

MR Imaging and MR Spectroscopy of Adenocarcinoma of the Prostate

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Abstract

Introduction: We examined the impact of magnetic resonance (MR) imaging and MR spectroscopy on the diagnosis and management of prostate cancer. **Methods:** A Medline search was performed and the relevant articles reviewed. The salient points are discussed and summarised. **Results:** MR imaging with phased-array and endorectal coils is not recommended for routine staging. It has a complementary role in improving the accuracy of local staging in patients with intermediate risk based on Partin's normogram. MR spectroscopy can be performed in conjunction with high-resolution anatomic MR imaging of the prostate. It exploits the increased choline and decreased citrate levels within malignant prostatic tissue compared with normal prostatic tissue, and can potentially improve the assessment of cancer location and extent within the prostate, as well as extracapsular spread in small retrospective studies. It also has the potential of providing a measure of the presence and extent of prostate cancer after therapy. **Conclusion:** MR imaging is indicated in staging patients with intermediate risk based on Partin's normogram. Combined MR imaging and MR spectroscopy of the prostate is a promising imaging tool which can contribute to the diagnosis and management of prostate cancer when combined with clinical, biochemical and histological data. Large prospective studies must be performed to ascertain the true clinical value of combined MR imaging/MR spectroscopy for the management of prostate cancer patients.

Ann Acad Med Singapore 2003; 32:500-6

Key words: Chemical shift imaging, Endorectal coil, Extracapsular invasion, MR spectroscopy imaging, Prostate cancer

Introduction

Prostate cancer is usually suspected due to an abnormal digital rectal examination, elevated serum prostate specific antigen (PSA) level or both. The diagnosis of prostate cancer depends on histopathologic examination of tissue obtained from systematic sextant core needle biopsy under transrectal ultrasound guidance. Although magnetic resonance (MR) imaging may demonstrate local extension of disease, it is not recommended as a routine staging procedure by the American College of Radiology.¹ There are also no existing guidelines on the use of MR imaging and MR spectroscopy for diagnosis of prostate cancer and evaluation of local tumour spread.

Local Staging

The most important factor in patient prognosis and treatment in prostate cancer is disease stage.² At diagnosis, clinical staging is performed by digital rectal examination and the TMN staging classification of the American Joint Committee on Cancer is applied. Staging of prostate cancer

must always include an evaluation of local and distant extent of disease. In the TMN staging, the T stage denotes the local extent of the disease, the N stage denotes the presence or absence of nodal metastases and the M stage denotes the presence or absence of haematogeneous metastases.

It is critical to distinguish between a stage T2 tumour (which is confined to the prostate) and a stage T3 tumour (in which the tumour has invaded beyond the prostatic capsule or into the seminal vesicle). Radical prostatectomy is a treatment option in stage T2 tumours, but is generally not indicated for stage T3 tumours. Clinical staging of locally confined disease by digital rectal examination is correct in <50% of the patients when correlated with pathologic staging.³ Other independent variables that influence prognosis include the PSA level and Gleason score.

PSA is a relatively sensitive test, but is non-specific in the diagnosis of prostate cancer. The upper limit of normal for PSA is 4 ng/mL. Increasing levels of PSA correlate to

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increasing clinical stage of prostate cancer. Patients with prostate cancer and a PSA <4 ng/mL generally have organ-confined disease; when the PSA ranges between 4 ng/mL and 10 ng/mL, only 53% of cases will be organ-confined.³

The Gleason score is a histological score based on the degree of differentiation of the prostatic cancer. A numerical score is assigned to the predominant histologic pattern and the secondary score to the next most dominant pattern. These scores are added to produce a total ranging from 2 to 10: the higher the score, the more poorly differentiated the tumour, the worse the prognosis. There is a good correlation between Gleason score and patient survival, with an excellent prognosis in patients with a score of 2 to 4 and a very poor prognosis in patients with a score of 8 to 10.⁴ A Gleason score >8 is almost twice as likely to be associated with extracapsular extension than a score <6. Normograms, which combine these parameters and digital rectal examination, have been developed to determine the probability of locally advanced disease in an individual patient, and are used routinely to plan treatment.⁵

MR Imaging

Imaging tests aimed at local staging must differentiate between disease confined to the prostate (stages T1 to T2) and locally invasive disease that extends beyond the prostatic capsule into the periprostatic fat, neurovascular bundles and seminal vesicles (stage T3) or adjacent organs (stage T4). MR imaging, with and without endorectal coils, has been investigated to improve the accuracy of local staging of prostate cancer. Endorectal MR imaging is generally considered as superior to phased-array MR imaging in the assessment of local extension.^{6,7} This is due to a higher signal-to-noise ratio, with the coil in the rectum

being closer to the prostate. However, the phased-array coil is more readily available in clinical practice and does not have the discomfort of endorectal coil insertion. Husband et al⁸ have shown that image quality from phased-array coils can be superior to that of endorectal coils.

Careful attention to technique is the key to image optimisation when performing MR imaging of the prostate. The authors' routine protocol includes a survey of the pelvis from the aortic bifurcation to the symphysis pubis with surface phased-array coils and a 1.5 Tesla MR system (Signa; General Electric Medical Systems, Milwaukee, WI, USA) (Table I). This is helpful in the evaluation of lymph nodes and bone marrow. The endorectal coil (Medrad, Pittsburgh, PA, USA) is then inserted and 40 mL to 60 mL of air insufflated. High-resolution fast recovery fast spin-echo T2-weighted sequences are then obtained in the axial and coronal planes to assess capsular invasion, seminal vesicle and neurovascular invasion with the endorectal coil (Table II). An additional high-resolution sagittal T2-weighted sequence has been found to assist evaluation of the prostatic apex. It can be performed if the patient can tolerate an increase in scan time with the endorectal coil *in situ*.^{6,7}

The use of the endorectal coil, together with the phased-array body coil, has the advantages of better signal-to-noise ratio and spatial resolution, resulting in higher accuracy in staging (77%) than the use of phased-array coils alone (68%).⁶ The main disadvantage of the endorectal coil is patient discomfort. Near-field artefacts may be corrected by image processing algorithms. Special caution should be exercised when inserting the endorectal coil in patients with inflammatory bowel disease, recent anal surgery and recent radiation therapy. Endorectal coils may be

TABLE I: SEQUENCES PERFORMED WITH SURFACE PHASED-ARRAY COILS

Sequence	Objective	TR/TE (msec)	FOV (cm)	Matrix (frequency/phase)	Frequency direction	NEX	Section thickness/ intersection gap (mm)	No. of slices	Average time taken (min)
Axial T1W FSE of whole pelvis	Identify pelvic lymphadenopathy and pelvic bony metastases	700/12-18 (minimum full); echo train length = 4	30 x 16	320 x 224	Right to left	4	8/1	20	3
Axial GRASS	Demonstrate flow in vessels and to distinguish lymph nodes from tortuous vessels	33/13; flip angle = 30	30 x 16	256/192	Right to left	2	8/1	20	4
Axial T1W FSE of the prostate	Define boundaries of prostate and detect presence of blood	600/10-18 (minimum full); echo train length = 4	16 x 16	320 x 224	Right to left	4	4/1	18	6

FOV: field of view; FSE: fast spin echo; GRASS: gradient-recalled acquisition in steady state; NEX: number of excitations; T1W: T1-weighted; TE: echo time; TR: repetition time

TABLE II: SEQUENCES PERFORMED WITH COMBINED ENDORECTAL-SURFACE PHASED-ARRAY COILS

Sequence	TR/TE (msec)	FOV (cm)	Matrix (frequency/phase)	Frequency direction	NEX	Section thickness/ intersection gap (mm)	No. of slices	Average time taken (min)
Axial T2W FRFSE	5000/90; echo train length = 16	12 x 12	320 x 224	Anterior/posterior	4	3/0.5	18	4
Coronal T2W FRFSE	5000/90; echo train length = 12	12 x 12	320 x 224	Superior/inferior	4	3/0.5	16	6
Axial T1W FSE (optional)	600 (minimum full)	12 x 12	320 x 224	Anterior/posterior	4	3/0.5	18	6

FOV: field of view; FRFSE: fast recovery fast spin echo; NEX: number of excitations; T1W: T1-weighted; T2W: T2-weighted; TE: echo time; TR: repetition time

contraindicated in these settings. The patient should ideally be scanned >3 weeks after biopsy to minimise inaccuracy due to the presence of post-biopsy haemorrhage.⁹ However, this requirement should be weighed against the need for timely surgery.

Normal Anatomy on MR Imaging

T2-weighted images best show the zonal anatomy of the gland (Fig. 1). The peripheral zone is hyperintense and horseshoe-shaped on axial images. The central and transitional zones are indistinguishable in the normal prostate and appear as an area of low signal. The true capsule of the prostate is very often microscopic in thickness. The visualised “capsule” is usually a combination of the true thin fibrous capsule and a relatively aglandular rim of prostate gland. This pseudocapsule is seen as a rim of low signal intensity around the gland on T2-weighted images.¹⁰ The tissue anterior to urethra is the fibromuscular stroma, which shows low signal intensity on T2-weighted images. The seminal vesicles show intermediate signal intensity on T1-weighted images and high signal on T2-weighted images due to fluid in the tubules. The main neurovascular bundles to the prostate enter posterolateral aspects of the gland at the 5 and 7 o’clock positions, midway between the base and the apex.¹⁰

MR Imaging Findings in Prostate Carcinoma

The histologic type of almost all (>96%) prostate cancers is adenocarcinoma. Others include sarcomas and non-epithelial tumours. Approximately 70% of cancers arise in the peripheral zone, 20% in the transitional zone and 10% in the central zone.¹¹ Most tumours are multifocal. Prostate cancer is isointense to the rest of the prostate gland on T1-weighted images and commonly appears as an area of low signal change in the background of high signal of the peripheral zone on T2-weighted images (Figs. 1 & 2). Unfortunately, this finding is non-specific and the differential diagnoses include benign prostatic diseases such as prostatitis, benign prostatic hyperplasia and fibrosis.

Peripheral zone tumours extend along the ejaculatory ducts and seminal vesicles and through the prostatic capsule into the neurovascular bundles and periprostatic tissue. Capsular invasion occurs most frequently at the apex, less commonly in the mid-gland and least commonly at the base.¹² Signs of capsular invasion on MR imaging include an irregular capsular bulge, angular bulge at the posterolateral margin of the gland, obliteration of the retroprostatic angle and breach of the capsule with direct tumour extension (Fig. 2).⁸ Asymmetry of the neurovascular bundle is an early indication of extracapsular tumour extension through the prostatic capsule along the branches of the neurovascular bundle.

Findings suggestive of invasion of seminal vesicles include demonstration of low signal intensity tumour extension from the base of the gland into and around the seminal vesicles, and abnormal low signal intensity within the lumen of the seminal vesicle.⁸ Potential pitfalls include extrinsic compression from benign prostate hyperplasia and post-biopsy haemorrhage. The presence of blood product can be confirmed when abnormal high signal intensity is identified on T1-weighted images.

Accuracy of MR Imaging Staging

There is a wide range of published accuracy, sensitivity and specificity for the identification of locally advanced disease with MR imaging. The reported performance of phased-array MR prostate for the detection of locally advanced carcinoma of the prostate is modest, with a sensitivity of 33% to 74% and specificity of 67% to 93%.^{6,7,13} The reported sensitivity and specificity of endorectal coil for the detection of locally advanced disease are 13% to 89% and 67% to 97%, respectively.^{6,7,14-16} Reader experience appears to play a part in the accuracy of interpretation.^{6,7}

To ensure that as few patients as possible are deprived of potentially curative surgery due to false positive findings, a high specificity for the diagnosis of locally advanced (stages 3 and 4) disease is desired. Ikonen et al¹⁶ achieved

TABLE III: PROSTATE SPECTROSCOPY AND IMAGING EXAMINATION (PROSE): A CLINICAL SPECTROSCOPY PULSE SEQUENCE FOR A 1.5T GENERAL ELECTRIC CLINICAL SCANNER

Sequence	TR/TE (msec)	Matrix (frequency/phase)	FOV (cm)	Frequency direction	NEX	Spacing (mm)	No. of locations per slab
PROSE (PRESS)	1000/130	16 x 8	11 x 11	Right to left	1	6.9	8

FOV: field of vision; NEX: number of excitations; PRESS: point resolved spatial selection; TE: echo time; TR: repetition time

a very high specificity of 97% with endorectal coil for the diagnosis of locally advanced prostate carcinoma, using very stringent MR imaging diagnostic criteria for extracapsular extension and seminal vesicle involvement, but at the expense of a low sensitivity of 13%.¹⁶

Although other studies with endorectal coils showed higher sensitivity than Ikonen et al, variable sensitivity remained a problem for MR imaging, with sensitivity of 50% for a senior reader and 14% for a junior reader in another series.⁷ Low sensitivity has been attributed to the early stage disease seen in the study populations in a few series. This suggests that microscopic invasion is not detectable on MR imaging.^{6,7,17}

Role of MR Imaging in Staging

MR imaging is not recommended in routine local staging of prostate cancer.^{1,17} The combination of PSA, clinical stage and Gleason score remains the norm for predicting the pathological stage of localised prostate cancer. The potential complementary role of MR imaging lies in improving the accuracy of local staging in patients with intermediate risk based on Partin's nomogram, allowing better patient selection for more aggressive therapy and sparing patients with locally advanced disease from unnecessary surgery.

D'Amico et al¹⁷ showed that in patients with an intermediate risk of local extension, endorectal MR imaging is an independent predictor of 5-year PSA failure. Endorectal MR imaging in this group of patients can improve prognosis by detecting a subgroup of patients at high risk of postoperative PSA failure, thus prompting additional treatment.¹⁷ This is currently the best evidence available for the use of MR imaging in staging. The study by D'Amico et al controlled for PSA level, biopsy Gleason score, clinical T stage and percentage of positive biopsy. The definition of intermediate risk includes PSA >20 ng/mL, Gleason score of 8 to 10 or stage T2c, and <34% positive prostate biopsy; <10 ng/mL, score ≤6, stage T1c or T2a, and >50%; 10 ng/mL to 20 ng/mL, score 7 or stage T2b, and 34% to 50%.

MR Spectroscopy

MR spectroscopy of the prostate detects the biochemical signature of metabolites within the prostate, thereby

improving the assessment of prostate cancer beyond the anatomic information provided by MR imaging. The development of the endorectal coil allows one to acquire MR spectroscopy data from the human prostate located deep in the pelvis. The examinations are performed with a clinical 1.5 Tesla MR system (Table III). Spectroscopic information can be overlaid on the corresponding anatomic images. A combined MR imaging/MR spectroscopy examination can be performed in about 45 minutes.

Current proton MR spectroscopy studies make use of a combination of point resolved spatial selection (PRESS) or stimulated echo acquisition mode (STEAM) with 3-dimensional (3D) phase encoding (3D MR spectroscopy, also called chemical shift imaging).¹⁸ The multi-voxel acquisition provides information about the spatial extent and heterogeneity of the cancer. The spatial position of the spectra can also be selected retrospectively by voxel shifting as 3D data is acquired. With current 3D MR spectroscopy, high-resolution (0.24 cm³ to 0.7 cm³) proton spectra can be achieved.¹⁹ The average time for the spectroscopy sequence is approximately 17 minutes.

MR Spectroscopic Identification of Prostate Cancer

In the normal prostate gland, high levels of citrate are found as the accumulation and secretion of citrate are the principal functions of this gland.²⁰ Citrate levels are higher in the peripheral zone than in the central gland.²¹ This is because the presence of high levels of intra-mitochondrial zinc in healthy prostatic epithelial cells inhibit mitochondrial aconitase, thereby preventing the oxidation of citrate in the Krebs cycle.²² Benign prostatic hypertrophy also results in increased citrate levels.²³ On the other hand, altered metabolism in malignant epithelial cells in prostate carcinoma results in a diminished capacity for net citrate production and secretion due to loss of capability to retain high levels of zinc.²⁴ It is also believed that the transformation of prostate epithelial cells into citrate-oxidising cells, which increases energy production capability, is essential to the process of malignancy and metastasis.²⁵ The elevation in the choline peak in prostate cancer is associated with changes in cell membrane synthesis and degradation that occur with the evolution and progression of cancer. Hence, in prostate cancer, there are high levels of choline and low levels of citrate. (Figs. 3 & 4).

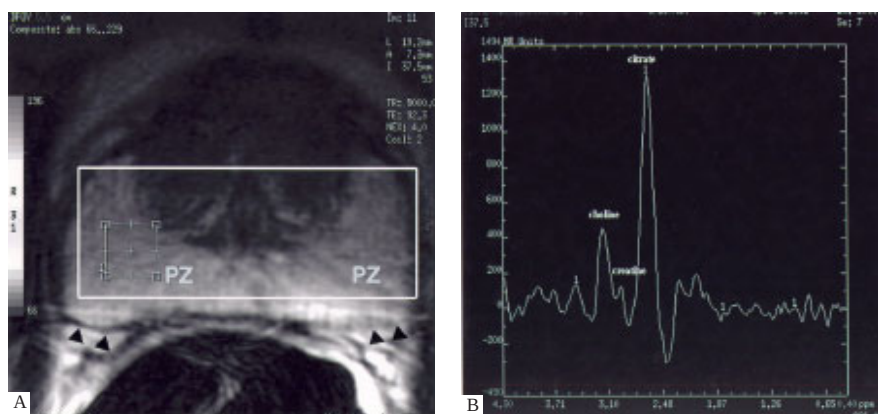


Fig. 1. (A) Axial T2-W fast recovery fast spin-echo (TR = 5000/TE = 92 msec) MR image through the prostate gland near the apex shows the hyperintense peripheral zone (PZ) surrounding the hypointense central gland. The thin hypointense rim around the peripheral zone represents the pseudocapsule (arrowheads). (B) The normal spectrum from the left peripheral zone (see voxel in Fig. 1A) shows a dominant citrate peak at approximately 2.6 ppm with no abnormal elevation of the choline/creatine peak at approximately 3.0 to 3.2 ppm.

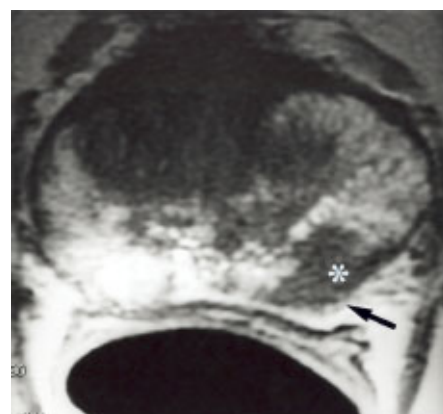


Fig. 2. A 61-year-old man with pathologic stage pT3c prostate cancer and Gleason score 4+3. Preoperative axial T2-W fast recovery fast spin echo (TR = 5000/TE = 90 msec) MR image shows a low signal area (asterisk) in the left peripheral zone with a focal bulge (arrow) in the capsule suspicious for tumour with extracapsular extension. This was subsequently confirmed on step-section whole-mount histopathology.

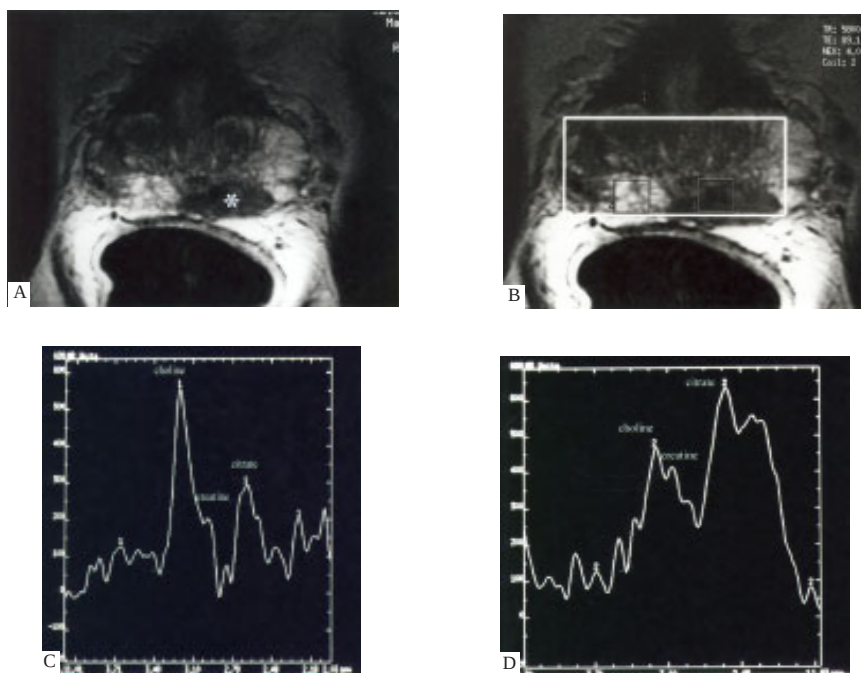


Fig. 3. A 61-year-old man with PSA of 14.0 ng/mL and previous negative transrectal ultrasound-guided biopsy. (A) Axial T2-W fast recovery fast spin-echo (TR = 5800/TE = 89 msec) MR image through the mid-gland using an endorectal coil. An area of low signal intensity (asterisk) in the peripheral zone of the left mid-gland is suspicious for a tumour focus. (B) The same section with information from MR spectra overlaid on the suspicious area in the left peripheral area and the corresponding area in the right peripheral area. (C) MR spectra from the area of imaging abnormality in the left peripheral zone shows elevated choline and reduced citrate, a pattern suspicious for cancer. This was confirmed on histology. (D) Normal MR spectra from the normal right peripheral zone shows a dominant citrate peak and no abnormal elevation of choline. The undulating baseline of this spectra is presumably related to artefacts from previous biopsy haemorrhage.

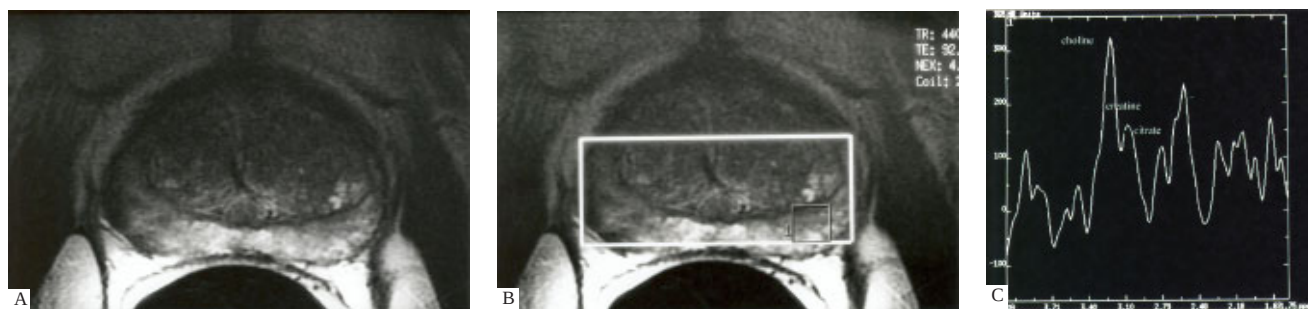


Fig. 4. A 64-year-old man with PSA of 18.1 ng/mL and previous negative tranrectal ultrasound-guided biopsy. (A) Axial T2-W fast recovery fast spin echo (TR = 4400/TE = 92 msec) MR image shows no definite focal areas of low signal intensity to suggest the presence of a tumour focus. (B) The same section with spectra voxel on the left peripheral zone. (C) MR spectra obtained from the right peripheral zone demonstrates elevated choline and reduced citrate, suspicious for cancer. This was confirmed on step-section whole-mount histology.

Improving Cancer Localisation with Combined MR Imaging and MR Spectroscopy

In a recent retrospective study of 53 patients with biopsy-proven prostate cancer and subsequent radical prostatectomy with step-section histopathologic examination, the addition of 3D MR spectroscopic imaging to MR imaging provides better tumour detection and localisation to a prostatic sextant (left and right: base, mid-gland and apex) than the use of MR imaging alone.²⁶ The 3D MR spectroscopic imaging diagnosis of definite cancer had higher specificity (75%), but lower sensitivity (63%), compared to MR imaging. High specificity (up to 91%) was obtained when combined MR imaging and 3D MR spectroscopic imaging indicated cancer, whereas high sensitivity (up to 95%) was obtained when either test alone indicated a positive result. In another study with 47 patients, MR imaging and MR spectroscopic imaging have accuracy similar to biopsy for intraprostatic localisation of cancer. They are more accurate than biopsy in the prostate apex.²⁷ Concordant positivity by both imaging tests and biopsy was highly specific at 98%. The addition of MR spectroscopy to MR imaging also significantly improves the ability to determine the presence of prostate cancer in the presence of post-biopsy changes, such as haemorrhage.²⁸ A prospective study with a large study population would be needed to validate these findings.

Another group of patients that can potentially benefit from the combined use of MR imaging and MR spectroscopy to localise cancer are those with elevated or rising PSA levels, but with prior negative transrectal ultrasound-guided biopsies. An example of such a patient is shown in Figure 3, where a region of metabolic abnormality corresponds to a focus of low T2-weighted MR imaging signal abnormality.²⁷

Improving Prostate Cancer Staging with Combined MR Imaging and MR Spectroscopy

The use of 3D MR spectroscopic imaging has been investigated as a tool for the prediction of extracapsular extension to improve the accuracy and reproducibility of interpretations of MR images. Histopathologic studies have demonstrated a strong correlation between the volume of prostate cancer and the presence of extracapsular extension.²⁹ This suggests the possibility that 3D MR spectroscopic imaging estimates of tumour volume may be used to assist the diagnosis of extracapsular extension. Another recent retrospective study, which combined tumour volume estimates based on MR spectroscopic imaging with MR imaging criteria for extracapsular extension, showed that the addition of 3D MR spectroscopic imaging improves accuracy for less experienced readers and reduces interobserver variability in the diagnosis of extracapsular extension.³⁰ Again, further prospective studies are required to establish the added value of MR spectroscopy.

Assessment of Cancer Therapy with Combined MR Imaging and MR Spectroscopy

Serum levels of PSA are often used to detect residual or recurrent tumour after surgery, radiation therapy or cryotherapy. However, PSA level is not specific to cancer and can be elevated in the presence of residual benign prostatic hypertrophy or normal prostate tissue. The only definite method of identifying residual or recurrent tumour is to obtain histological proof by ultrasound-guided biopsy, which may be limited by sampling errors. Combined MR imaging and MR spectroscopy can potentially provide a non-invasive assessment of the presence and location of residual cancer after unsuccessful therapy, and to detect locally recurrent prostate cancer.^{31,32} The detection of residual or recurrent tumour at an early stage allows for earlier additional therapy, which may potentially improve outcome.

Conclusion

Combined MR imaging and MR spectroscopy of the prostate is a promising imaging tool which can contribute to the diagnosis and management of prostate cancer when combined with clinical, biochemical and histological data. Large patient studies must be performed, with results validated at multiple institutions to ascertain the true clinical value of combined MR imaging and MR spectroscopy for the management of prostate cancer patients.

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