Fusion Biopsy, not Cognitive, Is the New Gold Standard

Alessandro Marquis, Giancarlo Marra, Paolo Gontero

Azienda Ospedaliera Universitaria Città della Salute e della Scienza, University of Turin, Department of Surgical Sciences, Division of Urology, Turin, Italy

Abstract

To date, although some benefits resulting from a software-guided technique are undeniable, no clear superiority of fusion over cognitive targeted biopsy (COG-TB) has been supported by strong evidence. We discuss potential causes of trials failing to show the superiority of fusion TB (FUS-TB) and highlight its advantages over the cognitive approach.

One possible reason why current literature showed contradictory evidence in supporting FUS-TB may be the lack of high-quality well-designed trials. Indeed, most of the studies addressing this issue have considerable limitations, such as underpowering, small sample size, lack of randomization, and poor generalizability. A second reason may be the inclusion in the majority of trials of a wide spectrum of MRI-lesions, a scenario in which the benefits of FUS-TB may be less evident. In fact, some of the few studies considering smaller targets demonstrated higher accuracy for the FUS technique. As concerns the advantages of FUS-TB, the opportunity offered by some fusion systems of storing information useful for planning and/or follow-up active surveillance, focal therapy, and radical prostatectomy, as well as a reported faster learning curve, are strong points supporting the fusion approach.

In conclusion, the potential advantages when targeting smaller lesions together with the storage capability to guide patient management after the biopsy and an easier learning curve may make the FUS approach the more appropriate technique for performing TB.

Commentary

When MRI is positive, current guidelines strongly recommend a prostate biopsy combining systematic (SB) and targeted (TB) cores[1]. The MRI target can be sampled through a cognitive guidance, a US/MRI fusion software or, less frequently, a direct in-bore guidance[2]. To date, there is no strong evidence to support the superiority of either one of these methodologies. However, when comparing the fusion and the cognitive approaches, it is undeniable that fusion has some advantages. We discuss potential reasons that trials fail to show clinically significant differences and highlight some advantages of a software over a cognitive-based TB.

Evidence from trials is contradictory

Some RCTs may have failed in capturing clinical benefits of the fusion over the COG-TB while others did not highlight significant advantages. Overall, all these studies suffer from considerable limitations. Notably, the FUTURE trial, which included 665 men with prior negative SB to undergo fusion versus cognitive versus in-bore TB, reported a higher clinically significant prostate cancer (PCa) detection rate for the fusion than the cognitive group, although not reaching statistical significance (34.2% versus 33.3%, $P > 0.9$)[3]. However, the primary endpoint resulted clearly underpowered with only 79 and 78 patients randomized for FUS and COG respectively versus 152 per group originally planned in the sample size calculation. Furthermore, only men with prior negative SB were included thus making the results not generalizable to all patients with PCa suspicion based on MRI findings.

Key Words

Prostate biopsy, targeted prostate biopsy, fusion prostate biopsy, cognitive prostate biopsy, prostate cancer

Competing Interests

None declared.

Article Information

Received on September 8, 2022
Accepted on January 3, 2023
This article has been peer reviewed.

Soc Int Urol J. 2023;4(2):142–144

DOI: 10.48083/RYRF4858

The PAIREDCAP study is a paired cohort trial which included 248 biopsy naïve patients undergoing 12 SB followed, in sequence, by 3-cores COG-TB and 3-cores FUS-TB[4]. The csPCa detection rate of FUS-TB was 7% higher than that of COG-TB (54.0% versus 46.8%) and similar difference was shown also at the per-core analysis (38.1% versus 33.3%). Although the trial was not powered to detect differences in the detection rate between the 2 techniques, these findings may support a potential advantage of FUS-TB even in the biopsy naïve population.

A more recent RCT investigated the diagnostic yield of fusion versus COG-TB in 199 men, all biopsy naïve and randomized head-to-head[5]. The study was powered with 200 patients under the authors' assumption of a 15% higher detection rate for FUS-TB. The results confirmed the hypothesised advantage of FUS: both the overall and csPCa detection rates were significantly higher in the fusion than in the cognitive group (44.4% versus 31.0%, $P = 0.035$ and 33.3% versus 19.0%, $P = 0.016$, respectively). The average positive cores number was also higher in the fusion arm (13% versus 8%, $P = 0.045$). Notably, the authors acknowledged in the discussion that in order to prove a 5% advantage of fusion over COG-TB (as current literature data seem to show), a total of 1776 patients would be needed, a number that exceeds the accrual of any available trial so far conducted and confirming that solid evidence in this respect is still lacking.

Size of MRI lesion

This may be another reason why some studies failed in showing clinically significant differences in favour of FUS-TB. It is reasonable that larger targets are likely to be more easily sampled using COG-TB, while with smaller lesions, FUS-TB may have significant advantages. Existing evidence has shown a high grade of targeting precision for the FUS system, with accuracy of 99% for lesions ≥ 6 mm and of 96% for 5 mm lesions. Smaller targets are less likely to be adequately sampled using only 1 targeted bioptic core (61% for 3 mm lesion), but the probability increases to 94% with 3 cores[6]. Therefore, fusion software is likely able to ensure levels of precision seldom achieved for small lesions in a cognitive setting.

Mean target size usually detected at MRI is 12 mm (IQR 8 to 15 mm)[7]; therefore, it is not surprising that in the majority of the main trials comparing fusion and COG-TB, mean lesion size ranged from 11 to 14 mm [3–5,8], more than double the minimum detection threshold of MRI. In this "wide-lesion" scenario, FUS-TB benefits may be less evident. The PROFUS trial analysed the fusion versus COG-TB diagnostic accuracy in a cohort with a slightly lower average size lesion (9 mm [IQR 7 to 13 mm]) and found a borderline significance in favour of FUS-TB in terms of per-target csPCa detection rate (20.3% versus 15.1%, $P = 0.052$). Smaller target diameter was identified as one of the most influential factors for cancer detection in the fusion group, further supporting the view that FUS-TB provides the greatest impact when targeting smaller lesions that may be difficult to sample using COG-TB[8]. Importantly, previous retrospective series observed a significant advantage for FUS-TB with a magnitude of effect that was larger in lesions below 1 cm (FUS-TB 64.0% versus 40% COG-TB, where targets ≤ 10 mm were 52% versus 21%, respectively)[9].

FUS-TB is more informative

Some fusion systems allow exact recording of the location of positive cores, which is key in the era of precision PCa diagnostics and treatment when planning future management. This has implications for (1) a more accurate follow-up biopsy during active surveillance; (2) a more precise delivery and then follow-up of focal therapy; (3) radical prostatectomy planning[8].

Fusion may be easier to learn

A higher operator expertise may be required to achieve comparable outcomes with a cognitive approach. Stabile et al. retrospectively evaluated both the detection rate and its improvement in 244 men during the learning curve[10]. There was no clear increase in detection of csPCa overall (58% versus 45% $P = 0.07$) but the detection of csPCa on a per-target analysis was higher with FUS-TB (57% versus 36%, $P = 0.002$). Interestingly, not only the fusion technology but also operator expertise was an independent predictor of cancer detection. In addition, the COG-TB learning curve was steeper, and the number of procedures needed to reach the plateau lower for FUS-TB.

Conclusion

While current evidence does not strongly support the superiority of fusion over cognitive TB, it seems plausible that FUS-TB is more accurate in targeting smaller lesions. Major trials have generally been underpowered and have yielded contradictory evidence; however, most have included large lesions, while the advantages of FUS-TB are likely more evident for smaller targets. The learning curve may also be shorter for fusion compared with COG-TB. In the era of precision medicine, advantages that are not clinically measurable, including storage capability to guide patient management after the biopsy, should also be considered.

References

1. Mottet N, van den Bergh RCN, Briers E, De Santis M, Gillesen S, Grummet J, et al. EAU Guidelines on Prostate Cancer 2022.

2. Yamada Y, Ukimura O, Kaneko M, Matsugasumi T, Fujihara A Vourganti S, et al. Moving away from systematic biopsies: image-guided prostate biopsy (in-bore biopsy, cognitive fusion biopsy, MRUS fusion biopsy)—literature review. *World J Urol.*2021;39:677–686. https://doi.org/10.1007/s00345-020-03366-x.

3. Wegelin O, Exterkate L, van der Leest M, Kummer JA, Vreuls W, de Bruin PC, et al. The FUTURE Trial: a multicenter randomised controlled trial on target biopsy techniques based on magnetic resonance imaging in the diagnosis of prostate cancer in patients with prior negative biopsies. *Eur Urol.*2018;75(4): 582-590. https://doi.org/10.1016/j.eururo.2018.11.040.

4. Elkhoury FF, Felker ER, Kwan L, Sisk AE, Merdie D, Natarajan S, et al. Comparison of targeted vs systematic prostate biopsy in men who are biopsy naive: The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) Study 2019. https://doi.org/10.1001/jamasurg.2019.1734.

5. Izadpanahi M-H, Elahian A, Gholipour F, Khorrami M-H, Zargham M, Mehrdad MS, et al. Diagnostic yield of fusion magnetic resonance-guided prostate biopsy versus cognitive-guided biopsy in biopsy-naive patients: a head-to-head randomized controlled trial 2021. *Prostate Cancer Prostatic Dis.*2021;24:1103–1109. https://doi.org/10.1038/s41391-021-00366-9https://doi.org/10.1038/s41391-021-00366-9.

6. Wegelin O, Henken KR, Somford DM, Breuking FAM, Bosch RJ, van Swol CFP, et al. An ex vivo phantom validation study of an MRI-transrectal ultrasound fusion device for targeted prostate biopsy. J Endourol.2016 Jun;30(6):685-691.doi: 10.1089/end.2015.0864. Epub 2016 Mar 16.

7. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al.;PRECISION Study Group Collaborators. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med.*2018 May 10;378(19):1767-1777. doi: 10.1056/NEJMoa1801993. Epub 2018 Mar 18.

8. Wysock JS, Rosenkrantz AB, Huang WC, Stifelman MD, Lepor H, Deng F, et al. A prospective, blinded comparison of magnetic resonance (MR) imaging – ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. *Eur Urol.*2014 Aug;66(2):343-351. doi: 10.1016/j.eururo.2013.10.048. Epub 2013 Nov 8.

9. Oderda M, Faletti R, Battisti G, Dalmasso E, Falcone M, Marra G, et al. Prostate cancer detection rate with koelis fusion biopsies versus cognitive biopsies: a comparative study. *Urol Int.*2016;97(2):230-237. doi: 10.1159/000445524. Epub 2016 Jun 4.

10. Stabile A, Dell'Oglio P, Gandaglia G, Fossati N, Scattoni V, Maga T, et al. Not all multiparametric magnetic resonance imaging – targeted biopsies are equal: the impact of the type of approach and operator expertise on the detection of clinically significant prostate cancer. *Eur Urol Oncol.*2018 Jun;1(2):120-128. doi: 10.1016/j.euo.2018.02.002. Epub 2018 May 15.2018;1.