Multiparametric Pelvic MRI Accuracy in Diagnosing Clinically Significant Prostate Cancer in the Reevaluation of Biopsy Microfocal Tumor

PIETRO PEPE[1], GIUSEPPE DIBENEDETTO[1], ANTONIO GARUFI[2], GIANDOMENICO PRIOLO[2] and MICHELE PENNISI[1]

[1]*Urology Unit, Cannizzaro Hospital, Catania, Italy;*
[2]*Imaging Department, Cannizzaro Hospital, Catania, Italy*

Abstract. *Aim: To evaluate the accuracy of multi-parametric pelvic magnetic resonance imaging (mpMRI) in diagnosing prostate cancer (PCa) in men with initial biopsy microfocal cancer. Patients and Methods: From January 2012 to July 2014, 40 patients before undergoing repeat transperineal saturation prostate biopsy (SPBx; median, 28 cores) for the presence of a microfocal PCa were submitted to 3.0-Tesla mpMRI. Results: A T1c clinical stage PCa was found in 23 (57.5%) patients submitted to SPBx; mpMRI was positive in 16/40 (40%) cases and in 11 of them a clinically significant PCa was found. On the contrary, the 12 men with negative mpMRI had a quantitative histology suitable for clinically insignificant cancer. Diagnostic accuracy of mpMRI in diagnosing significant PCa was equal to 100%. Conclusion: Multi-parametric pMRI should be suggested in the re-evaluation of microfocal cancer as a selection approach of patients at risk for clinically significant PCa.*

The widespread use of serum prostate-specific antigen (PSA) testing, associated with lower PSA threshold and extended biopsy protocols, has led to a marked increase of small, low grade prostate cancer (PCa) that cannot threaten patient's survival. The preoperative prediction (1, 2) of an insignificant PCa (organ confined, less than 0.5 ml cancer without Gleason grade 4 or 5 disease) remains a difficult task because PCa is a multifocal, heterogeneous disease and the employed prostate biopsy technique provides a limited amount of tissue that not necessarily reflects the biology of the disease; therefore, as a consequence, the potential aggressiveness of a small lesion can be underestimated. In the last years, the incidence of biopsy-proven microfocal PCa, characterized by a single positive core (5% or less) of Gleason score (GS) 6 (3-6) has significantly increased with an estimated risk to harbour a clinically significant PCa in about 30% of the cases (6). In the population-based screening study at the Rotterdam section of European Randomized Study on Screening of Prostate Cancer the proportion of focal cancers during the second screening after four years increased from 16% to 29% of all detected cancers (7). On the other hand, to reduce the risk of overtreatment active surveillance protocols (8) have been suggested, but still today the estimated understaging is equal to 30% of the cases. In this light, multiparametric magnetic resonance imaging (mMRI) has demonstrated a good sensitivity to detect only clinically significant PCa missing cancers at risk for indolent disease, especially, in patients submitted to repeat biopsy.

The accuracy of multi-parametric pelvic magnetic resonance imaging (mpMRI) in diagnosing significant PCa in men with initial microfocal biopsy cancer has been prospectively evaluated.

Correspondence to: Pietro Pepe, MD, Urology Unit, Cannizzaro Hospital, Via Messina 829, Catania, Italy. Tel: +39 957263285, Fax: +39 957263259, e-mail: piepepe@hotmail.com

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Patients and Methods

From January 2012 to July 2014 among 795 men submitted to prostate biopsy. 40 (5%) aged between 48 and 76 years (median, 62.5 years) underwent repeat saturation biopsy (SPBx; median, 28 cores; range, 24-34 cores) for the presence of a microfocal (Figure 1a) PCa (a single positive core of Gleason score of 6 with a greatest percentage of cancer <5%) diagnosed by extended prostate biopsy (median 18 cores) 6 months before (median; range, 3-9 months). In all cases digital rectal examination was negative and median PSA was equal to 8.9 ng/ml (range, 4.2-15 ng/ml). SPBx was accomplished in a transperineal way with a tru-cut 18 G needle through a GE Logiq 500 PRO ecograph supplied with a biplanar transrectal probe (5-6.5 MHz) under sedation and antibiotic prophylaxis (9).

All patients, who provided a written informed consent, underwent mpMRI 3-10 days before undergoing the SPBx. All examinations were performed using a 3.0 Tesla scanner, (ACHIEVA 3T; Philips Healthcare Best, Amsterdam, the Netherlands) equipped

with surface 16 channels phased-array coil placed around the pelvic area with the patient in supine position; multiplanar turbo spin-echo T2-weighted (T2W), axial diffusion weighted imaging (DWI), axial dynamic contrast enhanced (DCE) and spectroscopy were performed for each patient. The mpMRI lesions characterized by a prostate imaging reporting and data system PI-RADS score of 4 and 5 were considered at high risk for the presence of PCa (10). In detail, the criteria (11) for a positive lesion on T2W were the presence of a circumscribed, low signal intensity lesion (hypointense); a positive lesion on DCE was characterized by the presence of foci showing early and intense enhancement and rapid washout after power injection (3.0 ml/s) of gadobutrol 0.1 ml/kg (Gadovist®; Bayer Schering Pharma, Berlin, Germany) followed by a 15 ml saline flush. A positive lesion on spectroscopy was any area where the choline to citrate ratio was 3 or more standard deviations above the mean healthy value. Two radiologists (AF, GP) blinded to pre-imaging clinical parameters evaluated the MRI data separately and independently.

To ensure that histopatological findings matched with mpMRI images (cognitive fusion) the assessment of radiological images and SPBx scheme were performed dividing the prostate into 14 regions as previously reported (12). In the presence of mpMRI lesions suspicious for cancer, 4 targeted TRUS guided-biopsies -in addition to standard SPBx- were performed. A probability (*p*) level of less than 0.05 was considered statistically significant.

Results

A T1c clinical stage PCa was found in 23 (57.5%) and 11 (27.5%) patients submitted to SPBx and mpMRI targeted-biopsy, respectively; in the remaining cases a normal parenchyma (absence of cancer) was diagnosed. Multi-parametric pMRI was positive (Figure 1b) in 16/40 (40%) patients, in detail, in 11/23 (47.5%) and in 5/15 (33.3%) men with PCa and normal parenchyma, respectively. A total of 64 targeted-biopsies were performed; the median diameter of the suspicious mpMRI lesions was equal to 12 (range=8-15) mm *vs*. 6 (4-10) mm in the presence *vs*. absence of PCa (p=0.14), respectively; mpMRI targeted-biopsy found 9 and 2 cancers of the peripheric and anterior zone of the gland, respectively. In 15/23 patients the PCa was found in the same prostatic zone of primary microfocal disease; moreover, mpMRI targeted biopsy diagnosed 2 cancers of the anterior zone that were missed by SPBx.

Clinical parameters, mpMRI and histological biopsy findings of the 23 men with PCa are listed in Table I. All 11 men with PCa and positive mpMRI had a clinically significant cancer (1, 2). On the contrary, in the 12/23 patients with negative mpMRI quantitative histology was suitable for clinically insignificant cancer (median number of positive cores, GPC and GS equal to 1.5, 30% and 6, respectively) or a new microfocus of PCa was found for the second time (6 cases).

Fifteen (65.2%) out of 23 men underwent retropubic radical prostatectomy (RRP): 11 had a positive mpMRI targeted-biopsy combined with clinically significant PCa; moreover, in the 3/4 (75%) patients with negative mpMRI an indolent cancer was found (Table II). The remaining 25 patients were enrolled in an active surveillance protocol.

The diagnostic accuracy of mpMRI targeted-biopsy in diagnosing significant PCa was equal to 100%.

Table I. *Clinical, biopsy and mpMRI findings in the 23 patients with prostate cancer (PCa) diagnosed at repeat saturation biopsy.*

Clinical parameters in the presence of PCa No of patients	Overall 23	GS 6 20 (87%)	GS 7 3 (13%)
Median PSA (ng/ml)*	10.1	9.5	12.3
No of positive cores (median)*	2.7	2.1	7
Median GPC*	35%	20%	90%
Positive mpMRI	11 (47.9%)	8 (40%)	3 (100%)
No of positive cores (median)	4	3	7
Median GPC	55%	40%	90%
Negative mpMRI	12 (52.1%)	12 (60%)	-
No of positive cores (median)	1.5	1.5	-
Median GPC	30%	30%	-
Microfocus of PCa**	6 (50%)	6 (30%)	-

Overall*; mpMRI, multi-parametric pelvic magnetic resonance imaging; GS, Gleason score; GPC, greatest percentage of cancer; **a single positive core with GPC <5% and GS of 6.

Discussion

Microfocal cancer on prostate biopsy is defined by the presence of a single positive core with a minimal cancer involvement in terms of core length: 0.5-2 mm (3, 4) or in percent of cancer <5% (5, 6). In screen-detected PCa, the overall incidence of PCa that fulfilled the Epstein criteria for indolent cancer in surgical specimen varies from 5.8% to 14% (13). In the sub-group of patients with a preoperative diagnosis of focal cancer this incidence raises from 22-33% up to 60-70% of the specimens, including a 0.8% possibility not to find the cancer at all (vanishing cancer phenomenon) (14-18). Tumor volume and Gleason grading are considered the major determinants of the biological behaviour and clinical outcome of PCa; moreover, the correlation between biopsy findings (19, 20) and overall tumor burden is rather poor and even a single focus of low grade PCa in a biopsy specimen, *per se*, does not predict the pathologic stage of the disease. Thong *et al*. (18) reported that 42/192 (22%) patients with biopsy-proven microfocal disease were upgraded and/or upstaged after surgery. In a series of 55 patients with a microfocus of PCa submitted to radical retropubic prostatectomy (RRP) we previously reported in the 27.3 and 14.5% of the cases extraprostatic extent and positive surgical margins, respectively (6).

In the last years, to reduce the risk of overtreatment in the presence of histological biopsy findings predictive of clinically-indolent PCa active surveillance protocols have

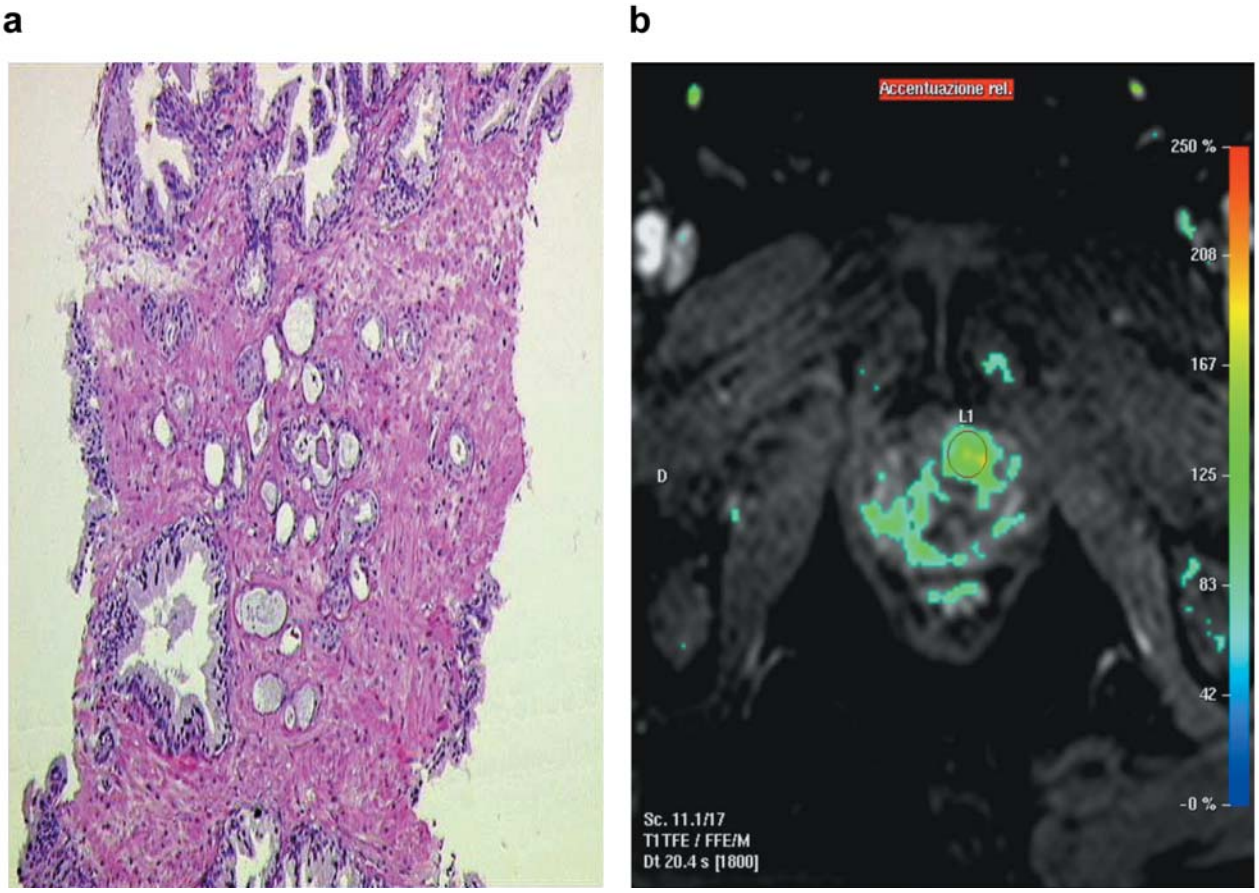

Figure 1. *A 67-year-old man with an initial biopsy showing a microfocus of prostate cancer (a) submitted to multi-parametric pelvic MRI (b) that demonstrated a lesion (diameter of 12 mm) suspicious for cancer of the anterior zone of the gland. MRI-targeted biopsy detected 3 cores of Gleason score 6 with a greatest percentage of cancer equal to 50%.*

Table II. *Multi-parametric pelvic magnetic resonance imaging (mpMRI), biopsy and pathological (pT) findings in the 15 patients who underwent radical retropubic prostatectomy.*

Clinical and biopsy findings	pT2a*	pT2b	pT2c	pT3a	GS 6	GS 7	psm	Nodes
15 patients	3 (20%)	5 (33.3%)	5 (33.3%)	2 (13.4%)	12 (80%)	3 (20%)	1 (6.7%)	neg
Positive mpMRI (11 cases-73.3%)	-	4	5	2	8	3	1 (9%)	neg
No of positive cores	-	2	4	7	3	7	-	-
Median GPC	-	10%	15%	75%	15%	90%	-	-
Biopsy GS	-	6	6	7	-	-	-	-
Negative mpMRI (4 cases-26.7%)	3	1	-	-	12	-	-	neg
No of positive cores	1	1	-	-	-	-	-	-
Median GPC	5%	5%	-	-	-	-	-	-
GS	6	6	-	-	-	-	-	-

pT2a*, Cancer volume <0.5 ml (clinically insignificant); GS, Gleason score; GPC, greatest percentage of cancer; psm, positive surgical margins; neg=negative.

been introduced in clinical practice; in this respect, mpMRI demonstrated high accuracy in detecting tumors larger than 0.5 ml (21, 22) and delineating clinically significant PCa demonstrating a sensitivity and negative predictive value equal to 85-93 *vs*. 84-100% (23-26), respectively. Multiparametric MRI has been suggested in the reevaluation of patients with minimal biopsy PCa enrolled in active surveillance protocols; moreover, Delonchamps *et al*. (27)

reported in 391 patients with suspected localized PCa a decreased detection of microfocal cancer performing mpMRI targeted-biopsy. Recently, Ouzzane *et al*. (28) stated that patients with nonsuspicious mMRI represent a special very low-risk group of men with either no disease or clinically insignificant disease, allowing them to be managed conservatively.

In our series, the first to our knowledge that evaluated mpMRI accuracy in the reevaluation of microfocal PCa, mpMRI targeted-biopsy found 11/23 cancers characterized by biopsy quantitative histology predictive of clinically significant PCa confirmed in the definitive specimen. On the other hand, the remaining 12 patients with PCa and negative mpMRI were at risk for indolent disease (3/4 patients submitted to surgery had a cancer volume <0.5 ml with a GS of 6). Finally, mpMRI demonstrated a diagnostic accuracy equal to 100% in diagnosing clinically significant PCa in men with initial microfocal disease.

Some limitations and considerations of the present study deserve annotation. Firstly, we do not know the true diagnostic accuracy of mpMRI in PCa diagnosis because the detection rate for cancer was compared only in 15 (37.5%) cases with definitive specimen and in 25 (62.7%) cases with SPBx results. Secondly, we do not know if the false-positive rate (5 cases) of mpMRI was secondary to false-negative SPBx results or biased because an mpMRI imaging/ultrasound fusion-guided biopsy, theoretically more accurate, was not performed. Finally, a greater number of patients should be evaluated.

In conclusion, mpMRI should be suggested in the presence of microfocal cancer as a selection approach of patients at risk for clinically significant PCa.

References

1 Epstein J, Walsh P and Carmichael M: Pathological and clinical findings to predict tumor extent of non palpable (stage T1c) prostate cancer. JAMA *271*: 368-374, 1994.

2 Kryvenko ON, Carter HB, Trock BJ and Epstein JI: Biopsy criteria for determining appropriateness for active surveillance in the modern era. Urology *83*: 869-874, 2014.

3 Bruce RG, Rankin WR, Cibull ML, Rayens MK, Banks ER and Wood DP Jr.: Single focus of adenocarcinoma in the prostate biopsy specimen is not predictive of the pathologic stage of disease. Urology *48*: 75-79, 1996.

4 Lee AK, Doytchinova T, Chen M, Renshaw AA, Weinstein M, Richie JP and D'Amico AV: Can the core length involved with prostate cancer identify clinically insignificant disease in low risk patients diagnosed on the basis of a single positive core ? Urol Oncol *21*: 123-127, 2003.

5 Guzzo TJ, Vira M, Hwang WT, D'amico A, Tomaszewski J, Whittington R, Wein AJ, Vanarsdalen K and Malkowicz SB: Impact of multiple biopsy cores on predicting final tumor in prostate cancer detected by a single microscopic focus of cancer on biopsy. Urology *66*: 361-365, 2005.

6 Pepe P, Candiano G, Fraggetta F, A Galia, G. Grasso and Aragona F: Is a single focus of low grade prostate cancer, diagnosed on saturation biopsy, predictive of clinically insignificant cancer? Urol Int *84*: 440-444, 2010.

7 Postma R, de Vries SH, Roobol MJ, Wildhagen MF, Schröder FH and van der Kwast TH: Incidence and follow up of patients with focal prostate carcinoma in 2 screening rounds after an interval of 4 years. Cancer *103*: 798-816, 2005.

8 Kryvenko ON, Carter HB, Trock BJ and Epstein JI: Biopsy Criteria for Determining Appropriateness for Active Surveillance in the Modern Era. Urology *83*: 869-864, 2014.

9 Pepe P and Aragona F: Saturation prostate needle biopsy and prostate cancer detection at initial and repeat evaluation. Urology *70*: 1131-1135, 2007.

10 Roethke MC, Kuru TH, Schultze S, Tichy D, Kopp-Schneider A, Fenchel M, Schlemmer HP and Hadaschik BA: Evaluation of the ESUR PI-RADS scoring system for multiparametric MRI of the prostate with targeted MR/TRUS fusion-guided biopsy at 3.0 Tesla. Eur Radiol *24*: 344-352, 2014.

11 Turkbey B and Choyke PL: Multiparametric MRI and prostate cancer diagnosis and risk stratification. Curr Opin Urol *22*: 310-315, 2012.

12 Pepe P, Garufi A, Priolo G, Candiano G, Pietropaolo F, Pennisi M, Fraggetta F and Aragona F: Prostate cancer detection at repeat biopsy biopsy: can pelvic phased-array multiparametric MRI replace saturation biopsy? Anticancer Res *33*: 1195-1199, 2013.

13 Augustin H, Hammerer P, Graefen M, Palisaar J, Noldus J, Fernandez S and Huland H: Insignificant prostate cancer in radical prostatectomy specimen: time trends and preoperative prediction. Eur Urol *43*: 455-460, 2003.

14 Jeldres C, Suardi N and Walz J: Validation of the contemporary Epstein criteria for insignificant prostate cancer in European men. Eur Urol *54*: 1306-1313, 2008.

15 Cheng L, Poulos C, Pan C, Jones TD, Daggy JK, Eble JN and Koch MO: Preoperative prediction of small volume cancer (less than 0.5 ml) in radical prostatectomy specimens. J Urol *174*: 898-902, 2005.

16 Harnden P, Naylor B, Shelly MD, Clements H, Coles B and Mason MD: The clinical management of patients with a small volume of prostatic cancer on biopsy: what are the risks of progression? A systematic review and meta-analysis. Cancer *112*: 971-981, 2008.

17 Anast J, Andriole G, Bismar T, Yan Y and Humphrey PA: Relating biopsy and clinical variables to radical prostatectomy findings: can insignificant and advanced prostate cancer be predicted in a screening population ? Urology *64*: 544-550, 2004.

18 Thong AL, Shikanov S, Katz MH, Gofrit ON, Eggener S, Zagaja GP, Shalhav AL and Zorn KC: A single microfocus (5% or Less) of Gleason 6 prostate cancer at biopsy- can we predict adverse pathological outcomes? J Urol *180*: 2436-2440, 2008.

19 Pepe P, Galia A, Fraggetta F, Grasso G, Allegro R and Aragona F: Prediction by quantitative histology of pathological stage in prostate cancer Eur J Surg Oncol *31*: 309-313, 2005.

20 Pepe P, Fraggetta F, Galia A, Grasso G, Piccolo S and Aragona F: Is quantitative histologic examination useful to predict nonorgan-confined prostate cancer when saturation biopsy is performed? Urology *72*: 1198-1202, 2008.

21 Abd-Alazeez M, Ahmed HU, Arya M, Charman SC, Anastasiadis E, Freeman A, Emberton M and Kirkham A: The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level – can it rule out clinically significant prostate cancer? Urol Oncol *32*: 17-22, 2014.

22 Turkbey B, Mani H, Aras O, Rastinehad AR, Shah V, Bernardo M, Pohida T, Daar D, Benjamin C, McKinney YL, Linehan WM, Wood BJ, Merino MJ, Choyke PL and Pinto PA: Correlation of magnetic resonance imaging tumor volume with histopathology. J Urol *188*: 1157-1163, 2012.
23 Styles C, Ferris N, Mitchell C, Murphy D, Frydenberg M, Mills J, Pedersen J, Bergen N and Duchesne G: Multiparametric 3T MRI in the evaluation of intraglandular prostate cancer: Correlation with histopatology. J Med Imaging Radiat Oncol *58*: 439-448, 2014.
24 Ouzzane A, Puech P and Villers A: How accurately can MRI detect indolent disease? Curr Opin Urol *24*: 264-269, 2014.
25 Chamie K, Sonn GA, Finley DS, Tan N, Margolis DJ, Raman SS, Natarajan S, Huang J and Reiter RE: The role of magnetic resonance imaging in delineating clinically significant prostate cancer. Urology *83*: 369-375, 2014.
26 Stamatakis L, Siddiqui MM, Nix JW, Logan J, Rais-Bahrami S, Walton-Diaz A, Hoang AN, Vourganti S, Truong H, Shuch B, Parnes HL, Turkbey B, Choyke PL, Wood BJ, Simon RM and Pinto PA: Accuracy of multiparametric magnetic resonance imaging in confirming eligibility for active surveillance for men with prostate cancer. Cancer *119*: 3359-3366, 2013.
27 Delongchamps NB, Peyromaure M, Schull A, Beuvon F, Bouazza N, Flam T, Zerbib M, Muradyan N, Legman P and Cornud F: Prebiopsy magnetic resonance imaging and prostate cancer detection: comparison of random and targeted biopsies. J Urol *189*: 493-499, 2013.
28 Ouzzane A, Puech P and Villers A: How accurately can MRI detect indolent disease? Curr Opin Urol *24*: 264-269, 2014.

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