When is a Negative Prostate Biopsy Really Negative? Repeat Biopsies in Detection and Active Surveillance

REPEAT biopsies are commonly performed in the diagnostic setting and increasingly for men on active surveillance. A prior study using SEER (Surveillance, Epidemiology, and End Results)-Medicare data reported that 11.8% of men with a negative prostate biopsy underwent repeat biopsy within 1 year and 38% did so within 5 years.[1] A major problem is the significant sampling error with the traditional random systematic biopsy and the resulting lack of confidence that a negative biopsy is really negative.

This sampling error also results in staging inaccuracies that affect decision making about prostate cancer management for newly diagnosed patients. Indeed, a recent review shows that a third or more of patients with very low or low risk prostate cancer at diagnosis have disease upgraded upon resampling within 6 months.[2] For men who opt for active surveillance, most protocols recommend repeat biopsy within the first year and then every 1 to 5 years thereafter.

It is noteworthy that despite the inaccuracy of diagnostic prostate biopsy, new data from the PLCO (Prostate, Lung, Colorectal and Ovarian) Cancer Screening Trial in this issue of The Journal (page 1014) show that men with an initial negative prostate biopsy have a low risk of prostate cancer specific mortality (1.1% at 12.9 years median followup).[3] Nevertheless, the frequent scenario of a man undergoing 1 or multiple repeat biopsies during a lifetime represents a significant source of morbidity and cost.

Although repeat biopsy procedures have a risk of infection similar to that of the initial biopsy,[4] a new study from the New York Statewide Planning and Research Cooperative System, also in this issue of The Journal (page 1020), shows that the risk of these complications continues to increase with time.[5] Meanwhile, techniques to reduce biopsy risks such as the transperineal approach and rectal swab cultures were rarely used. The American Urological Association recently issued an updated white paper on the prevention of prostate biopsy complications and increasing use of these strategies should be encouraged to reduce the morbidity of prostate biopsy.[6]

Meanwhile, multiparametric magnetic resonance imaging (MRI) and several new biomarkers are available to help with decisions about repeat biopsy and for monitoring patients during active surveillance. Indeed, the 2016 National Comprehensive Cancer Network® Guidelines offer 6 second line testing options for men with a persistently elevated prostate specific antigen (PSA) considering repeat biopsy, including 3 blood tests (free PSA, the Prostate Health Index [phi] and the 4Kscore®), urinary PCA3, the ConfirmMDx® tissue test and MRI.[7]

Free PSA is a component of the phi and the 4Kscore, which provide similar performance for predicting high grade prostate cancer on biopsy. PCA3 is a Food and Drug Administration approved urine test specifically for the repeat biopsy setting, but in head-to-head studies it was inferior to the phi for predicting high grade disease. ConfirmMDx examines negative biopsy tissue for hypermethylation suggestive of an occult cancer, with a high negative predictive value in multiple studies. Several other promising new markers have also recently become available, such as SelectMDx and urinary exosomes, but these have not yet been incorporated into guidelines and require further investigation, specifically in the repeat biopsy setting.

Finally, a recent joint consensus statement from the American Urological Association and the Society of Abdominal Radiology suggested that when high quality MRI is available, it should be strongly considered for any patient with a prior negative biopsy and persistent suspicion for prostate cancer.[8] These are exciting times for patients with prostate cancer with such a rapid expansion in available diagnostic modalities to help inform when repeat biopsy should be performed.

The next frontier is how to integrate all of these data to create personalized protocols for prostate cancer detection and active surveillance.[9] A study in this issue of The Journal by Macleod et al (page 1026) from the Canary PASS (Prostate Cancer

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Active Surveillance Study) showed that men with a body mass index greater than 35 kg/m^2 or a PSA density greater than 0.15 ng were more likely to have reclassification on the first surveillance biopsy.[10] The authors suggested that men with these risk factors may benefit from earlier surveillance biopsy (eg at 6 months), whereas a longer interval was not associated with an increased risk of reclassification for patients without any of these high risk features. Other new tests such as the phi and MRI may also be useful to inform the frequency of followup biopsies during active surveillance. Hopefully a risk stratified approach combining clinical data and noninvasive tests can help reduce our reliance on repeat biopsies and provide more individualized prostate cancer care in the future.

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