Prostate cancer detection rate of multiparametric magnetic resonance imaging/transrectal ultrasound fusion prostate biopsy. Impact of clinical indications on biopsy outcome

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Background & Aims. Multiparametric Magnetic Resonance Imaging has increased our ability to diagnose prostate cancer but questions remain about its proper use. Herein we evaluated potential differences between the clinically and multiparametric Magnetic Resonance Imaging-indicated and the non-clinically but multiparametric Magnetic Resonance Imaging-indicated fusion prostate biopsy.

Methods. Outcomes of 99 fusion prostate biopsies (Group A) were compared with those of a matched population having undergone standard prostate biopsy (Group B).

Results. The overall cancer detection rate was 60.6% in Group A and 29.2% in Group B (p < 0.001) whereas the rate of clinically-significant prostate cancer was 26.2% in Group A and 13.1% in Group B (p = 0.02). The cancer detection rate was 79.1% vs 13.1% for clinically-indicated and non clinically-indicated fusion biopsies, respectively; the clinically significant prostate cancer rate in these 2 populations were 45.6 and 0%, respectively. Cancer detection rate correlated with the Prostate Imaging-Reporting and Data System; in the setting of first biopsy, it was 84.6, 67.8%, and 100% for score 3, 4 and 5, respectively, whereas in the setting of repeat biopsy it was 28.5, 55.5% and 80% for score 3, 4 and 5, respectively. Complications rate was similar in both groups but all complications occurred in patients > 75y.

Conclusions. Fusion prostate biopsy provided better cancer detection rate than standard prostate biopsy providing proper clinical indications. The misuse of multiparametric Magnetic Resonance Imaging in patients with no clinical indication for prostate biopsy led, particularly in the elderly, to an extremely high number of unnecessary biopsies with their inherent problems.

Key words: Prostate Cancer, Magnetic Resonance Imaging, Fusion biopsy, Systematic biopsy, Detection rate

INTRODUCTION

Prostate cancer (PCa) is the most common malignancy in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed. The median age at diagnosis is 66y; though many elderly men who are diagnosed with PCa will die from other causes, 70% of deaths occur in men older than 75y. Moreover, elderly patients are more likely than younger patients to be diagnosed with aggressive cancers. Therefore, early diagnosis of PCa in the elderly represents a relevant clinical issue. Prostate biopsy (PBx) is the standard method for diagnosing PCa but the diagnostic yield of this procedure remains low. In current clinical practice the cancer detection rate (CDR) of a first extended PBx prompted by
an elevated serum PSA level and/or an abnormal digital rectal examination (DRE) is in the range of 40%\(^6\), dropping to approximately 25% in the setting of screening programs, i.e. patients with serum PSA between 2.5 and 10 ng/mL\(^7\).

In the last 20 years, efforts to improve the diagnostic yield of PBx have been oriented towards the construction of predictive models combining serum PSA and DRE findings with other readily available clinical information such as age, prostate volume (PVol), \%free PSA etc., as well as towards the development of novel biomarkers\(^8\) or imaging techniques. Among imaging techniques, multiparametric magnetic resonance imaging (mpMRI) of the prostate is increasingly been used given its postulated ability to identify lesions at high-risk of being clinically significant cancers, to improve PBx diagnostic yield by fusion of mpMRI and transrectal ultrasound (TRUS) images, and to increase the accuracy of models predicting PBx outcome\(^9\).

The optimal clinical application of mpMRI, however, remains under investigation. According to current EAU guidelines \(^10\), despite the use of the new PIRADS v2 scoring system, mpMRI has a low specificity, with high rates of false positives, especially among lesions scored 3/5 and 4/5. Moreover, the inter-reader reproducibility is moderate, limiting its broad use outside expert centres. Having said this, EAU guidelines recommend it before repeat biopsy (evidence level 1\(^\circ\); grade A).

In clinical practice, however, clinicians have to face two different problems. On one hand, there is a certain reluctance to advise PSA testing in men > 75y as well as to recommend prostate biopsy (PBx) for increased PSA levels, particularly in elderly men with PSA in the grey zone (4-10 ng ml) who suffer from lower urinary tract symptoms (LUTS). On the other hand, the increasing use of prostate mpMRI is leading to indicating PBx on the basis of this exam only, thus independently on clinical indications.

In this study we compared the outcome of mpMRI/TRUS fusion-guided PBx with that of “standard” systematic TRUS guided PBx and evaluated potential outcome differences between the clinically and mpMRI-indicated (CI) and the non-clinically but mpMRI-indicated (NCI) fusion PBxs.

**PATIENTS AND METHODS**

Data of patients scheduled for TRUS-guided transrectal PBx because of increased serum PSA (≥ 4 ng/mL) and/or abnormal digital rectal examination (DRE) were prospectively entered into our dedicated Institutional Review Board-approved database. In the present study we compared the first 99 patients having undergone mpMRI/TRUS fusion-guided PBx (Group A) with a matched population of patients having undergone standard TRUS-guided PBx (Group B) in the same period.

MpMRI was carried out using Intera Achieva by Philips with 1.5 tesla magnetic field strength, in T2WI, DWI axial at 3 b values and DCE-MRI (3Dt1W-THRIWE). PBx was carried under local non-infiltrative anaesthesia\(^11\)\(^12\). TRUS was used to determine prostate and transition zone volume and to guide transrectal prostate sampling according to our systematic 18-core biopsy scheme\(^13\). In Group A, care was taken to identify the position of the index lesion(s) within our 18-core scheme and to take 2 cores from it using the Navigo™ Workstation (UC-CARE Medical System).

Two senior uropathologists blind to procedural data evaluated the specimens according to contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP)\(^14\) of prostate, and PCa. The study protocol was approved by the University of Foggia Ethics Committee and was carried out in agreement with the provisions of the Declaration of Helsinki. Written informed consent to take part was given by all participants.

**STATISTICAL ANALYSIS**

Continuous variables were compared by the Mann-Whitney U-test. Rates were tested by the Fisher’s exact test or the chi-square test, as appropriate. Statistical significance was set at p < 0.05. Statistical calculations were carried out using STATA-SE software, version 14.0 for Mac OS X.

**RESULTS**

Table I reports the baseline characteristics of the 99 patients having undergone mpMRI/TRUS fusion-guided PBx (Group A) and those of a matched population of patients having undergone standard systematic TRUS-guided PBx (Group B). The percentage of patients aging > 75y was 20.2% (20/99). Procedural time was 37 ± 5.1 min in Group A and 11 ± 1.7 min in Group B (p < 0.001); there was no difference in complications rate (Group A 4% vs Group B 3%), but all complications occurred in patients > 75y.

The overall CDR (Tab. II) was 60.6% in Group A and 29.2% in Group B (p < 0.001) whereas the rate of clinically-significant PCAs (csPCAs), defined as cancers with Gleason sum ≥ 7\(^15\), was 26.2% in Group A and 13.1% in Group B (p = 0.02). In Group B, all PBxs were CI (elevated/raising PSA level and/or an abnormal DRE). In Group A, conversely, 72 PBxs were mpMRI and CI,
whereas 27 were mpMRI but NCI In the CI PBxs, the overall CDR was 79.1% as opposed to 11.1% in the NCI (p = 0.0001); the rates of csPCas in these 2 populations were 45.6 and 0%, respectively (p = 0.0001). Of the 27 patients having a NCI PBx, 9 (33.3%) were > 75y.

CDR correlated well with the Prostate Imaging-Reporting and Data System (PIRADS), being 50%, 61.8% and 90% for PIRADS 3, 4 and 5, respectively in the overall population, and 78.9, 75 and 100% for PIRADS 3, 4 and 5, respectively in the CI PBxs (Tab. III).

**DISCUSSION**

The identification of factors that could predict PBx outcome is of major clinical importance. Rising the CDR of PBx would significantly reduce the number of unnecessary PBxs, in other words those that are likely to result negative for PCa, with a significant reduction in costs and patient anxiety.

A commercially available assay combining serum PSA with urinary prostate cancer antigen 3 (PCA3) and the urinary transmembrane protease, serine 2: v-ets erythroblastosis virus E26 oncogene homolog (TMPRSS2:ERG fusion) has been shown to provide a 90% specificity and 80% sensitivity in diagnosing PCa. Similarly, we demonstrated that, in a small cohort of 40 patients scheduled for repeat PBx, Pentraxin 3 significantly outperformed PSA (AUC 0.92 vs 0.55) in predicting the risk of being diagnosed with PCa; these findings, however, await validation in a large series of patients scheduled for first PBx.

Another front of research has been addressed towards readily available clinical parameters related to benign prostatic obstruction (BPO). Prostate volume, which is directly correlated to BPO, has been shown to be inversely correlated with the risk of harboring PCa in men scheduled for PBx. In line with this, we found that, in patients scheduled for PBx because of increased PSA levels and/or abnormal DRE, the International Prostate Symptom Score (IPSS), the peak flow rate (PFR) and the post-void residual (PVR) independently predict the risk of being diagnosed with PCa. A novel nomogram based on BPO-related parameters (PFR, PVol, PVR) has recently been shown to predict the risk of prostate cancer at first prostate biopsy with a model predictive accuracy of 0.768 for overall PCa and of 0.8002 for clinical significant PCa. Question remains whether such clinical factors may impact on treatment outcome, like smoke in bladder cancer. In the field of imaging, mpMRI certainly represents the most promising technique in identifying neoplastic prostate lesions that should be sampled. The initial and

**Table I.** Patients descriptive characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Group A = 99 pts</th>
<th>Group B = 99 pts</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (y)</td>
<td>65.6 (58.6 ± 7.26)</td>
<td>66.4 (64 ± 6.88)</td>
<td>0.4958*</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>7.9 (4.9 ± 10.9)</td>
<td>7.3 (4.7 ± 9.9)</td>
<td>0.1558*</td>
</tr>
<tr>
<td>Suspicious DRE (%)</td>
<td>33.3 % (33/99)</td>
<td>33.3 % (33/99)</td>
<td>1*</td>
</tr>
<tr>
<td>Prostate volume (mL)</td>
<td>56.4 (30.8 ± 82)</td>
<td>55.1 (32.7 ± 77.5)</td>
<td>0.4811*</td>
</tr>
<tr>
<td>Previous PBx (%)</td>
<td>52.5 % (52/99)</td>
<td>52.5 % (52/99)</td>
<td>1*</td>
</tr>
<tr>
<td>Previous Surgery for BPH (%)</td>
<td>3 % (3/99)</td>
<td>3 % (3/99)</td>
<td>1*</td>
</tr>
</tbody>
</table>

Group A: mpMRI/TRUS fusion guided PBx; Group B: standard TRUS guided PBx. Data are expressed as means±standard deviations or percentages.

*Student’s t-test; * Fisher’s exact test.

**Table II.** Cancer Detection Rate (CDR).

<table>
<thead>
<tr>
<th></th>
<th>Group A All pts (99)</th>
<th>Group B 99 pts</th>
<th>P-value*</th>
<th>Group A- CI 72 pts</th>
<th>Group A - NCI 27 pts</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>all PCa, % (n)</td>
<td>60.6 % (60/99)</td>
<td>29.2 % (29/99)</td>
<td>&lt; 0.001</td>
<td>79.1 % (57/72)</td>
<td>11.1 % (3/27)</td>
<td>0.0001</td>
</tr>
<tr>
<td>First PBx</td>
<td>76 % (35/46)</td>
<td>31.9 % (15/47)</td>
<td>&lt; 0.001</td>
<td>79 % (34/43)</td>
<td>25 % (1/4)</td>
<td>0.0459</td>
</tr>
<tr>
<td>Repeat PBx</td>
<td>47.1 % (25/53)</td>
<td>26.9 % (14/52)</td>
<td>0.032</td>
<td>79.3 % (23/29)</td>
<td>8.6 % (2/23)</td>
<td>0.0001</td>
</tr>
<tr>
<td>csPCa, % (n)</td>
<td>26.2 % (26/99)</td>
<td>13.1 % (13/99)</td>
<td>0.02</td>
<td>36.1% (26/72)</td>
<td>0% (0/27)</td>
<td>0.0001</td>
</tr>
<tr>
<td>First PBx</td>
<td>34.7 % (16/46)</td>
<td>18.6 % (8/43)</td>
<td>0.08</td>
<td>38 % (16/42)</td>
<td>0 %</td>
<td>0.0001</td>
</tr>
<tr>
<td>Repeat PBx</td>
<td>18.8 % (10/53)</td>
<td>8.9 % (5/56)</td>
<td>0.132</td>
<td>33.3 % (10/30)</td>
<td>0 %</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Group A: mpMRI/TRUS fusion guided PBx; Group B: standard TRUS guided PBx; Group A-CI: mpMRI/TRUS fusion guided PBx with clinical indication; Group A-NCI: mpMRI/ TRUS fusion guided PBx without clinical indication.

* Fisher’s exact test.
simplest MRI-targeted biopsy strategy is the cognitive approach. Three RCTs have compared a TRUS-guided 12-core PBx with a cognitive mpMRI-guided PBx in the setting of first PBx yielding conflicting results 25-27. The first two studies pointed out that CDR was higher in the mpMRI-guided group 26 27, whereas the most recent one showed that the two procedures provided comparable results (25).

The mpMRI/TRUS fusion software has been developed with the aim of providing a more precise sampling of the lesions identified by mpMRI. Initial non-randomized studies comparing mpMRI/TRUS fusion PBx with “standard” TRUS-guided PBx in the setting of first PBx pointed out that fusion PBx provided better CDR than “standard” PBx 28 29.

The first RCT comparing mpMRI/TRUS fusion guided PBx with “standard” 12-core TRUS-guided PBx in the setting of first PBx 15 pointed out that “fusion” PBx provided a significantly greater overall CDR than “standard” PBx (50.5 vs 29.5%; p = 0.002) and such advantage was even greater for clinically significant PCa (43.9 vs 18.1%; p < 0.001). Such results can however be expected after having completed the learning curve of both radiologists and urologists with this procedure. Panebianco et al. 27 reported a learning curve of approximately 50 cases whereas Calio et al. 19 reported a learning curve of 270 cases.

Findings of the present study were clear. In matched populations, fusion PBx provided greater CDR than standard systematic PBx for overall PCa and csPCa. The novel and strong point of our study was assessing the impact of mpMRI on indications for PBx. A relevant (27%) number of patients had to undergo fusion PBx only on the basis on mpMRI; in other words, PBx was mpMRI indicated but NCI. This led to a disastrous 11.1% CDR, therefore, a huge number of unnecessary PBxs with all their burden in costs, risks, and patients anxiety. On the other hand, and this can be considered another strong point of our study, CI fusion PBxs yielded a very satisfactory 78.9, 75 and 100% CDR for PIRADS 3, 4 and 5, respectively. These findings somehow challenge the reported mpMRI low specificity and high rates of false positives among PIRADS 3 and 4 lesions 30.

It is worth mentioning that in Group A the percentage of patients aging > 75y was 20.2%, much higher than our historical 12% rate. Moreover, 33.3% of patients who had a NCI fusion PBx were > 75y. Overall, these findings suggest that potential misuse of fusion PBx is more likely to occur in the elderly. This is even more troublesome in view of the fact that complications, though always minor, were all seen in patients > 75y.

The main study limitation is the relatively small number of patients. Though case volume is known to play a relevant role in surgical procedures 31, the number of enrolled patients appeared to be sufficient to provide relevant information on performance and trend of use of this novel procedure particularly in the elderly population. In conclusions, mpMRI/TRUS fusion-guided PBx had greater CDR that standard TRUS-guided systematic PBx providing correct clinical indications. Clinicians, however, have to face the problem of inappropriate use of this imaging technique (NCI cases) resulting into an increase rather than a decrease in the number of unnecessary PBxs exposing patient to the risk of overdiagnosis and consequent overtreatment with possible procedure-related complications 32. Interestingly, elderly patients seemed to be those at higher risk of undergoing a NCI fusion PBx. Like for other common benign urological conditions, wise clinical judgment remains essential in the decision-making process 33-35.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**


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