

PROSTATE CANCER DETECTION YIELD IN REPEATED BIOPSY IS INDEPENDENT OF THE DIAGNOSIS OF EARLIER BIOPSIES

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Background. We analyzed data gathered from initial and repeated prostate biopsies at the University Hospital in Olomouc, Czech Republic. We evaluated the diagnostic yield of repeated transrectal ultrasound (TRUS) guided biopsies. We also assessed whether the result of the repeated biopsy depended on the benign diagnosis of the previous biopsy.

Methods. From June 2006 till December 2008, the total of 794 men underwent a TRUS guided biopsy. The following parameters were recorded for each patient: age, total Prostatic Specific Antigen (PSA) level, free PSA level, digital rectal examination record, total prostate volume, and the histo-pathological evaluation. For patients undergoing a repeated biopsy, the histo-pathological result of the previous biopsy was also available, as well as the total number of previous biopsies and the time since the last biopsy. These data were analyzed using standard statistical methods.

Results. Initial biopsy was positive for prostate cancer in 157 out of 566 men (27.7%). The total PSA level was confirmed to be a significant ($P < 0.001$) predictor of prostate cancer. The ratio of free PSA to total PSA (the so-called PSA index) was found to be significantly lower ($P < 0.001$) for patients suffering from adenocarcinoma. A total of 191 men underwent a repeated biopsy. The repeated biopsy was positive for adenocarcinoma in 39 cases (20.4%). Although this yield is lower, the significance is at the threshold ($P = 0.04700$). In the group of rebiopsied men, total PSA level and PSA index were again significant ($P = 0.0024$ and $P = 0.0015$ respectively) predictive factors for prostate carcinoma. The diagnostic yield of repeated biopsy was assessed with respect to the most common types of the benign findings in the previous biopsy – adenomyomatous hyperplasia, inflammation, high grade prostatic intraepithelial neoplasia, and suspected adenocarcinoma. No significant difference in the diagnostic yield was found ($P = 0.38431$).

Conclusions. Total PSA level and PSA index are the most significant precursors of adenocarcinoma in both initial and repeated biopsy. The histo-pathological result of a repeated biopsy was found to be independent of the type of benign diagnosis of the previous biopsy. A substantial number of prostate cancer is diagnosed in repeated biopsies which advocates for the indication of a repeated biopsy in case of a negative result of the initial one.

INTRODUCTION

According to the Czech system of oncology data visualization¹, prostate cancer has become the most common cancer in the Czech Republic with an incidence of 96.87 new cases per 100,000 men in 2005. The mortality had been growing steadily and has reached 28.52 cases per year per every 100,000 men with this diagnosis.

Multiple transrectal ultrasound (TRUS) guided biopsy is the standard method for obtaining biological material for adenocarcinoma diagnosis. Indications for biopsy are usually based on elevated prostatic specific antigen (PSA) and/or the findings of digital rectal examination. In rare occasions, an unusual transrectal ultra-sonography finding may result in biopsy indication. There has been an extensive debate about various biopsy indicators, especially about the sensitivity and specificity of the PSA

level². A group of patients with a serum PSA level between 4 and 10 ng/ml contains a large number of benign diseases. The cut-off level of 4.0 ng/ml does not detect 20% of adenocarcinoma cases but identifies about 65% of benign diseases³. For this reason, additional PSA-derived factors are considered, the most important being the age-specific PSA level⁵, PSA density (ratio of PSA level to total prostate volume)⁴, The PSA index (ratio of free to total PSA level), PSA velocity (increase in total PSA level per one year)⁶, and others. Even when these co-factors are taken into account, a considerable number of false negative biopsy results is to be expected. These include both “clinically insignificant” cases and also patients with an adenocarcinoma who would definitely benefit from treatment.

In the case of an initially negative biopsy and persistent indication factors, repeated biopsy may be indicated.

According to the European Prostate Cancer Detection Study², initially negative groups contain about 10% false negative results. There are some results that indicate repeated biopsy⁷, however, no proven biopsy scheme exists⁸. In particular, the influence of the histo-pathological result of the initial biopsy on indications for rebiopsy should be addressed. In ref.^{9,10}, the authors claim that high-grade prostatic intraepithelial neoplasia (HGPIN) has a higher yield of adenocarcinoma on repeated biopsy. In this prospective cohort study, we analyzed data gathered from repeated biopsy, briefly address the problem of repeated biopsy indication and evaluated how the result of the repeated biopsy depends on the benign diagnosis of the preceding biopsy.

PATIENTS AND METHODS

Data Origin. The University Hospital in Olomouc is the center for prostate cancer treatment for the region of Central Moravia with a population of about 500,000. About 400 biopsies per year are carried out at the Clinic of Urology. From June 2006 to December 2008 a total of 794 men underwent a TRUS guided biopsy here. The following parameters were recorded for each patient: age, total prostatic Specific antigen (PSA) level, free PSA level, digital rectal examination record (DRE), total prostate volume, and histo-pathological result. For patients undergoing repeated biopsy, the histo-pathological result of the previous biopsy was available, as well as the total number of previous biopsies and the time since the last biopsy. The indications for biopsy were an abnormal DRE and/or serum PSA level of > 2.5 ng/ml.

At each biopsy, a variable number of specimens was taken (median 12) with respect to the prostate gland volume and the patients' age. We used a BK Medical Viking 2400 scanner with bi-plane 10 MHz transducer for guiding the biopsies and Sydmed Pajunk Delta Cut Biopsy System with variable puncture depth between 15 and 22 mm and 18 gauge needles for obtaining the specimens. After the biopsy, the peripheral part of the specimen was marked with a stain/ink and separately sent for histo-pathological analyses where the following possible results were detected: adenocarcinoma, atypical gland suspected of adenocarcinoma, adenomyomatous hyperplasia (AH), atypical adenomyomatous hyperplasia (adenosis), atrophy, inflammation, and high grade prostatic intraepithelial neoplasia (HGPIN). Adenosis and atrophy were diagnosed in very few cases and were therefore excluded from further analyses.

Patients, whose diagnosis was other than prostate cancer on the first biopsy, underwent repeated biopsy after a median of 12 months (range 2–25).

Descriptive Statistics. All patients with a PSA level above 50 ng/ml were excluded from further analyses because they are almost definitely positive for adenocarcinoma – the biopsy was performed only to confirm the diagnosis before the start of treatment. The resulting group of 757

biopsies was divided into initial biopsies and repeated biopsies. The PSA index is calculated as the ratio of free PSA level [ng/ml] to total PSA level [ng/ml] and it is displayed as percent.

The index should be computed only for patients with a total PSA level below 10 ng/ml because no additional factors are needed for higher PSA levels. Consequently, all index values for men with a total PSA level above this threshold were excluded from the analysis. Table 1. describe the characteristics of both groups.

Statistical Analysis Methods. Continuous variables (such as PSA) are seldom normally distributed. If normal distribution needs to be assumed, it is tested here by the Jarque-Bera test. It tests the null hypothesis that the sample comes from a normal distribution with unknown mean and variance, against the alternative that it does not come from a normal distribution. For most of the comparisons (of two or more groups), the Kruskal-Wallis test is used. The test compares the medians of the samples, and returns the p-value for the null hypothesis that all samples are drawn from the same population (or equivalently, from different populations with the same distribution). The Kruskal-Wallis test is a nonparametric version of the classical one-way ANOVA, and an extension of the Wilcoxon rank sum test to more than two groups. For comparison of two variables containing categorial data (e.g. DRE record and positivity for adenocarcinoma) the Pearson Chi-square test was used. A probability below 5% was considered statistically significant.

RESULTS AND DISCUSSION

Improved knowledge of prostate cancer risk in the public and its growing incidence has increased the demand for prostate biopsy in urological practice. Although several studies have shown that extended or multiple prostate biopsy improves the diagnostic yield, many patients undergo biopsies unnecessarily. Accurate indication criteria could reduce the number of useless biopsies but a number of factors can influence the risk of prostate cancer. While a large number of studies are based on various tumor markers of prostate cancer, only PSA is widely used in clinical practice. It is essential to understand therefore the relevance of PSA in different contexts and conditions.

Initial biopsies. There were 566 initial biopsies, 157 of which were positive for adenocarcinoma (27.7%).

PSA: The total PSA level is significantly higher ($P < 0.001$) for patients positive for adenocarcinoma. We further posed the hypothesis that there is no difference in the total PSA level among the three prevailing benign diagnoses (adenomyomatous hyperplasia, HGPIN, inflammation). Medians for total PSA were 4.99 ng/ml for adenomyomatous hyperplasia, 5.20 ng/ml for high-grade PIN and 4.44 ng/ml for inflammation. This hypothesis cannot be rejected, i.e. the difference between the three diagnoses is insignificant ($P = 0.7759$, see Fig. 1). The

Table 1. Descriptive statistics of the initial biopsies and repeated biopsies group. Positive: histo-pathological result of adenocarcinoma, negative: all the other histo-pathological results.

		Initial biopsies group		Repeated biopsies group	
		Positive	Negative	Positive	Negative
Age [years]	Number of patients	157	409	39	152
	Median	65	62	64	62
	Mean	64.88	61.22	64.79	62.37
	Std	7.29	6.49	5.74	6.41
	Min	50	39	49	42
	Max	89	79	76	76
Total PSA [ng/ml]	Number of patients	157	409	39	152
	Median	7.60	4.90	10.11	7.39
	Mean	11.17	6.27	13.91	9.84
	Std	9.76	4.71	9.22	7.11
	Min	1.62	0.61	3.72	2.62
	Max	46.60	41.60	42.20	47.48
PSA index [%]	Number of patients	101	295	18	93
	Median	13.10	18	10.15	16
	Mean	15.00	18.69	11.56	16.90
	Std	7.66	8.05	4.86	6.62
	Min	1	2.90	5	6.90
	Max	39.5	55	19.93	40
Volume [ml]	Number of patients	155	407	39	150
	Median	35	44	40	51.50
	Mean	43.25	49.15	41.26	56.10
	Std	29.49	23.88	15.07	26.66
	Min	14	12	13.70	17
	Max	250	173	76	150

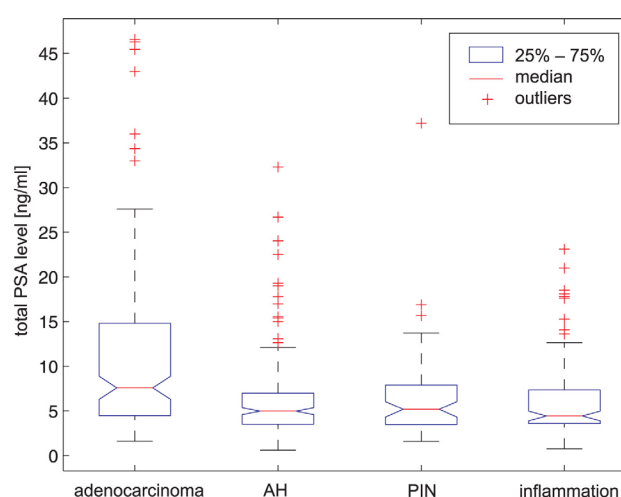
authors^{12,13} report that inflammation, particularly if it is acute, can contribute to an elevated PSA. Our results do not confirm this finding, on the contrary, the inflammation group appears to have the lowest PSA values.

PSA Index: The PSA index is found as the ratio of free PSA to total PSA. As already explained, the index was calculated for patients with a total PSA below 10 ng/ml only. The index is significantly lower ($P < 0.001$) for patients with positive histo-pathological findings.

The difference among the three benign diagnoses is insignificant ($P = 0.0668$) but inflammation appears to decrease the index value. Medians for PSA index were 18.7% for adenomyomatous hyperplasia, 18% for high-grade PIN and 16% for inflammation. However, testing the hypothesis that inflammation and adenocarcinoma have the same index medians results in rejecting the hypothesis ($P = 0.0225$), making the index value for adenocarcinoma still significantly lower.

Low values of PSA index in the inflammation group is in agreement with the literature¹⁴. Consequently, there is a risk that if the PSA index is considered alone, inflammation may conceal true cancer cases.

Per Rectum: We divide the digital rectal examination (DRE) results into two categories – positive and negative without further differentiating among the positive findings. It should be noted that a “positive” result is partly

**Fig. 1.** Comparison of the total PSA level in the initial-biopsy group. AH: Adenomyomatous Hyperplasia, PIN: Prostatic Intraepithelial Neoplasia.

subjective and dependent on the particular examiner. Sixty seven patients out of 113 with a positive DRE result were positive for adenocarcinoma (59%). Seventy nine patients out of 416 with a negative DRE result were positive for adenocarcinoma (20%). This shows that the specificity

Table 2. Influence of previous diagnosis on the result of the current biopsy. Horizontal: previous biopsy result, vertical: current biopsy result. Number of patients (% in parentheses).

AH: Adenomyomatous Hyperplasia, PIN: Prostatic Intraepithelial Neoplasia

	AH	PIN	Inflammation	Suspected adenocarcinoma
Adenocarcinoma	24 (27%)	4 (17%)	6 (17%)	1 (13%)
AH	40 (44%)	12 (50%)	11 (31%)	3 (37%)
PIN	10 (11%)	2 (8%)	1 (3%)	1 (13%)
Inflammation	16 (18%)	6 (25%)	17 (49%)	3 (37%)
Total	90	24	35	8

Table 3. Stratification of the diagnoses with respect to repeated biopsies.

AH: Adenomyomatous Hyperplasia, PIN: Prostatic Intraepithelial Neoplasia

	Adenocarcinoma	AH	PIN	Inflammation	Diagnostic yield
Initial initial biopsy	157	210	62	116	157/545 (29%)
First repeated-biopsy	24	51	12	32	24/119 (20%)
Second repeated-biopsy	9	16	3	11	9/39 (23%)
Third or higher repeated-biopsy	6	11	1	2	6/20 (30%)

of the DRE is not very high. However, the Pearson Chi-square test returns a P-value below 0.001 proving a significant difference in the DRE record between the malignant and the benign finding groups.

Volume: It is interesting that the total prostate volume (measured by ultra-sonography when guiding the biopsy needle) is significantly lower ($P < 0.001$) for patients positive for adenocarcinoma. Medians for prostate volume were 35 ml for adenocarcinoma, 46.5 ml for adenomyomatous hyperplasia, 42.5 ml for high-grade PIN and 44 ml for inflammation. The difference in volume among the three benign diagnoses is insignificant ($P = 0.740$).

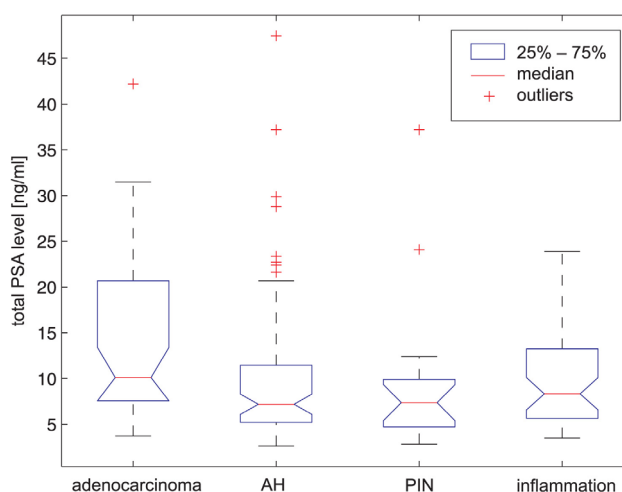
Moreover, there is small but significant correlation (Pearson's correlation coefficient of 0.3257, $P < 0.001$) between the total PSA level and the prostate volume. This makes lower prostate volume for positive patients even more significant and advocates for the use of PSA density (the ratio of the total PSA to the prostate volume) for biopsy indication (ref.¹⁶).

Repeated Biopsies. The yield of adenocarcinoma in the repeated biopsy group was 39 out of 191 (20.5%). This yield is not significantly lower than for the initial-biopsy group. However, the p-value of the Pearson Chi-square test reaches $P = 0.05084$, which is almost exactly on the threshold value of 0.05.

PSA: The total PSA level is significantly higher ($P = 0.0024$) for the patients positive for adenocarcinoma. In agreement with the initial-biopsy group, there is no significant difference ($P = 0.6072$) in PSA level among the three benign diagnoses. Medians for total PSA were 7.19 ng/ml for adenomyomatous hyperplasia, 7.37 ng/ml for high-grade PIN and 8.34 ng/ml for inflammation. Unlike the initial-biopsy group, inflammation does not have lower

values of PSA. The reverse appears to be true. However, both in the initial-biopsy and repeated-biopsy group, these differences are not significant (Fig. 2).

The total PSA level is the main indication criterion for rebiopsy. Consequently, there is no point in testing the difference in PSA between initial-biopsy and repeated-biopsy groups. However, it is interesting to see the stratification of the rebiopsy group with respect to the PSA level. It may be observed that at the cut-off level of about 8 ng/ml, there is a step in the diagnostic yield in the repeated-biopsy group (the ratio of positive to total patients changes from values around 20% to values over 50%). However, the

**Fig. 2.** Comparison of the total PSA level in the repeated-biopsy group. AH: Adenomyomatous Hyperplasia, PIN: Prostatic Intraepithelial Neoplasia.

number of patients is so small that we do not recommend that any clinical conclusions be drawn from these results.

PSA Index: Let us remember that the PSA index values were calculated only for patients with a total PSA level below 10 ng/ml. Like the initial-biopsy group, the index is significantly lower ($P = 0.0015$) for patients positive for adenocarcinoma. There is no significant difference ($P = 0.600$) in index among the three benign diagnoses. Medians for PSA index were 15.12% for adenomyomatous hyperplasia, 17.30% for high-grade PIN and 16% for inflammation.

Per Rectum: The same analysis of the digital rectal examination (DRE) as in the initial-biopsy group reveals a similar pattern. Twelve patients out of the 28 with a positive DRE result were positive for adenocarcinoma (43%). Twenty four patients out of 141 with a negative DRE result were positive for adenocarcinoma (17%). The specificity remains equally low in the repeated-biopsy group. There is no sense in testing the differences in DRE between initial-biopsy and repeated-biopsy groups because the DRE finding was one of additional factors indicating rebiopsy.

Volume: In the repeated-biopsy group, the total prostate volume is again lower for patients positive for adenocarcinoma, however, the difference is not significant anymore. Medians for prostate volume were 40 ml for adenocarcinoma, 50.5 ml for adenomyomatous hyperplasia, 42 ml for high-grade PIN and 60 ml for inflammation. Surprisingly, patients suffering from inflammation have significantly higher ($P < 0.001$) prostate volume than the three remaining groups.

This effect was not observed in the initial-biopsy group and we have no explanation for it. For some reason, patients suffering from inflammation in the repeated-biopsy group have much higher prostate volume than patients with the same diagnosis in the initial-biopsy group. It is possible that location of cancer in larger prostates is difficult in spite of more samples. The difference thus may be explained by the selection bias in the repeated-biopsy group.

Comparison of initial-biopsy and repeated-biopsy groups. We have shown that the result of the initial biopsy (provided it is negative) does not influence the total PSA level which is the primary criterion for rebiopsy indication. The PSA index is not influenced either. Therefore it is possible to analyze how the result of the previous biopsy affects the histo-pathological finding of the next biopsy (see Table 2).

It is apparent that there is slightly higher yield of positive rebiopsy in the group of patients suffering from AH. It is not reasonable to test the hypothesis that the current biopsy result is independent of the previous finding (it is to be expected that a patient previously diagnosed with e.g. AH will have a greater chance of being diagnosed with AH again). However, it can be tested that the percentage of patients positive for adenocarcinoma in the current biopsy is independent of the previous biopsy result. The Pearson Chi-square test returns $P = 0.38431$ which means that the difference in adenocarcinoma diagnostic yield among the groups is not significant. It is interesting that the yield is the lowest in the group where adenocarcinoma

was suspected on the previous biopsy. The number of such patients is so small that it does not allow us to draw any conclusion from this fact.

It should also be noted that the stratification of both groups (initial-biopsy and repeated-biopsy) with respect to the benign diagnoses is very similar, suggesting that the selection bias in the repeated-biopsy group does not relate to the histo-pathological findings, i.e. the type of (benign) diagnosis on the initial biopsy does not affect the probability of a rebiopsy indication. A closer look at the repeated biopsies reveals the following pattern (see Table 3).

Although the difference between the initial biopsy yield and the first repeated biopsy yield is at the threshold of significance (see above) we cannot conclude that the yield decreases with repeating biopsies. Observe that the yield in Table 3. is slightly different from the numbers already discussed – this is due to the fact that all histo-pathological results different from the four prevailing ones were ignored here.

CONCLUSIONS

(1) The results show that the diagnostic yield of adenocarcinoma in a repeated biopsy is independent of the type of benign diagnosis in the previous biopsy. Therefore, it should be recommended, not to take into consideration the result of the previous biopsy when making a decision about a repeated biopsy indication. In particular, HGPIN should not be considered as a precancerous any more if rebiopsy is indicated under conditions used in the study.

(2) Total PSA levels were confirmed as a very good indicator of prostate cancer. Total PSA is elevated in patients suffering from adenocarcinoma in both initial-biopsy and repeated-biopsy groups. We have not observed elevated PSA in patients suffering from inflammation. The PSA index is also a good indicator of adenocarcinoma for both initial-biopsy and repeated-biopsy groups although inflammation appears to decrease the index and mask true cancer cases. It can be concluded that PSA-derived factors (such as the PSA index) should definitely be used for biopsy indication, however, only in combination with the total PSA level¹⁵.

(3) Prostate cancer is associated with lower total prostate volume in both initial-biopsy and repeated-biopsy groups (or equally, all the benign diagnoses are associated with increased prostate volume). We have no explanation for this statistically significant result. This result advocates for the use of the so-called PSA density (total PSA level per prostate volume [ng/ml²]) because it makes PSA density correlate even more with adenocarcinoma occurrence.

(4) Adenocarcinoma diagnostic yield does not decrease in repeated biopsies.

Since the biopsy procedure is easy, fast, cheap and usually does not cause any complications, it can be recommended that the indication criteria be quite strict¹⁷.

LIST OF ABBREVIATIONS

PSA	Prostate specific antigen
TRUS	Transrectal ultrasound
HGPIN	High-grade prostatic intraepithelial neoplasia
DRE	Digital rectal examination
AH	Adenomyomatous hyperplasia

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