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Review Article

# Prostate pointers and pitfalls: the 10 most prevalent problems in prostate biopsy interpretation

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ABSTRACT

As small volumes of prostate cancer are being detected with ever-increasing frequency, the pathologist is challenged to make more diagnostically out of less. This photoessay explores ten diagnostic problems that are noted with regularity by a provider of second opinions in prostate biopsy interpretation. These include: suboptimal submission of prostate cores, atypia with small size of the focus of concern, cytologic ambiguity of the focus of concern, issues with ordering and interpreting immunostains, atypia arising with high-grade prostatic intraepithelial neoplasia, benign mimics of cancer, omitting mention of extraprostatic tumor extension or of Gleason pattern 5, not recognizing intraductal carcinoma, and the differential diagnosis of cancer of urothelial versus prostatic origin.

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The skills and techniques of prostate biopsy interpretation are acquired through many years of training and experience. Small or minute volumes of prostate cancer are being detected with ever-increasing frequency, so the pathologist is challenged to make more diagnostically out of less. As a provider of second opinions on prostate biopsies diagnosed at outside institutions, I observe that large or small diagnostic discrepancies occur in a substantial percent of cases, and follow certain recurring themes. Here, I present a photoessay of 10 of the most pervasive sources of variation and error in prostate biopsy interpretation.

## 1. Suboptimal submission

Since we first surveyed this topic 15 years ago [1], a wide variety of approaches to submitting prostate biopsy cores has been observable. The most common practice is to sample an apex, mid, and base specimen from the medial and lateral prostate on both sides, amounting to 3 × 4 or 12 cores, in each of 12 vials. However, the number of vials determines how many CPT 88305 charges will accrue, so there has always been an economic incentive for some urologists to submit 2 or more cores per vial. This results in some loss of topographic information. If all the right-sided cores are submitted in one vial and all the left-sided cores in another, there is an almost total loss of topographic information about the extent of tumor within the prostate. It should be emphasized to urologists that submitting more than 3 cores per vial is not recommended.

Technical processing work and expense can be minimized by submitting 2 or 3 specimens per cassette. Thus, many laboratories will use differential inking of biopsy cores and submit 2 per cassette—one with ink—or 3 per cassette—2 with ink of different colors. Kahane et al compared the cancer yield from submitting 1 core/cassette (3-6 slices/2 slides) vs 3 cores/cassette (3 slices/2 slides) with differential inks applied. Similar rates of benign (46.2%, 46.7%), atypical small acinar proliferation (ASAP, 8.2%, 6.3%), high-grade prostatic intraepithelial neoplasia (PIN) (4.5%, 4.4%), and cancer (41.1%, 42.6%) diagnoses were noted [2]. Submitting more than 3 cores or core fragments per cassette is highly problematic. The problem of core fragmentation owing to excessive cores per vial is exacerbated by submitting all of these core fragments in one cassette (Fig. 1). The resultant difference in the planes of tissue embedding between fragments hinders diagnosis and also sacrifices the ability to measure the linear extent of tumor. It also allows crossing-over of cores, sacrificing information provided by cores at the points of intersection (Fig. 2).

## 2. Small size (of focus of atypia)

The diagnosis of atypical small acinar proliferation (ASAP), suspicious for but not diagnostic of prostatic adenocarcinoma, was first described by us in 1997 [3]. ASAP represents our inability to render an incontrovertible diagnosis of cancer in about 2% to 5% of sets of needle biopsies (and more rarely in transurethral resection specimens). The focus of concern invariably has fewer than 2 dozen acini—less than the size of the head of a pin—and many have ≤5 acini. Rarely, ASAP may comprise not small, but medium-sized acini where the differential diagnosis is cystic atrophy versus atrophy-like cancer. Our recent review of ASAP [4] disclosed that its predictive value for cancer on repeat biopsies is about 40%-50% in multiple studies. Notably, when cancer is diagnosed subsequent to initial diagnosis of ASAP on a set of needle core biopsies, the clinicopathologic findings at radical prostatectomy are not significantly different from those of cancers diagnosed at initial biopsy [5].

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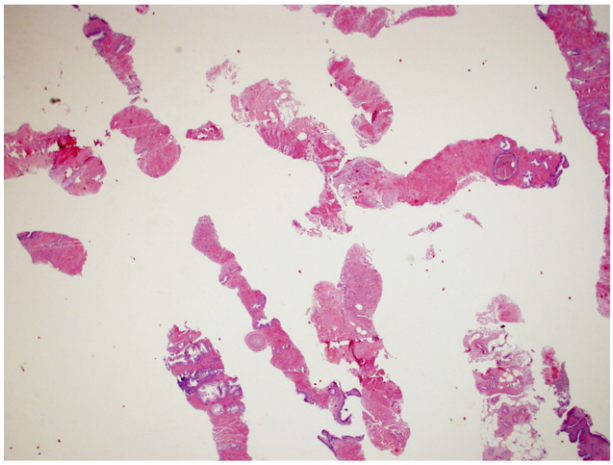

**Fig. 1.** Core fragmentation resulting from too many cores per vial, exacerbated by submitting too many core fragments per cassette.

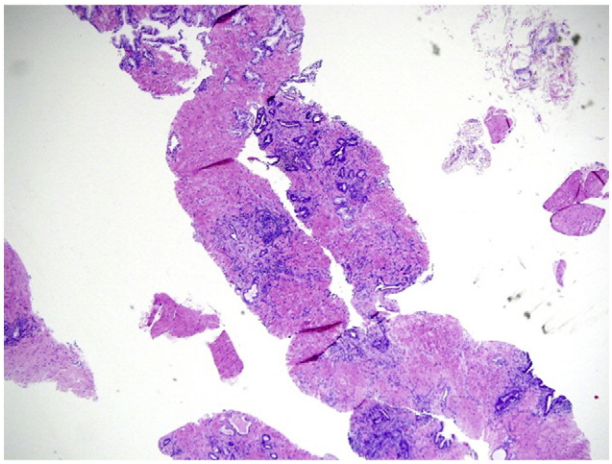

**Fig. 2.** Crossing-over of needle cores.

The ASAP diagnosis is justified in 2 main conditions. In 70% of cases [3], the size of the focal atypical acini is simply too small, often comprising one or a few atypical acini on the edge or tip of a needle core. A scant amount of acini with atypia and cytoplasmic basophilia is unable to be called cancer even with moderate support from an immunostain (Figs. 3 and 4). Even with stronger immunostain evidence favoring cancer, it is a mistake to it call cancer and such foci are often best diagnosed as ASAP. It is not unusual for just a single

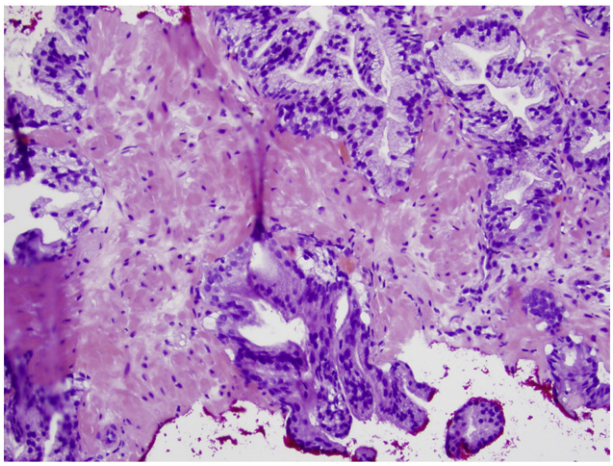

**Fig. 3.** Prostate biopsy specimen from a 35 y/o man with serum PSA of 1.35 ng/mL (normal, <4.0 ng/mL). Cytoplasmic basophilia of the glands at bottom, plus nuclear atypia, is suspicious for cancer. A few other cores had a similar finding.

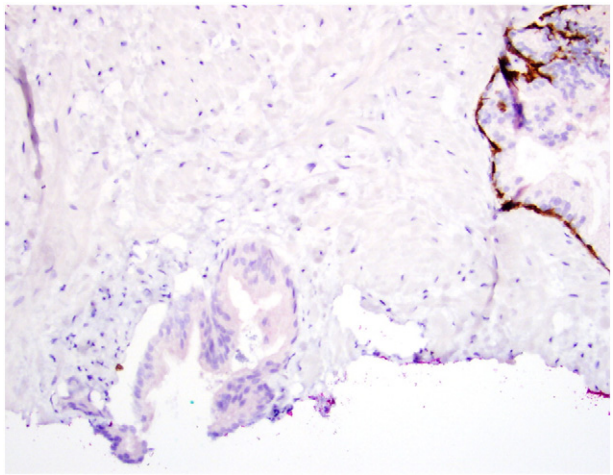

**Fig. 4.** ASAP. Triple immunostain on 35 y/o man's specimen shows apparent absence of basal cells, but racemase expression is not noted. Reactive atypia cannot be excluded with certainty.

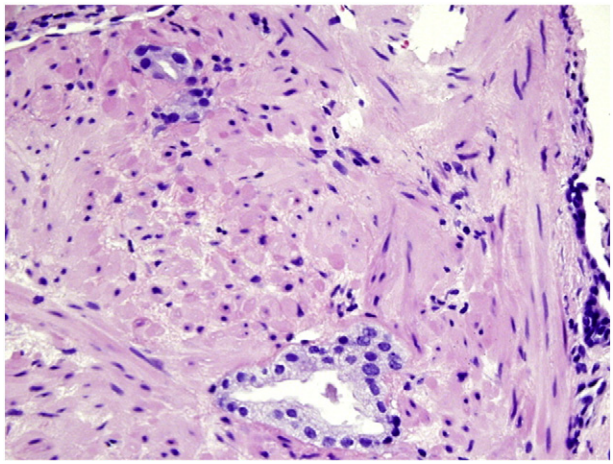

**Fig. 5.** ASAP. Minute size of atypical focus. Focus was lost on levels used for attempted immunostain.

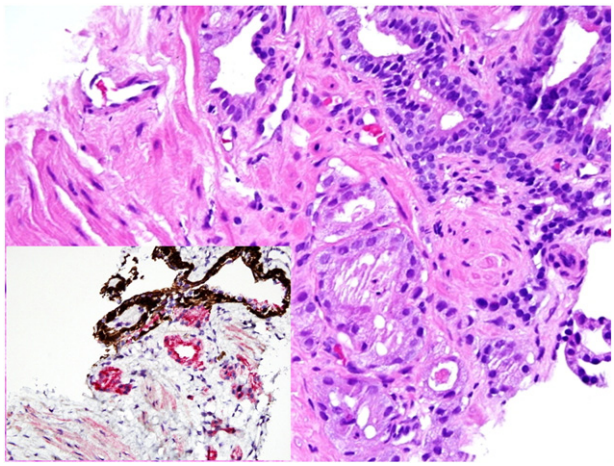

**Fig. 6.** Minimal cancer. Number and atypia of acini are sufficient to diagnose cancer.

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