MRI with a lymph-node-specific contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study

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Summary

Background **In patients with prostate cancer who are deemed to be at intermediate or high risk of having nodal metastases, invasive diagnostic pelvic lymph-node dissection (PLND) is the gold standard for the detection of nodal disease. However, a new lymph-node-specific MR-contrast agent ferumoxtran-10 can detect metastases in normal-sized nodes (ie, <8 mm in size) by use of MR lymphoangiography (MRL). In this prospective, multicentre cohort study, we aimed to compare the diagnostic accuracy of MRL with up-to-date multidetector CT (MDCT), and test the hypothesis that a negative MRL finding obviates the need for a PLND.**

Methods **We included consecutive patients with prostate cancer who had an intermediate or high risk (risk of >5% according to routinely used nomograms) of having lymph-node metastases. All patients were assessed by MDCT and MRL, and underwent PLND or fine-needle aspiration biopsy. Imaging results were correlated with histopathology. The primary outcomes were sensitivity, specificity, accuracy, NPV, and PPV of MRL and MDCT. This study is registered with ClinicalTrials.gov, number NCT00185029.**

Findings **The study was done in 11 hospitals in the Netherlands between April 8, 2003, and April 19, 2005. 375 consecutive patients were included. 61 of 375 (16%) patients had lymph-node metastases. Sensitivity was 34% (21 of 61; 95% CI 23–48) for MDCT and 82% (50 of 61; 70–90) for MRL (McNemar's test p<0·05). Specificity was 97% (303 of 314; 94–98) for MDCT and 93% (291 of 314; 89–95) for MRL. Positive predictive value (PPV) was 66% (21 of 32; 47–81) for MDCT and 69% (50 of 73; 56–79) for MRL. Negative predictive value (NPV) was 88% (303 of 343; 84–91) for MDCT and 96% (291 of 302; 93–98) for MRL (McNemar's test p<0·05). Of the 61 patients with lymph-node metastases, 50 were detected by MRL, of which 40 (80%) had metastases in normal-sized lymph nodes. The high sensitivity and NPV of MRL imply that in patients with a negative MRL, the chance of positive lymph nodes is less than 11/302 (4%).**

Interpretation **MRL had significantly higher sensitivity and NPV than MDCT for patients with prostate cancer who had intermediate or high risk of having lymph-node metastases. In such patients, after a negative MRL, the post-test probability of having lymph-node metastases is low enough to omit a PLND.**

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Introduction

If pelvic lymph-node metastases are present in a patient with prostate cancer, curative treatment by radical prostatectomy or radical radiotherapy is no longer the optimum treatment.[1] Non-invasive imaging with CT and MRI might be used to detect lymph-node metastases, but the sensitivity of these techniques is only 36%.[2] The specificity of these techniques is about 82%.[3] Therefore, CT and MRI imaging are only used before fine-needle aspiration biopsy (FNAB) in patients at high-risk of (ie, >45% risk of having metastases) to confirm the presence of metastases in enlarged lymph nodes.[4] However, imaging for these patients is only cost effective if the pre-test probability of positive lymph nodes is at least 45%,[2] which only occurs in around 5–10% of patients.[4] Additionally, FNAB is false-negative in about 40% of such patients.[5] Therefore, invasive diagnostic pelvic lymph-node dissection (PLND) is often done without imaging.

Because of its morbidity and high cost, PLND tends to be omitted if tables or routinely used tables or nomograms[6–8] suggest that the chance of detecting positive lymph nodes with this technique is less than 5%.[9–12] According to these nomograms, patients with a serum prostate-specific antigen (PSA) of over 10 ng/mL, a Gleason score of over 6, or a stage T3 tumour (according to the Tumour, Nodes, and Metastases [TNM] staging system) defined by digital rectal examination (DRE), have a 5–65% risk of lymph-node involvement.[6–9] Therefore, in these patients, a diagnostic PLND is done routinely.

With the introduction of multidetector CT (MDCT) and of a lymph-node-specific MR intravenous contrast agent called ferumoxtran-10 (an ultra-small particle of iron oxide [USPIO]), the potential diagnostic usefulness of CT and of MRI has increased. In this report, we refer to MRI as magnetic resonance lymphangiography (MRL). Initial studies in academic centres with extensive experience have

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	Repetition time, ms	Echo time, ms	Bandwidth, Hz/pixel	Acquisitions, n	Slice thickness, mm	Interslice distance, %	Matrix*, mm
Axial T1/PD-weighted sequence, turbo or fast spin echo	1800–2200	9–12	195	29 slices	5	≤10	230x512
Axial T2*-weighted sequence; two-dimensional gradient echo with flow compensation; flip angle (α)=30°	1400–1800	15	78	29 slices	5	≤10	230x512
Obturator T1/PD-weighted sequence, turbo or fast spin echo, parasagittal plane along iliac vessel axis	1800–2200	9–12	195	2x13 slices	3	≤10	230x512
Obturator T2*-weighted sequence; two-dimensional gradient echo with flow compensation; flip angle (α)=30°	1400–1800	15	78	2x13 slices	3	0	230x512

PD=proton density. All sequences had a 225x300 mm field of view, and included images from aortic bifurcation to the pelvic floor by use of cranial and caudal inflow presaturation and spatial presaturation on anterior abdominal wall. *Matrix is the number of acquired lines in X and Y directions.

***Table 1*: Pulse sequences used to obtain MR images**

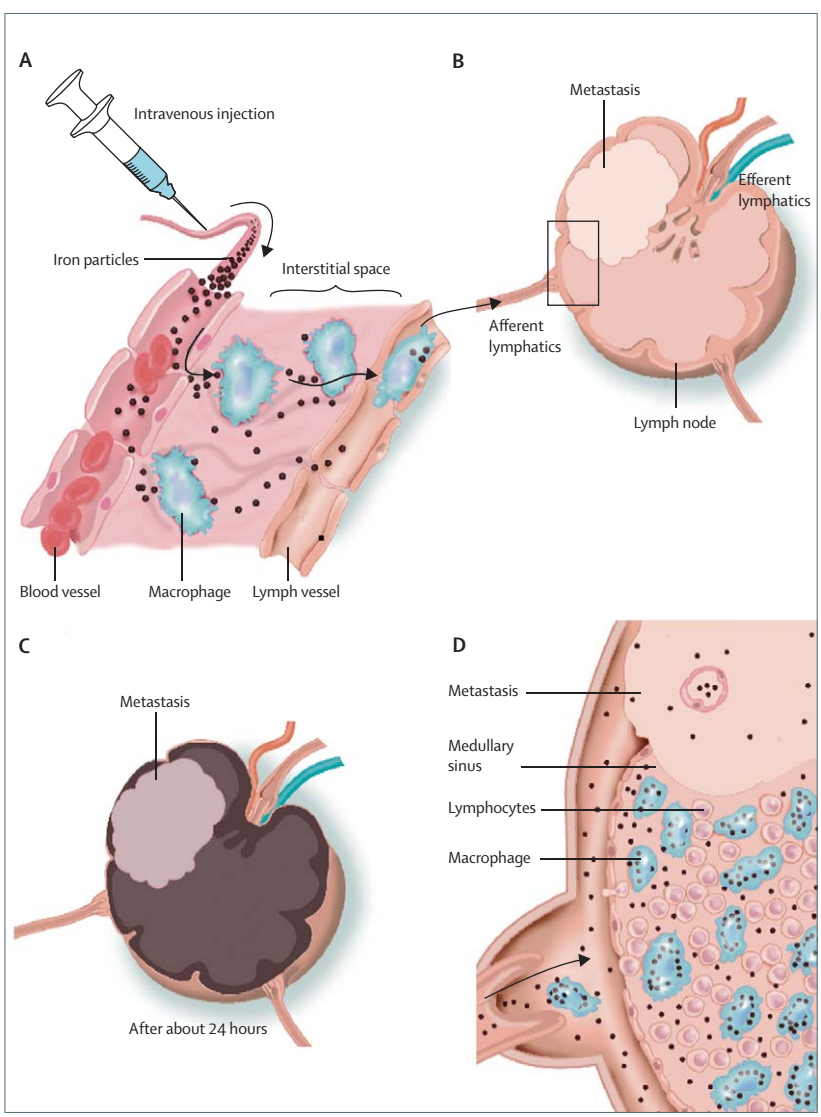

***Figure 1*: Mechanism of ferumoxtran-10**
(A) Infused iron-particles slowly extravasate from the vascular to the interstitial space and are internalised by macrophages. (B) and (C) Iron-loaded macrophages are transported to lymph nodes via lymphatic vessels and accumulate in normal-sized lymph node tissue. These iron-loaded macrophages cause low signal intensity on T2*-weighted MR image. Box in B shows area depicted in D. (D) Disturbances of lymph flow or nodal architecture by metastases leads to less macrophages, depicted at MR imaging by higher signal intensity.

shown that MRL has a high negative predictive value (NPV) for ruling out lymph-node metastases.[13–18] But, to our knowledge, no multicentre trials have studied one single disease entity. Harisinghani and colleagues[17] reported a sensitivity of 91%, a specificity of 98%, and an NPV of 98% for patients with prostate cancer. These findings suggested that after a negative MRL, the probability of lymph-node involvement is only 2%. Therefore, because of its high sensitivity and high NPV, MRL can be used to exclude reliably lymph-node metastases. This new approach could mean a paradigm shift. The main role of imaging would no longer be to detect and confirm metastases in large lymph nodes in high-risk patients, but to ensure the absence of metastases in patients at intermediate to high risk (ie, >5% risk) of having metastases. Also, there would be a change from having a high accuracy for a positive MRL result to a high accuracy for a negative MRL result. However, for the successful implementation of this new approach, the promising results of MRL that have been achieved in academic centres need to be replicated in clinical practice. Therefore, we aimed to ascertain the clinical effectiveness of MRL compared with MDCT in the detection of lymph-node metastases in patients with prostate cancer, and to test the hypothesis that a negative MRL finding can obviate the need for a PLND.

Methods

Patients and procedures

Between April 8, 2003, to April 19, 2005, 375 consecutive patients with biopsy-diagnosed prostate cancer were enrolled in to this prospective multicentre cohort study. Patients were enrolled from four university medical centres in the Netherlands (Radboud University Nijmegen Medical Centre, Radboud [n=106], University Medical Centre Amsterdam, Amsterdam [n=16], University Medical Centre Maastricht, Maastricht [n=9], Erasmus Medical Centre, Rotterdam [n=3]) and seven community hospitals (Catharina Hospital Eindhoven, Eindhoven [n=110], Hospital Zeeuws-Vlaanderen, Terneuzen [n=31], Antoni van Leeuwenhoek Hospital, Amsterdam [n=19], Rode Kruis Hospital, The Hague [n=15], Rijnstate Hospital Arnhem, Arnhem [n=9], Leyenburg Hospital, The Hague [n=9], and Canisius Wilhelmina Hospital, Nijmegen

[n=48]). Patients from Canisius Wilhelmina Hospital, had imaging at Radboud University Nijmegen Medical Centre. Inclusion criteria were: serum PSA concentration of over 10 ng/mL, or Gleason score of over 6, or T3 tumour defined by DRE; thus patients had a risk of lymph-node metastases greater than 5% according to routinely used nomograms. Mean age of the patients was 67 years (range 46–83), median serum PSA was 15 ng/mL (2–260), and median Gleason score was 7 (3–10). This study conforms to STARD guidelines of diagnostic accuracy studies. Institutional Review Board approval was obtained for all centres. Written informed consent was obtained from all patients.

All patients were scheduled for pelvic MDCT, MRL, and PLND. MDCT and MRL were done within 1 week of each other. MRL and PLND had to be done within 8 weeks of each other.

MDCT scanners were used for all CT assessments. Use of at least a two-detector scanner was needed for inclusion and the slice thickness used was 3 mm with 1 mm overlap. Images of the abdomen were obtained after administration of oral and 150 mL intravenous iodinated non-ionic contrast agent. Patients were scanned from the aortic bifurcation to the pubic symphysis.

MRI images were obtained on 1·5T imaging systems (Sonata/Symphony, Siemens, Erlangen, Germany; Gyroscan/Intera, Philips, Eindhoven, Netherlands; or Horizon, GE Medical Systems, Milwaukee, WI, USA) by use of pelvic phased array coils. T2*-weighted gradient echo (GRE) and T1-weighted fast-spin echo (FSE) MRI images were acquired from the entire pelvis, extending from the aortic bifurcation to the pubic symphysis within 24–36 h after intravenous drip infusion of ferumoxtran-10 (Sinerem, Guerbet, France). The T1-weighted and T2*-weighted MRI images were each acquired in two planes by use of identical position and resolution parameters to enable comparison. Image planes were a semi-sagittal (obturator) plane, which is a plane parallel to the psoas muscle, and an axial plane. The T1-weighted images were insensitive, and the T2*-weighted images were sensitive to the iron-containing contrast agent. Additionally, a three-dimensional T1-weighted GRE sequence was applied to allow exact anatomical localisation of the lymph nodes in relation to the vessels. The scan protocol is shown in table 1. All adverse events were recorded.

Image analysis

All findings were recorded on a specially designed electronic Case Record Form (TASK24, Nieuwegein, Netherlands). This form also consisted of a help file to instruct investigators. All images were analysed on-site at each hospital by the responsible radiologist by use of soft-copy reading at an electronic workstation with multiplanar reconstruction capability. At the start of the study only the primary investigator (JB) had substantial (8 years) experience with MRL. Anonymised MDCT images were read independently from the MRL images in random order. In addition to instructions in the Case Record Form help file, each radiologist from the individual centres received training before the study in reading MRL images. Image quality for the first ten MRL assessments at each centre was assessed by the principal investigator. During the study, the quality of MDCT and MRL images was reviewed every 3 months (by JB and RAMH).

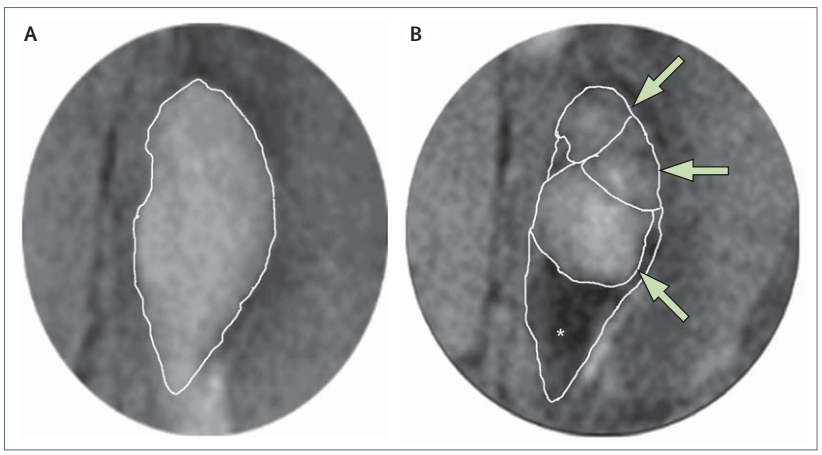

***Figure 2*: Image of a partially positive lymph node**
Arrows show lymph node and metastases. (A) T2*-weighted MR image with partial metastatic lymph node before infusion of ferumoxtran-10. Metastases and normal nodal tissue cannot be discriminated. (B) MRL image, shows low signal at caudal side of node (*), and three areas of high signal (arrows). Histopathology showed low signal area to be normal nodal tissue, and white areas to be metastases.

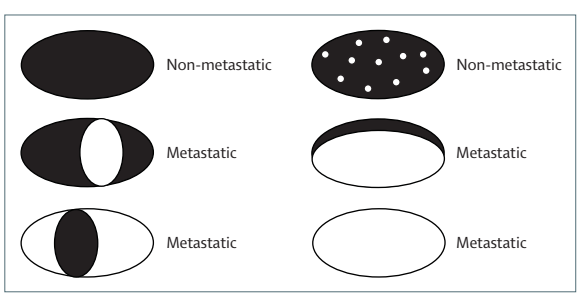

***Figure 3*: Classification of lymph nodes with MRL on T2*-weighted gradient echo images**

Lymph nodes were classified on the MDCT images based on size, according to existing criteria.[5] A lymph node was deemed malignant if its short axis exceeded 10 mm for an oval node or 8 mm for a round lymph node. Only positive lymph nodes were reported in the Case Record Form. Lymph nodes were classified on MRL based on their signal intensity on the iron-sensitive T2*-weighted sequences. The working mechanism of MRL is explained in figure 1. A lymph node was deemed healthy if it had predominant low signal intensity, suggesting the presence of iron-containing macrophages, and deemed metastatic if it showed a local area or total high signal (figures 2 and 3).[16] A patient was deemed positive when one or more metastatic lymph nodes were detected. The location and size of the metastatic lymph nodes on MDCT and MRL were independently recorded on a map embedded within the Case Record Form. A merged map that combined the MRL and MDCT results was provided to the surgeon before the PLND.

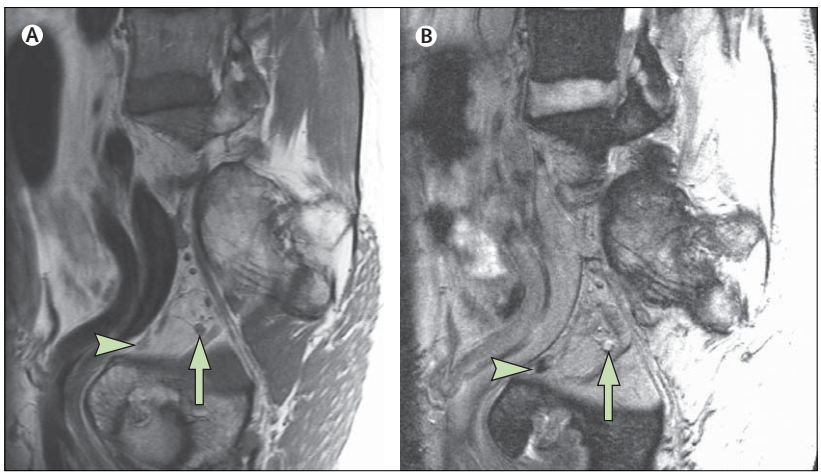

***Figure 4*: MRL images in the obturator plane**
(A) T1-weighted MRL image shows round 5·5 mm lymph node ventral to internal iliac vessels (arrow). This lymph node is benign according to its size and shape. There is another small, normal size (6 mm) lymph node in the obturator fossa (arrowhead). (B) T2*-weighted MRL image shows that the lymph node ventral of the internal iliac vessels (arrow) is white. This node is outside the regular PLND area. Based on the MRL images the PLND was extended and confirmed a malignant node. The node in the obturator fossa (arrowhead) is black due to iron uptake and was benign at histopathology following PLND.

	Prevalence 61/375 (16%)	
	MDCT	MRL
Sensitivity (%) (95% CI)	21/61 (34) (23–48)	50/61 (82) (70–90)
Specificity (%) (95% CI)	303/314 (97) (94–98)	291/314 (93) (89–95)
PPV (%) (95% CI)	21/32 (66) (47–81)	50/73 (69) (56–79)
NPV (%) (95% CI)	303/343 (88) (84–91)	291/302 (96) (93–98)
Post-test probability of false-negative result (%)	40/343 (12)	11/302 (4)

MDCT=multidetector CT. MRL=magnetic resonance lymphangiography.

***Table 2*: Results of MDCT and MRL in all centres**

Surgery

140 of 375 patients had open PLND and 221 patients had laparoscopic PLND. The choice between open and laparoscopic surgery was based on local experience and preference of the urologists. 30% more nodes were removed with open PLND than laparoscopic surgery, nonetheless, there was no difference in sensitivity or specificity between the two procedures (data not shown). 14 of 375 patients had lymph nodes that were accessible for biopsy and at least 6 mm in size and, therefore, underwent a FNAB, all with a positive finding. PLND was omitted in these patients.

PLND consisted of a routine limited (obturator) lymph-node dissection, including resection of the lymph nodes and fibro-fatty tissue along the external iliac vein and along the pelvic side wall, caudal to the femoral canal with the superior border being the bifurcation of the common iliac artery. The posterior border was the obturator nerve. However, in 15 patients the dissection was more extensive because it was guided by the findings of the MRL only, suggesting that there were positive lymph nodes outside the field of the limited routine PLND (figure 4). All lymphatic tissue was sent for final pathology testing en bloc on a grid identifying their location.[12] The surgeon noted the location of the removed lymph nodes. Finally, lymph-node location ascertained at surgical resection was compared with MRL and MDCT. Patients were asked about adverse events verbally and by questionnaire.

Statistical analysis

Histopathology was the standard of reference, and all histopathology results were included in the Case Record Form. The primary outcomes sensitivity, specificity, accuracy, NPV, PPV, and the 95% CIs were calculated for MRL and MDCT. Additionally, McNemar's test was applied to MRL and MDCT with a confidence level of 95% (a difference of $p<0·05$ was deemed significant). This study is registered with ClinicalTrials.gov, number NCT00185029.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

No serious adverse events occurred after ferumoxtran-10 administration. Six patients (2%) reported low-back pain during infusion. The pain ceased after drip infusion was stopped. When the infusion was resumed after about 10 min, the pain did not recur. Other minor adverse events were: diarrhoea or abdominal cramps (n=9 [2%]), itching and urticaria (n=4 [1%]), and headache (n=2 [<1%]). No adverse events were reported with the CT contrast agent.

61 of 375 (16%) patients had lymph-node metastases. Sensitivity was 34% (95% CI 23–48) for MDCT and 82% (70–90) for MRL (McNemar's test $p<0·05$). Specificity was 97% (94–98) for MDCT and 93% (89–95) for MRL. Positive predictive value (PPV) was 66% (47–81) for MDCT and 69% (56–79) for MRL. Negative predictive value (NPV) was 88% (84–91) for MDCT and 96% (93–98) for MRL (table 2). Sensitivity and NPV for MRL were significantly better compared with those for MDCT (McNemar's test $p<0·05$ for both). Of the 61 patients with lymph-node metastases, 21 were detected by MDCT and 50 by MRL. Of the 50 patients who were detected by MRL, 40 (80%) had metastases in normal-sized lymph nodes that had short axes (ie, shorter than 8 mm; figure 5). MDCT was false-negative in 40 patients and MRL was false-negative in 11 patients. MDCT was false-positive in 11 patients and MRL was false-positive in 23 patients. The positive lymph nodes of 18 of the 61 (30%) lymph-node-positive patients were detected by MRL and located by extended PLND or FNAB outside of the routine surgical PLND area.

Three hospitals (data from Radboud University Nijmegen Medical Centre and Canisius Wilhelmina Ziekenhuis were combined) enrolled 295 of the 375 patients and the other

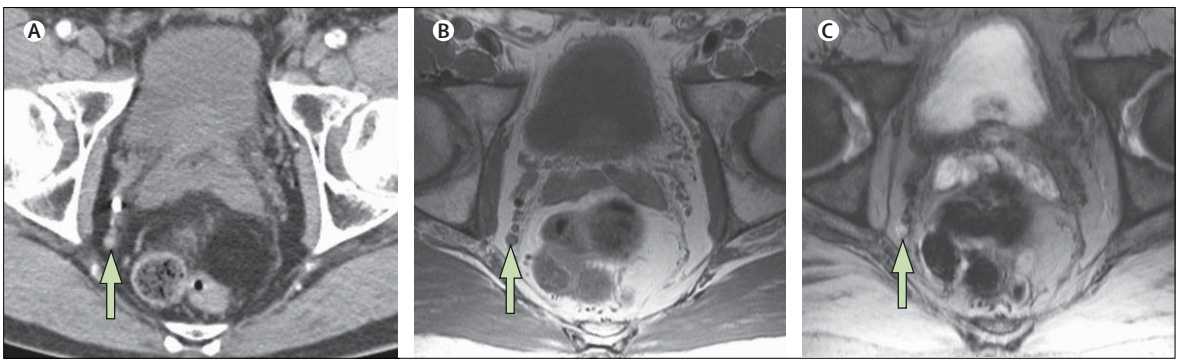

***Figure 5*: Axial CT and MRL images**
(A) No abnormal (enlarged) lymph nodes. (B) T1-weighted MRL image and (C) T2*-weighted MRL post image in the same patient. A normal-sized 6 mm lymph node is present in the internal iliac region (arrow). This node has high signal intensity on the T2*-weighted sequence and was malignant at histopathology.

seven hospitals enrolled 80 patients. None of these centres had technical difficulties. A sub-analysis of the MRL results from these two groups of hospitals was done (table 3). For the three major recruiting centres, sensitivity was 90% (95% CI 78–96), specificity was 94% (90–96), PPV was 75% (62–85), and NPV was 98% (95–99). For the remaining seven hospitals, sensitivity was 40% (14–73), specificity was 89% (78–96), PPV was 33% (11–65), and NPV was 91% (81–96). The sensitivity of the three major recruiting hospitals was significantly higher than that of the other seven (McNemar's test p<0·05). The main source of error in the seven hospitals was not technique-related, but because these hospitals had less time to undertake MR assessments and were inexperienced at interpreting them. The accuracy of the interpretation of the MDCT was equal between all the radiologists.

There were no substantial differences between the sensitivity, specificity, NPV, and PPV of the two inexperienced readers of the major recruiting hospitals and the experienced primary investigator (data not shown). In the seven low-recruiting hospitals, no region-to-region agreement could be made because of missing data in the pathology report. However, only four of ten of the patients with positive lymph nodes were recorded in these centres. In the three major recruiting centres, diagnoses of positive lymph nodes by MRL were confirmed by FNAB in 14 of 46 patients and by extensive PLND in 15 of 46 patients. Therefore, in these 29 patients, a-node-to-node agreement was obtained. In the remaining 17 patients, there was a correct region-to-region agreement in three regions: external iliac, obturator, and the combined internal/para rectal/common iliac/para aortic.

	Three experienced hospitals	Seven less experienced hospitals
Patients with MRL results, n	295	80
Sensitivity, n (%) (95% CI)	46/51 (90) (78–96)	4/10 (40) (14–73)
Specificity, n (%) (95% CI)	229/244 (94) (90–96)	62/70 (89) (78–96)
PPV, n (%) (95% CI)	46/61 (75) (62–85)	4/12 (33) (11–65)
NPV, n (%) (95% CI)	229/234 (98) (95–99)	62/68 (91) (81–96)
Post-test probability of false-negative finding (%)	5/234 (2)	6/68 (9)

***Table* 3: Results of MRL in experienced and less-experienced participating hospitals**

Discussion

To our knowledge, this is the largest prospective multicentre study that compares the performance of MRL with MDCT by use of PLND or positive FNAB as a standard of reference. Only minor adverse events were noted, the most severe was lumbar pain during infusion. The same adverse events have also been reported with other super paramagnetic iron particle agents. The mechanism behind this pain is still unexplained.[18–20] Our findings confirm that the safety profile of ferumoxtran-10 is good.[20–22]

The medical ethical committee and referring urologists did not allow a blind independent standard of reference, therefore, the study might have had some methodological flaws that make comparison with other studies difficult. Nonetheless, this study shows that the sensitivity and NPV of MRL are significantly higher than those of MDCT. The sensitivity of MDCT corresponds with the findings of single-slice CT as reported by Wolf and co-workers.[3] Due to its low sensitivity (34%) and NPV (88%), we have also shown that MDCT is of limited use in detecting and ruling out lymph-node metastases in patients with prostate cancer. This can be explained by the fact that MDCT relies on nodal size and shape as a diagnostic criterion.[5,23–26] Only round lymph nodes with a short axis larger than 8 mm and oval nodes with a short axis larger than 10 mm are deemed metastatic.[5,27–29] Because metastases in prostate cancer are mainly found in lymph nodes with a short axis smaller than 8–10 mm, the use of size and shape as criteria results in a low sensitivity of 36–40%.[3] Oyen and colleagues achieved a sensitivity of 78% with only CT staging of lymph nodes, with a lower threshold for size, combined with CT biopsy. However, this finding could not be reproduced,[29] possibly because of experience and expertise of that group.

The sensitivity of MRL in this study is in the range of other MRL studies done with iron-containing nanoparticles (82–100%).[16–18,30–33] Harisinghani and co-workers[17] used the same agent as us and reported a sensitivity of 100% on a

patient-to-patient basis (n=80). On a node-to-node basis, they assessed 334 lymph nodes and noted a sensitivity of 91%, which is slightly higher than our finding. The reason for this difference might be that they used expert readers. Our multicentre study was designed to assess the success of MRL in general practice, where it would be interpreted by radiologists who had never interpreted MRL before. In the three hospitals in which in each at least 30 patients were included, the findings were as accurate as (sensitivity 90%) those reported by Harisinghani and colleagues.[17]

Because our cohort was skewed towards these three institutions, the findings cannot be generalised for all hospitals. In the three main recruiting centres, MRL was easily implemented. In the other seven centres, implementation of MRL was difficult, as shown by the low inclusion numbers. Consequently, the radiologists in these centres had little experience with MRL (they assessed fewer than 20 patients), which might explain the significantly lower sensitivity (40%) noted for MRL in those centres.

The absence of substantial differences between sensitivity, specificity, NPV, and PPV of the two inexperienced readers of the major recruiting centres and the experienced primary investigator implies that a trained and dedicated radiologist could learn MRL, and emphasises the need for experienced radiologists to interpret MRL studies. MRL should only be implemented in specialised centres. In the main recruiting centres, MR scanners of two different manufacturers were used (Philips in Zeeuws-Vlaanderen Hospital and Catharina Hospital Eindhoven [n=141/295] and Siemens in Canisius Wilhelmina Hospital and Radboud University Nijmegen Medical Centre [n=154/295]), but there were no differences in the results between these scanners (data not shown).

The number of false-positive lymph nodes in our study (n=23) was high compared with that in other studies. This was not because of prostatitis, in which prostate lymph nodes are enlarged but are still reactive, ie, these nodes will have iron-containing macrophages. Therefore, in the case of prostatitis, lymph nodes will be black and will subsequently be diagnosed as healthy.

The high NPV and sensitivity imply that patients with a negative MRL result have less than a 4% chance of having positive lymph nodes. Usually, PLND is not done if the risk of lymph-node involvement is less than 5%.[9,10,12,34] This suggests that a PLND can be omitted in patients with a negative MRL who have an intermediate or high risk of lymph-node metastases according to tables or nomograms. Therefore, after a negative MRL, a urologist or radiation oncologist can immediately proceed to local treatment without PLND. With this approach, 302 of 375 (81%) patients in our study would not have had a PLND. Because a false-positive finding has serious clinical consequences, namely that a curative treatment might be withheld, a positive MRL should always be confirmed by MR-directed FNAB or PLND. In this study, there were no false-negative results of FNAB; however, others have reported a false-negative rate of 40%.[5]

The main limitation of this study was that the MRL findings affected the reference standard. As described by Bossuyt and colleagues,[35] a good diagnostic test should comply with strict criteria. One such criteria is that the reference test should be done independently of test results. In our study, a treatment plan based on the combined findings of MDCT and MRL was provided before surgery. This resulted in more extensive PLND, because MRL showed positive lymph nodes outside the normal surgical field. By this approach, additional positive lymph nodes were detected in 18 of 61 (30%) patients. Also, confirming small positive lymph nodes by FNAB in 14 of 61 (23%) patients might have increased the usefulness of the reference standard. Lymph nodes might have been successfully biopsied in areas where they were difficult to assess by PLND. These findings are in agreement with those reported by Burkhard and co-workers,[36] who did an extended PLND in all of their patients and yielded positive lymph nodes in 24% additional patients. This outcome of our study design is an advantage in terms of lower costs and morbidity. Another advantage is that our study design resembles routine clinical practice.

All findings in our study were based on patient-to-patient assessments. At the start of this study, a region-to-region test for correlation was intended, but despite extensive effort, eg, use of electronic Case Record Forms and a post-operative grid to localise lymph nodes, because of missing data in the pathology reports, it was not possible to reliably test this in the seven low-recruiting centres. In the four major recruiting centres, there was a 100% agreement on a region-to-region basis. Reverse transcriptase PCR studies of the lymph nodes would have been useful because up to 30% of pathologically negative lymph nodes are PCR-positive.[37] We did not include this new technique as we wanted to see the effect of introducing MRL to the existing standard diagnostic pathway. This PCR test was not routine in any of the participating hospitals. The clinical relevance of the RT-PCR test is debated,[38] but should be included in future MRL studies.

The new imaging MRL technique could change current practice by eliminating the need for PLND in patients with a negative MRL. Patients with a positive MRL could undergo FNAB or PLND to obtain histopathology or removal of the affected lymph node with minimum surgical effort. This approach might result in less direct post-operative morbidity for the patient, less time doing surgery for the surgeon, lower health-care costs, and a more accurate diagnosis.

In summary, we conclude that in patients deemed to be at intermediate or high risk of having lymph-node metastases and in those centres experienced in the use and interpretation of MRL, MRL had significantly higher sensitivity and NPV in the detection of lymph-node metastases than MDCT. In such patients, after a negative MRL, the post-test probability of having lymph-node metastases is low enough (less than 4%) to omit a PLND.

Contributors

JB, RAMH, and GJJ were the principal investigators. All authors were responsible for the study concept, design, and data acquisition, analysis,

and interpretation. JB, RAMH, GJJ, JAW, JLS, and EMMA drafted and revised the report. JB, RAMH, AMH, and GJJ did the literature search. JB, RAMH, AMH, HCMvdB, JAW, HPJR, and CH did the clinical studies. JB, RAMH, GJJ, JLS, and EMMA did the statistical analysis. All authors approved the final version of the report.

Conflicts of interest

The authors declared no conflicts of interest.

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