LITERATURE REVIEW

Should we perform systematic biopsies in case of suspicious MRI for prostate cancer in 2020? A review of literature

Faut-il réaliser des biopsies systématiques en cas d’IRM suspecte de cancer de prostate en 2020 ? Une revue de littérature

Q. Vesval\textsuperscript{a,b,*}, G. Fiard\textsuperscript{c,d,e,f}, A. Villers\textsuperscript{a,b}, J.M. Norris\textsuperscript{c}, J. Olivier\textsuperscript{a,b,c}

\textsuperscript{a} Department of Urology, Hospital Claude Huriez, CHRU Lille, France
\textsuperscript{b} Université de Lille 2, Faculté de médecine Henri Warembov, Lille, France
\textsuperscript{c} UCL Division of Surgery and Interventional Science, University College London, London, UK
\textsuperscript{d} Department of Urology, University College London Hospital NHS Foundation Trust, London, UK
\textsuperscript{e} Department of Urology, Grenoble Alpes University Hospital, Grenoble, France
\textsuperscript{f} Université Grenoble Alpes, CNRS, Grenoble INP, TIMC-IMAG, Grenoble, France

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Summary
Context. — Multiparametric magnetic resonance imaging (MRI) is now recommended before performing prostate biopsies, looking for suspicious lesions to perform targeted biopsies (TB). However, the association or exclusive performance of systematic biopsies (SB), criticized for its morbidity and for the detection of insignificant cancers, remains debated.

Objective. — To perform a literature review to answer three questions: (1) In the presence of a suspicious MRI lesion, should we always perform SB in addition to TB? (2) Can we avoid SB when considering focal treatment? (3) Is there an increase in adverse events when associating SB with TB?

Sources. — A non-systematic literature review was carried out on Medline in April 2020 using the keywords ‘‘MRI’’, ‘‘PROSTATE CANCER’’, ‘‘SYSTEMATIC BIOPSY’’, ‘‘TARGETED BIOPSY’’, ‘‘ADVERSE EVENTS’’. The references of the selected articles were analyzed for additional articles.

Selection of Studies published in the last five years were analyzed and retained if the available data made it possible to answer one of the three questions asked.

* Corresponding author at: Department of Urology, Hospital Claude Huriez, Centre Hospitalier Régional Universitaire, 2, avenue Oscar Lambret, 59000 Lille, France.
E-mail address: quentin.vesval@chru-lille.fr (Q. Vesval).

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Results. — In biopsy-naive patients, the added value of SB to TB for detection of significant cancer varied from +5 to +7% and was reduced to +1 to +3% in the case of a previous series of negative biopsies. For patients under active surveillance, this added value was higher, ranging from +8% to +17%. MRI has a negative predictive value of 85 to 95%, but this value drops to 55% for the detection of secondary or tertiary foci. The use of SB is necessary if focal treatment is considered. Serious complications from biopsies requiring hospitalization range from 1.4 to 6.9% and are increased by the number of previous biopsy series performed more than by the number of biopsies per series.

Conclusion. — In the presence of a suspicious MRI lesion, SB is indicated in addition to TB but can be discussed in patients with previous negative biopsies. They are necessary if focal treatment is considered to aid surgical planning. Severe complications from biopsies do not seem to increase when SB are associated to TB, but rather with the number of biopsy series performed.

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Introduction

Evidence suggests that multiparametric magnetic resonance imaging (mpMRI) before biopsy improves the detection of clinically significant prostate cancer (csPCa) with a high negative predictive value (NPV) of 85-95%, according to csPCa definition. Current guidelines recommend the use of mpMRI prior to biopsy in biopsy-naive patients with a suspected prostate cancer (PCa). When a suspicious lesion is present, it is recommended to perform targeted biopsy (TB) and systematic biopsy (SB) [1]. In patients with prior negative biopsy and a persistent suspicion of PCa, saturation biopsies may be performed, increasing PCa detection, mainly represented by anterior lesions [2] with a potential for increased morbidity [3]. Similarly, when active surveillance (AS) is being proposed as an alternative to active treatment, it is not clear how biopsies should be performed as part of follow-up.
In the era of TB, precision medicine and focal therapy, the indications of SB are still under discussion. They are criticized as being responsible for the over-diagnosis of insignificant cancers. However, significant cancers can still be under-detected by imaging alone [4]. Can we estimate the added value of SB to TB?

In the case of a multi-focal cancer, mpMRI appears less effective in the detection of secondary or tertiary foci [5,6]. When whole-gland treatment is planned, TB may be sufficient, and missing other foci may have no consequence besides a less adequate treatment planning and increased risk of surgical margin. However, what would be the consequences of omitting SB when considering focal therapy?

Finally, prostate biopsy is an invasive procedure, exposing the patient to a risk of morbidity, sometimes leading to severe complications and hospitalizations. To what extent does the multiplication of samples increase this morbidity?

We propose to answer these questions through a review of recent literature.

Methods
We performed a non-systematic review of the literature in April 2020, including the most recent articles (after 2015) in PubMed, using the following search terms: ‘’MRI’’, ‘’prostate cancer’’, ‘’systematic biopsy’’, ‘’targeted biopsy’’, ‘’adverse events’’. All English titles and abstracts were reviewed and included if providing sufficient data to answer the study questions. References of the selected articles were screened for additional articles.

Results
Should we continue adding systematic to targeted cores?
It appears that no ‘’one size fits all’’ answer can be provided to answer this question. Factors related to the patient (prostate volume, prior history of sepsis, prior history of biopsy), the targeting technique used (in-bore vs. cognitive vs. software fusion), the number of targeted cores obtained, the experience of the operator and the treatment planned (whole-gland vs. focal) all have to be taken into account.

Still, review of the most recent literature can provide us with some answers by looking at the added value of systematic biopsies in patients undergoing both diagnostic modalities in various situations. Details are presented in Table 1.

Biopsy-naïve patients
Two prospective studies provide us with good quality evidence regarding biopsy-naïve men. In the MRI-first trial, 251 biopsy-naïve patients received a combination of 12 systematic and three targeted biopsies (with cognitive or software guidance). Adding systematic cores led to the diagnosis of 13 (+5.2%) supplementary significant cancers [7]. In the 4M study, 317 patients were enrolled who underwent 2-4 in-bore targeted biopsies and systematic (12 cores) sampling. The added value of the latter was +7% [8]. Similarly, an added value of +6% was found in a retrospective analysis of 214 patients evaluated by a mean of 6 (range 2-15) targeted biopsies and 12 systematic cores (range 6-18) [9].

Prior negative biopsy
Although previously published studies showed a tendency toward an increased added value of SB among patients with a previous history of negative biopsy from 6.4% to 12.6% [10,11], other recent studies are in contradiction with these results, where added values were between 1.7% and 3.5% [12,13]. In the most recent prospective study (FUTURE trial), among 152 patients having both SB and TB, the detection rate for csPca was 35% (34% by TB and 16% by SB) and the added value of SB was only 1.3% [14].

A Cochrane review and meta-analysis determined an estimated added-value around +5% for biopsy-naïve patients and around +2.5% for patients with previous negative biopsies, with a significant uncertainty in both situations but especially for biopsy-naïve patients [15].

Active surveillance
In the ASIST trial, 273 patients on AS for PCa were randomized between SB alone and mpMRI with systematic and targeted biopsies (MRI arm) for confirmatory biopsy. No difference was observed in the detection rate of csPca (27% of patients in the SB arm and 33% in the MRI arm). In the MRI arm, upgrading was seen in 15% of patients and the added value of SB was 7.9% [16]. On confirmatory biopsy, overall upgrading to cancer grade group ≥2 was 26-33% and the added value of repeat SB in MRI-positive men was 36-48% [10,17,18] at one-year follow-up of low-risk PCa. A lower overall upgrading rate (14-16%) at confirmatory biopsy and lower added value of repeat SB in MRI-positive men (12-18%) were reported by Thurtle et al. [19] and Elkjaer et al. [20], which could be explained by a cohort of very-low-risk PCa men. In a recent retrospective study, on 101 men on AS who had follow-up MRI and SB + TB, the added value of SB was 17% [21].

Mixed population
In a very recent study including 2103 patients with a suspicious mpMRI, including biopsy-naïve, prior negative biopsy and active surveillance patients, Ahdoot et al. demonstrated an added value of 12 systematic cores around +5.8%, for the detection of clinically significant cancer [22]. Similarly, a prospective study enrolling 255 patients subjected to 2-4 targeted cores and 12 systematic cores reported an added value of 5% [11]. Furthermore, comparable results were obtained in two retrospective studies including 191 and 116 patients, with an added value of 12 systematic cores estimated at +6.8% and +6.9%, respectively [23,24]. Conversely, Oderda and colleagues determined an added value of +9% in a retrospective multicentre study including 2115 patients. However, this was probably explained by the high added value of systematic biopsies in the subgroup of patients under active surveillance in this study (+33%) [10]. Neale et al. have shown a +12% added value of SB on 282 patients, a higher value due to a higher proportion of biopsy-naïve patients. In this cohort, TB in patients with Likert score 3 lesion detect only 73% of csPca, the other 27% were picked by SB, while TB in patients with Likert score 5 lesion...
# Table 1  Added value of systematic biopsies in addition to targeted biopsies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Inclusion period</th>
<th>Design</th>
<th>MRI type</th>
<th>Patients having MRI + TBx + SBx (n)</th>
<th>TBx cores (n)</th>
<th>SBx cores (n)</th>
<th>Clinically-significant cancers on TBx n(%)</th>
<th>Clinically-significant cancers on SBx n(%)</th>
<th>Clinically-significant cancers total n(%)</th>
<th>Definition clinically-significant cancer</th>
<th>Added value SBx</th>
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<td><strong>Biopsy-naïve patients</strong></td>
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<td>Rouvière 2018 (MRI first) [7]</td>
<td>2015-2016</td>
<td>Prospective</td>
<td>1.5 T or 3 T 3 T</td>
<td>251</td>
<td>Cognitive/Fusion</td>
<td>12</td>
<td>81 (32.2)</td>
<td>75 (29.9 %)</td>
<td>94 (37 %)</td>
<td>GGG ≥ 2</td>
<td>+5.2 %</td>
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<tr>
<td>Van der Leest 2019 (4M) [8]</td>
<td>2015-2016</td>
<td>Prospective</td>
<td>3 T</td>
<td>317</td>
<td>In-bore</td>
<td>2-4</td>
<td>12</td>
<td>159 (50 %)</td>
<td>146 (46 %)</td>
<td>180 (57 %)</td>
<td>GGG ≥ 2</td>
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<td>Borkowetz 2018 [9]</td>
<td>2015-2017</td>
<td>Retrospective</td>
<td>3 T</td>
<td>214</td>
<td>Fusion</td>
<td>6</td>
<td>12</td>
<td>81 (38 %)</td>
<td>74 (35 %)</td>
<td>94 (44 %)</td>
<td>GGG ≥ 2</td>
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<td><strong>Prior negative biopsy</strong></td>
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<td>Exterkate 2020 [14]</td>
<td>2014-2017</td>
<td>Prospective</td>
<td>3 T</td>
<td>152</td>
<td>Fusion/Cognitive</td>
<td>10-12</td>
<td>51 (33.6 %)</td>
<td>24 (15.8 %)</td>
<td>53 (34.9 %)</td>
<td>GGG ≥ 2</td>
<td>+1.3 %</td>
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<tr>
<td>Mendhiratta 2015 [13]</td>
<td>2012-2014</td>
<td>Retrospective</td>
<td>3 T</td>
<td>172</td>
<td>Fusion</td>
<td>3-4</td>
<td>12</td>
<td>28 (16.3 %)</td>
<td>16 (9.3 %)</td>
<td>31 (18 %)</td>
<td>GGG ≥ 2</td>
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<tr>
<td>Salami 2015 [12]</td>
<td>2012-2014</td>
<td>Prospective</td>
<td>3 T</td>
<td>140</td>
<td>Fusion</td>
<td>2</td>
<td>12</td>
<td>67 (47.9 %)</td>
<td>43 (30.7 %)</td>
<td>72 (51.4 %)</td>
<td>GGG ≥ 2</td>
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<td><strong>Active surveillance</strong></td>
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<td>Klotz 2019 (ASIST) [16]</td>
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<td>Prospective</td>
<td>3 T</td>
<td>127</td>
<td>Fusion</td>
<td>2-3</td>
<td>12</td>
<td>19 (14.9 %)</td>
<td>21 (16.5 %)</td>
<td>29 (22.8 %)</td>
<td>GGG ≥ 2</td>
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<td>Osses 2020 [18]</td>
<td>2013-2019</td>
<td>Retrospective</td>
<td>1.5 T or 3 T 3 T</td>
<td>111</td>
<td>Fusion</td>
<td>2-5</td>
<td>10-12</td>
<td>20 (18 %)</td>
<td>28 (25 %)</td>
<td>35 (32 %)</td>
<td>GGG ≥ 2</td>
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<td>Hamoen 2018 [17]</td>
<td>2009-2013</td>
<td>Prospective</td>
<td>3 T</td>
<td>75</td>
<td>In-Bore</td>
<td>2-4</td>
<td>10</td>
<td>9 (12 %)</td>
<td>15 (20 %)</td>
<td>33 (44 %)</td>
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<td>Chesnut 2020 [21]</td>
<td>2013-2016</td>
<td>Retrospective</td>
<td>3 T</td>
<td>101</td>
<td>Fusion</td>
<td>2-3</td>
<td>14</td>
<td>22 (21.7 %)</td>
<td>35 (34.7 %)</td>
<td>39 (38.6 %)</td>
<td>GGG ≥ 2</td>
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<td><strong>Mixed population</strong></td>
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<td>Ahdoot 2020 [22]</td>
<td>2007-2019</td>
<td>Retrospective</td>
<td>3 T</td>
<td>2103</td>
<td>Fusion</td>
<td>5</td>
<td>12</td>
<td>795 (38%)</td>
<td>650 (31%)</td>
<td>918 (44%)</td>
<td>GGG ≥ 2</td>
</tr>
</tbody>
</table>

**Biopsy-naïve:** 436 Biopsy-naïve; 873 Prior negative biopsy; 794 Prior positive biopsy
Should we perform biopsies in case of suspicious MRI for prostate cancer?

Table 1  (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Inclusion period</th>
<th>Design</th>
<th>MRI type</th>
<th>Patients having MRI + TBx + SBx (n)</th>
<th>TBx type</th>
<th>TBx cores (n)</th>
<th>SBx cores (n)</th>
<th>Clinically-significant cancers on TBx n(%)</th>
<th>Clinically-significant cancers on SBx n(%)</th>
<th>Clinically-significant cancers total n(%)</th>
<th>Definition clinically-significant cancer</th>
<th>Added value SBx</th>
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<td>Mannaerts 2019</td>
<td>2015-2018</td>
<td>Prospective</td>
<td>1.5 T or 3 T</td>
<td>255</td>
<td>Fusion</td>
<td>2-4</td>
<td>12</td>
<td>113 (44%)</td>
<td>110 (43%)</td>
<td>126 (49%)</td>
<td>GGG ≥ 2</td>
<td>+5%</td>
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<td>94 (58%)</td>
<td>92 (57%)</td>
<td>101 (63%)</td>
<td>+4.3%</td>
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<td>Biopsy-naive</td>
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<td>19 (20%)</td>
<td>18 (19%)</td>
<td>25 (27%)</td>
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<td>Fourcade 2018</td>
<td>2013-2016</td>
<td>Retrospective</td>
<td>3 T</td>
<td>191</td>
<td>Fusion</td>
<td>2-4</td>
<td>10-12</td>
<td>73 (38%)</td>
<td>64 (33.5%)</td>
<td>86 (45%)</td>
<td>GGG ≥ 2+</td>
<td>+6.8%</td>
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<td>Biopsy-naive</td>
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<td>Prior negative biopsy</td>
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<td>Freifeld 2019</td>
<td>2016-2017</td>
<td>Retrospective</td>
<td>3 T</td>
<td>116</td>
<td>Fusion</td>
<td>2-3</td>
<td>12</td>
<td>47 (40.5%)</td>
<td>NA</td>
<td>55 (47%)</td>
<td>GGG ≥ 2</td>
<td>+6.9%</td>
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<td>Biopsy-naive</td>
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<td>Prior positive biopsy</td>
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<td>Oderda 2018</td>
<td>2010-2017</td>
<td>Retrospective</td>
<td>1.5 T or 3 T</td>
<td>2115</td>
<td>Fusion</td>
<td>4</td>
<td>10</td>
<td>716 (34%)</td>
<td>909 (43%)</td>
<td>420 (59.6%)</td>
<td>GGG ≥ 2</td>
<td>+9%</td>
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<td>371 (53%)</td>
<td>393 (53%)</td>
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<td>+6.9%</td>
<td>+12.6%</td>
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<td>Biopsy-naive</td>
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<td>Prior positive biopsy</td>
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TBx = targeted biopsies; SBx = systematic biopsies; NA = not available.

a When several definitions are used in the study, we present here the results for GGG ≥ 2.
b GGG ≥ 2+ means a broader definition is used.
allow detection of 100% of csPCa. As an alternative of both SB+TB, an “extended targeted” biopsy method, with four TB and six same-quadrant-only SB, allows detection of 97% csPCa but authors also concluded that contralateral SB allow better treatment planification, notably in a nerve sparing approach [25].

Correlation in Gleason Grade Group (GGG) between biopsy and radical prostatectomy specimen

Calio et al. showed that in a cohort of 208 patients, the proportion of patients who experienced upgrading of GGG at radical prostatectomy was 47.1%, 30.1% and 18.8% respectively, according to SB only, TB only and combined SB+TB [26]. Moreover, Diamond et al. evaluated the accuracy in GGG by comparing histopathology between SB, TB and SB+TB and RP among 443 patients in a retrospective study. Concordance was 49.4%, 51.2% and 63.2%, respectively, for overall PCa. Combining both techniques (SB+TB) achieves a 56.7% in concordance with final pathology, an upgrade of 30% and a downgrade of 13.3% for csPCa, with significant difference in comparison with the two biopsy techniques separately [27]. More recently, Gandaglia et al. have shown that SB+TB reduces the rate of upgrading at RP to 27% (versus 32% with TB alone) [28]. Same results were observed by Ahloot et al., where rates of any upgrading or cancer significant upgrading on whole mount was higher for SB (41.6% vs. 16.8%) and TB (30.9% and 8.7%) than for combined biopsy (14.4% and 3.5%), with low rates of downgrading to GGG 1 (2.2%, 2.5% and 3.7% respectively) [29].

Are systematic biopsies still necessary in the era of partial gland ablation?

Partial gland ablation (PGA) has emerged as a treatment option for men with clinically localized PCa. It is defined as an “individualized treatment that selectively ablates known disease and preserves existing function, with the overall objective of minimizing morbidity without compromising life expectancy” [29]. The principal pitfall of PGA lies in the multifocality of PCa. Histological studies have shown in men undergoing radical prostatectomy that approximately 42% harbor unifocal tumors and only 21% have unilateral disease [30].

As PCa is multifocal in the majority of cases, treatment of the index lesion and surveillance of clinically insignificant foci has been proposed.

The precise identification of the volume, grade and location of all significant tumors within the prostate is key to the selection of patients before PGA. Besides, mpMRI also provides information on anatomical features required for patient selection, treatment planning and the choice of focal treatment energy. Patients are currently selected based on the results of TB, SB and their concordance with the mpMRI, although the sole treatment of MRI-visible tumors is being increasingly considered. Are SB still necessary in the era of mpMRI and focal treatments?

The ideal study design to answer our question would include a longitudinal follow-up of patients treated by PGA after an evaluation consisting in MRI and TB alone, to evaluate the clinical consequence of the omission of SB. However, such studies are not available in the current literature.

To answer this question with extant evidence, it is important to distinguish the diagnostic performances of mpMRI at a prostate level versus at a lesion level. Indeed, the excellent NPV of mpMRI demonstrated at the prostate level around 85% to 95% for csPCa does not seem to hold when analyzing at a lesion level [7]. Whole-mount pathology is the not ideal reference standard for correlating individual prostate lesions to mpMRI findings in the context of PGA because it does not take into account the potential follow-up of untreated lesions, but it can help define the added value of SB offering whole-gland sampling. Nassiri et al. have shown in 175 men, eligible for focal therapy based on TB, and treated by radical prostatectomy, that mpMRI and TB alone offered a sensitivity of 73.3%, and a specificity of 47.9%, with an accuracy of 54.7% [5]. Johnson et al. showed on 1213 pathologically confirmed tumor foci in 588 patients that mpMRI missed 55% of all lesions, including 35% of csPCa and approximately 20% of high-grade PCa. Even though the majority of undetected multifocal tumors were clinically insignificant, 31% of the 629 undetected foci contained Gleason pattern 4 at final pathology. The low sensitivity at lesion level, and the proportion of men with undetected significant tumor foci are limitations of using mpMRI and TB alone when considering PGA treatment [6].

However, none of these studies looked at the proportion of patients with bilateral disease, including contralateral clinically insignificant tumor. Karavitakis et al. showed on 100 consecutive radical prostatectomy specimens that Gleason score and pathological stage were almost invariably defined by the index lesion. Satellite lesions tended to be small and well differentiated. However, these results should be interpreted with caution because no preoperative data were included and no absolute conclusions can be done from their analysis about the biological consequence of tumor focality due to the absence of follow-up data [31]. Furthermore, the presence of clinically insignificant cancer in the non-treated area had no influence on the radical treatment-free survival, nor on clinically significant cancer-free survival on a retrospective study on 55 patients [32].

Based on these results, it seems reasonable to recommend combining systematic biopsy with mpMRI-TB to improve patient selection and confirm eligibility to focal therapy. This was reinforced by a Delphi consensus on the use of mpMRI for the detection of PCa in focal therapy, stating that additional systematic biopsy remains crucial for accurate evaluation and patient selection [33].

Is there an increased morbidity when adding SB to TB?

The use of TB alone may decrease biopsy-related complications, but the clinical relevance of this remains unproven. While the impact of the transperineal versus transrectal route on adverse events (AEs) is still controversial, the assessment of the impact of the number of biopsy cores on AEs could help provide answers to this question. Few comparative studies have provided detailed complication rates (Table 2). Prostate biopsies are associated with a relatively frequent rate of bleeding events such as hema-
Should we perform biopsies in case of suspicious MRI for prostate cancer?

<table>
<thead>
<tr>
<th>Authors</th>
<th>Technique</th>
<th>Patients</th>
<th>TB Cores n (IQR)</th>
<th>SB Cores n (IQR)</th>
<th>Adverse Event reported at 30-d evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain (20%)</td>
</tr>
<tr>
<td>Eineluoto 2018 [35]</td>
<td>TB (Fusion) SB</td>
<td>59</td>
<td>3 (3.5)</td>
<td>0</td>
<td>12 (34%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>203</td>
<td>0</td>
<td>12 (all)</td>
<td>70 (34%)</td>
</tr>
<tr>
<td>Wegelin 2019 [36]</td>
<td>TB + SB (cog. TR)</td>
<td>78</td>
<td>3 (3-4)</td>
<td>10 (8-12)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>TB + SB (Fusion TP)</td>
<td>79</td>
<td>4 (3-5)</td>
<td>10 (8-12)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>TB (in-bore TR)</td>
<td>77</td>
<td>2 (2-3)</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Kasivisvanathan 2018 [45]</td>
<td>MRI-TB</td>
<td>252</td>
<td>4 (3-7)</td>
<td>0</td>
<td>27 (13%)</td>
</tr>
<tr>
<td></td>
<td>SB</td>
<td>248</td>
<td>0</td>
<td>10-12</td>
<td>48 (23%)</td>
</tr>
</tbody>
</table>

TB = targeted biopsy; SB = Systematic biopsy; IQR = interquartile range; COG: cognitive fusion transrectal biopsy; TR = transrectal; TP = transperineal.

a Significative result.
turia, hematochezia, haematospermia, reported with a high incidence variability (respectively 2-84%, 1.3-45% and 1.1-92.6%), but these AEs tend to be mild, self-limiting and transient [34]. Furthermore, there is no obvious correlation between the risk of bleeding and the number of biopsy cores taken. According to Eineluoto et al. [35], patients undergoing three-cores TB experienced less haematuria and pain compared with those undergoing 12-cores SB; however, the results regarding other bleeding events were not significant. Similarly, in the FUTURE trial, the in-bore MRI-TB group (with fewer biopsy cores taken) reported less episodes of haematuria and haematospermia, and anticoagulant usage was not associated with increased risk of bleeding complication [36].

A short term exacerbation of low urinary tract symptoms (LUTS) is another common side effect after PB with reported rates ranging from 6 to 25%, which may lead to acute urinary retention (AUR) [34]. In addition to the number of biopsy cores, the route used for biopsies and the transitional zone volume appeared associated to the occurrence of AUR. AUR was more frequent with the transperineal (1.7-11.1%) than transrectal approach (4.2% vs. 0.9%) [37]. In biopsy-naive patients, Murray et al. showed that the International Prostate Symptom Score (IPSS) was significantly increased at one week and four weeks after biopsy, but returned to baseline after three months [38]. In contrast, Wegelin et al. did not find any significant impact on self-reported LUTS at 30-days post biopsy [36]. According to Fujita et al., there was no significantly difference in IPSS regardless of the number of PBs performed in men on AS [39].

Erectile dysfunction may (ED) occur in a significant number of men undergoing PBs; however it appeared to be mild and transient, with complete recovery after one to six months [34]. As ED could be multifactorial, with physical and psychological aspects both involved (anxiety regarding the possibility of cancer, haematospermia and its detrimental effect on sexual activity), a relationship with the number of biopsy cores still has to be demonstrated. In 2016, Murray et al. described decreased IIEF5 score (International Index of Erectile Function) in biopsy-naive patients at 1 week, 4 weeks and 3 months [38]. In contrast, in patients with a history of prior negative biopsy, no significant impact on self-reported ED at 30 days after biopsy was noted [36]. In men on AS, increasing the number of biopsies was associated with a decrease in Sexual Health Inventory for Men score (SHIM). A past history of 3 or more biopsy series was associated with a greater decrease in SHIM compared to 2 or fewer biopsy series [39]. Klein et al. concluded that ED was transiently affected by prostate biopsy regardless of the number of cores [40].

The rate of clinical infectious complications ranges approximately from 1-17.5%. Fluoroquinolone-Resistant Escherichia Coli is the most recognized risk factor, independently of medical comorbidities (particularly diabetes and metabolic syndrome) and older age [34]. Transrectal biopsy was associated with a higher burden of sepsis than transperineal (0.8% vs. 0.1%) [37]. According to Pilatz et al., increasing the number of biopsy cores did not result in increased infectious complications [41]. However, repeating biopsy series did appear to increase the risk of infection, up to a rate of 15% for patient with five or more previous biopsy series [42]. Each additional biopsy session was associated with a 1.7-fold increase in overall hospitalizations and 1.7-fold increase in serious infectious complications [43]. Conversely, the low incidence of hospitalization and infectious complications after in-bore transperineal MRI-targeted biopsy appears related to the biopsy route rather than the number of cores taken [44].

In the PRECISION trial, complications in biopsy-naive patients reported at 30 days were less frequent in the mpMRI-TB group than in the SB group, but fewer biopsy cores were obtained in the former group; serious AEs, represented by prostatitis, sepsis and haematuria, were observed in 2% in both groups [45]. In the FUTURE trial, SB increased the risk of AEs with an odd-ratio of 1.1 per additional core taken [36].

The hospitalization rate within 30 days post biopsy for AEs ranged between 1.4-6.9%, mainly represented by infection, with age and comorbidity as independent predictor factor, and showed a steady increase over time [46]. Mortality after PB remains uncommon; to date, most PB-related deaths are due to septicemia and septic shock. Repeat biopsy does not appear to be associated with a higher overall mortality rate [43].

Discussion

The performance of mpMRI has now become key for the detection and treatment decision-making for patients suspected of having PCa. It is now endorsed by most guidelines before prostate biopsy, allowing the addition of TB. However, since its NPV is not 100%, there is a risk of non-detecting significant lesions, especially since PCa is usually a multifocal disease.

All three issues considered in this review rely on the risk-benefit balance of the performance of prostate biopsies. The added value of SB to TB in the most recently published studies ranged from 5 to 7% with a remarkable consistency between studies for the detection of significant cancers, defined by cancers greater than or equal to GGG 2. This added value appears significant for biopsy-naive patients, among whom a precise characterization of lesions is essential for treatment planning and stratification and allow for the detection of lesions that are not visible on mpMRI. Using SB and TB simultaneously provide less upgrading and better concordance with final pathological report on prostatectomy specimen. This is of particular importance when focal therapy is considered, while whole-gland treatment would alleviate the risk of neglecting a significant lesion outside the treated field. Gandaglia et al. are also suggesting adding concomitant SB leads to better risk stratification, with better concordance and less upgrading between GGG on biopsy and on radical prostatectomy specimen. Moreover, presence of csPCa at concomitant SB to TB was associated with an increased risk of extra-capsular extension and seminal vesicle invasion on RP specimen [28], and percentage of positive cores on SB is a significant predictor for positive margin during nerve sparing robot-assisted RP [47], confirming the value of SB implementation for treatment planning.

Conversely, in patients with a previous history of negative SB, the remaining significant lesions are more often found in the anterior part of the gland and likely to be missed by subsequent SB. Saturation biopsies, as performed before the emergence of mpMRI, are less likely to have a significant
added-value and are associated with greater morbidity, as showed in the PICTURE study, where AUR occurs in 24% of patients, with a median of 49 cores taken with a transperineal approach. In the FUTURE study, the added value of SB after a prior negative biopsy series appeared limited as the performance of these biopsies would detect only 1.3% additional significant cancers [14].

For patients on active surveillance, the performance of follow-up biopsies is recommended, but the replacement of this invasive procedure by an imaging-based surveillance, and biopsies triggered only in case of mpMRI changes, is being increasingly adopted. A recent review of the literature [48] reported 13 cohorts of patients under active surveillance, using many AS protocols. All authors agreed that repeated PSA measurements were important, and most authors recommended the performance of confirmatory biopsies within 12 months and up to 2 years after the initial diagnosis if mpMRI was not performed at inclusion. The latest EAU guidelines now support the absence of confirmatory biopsies provided the patient had an upfront mpMRI with TB and SB [49]. Patients under AS with positive MRI have higher risk of csPCa, explaining high added value of SB in these patients, especially since mpMRI could miss multifocal disease. Therefore, follow-up biopsies should include both TB and SB, as upgrading is key for the continuation of AS, and SB has been shown to add significant value in this regard [17–20]. In the ASIST trial, the addition of mpMRI with TB to SB initially did not significantly increase the upgrading rate compared with SB alone at time of confirmatory biopsy and the addition of 2-cores TB led to a non-statistically significant reduced upgrading than SB with 12 cores (14% vs. 23% respectively) [16]. However, the 2-year biopsy results recently published demonstrated a higher rate of progression in SB arm only vs. MRI-arm (13% vs. 27%, \( P = 0.021 \)) [50]. Conversely, Chesnut et al. concluded that performing biopsy only in clinical or mpMRI changes at 3 years in patients on AS could avoid many biopsies (estimated at 681 per 1000 men) but miss an unacceptable amount (16.9%) of clinically significant diseases [21].

The expertise of the centers should be taken into consideration since there may be major differences on the precision of TB, especially when performed under cognitive guidance [50]. All the studies included in this review were performed in expert centers, with trained physicians. In patients considered at higher risk of occult higher-grade disease, SB should be performed regardless of the mpMRI findings, and an increased sampling density should probably be offered.

Besides these considerations, the decision to biopsy and the biopsy technique used should also be based on the patients individualized risk of complications. All invasive procedures carry risk, and the tolerance for this risk depends on the potential benefits of the intervention and needs to be based on a shared decision-making approach. Post-biopsy infectious complications have been linked to older patient age and medical comorbidity status, emphasizing the importance of careful selection before biopsy. The transperineal approach appears to be safer regarding infectious complications, probably because of the avoidance of transrectal bacteria contamination. Similarly, the low incidence of infection after MRI-guided in-bore biopsy possibly resulted from the lower number of cores taken with this approach. Many patients experienced transient LUTS, and only a small proportion of these patients experienced urinary retention. Biopsy repletion, as opposed to number of biopsy cores taken, appears to drive the infectious morbidity in a cumulative fashion. A better upfront staging with pre-biopsy mpMRI and TB, and the implementation of mpMRI in AS protocols should help mitigate this risk. However, transperineal and limited sampling with MRI targeted biopsy appears to be associated with a reduced risk of severe infectious complications, and although not available for all patients, these approaches should certainly be considered for patients at higher risk of sepsis.

**Conclusion**

In the presence of a suspicious mpMRI lesion, SB added to TB appear to have a moderate added value in biopsy-naive patients, and a significant added value in patients under AS. However, SB can likely be omitted in patients with a history of prior negative biopsies, due to minimal additional benefit in this sub-group. If focal treatment is considered, SB appears to be necessary to aid with optimal surgical planning. Severe complications from biopsies do not appear to increase with the number of cores, but rather with the number of previous biopsy series.

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**Disclosure of interest**

The authors declare that they have no competing interest.

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