. 1.2 [SD, 0.5] in the non-HGPIN group, *P*=0.038), and that positive postoperative resection margins were statistically significantly less frequent (*P*=0.001). This would explain the lower incidence of relapses during the postoperative period in the HGPIN group (*P*=0.043). However, in our study, there was a statistically significant difference in the timing of HGPIN diagnosis between the HGPIN and non-HGPIN groups. Pierorazio et al. (6) also stated that the diagnosis of HGPIN is relatively new and that the frequency of diagnosed HGPIN and its association with PC may increase with time due to the progress in diagnostic techniques. In their study, the frequency of HGPIN diagnosis did not differ with respect to the year of surgery. In our study, we established the marginal value (24.5 months) for the timing of HGPIN diagnosis by applying the ROC test and found that the HGPIN group during the postoperative period more frequently demonstrated poorer tumor cell differentiation according to the Gleason score (≥7 vs. <7; *P*=0.001) and PC of higher postoperative TNM stages (T3a,b vs. T2a,b,c; *P*=0.001). These criteria are among the main ones in prognosticating the postoperative relapse in nomograms and are associated with higher probability of relapse (19–21). The fact that we found no difference between the groups concerning the number of relapses and time to biochemical relapse (*P*=0.598 and *P*=0.176, respectively) may be explained by a short follow-up period, because Pierorazio et al. (6) in their study detected statistically significant differences only after 5-year follow-up. We also tend to think that low frequency of HGPIN diagnosis in histological samples following surgery compared to the literature data (44.1% vs. 86.8–88.4%) may affect the results (6, 17) and may explain the fact that statistically significantly fewer positive resection margins were detected in the HGPIN group.

Conclusions

High-grade prostatic intraepithelial neoplasia was more often associated with the characteristics of poor prognosis for prostate cancer relapse: higher postoperative Gleason score and more cases of higher TNM stage. High-grade prostatic intraepithelial neoplasia did not have any influence on biochemical relapse of the disease during the short-term follow-up.

Aukšto laipsnio intraepitelinės neoplazijos įtaka biocheminiam prostatos vėžio atkryčiui po radikalios prostatektomijos

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Raktažodžiai: prostatos vėžys, prostatos aukšto laipsnio intraepitelinė neoplazija, radikali prostatektomija, biocheminis ligos atkrytis po radikalios prostatektomijos.

Santrauka. *Tyrimo tikslas.* Įvertinti ryšį tarp aukšto laipsnio intraepitelinės neoplazijos (ALPIN), diagnozuotos prostatos audiniuose po radikalios retropubinės prostatektomijos, ir prostatos vėžio klinikinių bei patologinių charakteristikų. Įvertinti laikotarpį be biocheminio ligos atkryčio grupės ligonių, turinčių ALPIN, ir neturinčių ALPIN.

Tiriamųjų kontingentas ir tyrimo metodika. Ligoniai, kuriems Kauno medicinos universiteto Urologijos klinikoje kliniškai nustatytos lokalios prostatos vėžio formos ir kurie buvo gydyti atliekant radikalias retropubines prostatektomijas, suskirstyti į dvi grupes pagal pooperacinėje medžiagoje nustatytą prostatos aukšto laipsnio intraepitelinę neoplaziją. Pirma grupė – ligoniai, turintys ALPIN, antra grupė – neturintys ALPIN. Šios dvi ligonių grupės buvo palygintos įvertinus priešoperacines pacientų charakteristikas (paciento amžius, PSA biopsijos metu, prostatos vėžio diferenciacijos laipsnis pagal Gleason, laikotarpis iki operacijos) bei pooperacines charakteristikas (pooperacinė stadija pagal TNM klasifikaciją, pooperacinis diferenciacijos laipsnis pagal Gleason, rezekciniai kraštai, perineurinis plitimas). Į tyrimą buvo įtraukiami pacientai, kurių

stebėsenos trukmė – bent 12 mėnesių. Biocheminis prostatos vėžio ligos atkrytis buvo fiksuojamas nustačius du iš eilės PSA pakilimus daugiau kaip 0,2 ng/ml arba tais atvejais, kai, gydančio gydytojo nuomone, tikslinga skirti adjuvantinį gydymą užfiksavus netgi vienkartinį PSA pakilimą daugiau kaip 0,2 ng/ml.

Rezultatai. 2006–2007 m. ligonių, turinčių ALPIN ir neturinčių ALPIN, grupėse laikotarpis iki biocheminio ligos atkryčio, biocheminio ligos atkryčio dažnis, ALPIN diagnozės nustatymo laikas, pacientų amžius, laikas iki operacijos, PSA, reikšmingai nesiskyrė.

ALPIN turinčių ligonių grupėje radikalios prostatektomijos medžiagoje statistiškai reikšmingai dažniau nustatyta blogesnė vėžio diferenciacija pagal Gleason (≥7 palyginti su <7; p=0,001), aukštesnė TNM stadija (T3a, b palyginti su T2a, b, c; p=0,001). ALPIN turinčiųjų ligonių grupėje mažiau diagnozuota ir teigiamų kraštų (p=0,05). Grupės pagal diferenciacijos laipsnį pagal Gleason biopsinėje medžiagoje, perineurinį plitimą nesiskyrė (atitinkamai – p=0,811 ir p=0,282).

Išvados. ALPIN buvo dažniau susijęs su prostatos vėžio blogos prognozės, ligos atkryčio charakteristikomis: blogesnė diferenciacija pagal Gleason po operacijos, daugiau aukštesnės stadijos pagal TNM atvejų. Trumpos stebėsenos metu ALPIN ligos biocheminiam atkryčiui įtakos nenustatyta.

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