Invited Review

Combined Magnetic Resonance Imaging and Spectroscopic Imaging Approach to Molecular Imaging of Prostate Cancer

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Magnetic resonance spectroscopic imaging (MRSI) provides a noninvasive method of detecting small molecular markers (historically the metabolites choline and citrate) within the cytosol and extracellular spaces of the prostate, and is performed in conjunction with high-resolution anatomic imaging. Recent studies in pre-prostatectomy patients have indicated that the metabolic information provided by MRSI combined with the anatomical information provided by MRI can significantly improve the assessment of cancer location and extent within the prostate, extracapsular spread, and cancer aggressiveness. Additionally, pre- and post-therapy studies have demonstrated the potential of MRI/MRSI to provide a direct measure of the presence and spatial extent of prostate cancer after therapy, a measure of the time course of response, and information concerning the mechanism of therapeutic response. In addition to detecting metabolic biomarkers of disease behavior and therapeutic response, MRI/MRSI guidance can improve tissue selection for ex vivo analysis. High-resolution magic angle spinning (1H HR-MAS) spectroscopy provides a full chemical analysis of MRI/MRSI-targeted tissues prior to pathologic and immunohistochemical analyses of the same tissue. Preliminary 1H HR-MAS spectroscopy studies have already identified unique spectral patterns for healthy glandular and stromal tissues and prostate cancer, determined the composition of the composite in vivo choline peak, and identified the polyamine spermine as a new metabolic marker of prostate cancer. The addition of imaging sequences that provide other functional information within the same exam (dynamic contrast uptake imaging and diffusion-weighted imaging) have also demonstrated the potential to further increase the accuracy of prostate cancer detection and characterization.

Key Words: prostate cancer; citrate; choline; polyamines; magnetic resonance spectroscopic imaging (MRSI); magnetic resonance imaging (MRI); HR-MAS; prostate specific antigen (PSA); hormone deprivation therapy; radiation therapy


THE AMERICAN CANCER SOCIETY estimates that 189,000 males will be newly diagnosed with prostate cancer in the United States in 2002, making it the most commonly diagnosed noncutaneous cancer among American men, with an incidence similar to that of breast cancer (an estimated 203,500 cases) in women (1). Due to increased prostate cancer screening using serum prostate-specific antigen (PSA) and transrectal ultrasound (TRUS) guided biopsy, thousands of prostate cancer patients are being identified at an earlier and potentially treatable stage (2). However, the decision on how to manage prostate cancer once detected still poses a great dilemma for both patients and their clinicians. The dilemma stems from the fact that prostate cancers demonstrate a tremendous range in biologic malignancy, and are treated with a broad spectrum of approaches from "watchful waiting" and hormone deprivation therapy to aggressive surgical, radiation, and cryosurgical therapies (3,4). Prostate cancer is one of the few cancers that can grow so slowly that they never threaten the lives of some patients, but at present this cannot be predicted in individual patients with current prognostic markers (5–8). However, if the cancer does metastasize there is currently no cure and the cancer becomes lethal, leading to an estimated 30,200 deaths in the United States in 2002 (1). A number of clinical (digital rectal exam [DRE]), pathologic (histologic grade from biopsy, and number and percentage of positive biopsies) (9), and biochemical parameters in serum (PSA, PAP) (10–13) and in tissue (MIB-1, bcl-2, p53, CD34) (14–19) can aid in assessing the extent and aggressiveness of the disease. However, these are often inaccurate or inadequate, particularly when used alone in individual patients. Additionally, with early detection, there has also been increased interest in focal "disease-targeted" therapies, including...
interstitial brachytherapy, intensity-modulated radiotherapy, and focal cryosurgery, which can potentially reduce treatment-related morbidity and allow patients to maintain their quality of life (20). These therapies require an improved knowledge of the location and spatial extent of the disease within the gland. Finally, the long natural history of prostate cancer and the increasingly younger age of patients at the time of detection underscores the need for shorter-term endpoints than survival in order to reduce the duration of therapeutic trials and the number of patients required (21,22).

New discoveries in the molecular and cellular biology of prostate cancer present opportunities for the development of noninvasive imaging modalities that could improve the characterization of prostate cancers in individual patients prior to and after therapy. The use of a combination of magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI) represents an exciting new approach that is currently being investigated. Conventional MRI of the prostate relies on abnormal signal intensities that result from morphologic changes within the prostate to define the presence and extent of cancer (23). Unfortunately, the morphologic changes observed by MRI often do not accurately reflect the presence and spatial extent of active tumor (23). The addition of metabolic information provided by MRSI complements the morphologic information provided by high-resolution MRI, and improves the discrimination of cancer from surrounding healthy tissue and necrosis (24). A combined MRI/MRSI exam can be performed in less than 1 hour using a standard clinical 1.5 Tesla MR scanner and the same coils used for MRI. A commercial package has recently been released and will be clinically tested in an upcoming multicenter trial. Since this molecular imaging technique will soon be more globally available to clinicians, it is timely to review what is already known about the utility of combined MRI/MRSI, and describe how it might be improved and used in the future.

MORPHOLOGIC IDENTIFICATION OF PROSTATE CANCER—MRI

High-spatial-resolution endorectal-coil T2-weighted images provide an excellent depiction of prostatic zonal anatomy, prostate cancer, and surrounding soft tissues in untreated patients (Fig. 1) (25,26). On T2-weighted MRI, regions of prostate cancer demonstrate decreased signal intensity relative to normal peripheral zone tissue due to increased cell density and a loss of the prostatic ducts (Fig. 1) (23,26). Currently, the prostate is best imaged using an endorectal coil combined with four external coils (pelvic phased array) (26). The use of the body coil for excitation and an endorectal coil/pelvic phased array coil system for signal reception allows for the acquisition of high-spatial-resolution images of the prostate as well as coverage to the bifurcation for assessment of pelvic lymph node and bone metastases within the same exam. The endorectal coil provides a ~10-fold increase in the signal-to-noise ratio (SNR) over the pelvic phased coil, thereby allowing for the acquisition of both high-resolution images and spectroscopic data from the prostate. However, the inhomogeneous reception profiles of the surface coils employed must be

Figure 1. Comparison of axial endorectal coil/pelvic phased array FSE prostate images (a) before and (b) after analytic correction for the reception profiles of the endorectal and pelvic phased array coils. In the corrected image, the high signal intensity close to the endorectal coil has been removed, allowing for improved visualization of prostate cancer (low T2 signal intensity, white arrows) compared to adjacent healthy prostate peripheral zone (high T2 signal intensity). Additionally, important anatomical features such as the prostatic capsule and the step-off angle in the prostatic capsule on the left side of the image (b) identifying extracapsular spread (black arrow) can be more clearly visualized.
taken into account when interpreting the data. If uncorrected, images exhibit very high intensity close to the coil and lower intensity further into the prostate (Fig. 1A). Even with windowing and leveling, it is difficult to interpret such images. One way to address this problem is to analytically correct the images for the reception profile of the endorectal coil, thereby eliminating near-field high signal intensity artifacts and producing images in which prostatic zonal anatomy and pathology can be more easily visualized (Fig. 1B) (24).

Knowledge of the spread of cancer outside the prostate is critical for determining whether focal, systemic, or a combination of both therapies is required. The use of T2-weighted fast spin echo imaging (27) and a pelvic phased-array incorporating an endorectal coil can markedly improve the evaluation of extracapsular extension (ECE: accuracy = 81%; sensitivity = 84%; and specificity = 80%) and seminal vesicle invasion (SVI: accuracy = 96%; sensitivity = 83%; and specificity = 98%), thereby improving the staging of prostatic cancer (26). However, the detection of extracapsular extension by MRI is becoming more difficult since men are being diagnosed at earlier stages of disease, and because the microscopic spread of cancer through the prostatic capsule cannot be directly seen on MR images (23). Additionally, there still remains great variability in the reported staging accuracy of endorectal/phased array MRI between individual readers. One recent study reported an overall staging accuracy of 93% and 56% for two different readers within the same study (28). Although inter-reader variability can be due to differences in reader experience and subjectivity, the addition of objective metabolic criteria provided by MRSI has been demonstrated to decrease this inter-reader variability (29).

In addition to staging, the assessment of prostate cancer location and extent is becoming increasingly important due to the emergence of disease-targeted therapies such as interstitial brachytherapy, intensitymodulated radiotherapy, and cryosurgery. Studies evaluating clinical data (DRE, PSA, and PSA density), systematic biopsy, TRUS, and MRI alone have so far shown disappointing results for tumor localization within the prostate (30–33). High-resolution endorectal/pelvic phased array MRI has demonstrated good sensitivity (78%) but low specificity (55%) in tumor location due to a large number of false-positives (26). These false-positives can be attributed to factors other than cancer, including post-biopsy hemorrhage, prostatitis, and therapeutic effects, which cause low signal intensity on T2-weighted images similar to that of prostate cancer (33,34). The addition of highly cancer-specific metabolic information to the sensitivity of MRI has resulted in a significant improvement in the overall accuracy of cancer localization to a sextant of the prostate (35).

**METABOLIC IDENTIFICATION OF PROSTATE CANCER—MRSI**

As with MRI, MRSI uses a strong magnetic field and radiowaves to noninvasively obtain metabolic information (spectra) based on the relative concentrations of endogenous chemicals (metabolites) that exist in the cytosol of the cell and in extracellular ducts. With prostate MRSI, the large tissue water and lipid signals must be suppressed in order to detect the prostatic metabolites citrate, choline, creatine, and polyamines that are present in much lower concentrations (36–39). The technology required for the robust acquisition of MRSI data from the prostate has just become available and requires very accurate volume selection (36,37) and efficient outer volume suppression (38). The resonances for citrate, choline, creatine, and polyamines occur at distinct frequencies or positions in the spectrum, although the peaks for choline, creatine, and polyamines overlap at 1.5T (Fig. 2D and E). The areas under these resonances are related to the concentration of the respective metabolites, and changes in these concentrations can be used to identify cancer with high specificity (39). Specifically, in spectra taken from regions of prostate cancer (Fig. 2D), citrate and polyamines are significantly reduced or absent, while choline is elevated relative to spectra taken from surrounding healthy peripheral zone tissue (Fig. 2E).

MRSI produces arrays of contiguous volumes (0.24–0.34 cc voxels) that can map the entire prostate, and because MRSI and MRI are acquired within the same exam, the data sets are already in alignment and can be directly overlaid (Figs. 2–7) (39). In this way, areas of anatomic abnormality (decreased signal intensity on T2-weighted images) can be correlated with the corresponding area of metabolic abnormality (increased choline, and decreased citrate and polyamines). It is the concordance of MRI and multiple metabolic changes observed by MRSI that leads to the most confident identification of cancer (35,40). Additionally, since three-dimensional, volume MRI and MRSI data are collected, the data can be viewed in any plane (axial, coronal, or sagittal) (Fig. 3), and the position of spectroscopic voxels can be retrospectively changed to better examine a region of abnormality on MRI after the data is acquired (Fig. 4). This method of interactive analysis will be the way that MRI/MRSI data is used in the future and should reduce interpretative errors associated with the overlap of normal and cancerous tissues.

One of the strengths of prostate spectroscopy is that many of the biochemical mechanisms that result in the observed metabolic changes are now known and correlate with stage of carcinogenesis and response to therapy. Healthy prostate epithelial cells possess the unique ability to synthesize and secrete enormous quantities of citrate (41). The decrease in citrate with prostate cancer is due to changes in both cellular function (41,42) and the organization of the tissue, resulting in a loss of its characteristic ductal morphology (43,44). Biochemically, the loss of citrate in prostate cancer is intimately linked with changes in zinc levels that are extraordinarily high in healthy prostate epithelial cells (45,46). In healthy prostatic epithelial cells, the presence of high levels of zinc inhibits the enzyme aconitase, thereby preventing the oxidation of citrate in the Krebs cycle. Consequently, high levels of citrate are observed in the MRSI spectra of healthy glandular prostate tissues. Zinc levels are dramatically reduced in prostate cancer, and the malignant epithelial cells demonstrate...
a diminished capacity for net citrate production and secretion (45,46). There exists strong evidence that the loss of the capability to retain high levels of zinc is an important factor in the development and progression of malignant prostate cells (45,46). It is also believed that the transformation of prostate epithelial cells to citrate-oxidizing cells, which increases energy production capability, is essential to the process of malignancy and metastasis (47).

As in other human cancers, the elevation of 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 (48,49). Phosphatidylcholine is the most abundant phospholipid in biological membranes, and together with other phospholipids, such as phosphatidylethanolamine and neutral lipids, it forms the characteristic bilayer structure of cells and regulates membrane integrity and function (50,51). High-resolution $^{31}$P and $^1$H NMR studies of surgical prostate cancer tissue extracts have demonstrated that many of the compounds involved in phosphatidylcholine and phosphatidylethanolamine synthesis and hydrolysis (choline, phosphocholine, glycerophosphocholine, ethanolamine, phosphoethanolamine, and glycerophosphoethanolamine) contribute to the magnitude of the in vivo "choline" resonance (52–56). There is also evidence that changes in the cytosolic levels of these phospholipid metabolites correlate with cellular proliferation (57–60) and cellular differentiation (61–63). Additionally, changes in epithelial cell density can also contribute to the observed increase in the "in vivo" choline resonance in prostate cancer, since densely packed malignant epithelial cells replace the normal ductal morphology, forming prostate cancer.

Figure 2. a: A representative reception-profile corrected T2-weighted FSE axial image taken from a volume data set demonstrating a large tumor in the right midgland to base (same patient as in Fig. 1). The selected volume for spectroscopy (bold white box) and a portion of the $16 \times 8 \times 8$ spectral phase-encode grid from one of eight axial spectroscopic slices is shown overlaid (fine white line) on (b) the T2-weighted image with (c) the corresponding $0.3 \text{ cm}^3$ proton spectral array. Spectra in (d, red box) regions of cancer demonstrate dramatically elevated choline, and a reduction or absence of citrate and polyamines relative to (e, green box) regions of healthy peripheral zone tissue. In this fashion, metabolic abnormalities can be correlated with anatomic abnormalities from throughout the prostate. The strength of the combined MRI/MRSI exam is demonstrated when changes in all three metabolic markers (choline, polyamines, and citrate) and imaging findings are concordant for cancer. The focus of future studies will be to increase the number of metabolic markers and to better understand the cause of these changes through correlation with earlier protein and genetic changes.
nodules that are often palpable by digital rectal examination (44). In more recent high-resolution NMR studies of human prostate cell extracts, strong evidence was provided associating elevated phosphocholine and glycerophosphocholine in prostate cancer with altered phospholipid metabolism and not simply to increased cell density, doubling time, or other nonspecific effects (64).

Another strength of prostate spectroscopy is that multiple metabolic changes occur within the same voxels that indicate the presence of cancer. Historically, two metabolic markers (choline and citrate) have been relied upon for the metabolic detection of prostate cancer (65). However, high-resolution NMR studies of ex vivo prostatic tissues have identified several new metabolic markers for prostate cancer, including polyamines, myo-inositol, scyllo-inositol, and taurine (53,55,56,66–70). Of these the most promising are the polyamines, which appear very elevated in spectra of healthy prostatic peripheral zone tissues and predominantly glandular benign prostatic hyperplasia (BPH), and dramatically reduced in prostate cancer (67,70).

Similar to changes in choline-containing compounds, changes in cellular polyamine levels have been associated with cellular differentiation and proliferation (71,72). Moreover, it has recently been demonstrated that the loss of polyamines in regions of cancer can be detected by MRSI as an improvement in the resolution of the choline and creatine peaks (Fig. 2D) (73). Studies are under way to determine how the addition of this metabolic change further improves the detection and characterization of prostate cancer.

**CURRENT CLINICAL FINDINGS**

Over the past decade, thousands of prostate cancer patients have received combined MRI/MRSI exams. Many of these patients subsequently underwent radical prostatectomy, thereby providing a “gold standard” (i.e., step-section histopathology of the resected gland) for determination of the utility and accuracy of combined MRI/MRSI in the assessment of prostate cancer. The following studies in pre-prostatectomy patients provide compelling evidence of the clinical potential of

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**Figure 3.** a: Coronal T2-weighted FSE image of the same prostate cancer patient shown in Fig. 2. b: Coronal image with overlying spectroscopic selected volume (bold white box) and phase-encode grid (fine white line) taken from a portion of the 3-D array of spectra and (c) corresponding 0.3-cm³ proton spectra. The coronal slice is taken at the level of the peripheral zone, and MRI/MRSI (red arrows and outlined grid) are concordant for a large volume of tumor involving all of the right peripheral zone from apex to base and extending into the right seminal vesicles (black arrows). The metabolic pattern in the region of cancer is characteristic of a high Gleason score.
combined MRI/MRSI for the improved characterization of prostate cancer in individual patients.

**Improved Prostate Cancer Staging Using Combined MRI/MRSI**

MRI alone has good accuracy in detecting seminal vesicle invasion (96%; Fig. 3) (26). However, the assessment of cancer spread through the prostatic capsule is more difficult (81% accuracy) (26) and is becoming even harder to assess as fewer men demonstrate gross cancer spread (directly visible on MRI) due to earlier cancer detection. In a recent study of 53 patients with early-stage prostate cancer, tumor volume estimates based on MRSI findings were combined with high-specificity MRI criteria (74) in order to assess the ability of combined MRI/MRSI to predict extracapsular cancer spread. This study was based on prior histopathologic studies that demonstrated that tumor volume was a significant predictor of extracapsular extension (ECE) of prostate cancer (75,76). It was found that tumor volume per lobe estimated by MRSI was significantly ($P < 0.01$) higher in patients with ECE ($2.14 \pm 2.3 \text{ cm}^3$) than in patients without ECE ($0.98 \pm 1.1 \text{ cm}^3$) (29). Moreover, the addition of an MRSI estimate of tumor volume to high-specificity MRI findings for ECE (74) improved the diagnostic accuracy and decreased the inter-observer variability of MRI in the diagnosis of extracapsular extension of prostate cancer (Fig. 2) (29). In a recent study of 37 patients prior to radical prostatectomy, it was demonstrated that the addition of MRSI to MRI increases the overall accuracy of prostate cancer tumor volume measurement, although measurement variability still limits consistent quantitative tumor volume estimation, particularly for small tumors ($<0.5 \text{ cm}^3$) (77).

**Improved Intraglandular Cancer Localization Using Combined MRI/MRSI**

It has been demonstrated that the high specificity of MRSI to metabolically identify cancer can also be used to improve the ability of MRI to identify the location and extent of cancer within the prostate (35). A study of 53
biopsy-proven prostate cancer patients prior to radical prostatectomy and step-section pathologic examination demonstrated a significant improvement in cancer localization to a prostatic sextant (left and right—base, midgland, and apex) using combined MRI/MRSI vs. MRI alone (35). A combined positive result from both MRI and MRSI indicated the presence of tumor with high specificity (91%), while high sensitivity (95%) was attained when either test alone indicated the presence of cancer (Figs. 2–5) (35). In another recent study it was found that the addition of a positive sextant biopsy finding to concordant MRI/3D MRSI findings further increased the specificity (98%) of cancer localization to a prostatic sextant, whereas high sensitivity (94%) was again obtained when any of the tests alone were positive for cancer. Both of these studies used only the (choline/creatinine)/citrate ratio to metabolically detect prostate cancer. The addition of other metabolic ratios (choline/creatine, citrate/normal citrate) as well as the addition of new metabolic markers, such as polyamines, offers the possibility of further increasing the accuracy of the metabolic assessment of cancer within the prostate.

Assessment of Prostate Cancer Aggressiveness

MRSI information may also provide new insights into tumor aggressiveness, which may lead to improved risk assessment for patients with prostate cancer (24). In a preliminary MRI/MRSI study of 26 biopsy-proven prostate cancer patients prior to radical prostatectomy, spectroscopic voxels were shifted in postprocessing to be within a region of cancer as defined by step-section pathology and T2-weighted MRI. Spectra obtained from these voxels demonstrated a linear correlation between the magnitude of the decrease of citrate and the elevation of choline with the pathologic Gleason score. The magnitude of the elevation of choline was the most significant predictor of the Gleason score, with choline being significantly \( P < 0.0001 \) higher in high grade (Gleason 7 + 8) vs. moderate grade (Gleason 5 + 6) cancers (78).

CURRENT CLINICAL APPLICATIONS

In untreated patients, the improved intraglandular cancer localization, staging, and assessment of cancer aggressiveness provided by combined MRI/MRSI are currently being used in two main ways. The primary reason for patient referral for MRI/MRSI has been for improved therapeutic selection. A representative example of MRI/MRSI having an impact on therapeutic selection is provided by a patient who was considering "watchful waiting." This patient had a PSA of 4.7 ng/ml (7.5% free PSA) and two of six biopsy cores positive for Gleason (3 + 3) and (3 + 4) prostate cancer in the right lobe (Figs. 1–3). Based upon just these clinical and pathologic findings, watchful waiting appeared to be a plausible option. However, MRI/MRSI findings were concordant for a large volume of abnormality involving almost the entire right peripheral zone (left side of image) from apex to base (Fig. 3). The metabolite abnormality consisted of an almost complete loss of citrate and polyamines, and a very elevated choline-to-creatine ratio (Cho:Cr = 5 to 10), and corresponded to a region of low signal intensity on T2-weighted MRI. Based on the
large volume of aggressive-appearing cancer on MRSI and capsular irregularity on MRI, extracapsular extension of cancer was predicted (Fig. 2). There was also MRI evidence of seminal vesicle invasion (Fig. 3). Based on these findings it was decided that the patient should receive a combination of hormone deprivation and external beam radiation therapy as soon as possible.

Another important group of patients being referred for an MRI/MRSI exam prior to therapy is comprised of men who have elevated or rising PSA levels but negative TRUS-guided biopsies. These patients tend to have very enlarged central glands due to BPH, which present sampling problems for TRUS-guided biopsies, or they have cancers in locations that are difficult to biopsy, such as the apex (79). In a preliminary study it was found that MRI/MRSI targeting of cancer in these patients can significantly increase the positive yield of subsequent TRUS-guided biopsies (80). An example of such a patient is shown in Fig. 4. The patient had a PSA of 6.0 ng/ml at the time of the scan, which was up from a PSA of 3.8 ng/ml 1 year prior to the scan, and had a prior negative biopsy. A very small region of clear-cut metabolic abnormality corresponding to a small focus of low T2-weighted MRI signal was observed in the left lateral aspect of the apex abutting the prostatic capsule. A subsequent TRUS-guided biopsy confirmed prostate cancer (Gleason score = 3 + 3, 10% of core) in this region. A study is currently under way to determine the value of MRI/MRSI targeting of cancer, compared to a second systematic TRUS-guided biopsy without MRI/MRSI targeting, in a large cohort of patients with prior negative biopsies.

Growing numbers of patients receiving MRI/MRSI are referred for suspected local cancer recurrence after...
various therapies (hormonal deprivation therapy, radiation therapy, cryosurgery, and radical prostatectomy). Recurrent cancer is typically suspected in these patients due to a detectable or rising PSA. However, the use of PSA testing to monitor therapeutic efficacy is not ideal, since PSA is not specific for prostate cancer. Additionally, it can take 1–2 years or more for PSA levels to reach nadir values following radiation therapy (both external beam and brachytherapy) (81,82). Further, the interpretation of PSA data is more complicated for patients undergoing therapies, such as hormone deprivation therapy, that have a direct effect on the production of PSA. Conventional imaging methods, including TRUS, computed tomography (CT) and MRI, often cannot distinguish healthy from malignant tissue following therapy because of therapy-induced changes in tissue structure (83,84). The only definitive way to determine whether residual or recurrent tissue is malignant is the histologic analysis of random biopsies, which are subject to sampling errors and are more difficult to pathologically interpret after therapy.

Studies have indicated that MRI/MRSI can discriminate residual or recurrent prostate cancer from normal and necrotic tissue after cryosurgery (39,85,86). In a study of 25 patients before and after cryosurgery, histologically confirmed necrotic tissue (N = 432 voxels) demonstrated a loss of all observable prostatic metabolites, while the (choline + creatine)/citrate ratio in regions of histologically confirmed benign prostatic hyperplasia (0.61 ± 0.21, N = 52 voxels) and cancer (2.4 ± 1.0, N = 65 voxels) after cryosurgery were not significantly different from those observed prior to therapy, but were significantly different from each other. These initial studies suggested that MRSI could discriminate successful therapy (complete loss of prostatic metabolites) from residual disease. Subsequent studies have indicated that MRSI can also detect residual disease after unsuccessful hormone deprivation therapy (87,88) and radiation therapy (89). Figure 5 shows an example of a patient with biopsy-proven cancer in the left lobe, who had a PSA of 0.6 ng/ml at the time of the MRI/MRSI exam, which was almost 3 years after intensity modulated radiation therapy was administered. Consistent with effective radiation therapy, many spectroscopic voxels (left side of image) demonstrate a complete loss of all prostate metabolites (metabolic atrophy). However, on the right side of the image, several spectroscopic voxels demonstrate abnormal prostatic metabolism (choline + creatine)/citrate > 3 SD above normal values). This region of abnormal metabolism was later confirmed by biopsy to be residual cancer.

Figure 7. a T2-weighted MRI image and b: in vivo MRSI spectrum concordant for the presence of prostate cancer at the right base (left side of image). c Ex vivo 1H HR-MAS spectrum. d H&E stain, and e MIB-1 immunohistochemical stain of a single piece of prostate cancer tissue (Gleason 3 + 3) resected from this region.
In addition to the potential of MRI/MRSI to provide a direct measure of the presence and spatial extent of prostate cancer after therapy, there is evidence that MRI/MRSI can provide a measure of the time course of response and information concerning the mechanism of therapeutic response (88). For example, prostatic citrate production and secretion have been shown to be regulated by testosterone and prolactin (42), and an early dramatic reduction of citrate after initiation of complete hormonal blockade has been observed by MRSI (88). Additionally, there is a time-dependent loss of all prostatic metabolites in both regions of cancer and healthy tissue following the initiation of hormone deprivation therapy (88). This finding is consistent with the increased frequency of tissue atrophy that occurs with increasing duration of hormone deprivation therapy, and is considered to be a indicator of effective therapy (90). An example of the morphologic and metabolic consequences of long-term (12 months) complete hormone deprivation therapy (Lupron and Casodex) in a prostate cancer patient is shown in Fig. 6A. On MRI, the entire peripheral zone demonstrates diffuse low signal intensity, making identification of zonal anatomy and pathology very difficult. On MRSI, there was a complete loss of signals from all prostatic metabolites (metabolic atrophy).

Moreover, recent studies of patients on intermittent hormone deprivation therapy have demonstrated that the time course of metabolic recovery after cessation of therapy can also be monitored by MRI/MRSI. As shown in Fig. 6B, which is the same patient as shown in Fig. 6A 1 year after cessation of hormone deprivation therapy, significant recovery of prostatic zonal anatomy on MRI and a recovery of metabolism on MRSI were observed. Additionally, recovery of bilateral metabolic abnormalities consistent with biopsy findings prior to therapy was observed. Studies are currently under way to investigate the accuracy of MRI/MRSI in assessing the presence and spatial extent of prostate cancer after these therapies (87): the prognostic value of the time course to metabolic atrophy; the duration of undetectable metabolism; and the rate of metabolic recovery, particularly of cancer. The detection of residual cancer at an early stage following treatment, and the ability to monitor the time course of therapeutic response would allow earlier intervention with additional therapy and provide a more quantitative assessment of therapeutic efficacy.

**FUTURE DIRECTIONS**

The studies described above provide compelling evidence that the addition of MRI/MRSI data to PSA and biopsy data can improve the characterization of prostate cancer in individual patients prior to therapy and provide information about its response to therapy. However, as promising as this may seem, there are currently only a few academic medical centers worldwide that have experience with this new technology. In the next stage, MRI/MRSI must be implemented and validated at multiple institutions, and large-scale patient studies must be performed to determine the true clinical value of MRI/MRSI for the improved management of prostate cancer patients. There is also a clinical need to further improve the sensitivity and specificity of prostate cancer detection and characterization, particularly for small tumors and early-stage disease.

There are several new applications of MRI/MRSI that are currently under investigation. One area of great potential is the use of MRI/MRSI for improved radiation treatment planning. The motivation for MRI/MRSI treatment planning is that non-contrast CT overestimates the volume of the prostate as compared to MRI, and is inadequate for identifying the complex anatomy of the prostate (91). MR images obtained using a pelvic phased array and endorectal coil provide improved definition of the prostate, its complex zonal anatomy, and important surrounding structures. The integration of this information into the treatment plan has the potential to reduce the dose delivered to anatomic structures close to the prostate (i.e., the rectum, bladder, and neurovascular bundles) and hence decrease the incidence of damage to normal tissue. MRI, MRSI, and biopsy results can also be used to define the distribution of dominant intraprostatic lesions (DILs) within the prostate (79). Two recent studies indicated the potential of MRI/MRSI data in combination with CT to optimize radiation dose selectively to regions of prostate cancer using either intensity modulated radiotherapy (IMRT) (92) or brachytherapy (93).

Another area of recent work is the use of MRI/MRSI to improve tissue selection for ex vivo spectroscopic analysis. Previous ex vivo high-resolution nuclear magnetic resonance (NMR) studies of human prostate tissues have involved relatively blind tissue sampling and required laborious tissue extraction procedures. In a preliminary study, prostate cancer was identified in 25 out of 25 samples targeted using presurgical MRI/MRSI data (69). This study indicates that MRI/MRSI guidance can significantly improve the quality of tissue samples used for biomarker discovery. Tissue extraction was previously necessary because the motional restriction of the molecules in the intact tissue results in extreme spectral broadness under normal spinning conditions. Two major drawbacks of tissue extraction are that 1) the tissue is completely destroyed, preventing any subsequent histopathologic analysis; and 2) lable metabolites can be lost during the extraction process. Solid-state “magic angle spinning” (MAS) NMR techniques have existed for decades; however, they have only recently been applied to intact tissues (94,95). By spinning the sample at a fast rate (\( \approx 2 \text{ kHz} \)) and a specific angle (\( \theta = 54.7^\circ \)), MAS dramatically reduces chemical shift anisotropy and dipole-dipole interactions such that solution-like spectra with narrow linewidths can be obtained. Since HR-MAS spectroscopy is nondestructive, samples can subsequently undergo histopathologic, immunohistochemical, genetic, or other analyses, thereby providing the previously missing link between the pathologic, biochemical, and metabolic assessment of prostate cancer. As shown in Fig. 7, elevation of the composite in vivo choline resonance is due to significant increases in phosphocholine, glycerophosphocholine, and choline. Additionally, dramatic reductions in citrate and polyamines have been observed in cancer as compared to normal periph-
eral zone tissues. Ongoing studies are aimed at identifying new metabolic markers of prostate cancer and correlating metabolic patterns with specific tissue types, as well as markers for cellular proliferation (MIB-1), apoptosis (p53), and angiogenesis (53,55,56,66–70). Future studies are required to determine whether metabolic changes can be correlated with specific protein or genetic changes. Additionally, continuing improvements in MR technology, such as higher magnetic field clinical scanners (3–7 Tesla), will allow the exploitation of new metabolic markers in patients, and will also allow the acquisition of MRI/MRSI with higher spatial resolution, and the visualization of even finer anatomic and metabolic details.

The addition of other types of imaging sequences that provide additional functional information within the same exam should further increase confidence in prostate cancer detection and characterization. The enhancement of prostate cancer during the first pass of contrast with fast dynamic imaging can provide valuable information concerning prostate cancer microvascularity and angiogenesis (96–101). Regions of prostate cancer, particularly high-grade tumors, have been characterized by early and rapidly accelerating enhancement and faster rates of wash-out compared to surrounding tissues.

Additionally, several recent studies (102,103) have demonstrated the feasibility of performing single-shot echo-planar imaging (EPI)-based diffusion-weighted imaging of the prostate, and the potential of this technique to identify cancer in the peripheral zone based on a significant reduction in the apparent diffusion coefficient (ADC). Another recent study (104) has demonstrated that a single-shot Fast Spin Echo/Rapid Acquisition with Relaxation Enhancement (FSE/RARE) diffusion tensor imaging sequence could produce images superior in quality to EPI sequences, and that both the ADC and anisotropy were observed to be significantly different for biopsy-confirmed cancer as compared to the normal peripheral zone (104). Future studies will need to address the incremental value of these new functional parameters when added to an MRI/MRSI patient exam.

REFERENCES


Combined MRI/MRSI of Prostate Cancer


