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Reducing or Increasing Overtreatment? How Do We Measure the Impact of Magnetic Resonance Imaging–targeted Biopsy on Prostate Cancer Mortality?

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The use of prebiopsy prostate magnetic resonance imaging (MRI) and subsequent MRI-targeted biopsy has truly revolutionized the diagnostic paradigm for prostate cancer, and the underlying belief among proponents of the technique is that it has allowed superior baseline risk stratification of patients. This improved risk stratification, in theory, may allow better counseling of patients and selection of a management strategy. Intrinsically, since the inception of MRI-based prebiopsy risk stratification, the belief has been that MRI has the potential to reduce the problem of overdetection and subsequent overtreatment, and thereby improve the impact of prostate cancer treatment on mortality via better candidate selection.

To date, countless studies have confirmed that the application of MRI-targeted sampling to prostate biopsy increases the detection of clinically significant cancer (defined typically by Gleason score), reduces the detection of indolent or low-grade cancer, and reduces the need for unnecessary biopsy in men deemed at low risk according to risk stratification [1–3]. When MRI is applied in a prostate-specific antigen (PSA)-based screening paradigm, the rate of indolent cancer detection is reduced if systematic biopsy is avoided and if biopsy is avoided altogether in men with elevated PSA and low suspicion on MRI [4]. Collectively, the data highly suggest an improved diagnostic paradigm whereby men who need therapy will be more likely to receive it and those who do not will be less likely to receive treatment.

As in all cases, the data could be viewed through a different lens. It has been asserted that rather than reducing overtreatment, MRI-targeted biopsy may actually fuel overtreatment of men who would have been appropriate for surveillance had they undergone systematic biopsy alone [5]. Logically, as the outcomes of surveillance have been quite good, with low rates of metastatic progression and up to half of men avoiding treatment in their lifetime, this is an important question. Does the use of MRI-targeted biopsy result in treatment for men who really did not need it? Moreover, data from large cohort studies indicate that men who were not diagnosed with prostate cancer on first-round biopsy rarely die of prostate cancer [6]. While the prevalence of missed occult high-grade tumors in such men is quite low, this further draws into question the benefit of finding such cancers at a population level.

In this issue of *European Urology*, Baboudjian et al [7] attempt to answer this question via a retrospective evaluation of rates of downgrading on radical prostatectomy following MRI-targeted biopsy that demonstrated grade group (GG) ≥2 cancer. The authors found a very low rate of downgrading (2.7%) to low-risk disease in a multicenter cohort of 1020 men, and it is notable that this is much lower than rates observed in most of the previous correlative

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studies. The authors conclude that their study shows no evidence of overtreatment as a result of MRI-targeted biopsy. The question is, perhaps, whether the correct population was studied. In determining overtreatment rates, the group in question would be those with GG $\geq$2 cancer on MRI-targeted biopsy and GG $\leq$1 on systematic biopsy, as treatment in this group would have been fueled purely by the targeted sample. It appears that two-thirds of men in this study had a systematic sample showing GG $\geq$2 cancer.

The observation that the rate of relapse is essentially equivalent for men with and men without downgrading in this study further suggests that downgrading may not be a robust measure of overtreatment. The fundamental difficulty in drawing this conclusion is that the authors still rely on the concept that Gleason grade alone justifies treatment, and that the arbitrary cutoff of GG 2 cancer represents true clinical significance. Given the known subjectivity of Gleason grading (particularly for men with minimal pattern 4), the demonstrated safety of surveillance for men with favorable-risk GG 2 cancer, and the low rates of prostate cancer mortality by 15 yr in the recent update of the ProtecT trial [8], I do not believe that we can safely conclude that MRI-targeted biopsy does not increase overtreatment on the basis of this study alone. It is reassuring that the authors have found a strong correlation between MRI-targeted biopsy and Gleason score on radical prostatectomy, as this suggests that the techniques for MRI-targeted biopsy are improving and providing accurate data regarding risk. Ultimately, better definitions of clinical significance, perhaps rooted in radiogenomic characteristics, and long-term follow-up for men treated or not treated on the basis of MRI-targeted sampling will be necessary to determine the true impact of MRI-targeted biopsy on prostate cancer mortality.

Conflicts of interest: The author has nothing to disclose.

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