Original Article

Increased rate of positive biopsies using a combination of MR-Tomography, spectroscopy and diffusion-weighted magnetic resonance imaging prior to prostate biopsies in patients with persistent elevated prostate-specific antigen values: A retrospective analysis

A. Lunacek, J. Simon[1], R. Bernt[1], M. Huber[2], E. Plas, C. Mrstik

Departments of Urology, [1]Radiology, and [2]Pathology, Hanusch Krankenhaus, Vienna, Austria

Abstract

Purpose: Persistently elevated prostate-specific antigen (PSA) values following negative biopsies result in a diagnostic dilemma. In order to improve detection rates in patients with former negative biopsies and persistently elevated PSA values, magnetic resonance tomography (MRT), magnetic resonance spectroscopy (MRS), and diffusion-weighted magnetic resonance imaging (DW-MRI) were performed prior to prostate rebiopsies.

Materials and Methods: Over a 14-month period, 67 patients (mean age of 66 years) with a history of 1-5 negative biopsies underwent endorectal magnetic resonance imaging (MRI) using T2-weighted MRT MRS and DW-MRI before an additional prostate biopsy was performed. Subsequently, 5 contrast-enhanced transrectal ultrasound-guided biopsies were performed according to a 10-core systematic scheme. Out of the 67 men, 25 patients had positive biopsies and opted for radical prostatectomy. Histological evaluation of cancer localization, PSA, diameters of primary tumors, numbers and diameters of satellite tumors, prostate volume, and staging pathology was performed. These findings were compared with MRI and MRS results.

Results: Serum PSA levels ranged from 3.1 to 19.5 g/ml (median level of 7.96 ng/ml). After the 25 patients underwent radical prostatectomy, analysis of 20 whole-mount sections of 25 radical retropubic prostatectomy (RPE) specimens presented results agreeing with the tumor location from MRI and MRS data.

Conclusions: The aim of image-guided diagnostics should be to provide more critical information prior to biopsy. Furthermore, the acquisition of such data is important for better risk stratification in therapeutic decisions.

Key Words: Biopsy, detection, magnetic resonance imaging, prostate cancer

Address for correspondence:
Dr. Andreas Lunacek, Department of Urology, Hanusch Krankenhaus, Heinrich Collin Strasse 30, A-1140 Vienna, Austria. E-mail: andreas.lunacek@acmp.at
Received: 27.11.2011, **Accepted:** 03.03.2012

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/0974-7796.110001

INTRODUCTION

Prostate cancer is the most commonly diagnosed malignancy in the western world. The standard detection is from assessment of prostate-specific antigen (PSA) and digital rectal examination (DRE). In patients with increased levels of serum PSA or suspicious DRE, systematic grey-scale biopsies are performed. To minimize side effects compared to

saturation biopsies, fewer needle biopsies with higher accuracy are recommended. The major aim is to develop more accurate techniques in order to avoid saturation biopsies.

There are several methods used for imaging the prostate and surrounding tissues. Among these are contrast medium-enhanced transrectal ultrasound (CEUS), magnetic resonance imaging (MRI), spectroscopy (MRS) and DW-MRI. The CEUS technique has been used for detection for about 10 years.[1,2] MRI has an advantage of allowing a detailed evaluation of prostatic, periprostatic, and pelvic anatomy, and neither TRUS nor CT can offer this broad coverage. Spectroscopy relies on tissue metabolism, DW-MRI is based on diffusion of hydrogen molecules denoting pathological changes. They therefore clearly differ from other imaging modalities such as MRI, CT, or TRUS, which assess abnormalities of structure only.[3] Suspect results based on the T2 weighted images with regions of low signals and minimum one additional suspicious MRS or DW-MRI. Magnetic resonance spectroscopy (MRS) and diffusion-weighted magnetic resonance imaging (DW-MRI) have the potential to significantly increase the detection rate of prostate cancer. Clearly, the combination of imaging modalities may represent a powerful tool for the management of prostate cancer in most of its aspects: initial diagnosis, cancer localization, local staging, and additional detailed information for surgery and radiotherapy.[4,5]

The objectives of the present study were to evaluate whether MRI is useful for localization prior to prostate biopsy, and to increase the prostate cancer detection rate in selected patient cohorts with persistently elevated or increasing PSA values.

MATERIALS AND METHODS

Subjects in the study

A total of 25 males with a history of 1-5 previous negative biopsies underwent endorectal MRI/MRS/DW-MRI 1 week before transrectal contrast-enhanced targeted and grey scale ultrasound (GSUS) guided prostate biopsy in a single center. None of these patients had signs of acute prostatitis, urinary tract infection, contraindication to the contrast medium Sonovue® (Bracco, Milan), or had been using nonsteroidal anti-inflammatory medications 10 days prior to biopsy. A written informed consent was obtained in each case. After obtaining informed consent from patients, specimens were donated to the Department of Pathology for research and teaching purposes according to the regulations of the National Ethical Review Board.

Imaging equipment and methods

Magnetic resonance was performed on a 1.5-Tesla MR scanner (PhilipsAchieva Version 2 Series) using an endorectal coil (Philips Medical Systems Type Ecca 64 MHZ). The imaging protocol included transverse and coronal high-resolution T2-weighted Turbo Spin Echo sequences (TSE; T2 paraaxial 4 min 41 s, TSE T2 coronal 3 min 17 s, TSE; T2 axial 5 min 3 s, and 3-D spectroscopic TE 120; 0; paraaxial 11 min 58 s). The interpretation of the MRS results correspond to methods described by Müller-Lisse.[6]

Contrast medium-enhanced ultrasound (CEUS) assisted was performed by one radiologist (JS) using a Toshiba Aplio XG and an endocavital probe (Toshiba PVT 661VT) with 6 MHz.

For GSUS, a B-K Medical®, 2001 (Leopard, Denmark) was used with a mechanical (single-element) multiplane transducer for rectal scanning (Mod 8551) at a frequency of 7.5 MHz.

Biopsy procedures

One day before biopsy, all participants began a 5-day course of a fluoroquinolone antibiotic, or an appropriate alternative antibiotic if there was a fluoroquinolone allergy. Furthermore, a cleansing enema (Mikroklist® Pfizer) was administered on the morning of biopsy and MR imaging.

CEUS and GSUS biopsies were performed using a needle guidance device. SonoVue® contrast agent was prepared according to the instructions of the manufacturer. Four to 5 targeted biopsy cores were obtained during intravenous injection of the contrast agent. Contrast enhanced imaging was always performed prior to grey scale biopsies, in accordance with the MRI, MRS, and DW-MRI results. CEUS guided biopsies were performed in any areas that appeared suspect by MR and in hypervascular areas of the peripheral zone (PZ) of the prostate.

Each biopsy core was reviewed by a pathologist and reported as a prostate cancer with an assigned Gleason score, an atypical small acinar proliferation, benign prostatic tissue, or prostatic inflammation.

Treatment of specimens

A total of 25 prostatectomy specimens were serially step-sectioned at 4-mm intervals, perpendicular to the long axis (apical-basal) of the gland, and whole mounted according to a standard protocol. The sections were then covered with histological dye using a standard protocol (left lobe, yellow; right lobe, green; ventromedial, black) and then fixed in 7.5% neutral buffered formalin for 24 h. The cut slices were placed in super-mega-cassettes (Sanova®), fixed in formalin for an additional 24 h and then paraffin-embedded according to routine histological methods in a Tissu-Tek® VIM™ 5 (Sakura®) vacuum infiltration processor. Specimens were cut as 2-4 μm whole-mount sections, placed on 50 × 76-mm microscope slides (Menzel® Gläser) and then dried at 60°C overnight. The dried tissue specimens were deparaffinized and then rehydrated using xylene and a decreasing alcohol series, stained with hematoxylin and eosin, and permanently mounted using Pertex quick hardening mounting medium (Medite®)

and 50 × 55-mm cover glasses (Menzel® Gläser). The slices were subsequently examined using a Nikon® eclipse E400 light microscope and scanned by an Acer/Benq® Prism 620 ST transmitted-light scanner.

Analysis of results

Cancer localization within the whole-mount sections was assessed and compared with the MR results by 1 pathologist (MH), 2 radiologists (JS, RB), and 3 urologists (AL, CM, EP). Any single analysis of the MRI results as well as the histological work-up was done blinded. As a last step, the pathological and radiological findings were compared. The analysis included the extension and location of the primary tumor and, in addition, the number and sizes of satellite tumors.

The results are expressed as odds ratios with 95% confidence intervals and their respective *P* values. The IBM® SPSS® Statistics 18 software program was used for the statistical analyses.

RESULTS

Patient ages ranged from 49 to 78 years (mean value of 66), with a median PSA of 7.96 ng/ml (range of 3.1-19.5 ng/ml). A total of 67 males underwent the MRI/MRS/DW-MRI procedure followed by CEUS and GSUS biopsies. All participants had at least 1 former biopsy (median of 1.96 biopsies). Prostate cancer was detected in 25 participants. The Gleason scores of the prostatectomy specimens ranged from 6 to 9 (median value of 7.04). The 25 whole-mount sections of the retropubic radical prostatectomy (RPE) specimens were compared to the MRT and MRS results.

The primary tumor, as well as satellite tumors, was found in the PZ. No tumor was found in the transitional zone. The total number of detected tumors (i.e., primary and satellite tumors) was 86 (median value of 3.3). The primary tumor diameters ranged from 4 to 23 mm (median value of 10.92 mm), and the size of the satellites ranged from 2 to 6 mm.

The correlation between the histological specimens and the MR results correspond to the primary cancer within the prostate [Figure 1a, b]. The detectable tumors had a minimum diameter of 7 mm, and the size of satellites was less than 6 mm. The location of the cancer in 20 histological specimens (80%) showed identical results to MR findings, whereas 5 specimens (20%) had no analogy (maximum diameter of primary tumors 5 mm).

Within the group of 42 men with negative biopsies, there was no evidence of cancer in two MRI modalities at least.

The interrelationships of these different variables were correlated.

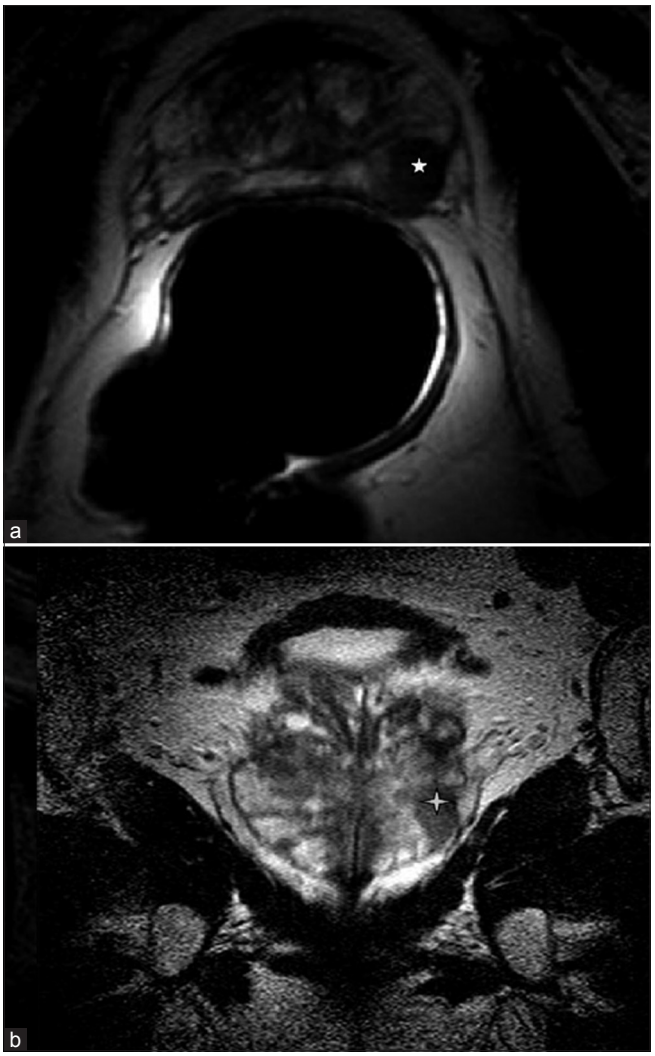

Figure 1: Sixty nine year old male patient with a biopsy proven Gleason 9 cancer, PSA 11 ng/ml. MRT was referred before CEUS and GSUS biopsy and radical prostatectomy. (a) An axial T2-weighted MRT shows large volume tumor on the left side (asterisk). (b) A coronal T2-weighted MRI reveals tumor (asterisk) invading left prostatic capsule, indicating stage T3 a disease

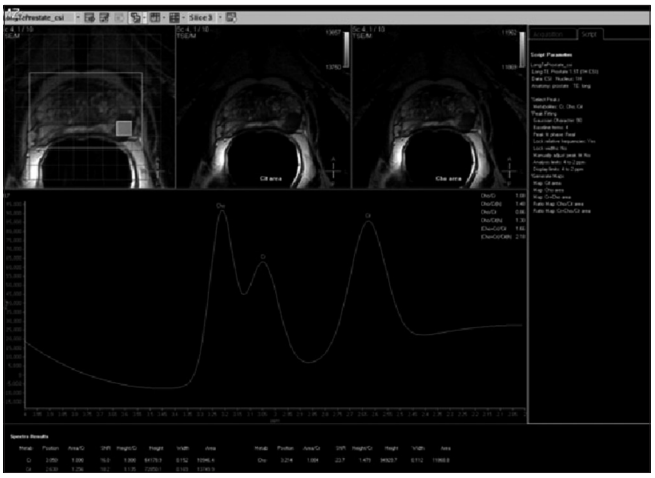

Figure 2: Corresponding MRS of the region of interest. The spectroscopic measurement shows a reduced citrate signal and increased choline-creatine to citrate ratio in the center of the tumor lesion (full square)

DISCUSSION

A major goal for prostate cancer treatment is to accurately diagnose the cancer, particularly in the early stages of the disease. Persistently high and/or increasing PSA levels and 1 or more negative biopsies are a major concern in clinical practice. Elevated PSA is the most common indication for performing a prostate biopsy. In case PSA levels are still rising after the first negative biopsy, the detection rate of prostate biopsies after a first and second negative set is approximately 20%,[7,8] whereas 70% of all rebiopsies in the third to fifth set show a Gleason score of ≥6.[9]

The prediction of positive needle biopsy is directly related to cancer volume and the number of cores obtained.[9,10] Prostate cancer detection in men who have never had a biopsy is undervalued by the sextant biopsy regimen, which yields cancer detection rates of only 20-25%.[10] In the last few years, the use of more effective biopsy techniques has improved patient tolerability of increased sampling.[11,12] To further improve detection of prostate cancer while limiting the number of biopsy cores, microbubble contrast agents have been used to optimize the US diagnostic as reasonable approach for detecting a greater number of clinically significant cancers with fewer biopsy cores.[13,14]

One of the most accurate modalities for the evaluation of extracapsular cancer extension and seminal vesicle invasion is endorectal MRI. However, its value for staging prostate cancer is the subject of considerable controversy, and widespread use has been deterred by the lack of uniform image quality, interobserver variability, and differences of consensus about specific MRI findings in the diagnosis of extracapsular extension. The technology continues to evolve, and large sets of data are becoming available. The opportunity to combine anatomical and metabolic information with combined MRI, spectroscopic MR, and DW-MRI promises much potential for the future.[14]

Dynamic MR imaging, MRS [Figure 2], and DW-MR imaging to localize prostate cancer, as compared to T2-weighted MR imaging, significantly improves accuracy. Combined morphologic and metabolic information is very useful for localizing prostate cancer for MR imaging in clinical practice. An accuracy of up to 88% was achieved for tumor localization focused on the PZ. Improved prostate cancer localization with MRT and MRS imaging is used for patients with increasing PSA levels and negative image guided biopsy results. These imaging modalities may be used to gather more detailed information about tumor location, distance between tumor and neurovascular bundle, and assessment of the prostate capsule to determine if nerve sparing surgery is possible. This type of information would be particularly useful in laparoscopic procedures where no tactile information is provided.[15-17]

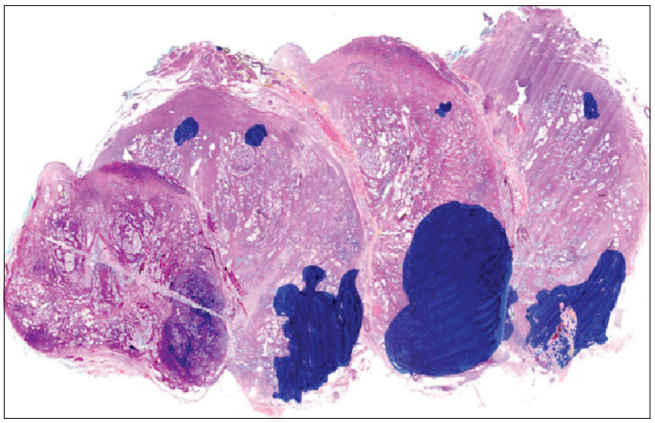

Figure 3: Corresponding histopathological step-section map of apex mid gland and base pT3 a Gleason 9 (5 + 4) tumor with extracapsular extension on mid posterior left aspect of prostate

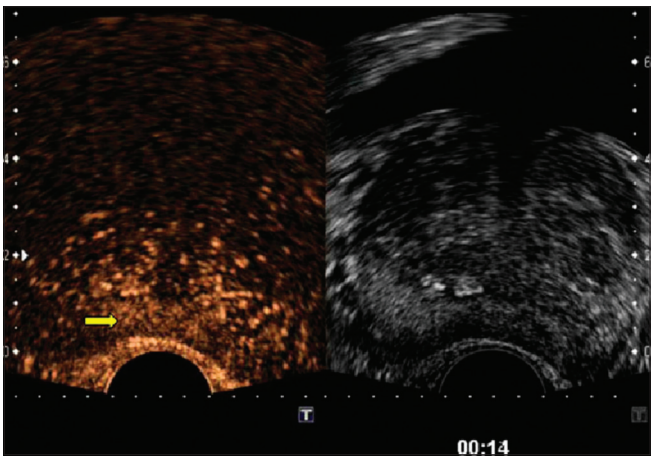

Figure 4: US 1 (14 sec after conrast medium application). Grey scale picture (right side): Hypoechoic lesion middle base and laft base/ coronar section. Contrast medium enhanced (left side): Early uptake of SonoVue contrast agent (yelloy arrow)

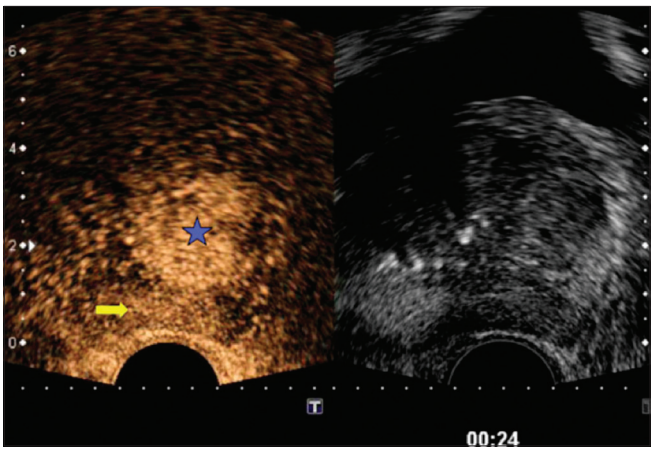

Figure 5: US 2 (24 sec after conrast medium application). The hypoechoic lesion is well depictable in the contrast mode (yellow arrow). Further contrast agent is accumulated in the TZ (blue asterix)

In our series of 80% histologically proven prostate cancer [Figure 3], tumors were detected using MR modalities. Based on the MR findings, a significant biopsy detection rate was

achieved. Some factors may have contributed to these results. Contrast-enhanced biopsies were collected from hypervascular areas in the PZ, based only on the MR findings. No targeted biopsies were collected in the transition zone because the changes of benign prostatic hyperplasia demonstrate hypervascularity, which is impossible to differentiate from the hypervascularity caused by cancer [Figures 4-5].[13] Furthermore, no suspicious areas were found in the transition zone using MR modality.

Magnetic resonance performed prior to biopsy provided evidence for possible malignancies within the gland. A more accurate assessment in specimens with a Gleason score of >7 was noticed in the present series. Chronic inflammatory disease of the prostate and prostatic hyperplasia with negative targeted biopsies on CEUS as well as GSUS was the major cause for negative results.

In 20 of the 25 radical prostatectomy specimens, results matched those obtained from MR imaging. Results of only 5 specimens showed no match to those of the imaging modalities. The smallest detectable cancer lesion found with magnetic resonance tomography (MRT) had a diameter of about 7 mm. Tumors smaller than 6 mm in diameter were not detected in the MR modality.

Hypoechoic lesions in the transitional zone presented no pathological findings in the spectroscopic analysis. The additional use of MRT/MRS/DW-MRI prior to biopsy increased the probability to achieve a higher positive rebiopsy rate. Prebiopsy MRI provided information on the position of the cancer, specifically for considering adjustments to be made to the needle depth and direction before biopsy to ensure proper sampling of lesions.[18-20]

CONCLUSIONS

This study facilitates a more accurate assessment for US-targeted biopsies by conducting MRI/MRS/DW-MRI prior to prostate biopsy, which in turn provides important information on possible malignancies and extracapsular extension. These MRI modalities, in addition to the US-guided biopsies, increase the overall detection rate in re-biopsies and may represent an approach to avoid routinely performed saturation biopsies. The study should not conceal limitations of all mentioned modalities but in summary one more step in detection of prostate cancer is done. Additional MR information provides guidance for making therapeutic decisions.

REFERENCES

1. Frauscher F, Klauser A, Halpern EJ, Horninger W, Bartsch G. Detection of prostate cancer with a microbubble ultrasound contrast agent. Lancet 2001;357:1849-50.
2. Roy C, Buy X, Lang H, Saussine C, Jacqmin D. Contrast enhanced color Doppler endorectal sonography of prostate: Efficiency for detecting peripheral Zone tumors and role for biopsy procedure. J Urol 2003;170:69-72.
3. Lawrentschuk N, Fleshner N. The role of magnetic resonance imaging in targeting prostate cancer in patients with previous negative biopsies and elevated prostate-specific antigen levels. BJU Int 2009;103:730-3.
4. Sciarra A, Salciccia S, Panebianco V. Proton spectroscopic and dynamic contrast-enhanced magnetic resonance: A modern approach in prostate cancer imaging. Eur Urol 2008;54:485-8.
5. Bonekamp D, Jacobs MA, El-Khouli R, Stoianovicic D, Macura KJ. Advancements in MR imaging of the prostate: From diagnosis to interventions. Radiographics 2011;3:677-703.
6. Mueller-Lisse UG, Scherr M. 1H magnetic resonance spectroscopy of the prostate. Radiologe 2003;43:481-8.
7. Puppo P, Introini C, Calvi P, Naselli A. Role of transurethral resection of the prostate and biopsy of the peripheral zone in the same session after repeated negative biopsies in the diagnosis of prostate cancer. Eur Urol 2006;49:873-8.
8. Puppo P. Repeated negative prostate biopsies with persistently elevated or rising PSA: A modern urologic dilemma. Eur Urol 2007;52:639-41.
9. Djavan B, Mazal P, Zlotta A, Wammack R, Ravery V, Remzi M, *et al.* Pathological features of prostate cancer detected on initial and repeat prostate biopsy: Results of the prospective European Prostate Cancer Detection study. Prostate 2001;47:111-7.
10. Steiner H, Moser P, Hager M, Berger AP, Klocker H, Spranger R, *et al.* Clinical and pathologic features of prostate cancer detected after repeat false-negative biopsy in a screening population. Prostate 2004;58:277-82.
11. Stricker HJ, Ruddock LJ, Wan J, Belville WD. Detection of non-palpable prostate cancer. A mathematical and laboratory model. Br J Urol 1993;71:43-6.
12. Patel A. Finding a balanced strategy in prostate cancer diagnosis for case detection by prostate needle biopsy at first presentation: "All for more cores and more cores for all" or individualised sampling regimens? Which way forward? Eur Urol 2007;52:313-5.
13. Guichard G, Larré S, Gallina A, Lazar A, Faucon H, Chemama S, *et al.* Extended 21-sample needle biopsy protocol for diagnosis of prostate cancer in 1000 consecutive patients. Eur Urol 2007;52:430-5.
14. Frauscher F, Klauser A, Volgger H, Halpern EJ, Pallwein L, Steiner H, *et al.* Comparison of contrast enhanced color Doppler targeted biopsy with conventional systematic biopsy: Impact on prostate cancer detection. J Urol 2002;167:1648-52.
15. Hricak H: Imaging prostate cancer. J Urol 1999;162:1329-30.
16. Fütterer JJ, Heijmink SW, Scheenen TW, Veltman J, Huisman HJ, Vos P, *et al.* Prostate cancer localization with dynamic contrast-enhanced MR imaging and proton MR spectroscopic imaging. Radiology 2006;241:449-58.
17. Mazaheri Y, Shukla-Dave A, Hricak H, Fine SW, Zhang J, Inurrigarro G, *et al.* Prostate cancer identification with combined diffusion-weighted MR imaging and 3D 1H MR spectroscopic imaging – correlation with pathologic findings. Radiology 2008;246:480-8.
18. Mullerad M, Hricak H, Kuroiwa K, Pucar D, Chen HN, Kattan MW, *et al.* Comparison of endorectal magnetic resonance imaging, guided prostate biopsy and digital rectal examination in the preoperative anatomical localization of prostate cancer. J Urol 2005;174:2158-63.
19. Ahmed HU, Kirkham A, Arya M, Illing R, Freeman A, Allen C, *et al.* Is it time to consider a role for MRI before prostate biopsy? Nat Rev Clin Oncol 2009;6:197-206.
20. Pinto F, Totaro A, Calarco A, Sacco E, Volpe A, Racioppi M, *et al.* Imaging in prostate cancer diagnosis: Present role and future perspectives. Urol Int 2011;86:373-82.

How to cite this article: Lunacek A, Simon J, Bernt R, Huber M, Plas E, Mrstik C. Increased rate of positive biopsies using a combination of MR-Tomography, spectroscopy and diffusion-weighted magnetic resonance imaging prior to prostate biopsies in patients with persistent elevated prostate-specific antigen values: A retrospective analysis. Urol Ann 2013;5:76-80.

Source of Support: Nil, **Conflict of Interest:** None.