The Role of Combined MRI & MRSI in Treating Prostate Cancer

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Clinical assessment of the extent of prostate cancer (PC) is often difficult because of the relatively small size and complex anatomy of the prostate and its inaccessible location deep within the pelvis. Traditionally, the extent of PC has been evaluated by digital rectal examination (DRE) in combination with other clinical data (PSA, number of positive biopsies or core percentage positive for PC). Increased awareness of limitations of traditional methods for diagnosis and staging of PC has mobilized the development and application of new imaging modalities for its assessment. Several new non-invasive imaging techniques, such as transrectal ultrasound of the prostate (TRUSP) have been developed to aid in this evaluation. However, these diagnostic modalities still have limitations. Even when combined with other clinical tools they often cannot consistently provide all the information needed by physicians.

Magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI) examinations are techniques that are FDA-approved, and the clinical utility of MRI in assessing PC has been well studied.[1-8] MRSI has been integrated into an MRI staging exam at UCSF and the combined metabolic and anatomic data has proven more accurate than MRI alone in identifying the location and spatial extent of the cancer within the prostate[9] and determining whether it has spread outside the gland.[10] Additionally, recent studies have indicated that MRSI may provide an assessment of cancer aggression and can detect residual or recurrent cancer after therapy.[4,11-14] This review will focus on the combined use of MRI and MRSI for the assessment of PC.

MRI as a Staging Technique

MRI emerged in the1980s as an outgrowth of the use of nuclear magnetic resonance to study the structure of chemical compounds. It quickly became the best imaging technique to assess problems associated with soft tissues. MRI uses a strong magnetic field and radio frequency waves to non-invasively obtain morphologic pictures (images) based on tissue water. It has the following advantages over other radiological techniques used for PC diagnosis:

- It does not use ionizing radiation.
- It can obtain images in sagittal, coronal, axial, and/or oblique planes.
- It provides more soft tissue contrast than other radiological techniques, and PC has low signal intensity as compared to surrounding regions of healthy tissue. This decrease in signal intensity is due to differences in structure between cancerous and normal prostate tissue.
- Endorectal/pelvic phased array coil MRI has demonstrated higher accuracy than other modalities in assessing seminal vesicle invasion and extra-capsular extension (ECE) of PC (96% and 81%r respectively).[1]

Within the same exam, endorectal MRI can also be used to assess the possibility of PC spread to lymph nodes and bones within the pelvis and close to the

prostate. However, even with all of these advantages, MRI has the following limitations:

- Localization of cancer within the prostate: MRI used alone has demonstrated a good sensitivity (79%) but low specificity (55%) in determining tumor location and spatial extent within the gland. This results from a large number of false positives[1] that are caused by factors other than cancer (e.g. post-biopsy hemorrhage, chronic prostatitis, benign prostatic hyperplasia (BPH), intra-glandular dysplasia, trauma, and therapy) that yield the same low signal intensity as cancer.[2-4, 8]
- Lymph node metastases: Both MRI and CT have demonstrated high specificity (98% and 97%, respectively) but low sensitivity (36% and 34%, respectively)[11,15] in detecting lymph node disease. This low sensitivity results from a high occurrence of false negatives, rather than false positives.

Improving MRI with New Technology & Experience

Recently, there has been a dramatic improvement in MRI assessment of PC. The latest endorectal MRI studies have demonstrated staging accuracies consistently between 75% and 90%[5, 10, 16] that are higher than staging accuracies reported using TRUS.[17] This increased accuracy has been the result both of improved MRI technology and of greater experience in interpreting MRIs of the prostate.

Multiple Coils

One important technical improvement is the user of multiple coils to image the prostate. Currently the prostate is imaged using an endorectal coil combined with four external coils.[18] This approach provides both the sensitivity to acquire high-resolution images of the prostate and the ability to image the entire pelvis. The use of the endorectal coil provides the necessary sensitivity to zoom in on the prostate and to acquire the MRSI data, while the pelvic phased array (four external coils) allows a large enough field-of-view (FOV) to assess pelvic lymph nodes and pelvic bones for metastatic disease.

Computer Post-processing

However, variability in image quality due to image intensity dramatically decreasing with distance from the surface coil and subsequent difficulties in interpretation may present a problem. To correct for this, the UCSF MR research team has developed computer post-processing to create uniform images and thereby greatly improve image interpretation.[11, 19] The improvement in image quality can be clearly seen in the anatomic image through the middle of the prostate of a patient with cancer (as shown on the left side of the image in Figure 1).

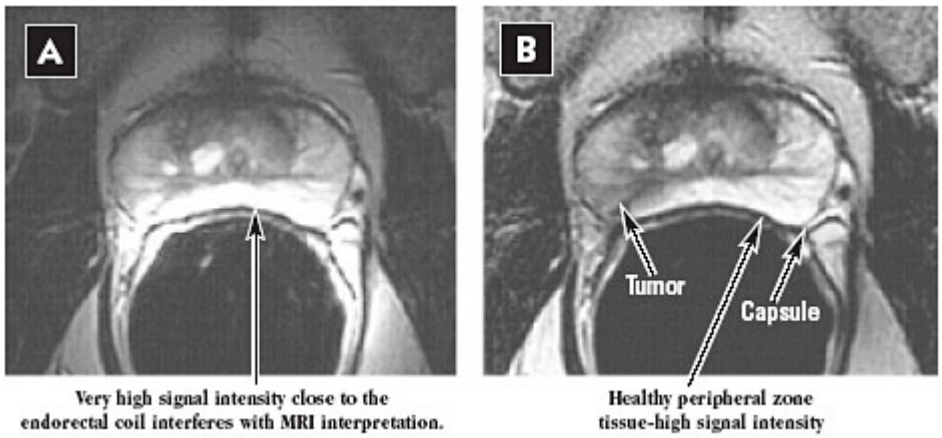

Figure 1. Comparison of axial endorectal coil/pelvic phased array FSE prostate images A (prior to) and B (after) performing an analytic correction for the reception profiles of the endorectal and pelvic phased array coils. The slight (10°) tilt in the placement of the endorectal coil hindered the ability to identify the low signal intensity cancer in the left peripheral zone of the uncorrected image. In the corrected image, the high signal intensity close to the endorectal coil has been removed allowing for improved visualization of the PC (low T2 signal intensity on the left side, short arrow on left) and the prostatic capsule (thin dark line encompassing the prostate, arrows on the right side).

After the high (bright) signal intensity close to the endorectal coil (Figure 1A) has been corrected for, the anatomy of the prostate as well as the tumor process can be more clearly visualized. The cancer can now be identified as a region of low (dark) signal intensity in the peripheral zone of the prostate as indicated by the arrow on the left in Figure 1B. The correction also improves visualization of the prostatic capsule (Figure 1B, right side), which is critical to an assessment of cancer spread outside the prostate.

Reader Experience

Additionally, increased experience in interpreting endorectal coil MR images[7] and a better understanding of the morphologic criteria used to diagnose extra-prostatic disease has also improved the performance of endorectal MRI.[16] This improvement in the performance of endorectal MRI should continue in the future as the UCSF image correction becomes available to other sites and as radiologists gain additional experience concerning what morphologic and metabolic findings are most predictive of early cancer spread. Increased experience should result in improved guidelines for those patients most likely to benefit most from an MRI exam, and should allow integration of MRI results with other radiological and clinical findings.

Objectified Reporting

The graphic reporting of MR findings in an objectified format will need to become routine in order to avoid ambiguities due to the English language. This commits the reader to evaluate all aspects of the MRI and MRSI that may have clinical relevance. An example of a proposed format for such objectified reporting is shown below:

ENDORECTAL MRI & MRSI REPORT

Patient's Name (First-Last)	Date of Exam	PSA	Volume ( ) cc PSAD density ( )

Indicate in each anatomic area below the presence of cancer (Yes) or the absence (No) by circling the findings.

MRI Results	MRSI Results	Concordance
I. GLAND EVALUATION		
Right Base Yes vs No Right Midgland Yes vs No Right Apex Yes vs No	Right Base Yes vs No Right Midgland Yes vs No Right Apex Yes vs No	Yes vs No Yes vs No Yes vs No
Left Base Yes vs No Right Midgland Yes vs No Right Apex Yes vs No	Left Base Yes vs No Right Midgland Yes vs No Right Apex Yes vs No	Yes vs No Yes vs No Yes vs No

II. CAPSULE, SEMINAL VESICLE AND PERI-PROSTATIC LYMPH NODE ASSESSMENT		
Extra-Capsular Extension	**Seminal Vesicle Involvement**	**Lymph Node Involvement**
Right Yes vs No Left Yes vs No	Right Yes vs No Left Yes vs No	Right Yes vs No Left Yes vs No
Stage per MRI	Stage per MRSI	Stage per Concordance
T2a, T2b, T2c, T3a, T3b, T3c	T2a, T2b, T2c, T3a, T3b, T3c	T2a, T2b, T2c, T3a, T3b, T3c

Comments (also see attached narrative report if more detailed reporting needed)

Magnetic Resonance Spectroscopic Imaging

While the staging accuracy of MRI has recently improved, the assessment of location and extent of PC within the prostate still remains problematic. Studies evaluating clinical data, systematic biopsy, TRUS, and MRI have shown disappointing results for tumor localization within the prostate.[6, 8, 20, 21] The problem lies in (1) the lack of specificity that TRUS and MRI alone have in identifying cancer and (2) the sampling error associated with systematic biopsies. Spectroscopy, however, has demonstrated high specificity in identifying cancer.[12]

Expanding the Effectiveness of MRI by Including MRSI

The recent development and use of MR spectroscopic imaging (MRSI) expands the diagnostic assessment of PC beyond the morphologic information provided by MRI.[12, 13, 22] As with MRI, **MRSI uses a strong magnetic field and radio waves to non-invasively obtain metabolic pictures (spectra) based on the relative concentrations of cellular chemicals (**choline**,** creatine**,** citrate**).**

With MRSI, one observes specific resonances (peaks) for citrate, choline and creatine from contiguous small volumes throughout the gland. The peaks for these different chemicals occur at distinct frequencies or positions in the MRSI spectrum (Figure 2, plots 1 and 2). The area under these peaks is related to the concentration of these metabolites, and changes in these concentrations can be used to identify cancer. Figure 2 shows cancer in the low signal intensity region labeled by box 1 versus the normal peripheral zone high signal intensity labeled by box 2. These are two 0.24 cc volumes (a cube 6.5 mm on a side) pulled out of the entire MRSI array of volume (that consists of hundreds of these volumes covering the entire prostate).

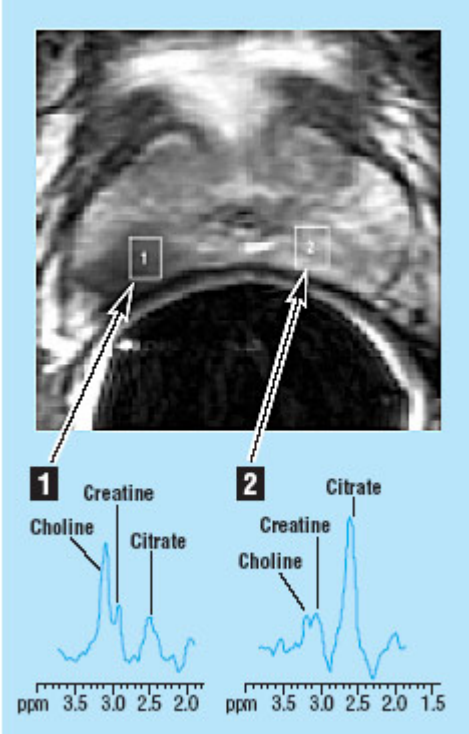

Figure 2. Fifty-eight year old man with pathologic stage pT3a PC, Gleason score (GS) 5. Corrected T2-weighted axial MR image through the mid-prostate obtained using an endorectal coil. A 0.24 cc spectrum obtained from the area of imaging abnormality (1) demonstrates elevated choline at 3.2 ppm, creatine at 3.0 ppm, and reduced citrate at 2.6 ppm; this is a pattern consistent with cancer. MR spectra obtained from the right side of the image (2) demonstrate a normal spectral pattern with citrate dominant and no abnormal elevation in choline.

In a study of 85 PC patients who had combined MRI/MRSI evaluation prior to radical prostatectomy, significantly higher choline levels, and significantly lower citrate levels were observed in regions of cancer as compared to BPH and normal prostatic tissues. The ratio of these metabolites (choline + creatine/citrate) in regions of cancer had minimal overlap vs normal prostate tissue or BPH values (high specificity).[22] This study indicated that MRSI could provide the degree of specificity for identifying cancer within the prostate that was lacking with MRI alone.

Recent studies have, in fact, demonstrated that an improved assessment of the presence and spatial extent of cancer within the prostate[9], as well as its spread outside the gland,[16] can be obtained by combining the information from MRI and MRSI (See Figure 3).

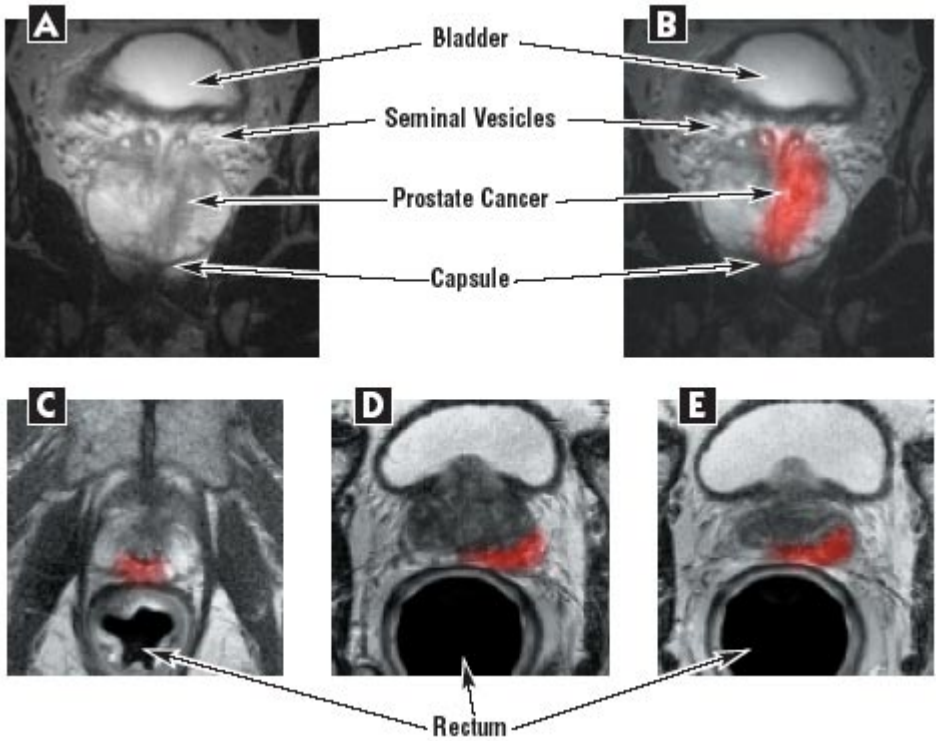

Figure 3. PC can be more accurately identified based on a concordant decrease in signal intensity demonstrated on the MRI image (A) and metabolic abnormality detected by MRSI (B). Image B shows a region of abnormal metabolism (in red) overlaid on the corresponding T2 weighted MR image. The region of abnormal metabolism in red corresponded with the area of decreased T2 signal intensity (image A) allowing for the identification of cancer with increased confidence. The region of cancer can be viewed volumetrically in multiple planes as seen from selected axial images taken from the base (C), mid-gland (D), and apex (E) of the prostate. Normally, 30-40 axial images are acquired contiguously through the prostate. By stepping through these high-resolution axial images, the trained radiologist can assess the spread of cancer through the capsule as seen in images D and E.

In a study of 62 patients undergoing MRI/MRSI evaluation prior to RP, with step-section histopathology, **it was demonstrated that PC could be localized to a sextant of the prostate (i.e. left/right base, mid-gland and apex) with a specificity of up to 91% when both MRI and MRSI were positive for cancer and a sensitivity of up to 95% when either MRI or MRSI were positive for cancer** (See Table 1[9]).

TABLE 1: Sensitivity & Specificity of MRI/MRSI for Intra-Glandular PC Determination

MRI/MRSI Findings[9]	Sensitivity[(a)]	Specificity[(b)]
MRI or MRSI suggests PC is present within prostate	95%	41%
MRI and MRSI suggests PC is present within prostate	55%	91%

(a) Sensitivity = True Positives ÷ (True Positives + False Negatives)
(b) Specificity = True Negatives ÷ (True Negatives + False Positives)

A high sensitivity study is associated with only a few patients being told they do not have PC when in fact they do have PC (false negative results are minimal-therefore sensitivity high) A high specificity study is associated with only a few patients being told they do have PC when in fact they do not have PC (false positive results are minimal-therefore specificity high)

It has also been demonstrated that assessment of cancer spread outside the prostate can be significantly improved by combining MRI findings that are predictive of cancer spread (based on studies of patients who received surgery after MRI/MRSI) with an estimate of the spatial extent of metabolic abnormality provided by MRSI.[16] In a study of 53 patients who received an MRI and MRSI exam prior to surgery, it was demonstrated that the addition of MRSI information increased the accuracy (from 0.77 to 0.83) in predicting early cancer spread outside the prostate (See Figure 4 below).

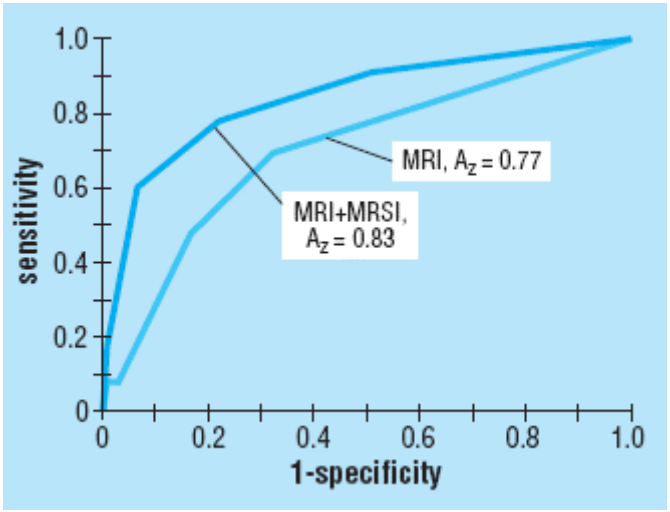

Figure 4. This graph demonstrates the trade-off between sensitivity and specificity when using MRI/MRSI to predict ECE. A perfect test (100% sensitive and 100% specific) would be a straight line up the vertical axis. The area under the curve (A_z) represents the overall accuracy of

the test. It can be clearly seen that combining MRI and MRSI increases the accuracy (increased area under the ROC curve) of predicting early ECE.

Metabolic information can also provide new insights into tumor aggressiveness, which may lead to improved risk assessment of patients with PC. An MRI/MRSI study of 26 biopsy-proven PC patients prior to RP and step-section pathologic examination was recently reported. It demonstrated a correlation between the magnitude of the decrease in citrate and the elevation of choline with cancer aggressiveness as reflected in the Gleason Score (See Figure 5).[11] When comparing higher GS (>6) to lower GS (=6) cancers, a statistically significant ($P<0.0001$) difference in (cancer choline)/(normal choline) ratios was observed. There was also a significant ($P<0.05$) correlation between the elevation of choline and (choline + creatine)/citrate ratio, and reduction in citrate with GS.

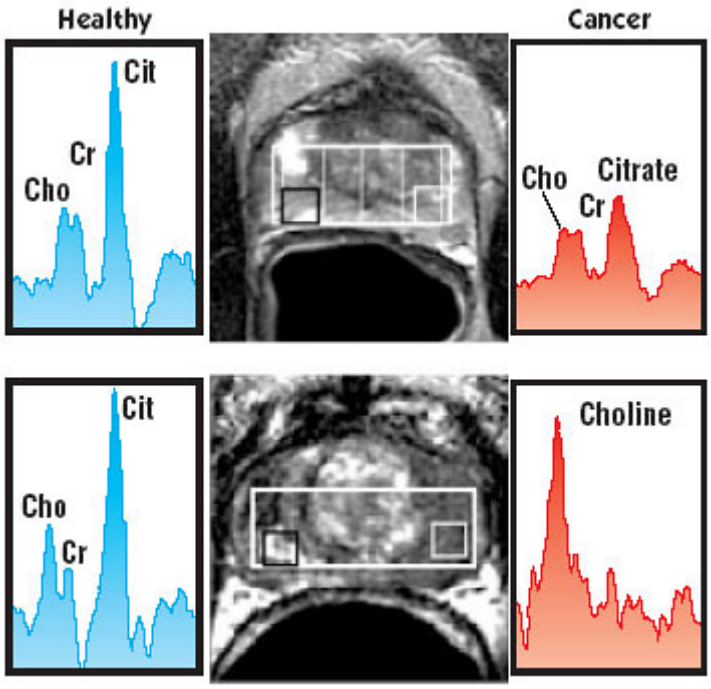

Figure 5 shows aggressive PC (bottom image right side) and non-aggressive PC (upper image-right side). The cancerous area can be visualized as a region of lower signal intensity on the right side of the image; the corresponding spectra are shown to the right. In not very aggressive cancer (GS 5 top right), citrate was reduced but choline was not elevated. Conversely, in aggressive cancer (GS 8, bottom right), citrate was absent and choline was very elevated.

(**Cho** = choline, **Cr** = creatine and **Cit** = citrate)

While the GS still remains the standard for confirming the presence of PC and predicting biologic behavior, the potential of MRSI to provide similar information is very exciting. Due to the great heterogeneity of prostate cancers as well as biopsy sampling errors, cancers are often inaccurately graded or not detected. In these cases, 3D-MRSI might be valuable in providing an additional

assessment of cellular function and organization, non-invasively and throughout the gland.

MRI/MRSI Findings in Response to Anti-Cancer Therapy

MRSI will probably have its greatest impact on the assessment of PC therapy and on the selection of additional therapy. After therapy, the ability to detect the presence and spatial extent of cancer by MRI alone is reduced due to the morphologic changes induced by the therapy (See Figure 6). However, studies have indicated that residual or recurrent PC can be metabolically discriminated from normal and necrotic tissue after therapy. Basically, the pattern of elevated choline and reduced citrate observed in regions of cancer prior to therapy are also seen in areas of persistent or recurrent PC after therapy.[4, 12, 13]

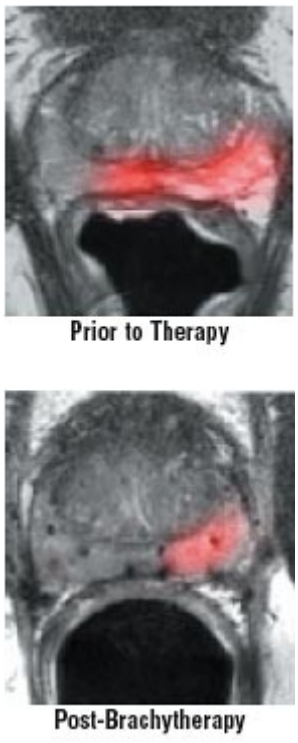

Figure 6 illustrates recurrent cancer after brachytherapy. The axial images shown represent one 3-mm section through the prostate (before and after therapy) selected from a contiguous series of 32 images through the prostate. The regions colored in red are areas determined to be abnormal by MRSI. These regions had (choline + creatine)/citrate peak area ratios that were more than three standard deviations greater than healthy values. Radiation seeds can be seen as very dark spots in the peripheral zone of the prostate in the bottom image. Although cancer was dramatically reduced after brachytherapy, a region of residual abnormal metabolism consistent with cancer is seen on the right side of the image. This area also corresponded to a region of low radiation dose. This information allows for earlier intervention with additional therapy.

In some cases, such as after androgen deprivation therapy (ADT), the treatment directly affects one of the metabolites. For example, **prostatic citrate production and secretion have been shown to be regulated by the hormones testosterone and prolactin**[23, 24], **and we have observed an early dramatic reduction of citrate after initiation of combined ADT.**[11]
Additionally, there is a time-dependent loss of all prostatic metabolites in regions of both cancer and healthy tissue following the initiation of ADT.[11] This finding is consistent with the increased frequency of tissue atrophy that occurs as the duration of ADT increases.[25] These findings indicate the potential of MRI/3D MRSI to provide a measure of the time course of response and information concerning the mechanism of therapeutic response.[11] The improved assessment of therapeutic response provided by combined MRI/MRSI should allow for earlier intervention in patients with recurrent disease.

The determination of the accuracy of combined MRI/3D-MRSI for detecting residual cancer after therapy is more difficult than it is prior to therapy due to the lack of a gold standard (pathology of the surgically removed prostate) and the long natural history of PC. Therefore, large-scale outcome studies are required to determine if MRI/3D-MRSI can morphologically and metabolically assess the early efficacy of therapy. These studies are currently underway. **If successful, MRI/MRSI should again allow for earlier intervention in patients with recurrent cancer after therapy and shorten clinical trials of PC therapy by providing surrogate endpoints of therapeutic success.**

Current Status of the Clinical Use of MRI/MRSI in PC Assessment

Over the last ten years at UCSF, the combined MRI/MRSI PC-staging exam has gone from a research to a clinical exam.

- 3D MRSI has been integrated into a clinical MRI staging exam for PC taking a total of 50 minutes.
- The fact that over 2000 MRI/MRSI exams have been performed to date at UCSF has allowed a determination of the utility of combined MRI/MRSI in assessing PC.
- A majority of these patients were covered by insurance. Patients are encouraged to check with their insurance company to ensure coverage. The following CPT codes may be quoted: 72196(MRI) and 76390(MRS).

MRSI data is factored into all clinical MRI reports by radiologists at UCSF. These reports summarize the location and extent of disease within the prostate, the possibility of cancer spread through the capsule, any involvement of nearby tissues (surrounding nerves and blood vessels, and seminal vesicles), and any cancer spread to lymph nodes and bones within the pelvis. Additionally, the report will provide a prostate volume (by MRI) and PSA density if a recent PSA is given. Currently however, the report will not provide a cancer volume. The ability of MRI and MRSI to provide an estimate of cancer volume is under investigation.

A clinical package is under development in conjunction with GE Medical Imaging and will be available in the future to hospitals in other locations. PC patients have opted for an MRI/MRSI exam prior to therapy for a number of reasons. Last year at UCSF 69% of the patients receiving an MRI/MRSI exam did so prior to therapy, and had the exam for the following reasons:

- To determine the location, extent, and potential of cancer spread so that this information can be used to decide which therapy is best for individual patients.
- To improve therapeutic planning and evaluation (Figure 7 below).
- To improve diagnosis: There are a growing number of patients with negative biopsies and elevated or rising PSAs, who are using MRI/MRSI to target regions for subsequent ultrasound guided biopsy.

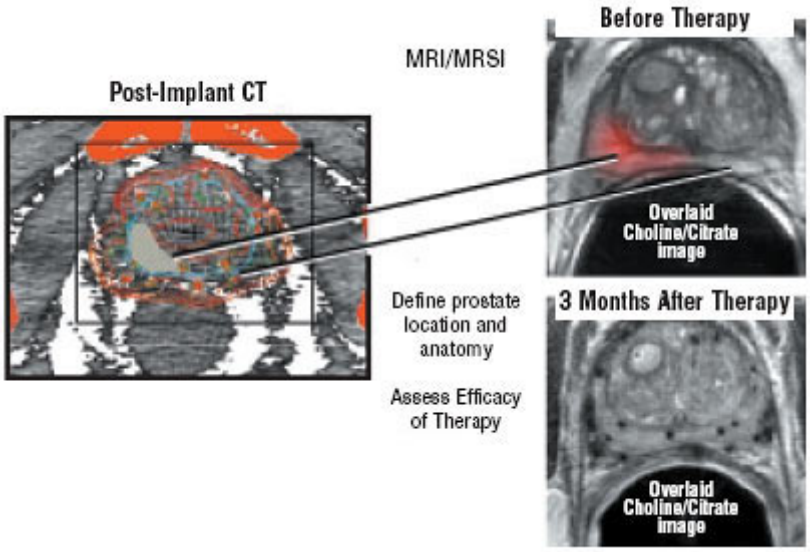

Figure 7. On the right side are two representative axial MRI/MRSI images (cancer in red) taken prior to (top) and after Brachytherapy (bottom). On the left side is an axial CT image taken through the same prostate, with overlaid MRI/MRSI information (white lines). Oncologists currently use CT images to plan radiation therapy (red lines is a contour map of radiation dose). CT is very good at visualizing bones within the human body, but does not visualize soft-tissues such as the prostate very well.[26] Moreover, CT cannot accurately detect cancer within the prostate. The superior anatomic detail provided by high resolution MRI can be used to better define the prostate (traced in white on the CT image) and surrounding radiation-sensitive tissues for improved radiation treatment planning. The combination of MRI and MRSI can also better define the location and extent of cancer within the prostate (hash-marked area on CT image) thereby allowing radiation oncologists to give these regions increased doses of radiation while minimizing radiation to surrounding tissue.[27]

A growing number of patients with suspected cancer recurrence after therapy are getting an MRI/MRSI restaging exam. In fact, last year 34% of the MRI/MRSI exams were performed post therapy as follows:

- 103 patients after hormone ablation therapy
- 76 patients after radiation therapy
  - 49 after brachytherapy
  - 27 after external beam radiation
- 11 patients after RP
- 40 patients before and after nutritional/lifestyle intervention.

For More Information

Patients or physicians wanting more information about MRI/MRSI at UCSF can contact Penny Wood or Kristin Wright at (415) 476-4159 or may e-mail them at:

penny@mrsc.ucsf.edu and
kristin@mrsc.ucsf.edu

Physicians wanting to arrange an MRI/MRSI study should call (415) 353-2573 for additional details. The clinical data form that must be completed by the physician & patient can be printed from the following Internet address: www.mrsc.ucsf.edu/prostate.html and sent by fax to (415) 476-8809 or e-mailed directly from the above Web site.

Editor's Notes:

(1) For current MRI contact information click here.

(2) This technology is now marketed by GE Healthcare using the name PROSE (PROstate Spectroscopy and imaging Examination). For more information about PROSE, click here.

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