Outcome for Repeated Biopsy of the Prostate

Roles of Serum PSA, Small Atypical Glands, and Prostatic Intraepithelial Neoplasia

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Abstract

We studied the relationships between the outcome in the last follow-up prostate biopsy specimen and serum prostate-specific antigen (PSA), prostatic intraepithelial neoplasia (PIN), and atypical small acinar proliferations (ASAPs) at the occasion of the initial biopsy in 244 cases in which the initial specimen was negative for tumor and at least 1 follow-up biopsy was done. PSA levels and ASAPs were significantly associated with cancer in the follow-up biopsy specimen (P < .005; logistic regression analysis); however, the presence of PIN in the initial biopsy specimen did not relate to cancer in the follow-up specimen (P > .1). Thus, the probability that a follow-up biopsy demonstrates cancer depends on PSA and ASAPs, and even when ASAPs are present, serum PSA exerts an influence. For example, low PSA values, 5 ng/mL (5 µg/L) or less, are associated with low probabilities of a positive follow-up biopsy result, even when ASAPs were present in the first biopsy specimen. For higher PSA values, the presence of ASAPs dramatically increases the probability of a positive follow-up biopsy result compared with cases with no atypia or PIN in the first biopsy specimen.

For needle biopsies of the prostate, surgical pathologists have 3 broad choices for their diagnoses: benign, malignant, and atypical. The benign categories include changes of hyperplasia, inflammation, atrophy, adenosis, and a few other, less common pathologies, and the malignant categories comprise predominantly several patterns or types of adenocarcinoma. The category of atypia largely comprises 2 subcategories: high-grade prostatic intraepithelial neoplasia (hereafter denoted PIN)1–3 and foci of small atypical glands that are too small to be diagnostic as benign or malignant or have cytologic or tissue patterns that are not clearly benign or malignant.4–6 The second category of atypia has been labeled by some as “atypical small acinar proliferation”4 and by others as “atypical foci suspicious for carcinoma,”7 and to be concise we will hereafter symbolize this subcategory as ASAP.

Whereas clinicians have workable algorithms for dealing with biopsy results that are benign or malignant, there is far greater uncertainty and controversy about what to do when a set of prostate biopsy specimens yields PIN or ASAP.7 An effective way to study the issue is to examine the results of follow-up biopsies of patients who had PIN or ASAP in their first biopsy specimens, and many groups have done this.7 For example, Epstein and Herawi7 recently reviewed follow-up studies with a total of 3,754 patients with PIN and 2,762 with ASAP. Their tabulated data demonstrated that for patients with PIN, the weighted mean percentage of patients who had cancer in a follow-up biopsy specimen was 24%. For patients with ASAP, the weighted mean was 41%. Furthermore, in the same review, data demonstrated that for patients without PIN or ASAP, the weighted mean percentage of patients who had cancer in a follow-up biopsy specimen was 19%.7 Thus, the collective
results of all of the reviewed studies suggested that approximately twice as many patients with ASAP will have cancer in a follow-up biopsy specimen than if PIN or no atypia were found in the initial biopsy specimen. Furthermore, the results suggested that the outcomes in follow-up biopsies for patients with PIN may not differ from the outcomes for patients without any atypia.

When a urologist is deciding how to follow up a patient with PIN or ASAP, there are at least 2 additional variables he or she should heed: the value of the serum prostate-specific antigen (PSA) and results of digital rectal examination (DRE). For example, PSA, although not always specific, is clearly associated with the presence of prostate cancer and the outcome of a positive biopsy.8,9 Yet, Epstein and Herawi7 found that just 14 of 34 PIN studies examined PSA and just 10 of 21 ASAP studies examined PSA. Most surprising was the finding that few studies found that PSA or DRE were important to outcomes in follow-up biopsies.7 Because such results seem counterintuitive to us, we examined the relative importance of PSA, PIN, and ASAP to outcomes in 244 men who had follow-up prostate biopsies after initial biopsies failed to demonstrate tumor. Herein we report the results.

Materials and Methods

Study Cases

The patients comprised 244 whose initial biopsy of the prostate failed to demonstrate cancer and who underwent 1 or more repeated biopsies between January 2000 and November 2005. All biopsy specimens examined were selected from the Department of Pathology, Jewish General Hospital, Montreal, Canada. The cases were diagnosed by 2 department pathologists with community-based training and prostate needle biopsy expertise by practice. About 20% of the cases (between June 2004 and November 2005) were diagnosed by a third dedicated urological pathologist (T.A.B). There was no centralized review of cases, although the majority of cases with ASAP diagnoses were agreed on by at least 2 of the examining pathologists. The mean age of patients was 67 years (range, 38-82 years).

The median number of cores obtained in the first biopsy was 8 (range, 3-12). In 55 men, the initial biopsy revealed no atypia; in 42, just ASAP; in 93, just PIN; and in 54, ASAP and PIN. Of note, the newly described marker, α-methylacyl coenzyme A racemase was not introduced in our institution at the time the cases were signed out. However, the majority of cases (>95%) with equivocal or “suspicious” diagnoses were tested with the basal cell marker, 34βE12. Examples of cases included in this study as ASAP are given in Image 11 and Image 21.

Statistical Analysis

The outcome for this study was the presence or absence of cancer in the final follow-up prostate biopsy specimen. Because this outcome is a binary variable, we used logistic regression to model the dependence of the outcome on the variables of PSA, PIN, and ASAP, and to illustrate the combined influences of PSA, PIN, and ASAP on the probability of being free of tumor in the last follow-up biopsy specimen, we used Kaplan-Meier plots.

Results

Repeated biopsy demonstrated cancer in 74 (30.3%) of study cases. Of the tumors, 55 (74.3%) were found in the first repeated biopsy specimen, 12 (16.3%) in the second, 5 (6.7%) in the third, and 2 (2.7%) in the fourth. In cases with tumor, the Gleason scores ranged from 5 to 9 (median, 7). The results of the logistic regression analysis are given in Table 11. They demonstrated that PSA and ASAP were significantly and positively associated with the presence of cancer in the final follow-up biopsy specimen; however, the presence of PIN, alone or in combination with ASAP, was not associated with cancer in the follow-up biopsy specimen. In separate logistic regression analyses controlling for the combined effects of PSA and ASAP, we found no association between cancer in the follow-up biopsy specimen and DRE results (P > .2), the number of cores obtained (P > .2), the number of biopsy occasions (P > .1), the number of foci of ASAP (P > .6), or the number of foci of PIN (P > .05).

The composite effect of PSA and ASAP on outcomes in follow-up biopsies is best illustrated in Kaplan-Meier plots Figure 11, in which the probability of a tumor-free follow-up biopsy specimen is plotted against PSA for 3 patient groups: the control group without atypia in the first biopsy specimen, the group with just PIN present in the first biopsy specimen, and the group with ASAP present in the first biopsy specimen. The plots demonstrate that as PSA increases, the chance of a negative follow-up biopsy decreases. The plots also demonstrate that for any value of PSA, the presence of ASAP in the first biopsy specimen decreases the chance of a negative follow-up biopsy result compared with the control or PIN group. On the other hand, the near overlap of the lines for the control and PIN groups demonstrates that outcomes for these 2 groups are nearly the same when controlled for the effect of PSA.

Table 21 lists the Kaplan-Meier estimates for the probability of a positive follow-up biopsy result by PSA value and by absence and presence of ASAP in the first biopsy specimen. The entries in Table 2 are the expected probabilities obtained from our data. For example, our results suggest that 17% of patients with a PSA of 8 ng/mL (8 μg/L) and without ASAP would be expected to have a positive follow-up biopsy result,
whereas 46% of patients with this PSA value and prior ASAP would be expected to have a positive follow-up biopsy result.

**Discussion**

We believe that our results establish the importance of initial PSA for outcomes in repeated biopsies of the prostate after initial biopsies are negative for cancer, and, like other recent studies,\textsuperscript{10-13} we have found that the presence of ASAP in initial biopsy specimens is more important than PIN for the outcome of cancer in a repeated biopsy specimen. Furthermore, Figure 1 and Table 2 demonstrate that the probability of cancer in repeated biopsy specimens is strongly connected to the initial PSA level, even when ASAP was present in the first biopsy specimens. For example, when ASAP was present, the probability of a positive repeated biopsy result does not exceed 0.5 until the initial PSA level exceeded 8 ng/mL (8 µg/L). In this way, our
results should help urologists and their patients plan about repeated biopsies.

Our results also demonstrate that one cannot effectively study outcomes in prostate cancer without doing multivariate analyses like logistic regression. In other words, one cannot simply examine the binary relationship between the presence of ASAP or PIN and the outcome of a repeated biopsy without controlling for a variable known to be as important as PSA. Multivariate analyses are even more critical when examining the importance of secondary variables such as the number of cores obtained or the number of cores with atypia. Finally, when accounting for the role of a continuous variable like PSA, it is important to use it continuously, as we have in Table 2 and Figure 1. Using arbitrary cut points in PSA can yield misleading results, and perhaps this is why so many studies failed to demonstrate the importance of PSA.7,11,14

The main focus of this study was to examine the relationship between serum PSA as a variable in the presence of 2 important and widely encountered diagnoses in needle prostate biopsy specimens, ASAP and high-grade PIN. It did not address the issue of using additional biomarkers to aid surgical pathologists in establishing a definite cancer diagnosis. It also did not address the morphologic quantitative or qualitative heterogeneity of cases in the ASAP category and its relation with a subsequent cancer diagnosis. Future directions will be to examine the histologic and immunohistochemical details of cases of ASAP that were followed by a cancer diagnosis on repeated biopsy with emphasis on using additional markers such as α-methylacyl coenzyme A racemase.

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References


