Clinical applications of image-based radiation therapy for the study of prostate cancer have expanded significantly over the past years. The results of recent studies of magnetic resonance imaging (MRI) combined with magnetic image-based therapy is not only a buzzword for researchers but a major key to the future of cancer staging and therapy. Knowing the precise distribution of a patient’s cancer enables clinicians to determine whether a cure is possible with local therapy alone. A true stage T1 lesion could be excised without the necessity of adjuvant therapy. Radiation fields and surgical approaches could be designed to minimize complications. A more accurate estimate of prognosis could facilitate the design of prospective clinical trials. With better modeling, trials could be completed more quickly with fewer patients, thus reducing cost and follow-up time.

Advances are being pioneered in just about every area of imaging. Despite these advances, imaging is still hampered by the poor spatial resolution of modalities that are based on measurements of differences in density or structure that originate from the atomic number, the hydrogen concentration, or the concentration of an antigen or metabolic by-product. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI), collectively called MRI/MRSI, represent one of the most exciting avenues currently being pursued at numerous institutions throughout the country. This strategy takes advantage of the two different approaches: MRI provides excellent spatial resolution and MRSI delineates the metabolic activity of differentiated soft tissue. This article summarizes the current state of this technology as it applies to the management of prostate cancer. It is our view that this approach offers more hope than hype.

Understanding the MRI/MRSI Exam

More than 2,500 prostate cancer patients have been imaged at the University of California, San Francisco (UCSF) since development of the combined MRI/MRSI exam for staging. The exam is performed using a standard clinical 1.5-T magnetic resonance scanner applied through commercially available coils. A commercial package is being developed that allows the MRI/MRSI exam to be performed in routine clinical practice.

A multi-institutional clinical trial to test the robustness and clinical significance of combining metabolic and anatomic information for localizing and staging prostate cancer is now being planned. Therefore, it is timely to present what is already known about combined MRI/MRSI, how this technology is currently being used in the clinic, and how it might be used in the future.

Basic Principles

Magnetic resonance imaging is a noninvasive technique that uses strong magnetic fields and radiofrequency waves to obtain morphologic images based on physical properties (ie, T1 and T2 relaxation times) of water contained in body tissues. Magnetic resolution images, especially high spatial resolution endorectal coil T2-weighted images, provide an excellent depiction of prostatic zonal anatomy, the urethra, neurovascular bundles, surrounding soft tissues, and prostate cancer.[1] Currently, the prostate is imaged using an endorectal coil combined with four external coils.[2] The endorectal coil provides the sensitivity necessary for acquiring prostate imaging and MRSI data, while the pelvic-phased array of four external coils allows a field of view large enough to assess pelvic lymph nodes and bones for metastatic disease.

On T2-weighted images, regions of cancer within the prostate demonstrate lower signal intensity relative to healthy peripheral zone tissue owing to loss of normal ductal morphology and associated long-T2 water (Figure 1). The anatomic information provided by MRI has demonstrated utility as a staging modality for the differentiation between organ-confined cancers and those with extracapsular extension.[1,3-5] The use of fast spin echo imaging and a pelvic phased-array incorporating an endorectal coil can markedly improve the evaluation of extracapsular extension (accuracy: 81%; sensitivity for extracapsular extension: 91%) and seminal vesicle invasion, thereby
improving the staging of prostatic cancer.[1] The use of fast spin echo imaging has also reduced the MRI exam time from over 60 minutes to less than 30 minutes, thereby allowing the addition of MRSI to clinical MRI exams.

With the emergence of disease-targeted therapies such as interstitial brachytherapy and intensity-modulated radiotherapy (IMRT), the assessment of prostate cancer location and extent has become an important consideration in treatment selection and planning. Studies evaluating clinical data (eg, digital rectal examination, prostate-specific antigen [PSA], and PSA density), systematic biopsy, transrectal ultrasound, and MRI have so far shown disappointing results for tumor localization within the prostate.[6-9] High-resolution endorectal-pelvic-phased array MRI has demonstrated good sensitivity (78%) but low specificity (55%) in identifying tumor location because of a large number of false-positives.[1] These false-positives can be attributed to factors other than cancer, including postbiopsy hemorrhage, prostatitis, and therapeutic effects that can cause imaging appearances similar to prostate cancer.[9,10] An accurate assessment of the presence and extent of cancer requires additional methods such as functional or metabolic imaging of the prostate.

**Addition of MRSI**

The recent development of MRSI expands the diagnostic assessment of prostate cancer beyond the morphologic information provided by MRI.[11-13] As with MRI, MRSI uses a strong magnetic field and radio waves to noninvasively obtain metabolic spectra based on the relative concentrations of cellular chemicals. With MRSI, specific resonances (peaks) for the metabolites citrate, choline, creatine, and various polyamines from contiguous small volumes throughout the gland are observed (Figure 2).

The peaks for these different chemicals occur at distinct frequencies or positions in the MRSI spectrum. The areas under these peaks are related to the concentration of the respective metabolites, and changes in these concentrations can be used to identify cancer with reasonably high specificity.[13] As seen in Figure 2, prostate cancer (right side of image) can be metabolically discriminated from the healthy peripheral zone (left side of image) based on significant decreases in citrate and polyamines and an increase in choline.

**Biochemical Mechanisms**

Many of the biochemical mechanisms that result in these metabolic changes are known. The decrease in citrate with prostate cancer is due to both changes in cellular function[14,15] and changes in the organization of the tissue, which loses its characteristic ductal morphology. [16,17] The elevation of the choline peak in prostate cancer is associated with changes in cell membrane synthesis and degradation that occur with the evolution of human cancers.[18,19] The polyamines spermine, spermidine, and putrescine also are abundant in healthy prostatic tissues and reduced in cancer. Polyamines have been associated with cellular differentiation and proliferation.[20,21]

The high specificity of spectroscopy arises from the observation of multiple metabolic changes within the same spectrum. To enhance the display of the metabolic data and to correlate it with the prostatic anatomy and pathology, spectral arrays with metabolite peak areas and ratios can be displayed simultaneously with the corresponding magnetic resonance image (Figure 3). Thus, maps of metabolite concentrations can be overlaid on the corresponding anatomic images (Figure 4). Because the same gradients are used for imaging and spectroscopy acquisitions, the data sets are already in alignment and can be directly overlaid. In this manner, 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).

Additionally, since volume MRI and MRSI data are collected, spectral voxels can be moved to optimally encompass the abnormality on MRI after the data are acquired (Figure 4). This kind of interactive analysis will be the way MRI/MRSI data are interpreted in the future and should reduce interpretive errors associated with overlapping regions of normal and cancerous tissue.

**Cancer Staging by MRI/MRSI**

**Sensitivity and Specificity**

The accuracy of MRI/MRSI staging is best considered when compared to findings on radical prostatectomy, as assessed by comparing localization on biopsy specimens. Recent studies in preprostatectomy patients have indicated that the metabolic information provided by MRSI, combined with the morphologic information provided by MRI, can significantly improve the assessment of cancer spread outside the prostate as well as assessment of cancer location and extent within the prostate (Table 1).[13,22-24] Additionally, a further improvement in sensitivity and specificity of cancer localization can be attained when MRI/MRSI data are combined with biopsy
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Published on Cancer Network (http://www.cancernetwork.com)

Recently, investigators from UCSF conducted a study in 62 patients who underwent an MRI/MRSI exam before radical prostatectomy, followed by step-section histopathologic evaluation. They determined that the addition of MRSI (with its high specificity) to MRI (with its high sensitivity) resulted in improved localization of prostate cancer within the prostate.[19] Using only anatomic landmarks, the prostate was divided into six sites: left/right base, midgland, and apex. On a site-by-site basis, specificity and sensitivity for MRI were 60% and 79%, respectively. Compared to MRI, MRSI rendered significantly higher specificity (73%, P < .05), but lower sensitivity (61%, P < .05).

Combined MRI/MRSI allowed localization of cancer to a sextant of the prostate with a sensitivity of up to 95% compared to MRI alone (P < .05), when either MRI or MRSI were positive. When both MRI and MRSI were positive, investigators found a specificity of up to 91% vs MRI alone (P < .05). For patients with postbiopsy hemorrhage, which was present in a large percentage of newly diagnosed patients, MRSI also significantly improved the accuracy and specificity of cancer detection over MRI by overcoming limitations in estimating the extent of intraglandular cancer and assessing extracapsular spread.[20]

In another recent study of 47 patients, the addition of a positive sextant biopsy to concordant MRI/MRSI findings increased the specificity of cancer localization to a prostatic sextant to 98%. The addition of positive biopsies also increased the sensitivity (to 94%), compared with when any test alone was positive for cancer (Table 2).[21]

Studies are currently under way to determine how effectively MRI/MRSI data in combination with systematic biopsy data can estimate tumor volume. These studies are based on the ability of MRI/MRS to localize prostate cancer to a sextant. It will be interesting to know if this localization can accurately depict the cancer within the sextant. Merger of images from MRI/MRSI with step-sectioned pathology specimens is required and currently under way to address this issue.

**Prediction of Extracapsular Spread of Cancer**

Knowledge of the spread of cancer outside the prostate is critical for choosing an appropriate therapy. Although endorectal MRI has a sensitivity that has been reported to be highly variable (23% to 100%), it has an excellent negative predictive value (80% to 96%) and specificity (83% to 100%) for detecting seminal vesicle invasion.[1,3,26-33] Assessment of the spread of cancer beyond the prostatic capsule (ie, extracapsular extension) is more difficult. Sensitivity of endorectal MRI for detection of extracapsular extension varies from 13% to 95%, the negative predictive value from 67% to 90%, and the specificity from 47% to 100%.[1,3,26-34]

These highly variable results are partially explained on the basis of patient selection. D'Amico and colleagues reported that endorectal MRI was best reserved for patients with intermediate-risk factors, rather than for low-risk patients, because of the unacceptably high risk of false-positives in the latter group.[26] With fewer men demonstrating gross cancer spread directly visible on MRI at the time of diagnosis, this risk has become an even more challenging problem.

Assessment of cancer spread outside the prostate can be significantly improved by combining MRI findings that are predictive of cancer spread with an estimate of the spatial extent of metabolic abnormality provided by MRSI.[22] A study of 53 patients found that tumor volume per lobe was significantly higher (P < .01) in patients with extracapsular extension (2.14 ± 2.3 cc) than in patients without extracapsular extension (0.98 ± 1.1 cc). Using a threshold of 1-cc tumor volume per lobe as predictive of extracapsular spread, the addition of MRSI information increased the accuracy of MRI from 0.77 to 0.83 in predicting early spread outside the prostate.[22]

**Assessment of Cancer Grade by MRI/MRSI**

A preliminary MRI/MRSI study of 26 biopsy-proven patients prior to radical prostatectomy and step-section pathologic examination has demonstrated a strong linear correlation between cancer aggressiveness (ie, Gleason grade) and tumor metabolic parameters (ie, decrease in citrate and an elevation of choline).[11] When comparing high-grade (Gleason score of 7 or more) to moderate-grade (Gleason score 5 or 6) cancers, a statistically significant (P < .0001) difference in the ratio of cancer choline to normal choline was observed. Increasing cancer grade also was significantly (P < .05) correlated with the elevation of choline, the ratio of choline plus creatine to citrate, and reduction in citrate.

Although histologic scores will remain the standard for confirming the presence of prostate cancer and predicting biologic behavior, the potential of MRSI to provide additional information is very exciting. Owing to the great heterogeneity of prostate cancers and biopsy sampling errors, cancers often are not detected or are graded inaccurately. Since patient management can be critically
dependent on the Gleason score, this technology could be used to identify patients who might benefit from repeat biopsies to selected regions of the gland. Gleason scores are undergraded in 20% to 35% of these cases because of sampling errors associated with biopsies.[35]

Three-dimensional MRSI could noninvasively provide a valuable assessment of cellular function and organization throughout the gland.

**Current Applications to Radiotherapy**

At UCSF, the MRI/MRSI data presented above have been combined with biopsy and other clinical data to select the best therapy, or combination of therapies, for individual patients. Also, MRI/MRSI data have been used in combination with computed tomography (CT) to selectively optimize radiation dose distribution using intensity-modulated radiotherapy (Figure 5 and Figure 6).

Use of MRI/MRSI can improve the radiation dose distribution in two ways. First, high-spatial-resolution MRI can provide improved definition of the prostate, its complex zonal anatomy, and important surrounding structures. It has previously been demonstrated that the noncontrast CT scan cannot adequately identify the complex anatomy of the prostate and, on average, overestimates the volume of the prostate by 32% compared to MRI.[36] Second, a combination of MRI/MRSI and biopsies can be used to define the distribution of dominant lesions within the prostate.

We have shown that it is feasible to use IMRT to treat dominant intraprostatic lesions as defined by MRI/MRSI (Figure 5).[37] We have also demonstrated that a similar approach can be used to selectively target tumor-bearing areas during brachytherapy planning (Figure 6). Other investigators have followed this lead and argued for the theoretical reasons this approach might be valuable.[38] One confounding factor in merging CT data with MRI/MRSI data for treatment planning is distortion of the prostate by the inflatable endorectal coil. A comparison of the CT anatomy with and without the endorectal coil has demonstrated substantial displacement differences when the expandable endorectal coil was used.[39,40] We address this problem by placing gold seeds at the base, midgland, and apex of the prostate prior to MRI/MRSI and the acquisition of the treatment planning CT.

CT data acquired with the endorectal coil in the rectum allows direct and reproducible fusion with the MRI/MRSI (Figure 7).[39] With the endorectal coil inserted, registration discrepancies between CT and MRSI are eliminated by image correlation using both the bony anatomy and gold seeds to ensure precise alignment. Immobilization of the prostate by the coil also allows a reduction to be made in the margins used to account for organ movement. A newly designed, noninflatable, rigid endorectal coil for MRI/MRSI may reduce deformity of the prostate and the magnitude of the discrepancies between the prostate position on MRI/MRSI vs CT (unpublished data).

**MRI/MRSI and Biopsy-Directed IMRT**

We have concluded that MRI/MRSI can define regions within the prostate that are at the highest risk for involvement by bulky tumor.[13] Based on numerous studies suggesting that MRI combined with MRS could potentially enhance the sensitivity of biopsies, we chose to combine endorectal MRI/MRSI with biopsy information. This conclusion is supported by studies suggesting that the traditional sextant biopsy schemes have relatively low sensitivity (Table 2).[41-43] Extended-pattern biopsy schemes are being used routinely, and these techniques have resulted in improved cancer detection and a reduction in undergrading. Thus, we combine information from multiple (more than six) biopsies as well as MRI/MRSI to improve sensitivity and specificity and believe that this approach allows us to identify the dominant intraprostatic lesions.

**SF-IMRT**

Most prostate cancer patients treated with IMRT at UCSF over the last few years have received what is known as static-field intensity-modulated radiotherapy (SF-IMRT). Based on conventions proposed by the National Cancer Institute (NCI) IMRT working group, SF-IMRT is now considered a type of segmental multileaf collimation (SMLC) IMRT. Using the NCI IMRT working group convention, SF-IMRT is equivalent to forward-planned SMLC IMRT (unpublished data). At UCSF, forward-planned SMLC evolved from a previously described six-field three-dimensional conformal radiotherapy (3D CRT) technique.[37,44]

In 1996, we demonstrated the feasibility of selectively intensifying the dose to a dominant intraprostatic lesion.[37] Using forward-planned SMLC and online portal imaging, we treated the whole prostate at 180 cGy daily to a dose exceeding 73.8 Gy and simultaneously treated tumor-bearing regions of the prostate to 90 Gy. This approach begged the question, "If the disease is not uniformly distributed throughout the gland, why uniformly distribute the dose?" Uniformly delivering a high dose to the entire prostate uniformly increases the risk of complications to
surrounding normal tissues[even those tissues not immediately adjacent to sites of bulky disease. Other IMRT Techniques[]Prostate cancer is usually a multifocal disease and, unfortunately, most patients do not have a single dominant lesion.[41-43] In 1998, we found that selective dose intensification to multiple dominant intraprostatic lesions was also feasible with forward-planned SMLC, inversely planned SMLC, or sequential tomotherapy.[45] All three IMRT techniques were capable of ensuring that 90 Gy could be delivered to two dominant intraprostatic lesions while treating the entire prostate to 75.6 Gy without exceeding normal tissue tolerance.

Several hundred patients at UCSF have been treated with forward-planned SMLC to doses exceeding 73.8 Gy, and the complication rates have been quite low. An analysis of patients who received doses to portions of the prostate well in excess of 82 Gy has recently been completed.[46] Forty-four patients treated between 1992 and 1998 received a maximal dose within target volume (D$_{max}$ of 82 Gy. Of these patients, 18 received radiotherapy boosts selectively to limited portions of their prostate using IMRT; the remaining patients were treated with 3D CRT and had "hot spots" within their prostate. The Radiation Therapy Oncology Group (RTOG) acute and late toxicity scales were used to score gastrointestinal and genitourinary morbidity. Median follow-up and D$_{max}$ for this series were 23.0 months (range: 4.4 to 84.7 months) and 84.5 Gy (range: 82.0 to 96.7 Gy). Acute-grade gastrointestinal and genitourinary toxicities developed in 34.1% and 59.1% of patients, respectively. One patient experienced acute (grade 3) gastrointestinal toxicity; no other grade 3 or greater acute toxicity was observed. Three patients experienced grade 3 gastrointestinal late morbidity; these cases involved rectal bleeding and were effectively managed with laser coagulation/fulguration. No grade 3 or greater late genitourinary morbidity has been observed.

We concluded that doses of 82 Gy could be delivered by external-beam radiotherapy to at least a portion of the prostate gland and be tolerated with acceptable morbidity. This observation supports the continued investigation of IMRT as a means of improving disease control in prostate cancer. Great effort must be made, however, to compensate for day-to-day set-up variations and organ movement.[37,45] It also remains to be seen whether the shapes of the dose-response curve and complication-probability curves justify higher doses.[47] Reducing doses to surrounding normal tissues may turn out to be a greater asset to IMRT than increasing the dose of radiation to the prostate.

**MRI/MRSI and Treatment Follow-up**

The morphologic changes induced by therapy reduce our ability to detect the presence and spatial extent of cancer after therapy using only MRI.[48-51] Following radiation therapy, there is a homogeneous reduction in T2 throughout the prostate that reduces our ability to visualize both prostatic anatomy and cancer.[39] Studies have indicated, however, that residual or recurrent prostate cancer can be metabolically discriminated from normal and atrophied/necrotic tissue after therapy,[48-51] and can be identified as regions having elevated choline levels (ie, ratio of choline to creatine = 1.5, Figure 8). A prospective evaluation of several hundred patients treated with either brachytherapy or 3D CRT is currently under way at UCSF to establish the accuracy of using residual elevated choline to identify cancer after radiation therapy.

In addition to the potential for directly measuring the presence and spatial extent of prostate cancer after therapy, there is evidence that MRI/ MRSI can measure the time course of metabolic response. Early after radiation therapy, prostatic citrate levels are reduced or lost in both healthy and malignant tissues, followed by a slower loss of choline and creatine, and, eventually, by an absence of all metabolism, or metabolic atrophy (Figure 9). Citrate metabolism is very sensitive to therapy, and regions of residual citrate metabolism have correlated with regions of low radiation dose. The complete loss of all MRSI-detectable prostatic metabolites appears to correlate with effective therapy (Figure 9). Serial studies after therapy have indicated that metabolic abnormalities observed early posttherapy continue to decrease in size and magnitude and often disappear, which is consistent with the fact that cells continue to die for a long time after radiation therapy (Figure 10). Although prostate metabolite levels can be reduced to below MRSI-detection levels, viable normal and malignant cells may still be present, and the metabolism of both types of cells has been observed to recover with time after therapy. The phenomenon of metabolic recovery, most notable after the temporary use of androgen-suppressive therapy, can also occur following radiotherapy. Longer follow-up will be required to identify which patients are cancer-free and to determine the prognostic value of early metabolic changes, as well as the time course to metabolic atrophy and recovery.
Future Directions for MRI/MRSI

Several technical challenges hampered the successful application of MRI/MRSI technology before 1996. First, the time required to acquire high-quality images was prohibitively long. Second, only a limited volume could be imaged, and a portion of either the base or apex was excluded in patients with large glands. Third, failure to recognize the potential impact of postbiopsy artifacts and the impact of hormonal therapy compromised efforts at defining the extent of disease and the accuracy of readings.

Another technologic limitation was that only the peripheral zone portions of the prostate could be accurately imaged. Periurethral and transition zone tissues normally have reduced citrate levels (due to a reduction of glandular cells) and may have slightly elevated choline (due to the presence of benign prostatic hyperplasia). In light of this, overlapping voxels between these tissues and normal prostate tissues may create small regions that yield false-positive results. Similarly, a region containing a small focus of cancer with a high choline-to-citrate ratio might be partially diluted by the presence of normal tissue within the same spectroscopic voxel, creating a false-negative reading. Both of these problems may be exacerbated by human error—either in determining whether a voxel belongs to transition zone or to peripheral zone tissues. Portions of large and irregularly shaped glands may inadvertently be excluded because the shape does not fit into the square corner of the voxels.

Future developments in the design of endorectal coils, the deployment of higher-strength magnetic resonance scanners, the investigation of new imaging compounds, and the use of real-time displays that allow selection of different imaging positions should substantially reduce these problems.

Conclusions

The data presented suggest that there may be great potential for the use of MRI/MRSI to stage and treat prostate cancer. Thus, there is hope; but there may also be some hype. Much work remains before we can recommend that every medical center in the country acquire this technology. Initially, we need to prove that the use of this technology results in a measurable improvement in clinically meaningful outcomes. Then, we must demonstrate that these outcomes can be reproduced elsewhere.

From our perspective, there is great hope for MRI/MRSI. From the vantage point of the rest of the uninitiated world, however, much remains to be proven.

References:


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