



European Association of Urology

Open to Debate: For

Prostate Cancer: Is There Still a Role for Systematic Biopsies? Yes

Giorgio Gandaglia^{*}, Antony Pellegrino, Francesco Montorsi, Alberto Briganti

Unit of Urology/Division of Oncology, IRCCS Ospedale San Raffaele, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy

Article info

Article history

Accepted June 30, 2021

Associate Editor:

Guillaume Ploussard

The introduction of multiparametric magnetic resonance imaging (mpMRI) in the diagnostic pathway for prostate cancer (PCa) marked a paradigm shift, whereby MRI-targeted biopsy (MRI-TBx) improves the detection of clinically significant PCa (csPCa) compared to random systematic biopsy [1]. Moreover, MRI-TBx is associated with a decrease in the incidental diagnosis of clinically insignificant PCa and, therefore, with the risk of overtreatment compared to systematic biopsy [1]. Given these premises, one may ask what role random systematic sampling of the prostate has in the mpMRI era.

First, prospective studies demonstrating the superiority of a pathway based on MRI-TBx over systematic biopsy mainly include asymptomatic men with a prostate-specific antigen (PSA) level between 2 and 20 ng/ml and negative digital rectal examination (DRE). In particular, the median PSA at enrolment in the PRECISION, MRI-FIRST, and 4M studies was below 6.8 ng/ml and up to 85% of the participants had a normal DRE [1–3]. Conversely, the risk of harbouring csPCa at systematic biopsy for a man with an abnormal DRE or PSA of 20 ng/ml ranges between 25% and 45% according to the Rotterdam ERSPC risk calculator [4]. Since these patients were under-represented in avail-

able studies assessing the role of mpMRI and targeted biopsy, one might hypothesise that systematic biopsy would not be inferior to MRI-TBx in this setting. The use of upfront random systematic biopsy for men with a clinical suspicion of PCa based on an abnormal DRE or PSA ≥ 20 ng/ml would reduce the number of mpMRI examinations performed with timelier diagnosis and savings for the health care system.

Second, concomitant systematic biopsy might improve the ability to diagnose csPCa for men undergoing MRI-TBx. Indeed, the disease itself is multifocal, a feature that current mpMRI techniques cannot fully grasp, as this imaging modality is able to detect only 65% of all the foci of csPCa identified at whole-mount pathology [5]. This is particularly true when considering small (<1 cm) lesions, for which the risk of missing csPCa at mpMRI increases with the Prostate Imaging-Reporting and Data System score of the index tumour [6]. In terms of evidence from prospective trials, MRI-FIRST demonstrated that addition of concomitant systematic biopsy would allow detection of approximately 5% more men with csPCa compared to MRI-TBx [2]. Similar figures were observed in the 4M study, and a recent Cochrane meta-analysis estimated that omitting systematic biopsy at the time of MRI-TBx would miss approximately 15% and 10% of ISUP grade group ≥ 2 PCa in the biopsy-naïve and repeat biopsy settings, respectively [3,7]. On the basis of these findings, the European Association of Urology guidelines currently recommend combining targeted and systematic biopsy for biopsy-naïve patients [8]. Of note, the attempt to develop multivariable models to identify men who could receive MRI-TBx alone failed and currently there is no way to avoid systematic biopsy in this setting [9].

Third, systematic biopsy at the time of MRI-TBx provides important prognostic information and should guide the sur-

DOI of original articles: <https://doi.org/10.1016/j.euro.2022.01.006>; <https://doi.org/10.1016/j.euro.2021.07.010>.

^{*} Corresponding author. Unit of Urology/Division of Oncology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy. Tel. +39 02 26434066; Fax: +39 02 26437286.

E-mail address: gandaglia.giorgio@hsr.it (G. Gandaglia).

<https://doi.org/10.1016/j.euro.2021.06.016>

2666-1683/© 2022 The Author(s). Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



gical approach. Random prostate sampling may serve as an “index of multifocality”, which is important when formulating a therapeutic strategy. The presence of csPCa outside the index lesion is associated with higher risk of adverse pathologic features at radical prostatectomy and this variable has been included in models predicting lymph node invasion, extracapsular extension, and seminal vesicle invasion [10–12]. The accurate knowledge of the prostate gland outside the index lesion obtained via systematic sampling allows for accurate surgical planning, potentially reducing the risk of positive surgical margins. The presence of csPCa outside the index lesion in men treated with surgery has also been associated with greater risk of biochemical recurrence and therefore has important prognostic implications [13]. Performing both systematic biopsy and mpMRI-TBx provides the physician with complementary information. On the one hand, targeted biopsy allows confident detection of the main lesion of interest. On the other hand, systematic sampling of the prostate allows detection of the few csPCa lesions missed by mpMRI and provides information regarding the multifocal nature of the disease, which is important for risk stratification and prognosis.

Finally, systematic biopsy still represents the cornerstone for follow-up of patients included in active surveillance programs. Indeed, mpMRI is characterised by suboptimal sensitivity for low-grade and low-volume disease and it misses a substantial proportion of csPCa at confirmatory or surveillance prostate biopsy in active surveillance. Previous studies demonstrated that an active surveillance strategy based on mpMRI to trigger MRI-TBx would miss an unacceptable rate of csPCa [14]. Therefore, systematic random confirmatory and/or surveillance biopsies should be performed even in patients with a negative mpMRI.

To conclude, systematic biopsy still plays an important role in the diagnostic and therapeutic pathways for PCa. Future advances in imaging may result in a more detailed picture of the prostate and therefore imaging could potentially replace systematic biopsy. That said, as of today, random sampling of the prostate should be considered an integral part of prostate biopsies, as omitting them may have repercussions for therapeutic management.

Conflicts of interest: The authors have nothing to disclose.

References

- [1] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018;378:1767–77.
- [2] Rouvière O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol* 2019;20:100–9.
- [3] van der Leest M, Cornel E, Israël B, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naïve men with elevated prostate-specific antigen: a large prospective multicenter clinical study. *Eur Urol* 2019;75:570–8.
- [4] Roobol MJ, Verbeek JFM, van der Kwast T, et al. Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer risk calculator for initial prostate biopsy by incorporating the 2014 International Society of Urological Pathology Gleason grading and cribriform growth. *Eur Urol* 2017;72:45–51.
- [5] Johnson DC, Raman SS, Mirak SA, et al. Detection of individual prostate cancer foci via multiparametric magnetic resonance imaging. *Eur Urol* 2019;75:712–20.
- [6] Stabile A, Dell’Oglio P, de Cobelli F, et al. Association between Prostate Imaging Reporting and Data System (PI-RADS) score for the index lesion and multifocal, clinically significant prostate cancer. *Eur Urol Oncol* 2018;1:29–36.
- [7] Drost F-JH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database Syst Rev* 2019;2019:CD012663.
- [8] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2021;79:243–62.
- [9] Dell’Oglio P, Stabile A, Soligo M, et al. There is no way to avoid systematic prostate biopsies in addition to multiparametric magnetic resonance imaging targeted biopsies. *Eur Urol Oncol* 2020;3:112–8.
- [10] Gandaglia G, Ploussard G, Valerio M, et al. A novel nomogram to identify candidates for extended pelvic lymph node dissection among patients with clinically localized prostate cancer diagnosed with magnetic resonance imaging-targeted and systematic biopsies. *Eur Urol* 2019;75:506–14.
- [11] Gandaglia G, Ploussard G, Valerio M, et al. The key combined value of multiparametric magnetic resonance imaging, and magnetic resonance imaging-targeted and concomitant systematic biopsies for the prediction of adverse pathological features in prostate cancer patients undergoing radical prostatectomy. *Eur Urol* 2020;77:733–41.
- [12] Gandaglia G, Martini A, Ploussard G, et al. External validation of the 2019 Briganti nomogram for the identification of prostate cancer patients who should be considered for an extended pelvic lymph node dissection. *Eur Urol* 2020;78:138–42.
- [13] Gandaglia G, Ploussard G, Valerio M, et al. Prognostic implications of multiparametric magnetic resonance imaging and concomitant systematic biopsy in predicting biochemical recurrence after radical prostatectomy in prostate cancer patients diagnosed with magnetic resonance imaging-targeted biopsy. *Eur Urol Oncol* 2020;3:739–47.
- [14] Chesnut GT, Vertosick EA, Benfante N, et al. Role of changes in magnetic resonance imaging or clinical stage in evaluation of disease progression for men with prostate cancer on active surveillance. *Eur Urol* 2020;77:501–7.