

## Optimizing Prostate Biopsy Techniques

What is the optimal biopsy strategy for detecting clinically important prostate carcinoma? I am not sure we are any closer in 2007 than we were in 1989 when the 6-core biopsy technique became the standard of care.<sup>1</sup> Take too few cores and clinically significant cancers might be missed. However, take too many cores and clinically indolent cancer may be identified. Data from the early 1990s demonstrated that a significant number of cancers were being missed with a 6-core approach, particularly in larger glands.<sup>2</sup> The solution has been to increase the number of cores which has improved the cancer detection rate to approximately 40%.<sup>3,4</sup> The cost has been potential over detection.

The 3 variables of tumor volume, tumor location and prostate gland size alter the likelihood of cancer detection. There is increasing evidence that we should take these 3 variables into account when tailoring our biopsy schemes to maximize the detection of clinically significant prostate cancer and minimize the identification of potentially indolent cancers.

Transperineal saturation biopsies hold the promise of detecting anterior tumors that may have been missed with transrectal biopsy strategies. Furuno et al demonstrated that on repeat biopsy in high risk patients, the anterior region of the prostate harbors cancers which cannot be detected with standard biopsy techniques.<sup>5</sup> Increasing the number of cores for larger prostates allows us to find prostate cancer foci that may be missed with standard techniques. Remzi et al developed a nomogram that incorporates prostate size and patient age to maximize the detection of prostate carcinoma in the prostate specific antigen (PSA) range of 2 to 10 ng/ml. In a prospective evaluation of the nomogram they demonstrated an improved cancer detection rate, particularly in younger patients.<sup>6</sup>

Unfortunately both of these strategies potentially increase the likelihood of detecting indolent disease. In this issue of *The Journal* Serfling et al (page 2352) address this important concept by constructing a mathematical model that examines the effect of prostate volume, number of cores, biopsy core location and tumor volume on cancer detection. The tumor volumes examined were 1.0 and 3.0 cc, well above the conventional thresholds of 0.2 and 0.5 cc for a pathologically indolent tumor.<sup>7</sup> Prostate volumes of 20 to 80 cc were placed in the model, resulting in core number recommendations ranging from 4 to 22. The novel concept is that a smaller prostate with a larger tumor needs fewer cores to maintain a detection probability of 0.90. Implicit in this approach is that some smaller, presumably less significant tumors will be missed.

Conceptually this model is attractive. If it is accurate, urologists could limit the number of cores in a small gland, maintaining the ability to detect larger tumors but decreasing the likelihood of detecting insignificant tumors. Before

this concept moves into the clinic, one needs to remember that this is not a trial but a model that needs to be validated in a patient population. Models are only as good as the assumptions from which they are built and how well those assumptions reflect the population of interest. While the assumptions in this model are reasonable, individual patient prostate and prostate tumors will not necessarily fit the model.

In addition, tumor volume is a surrogate for tumor aggressiveness. The 40-year-old patient with a 0.5 cc tumor is of much greater concern than the 80-year-old with a 1.0 cc tumor. In addition to age there are many factors that influence the decision to biopsy. Comorbidity, absolute PSA, PSA kinetics and family history must be assessed before aggressively pursuing prostate cancer in a given individual.

In a secondary analysis Serfling et al expanded their analysis by using the model to examine the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. Both of these large, well designed trials examine the role of 5 $\alpha$ -reductase in preventing prostate carcinoma.<sup>8,9</sup> According to author estimates tumor detection would have increased substantially in PCPT and REDUCE if tumor volumes had remained constant. Since the PCPT actually demonstrated a decrease in tumor detection of 24.8%, the model predicts tumor volume was 51% to 66% less than expected, representing substantial inhibition of tumor growth.

This secondary analysis provides a potential explanation into the increase in higher grade prostate cancer in the PCPT trial. While there was a 24.8% decrease in overall prostate carcinoma in PCPT, there was a 26.9% increase in Gleason 7–10 prostate cancer. It is unknown at this time if the increase in high grade tumors is real or artifactual. Possible explanations have ranged from subtle alterations in grade due to incomplete androgen ablation to decrease in prostate volume resulting in more accurate sampling of the tumor.<sup>10</sup> However, an alternative hypothesis consistent with the Serfling et al model is that higher grade tumors would be less responsive to 5 $\alpha$ -reductase inhibition, shrink less and, as a result, be more easily detected on needle biopsy. This hypothesis is consistent with the finding that the increased hazard ratio for high grade tumors appeared early in the PCPT study and did not increase with time.<sup>9</sup>

In summary, our focus has been on improving the detection of prostate carcinoma, which has resulted in a substantial over diagnosis. What we need are tools to detect clinically significant disease while minimizing the detection of clinically indolent disease. The model presented by Serfling et al provides a possible framework to tailor biopsies to detect more clinically relevant tumors.

**Adam S. Kibel**

Division of Urology

Washington University School of Medicine

St. Louis, Missouri

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