JGG 2018;66:205-210

Short Communication

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

G. Silecchia[1], O. Selvaggio[1], P. Milillo[2], A. Tewari[3], G. Stallone[4], G. Carrieri[1]

[1] Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; [2] Department of Radiology, University of Foggia, Italy; [3] Department of Urology, Mount Sinai School of Medicine, New York, USA; [4] Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy.

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 [1]. 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 [2 3]. Moreover, elderly patients are more likely than younger patients to be diagnosed with aggressive cancers [4 5]. 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

Received: October 29, 2018 - Accepted: December 09, 2018
Correspondence: Luigi Cormio, Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, viale Luigi Pinto 251, 71122 Foggia, Italy. Tel .+39 0881 732111. Fax +39 0881 736056. E-mail: luigi.cormio@unifg.it

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°; grade A).

In clinical practice, however, clinicians have to face two different problems. On one hand, there is a certain reluctancy 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 mpMR-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 anesthesia [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 PCa (csPCa), 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,

Table I. Patients descriptive characteristics.

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

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).

	Group A All pts (99)	Group B 99 pts	P-value*	Group A- CI 72 pts	Group A - NCI 27 pts	P-value*
all PCa, % (n)	60.6 % (60/99)	29.2 % (29/99)	< 0.001	79.1 % (57/72)	11.1 % (3/27)	0,0001
First PBx	76 % (35/46)	31.9 % (15/47)	< 0.001	79 % (34/43)	25 % (1/4)	0,0459
Repeat PBx	47.1 % (25/53)	26.9 % (14/52)	0.032	79.3 % (23/29)	8.6 % (2/23)	0,0001
csPCa, % (n)	26.2 % (26/99)	13.1 % (13/99)	0.02	36,1% (26/72)	0% (0/27)	0,0001
First PBx	34.7 % (16/46)	18.6 % (8/43)	0.08	38 % (16/42)	0 %	0,0001
Repeat PBx	18.8 % (10/53)	8.9 % (5/56)	0.132	33.3 % (10/30)	0 %	0,0009

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.

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 [16]. 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 [17]; 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 [18 19]. 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 [20-22]. 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 [23]. Question remains whether such clinical factors may impact on treatment outcome, like smoke in bladder cancer [24].

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 III. Cancer detection rate by prostate imaging-reporting and data system (PIRADS) scores in patients having undergone mp-MRI/TRUS fusion-guided PBx.

	Group A All pts (99)	Group A CI pts (72)	Group A NCI pts (27)
PIRADS 3, % (n)	50 % (17/34)	78.9 % (15/19)	14.2 % (2/14)
PIRADS 4, % (n)	61.8 % (34/55)	75 % (33/44)	9 % (1/11)
PIRADS 5, % (n)	90 % (9/10)	100 % (9/9)	0 % (0/2)
Overall	60.6 % (60/99)	79.1 % (57/72)	11.1 % (3/27)

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 PCas (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

1 Mottet N, Bellmunt J, Bolla M, et al. *EAU-ESTRO-SIOG Guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent.* Eur Urol 2017;71:618-29.

2 Smith BD, Smith GL, Hurria A, et al. *Future of cancer incidence in the United States: burdens upon an aging, changing nation.* J Clin Oncol 2009;27:2758-65.

3 Droz J-P, Albrand G, Gillessen S, et al. *Management of prostate cancer in elderly patients: recommendations of a task force of the International Society of Geriatric Oncology.* Eur Urol 2017;72:521-31.

4 Ko J, Falzarano SM, Walker E et al. *Prostate cancer patients older than 70 years treated by radical prostatectomy have higher biochemical recurrence rate than their matched younger counterpart.* Prostate 2013;73:897-903.

5 Brassell SA, Rice KR, Parker PM et al. *Prostate cancer in men 70 years old or older, indolent or aggressive: clinicopathological analysis and outcomes.* J Urol 2011;185:132-7.

6 Serag H, Banerjee S, Saeb-Parsy K, et al. *Risk profiles of prostate cancers identified from UK primary care using national referral guidelines.* Br J Cancer 2012;106:436-9.

7 Bokhorst LP, Zhu X, Bul M, et al. *Positive predictive value of prostate biopsy indicated by prostate-specific-antigen-based prostate cancer screening: trends over time in a European randomized trial*. BJU Int 2012;110:1654-60.

8 Falzarano SM, Ferro M, Bollito E, et al. *Novel biomarkers and genomic tests in prostate cancer: a critical analysis.* Minerva Urol Nefrol 2015;67:211-31.

9 Shukla-Dave A, Hricak H, Akin O, et al. *Preoperative nomograms incorporating magnetic resonance imaging and spectroscopy for prediction of insignificant prostate cancer.* BJU Int 2012;109:1315-22.

10 Mottet N, Bellmunt J, Bolla M, et al. *EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent*. Eur Urol 2017;71:618-29.

11 Cormio L, Lorusso F, Selvaggio O, et al. *Noninfiltrative anesthesia for transrectal prostate biopsy: a randomized prospective study comparing lidocaine-prilocaine cream and lidocaine-ketorolac gel.* Urol Oncol 2013;31:68-73.

12 Cormio L, Pagliarulo V, Lorusso F, et al. *Combined perianal-intrarectal (PI) lidocaine-prilocaine (LP) cream and lidocaine-ketorolac gel provide better pain relief than combined PI LP cream and periprostatic nerve block during transrectal prostate biopsy.* BJU Int 2012;109:1776-80.

13 Cormio L, Scattoni V, Lorusso F, et al. *Prostate cancer detection rates in different biopsy schemes. Which cores for which patients?* World J Urol 2014;32:341-6.

14 Sanguedolce F, Cormio A, Musci G, et al. *Typing the atypical: Diagnostic issues and predictive markers in suspicious prostate lesions.* Crit Rev Clin Lab Sci 2017;54:309-25.

15 Porpiglia F, Manfredi M, Mele F, et al. *Diagnostic pathway with multiparametric magnetic resonance imaging versus standard pathway: results from a randomized prospective study in biopsy-naïve patients with suspected prostate cancer.* Eur Urol 2017;72:282-8.

16 Sanguedolce F, Cormio A, Brunelli M, et al. *Urine TMPRSS2: ERG fusion transcript as a biomarker for prostate cancer: literature review.* Clin Genitourin Cancer 2016;14:117-21.

17 Stallone G, Cormio L, Netti GS, et al. *Pentraxin 3: a novel biomarker for predicting progression from prostatic inflammation to prostate cancer.* Cancer Res 2014;74:4230-8.

18 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.

19 Calio B, Sidana A, Sugano D, et al. *Changes in prostate cancer detection rate of MRI-TRUS fusion vs systematic biopsy over time: evidence of a learning curve*. Prostate Cancer Prostatic Dis 2017;20:436-41.

20 Cormio L, Lucarelli G, Netti GS, et al. *Post-void residual urinary volume is an independent predictor of biopsy results in men at risk for prostate cancer.* Anticancer Res 2015;35:2175-82.

21 Cormio L, Lucarelli G, Selvaggio O, et al. *Absence of bladder outlet obstruction is an independent risk factor for prostate cancer in men undergoing prostate biopsy.* Medicine (Baltimore) 2016;95:2551-7.

22 Cicione A, Cormio L, Cantiello F, et al. *Presence and severity of lower urinary tract symptoms are inversely correlated with the risk of prostate cancer on prostate biopsy.* Minerva Urol Nefrol 2017;69:486-92.

23 Cormio L, Cindolo L, Troiano F, et al. *Development and internal validation of novel nomograms based on benign prostatic obstruction-related parameters to predict the risk of prostate cancer at first prostate biopsy*. Front Oncol 2018;8:438.

24 Serretta V, Altieri V, Morgia G, et al. *Cigarette smoking status at diagnosis and recurrence in intermediate-risk non muscle invasive bladder carcinoma.* Urology 2013;81:277-81.

25 Tonttila PP, Lantto J, Paakko E, et al. *Prebiopsy multiparametric magnetic resonance imaging for prostate cancer diagnosis in biopsy-naıve men with suspected prostate cancer based on elevated prostate-specific antigen values: results from a randomized prospective blinded controlled trial.* Eur Urol 2016;69:419-25.

26 Park BK, Park JW, Park SY, et al. *Prospective evaluation of 3-T MRI performed before initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-specific antigen and no previous biopsy.* Am J Roentgenol 2011;197:W876-81.

27 Panebianco V, Barchetti F, Sciarra A, et al. *Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study.* Urol Oncol 2015;33:1-7.

28 Mozer P, Roupret M, Le Cossec C, et al. *First round of targeted biopsies with magnetic resonance imaging/ultrasound fusion images compared to conventional ultrasound-guided transrectal biopsies for the diagnosis of localised prostate cancer.* BJU Int 2015;115:50-7.

29 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;313:390-7.

30 Mertan FV, Greer MD, Shih JH, et al. *Prospective evaluation of the prostate imaging reporting and data system version 2 for prostate cancer detection*. J Urol 2016;196:690-7.

31 Kandasami SV, Mamoulakis C, El-Nahas AR, et al; CROES URS Global Study Group. *Impact of case volume on outcomes of ureteroscopy for ureteral stones: the clinical research office of the endourological society ureteroscopy global study*. Eur Urol 2014;66:1046-51.

32 Cormio L, Massenio P, Lucarelli G, et al. *Hem-o-lok clip: a neglected cause of severe bladder neck contracture and*

consequent urinary incontinence after robot-assisted laparoscopic radical prostatectomy. BMC Urology 2014;14:21-6.

[33] Wollin DA, Joyce AD, Gupta M, et al. *Antibiotic use and the prevention and management of infectious complications in stone disease*. World J Urol 2017;35:1369-79.

[34] Cormio L, Preminger G, Saussine C, et al. *Nephrostomy in percutaneous nephrolithotomy (PCNL): does nephrostomy tube size matter? Results from the Global PCNL Study from the Clinical Research Office Endourology Society*. World J Urol 2013;31:1563-8.

[35] Cormio L, Gonzalez GI, Tolley D, et al. *Exit strategies following percutaneous nephrolithotomy (PCNL): a comparison of surgical outcomes in the Clinical Research Office of the Endourological Society (CROES) PCNL Global Study.* World J Urol 2013;31:1239-44.