



Michael Mahany. *Autumn Ptarmigan*. Photograph. Denali National Park, Alaska.

*Recent advances in imaging techniques for prostate cancer are reviewed.*

## Newer Imaging Modalities to Assess Tumor in the Prostate

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**Background:** *Several advances in the imaging of prostate cancer have been made in recent years. Diagnostic staging has become increasingly complex and confusing as newer technologies have developed more rapidly than research has been able to confirm or refute the accuracy of these technologies. By the time research has been performed, the technology used for a study has often become outdated and newer and more sophisticated imaging has become available.*

**Methods:** *We reviewed the literature on local and nodal staging of prostate cancer, as well as the role of magnetic resonance imaging (MRI), magnetic resonance spectroscopic imaging (MRSI), dynamic contrast-enhanced MRI, positron emission tomography (PET), endorectal power Doppler, lymphotropic MRI contrast agents, and future possibilities such as diffusion MRI. This review is not systematic, but rather focused on these imaging modalities.*

**Results:** *Advances in MRI, ultrasound, and lymphotropic contrast agents have improved our ability to differentiate between T2 and T3 prostate tumors. PET imaging has proven less successful at staging prostate cancer. A literature review suggests patients with moderate risk of extracapsular extension benefit most from endorectal MRI evaluation. Spectroscopy, dynamic imaging, and lymphotropic contrast agents are expected to continue to improve sensitivity and specificity of staging of prostate cancer. Power Doppler evaluation with endorectal ultrasound has proved useful for evaluation during endorectal biopsy for identifying hypervascular tumors for directed biopsy. Diffusion-weighted MRI remains untested clinically and represents a future direction for research.*

**Conclusions:** *Future studies using these new techniques are needed to demonstrate changes in outcomes in large patient populations.*

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*Abbreviations used in this paper: CT = computed tomography, MRI = magnetic resonance imaging, MRSI = magnetic resonance spectroscopic imaging, PET = positron emission tomography.*

## Introduction

Ultrasound and computed tomography (CT) have been the "standard" measures to evaluate the prostate in patients with prostate cancer. Sonographic examination of the prostate is insufficiently sensitive or specific to detect prostate cancer.<sup>1</sup> Transrectal ultrasound is used to guide sextant biopsy, but its usefulness for staging is limited. CT has traditionally been used to evaluate the extent of local disease. More recently, magnetic resonance imaging (MRI) has also been used to evaluate for local disease. Borley et al<sup>2</sup> have shown that while CT and MRI have a high sensitivity for detecting lymph node metastases, they have poor sensitivity. Indium-111-capromab pendetide (ProstaScint, Cytogen Corp, Princeton, NJ) has also been used to evaluate lymph node involvement, relapse after prostatectomy, and occult malignancy.<sup>3</sup> However, Wilkinson and Chodak<sup>4</sup> recently reviewed 42 cases and concluded that ProstaScint did not offer additional benefit in assessing postprostatectomy patients for further therapy. Currently, ProstaScint imaging is not thought to provide sufficient additional staging information to warrant its use. Although MRI of the prostate has been available since 1984, there is a large variation in reported staging performance in the literature.<sup>5,6</sup> These wide variations are presumably due to sample size, variations in technique, study population, and the constant change in state-of-the-art technology. This review addresses the new imaging techniques for evaluating tumor in the prostate and their degree of support in the literature. We also review other techniques such as ultrasound for their role in staging of prostate cancer.

## Magnetic Resonance Imaging

As with all radiologic modalities, MRI continues to change rapidly. Several changes have improved the examination of the prostate. When endorectal coils became available in 1984, they were large and uncomfortable for the patient. Currently, a flexible endorectal coil is positioned in a balloon that expands into the rectal vault after placement, holding the coil reliably into position with minimal discomfort. Until recently, one of the difficulties with endorectal coil examination was the inability to utilize more than one coil. If an endorectal coil was employed, other coils could not be utilized, and thus the pelvis could not be imaged simultaneously with the prostate. In a comparison of pelvic phased-array (PPA) coils and integrated endorectal coils, staging accuracy was better with integrated endorectal PPA coils than for PPA coils.<sup>7</sup> Newer software and technology have allowed simultaneous multi-channel image acquisition. This advance reduces signal drop-off throughout the pelvis.

In a recent meta-analysis of the current literature by Engelbrecht et al,<sup>6</sup> factors improving staging performance

included publication year, sample size, histologic gold standard, number of imaging planes, turbo spin echo, endorectal coil, and contrast agents. This meta-analysis demonstrates the improving staging sensitivity as the technology has improved. Due to time constraints, the number of imaging planes is usually limited to two. As sequences have decreased in acquisition time, the sagittal plane has been added to many evaluations. However, the addition of the sagittal plane has not been shown to increase specificity or sensitivity. Turbo spin-echo is a sequence that allows more rapid acquisition, thereby decreasing motion artifact and increasing patient comfort by shortening the length of the examination. Interestingly, this study did not show improved sensitivity with magnetic resonance spectroscopic imaging (MRSI), dynamic contrast-enhanced imaging, or field strength, possibly because there is not enough improvement with these techniques or because not enough studies have been performed with newer techniques such as multivoxel spectroscopy. This meta-analysis suggested that currently, MRI in prostate cancer staging (T2c vs T3c) has a combined sensitivity and specificity of 71%. At a specificity of 80% on this curve, sensitivity was 62%. A sensitivity of 62% is an "improvement over the sensitivity of clinical examination, which, by definition, has not helped detect periprostatic invasion in patients with clinically localized disease."<sup>8</sup>

Given these findings, many urologists have elected to proceed with patient treatment of prostate cancer based only on Gleason score, prostate-specific antigen (PSA) level, and digital rectal examination. In 1997, only 10% of the urologists in the United States used preoperative prostatic MRI, and 31% of urologists reported that MRI was not available to them.<sup>9</sup> In 2000, Jager et al<sup>10</sup> demonstrated that MR staging was cost-effective for patients at intermediate risk of extracapsular disease: PSA 10–20 ng/mL and Gleason score of 5–7. Their study also suggested cost-effectiveness for patients at low risk. These benefits were derived from the cost savings created when patients with clinically T2 disease were converted to T3 disease based on imaging and consequently did not undergo surgical prostatectomy. Many urologists will not perform prostatectomy on patients with high risk of extracapsular extension despite the lack of evidence of extracapsular extension (Fig 1). The surgery-MRI threshold has not been evaluated prospectively; however, retrospective analysis has suggested that patients with an intermediate to high risk of having T3 or greater disease benefit from MRI.<sup>11</sup> Therefore, utilizing MRI for patients in this category depends on the urologist's practice parameters and patient choice. Occasionally, patients with high risk of extracapsular extension request prostatectomy despite advice to the contrary. At our institution, we perform endorectal MRI to evaluate these patients (Fig 2), and we often find definitive evidence of extracapsular extension. This information is shown to the patient to assist in choosing the best treatment.

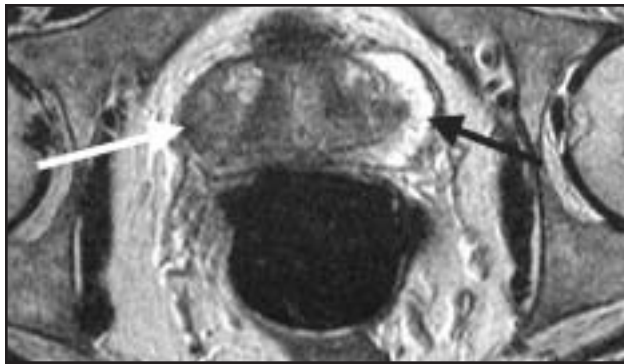


Fig 1. — Axial T2 demonstrates normal peripheral zone (black arrow) and site of prostate cancer without extracapsular invasion (white arrow).

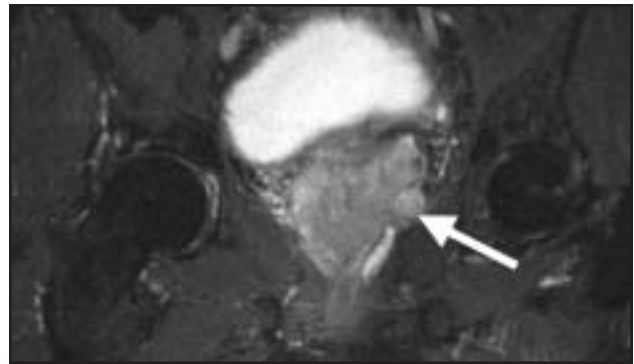


Fig 2. — Coronal T2-weighted STIR (short tau inversion recovery) imaging demonstrates extracapsular extension (arrow).

Other studies confirm this approach and also confirm the sensitivity and specificity of MRI for staging. A French study<sup>12</sup> of 336 patients undergoing radical prostatectomy demonstrated sensitivity of 50% for occult T3 staging and 69% for extensive T3 tumor with a specificity of 95%. This study also showed that MRI was likely to confirm T3 tumor with three or more sextants involved at biopsy. The authors concluded that endorectal MRI was appropriate in patients with three or more positive sextant biopsies, a palpable tumor, and/or a PSA level greater than 10 ng/mL.

The future of MRI imaging includes the advance in field strength. Three Tesla (3T) magnets promise increased resolution and improved spectroscopy that is likely to enhance specificity and sensitivity in differentiating T2 from T3 tumors. Another advance will be the continued increase in the number of channels that can be sampled simultaneously. However, the effect that advanced multi-channel detection will have on staging of prostate cancer is unclear.

## Magnetic Resonance Spectroscopic Imaging

MRSI utilizes the magnetic field to obtain spectra based on the in vivo endogenous chemicals present in tissue. This technique is frequently used in neurologic imaging to differentiate tumor from radiation necrosis. With prostate tissue, MRSI must suppress the water and lipid content in order to detect the prostatic metabolites citrate, choline, and creatine.<sup>13</sup> In normal prostatic tissue, citrate is as plentiful as creatine. Choline, a marker of cell membranes, is elevated in prostate cancer, likely the result of more rapid cell turnover (Fig 3). Until recently, MRSI required a relatively large volume of tissue from which the spectra was analyzed and also required manual placement of the voxel that was to be sampled.

This made sampling of the small peripheral zone of the prostate somewhat impractical. Newer technology now allows multivoxel sampling of the entire gland and also provides spectral arrays from a volume as little as 0.24 cc.<sup>13</sup> The MRSI data can be obtained within the same examination as the endorectal MRI. MRSI evaluation improves estimation of tumor volume (which correlates with extracapsular extension<sup>6</sup>) and enhances the ability to identify the location of the tumor within the prostate gland,<sup>14</sup> and it may show a relationship between outcome, response to therapy, and the spectral evaluation of the tumor. Vigneron et al<sup>15</sup> demonstrated in an abstract that “a linear correlation between the magnitude of the decrease of citrate and the elevation of choline with the pathologic Gleason score.” Despite these recent advances in MRSI, research has yet to prove its value for patient outcomes in a multicenter randomized trial.

## Lymphotropic Contrast Agents

In June 2003, Harisinghani et al<sup>16</sup> described utilization of lymphotropic superparamagnetic nanoparticles to identify prostate metastasis to lymph nodes. In this landmark article, the authors reported improved sensitivity of MRI for detection of nodal metastasis from 35.4% to 90.5%. Their study correctly identified all patients with nodal

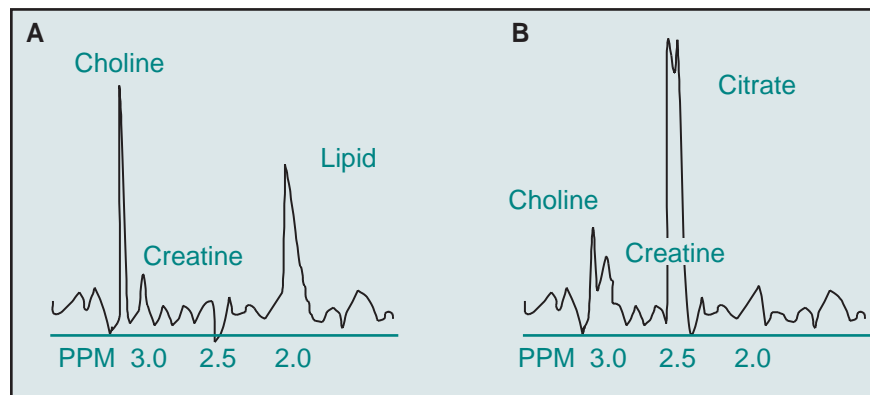


Fig 3. — A cartoon example of the spectra from prostate tissue. (A) demonstrates high choline and absent citrate, indicating carcinoma. (B) is normal with a high citrate peak.

metastases. Conventional evaluation of lymph nodes suggests malignancy if the short-axis diameter is greater than 10 mL or if the short axis diameter is 8 mL and the lymph node is spherical. However, with the monocrystalline iron oxide (Combidex, Advanced Magnetics Inc, Cambridge, Mass), three criteria were used: a decrease in signal intensity of less than 30% on T2-weighted fast spin-echo, a heterogeneous signal giving the node a mottled appearance or discrete focal defects, and nodes with a central area of hyperintensity with peripheral decrease in signal.<sup>9</sup> These findings significantly improve the ability of imaging to detect lymph node metastasis.

## Future Directions in Magnetic Resonance Imaging

Dynamic contrast-enhanced MRI evaluation utilizes a rapid T1-weighted MR sequence to sample a single plane of tissue as the tissue enhances from intravenous injection of gadolinium MR contrast (Fig 4). Using differences in enhancement characteristics, this technique attempts to differentiate prostate carcinoma from normal peripheral zone and central gland tissue. The main features used for differentiation are the start of enhancement, time to peak, peak enhancement, and washout. The peak-enhancement was the optimal enhancement feature for differentiation of carcinoma in the peripheral zone and central gland.<sup>17</sup>

Diffusion MRI utilizes the ability of MR to detect the Brownian motion of water molecules. The technique has become especially useful in the detection of acute infarcts in neurological imaging. Several attempts have

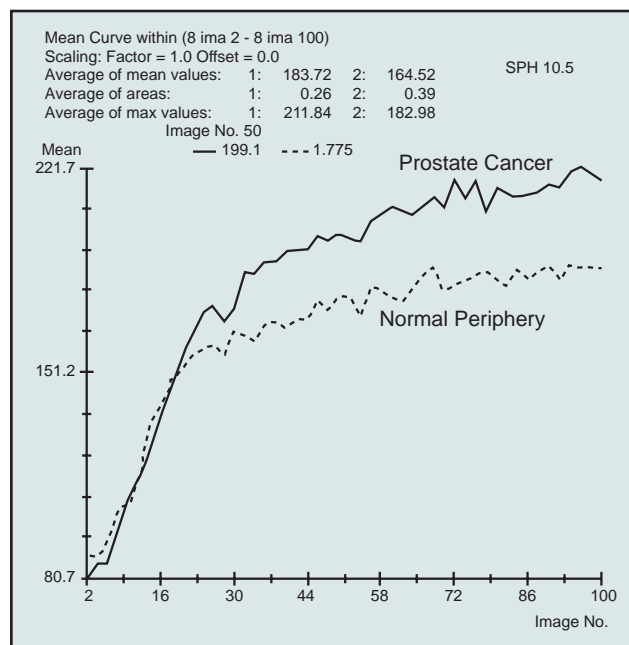


Fig 4. — Dynamic contrast-enhancement of prostate cancer achieves a higher peak than benign tissue.

been made to utilize the technique to evaluate the response to radiation therapy in other body sites. A literature search revealed just one journal article describing early evaluation of this technique in prostate cancer. Jennings et al<sup>18</sup> demonstrated that prostate carcinoma xenografts exposed to docetaxel chemotherapy developed an increased apparent diffusion coefficient (ADC). This early study suggests that MR diffusion imaging may be able to demonstrate the degree of response to radiation and chemotherapy.

## Positron Emission Tomography

A recent review by Shvarts et al<sup>19</sup> discusses the difficulties of using positron emission tomography (PET) to stage prostate cancer. The authors note that the use of PET with the glucose analog [<sup>18</sup>F]-fluoro-2-deoxy-D-glucose (FDG) in the diagnosis of localized prostate cancer has been disappointing. Prostate cancer has a low glycolytic rate, which results in decreased accumulation of fluorodeoxyglucose. Other research radiopharmaceuticals exist that show promise for evaluation of locally extensive prostate cancer.<sup>11</sup> C-choline has been used successfully in identifying both local and metastatic disease.<sup>20</sup> This radiotracer has a short half-life, which limits its clinical usefulness. FDG-PET has been used successfully for the evaluation of metastatic disease, tumor burden, and location of disease. Oyama et al<sup>21</sup> demonstrated a decrease in PET uptake at metastatic sites in patients undergoing androgen ablation. At our institution, PET is not routinely used to stage prostate cancer or to follow metastatic prostate cancer.

## Advances in Ultrasound

A new study utilizing Doppler sonography and power Doppler techniques has demonstrated that hypervascularity correlates with increased Gleason score.<sup>22</sup> This study prospectively evaluated ninety-four patients with color Doppler sonography before radical prostatectomy. Thus color Doppler sonography evaluation of hypoechoic lesions at time of biopsy is useful in predicting increased Gleason score and the aggressiveness of the tumor.

## Conclusions

At our institute, we use ultrasound to guide prostate biopsies (Table). Staging of the pelvis has traditionally been completed with CT, but MRI is better in evaluating for lymph nodes and the use of MRI is becoming more widespread. MRI with the endorectal coil is being used to evaluate for residual prostate tumor in patients who have undergone prostatectomy. Bone scan is used to evaluate for distant metastasis.

### Imaging Modalities to Evaluate Patients With Prostate Cancer at Our Center

Biopsy direction:	Ultrasound
Local staging:	Computed tomography Magnetic resonance imaging (replacing CT due to increased sensitivity for evaluating lymph nodes)
Metastasis:	Bone scan
Residual prostate:	Magnetic resonance imaging with endorectal coil

Despite the rapid advancement of imaging technology large studies demonstrating their usefulness have yet to be completed. Currently, there is a large multi-institutional trial underway to evaluate the usefulness of MRSI but the results are likely several years away. As Langlotz et al<sup>23</sup> noted in 1995, "One may wonder about the relevance of results of large multi-institutional studies charged with assessing technology such as prostatic MRI imaging ... Because such projects cannot be designed, implemented, and evaluated in a short time, the results of a scientific interrogation ... are likely to be outdated and of limited value by the time they are published." Given these complex issues the clinician is left with utilizing the technology available at their own institution and determining if the technology benefits their patients. Current literature suggests that patients with moderate to high risk of extracapsular extension of disease benefit most from endorectal MRI. Spectroscopy remains unproven. Despite these limitations, ongoing advances in imaging modalities will help to allow imaging to equal the gold standard of pathologic evaluation in the staging of prostate cancer.

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