

Feraheme®: A New Tool in the Prostate Cancer Toolbox



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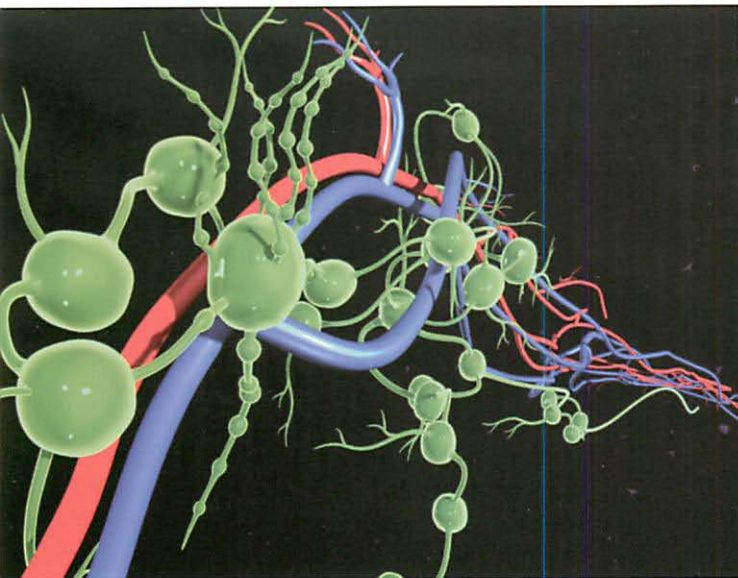
I started my prostate cancer research decades ago. As each year has gone by, we have learned much more about the diagnosis and treatment of this disease. In my early days, the challenge was merely to be equipped to diagnose the disease early enough to be able to actually thwart its progress. Today, it feels like light years beyond those rudimentary steps.

We continue to explore what the causes of the disease might be; we are beginning to be able to accurately predict the course of the disease; and we are learning about the great varieties in this common cancer. We are still challenged to know why one man develops the disease while another man with nearly identical features and experience does not. We strive to uncover the key as to why one case of prostate cancer persists in an indolent state for years, while another appears rapidly and explodes to a fatal disease state almost overnight.

My most recent research effort has focused on metastatic prostate cancer in the lymph system. We have long known that the lymph



system is a convenient runway for the escape of active prostate cancer cells. Having experienced great success over 20+ years in treating even high-risk prostate cancer with our exquisite pinpoint radiation and seed implant combination, our Center has gained an international reputation as one that continues to push the envelope in regards to



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the tough cases. As a result, we find many men coming to us following some initial treatment elsewhere that was felt to be successful until a few years down the road. These are men who began to see gradual increases in PSA following years of stable low numbers.

Suspecting the presence of active prostate cancer cells in the lymph nodes presents a daunting challenge: How can we know where the cells had traveled? How many lymph nodes are involved? How can we prove

that cancer is present in the nodes? The traditional method of lymph node biopsy is problematic, as there are between 500 and 700 lymph nodes in the body and around 100 in the pelvis and groin alone.

As it so often happens, a few years ago a surprising and unexpected result occurred in a laboratory investigating a ferromagnetic nanoparticle called Feraheme® (ferumoxytol). This product had originally been used in the treatment of iron deficiency anemia. It was noted that when infused intravenously, MRI images of the patient revealed an interesting pattern. Lymph nodes containing prostate cancer cells could be identified and distinguished from those lymph nodes that do not contain prostate cancer cells. This was a “eureka” moment for prostate cancer researchers.

Although this discovery heralded great utility for prostate cancer research and treatment, it required extensive new research to prove its efficacy and to gain approval for its use by the FDA.

If you have read past issues of *Journey*, you will have read about the evolution of a test named USPIO (ultra-small super paramagnetic iron oxide) – this is the Feraheme scan test. In February 2018, Dr. Kaminski and I presented our research abstract reporting on the success of Feraheme

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Feraheme: New Tool

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in diagnosing lymph node-positive prostate cancer to two major radiation and clinical oncology research organizations. We are happy to report that at the ASCO (American Society of Clinical Oncology) Genitourinary meeting in San Diego, it was the most viewed abstract out of more than 1000, and it was voted the #1 Abstract and Presentation at the Clinical Interventional Oncology meeting in Hollywood, Florida. Our abstract, below, appeared on the front page of the CIO February 2018 newsletter.

Efficacy of Feraheme as Lymphatic Contrast Agent in Prostate Cancer

Dattoli MJ, Bravo SM, Kaplan DM, Hayes M, Osorio A, Dycus PM, Bostwick D, Kaminski JM

BACKGROUND: Ferumoxytol (Feraheme), a ferromagnetic nanoparticle with lymphotropic biokinetics, is delivered to lymph nodes via normal macrophages. MRI suppresses normal lymph nodes containing Feraheme. Objective is to validate the agent's safety and efficacy in finding lymph node positivity in prostate cancer (PCa).

METHODS: Nonrandomized prospective evaluation of 178 consecutive PCa patients (pts) at high risk for prostate lymph node spread were enrolled 2/13-3/15. All received IV Feraheme. 177 received infusion of 6mg/kg given over 20 minutes. One pt received 3 mg/kg infusion. T2 MEDIC and T2* sequence imaging of the abdomen and pelvis, performed 24 hours later.

Images were reviewed by 2 board certified radiologists with same interpretations, blinded to clinical and histo-path informa-

tion (pre-MRI TNM stage, PSA or Gleason score). Lymph nodes were deemed abnormal if they did not suppress after Feraheme infusion (group 1, 94 patients). Lymph nodes were deemed suspicious by MRI if suppressed and met usual size criteria with high signal intensity on DWI and decreased ADC map values and morphologic features (group 2, 84 pts). 83 group 1 pts had CT biopsies (77 pelvis, 6 retroperitoneum); 11 pts had open PLND. 382 lymph nodes were sampled. 76 group 2 patients had CT biopsies (73 pelvis, 3 retroperitoneum); 9 pts had open PLND. 340 lymph nodes were sampled. Rad-path correlation was performed. Resected nodes were stained; reviewed by a single pathologist with no knowledge of MRI findings. The histo-path results for each node were cataloged for later MRI comparison.

RESULTS: 90 group 1 pts (96%) proved metastatic PCa; 4 pts (4%) were normal. 68 group 1 pts (77%) contained malignant lymph nodes not meeting usual imaging criteria for malignancy. 39 group 2 pts showed metastatic PCa; 46 pts (53%) were normal. One group 2 pt experienced an allergic reaction with hives; infusion ceased at 3mg/kg; pt treated to full resolution with 50 mg IV Benadryl.

CONCLUSION: Feraheme can be used to evaluate for lymphatic dissemination of metastatic disease in PCa patients, with a lower limit of resolution of focal lymph node metastases of 2-3 mm. Improved resolution brings implications for therapeutic radiation planning in setting of newly diagnosed or recurrent/metastatic PCa. Toxicity was very acceptable at 6mg/kg. Feraheme may play a significant role as a lymphatic contrast agent in the early dissemination of lymphatic metastatic disease. ①

In October 2017, Dr. Dattoli was interviewed prior to these meetings by Laura LeBano, managing editor of *Vascular Disease Management – Interventional Oncology* 360.

Why did you decide to study ferumoxytol, and what sets your study apart from what is already in the literature?

In recent years, there has been an unprecedented expansion in the field of nanomedicine for both diagnostics and therapeutics. Current standard of care diagnostics for prostate cancer staging typically includes CT scans and bone scans, both of which are insufficient, leading to unacceptably high false positive and false negative rates, especially in high risk and recurrent disease. Previous studies using nanoparticle Ferumoxtran-10 (Combidex®) demonstrated substantially increased rates of detecting lymphatic dissemination when coupled with MR imaging, although Combidex is currently a non-FDA-approved reagent. Ferumoxytol (Feraheme®) is an FDA-approved ferromagnetic reagent with lymphotropic biokinetics similar to Combidex, which led to our interest in the current analysis.

Can you briefly describe your findings?

As expected, coupling Feraheme with MRI resulted in a 96% predictive accuracy in a cohort of patients comprised entirely of high-risk disease, with results comparable to previous studies using Combidex.

Tell me about something surprising you encountered while doing this research.

Resolution of focal lymph node metastasis down to 2-3 mm was established in patients undergoing nodal dissection, setting a new lower limit of resolution using any molecular or functional imaging currently available. Independent of this study, patients having recurrent disease and low PSAs (<1ng/ml) have also benefited with Feraheme detection of malignant lymph nodes down to 2-3 mm.

How might your findings eventually affect clinical practice?

CT scans and bone scans must be challenged as tools for staging in patients having high risk and recurrent disease. The inherent problem is the increased cost associated with advanced MRI/Feraheme imaging. Meanwhile, this imaging coupled with Sodium Fluoride F-18 PET would arguably be the most accurate staging possible, although F-18 PET adds even further cost. This increased cost, however, must be weighed against the poor staging associated with standard methods, the latter potentially leading to inappropriate treatment and increased future costs. Results using other advanced diagnostics, especially PSMA-PET scans, are promising, although also at increased cost when compared to current standard diagnostic testing.

What are your plans for further studies?

In view of the absence of toxicities at Feraheme infusions of 6mg/kg, along with increased rate of lymph node detection when compared to currently used diagnostics, we look forward to others duplicating our results.

What are you hoping that attendees take away from your presentation?

The improved accuracy of staging using MRI/Feraheme imaging could have significant therapeutic implications, allowing for individual tailoring of treatment in the setting of high risk and recurrent prostate cancer, which is simply not possible with current staging methods. ❶

Lymph Node-Positive Prostate Cancer

LATEST BOOKLET IN OUR SERIES UNDERSCORES A PROGRESSIVE APPROACH.

The latest addition to the *Prostate Cancer Essentials for Survival Series* is timely, coming on the heels of the release of “Efficacy of Feraheme® as Lymphatic Contrast Agent in Prostate Cancer” (February 2018). As noted in the introduction of the Feraheme article (page 4), much of the current prostate cancer research today is focusing on the spread of disease through the lymph system.

This new booklet underscores our progressive thinking in considering many instances of lymph node-positive prostate cancer to be “curable.” While most prostate cancer specialists throw in the towel when presented with a case of metastatic disease in the lymph nodes, our approach is the same as that used when facing metastatic breast cancer, or colo-rectal and other cancers, in the lymph nodes. If those cancers are aggressively treated, why shouldn’t metastatic lymph node-positive prostate cancer be treated aggressively as well?

The first challenge comes from the fact that there are hundreds of lymph nodes in close proximity to the prostate gland. The traditional method of biopsying each node to find cancer would be an invasive nightmare.

Identifying just which nodes are harboring active prostate cancer cells has always been a daunting task – until now. In the past decade, several diagnostic breakthroughs have offered progress in discerning where the cancer cells may have traveled. For a while, Dr. Jelle Barentsz, of The Netherlands, was leading the charge with developing and

offering Combidex® screening for metastatic prostate cancer. Drs. Dattoli and Sorace sent many men to his clinic in Nijmegen for the diagnostic scan. When the FDA failed to approve the drug used in the scanning process for use in the United States, the company that manufactured it went out of business.

Leading-edge technology research involving nanoparticle science and advanced imaging continued, however, and it has now made locating these lymph nodes possible – with accuracy to a degree that makes individual lymph node biopsies unnecessary. And you don’t have to leave the country to take advantage of it!

All prostate cancer patients should be aware of the potential for their disease to advance to the lymph nodes at some point, even many years after “successful” treatment. This is why continued vigilance with regular PSA tests is so important. As soon as an upward tick in PSA is noted, we suggest a consultation to determine what is going on. If there is a suspicion of persistence of disease, the sooner it can be addressed, the better.

If you are interested in receiving a copy of this new booklet, just make a notation on the enclosed donation envelope and we will be happy to send you a copy. ①

