Title: Risk of prostate cancer after isolated high-grade prostatic intraepithelial neoplasia (HGPIN) detected on extended core needle biopsy: a UK hospital experience

Version: 1 Date: 5 January 2009

Reviewer: Kenneth Iczkowski

Reviewer’s report:

1. Is the question posed by the authors well defined? YES
2. Are the methods appropriate and well described? YES
3. Are the data sound? YES BUT MORE ANALYSIS NEEDED ON CERTAIN THINGS
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? YES
5. Are the discussion and conclusions well balanced and adequately supported by the data? YES
6. Are limitations of the work clearly stated? YES
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? YES
8. Do the title and abstract accurately convey what has been found? YES
9. Is the writing acceptable? YES

- Major Compulsory Revisions

1. Abstract:

Don’t say HGPIN may be a precursor lesion. Say that it IS. There is enough evidence out there that such hesitation is not justified.

In the Results section of the Abstract, spell out what the predictive values for each PSA value were, don’t just say the rate was low. That is, “PSA ranges and their associated predictive values for cancer were: 0-5, 11%, 5-10, 34%……respectively.” This is a big enough finding to belong in the Abstract.

2. Background: 1st sentence: Again, avoid saying “may be....”

For the sentence about a lowered rate of CaP, along with reference [5], the Cory Schlesinger et al. paper [8], from 2005 should be cited, since that study also suggested a lowered risk of CaP after HGPIN, in contrast to prior literature. In fact, Schlesinger et al. came out before [5].

Patients and methods: OK
3. Results: I would like to know two additional facts. First, it is stated that the
mean number of cores was 12 (range 8-14). Was there a statistically significant increase in CaP detection according to number of cores taken?

It is also stated that 71% of the patients diagnosed with isolated HGPIN had it unifocally. That means it was multifocal in 29%. Did those 29% with multifocal HGPIN have significantly higher detection rate of cancer than the 71% with a unifocal finding? This is an important consideration as the authors state in the Discussion [13,14]. It may also be of interest to determine whether the cancer was ipsilateral versus contralateral to the site of the HGPIN. When the authors complete this and discuss their findings, they should be aware of Kronz JD et al. Am J Surg Pathol 2001;25:1079-85 (which is referenced in Zynger et al—see below).

4. In the paragraph about Table 2, please present all the percent values for prediction of CaP according to PSA stratification. This finding in Table 2 is quite striking and the numbers deserve mention in the text. Saying it was “higher” in men with PSA over 10 is an understatement, especially since it was 88% when PSA was >20. So this needs to be highlighted in the text.

5. Discussion: Reference [8] should be mentioned alongside [5] as to the incidence of HGPIN and predictive value for cancer, as the numbers were quite similar between these two studies. The authors are referred to a recent HGPIN review in the International Journal of Clinical and Experimental Pathology, an online journal (Debra L Zynger and Ximing Yang: High-grade Prostatic Intraepithelial Neoplasia of the Prostate: The Precursor Lesion of Prostate Cancer. Int J Clin Exp Pathol 2(4), 327-338; 2009. (Abstract, full text PDF). ) in which the authors found a 4.26% incidence of HGPIN, identical to that in the current work.

6. Line 6, capitalize P (Capà CaP)

7. Page 7. The authors found a 42% predictive value of HGPIN for cancer. This is higher than most contemporary US studies but if you compare it to mid-1990s U.S. studies, based on an era when there was less PSA screening and fewer cores were sampled (not 8-14 as nowadays) then the rate is quite comparable. I am specifically thinking of citing the Deborah Davidson J. Urol. 154:1791-94 paper of 1995 (with Bostwick) where she found a predictive value of 35% of HGPIN for subsequent cancer—not too far off from 42%. This paper was the very first to come out with a predictive value of HGPIN for cancer. This suggests that the different rates in PSA screening between UK and US are responsible for that difference in predictive values. Also, the Davidson paper found a significant interaction of HGPIN with PSA in predicting cancer. This is depicted in their Figure 2C. The authors should use their data to make a Kaplan-Meier plot like that of Figure 2C (although they won’t have an age-matched group without HGPIN). The benefit of doing this is that the x-axis depicts “Time from first biopsy,” providing a very clear picture of the time-dependence of the risk as stratified by PSA.

**Level of interest:** An article of importance in its field
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.