benefit of extended therapy is likely to be meaningful in patients at higher risk of recurrence (eg, those with nodal involvement or genomic risk signatures for late relapse) and in those who are less likely to have substantial competing risks of death (eg, younger patients and those without comorbidities, especially cardiovascular disease). Data from trials such as NSABP B-42 should be used to validate models incorporating breast cancer and competing risks, thereby allowing clinicians to tailor therapy to individual patients.

Eitan Amir
Division of Medical Oncology, Princess Margaret Cancer Centre and the University of Toronto, Toronto M5G 2M9, Canada
eitan.amir@uhn.ca

I have received personal fees from Genentech/Roche and from Apobiologix, outside the submitted work.

1 Anderson GM. Breast-cancer recurrence after stopping endocrine therapy. *N Engl J Med* 2018; **378:** 870.
2 Al-Mubarak M, Tibau A, Templeton AJ, et al. Extended adjuvant tamoxifen for early breast cancer: a meta-analysis. *PLoS One* 2014; **9:** e88238.
3 Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005; **97:** 1262–71.
4 Mamounas EP, Bandos H, Lembersky BC, et al. Use of letrozole versus after aromatase inhibitor-based therapy (NRG Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol* 2018; published online Nov 30. http://dx.doi.org/10.1016/S1470-2045(18)30621-1.
5 Goldvaser H, Barnes TA, Seruga B, et al. Toxicity of extended adjuvant therapy with aromatase inhibitors in early breast cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2018; **110:** 31–39.
6 Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase inhibitors adjuvant therapy to 10 years. *N Engl J Med* 2016; **375:** 209–19.
7 Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. *Lancet Oncol* 2017; **18:** 1502–11.
8 Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al. Optimal duration of extended adjuvant endocrine therapy for early breast cancer; results of the IDEAL Trial (BOOG 2006-05). *J Natl Cancer Inst* 2018; **110:** 40–48.
9 Algorashi I, Goldvaser H, Ribnikar D, Cescon DW, Amir E. Evolution in sites of recurrence over time in breast cancer patients treated with adjuvant endocrine therapy. *Cancer Treat Rev* 2018; **70:** 138–43.
10 Abdel-Qadir H, Austin PC, Lee DS, et al. A population-based study of cardiovascular mortality following early-stage breast cancer. *JAMA Cardiol* 2017; **2:** 88–93.

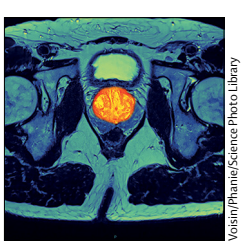
Exclusive MRI-targeted biopsy: not so fast

The MRI-FIRST trial reported by Olivier Rouvière and colleagues[1] in *The Lancet Oncology* is a thoughtfully designed, prospective investigation of men with suspected prostate cancer. This French multicentre study investigated the sensitivity of systematic versus targeted biopsy in the detection of clinically significant cancer. The greatest sensitivity in detecting prostate cancer was found by combining the two methods. Notably, only a third of clinically significant tumours were detected by either biopsy technique alone, which argues in favour of combining the two methods.

Previously, two of the most noteworthy investigations into MRI-guided prostate biopsy were the studies of Kasivisvanathan and colleagues (the PRECISION trial)[2] and Siddiqui and colleagues.[3] These studies both found that the proportion of prostate cancers detected by targeted biopsy was significantly greater than by systematic biopsy, thus providing a rationale for using targeted biopsy and omitting conventional systematic biopsy. However, in the PRECISION study,[2] men were randomly assigned to have either targeted or systematic biopsy. Combined biopsy was not done. In the study by Siddiqui and colleagues,[3] men with no MRI-visible lesions were excluded.

The design of the trial by Rouvière and colleagues differs from that of the aforementioned studies in one important way: all men had systematic biopsy, regardless of MRI results, and if a lesion was visible on MRI, targeted biopsy was also done. Thus, a proportion of false-negative diagnoses could be calculated for men with no MRI-visible lesion. Furthermore, a comparison of targeted and systematic biopsies in the same individuals could be obtained. Of the 94 men diagnosed with clinically significant prostate cancer of International Society of Urological Pathology grade group 2 or higher, 13 were diagnosed by systematic biopsy only, 19 by targeted biopsy only, and 62 by combining both methods. By employing each patient as his own control, this study design provided a conclusion that was not apparent in either of the earlier investigations: although targeting might be somewhat more sensitive than systematic sampling, the combination of the two methods provides the greatest detection. These results are similar to those reported by Filson and colleagues in a large prospective study.[4]

It is not yet clear why MRI does not detect some foci of clinically significant prostate cancer. Many of the undetected lesions are small, and lesions less than 0·5 cc are often invisible on MRI.[5] Systematic biopsy will detect some of these foci because small-volume lesions might have relatively large surface areas. Specific morphologies of prostate cancer, such as the aggressive


Voisin/Phanie/Science Photo Library

Published **Online** November 20, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30607-7

See **Articles** page 100

cribiform or mucinous varieties, might not be readily distinguishable from surrounding tissue with MRI.[6] The heterogeneity of the transition zone can shroud cancers in the inner prostate, a place where roughly 30% of all cases of clinically significant prostate cancer seem to reside. And although a standardised reporting system has been devised (Prostate Imaging Reporting and Data System version 2), no system of credentials has been established for radiologists to become experts in prostate MRI performance and interpretation. Inter-reader agreement of MRI scoring could therefore vary substantially; a κ score of 0·5 has been reported among experienced readers.[7] Thus, systematic sampling will probably persist as an adjunct to targeted sampling. Systematic biopsy can also have high relevance when planning focal therapies. Ideally, systematic sampling will employ template guidance, as provided in image-fusion devices.

Increased detection of clinically significant prostate cancer via the combination method described in the MRI-FIRST trial might also increase the detection of non-clinically significant or low-risk tumours. Previously, the resulting overtreatment of such tumours was often an undesirable side effect of extended biopsy—ie, over-detection led to over-treatment. Now, however, excessive treatment has been considerably mitigated by the advent of active surveillance for small, well differentiated tumours. A sharp and notable upturn in the use of active surveillance began a decade ago and is still gaining momentum.[8,9] Therefore, previous concerns about overtreatment of non-threatening tumours seems to be receding.

The MRI-FIRST trial was pragmatically designed to reflect the real-world implementation of MRI-targeted biopsy. Unlike some other contemporary trials, wherein imaging was done and interpreted at high-volume centres, in MRI-FIRST, MRI was strictly a local affair at each participating site, and radiologists did not have centralised training. As MRI-targeted biopsy is adopted in community settings, its implementation will probably have results similar to those of the MRI-FIRST trial. At the beginning of a new programme, the sensitivity of targeted biopsy alone might be less than is reported in previous clinical trials. Thus, as elegantly shown in MRI-FIRST, combined biopsy should be considered as the present standard. The decision of whether to perform biopsy in the first place will continue to be based on overall clinical suspicion, including palpable abnormalities, family history, race, prostate-specific antigen concentrations, and MRI findings (or lack thereof).

*Rajiv Jayadevan, *Leonard S Marks*
Department of Urology, Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA
lmarks@mednet.ucla.edu

We declare no competing interests.

1 Rouviere O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol* 2018; published online Nov 20. http://dx.doi.org/10.1016/S1470-2045(18)30569-2.
2 Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis (PRECISION study). *N Engl J Med* 2018; **378:** 1767–77.
3 Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion–guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA* 2015; **313:** 390.
4 Filson CP, Natarajan S, Margolis DJA, et al. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: the role of systematic and targeted biopsies. *Cancer* 2016; **122:** 884–92.
5 Le JD, Stephenson S, Brugger M, et al. Magnetic resonance imaging-ultrasound fusion biopsy for prediction of final prostate pathology. *J Urol* 2014; **192:** 1367–73.
6 Truong M, Feng C, Hollenberg G, et al. A comprehensive analysis of cribriform morphology on magnetic resonance imaging/ultrasound fusion biopsy correlated with radical prostatectomy specimens. *J Urol* 2018; **199:** 106–13.
7 Rosenkrantz AB, Ginocchio LA, Cornfeld D, et al. Interobserver reproducibility of the pi-rads version 2 lexicon: a multicenter study of six experienced prostate radiologists. *Radiology* 2016; **280:** 793–804.
8 Cooperberg MR. Active surveillance for low-risk prostate cancer—an evolving international standard of care. *JAMA Oncol* 2017; **3:** 1398.
9 Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990–2013. *JAMA* 2015; **314:** 80.

Drug development for glioma: are we repeating the same mistakes?

Published Online December 3, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30827-1

See Articles page 110

Treatment of recurrent glioma remains challenging, variable, and controversial. Despite repeated surgery, re-irradiation, and several lines of salvage chemotherapy, prognosis remains poor and most patients will die from their disease. Recent large randomised trials aiming at VEGF neutralisation with bevacizumab[1] or checkpoint inhibition with nivolumab (NCT02017717) have not shown a survival benefit.