Prostate Cancer: Detection of Lymph Node Metastases Outside the Routine Surgical Area with Ferumoxtran-10–enhanced MR Imaging[1]

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Purpose: To prospectively evaluate the feasibility of magnetic resonance (MR) imaging with ferumoxtran-10 in patients with prostate cancer to depict lymph node metastases outside the routine pelvic lymph node dissection (PLND) area.

Materials and Methods: The study was approved by the institutional review boards at all four hospitals; patients provided written informed consent. Two hundred ninety-six consecutive men (mean age, 67 years; range, 47–83 years) with prostate cancer and an intermediate-to-high risk for nodal metastases (prostate-specific antigen level >10 ng/mL, Gleason score >6, or stage T3 disease) were enrolled. MR lymphography of the pelvis was performed 24 hours after intravenous drip infusion of ferumoxtran-10. Positive nodes at MR lymphography were indicated to be inside or outside the routine dissection area (RDA). On the basis of MR lymphography computed tomographic (CT)–guided biopsy, routine PLND, or MR imaging–guided minimal extended PLND was performed.

Results: MR lymphography findings were positive in 58 patients. Of these, 44 had histopathologic confirmation of lymph node metastases. In 18 of 44 patients (41%), MR lymphography findings showed nodes exclusively outside the RDA, which were confirmed with MR lymphography–guided extended PLND (n = 13) and CT-guided biopsy (n = 5). In another 18 patients (41%), positive nodes were located both inside and outside the RDA at MR lymphography. In these 18 patients, routine PLND was used to confirm the nodes inside the RDA (n = 11); CT-guided biopsy was used to confirm nodes outside the RDA (n = 7). In the remaining eight patients, MR lymphography findings showed only nodes inside the RDA, which was confirmed with PLND (n = 5) and CT-guided biopsy (n = 3). In 14 of the 58 patients (24%), there was no histologic confirmation.

Conclusion: In 41% of patients with prostate cancer, nodal metastases outside the area of routine PLND were detected by using MR imaging with ferumoxtran-10.

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The detection of nodal metastases is of utmost importance to determine prognosis and choice of treatment in patients with prostate cancer. A metastasis in one lymph node turns prostate cancer from a local to a systemic disease, with fewer curative options. In patients with an intermediate-to-high risk of having node metastatic disease, a bilateral pelvic lymph node dissection (PLND) is the standard procedure before curative treatment with either radical prostatectomy or curative radiation therapy (1–3).

It has become increasingly clear that PLND, as it is routinely performed, is itself far from perfect. Several studies have reported a considerable percentage of positive lymph nodes outside the routine dissection area (RDA) (4–11). These positive lymph nodes are missed during routine PLND. Disease will be understaged and subsequently incorrectly treated as N0. For this reason, some urologists will perform an extended lymphadenectomy in all of their patients. This, unfortunately, leads to a higher complication rate and an increase in operating time (12).

The value of computed tomography (CT) and conventional magnetic resonance (MR) imaging is also limited, as lymph nodes are evaluated according to size and shape. A node is considered to be malignant if the short axis is more than 8 mm in a round node or more than 10 mm in an oval node. With use of these size and shape criteria, the sensitivity is low (13). When using ferumoxtran-10, a contrast agent specific to lymph nodes, the sensitivity of MR imaging improves substantially. Harisinghani et al (14) reported a sensitivity of 100% and a specificity of 96% in the detection of patients with nodal involvement in prostate cancer. Furthermore, ferumoxtran-10 MR imaging (also called MR lymphography) can depict lymph nodes in the entire pelvic area as well as in the abdominal nodal region.

Thus, the purpose of our study was to prospectively evaluate in patients with prostate cancer the feasibility of using MR lymphography to detect lymph node metastases outside the RDA.

Advances in Knowledge

- At least 30% of patients with prostate cancer had nodal metastases outside the area of routine pelvic lymphadenectomy.
- These additional positive nodes can be detected with MR imaging by using iron oxide nanoparticles (ferumoxtran-10).

Materials and Methods

Guerbet (Paris, France) provided the contrast agent. Ferumoxtran-10 (in Europe called Sinerem and in the United States called Combidex) has not yet been approved by the European Medicines Agency or the U.S. Food and Drug Administration.

Patient Selection and Characteristics

Between April 2003 and June 2005, 296 consecutive men (mean prostate-specific antigen level, 25.5 ng/mL; median Gleason score, 7) with histologically proved prostate cancer, a mean age of 67 years (range, 47–83 years), and an intermediate-to-high risk of lymph node metastases (serum prostate-specific antigen level >10 ng/mL, Gleason score >6, or T3 clinical stage at digital rectal examination) were enrolled. Our study is a part of a large national study and included four hospitals: Radboud University Medical Centre, Canisius Wilhelmina Hospital, Catharina Hospital Eindhoven, and Hospital Zeeuws-Vlaanderen. Patients from Canisius Wilhelmina Hospital underwent imaging at Radboud University Medical Centre but underwent surgery at Canisius Wilhelmina Hospital. Exclusion criteria were positive findings at bone scintigraphy, previous androgen therapy, or radiation therapy to the pelvic area. The study was approved by the institutional review boards at all four hospitals, and all patients provided written informed consent.

Implication for Patient Care

- MR imaging with intravenous iron oxide nanoparticles in patients with prostate cancer will allow detection of lymph node metastases missed with routine lymph node dissection.

MR Imaging and Interpretation

MR images were obtained with 1.5-T imaging systems from two commercial vendors. (Sonata/Symphony, Siemens, Erlangen, Germany was used at Radboud University Medical Centre; and Gyroscan/Intera, Philips, Eindhoven, the Netherlands, was used at Canisius Wilhelmina Hospital and Hospital Zeeuws-Vlaanderen.) Pelvic phased-array coils were used. Two-dimensional $T2^*$-weighted gradient-echo and two-dimensional T1-weighted fast spin-echo MR images were acquired from the pelvis, extending from the aortic bifurcation to the pubic symphysis, 24 hours after intravenous injection of ferumoxtran-10. The T1- and $T2^*$-weighted MR images were each acquired in two planes, with use of identical position and resolution parameters, to allow comparison. Image planes were a semisagittal (obturator) plane, that is a plane parallel to the psoas muscle, and an axial plane. The T1-weighted (fast spin-echo) images are insensitive, and the $T2^*$-weighted images are sensitive to the iron-containing contrast agent. In addition, a three-dimensional T1-weighted gradient-echo sequence was applied to allow anatomic localization of the lymph

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Abbreviations:
PLND = pelvic lymph node dissection
RDA = routine dissection area

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See Materials and Methods for pertinent disclosures.

nodes in relation to the vessels. Details of the specific pulse sequences are presented in Table 1. All images were obtained 24 hours after intravenous drip infusion of ferumoxtran-10 (particle size, 35 nm). In each hospital, all images were analyzed by an experienced radiologist affiliated with the corresponding hospital. These radiologists have experience in evaluating lymph nodes and are familiar with the ferumoxtran-10 criteria for nodal involvement (J.O.B., 8 years of experience; H.C.M.v.d.B., 3 years of experience; and F.R., 3 years of experience). The size and shape of the nodes were evaluated on the T1-weighted fast spin-echo images, and its signal intensity was evaluated on the T2*-weighted images. A node was considered normal if it showed a homogeneous low signal intensity and metastatic if the entire node or a focal area did not show low signal intensity (14–16). The location of a node was classified as "inside the RDA" when it was located in the obturator fossa, a region bound by the iliac vein and around the obturator nerve. Nodes were classified as "outside the RDA" when they were located anywhere else (Figs 1, 2).

Acquiring Nodes for Histologic Examination

MR lymphography–positive nodes were obtained for histopathologic examination by means of three approaches. First, when MR lymphography findings showed a positive node larger than 6 mm, CT-guided biopsy was performed with knowledge of the MR images. After a positive result at biopsy, no further action was taken to evaluate the other nodes. In patients with a positive biopsy result, PLND was omitted. These patients were not treated as "free of nodal metastases" (N0) and thus did not undergo an unnecessary radical prostatectomy or other local therapy. Second, when a CT-guided biopsy was not possible or results were negative, surgical dissection was performed. This consisted of routine PLND if the node was inside the RDA at MR lymphography. Third, on the basis of outcome at MR lymphography, a minimal extended PLND was performed if the node was outside the RDA. A minimal extended PLND

Figure 1

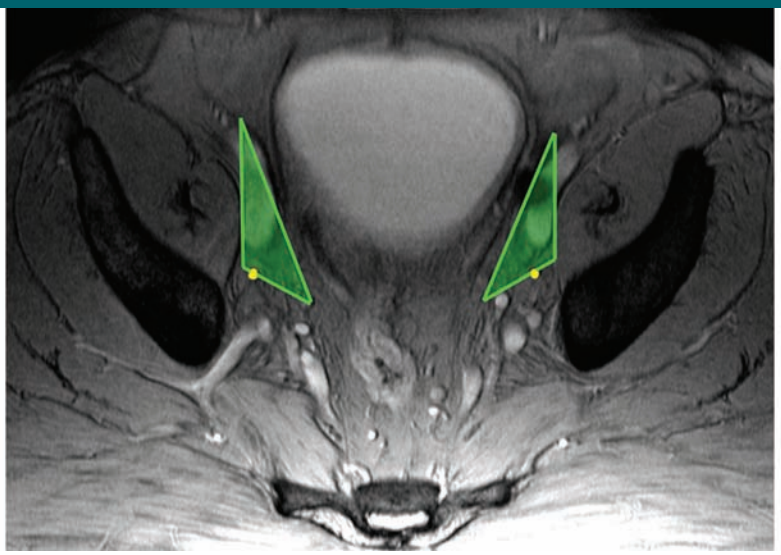

Figure 1: Axial T2*-weighted gradient-echo (repetition time msec/echo time msec, 2200/18) MR image. The green triangles indicate the RDA. The dorsal border is the obturator nerve, which is indicated by a yellow spot. Positive lymph nodes more dorsal of the obturator nerve (internal iliac and presacral region) will be missed.

Table 1

Pulse Sequences Used to Obtain MR Images

Sequence	Repetition Time (msec)	Echo Time (msec)	Bandwidth (Hz/pixel)	No. of Sections	Section Thickness (mm)	Gap (%)	Matrix	Field of View (mm)*
Axial T1 and proton density weighted fast spin echo	1800–2200	9–12	195	29	5	≤10	230 × 512	225 × 300
Axial T2* weighted two dimensional gradient echo with flow compensation	1400–1800	15–18 (α × 30°)	78	29	5	≤10	230 × 512	225 × 300
Obturator T1 and proton density weighted fast spin echo, parasagittal plane along iliac vessel axis	1800–2200	9–12	195	2 × 13	3	≤10	230 × 512	225 × 300
Semisagittal (obturator) T2* weighted two dimensional gradient echo with flow compensation	1400–1800	15–18 (α = 30°)	78	2 × 13	3	0	230 × 512	225 × 300

* From aortic bifurcation to pelvic floor, with cranial and caudal inflow presaturation and spatial presaturation on anterior abdominal wall.

meant that surgery was only extended to the region where the positive lymph node was found at MR lymphography. The local pathologists with more than 6 years of experience evaluated the lymph nodes for metastases. The routine protocol of their own hospital was used. No additional slices were made or additional staining was used for our study.

Surgery and Histologic Examination

A maximum of three different urologists per hospital performed PLND. All urologists had at least 10 years of experience in genitourinary surgery (J.A.W., 15 years of experience). Routine PLND was performed along the lymphatics of the external iliac artery and vein with the genitofemoral nerve as the lateral limit. All connective and lymphatic tissue was removed up to the bifurcation of the common iliac artery. Medially, the dissection proceeded along the bladder and caudal to the endopelvic fascia, where the node of Cloquet was removed (first node underneath the inguinal ligament). The dissection terminated with the obturator nerve. The urologist tagged the specimen by location where the lymph nodes were removed. The location was divided into six regions: the obturator fossa, external iliac, internal iliac, common iliac, presacral and/or pararectal, and paraaortic regions. The urologist also noted if the dissected node would have been removed during routine surgery, and thus if the node could be considered "outside the RDA." Lymphatic tissue was sent for final pathologic examination en bloc on a grid identifying its location. The entire specimen was processed histologically to identify all pelvic lymph nodes.

Figure 2

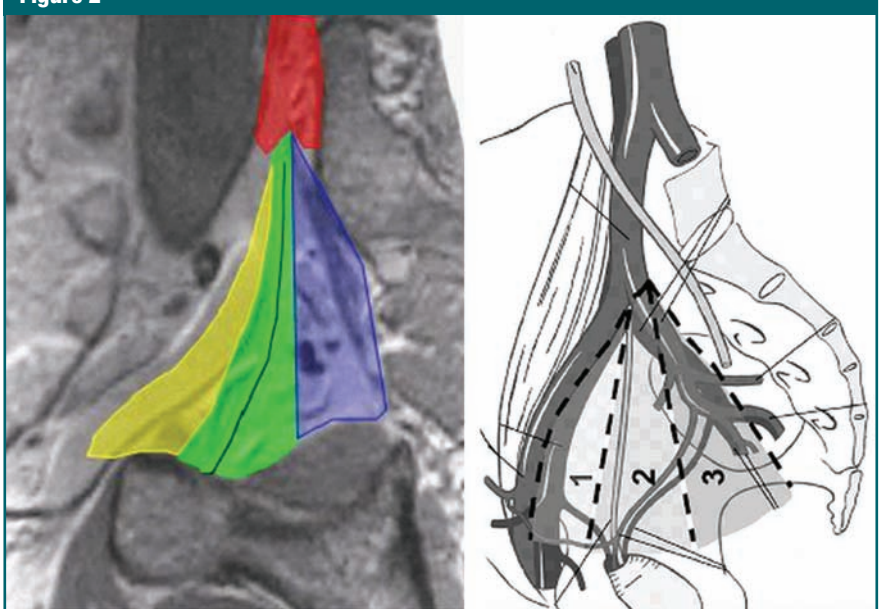

Figure 2: Semisagittal T2*-weighted gradient-echo (2200/18) MR image (left) and schematic drawing (right) of the PLND fields. *1* = external iliac region (medial part), *2* = obturator fossa region, *3* = internal iliac region (hypogastric) and presacral region, *4* = common iliac and paraaortal region.

Figure 3

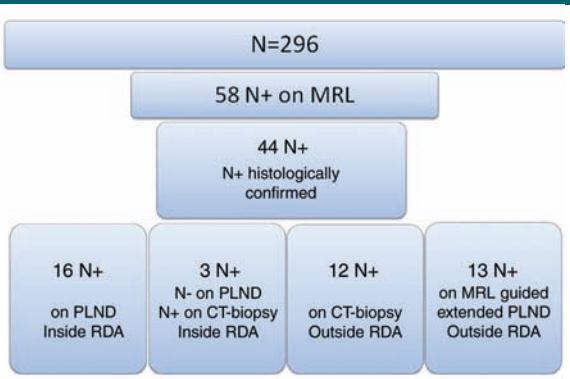

Figure 3: Breakdown of the 44 patients with histologically confirmed abnormal MR lymphographic (*MRL*) findings outside the RDA.

Results

Fifty-eight of the 296 patients (20%) had positive findings at MR lymphography. In 44 patients (mean prostate-specific antigen level, 48.4 ng/mL), the positive nodes were proved with histologic examination. In the remaining 14 patients, no pathologic nodes were found with routine PLND. All of these nodes were located outside the RDA at MR lymphography. In 16 of the patients with a positive node, their metastatic nodes were found by using routine PLND. An additional 15 cases were confirmed with CT-guided biopsy. These include three patients with a previous negative finding at routine PLND. The remaining 13 cases were found with MR lymphography–guided minimal extended PLND (Fig 3).

In 18 of the 44 patients with positive findings at histologic examination, the malignant nodes were found exclusively outside the RDA at MR lymphography (Figs 4 and 5). This was confirmed with minimal extended PLND in 13 of the 44 patients (30%) and with CT-guided biopsy in five (11%) (Table 2).

In another 18 patients, MR lymphography findings showed lymph nodes both inside and outside the RDA. Malignant involvement of lymph nodes outside the RDA could be confirmed with CT-guided biopsy in seven of these patients. The positive nodes outside the RDA at MR lymphography were not further explored. In the remaining 11 pa-

Figure 4

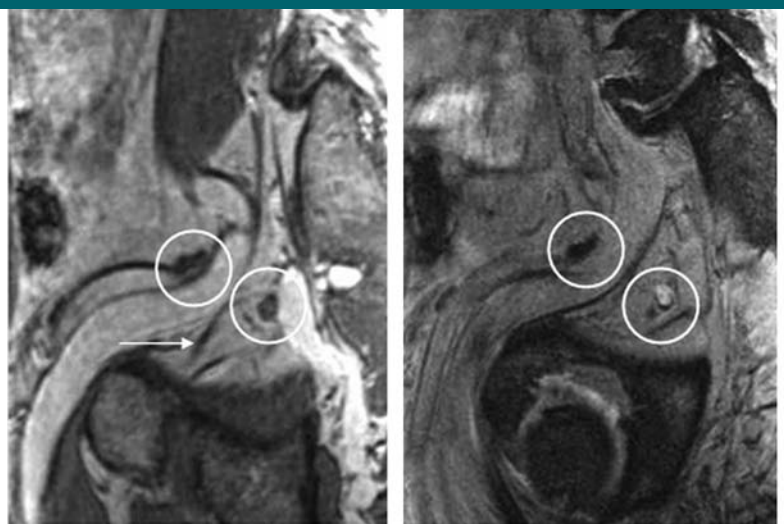

Figure 4: Left: Semisagittal T1-weighted fast spin-echo (1800/12) MR image. Two lymph nodes (circles) and an obturator nerve (arrow) are visible. With use of size criteria, both lymph nodes (axial size, 5 mm) are considered to be negative (13). Right: Semisagittal T2*-weighted gradient-echo (2200/18) MR image obtained after the administration of ferumoxtran-10. The black lymph node (top circle) is normal, but the white node (bottom circle) is metastatic. This lymph node is located about 2 cm behind the obturator nerve and will not be removed during routine PLND.

Figure 5

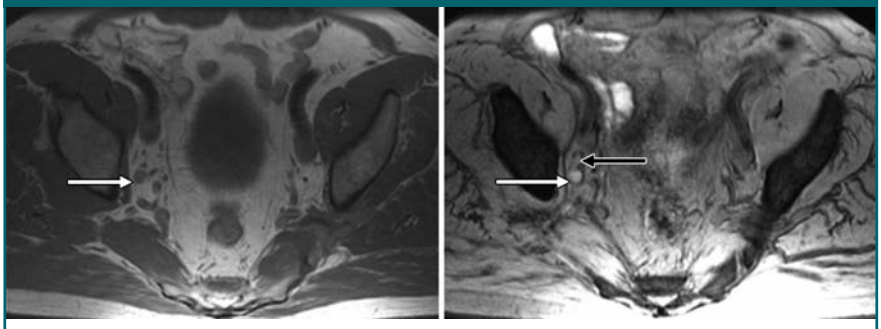

Figure 5: Left: Axial T1-weighted fast spin-echo (1800/12) MR image shows one lymph node (arrow). With use of size criteria (axial size, 4 mm), this lymph node is considered negative (13). Right: Axial T2*-weighted gradient-echo (2200/18) MR image obtained after the administration of ferumoxtran-10. The lymph node is white (white arrow) and, thus, positive. This node is located dorsal to the obturator nerve (black arrow), and thus outside the RDA.

Table 2

Analysis of 44 Positive Lymph Nodes according to Location

Location	No. of Patients ($n = 44$)
On MR lymphograms in the RDA only	8
Routine PLND (inside the RDA)	5
CT-guided biopsy after routine PLND (inside the RDA)	3
On MR lymphograms in and out of the RDA	18
Routine PLND (inside the RDA)	11
CT-guided biopsy (outside the RDA)	7
On MR lymphograms outside the RDA only	18
Minimal extended PLND (outside the RDA)	13
CT-guided biopsy (outside the RDA)	5
Total	44

tients in this group, histologic confirmation of positive nodes inside the RDA was documented with routine PLND.

In the final eight patients, the positive nodes at MR lymphography were inside the RDA, which was confirmed with CT-guided biopsy in three patients and with routine PLND in five. Three patients in whom the nodes were confirmed with CT-guided biopsy had a negative finding at previous routine PLND.

Of all nodes outside the RDA, 35 of the 76 (46%) were found in the internal iliac region, 18 (24%) in the common iliac region, six (8%) in the external iliac region, six (8%) in the pararectal and/or presacral region, and 11 (14%) in the paraaortic region.

Discussion

With use of MR lymphography, we found that at least 30% of patients with prostate cancer and an intermediate-to-high risk of having positive nodes had nodal metastases exclusively outside the RDA. Earlier surgical studies in patient groups similar to ours have also reported a high rate of nodal metastases detected exclusively in areas outside RDA. Raghavaiah and Jordan (17), who described the lymphatic drainage of the prostate in 1979, found that drainage areas include not only the obturator fossa but also the internal and external iliac and presacral and/or perirectal regions, which is confirmed by our findings at MR lymphography.

Heidenreich et al (5) compared routine with extended PLND. Nodal metastases were found more than twice as frequently with extended dissection than with routine PLND. They found 42% of the positive nodes outside the field of

standard routine PLND. Their results are supported by those of our study. Burkhard and Studer (4) found additional positive nodes outside the field of routine PLND. Nodes were detected along the internal iliac vessels in up to two-thirds of all positive nodes. Up to one-fifth of all patients had positive lymph nodes exclusively at this location. In contrast, Allaf et al (9) found a detection rate of only 3.2% and 1.1% for nodal metastases with extended and routine PLND, respectively. Although the gain of malignant nodes outside the routine dissection area they found was modest, these numbers were small probably due to the predominance of low-risk patients in their study population. Clark et al (18) described a higher complication rate with a gain of only a few additional nodal metastases when performing extended PLND. However, their study also included mainly low-risk patients. Furthermore, they performed an extended PLND on only one side of the pelvis, independent of tumor localization.

Our data, as well as those of Heidenreich et al (5) and Burkhard and Studer (4), show that routine PLND results in understaging and that a more extensive PLND depicts many more positive nodes. However, a routinely performed extended PLND is not the preferred standard because it is associated with higher complication rates and health care costs (8,18,19). In contrast, with use of MR lymphography, it is possible to detect positive nodes outside the RDA: In 18 of the 44 patients (41%), MR lymphography depicted nodes only outside the RDA. In another 18 patients, their positive nodes were found inside and outside the RDA at MR lymphography. In seven of these patients, the location of the metastatic nodes outside of the RDA was confirmed with CT-guided biopsy. Thus, we have histologic confirmation that MR lymphography was able to help detect 25 of 44 patients (57%) with lymph node involvement outside the RDA. Furthermore, due to MR lymphography, in some patients PLND was omitted and replaced with a less-invasive CT-guided biopsy. More important is the fact that these patients were not treated as "free of nodal metastases" (N0) and thus did not undergo an unnecessary radical prostatectomy or other local therapy.

A study by Daneshmand et al (20) showed that the number of positive lymph nodes corresponds with the recurrence-free survival rate. If a patient had one or two positive lymph nodes, the disease-free 10-year survival was 70%. For patients with more than five positive nodes, the 10-year survival was 49% (20). Other recent studies (9,21) suggest an improvement in disease-free interval when positive nodes are removed, but this is not statistically proved. If it is true that the removal of metastatic nodes in patients with only one or two positive nodes improves the recurrence-free survival even more, then the potential of MR lymphography to show lymph node metastases outside the RDA becomes even more important.

Our study had several limitations. Our study is part of a larger multicenter study in which the diagnostic performance of MR lymphography was evaluated. This part of the study was designed with the purpose of showing the ability of MR lymphography to depict lymph nodes in areas where surgeons routinely do not dissect them. This induced bias and influenced the reported sensitivity and specificity of the multicenter trial. Not all patients who underwent MR lymphography underwent extended PLND because not all urologists would routinely perform an extended PLND, as it is not the standard surgical technique used in their hospital.

Of the 58 patients with positive nodes at MR lymphography, 44 had histologically proved lymph node metastases. Reported high positive predictive values and specificity (14), and the fact that in our study three patients had a negative finding at routine PLND, suggest that probably the MR lymphography–positive nodes were not found with routine PLND.

Of the 18 patients whose positive nodes were located outside the RDA at MR lymphography, 13 were confirmed with minimal extended PLND (30%). Five had a positive finding at CT-guided biopsy. Because lymph nodes in the RDA in these five patients were not sampled anymore for ethical reasons, a verification bias is introduced. Because it was not proved that the RDA was negative in these five patients, we excluded them from the number of patients with positive nodes exclusively outside RDA. If we do include them, the percentage of positive nodes detected with MR lymphography outside the RDA is even higher (18 of 44 [41%] instead of 13 of 44 [30%]).

In conclusion, in 30% of patients with prostate cancer and an intermediate-to-high risk of having nodal metastases, nodal metastases were exclusively found outside the area of routine pelvic lymphadenectomy. These positive nodes were detected with iron oxide nanoparticle (ferumoxtran-10)–enhanced MR imaging.

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