A comparison of tumor progression in patients with simultaneous prostate cancer and prostate premalignant condition to patients with prostate cancer alone

Mieczysław Fryczkowski[1], Maciej Szczębara[1], Andrzej Kupilas[1], Aleksandra Sitko-Saucha[2], Andrzej Paradysz[1]

[1]Department of Urology in Zabrze, Medical University of Silesia in Katowice, Poland
[2]Helimed Urology Center in Kędzierzyn-Koźle, Poland

KEY WORDS

prostate ◗ prostate cancer ◗ premalignant condition ◗ prostatectomy

ABSTRACT

Introduction. An evaluation of prostate cancer progression in group 1 (n – 30) with simultaneous prostate cancer (PCa) and premalignant lesions (PL) in comparison with group 2 (n – 159) with prostate cancer alone was carried out.

Materials and methods. All patients underwent radical prostatectomy (RP). The assessment consisted of PSA levels, Gleason score (Gs), clinical staging, percentage of multifocal tumors, and tumor volume in both groups. Postoperative follow-up was evaluated: including clinical recurrence and biochemical recurrence (BCR) rate, metastases, and cancer specific deaths.

Results. Sixty percent of patients in group 1 had clinically insignificant prostate cancer. Although in this group PSA levels, Gs, and tumor staging were statistically lower. Tumor progression was similar to group 2. A considerably prevalent presence of multifocal tumors in group 1 did not result in their greater volume.

INTRODUCTION

Both, high grade prostatic intraepithelial neoplasia (HG PIN) and atypical small acinar proliferation (ASAP), are presently accepted predictors of PCa. Frequency of HG PIN incidence at first biopsy amounts to 0.7 – 16.5%, whereas in rebiopsy in these patients the frequency of PCa is approximately 23 – 50%. ASAP incidence is approximately 0.4 – 23.3% in first biopsy, while second biopsy detects PCa in 21-57% of patients [1]. In addition, 8 – 63% of patients with recognized ASAP are not submitted to successive biopsies [2]. Is there a similarity to other organs like the uterus, urinary bladder, or intestines that premalignant lesions always precede malignancy or in a prostate they are somehow competitive? None of the premalignant prostate conditions have a specific biological marker or other prognostic factor that would allow us to estimate the risk of developing prostate cancer and recognizing it in consecutive biopsies or in specimen after radical prostatectomy (RP) [3]. Some authors suggest that growth in the percentage of diagnosed prostate cancers after previous recognition of PL is the result of the extended protocol for rebiopsies. They accent that after performing the first saturation prostate biopsy, growth of PCa detection in the subsequent one is significantly lower [4, 6]. Lack of evidence supporting the difference in progression of simultaneous PCa and PL in comparison with PCa alone in major clinical studies does not allow for firm evaluation of the results of their surgical treatment [1, 3, 5]. Therefore the analysis of patients after RP with PCa and with coexisting PCa and premalignant lesions was performed.

MATERIAL AND METHODS

The study involved 189 patients operated between February 2001 and March 2009 who underwent control examinations during a period from 8 to 105 months (average 51 months) after surgery. Patients were divided into two groups. Group 1 (n = 30) included patients with coexisting PCa and PL. Group 2 (n = 159) consisted of patients in whose specimens after RP showed only histological findings of PCa. Each specimen was inspected by two pathologists. HG PIN was recognized according to generally acknowledged standards of evaluating changes in cytoarchitectonic criteria of prostate epithelium. The recognition of ASAP in doubtful cases was accomplished using immunohistochemical markers of the basal epithelial layer. In each patient, before surgery, PSA level, clinical tumor stage, Gleason sum, CT of pelvis, transrectal ultrasound examination (TRUS), and bone scintigraphy were performed. Survival rate (SR) and cancer specific survival rate (SRCS) as well as progression-free survival rate (SRPF) were estimated. Radical prostatectomy was performed using the suprapubic retroperitoneal approach in all cases except 3 (10%) in group 1 and 26 (16.3%) in group 2 in which we used laparoscopy. Control examinations included PSA levels, chest x-ray (CXR), and, in cases of biochemical recurrence, bone scintigraphy. In specimens after RP, the presence of multifocal changes and tumor volume to prostate volume ratio (vT/vP) was estimated in 27 cases from group 1 and 146 from group 2. Recurrence was recognized after positive histological examination of biopsies of paraurethral tissue, while biochemical recurrence was recognized after obtaining a twofold excess in total serum PSA level over 0.2 ng/ml. Results were statistically analyzed and calculated using Statistica™ software version 4.3 En. To estimate normality in distribution of examined parameters we used the Shapiro-Wilk test. To compare the differences between measurements we used the non-parametric Mann-Whitney-Wilcoxon signed-rank test. The Pearson X^2 statistic was used to calculate a p-level by comparing the value of the statistic to a chi-square distribution. We accepted the significance level at $\alpha = 0.05$.

RESULTS

Altogether the study involved 189 patients in the age bracket of 49 to 73 years (mean = 62.0).

Table 1. Comparison of prostatectomy results.

	Group 1	Group 2	P
No. of patients	30 – 15.9%	159 – 84.1%	–
Age (years)	61.8	62.9	ns
PSA T (ng/ml)	10.7	13.5	0.027074
PCa clinically insignificant	18 - 60%	36 - 23%	0.00028
PSA T <4 4-10 >10	2 – 6.7% 15 – 50% 13 – 43.3%	9 – 5.1% 68 – 42.8% 52 – 51.6%	ns ns ns
Gleason (sum) 0 <7 =7 >7	7 – 23% 16 – 53.3% 5 – 16.7% 2 – 6.7%	7 – 4.4% 23 – 14.5% 30 – 18.9% 99 – 62.2%	0.00028 0.09568 0.35558 0.01848
Gleason (average)	4.3	5.9	0.003933

Table 2. Differences in clinical staging.

	Group 1	Group 2	P
Metastases	0	4 – 2.5%	0.37990
Tumor vol.	14.5%	31.3%	0.00014
Deaths	0	8 – 5%	0.20933
Biochemical recurrence Clinical recurrence	10 – 33.3% 1 – 3.3%	36 – 22.6% 8 – 5%	0.21069 ns
Staging pT0 pT1 pT2 pT3 pT4	7 – 13.3% 16 – 53.3% 5 – 16.7% 1 – 3.3% 1 – 3.3%	7 – 4.4% 58 – 36.4% 51 – 32.1% 39 – 24.6% 4 – 2.5%	0.02288 0.00026 0.01883 0.03140
Multifocality	20 – 66.7%	42 – 26.4%	0.00011
Time (months)	45.3	53.8	–

There were no differences in age of operated patients between groups (Tab. 1). Mean total PSA level in group 1 was significantly lower than in group 2 (p = 0.027) while the percentage of patients who were operated with normal (4 ng/ml) PSA levels was similar. Also, there were no statistically significant differences between groups in percentage of patients with initial PSA levels 4-10 ng/ml and above 10 ng/ml. Average Gleason score was lower in group 1 (p = 0.037), which followed the higher number of patients with Gs >7 in group 2 (p = 0.018) and higher number of patients with Gs <7 in group 1 (p = 0.095).

Table 2 presents the distinction in clinical staging between the studied groups. A weighty difference in the number of patients with a pT0 tumor appeared, 16.7% in group 1 versus 4.4% in group 2 (p = 0.0028), even though each patient qualified to RP had previously recognized PCa. In general, in group 1 there were more pT0 (p = 0.0028) and pT1 (p = 0.0026) tumors whereas in group 2 more pT2 (p = 0.18) and pT3 (p = 0.031) were observed. Control examinations after RP revealed 10 cases of biochemical recurrence and 1 clinical recurrence in group 1, which generally amounted to 36% of patients. In group 2, BCR was noted in 36 and clinical recurrence in 8 cases which amounts to 27% and was not significantly different from group 1 (p = 0.21). The survival rate was approximately 100% in group 1 *vs.* 95% in group 2 and progression-free survival rates were 63.4% vs. 67.8% respectively. Despite a higher percentage of multifocal tumors in group 1 (p = 0.0011) their summed volume equaled 15.5% of prostate volume, which was significantly less than 31.3% (p = 0.0014) in group 2 (Tab. 3).

Only in group 1 was the number of multifocal tumors higher than unifocal tumors. Comparison of both groups revealed a higher percentage of pT0 among multifocal changes, 25% *vs.* 0% with an associated insignificantly lower Gleason score. Five patients with pT0 had a similar total PSA level to the remaining 25 patients in group 1 – 9.4 ng/ml *vs.* 10.4 ng/ml. Recurrence rate among those with pT0 amounted to 20%, which in comparison with 44% of the remaining is significantly smaller.

Histological examination of specimens in group 1 revealed the simultaneous presence of PCa with HG PIN in 22 patients (73.3%), PCa with ASAP in 3 (10.0%), PCa with HG PIN + ASAP in 4 (13.3%), and PCa with LG PIN in 1 (3.3%). A small number of patients with a particular combination of PCa and PL were not statistically analyzed. According to Epstein's definition of clinically insignificant PCa, group 1 contained 18 (60%) such cases vs. 38% in group 2 (p = 0.0023) (Tab. 4).

DISCUSSION

HG PIN and PCa demonstrate extensive morphological similarity and frequent coexistence, mainly in multifocal tumors [1, 2, 4]. ASAP is not a variant of HG PIN and at present is ambiguously defined as a complex of atypical histological changes. It is quantified by its similarity to PCa, which still does not accomplish all the criteria of cancer recognition [2, 5]. It results in premalignant lesions being defined as ASAP, however they may have different malignant potentials [1, 6]. Only using immunohistochemistry, can we often distinguish ASAP from PCa. This method utilizes antibodies to markers of the basal epithelial layer [7, 8].

Is the coexistence of PL and PCa in one specimen proof of their common origin or are they rather coexisting incidentally [2, 9]?

Table 3. Tumor focality impact.

	No. – %	PSA (ng/ml)	Gleason sum	Recurrence	Time (months)
Multifocality	20 – 86.7%	10.2	3.3	8 – 40%	53.2
Unifocality	10 – 33.3%	10.8	5.2	3 – 30%	38.1
pT0	7 – 23.3%	8.4	0	1 – 28.6%	59.4
P	0.0038	ns	0.01	0.05	–

Table 4. Distribution of premalignant lesions types.

Lesion type	Frequency	PSA (ng/ml)	Gleason (sum)	Recurrences	Time (months)
HG PIN + PCa	22 – 73.3%	10.4	5.3	7 – 31.8%	41.9
ASAP + PCa	3 – 10%#	13.6	2.7	2 – 66.7%	81.0
HG PIN + ASAP	4 – 13.4%	10.9	0	2 – 66.7%	63.0
HG PIN	1-3.3%	6.4	0	0	17.0

The answer could be given partly by evaluating tumor progression and survival in these cases. In 2006, Epstein and coworkers analyzed 54 patients, described earlier in smaller groups by 6 different authors, who had diagnosed PCa with PL or PCa following recognition of PL. In this study 85.2% of prostate specimens were locally confined without seminal vesicle and lymph node involvement. In 66% of these patients, summed Gs did not exceed 6 points. In comparison with patients with only PCa, authors did not find any changes in terms of tumor progression [1, 9].

In the last four years there were at least several studies devoted to the coexistence of PCa and PL in patients who underwent prostatectomy. Analysis of 8 successive studies, involving a total of 2,368 patients, does not allow an unequivocal answer to the question of tumor progression and survival time in this group [3, 9, 10, 12, 13, 14, 15, 17]. Most investigators agree that neither total, or free PSA, nor free/total ratio are adequate predictors of PL [3, 5, 18]. There is a similar opinion about the predictive suitability of the digital rectal examination and TRUS in recognizing premalignant conditions [11].

As an odd one, Roscigno and coworkers revealed statistically important differences in PSA density (PSA D) in patients with PCa in comparison to patients with HG PIN. Seventy percent of tumors in their material were multifocal [8]. Krishanmurti and coworkers found that in patients with PSA below 10 ng/ml they recognized HG PIN in the group with a higher PSA D – average 0.3 (ng/ml/cm^2) in comparison to 0.18 in the group with PCa. The other finding of these authors was that an increase in PSA above 0.75 ng/ml a year strongly correlates with the presence of PCa in second biopsy [4]. Zuniga and coworkers concluded that total PSA has a good predictive value only in patients with HG PIN, but not with ASAP. According to Mansfield and coworkers these non-randomized studies may have limited value due to the variation in time period between biopsy and prostatectomy in each group of patients, resulting in poor conformity of the histological examinations. In their material, consisting of 368 patients, only 21.9% had the same Gs after biopsy and prostatectomy and this conformity was higher in the group with the highest Gs [11]. An influence of the time period was confirmed in a study by Lefkowitz and coworkers who, during three years of observation, after recognition of HG PIN later diagnosed PCa in 26.8% of cases while the increase in PSA level was insignificant and averaged 1 ng/ml. Another confirmation of this hypothesis that the time between biopsy and prostatectomy have an influence on histological findings was given by Fandella and coworkers [9, 16].

In our study, patients in group 1 with coexisting PCa and PL had significantly lower PSA T levels as well as Gleason sum. Furthermore, Gs was lower in patients with multifocal tumors. Despite the lower average PSA level in group 1 compared to group 2, a detailed analysis excluded its value in differentiating between them. However, Gleason sum and clinical staging were significantly higher in group 2.

While discussing the matter, some authors focused on tumor volume and tumor volume to prostate volume ratio. Guzo and coworkers estimated that the volume of premalignant lesions was smaller than the changes in PCa. They concluded that there is also a difference in estimation of this volume between biopsy and prostatectomy specimen examination [10]. According to Kutzman and coworkers, there is an overestimated number of clinically insignificant PCa with accompanying HG PIN tumors recognized by TRUS driven biopsy, which after prostatectomy are in fact clinically significant pT2c and pT3a tumors in 63% of patients [13]. The number of falsely estimated biopsy specimens may be even higher if we take into account the results of the study by Humphrey and coworkers, who recognized PCa in all of the 10 patients who underwent prostatectomy for HG PIN [19]. Aside from the exceptions mentioned above, most studies prove a higher percentage of clinically insignificant PCa when a premalignant condition is co-recognized [1, 2, 9, 14].

In our study, group 1 showed significant supremacy of multifocal tumors as opposed to group 2, 66.7% to 26.4% respectively ($p = 0.0011$), which resulted in the larger volume of these tumors ($p = 0.0014$). There is support for our data in the study by Gavorov and coworkers [20]. The influence of multifocality on the risk of PCa progression was previously investigated by only a few authors. They concluded that multifocality worsens prognosis due to earlier recurrence [21, 22]. Guzza and coworkers confirmed these observations, having quite similar groups to ours, with the frequency of multifocal tumors being 63.9% *vs.* 38.7% respectively. In addition they noticed a higher percentage of neurovascular bundle involvement in the group with coexisting PCa and HG PIN, which resulted in 1.9 times higher risk of BCR in this group and lower SRCS – 62% *vs.* 73% in 10 years follow-up [11].

In our study, the progression of PCa was insignificantly higher in group 1. However, when we analyzed this group separately, the progression was significantly higher in patients with multifocal tumors. In our opinion these results are influenced by a different number of clinically insignificant PCa tumors in both groups: 60% *vs.* 38.4% respectively ($p = 0.0023$). The problem of clinically insignificant tumors is widely discussed in literature, but there is only poor response to its connections with premalignant conditions. Salomon and coworkers investigated 30 patients with coexisting PCa and PL after RP and recognized that 76.7% of patients with insignificant tumors resulted in 4-years progression free survival in 78.3% of these cases [23].

Sangupta and coworkers operated 25 patients with previously diagnosed simultaneous PCa and PL and recognized clinically significant tumors in only 8% [13]. Most authors confirm that in re-biopsies and in specimens after RP the malignant lesions are located where they originally were in first biopsy, recognizing HG PIN or ASAP in about 70% of cases. It proves close biological connections, described as the so-called "field symptoms" [15]. Assessment of ASAP is more difficult due to the various potential in malignancy of these lesions [17, 22]. There is some evidence that proves ASAP as a powerful PCa predictor, such as Braussi and coworkers study, which included patients who underwent radical prostatectomy for ASAP and a detailed specimen examination revealed PCa in all of them [14]. However, the majority of urological societies do not justify RP for ASAP; regarding it as overtreatment [19, 24]. There are some observations concerning the high percentage of pT0 Gs0 tumors in such patients, supporting their recommendations. Finally, there are other non-radical possibilities such as chemoprevention of premalignant cases with drugs, food, or hormones. However, there are limited studies which confirm the abilities of these individual substances [25, 26 ,27].

The phenomenon of coexisting PCa and PL and its frequency are not precisely estimated in large randomized trials. Previous studies evaluate this frequency from a few to a few dozen percent. Prange and coworkers, in 83 specimens after cystoprostatectomy, recognized ASAP in 5% of cases, HG PIN in 35%, and PCa with HG PIN in 7% [4]. Flury and coworkers, after RP, recognized coexisting ASAP in 7%, ASAP+HG PIN in 18%, and HG PIN alone in 43% of cases [28]. Finally, Salomon et al. found 56% of patients with ASAP and/or HG PIN in their material [23]. There were 15.9% of such patients in our present study. We should also remember that some authors regard chronic non-bacterial prostatitis as PL [29]. In our investigated group, in 10% of patients, PCa followed inflammatory changes.

CONCLUSIONS

1. Simultaneous appearance of premalignant lesions and prostate cancer was recognized in 15.9% patients.

2. Either total PSA level, Gleason sum, or clinical staging were lower in the group with coexisting prostate cancer and premalignant condition, which resulted for a higher percentage of clinically insignificant tumors in these patients.

3. There were no differences in progression for five-years survival between the groups after radical prostatectomy.

4. Multifocality of neoplastic lesions has an influence on lower progression-free survival rate and lower tumor volume.

Acknowledgements:

Scientific research financed from science financing resources for years 2007-2010, as development project No. R 13 015 03.

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Correspondence

Mieczysław Fryczkowski
Department of Urology in Zabrze
Medical University of Silesia in Katowice
13/15, 3 Maja Street
41-800 Zabrze, Poland
phone: +48 342 716 511
klinurolzabrze@slam.katowice.pl