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ORIGINAL ARTICLE **CME**

Institutional Experience of Magnetic Resonance Imaging–directed Targeted Transrectal Ultrasound–guided Prostate Biopsy

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ABSTRACT

Objective: *To evaluate the efficacy of magnetic resonance imaging (MRI)–directed targeted transrectal ultrasound (TRUS) prostate biopsy in the detection of clinically significant prostate cancer.*

Methods: *The records of patients who underwent MRI-directed targeted TRUS prostate biopsy from August 2013 to December 2014 in a regional hospital in Hong Kong were retrospectively reviewed. The procedure was indicated in patients with persistently elevated prostate-specific antigen (PSA) and at least two consecutive negative random systematic TRUS prostate biopsies. Pre-biopsy MRI localisation was arranged. Multiparametric MRI of the prostate (T2-weighted, diffusion-weighted imaging, apparent diffusion coefficient, dynamic contrast–enhanced imaging, and spectroscopy) was performed and each lesion was mapped to one of 16 sectors of the prostate. Prostate Imaging–Reporting and Data System (PI-RADS) classification was used to score each suspicious lesion. TRUS-guided prostate biopsy was then performed at the sector with PI-RADS score of ≥3. Pathological reports were reviewed and cancer detection rate was calculated.*

Results: *Overall, 27 patients were referred during the study period. Of these patients, seven (25.9%) had positive findings: prostatic acinar adenocarcinoma was identified in six, and high-grade prostatic intra-epithelial neoplasia in one. Among the six patients with adenocarcinoma, three had a Gleason score of ≥7, and three had a score of 6. There was a cancer detection rate of 25.9% in our population with negative random TRUS biopsies and persistently elevated PSA.*

Conclusion: *MRI-directed targeted TRUS prostate biopsy is able to further detect prostate cancer that requires treatment in patients with persistently elevated PSA and repeated negative random TRUS biopsy. The cancer detection rate from our institution is comparable to other reported studies. MRI-directed targeted TRUS prostate biopsy requires no significant extra resources, and may help selected patients in our locality.*

Key Words: *Magnetic resonance imaging; Prostatic neoplasms; Ultrasound, high-intensity focused, transrectal*

中文摘要

根據磁共振成像經直腸超聲引導下的前列腺穿刺活檢：一所機構的經驗

曾彥豪、林卓恆、姚寶平、曹慶恩

目的：探討根據磁共振成像（MRI）經直腸超聲引導下（TRUS）的前列腺穿刺活檢用作檢測前列腺癌的效果。

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方法：研究對象為在2013至8月至2014年12月期間到香港一所分區醫院接受MRI指導TRUS前列腺穿刺活檢的病人，回顧分析其病歷紀錄。病人均有持續高水平的前列腺特異性抗原（PSA），以及至少兩個連續TRUS的前列腺活檢陰性。活檢前先以MRI定位，並進行多參數MRI（T2加權、擴散加權成像、表觀擴散係數、動態對比增強成像和磁共振波普），把每個病變定位到前列腺16個分區中的其中一個。再利用前列腺影像學報告和數據系統指南（PI-RADS）為每個可疑的病變評分。PI-RADS分數≥3時進行TRUS前列腺穿刺活檢。最後審查患者的病理報告，並計算出癌症檢測率。

結果：研究期間27名患者中7例（25.9%）有陽性結果，包括6例前列腺腺泡腺癌及1例高級別前列腺上皮內瘤。6例腺癌中，3例Gleason評分≥7，另3例評分為6。在這研究中，有持續高水平PSA和TRUS引導下前列腺活檢陰性樣本的癌症檢測率為25.9%。

結論：對於有持續高水平PSA和前列腺活檢陰性樣本的患者，以MRI定位的TRUS引導下前列腺穿刺活檢能進一步提高前列腺癌檢出率。我們醫院的癌症檢出率與其他研究報導相近，而且這種檢測方式無需額外設備。以MRI定位的前列腺穿刺活檢可以在本地選擇性地應用於患者身上。

INTRODUCTION

Prostate cancer has recorded the largest increase in incidence rate among common male cancers in Hong Kong over the past two decades. In 2011, prostate cancer was the third most common cancer in men, accounting for 11.7% of all new cancer cases in males.[1] The most widely used tests to screen for prostate cancer are digital rectal examination and the prostate-specific antigen (PSA) blood serum test. Increased PSA is not cancer-specific since numerous benign prostate conditions can increase its level. Urologists increasingly encounter patients with increased PSA in whom repeated transrectal ultrasound (TRUS)–guided biopsy reveals no cancer. Systematic random prostate TRUS biopsy is the standard procedure for prostate histological sampling and involves taking 8 to 12 cores depending on prostate size. Large prostate size, the multifocal nature of prostate cancer, and the relatively small tissue volume sampled by random biopsy — all these contribute to the persistently low cancer detection rate of random biopsy. Studies also show that the cancer detection rate falls with repeated random TRUS, from 22%-38% at initial biopsy, to 10%-17% at second biopsy, and 5%-15% at third biopsy.[2] Improvements in magnetic resonance imaging (MRI) technology over the last few decades have led not only to the potential for MRI in staging biopsy-confirmed prostate cancer but also to detecting cancer prior to biopsy. The value of MR in accurate localisation of prostate cancer is well established.[3-9] Various techniques for using MR images to improve prostate biopsies have been explored. Among them, MRI-directed TRUS biopsy, which is also called cognitive-fusion MR-TRUS-guided biopsy, has been initiated in our department for selected patients. As the name implies, MRI-directed TRUS biopsy means the radiologist uses MR images to target suspicious areas when performing TRUS-guided biopsy. The objective of this study was to evaluate the improvement in cancer detection rate when using MRI-directed targeted TRUS biopsy. To date, similar studies have not been performed in Hong Kong.

METHODS

This was a single-centre, retrospective study. The MR-directed targeted TRUS biopsy service started in August 2013, and all patients referred to this service between August 2013 and December 2014 were included. Patients in whom MRI-directed targeted TRUS biopsy was indicated had persistently elevated PSA level (>10 μg/l), and at least two consecutive negative random systematic TRUS prostate biopsies. These patients were arranged pre-biopsy MRI localisation according to departmental protocol. A 1.5T machine (Philips Achieva 1.5; Philips Healthcare, The Netherlands) was used without endorectal coil. Multiparametric MRI prostate — including T2-weighted (T2W) diffusion-weighted imaging (DWI, including apparent diffusion coefficient [ADC] map), dynamic-contrast enhancement (DCE), and MR spectroscopy (MRS) — was performed for detection purposes (not for staging) according to departmental protocol (T2W turbo spin-echo axial / sagittal / coronal; DWI / ADC map with b values = 0, 100, 500, 1000; dynamic T1 contrast THRIVE delay 5 minutes, 9.9 s per acquisition for 30 times; MRS). All MR studies were interpreted by a consultant radiologist. A PI-RADS score (Figure 1[10]; PI-RADS is the acronym

Score **Criteria**

A1. T2WI for the peripheral zone (PZ)

1 Uniform high signal intensity (SI)
2 Linear, wedge shaped, or geographic areas of lower SI, usually not well demarcated
3 Intermediate appearances not in categories 1/2 or 4/5
4 Discrete, homogeneous low signal focus/mass confined to the prostate
5 Discrete, homogeneous low signal intensity focus with extra-capsular extension/invasive behaviour or mass effect on the capsule (bulging), or broad (>1.5 cm) contact with the surface

A2. T2WI for the transition zone (TZ)

1 Heterogeneous TZ adenoma with well-defined margins: "organised chaos"
2 Areas of more homogeneous low SI, however well marginated, originating from the TZ/BPH
3 Intermediate appearances not in categories 1/2 or 4/5
4 Areas of more homogeneous low SI, ill defined: "erased charcoal sign"
5 Same as 4, but involving the anterior fibromuscular stroma or the anterior horn of the PZ, usually lenticular or water-drop shaped.

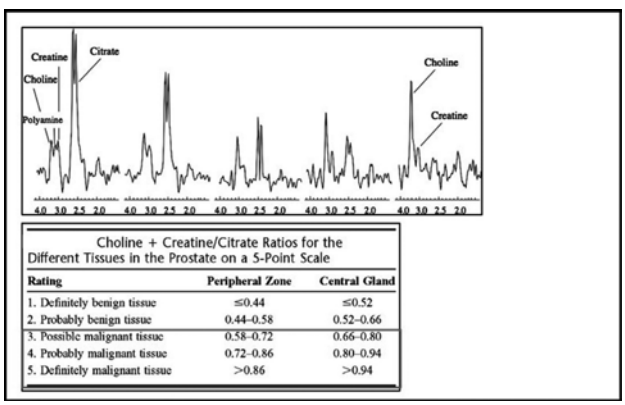
B. Diffusion weighted imaging (DWI)

1 No reduction in ADC compared with normal glandular tissue. No increase in SI on any high b-value image (≥b800)
2 Diffuse, hyper SI on ≥b800 image with low ADC; no focal features, however, linear, triangular or geographical features are allowed
3 Intermediate appearances not in categories 1/2 or 4/5
4 Focal area(s) of reduced ADC but iso-intense SI on high b-value images (≥b800)
5 Focal area/mass of hyper SI on the high b-value images (≥b800) with reduced ADC

C. Dynamic contrast enhanced (DCE)-MRI

1 Type 1 enhancement curve
2 Type 2 enhancement curve
3 Type 3 enhancement curve
+1 For focal enhancing lesion with curve type 2–3
+1 For asymmetric lesion or lesion at an unusual place with curve type 2–3

D1. Quantitative MRS for 1.5 T.



Choline + Creatine/Citrate Ratios for the Different Tissues in the Prostate on a 5-Point Scale

Rating	Peripheral Zone	Central Gland
1. Definitely benign tissue	≤0.44	≤0.52
2. Probably benign tissue	0.44–0.58	0.52–0.66
3. Possible malignant tissue	0.58–0.72	0.66–0.80
4. Probably malignant tissue	0.72–0.86	0.80–0.94
5. Definitely malignant tissue	>0.86	>0.94

D2. Qualitative magnetic resonance spectroscopic imaging (MRSI)

1 Citrate peak height exceeds choline peak height >2 times
2 Citrate peak height exceeds choline peak height times >1, <2 times
3 Choline peak height equals citrate peak height
4 Choline peak height exceeds citrate peak height >1, <2 times
5 Choline peak height exceeds citrate peak height >2 times

In qualitative analysis, the relative peak heights of citrate and choline are visually compared (pattern analysis), rather than quantified. The criteria apply for 1.5: for at least three adjacent voxels
Score 1 = Clinically significant disease is highly unlikely to be present
Score 2 = Clinically significant cancer is unlikely to be present
Score 3 = Clinically significant cancer is equivocal
Score 4 = Clinically significant cancer is likely to be present
Score 5 = Clinically significant cancer is highly likely to be present

Figure 1. PI-RADS scoring system (diagram reference from ESUR Prostate MR guidelines 2012[10]). Copyright permission granted by Dr J Barentsz.

for Prostate Imaging–Reporting and Data System, a structured reporting scheme for prostate cancer, to be discussed later) of 1-5 was assigned to each lesion, with 1 being most probably benign and 5 being highly suspicious of malignancy. A standardised 16-sector scheme with modified naming was used to divide the prostate (Figure 2[10-12]). Four to five targeted biopsies were performed at each suspicious sector. Targeted TRUS prostate biopsy was subsequently performed (within 2 weeks after pre-biopsy MRI) at the sector with PI-RADS score of ≥3, using a 20G Temno needle. Biopsies were performed by different fellow radiologists in the department. Four to five passes were performed at each target according to MR findings.

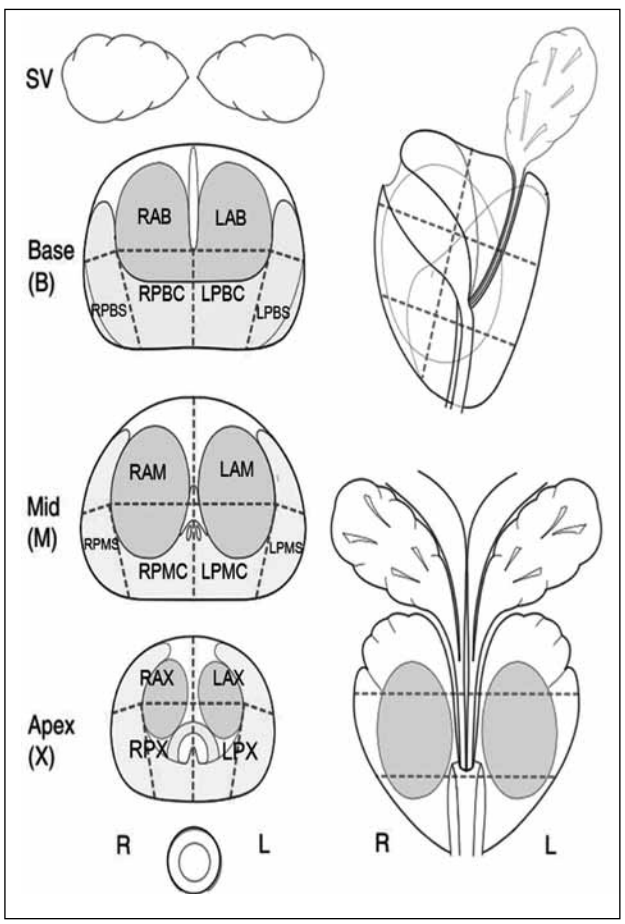


Figure 2. 16-Sector standardised magnetic resonance imaging (MRI) prostate reporting scheme with modified naming. The anterior region starts 17 mm from the prostatic posterior surface (biopsy core length). Anteriorly (A), prostate base (B), midgland (M), and apex (X) are divided into left (L) and right (R). Posteriorly (P), average axial sections at prostate base and midgland are subdivided into four regions, right and left, side (S) and central (C) and at the prostate apex into two regions, left and right (diagram reference from J Barentsz et al[10,11] and PP Iu[12]). Copyright permission granted by Dr J Barentsz.

Their pathological reports were reviewed and cancer detection rate was calculated.

This study was approved by ethics committee of the author's institution, with the requirement of patient's informed consent waived because of its retrospective nature.

RESULTS

During the study period, 27 patients were referred with a mean age of 68 years. The mean PSA level of all patients was 17.7 μg/l, and mean prostate size was 52.9 cc. Of the MR images, one showed evidence of extracapsular extension. Of the 27 patients, only seven had positive biopsy findings — six were found to have prostatic acinar adenocarcinoma and one yielded high-grade prostatic intra-epithelial neoplasia (HGPIN). Among the six patients with adenocarcinoma, three had a Gleason score of ≥7 (of which one was 10) and three had a score of 6. There was a 25.9% cancer detection rate in these patients with previous negative TRUS biopsies. All three patients with a Gleason score of 6 underwent radical prostatectomy. Those three with a Gleason score of ≥7 received neoadjuvant chemotherapy pending prostatectomy.

DISCUSSION

The limitations of random TRUS prostate biopsy underscore the need for an imaging modality that can detect and localise regions with an appearance suggestive of prostate cancer, and thus allow targeted sampling. MRI has been increasingly used in the work-up of patients with prostate cancer, mainly to detect extracapsular seminal vesicular, neurovascular bundle, and lymph node involvement for preoperative staging.

Multiparametric Magnetic Resonance for Carcinoma Prostate Detection: What Sequences to Include

Over the past two decades, MRI of the prostate has evolved to the point where it can directly depict the location of prostate cancer within the prostate gland. A multiparametric technique — including T2W images, a DCE, DWI, and MRS — is now well-described in the assessment of prostate cancer. Traditionally T2W imaging alone has been performed and is the best technique to look at anatomy, but it has limited sensitivity. Advanced techniques, namely DCE, MRS, and DWI have higher sensitivities and better detection rates. There has been some discussion about what advanced imaging techniques in addition to T2W

imaging should be used. In a study by Riches et al,[13] in which location of histologically confirmed cancer in prostatectomy specimens was correlated with the regions of abnormality seen on MRI, and receiver operating characteristic curves calculated for various combinations of advanced MR-based techniques, the combined use of two advanced techniques was significantly more accurate than the use of a single advanced technique for the detection of prostate cancer. The addition of a third advanced technique did not lead to further improvement in either sensitivity or specificity, however.[13] Another study by Franiel et al[14] showed that use of a combination of two advanced techniques would have reasonably reduced the number of areas targeted for biopsy although approximately 6% of lesions would have been missed. Thus it is recommended that diagnostic MRI examinations that are performed to detect and localise abnormal prostate regions for targeted biopsy include a combination of T2W imaging and at least two advanced imaging techniques. The most effective two-technique combinations have been shown to be DWI plus contrast-enhanced imaging and DWI plus MRS.[14] According to PI-RADS, T2W, DWI, and DCE should all be routinely acquired, while MRS is considered optional. In our institution, we used T2W imaging with a combination of DCE, DWI, and MRS.

Mapping and Grading of Lesions

A 16 region-of-interest dividing system of the prostate is used in our institution. Each lesion is described as entirely located within one sector, or crossing different sectors but with identification of the predominant sector. Each lesion is assigned a PI-RADS score from 1 to 5 according to its appearance on MRI. PI-RADS is a scoring system that makes use of various MRI techniques (T2W, DCE, DWI, and/or MRS) to derive a 5-point scale that stratifies the likelihood that a focal prostatic abnormality represents tumour, with 1 being clinically significant disease highly unlikely to be present, and 5 being clinical cancer highly likely to be present. A typical prostate cancer would appear T2 hypointense, have restricted diffusion on DWI/ADC map, demonstrate a type 3 enhancement curve with rapid arterial enhancement and subsequent washout on dynamic enhancement, and have high (choline + creatinine)/citrate ratio on MRS (Figure 3). The PI-RADS score also includes scoring extracapsular extension features, but this matters more during staging and it is beyond the scope of discussion in this article.

Since lesions with a PI-RADS score of ≥3 would be biopsied, it is important to discuss how the PI-RADS score is derived. Different methods have been proposed to derive the final PI-RADS score. Some advocate using a sum scoring system in which each lesion is assigned a score from 1 to 5 for each individual imaging parameter, resulting in lesions being scored 3 to 15 if MRS is not included in the imaging protocol, or 4 to 20 if MRS is included. The idea of a sum score suggests that each MR sequence contributes equally to the final PI-RADS score. Others advocate that the diagnostic value of each MRI parameter is not the same and that they should be weighted differently, meaning the PI-RADS score depends more on the primary determining sequence. Studies have shown that T2W and DWI are the major sequences to be inspected. For the peripheral zone, DWI is the primary determining sequence,[15] while for transition zone one T2W is the determining sequence.[16] DCE does not contribute to the overall score assessment if T2W or DWI can determine the lesions to be PI-RADS 1, 2, or 4, 5.[17] DCE is an unreliable tool to diagnose prostate cancer in the transition zone, given the significant overlap with benign prostatic hyperplasia.[18] Nonetheless, when DWI is PI-RADS 3 in the peripheral zone, a positive DCE may upgrade the lesion to PI-RADS 4.[17] In our institution, we give the final PI-RADS score based more on T2W, DWI, DCE, with MRS as an accessory tool.

Performance of Magnetic Resonance (MR)–directed Targeted Transrectal Ultrasound Biopsy, Other MR-assisted Biopsy Techniques, and Current Views on Their Roles

There are several techniques wherein MR can assist in prostate biopsy, including MRI-directed targeted TRUS biopsy or cognitive fusion of MR-TRUS guided biopsy, computer or software fusion of MR- and TRUS-guided biopsy, and direct MR-guided biopsy. The first method, MRI-directed targeted TRUS biopsy, is in use in our institution. Our results showed a cancer detection rate of 25.9% among patients with elevated PSA and repeated negative random TRUS biopsy, which is comparable to other reported studies that demonstrated a cancer detection rate of 16% to 44% by cognitive-fusion MR/TRUS biopsy in patients with previous negative TRUS biopsies.[19-22] Other MR-assisted prostate biopsy techniques include direct MR-guided biopsy, and computer-fused MR- and TRUS-guided biopsy although these are not yet available at our institution. The former method uses real-time MRI and MR-compatible biopsy instruments, with biopsy performed in the MR suite, and

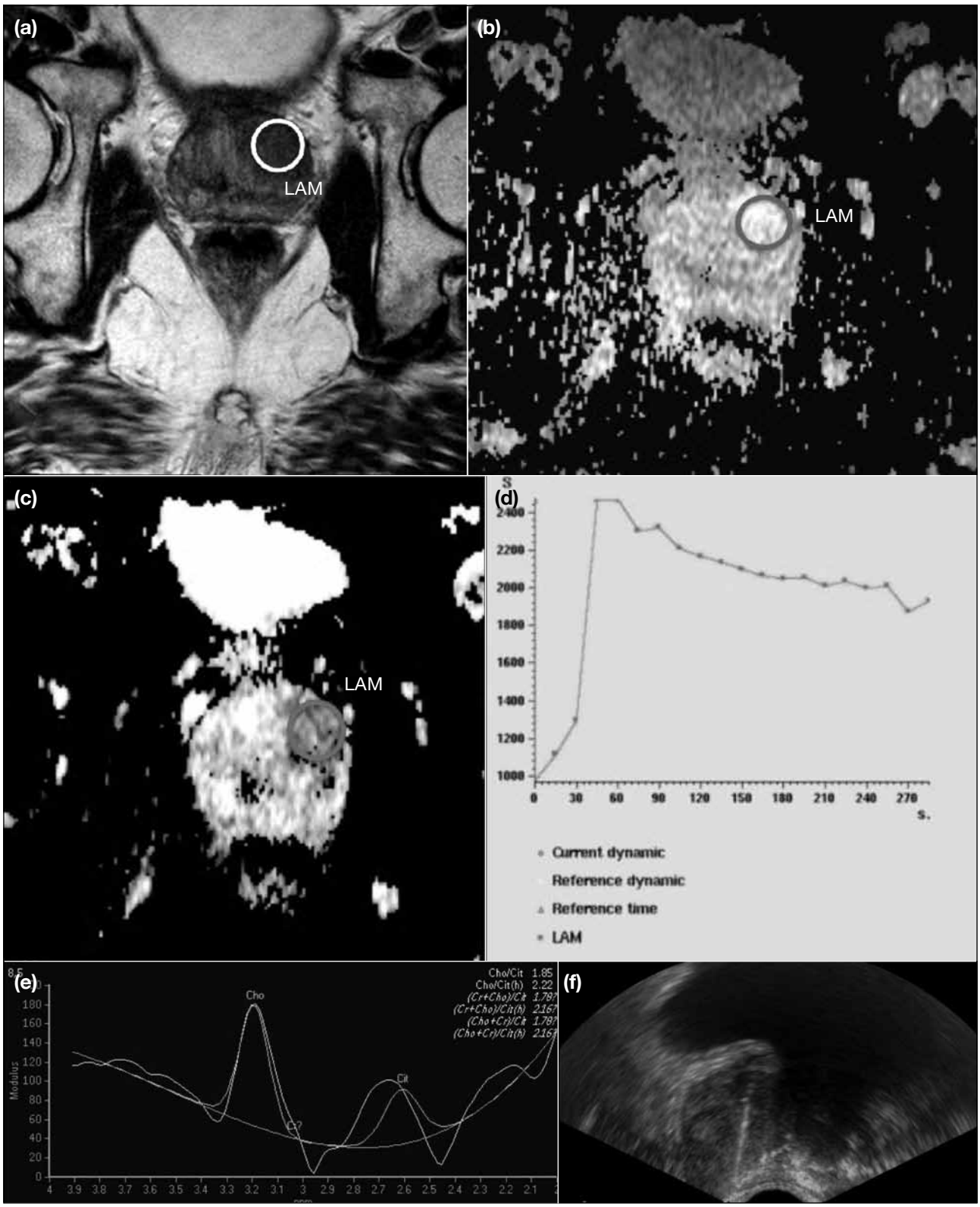


Figure 3. Magnetic resonance (MR) and transrectal ultrasound (TRUS) images of a PI-RADS 5 lesion over left anterior midgland (LAM), subsequent biopsy-proven adenocarcinoma. Images of (a) T2-weighted hypointense and (b and c) diffusion-weighted imaging / apparent diffusion coefficient show restricted diffusion; (d) dynamic-contrast enhancement shows type 3 curve; (e) MR spectroscopy shows elevated (choline + creatinine)/citrate ratio; (f) TRUS image with biopsy needle targeting the lesion.

the latter method uses software to fuse the MR image with TRUS image to allow targeted biopsy. These two methods allow visualisation of the suspected lesion by the surgeon performing the biopsy, while MRI-directed TRUS biopsy still requires estimation as lesions are seen on the previously performed MRI, not on TRUS. Studies that compare performance of cognitive fusion with software fusion of MR-TRUS prostate biopsy have shown controversial results. One multicentre prospective study showed similar performance[23] and others showed superior performance of software fusion.[24,25] Studies that reviewed the performance of direct MR-guided biopsy in patients with previous negative TRUS biopsies have shown a cancer detection rate of 38% to 59%.[26-29] No large-scale study has directly compared these three modalities. Nonetheless, an advantage of cognitive-fusion MR-TRUS biopsy over the other two modalities is that the method is quick, and no additional hardware or software or special training is required.

Despite firm evidence of the ability of MRI to detect and localise early intraprostatic prostate cancer,[3-9] current practice guidelines outline only a narrow diagnostic role for MRI in targeting prostate lesions for biopsy.[2] According to the most recent guidelines of the European Association of Urology, MRI may be used to investigate the possibility of an anteriorly located prostate cancer if clinical suspicion persists despite negative TRUS-guided biopsies.[30] The guidelines of the European Society of Urogenital Radiology in 2012 also suggested performing detection MRI followed by MR-guided TRUS biopsy or direct MR biopsy in patients with a previous negative TRUS biopsy and interval rise in PSA.[10] In US and Canadian guidelines, however, no role is outlined for MR-assisted targeted prostate biopsy at all.[31,32] This discrepancy reflects a lack of widely accepted definitions of roles, therefore large-scale multicentre trials and consensus statements are needed before algorithms incorporating targeted biopsy techniques can be widely accepted. We consider cognitive-fusion MR-TRUS biopsy, which requires no significant extra resources, to be a good first step to exploit the potential of MRI-directed prostate biopsy in selected patients in our locality.

Biopsy Results

In our study, three (50%) of the six patients with prostatic adenocarcinoma had a Gleason score of ≥7, of whom one had a score of 10, and three (50%) had a Gleason score of 6. Localised prostate cancer can be stratified into three groups based on the likelihood of tumour spread and recurrence: Gleason score of ≤6 is low risk and a score of ≥7 is high risk.[10] High-risk patients are at higher risk of extracapsular extension, and nodal and skeletal metastasis. Management of patients with high-risk disease requires staging MRI and bone scan, with increased likelihood of neoadjuvant chemotherapy prior to prostatectomy. Patients with high-risk disease in our study did receive the above investigations and treatment. In our study, one patient had histology indicative of HGPIN. HGPIN is believed to precede the development of prostate adenocarcinoma and HGPIN in isolation does not require treatment. Further, it has been shown that in prostate biopsies, HGPIN is not predictive of prostate cancer within 1 year.[33] Exact timing of repeated biopsies remains an area of controversy, as the time required for and probability of HGPIN transformation to prostate cancer is undetermined. The MR appearance of HGPIN is not yet well-described, but with more sensitive detection of abnormal foci in the prostate, biopsies yielding HGPIN are expected to increase in frequency.

Limitations

This study has some limitations. First, the study population was relatively small. Second, there was a time gap between last negative random biopsy and MRI-directed targeted biopsy. It is therefore difficult to determine whether the apparent improvement in cancer detection rate is due to natural disease progression or due to genuine improvement in sampling. This could be solved if there were a control group who could undergo another random TRUS biopsy instead of MR-directed biopsy. Nonetheless, this is technically difficult as most patients after at least two negative repeated random TRUS are reluctant to repeat the procedure again. Third, the MRI-directed targeted TRUS biopsy is performed by cognitive fusion. This means the location of the suspicious lesion on TRUS is estimated by the operator by correlating with MR images. There may remain sampling error due to inaccurate localisation without actual overlay of images unlike in the case of software fusion, in which this kind of sampling error should be reduced. Interval MR follow-up may be helpful in documenting whether the sampled area is the area of suspicion. Software MR/TRUS image fusion is not available in our institution yet, although it remains controversial whether software fusion performs better than cognitive fusion.

CONCLUSIONS

MRI-directed targeted TRUS prostate biopsy enabled

further cancer detection in patients with persistently elevated PSA and repeated negative random systematic TRUS biopsy in our study of limited sample size. Cancer detection rate was comparable to other studies. A future comparative study with larger sample size would be helpful to validate its efficacy. With better MR detection of localised prostate cancer, MRI-directed biopsy is expected to be more commonly used and alter patient management. MRI-directed targeted TRUS prostate biopsy using cognitive fusion, which requires no significant extra resources, might be a good first step to explore the potential of MRI-directed prostate biopsy in selected patients in our locality.

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