EDITORIALS

Prostate Biopsy in Men with an Elevated PSA Level — Reducing Overdiagnosis

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Research into magnetic resonance imaging (MRI) for prostate cancer screening and diagnosis has been ongoing for more than a decade. Initially, MRI was thought to be important for achieving two goals. Among patients with low-grade (International Society of Urological Pathology [ISUP] grade 1, also called Gleason grade group 1) disease diagnosed on the basis of systematic biopsy, there was some hesitation to undergo active surveillance because of the possibility of missed higher-grade disease. An absence of high-grade lesions on MRI could help to allay those concerns.[1,2] In addition, systematic biopsy could miss high-grade disease when it is actually present and therefore lead to a delay in warranted initiation of curative therapy. MRI could potentially be used to detect such high-grade disease with targeted biopsies, thus guiding patients to timely appropriate treatment.[2]

Although active surveillance has been successful in allowing patients who have ISUP grade 1 disease, which is generally regarded as being overdiagnosed, to forego, at least for a time, curative therapy with its attendant costs and harms, it is not a panacea. Active surveillance has its own costs and harms, and a substantial proportion of patients eventually choose curative therapy as a result of psychological and family pressures, even in the absence of evidence of disease progression (which is relatively infrequent).[3,4] Furthermore, even for patients who continue to undergo active surveillance in the long term, important downsides include anxiety, health care system costs, and complications of the required periodic biopsies. In addition, evidence from randomized trials has shown that mortality from prostate cancer among patients undergoing active surveillance, or even watchful waiting, is relatively low and not significantly higher than that among patients who undergo initial curative treatment.[5,6] Therefore, a consensus is emerging that avoiding detection of ISUP grade 1 disease is a worthy goal of screening strategies.

After the introduction of MRI into clinical use, the generally accepted strategy was to perform systematic biopsy regardless of MRI results, with targeted biopsy added if lesions are found on MRI. However, recent studies have shown that identification of ISUP grade 2 or higher disease only by systematic biopsy in patients with lesions visible on MRI is relatively infrequent. For example, in the Trio study, in which patients underwent both systematic and targeted biopsy, only 6% of those who had a lesion with a Prostate Imaging–Reporting and Data System (PI-RADS) score of 3, 4, or 5 on MRI would have been upgraded to ISUP grade 2 or higher (from no disease or ISUP grade 1 disease) on the basis of added systematic biopsy.[7] Moreover, eliminating targeted biopsy reduced the detection of ISUP grade 1 disease by 41%, which is a plus, given the emerging consensus. Other data show a high negative predictive value of MRI for ISUP grade 2 or higher disease; thus, avoiding biopsy in this group is likely to be low risk and would reduce the diagnosis of low-grade disease.[8]

This brings us to the Swedish GÖTEBORG-2 trial, which aimed to contribute additional evidence about how best to use MRI in the context of PSA screening.[9] Approximately 13,000 men 50 to 60 years of age were randomly assigned to a

systematic biopsy group or an MRI-targeted biopsy group. All were invited to undergo PSA screening; men in either group with a PSA level of 3 ng per milliliter or higher were invited to undergo MRI. Men in the systematic biopsy group underwent systematic biopsy, as well as MRI-targeted biopsy if suspicious lesions were found, whereas those in the MRI-targeted biopsy group generally did not undergo systematic biopsy and underwent only MRI-targeted biopsy if lesions were noted on MRI. Men underwent postbaseline screening 2, 4, or 8 years later, depending on initial screening results. At a median of 3.9 years of follow-up, the trial showed a 57% lower risk of detecting ISUP grade 1 disease in the MRI-targeted biopsy group than in the systematic biopsy group, along with a 57% lower risk of undergoing biopsy, while also showing a 16% lower proportion of men with ISUP grade 2 or higher disease detected. From a public health perspective, these results are best expressed in absolute terms: per 1000 enrolled men, the MRI-targeted biopsy approach led to 51 fewer men undergoing biopsy and 14 fewer men receiving a diagnosis of ISUP grade 1 disease, but it also led to a delay in the diagnosis of ISUP grade 2 or higher disease in 3 men. The meaning of this delay is not immediately clear, but such a delay could lead to worse outcomes in a fraction of those men.

Performing MRI in everyone with an elevated PSA level is a resource-intensive strategy. However, the required resources can be offset by the experimental approach used in the GÖTEBORG-2 trial, which minimized the number and extent of biopsies. A systematic review of cost-effectiveness studies showed that for patients with an elevated PSA level, a strategy of first performing MRI and then proceeding to biopsy only if MRI targets were found was generally more cost-effective than a strategy in which the first step was performing systematic biopsy in everyone.[10]

The way in which MRI is used in the context of PSA-based screening is evolving. This trial gives additional evidence regarding the comparative effectiveness and resource utilization of MRI-based strategies designed to reduce biopsies and the diagnosis of clinically insignificant (ISUP grade 1) disease. This information contributes to the ultimate goal of designing screening strategies that preserve most of the benefits of PSA-based screening while reducing harms and costs.

Opinions expressed by the author are his own, and this material should not be interpreted as representing the official viewpoint of the U.S. Department of Health and Human Services, the National Institutes of Health, or the National Cancer Institute.

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