

High-resolution MRI with magnetic nanoparticles allows the detection of small and otherwise undetectable lymph-node metastases

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<http://content.nejm.org/cgi/content/abstract/348/25/2491>

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Noninvasive Detection of Clinically Occult Lymph-Node Metastases in Prostate Cancer

Mukesh G. Harisinghani, M.D., Jelle Barentsz, M.D., Ph.D., Peter F. Hahn, M.D., Ph.D., Willem M. Deserno, M.D., Shahin Tabatabaei, M.D., Christine Hulsbergen van de Kaa, M.D., Ph.D., Jean de la Rosette, M.D., Ph.D., and Ralph Weissleder, M.D., Ph.D.

ABSTRACT

Background Accurate detection of lymph-node metastases in prostate cancer is an essential component of the approach to treatment. We investigated whether highly lymphotropic superparamagnetic nanoparticles, which gain access to lymph nodes by means of interstitial/lymphatic fluid transport, could be used in conjunction with high-resolution magnetic resonance imaging (MRI) to reveal small nodal metastases.

Methods Eighty patients with presurgical clinical stage T1, T2, or T3 prostate cancer who underwent surgical lymph-node resection or biopsy were enrolled. All patients were examined by MRI before and 24 hours after the intravenous administration of lymphotropic superparamagnetic nanoparticles (2.6 mg of iron per kilogram of body weight). The imaging results were correlated with histopathological findings.

Results Of the 334 lymph nodes that underwent resection or biopsy, 63 (18.9 percent) from 33 patients (41 percent) had histopathologically detected metastases. Of these 63 nodes, 45 (71.4 percent) did not fulfill the usual imaging criteria for malignancy. MRI with lymphotropic superparamagnetic nanoparticles correctly identified all patients with nodal metastases, and a node-by-node analysis had a significantly higher

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sensitivity than conventional MRI (90.5 percent vs. 35.4 percent, P<0.001) or nomograms.

Conclusions High-resolution MRI with magnetic nanoparticles allows the detection of small and otherwise undetectable lymph-node metastases in patients with prostate cancer.

Source Information

>From Massachusetts General Hospital and Harvard Medical School, Boston (M.G.H., P.F.H., S.T., R.W.); and University Medical Center, Nijmegen, the Netherlands (J.B., W.M.D., C.H.K., J.R.).

Drs. Harisinghani and Barentsz contributed equally to the article.

Address reprint requests to Dr. Weissleder at the Center for Molecular Imaging Research, Department of Radiology, Massachusetts General Hospital, Bldg. 149, 13th St., Rm. 5403, Charlestown, MA 02129-2060, or at weissleder@xxxxxxxxxxxxxxxxxxxxxxxxxxxx

Currently recruiting in clinical trial in Texas
<http://www.clinicaltrials.gov/ct/gui/show/NCT00147238>
A Validation Study of MR Lymphangiography Using SPIO, a New Lymphotropic Superparamagnetic Nanoparticle Contrast

This study is currently recruiting patients.
Verified by M.D. Anderson Cancer Center September 2005
urpose

The objective of the study is to re-validate the accuracy of ferumoxtran-10, a new ultra-small superparamagnetic oxide (USPIO) particles, using currently available a high-resolution MR imaging technique in patients with surgically resectable carcinomas of prostate, penis, and urinary bladder in their initial staging work-ups.

In most, if not all, tumor staging work-up, the knowledge of nodal disease (?N? staging) is important in treatment planning and predicting the outcome of the treatment.

Conventional way to evaluate the nodal disease is based on the ?size? on CT, MRI, or ultrasound. Unfortunately, despite continuous improvement, the accuracy of the current imaging techniques detecting metastatic nodal disease is notoriously suboptimal and varies greatly depending on the criteria. Surgical exploration, either by an open surgery for lymph nodes dissection or a laparoscopy, is required for accurate ?N? staging in some urologic tumors.

The new, ultra-small superparamagnetic agent, iron oxide (SPIO) particles

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(Combidex; ferumoxtran-10), is taken primarily by reticuloendothelial system (RES) of the liver and spleen and lymph nodes following the initial vascular distribution. Multiple pre-clinical and clinical studies have shown that the contrast injected intravenously accumulates in the lymphatic system and decrease the signal intensity of normal lymph nodes on MRI. The recent feasibility studies conducted in human have also shown promising results to detect the malignant nodes in patients with Head and Neck tumors, breast carcinomas, and prostate carcinomas. The most recent report from Massachusetts General Hospital has shown about 90 % sensitivity and 98 % specificity in detecting the metastatic pelvic lymph nodes in patients with prostate carcinomas with a 41 % sensitivity and 98 % specificity for the nodes less than 5 mm.

Bladder cancer, Genitourinary cancer, Prostate cancer
Drug: Combidex- MR contrast agent

Study Type: Interventional
Study Design: Diagnostic, Non-Randomized, Open Label, Uncontrolled, Single Group Assignment, Efficacy Study
Further Study Details:

Expected Total Enrollment: 80

Study start: July 2005

1. MRI will be performed prior to and 24- 36 hours after intravenous infusion of 2.6 mg/kg of ferumoxtran-10.
2. Location and degree of suspicion of all nodes noted on MR images will be marked on a diagram for each lymphatic chain in the pelvis and each nodal group or node, if possible, will be correlated with the surgical pathology. Also any malignant nodes seen only during the surgery will be noted.

A total of 80 patients will be recruited as follows.

Each patient will have two images. One with and one without ferumoxtran-10, thus this is a paired experiment, where sensitivity on a per patient basis is the major endpoint. The null hypothesis is that the sensitivity of both images are the same versus the alternative that the sensitivity of MRI with nano particles is greater than that for MRI only

Of the 80 patients we expect 40% or 32 to have lymph node metastasis. Based on the Harisinghani et. al. study(18), the sensitivity of MRI only was 45% and that of MRI with nano particles 100%.

Given below is the power of the two-sided McNemar test to detect differences in the sensitivities of the two paired images, using alpha = .01.

Sensitivity Pre-contrast Sensitivity Post Contrast Power
0.40 .90 0.957*
0.40 .95 0.992 0.40 .99 0.999 0.45 .90 0.897 0.45 .95 0.980 0.45 .99 0.998

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0.50 .90 0.814 0.50 .95 0.946 0.50 .99 0.995

*From the above table, 32 patients (with lymph node metastasis) should be sufficient to detect a significant ($P < .01$) difference between a sensitivity of 0.45 without contrast agent and a sensitivity of .90 with ferumoxtran-10 using the McNemar test.

The sensitivity, specificity, accuracy, and positive and negative predictive values will be calculated on a per patient basis and on a per lymph node basis. The effect of tumor size on test accuracy will be estimated (24).

Eligibility

Genders Eligible for Study: Both
Criteria

Inclusion Criteria:

1. Patients with newly diagnosed pelvic urological tumors, including prostate carcinomas, bladder carcinomas, and penile carcinomas.
2. Planned to have a surgical exploration or a laparoscopy for pelvic lymph node dissection/biopsy within 4 weeks.
3. No previous treatment.
4. Signed written consent and HIPAA authorization

Exclusion Criteria:

1. Contraindications for MRI
2. Claustrophobia, metals in the pelvis, previous pelvic surgery
3. Allergy or hypersensitivity to iron products, dextrans, iron-dextran complex
4. Previous treatment related to the primary disease or any pelvic surgery a. Prostate cancer: metastases demonstrated on preoperative imaging; prior hormonal therapy greater than 3 months; prior local therapy for prostate cancer b. Penile Cancer: prior systemic therapy for penile cancer; prior inguinal radiation c. Bladder Cancer: prior systemic therapy for bladder cancer (does NOT include intravesical chemotherapy or immunotherapy); prior pelvic radiation; history of partial cystectomy or prior pelvic lymph node dissection
5. Women of child-bearing potential. (Women who will be having hysterectomy as part of bladder surgery will not be excluded.)
6. Clinically documented or risk of primary or secondary iron overloading (e.g. History of thalassemia, sickle cell anemia, hereditary hemochromatosis, multiple transfusions with any reason)

Location and Contact Information

Please refer to this study by ClinicalTrials.gov identifier NCT00147238

Haesun Choi, M.D. 713-792-8177 hchoi@xxxxxxxxxxxxxxxx

Texas

The University of Texas M.D. Anderson Cancer Center, Houston,
Texas, 77030, United States; Recruiting
Haesun Choi, M.D. 713-792-8177 hchoi@xxxxxxxxxxxxxxxxxxxx

Study chairs or principal investigators

Haesun Choi, M.D., Principal Investigator, University of Texas M.D.
Anderson Cancer Center

More Information

Study ID Numbers: 2004-0003

Last Updated: September 6, 2005

Record first received: September 6, 2005

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Health Authority: United States: Food and Drug Administration

ClinicalTrials.gov processed this record on 2005-09-30

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