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CLINICAL IMAGING

Lymphotropic nanoparticle-enhanced magnetic resonance imaging (LNMRI) identifies occult lymph node metastases in prostate cancer patients prior to salvage radiation therapy☆

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Abstract

Twenty-six patients with prostate cancer status post-radical prostatectomy who were candidates for salvage radiation therapy (SRT) underwent lymphotropic nanoparticle enhanced MRI (LNMRI) using superparamagnetic nanoparticle ferumoxtran-10. LNMRI was well tolerated, with only two adverse events, both Grade 2. Six (23%) of the 26 patients, previously believed to be node negative, tested lymph node positive by LNMRI. A total of nine positive lymph nodes were identified in these six patients, none of which were enlarged based on size criteria.

Keywords: Nanoparticle MR imaging; Ferumoxtran-10; Lymph nodes; Metastases; Salvage radiation therapy

1. Introduction

Patients with prostate cancer can have a heterogeneous clinical course. In every stage of the treatment of prostate cancer, appropriate patient selection is critical to maintaining high efficacy while decreasing side-effects. A good example of this principle is in the area of salvage radiation therapy (SRT) after radical prostatectomy (RP). Within 5 years of RP, approximately 20–40% of men will have prostate-specific antigen (PSA) recurrence (also called biochemical recurrence), accounting for approximately 30,000 men per year in the United States [1–3]. Many of these patients go on to receive radiation therapy to the prostate bed [4]. Unfortunately, treatment outcomes are suboptimal, with 5-year PSA progression free rates of approximately 35% [5,6].

The efficacy of SRT after RP as a potentially curative treatment depends upon the pattern of recurrence [7]. Patient selection for SRT has focused on imaging modalities that indicate lymph node and distant metastases and clinicopathologic features that are correlated with distant failure. Conventional magnetic resonance imaging (MRI) is able to provide excellent anatomic detail, but it is relatively insensitive for

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detecting pelvic lymph node metastases. However, this sensitivity is improved dramatically with the use of lymph node targeted magnetic nanoparticles (LNMRI). Prototypic, lymph node avid nanoparticles have a monocrystalline, inverse spinel, superparamagnetic iron oxide core containing a dense packing of dextrans to prolong their time in circulation and are avidly taken up by macrophages in lymph nodes [8,9]. Disturbances in lymph flow or nodal architecture caused by metastases lead to an abnormal pattern of accumulation of the nanoparticles within lymph nodes that is detectable by MRI and is independent of the size or location of the lymph nodes [10]. Our group has previously performed a clinical trial to assess the efficacy of LNMRI in nonmetastatic prostate cancer, comparing it to careful node-by-node histopathological analysis [11]. LNMRI had excellent test characteristics (96.4% sensitivity and 99.3% specificity) when considering lymph nodes with a short axis diameter of 5–10 mm.

The selection of appropriate patients for SRT after RP is critical to maximizing the benefits while minimizing the toxicity of this procedure. Given our previous experience with LNMRI in detecting prostate cancer nodal metastases, we performed a pilot study of LNMRI in subjects with a rising PSA post-RP to identify whether LNMRI can help select patients for SRT. In this report, we present the initial data from this prospective clinical trial.

2. Materials and methods

2.1. Patients

Eligible patients had histologically confirmed adenocarcinoma of the prostate and had undergone a prior RP. Patients who had prior lymphadenectomy had to be pathologically N0. At the time of entry into the study, patients were required to have a PSA between 0.2 and 4.0 ng/ml with no evidence of disease outside the prostatic fossa [as evidenced by a negative bone scan and a negative pelvic computed tomography (CT) scan within 16 weeks of study entry]. Eligible patients could not have received androgen deprivation therapy or prior radiation therapy to the prostate. All patients provided written informed consent. The study was approved by our institutional review board in accordance with international standards of good clinical practice.

2.2. Study procedures

Eligible patients had a baseline pelvic MRI, followed by a 30-min intravenous infusion of ferumoxtran-10 (Combidex, AMAG Pharmaceuticals, Cambridge, MA, USA) at a dose of 2.6 mg Fe/kg. One day later a repeat pelvic MRI (LNMRI) was performed with identical parameters. Patients with a positive LNMRI also underwent an image-guided biopsy if technically feasible, i.e., if the LN in question was of sufficient size and was anatomically accessible. Patients were then followed prospectively.

MR imaging was performed on a 1.5-T clinical imaging system (Signa, GE Healthcare, Milwaukee, WI, USA) using a pelvic phased array coil. The MR protocol included T2-weighted fast spin-echo, T2* (T2-star) gradient-echo and T1 2D/3D gradient echo sequences in different planes. The scans were performed to include the anatomical pelvis extending from the level of the aortic bifurcation to the pubic symphysis.

2.3. Image analysis

Analysis of the LNMRI has been previously described [11]. In brief, nodes were considered malignant when one of the following three criteria were present on the T2*-gradient echo sequences 24 h after the administration of ferumoxtran-10: a decrease in signal intensity of less than 30%; a heterogeneous signal, discrete focal defects or both; and nodes with a central area of hyperintensity (excluding the fatty hilum) but a peripheral decrease in signal intensity. Two radiologists reviewed all images independently and a third radiologist resolved discrepancies.

2.4. Outcomes

The primary objective of the study was to evaluate the number of patients with LNMRI-defined lymph node involvement. Secondary outcomes included the safety of ferumoxtran-10 infusion and estimation of the progression free survival in these patients after SRT. Post-LNMRI therapy was not dictated by the protocol.

2.5. Statistical analysis

This was a prospective cohort pilot study. All statistical analyses were descriptive. Patients were summarized as *n* (%) and median (range) of values. PSA doubling time (PSADT) was calculated as the natural logarithm of 2 divided by the slope from a linear regression of the natural log of PSA values over time (months). For this calculation, we used all PSA values $\geq$0.2 ng/ml (when PSA became detectable) post-RP and prior to study entry. All PSA values obtained were over a minimum period of 3 months and separated in time by at least 4 weeks between measurements if there were only three PSAs. The PSA values needed to follow a rising trend but did not need to be consecutively rising. We only report results for the primary analysis; estimation of the progression free survival is pending longer follow-up.

3. Results

3.1. Baseline characteristics

From December 2005 until May 2006, 26 patients were enrolled onto this trial. The median age at the