Intravenous Ferumoxtran-10 MRI: a cellular MR contrast agent with high clinical potential for the detection of small metastases

Jelle Barentsz

Department of Radiology, Radboud University Medical Center, Nijmegen, The Netherlands

Introduction

Pelvic lymph node metastases have a significant impact on the prognosis of patients with malignancies. In prostate cancer, for example, even micro metastases in a single node rule out surgical cure by the available treatment protocols. For bladder cancer, lymph node metastasis is also significant and more than five lymph node metastases or extra capsular growth precludes curative surgical treatment. Thus, the status of the lymph nodes largely dictates the management of the primary tumour.

Surgical open pelvic lymph node dissection (PLND), which is considered to be the only reliable method for assessing lymph node status, is an invasive procedure associated with potential complications and side effects. A noninvasive, reliable method for detecting and staging nodal metastasis would reduce unnecessary surgery. Routine cross-sectional imaging modalities like CT and MRI lack the desired sensitivity in identifying metastases as they largely rely on size criteria only, and small metastases in normal size nodes can be missed. Moreover, differences in signal intensity on MR images between normal and cancerous nodes as well as gadolinium enhancement have also proven to be unreliable.

Although very promising in metastatic lung cancer, the role of ^{18}FDG PET-scanning is limited in the urinary tract region, as ^{18}F-fluorodeoxyglucose accumulates in the urinary bladder and kidneys. This makes an evaluation of metastases at this site difficult. Also in various tumours like prostate and bladder cancer, this method is further limited by its low uptake in metastatic nodes. Although the sensitivity of ^{18}FDG PET is slightly better (67%) compared to those of CT and unenhanced MR imaging, it is not high enough to replace pelvic lymph node dissection.

Ultra small super paramagnetic iron oxide particles (ferumoxtran-10) with a long plasma circulation time have been shown to be suitable as a MR contrast agent for intravenous (IV) MR lymphangiography [1,2].

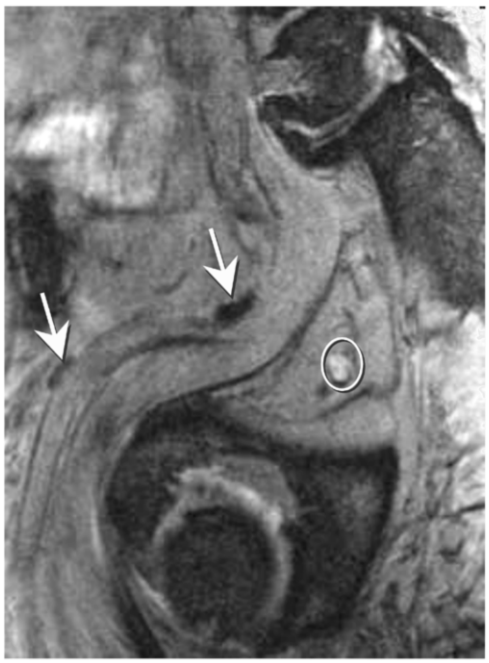

Fig. 1. Patient with prostate cancer. Fe-sensitive (T2*-weighted) MR images 24 hours post IV administration of ferumotran-10 show normal size black nodes (arrows), and normal size (6 mm) white node (circle). Lymphadenectomy showed the black nodes to be normal (filled with iron loaded macrophages) and the white node to be metastatic.

After IV injection, the ferumoxtran-10 particles are taken up by macrophages are transported to the interstitial space and from there through the lymph vessels to the lymph nodes (Fig. 1). Thus this contrast agent is cell specific (for macrophages). Once within normally functioning nodes, the intracellular ferumoxtran-10 within the macrophages reduces the signal intensity of normal node tissue due to T1 and T2*- susceptibility effect of iron oxide and produces a signal drop or negative enhancement. In areas of lymph nodes that are involved with malignant cells, macrophages are replaced by cancer cells. Therefore, in these areas there is no uptake of the ferumoxtran-10 particles. In addition, due to increased vascular

permeability and increased diffusion in cancer tissue, there is minimal leakage of ferumoxtran-10 particles into the extracellular space of malignant metastatic areas, which produces a low local concentration and non-clustering of ferumoxtran-10 particles at these sites [3]. Through their T1-relaxivity this can induce an increase in signal intensity on T1-weighted images, producing positive enhancement [4]. Thus the ability of post ferumoxtran-10 MRI to identify metastatic areas in the lymph nodes depends primarily on the degree of uptake of ferumoxtran-10 by the macrophages in normal lymph node tissue and the leakage of ferumoxtran-10 particles in the metastatic area itself. Twenty-four hours after IV injection of ferumoxtran-10, normal lymph node and malignant tissue have different signal intensity on MR images and could result in the detection of metastatic deposits in normal-size nodes (Fig. 1) [4].

Clinical value

When using high resolution MR-technique small metastases can be prospectively recognized in small (3–10 mm) size lymph nodes [5]. These small lymph nodes would be considered to be benign in plain MRI or CT examinations. In addition, hyperplastic enlarged nodes can be correctly recognized as non metastatic, based on their low signal intensity resulting in improved sensitivity (~90%), with remaining equal high specificity (~95%) in various tumours [5–8]. In prostate cancer contrast-enhanced CT and conventional MRI have a low sensitivity (40%), which is improved to 100% on a patient level and to 90% on a nodal level [5].

In urinary bladder cancer 10/12 metastatic normal size lymph nodes were detected with ferumoxtran-10 MRI only and resulted in improved sensitivity (from 76% to 96%), whereas the specificity did not change significantly (from 99% to 95%) [6]. When using ferumoxtran-10 MRI patients may be reliably selected for cystectomy, prostatectomy or radiotherapy without the need for invasive and costly procedures such as open and laparoscopic PLND. Furthermore, if the node is >5 mm the presence of malignancy can be confirmed by image guided biopsy, and thus also avoid PLND in these patients. This was the case in 5/80 (6%) patients in the study of Harisinghani & Barentsz and all 5 nodes were confirmed positive. Finally with Ferumoxtran-10 MRI, all pelvic nodes can be visualized. Harisinghani & Barentsz showed that in 11% of their patients, thanks to ferumoxtran-10 MRI, metastatic nodes were detected that were outside the classical field of lymph node resection [5]. In patients with a suspicion for a recurrence, e.g. in patients with a PSA-relapse after treatment, this technique may show metastatic nodes when they still are small, thus allowing earlier adequate therapy. Finally, identifying small pathologic nodes will facilitate more appropriate use of sophisticated radiation therapy, for example when positive nodes are accurately identified, precise intensity modulated radiotherapy can be performed. This results in an increased dose on the malignant nodes and a decreased dose, with reduced side-effects, on normal tissues.

In head and neck cancers 25% lymph nodes are positive despite negative preoperative imaging (contrast CT and US biopsy) as metastatic nodes are small (5–10 mm). In addition PET is nonspecific and does not provide anatomic location. Therefore, extensive surgery -radical neck dissection- is performed in virtually all patients to result in cosmetic deformity and a complication rate of 36–54%. However, Mack and colleagues reported that ferumoxtran-10 MRI was accurate in 26/27 (96%) patients, which resulted in reduced extent of surgery in 26% of patients [7].

Early results with ferumoxtran-10 MRI in breast cancer show a sensitivity of 78%, a specificity of 96% and a negative predictive value of 97% [8]. The sentinel lymph node procedure in breast cancer has a 3% to 10% false negative rate, furthermore, positive internal mammary lymph nodes are missed in 17%. Finally, the sentinel lymph node is the only positive node in 61% lymph node positive patients These patients all undergo axillary dissection, with subsequent high rate of clinically significant lymph edema. Thanks to its high negative predictive value, in patients with a negative ferumoxtran-10 MRI the axillary dissection may be potentially avoided. Further studies are under way to validate this statement.

Summary

Using a macrophage, specific MR-contrast agent and high resolution MR imaging allows the detection of small and otherwise undetectable lymph node metastases in patients with cancer. This has an important clinical impactions, as the diagnosis will be more precise and less invasive to obtain. Subsequently this will reduce morbidity and health care costs. However, solid knowledge of sequence parameters and planes; lymph node anatomy; appearance of normal and abnormal nodes; and other pitfalls is essential when using this technique. A very important role for education by expert radiologists, MR-manufacturers, and contrast agent companies is therefore also required.

References

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