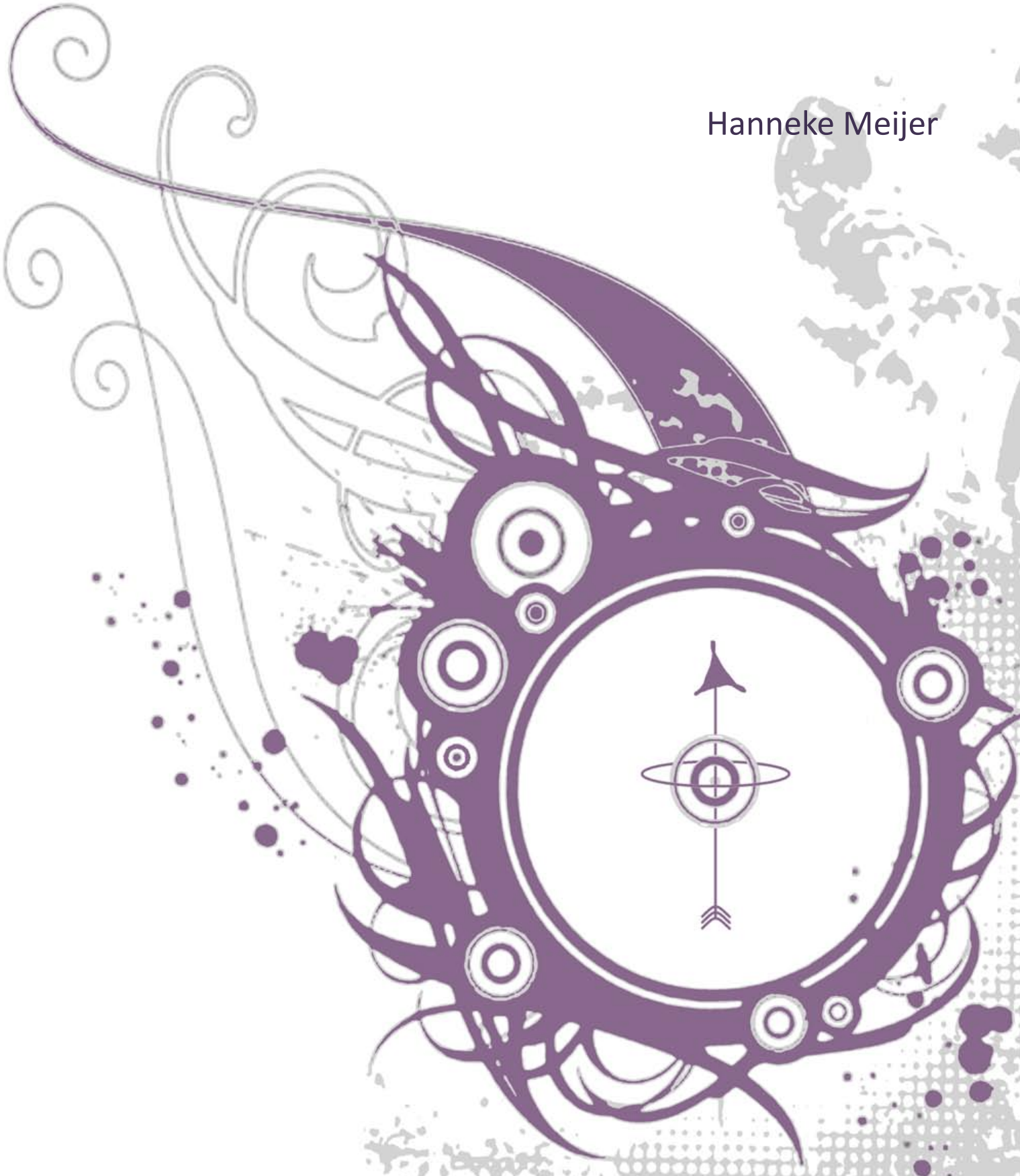
# MAGNETIC RESONANCE LYMPHOGRAPHY AND LYMPH NODE IRRADIATION IN PROSTATE CANCER

Hanneke Meijer



# Magnetic resonance lymphography and lymph node irradiation in prostate cancer

Hanneke Meijer

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Thesis Radboud University Nijmegen

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# Magnetic resonance lymphography and lymph node irradiation in prostate cancer

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Voor mijn ouders
Voor Frank

## Contents

**Chapter 1** **9**
General Introduction and Outline

**Chapter 2** **15**
Geographical distribution of lymph node metastases on MR lymphography in prostate cancer patients
*Radiat Oncol 2013;106(1):59-63*

**Chapter 3** **27**
Magnetic resonance lymphography findings in patients with a biochemical recurrence after prostatectomy and the relation with the Stephenson nomogram
*Int J Radiat Oncol Biol Phys 2012*;*84(5): 1186-1191*

**Chapter 4** **39**
High occurrence of aberrant lymph node spread on magnetic resonance lymphography in prostate cancer patients with a biochemical recurrence after radical prostatectomy
*Int J Radiat Oncol Biol Phys 2012;82(4):1405-10*

**Chapter 5** **53**
Magnetic resonance lymphography-guided selective high-dose lymph node irradiation in prostate cancer
*Int J Radiat Oncol Biol Phys 2012; 82(1):175–183*

**Chapter 6** **67**
Prognosis of prostate cancer patients with lymph node involvement on MR lymphography: who might be cured?
*Radiat Oncol, submitted*

**Chapter 7** **81**
General Discussion and Future Perspectives
Future perspectives for lymph node irradiation in prostate cancer: towards an image-based individualized treatment
*Nature Reviews Urology, submitted*

**Chapter 8** **105**
Summary and Conclusions

**Chapter 9** **109**
Summary in Dutch (Nederlandse samenvatting)

**Dankwoord** **117**
**Curriculum Vitae** **119**
**List of Publications** **121**

# 1

# General Introduction and Outline

## General Introduction

Prostate cancer is the most frequently occurring malignancy in men over 45 years. In 2010, over 10.000 men in the Netherlands were diagnosed with prostate cancer (1).
There are several treatment options for prostate cancer patients with disease confined to the prostate. The most frequently used treatments are prostatectomy and radiotherapy. While brachytherapy is generally reserved for patients with early stage disease, external beam radiotherapy is a treatment option for all patients (2).

Patients with locally advanced disease have a substantial risk of having lymph node metastases (3). A major limitation in the treatment of prostate cancer is that for a long time, no accurate non-invasive manner to determine lymph node status was available. Computed tomography (CT) and magnetic resonance imaging (MRI) cannot detect nodal metastases until enlargement of the lymph node occurs, usually in a late stage of the disease, and therefore have a low sensitivity (4). For this reason, predictive tools, such as the Partin tables (3) and the Roach formula (5), are being used to predict the chance of lymph node involvement. This prediction is based on clinical T-stage, Gleason score and prostate-specific antigen (PSA). In patients with a substantial risk of lymph node involvement, a pelvic lymph node dissection can be performed to determine lymph node status. However, this is an invasive procedure, with consequential morbidity and high costs (6).

The Partin tables and Roach formula can also be used to select patients for nodal irradiation. In many solid tumors, lymph node irradiation is a standard part of the radiation treatment, especially in more advanced disease (2). However, for prostate cancer, lymph node irradiation, often referred to as whole pelvis irradiation (WPRT) when combined with irradiation of the prostate, is controversial. Many retrospective trials comparing WPRT to prostate-only radiotherapy (PORT) have shown a benefit for WPRT, mainly for patients with a high risk of lymph node involvement (7-11). Two randomized controlled trials have, however, reported contradictory results (12-14). As a result, the use of WPRT varies largely throughout the world.

After treatment with prostatectomy, about 25% of the patients develops a recurrence, initially presenting as a rise in PSA (15). A treatment option for these patients is salvage radiotherapy, at which generally only the prostate bed is irradiated. Therefore, this treatment can only be curative for patients with an isolated local recurrence. Further, the best results are achieved when salvage radiotherapy is administered at a low PSA value (16). However, tumor burden is low at low PSA values, and imaging methods are not accurate enough to detect the disease (4, 17, 18). The site of the recurrence -local, regional or distal- can therefore often not be determined at this time. For this reason, patients are often selected for curative salvage radiotherapy directed only at the prostate bed based on the Stephenson nomogram (19). This predicts the chance of success after this treatment, based on clinical and histopathological features: prostatectomy PSA, Gleason score, seminal vesicle invasion, extracapsular extension, surgical margins, lymph node metastases at lymph node dissection, postprostatectomy PSA, PSA doubling time, preradiotherapy PSA, neo-adjuvant hormonal treatment and radiation dose.

Very little is known about lymph node involvement and nodal irradiation in these patients. The results of three retrospective studies suggest that there might be a benefit of WPRT compared to irradiation of only the prostate bed, especially for patients with a high risk of lymph node involvement (20-22). Currently, a randomized controlled trial, the RTOG 0534 is ongoing, comparing these treatments prospectively. The results of this trial will have to be awaited before WPRT in the salvage setting will be implemented into clinical use.

Recently, imaging techniques have been developed that can more accurately detect lymph node metastases, even in non-enlarged lymph nodes. Positron emission tomography (PET) (23), and single photon emission computed tomography (SPECT)/the sentinel node procedure (24, 25) are appealing imaging techniques from the field of nuclear medicine. Also in the field of radiology, new imaging techniques have been developed, such as diffusion-weighted MRI (26) and perhaps the most promising technique: magnetic resonance lymphography (MRL) (27).

MRL is an MRI technique that uses the contrast agent ferumoxtran-10, which contains ultrasmall superparamagnetic particles of iron oxide (USPIO). It is injected intravenously 24-36 hours before the MRI is performed. The iron oxide particles extravasate, and are transported to the lymph nodes by macrophages. Normal lymph nodes are filled with these iron particles, which causes them to have a low signal intensity on a T2* MRI image. In pathological lymph nodes, however, accumulation of these particles is blocked by metastasis formation, and these lymph nodes retain their high signal intensity on a T2* image. This technique has a sensitivity of 80-100% and a specificity of 87-99% for the detection of lymph node metastases in prostate cancer patients (27).

These imaging techniques will contribute to further knowledge about lymph node involvement in prostate cancer patients. For example, the pattern of spread of lymph node metastases has not been mapped precisely. Because conventional imaging has very limited value for the detection of lymph node metastases, most data come from extended pelvic lymph node dissection (28). This procedure does, however, not address all lymph node regions. For example, the pararectal and para-aortal lymph node region are generally not dissected (29), and therefore mapping is incomplete. Modern imaging can complement this.
In patients with a biochemical recurrence after prostatectomy, a lymph node dissection is usually not performed as there is no evidence on its diagnostic value in this setting (30). Knowledge about the incidence of nodal involvement and pattern of nodal spread is therefore especially sparse in these patients. And that, while the lymph drainage may have been changed due to previous surgery, as has been described in other tumor types such as breast cancer (31). Also here, accurate imaging methods can increase our knowledge.
This increase in knowledge about nodal involvement can improve standard WPRT, for example by enabling the definition of a more accurate target volume.

Moreover, the use of accurate imaging methods might be of benefit for individual patients too. Node-negative patients can be spared from a lymph node dissection. Further, it creates the possibility to treat patients with minimal nodal involvement with nodal irradiation according to individualized image-based radiotherapy treatment plans with a boost to the

pathological lymph nodes. The emergence of this new possibility has raised many questions. Patients with lymph node involvement are generally regarded incurable. However, modern imaging techniques can detect lymph node involvement at an early stage, before enlargement of the lymph nodes occurs. This is a new category of patients, whose prognosis and the treatment from which they benefit the most are unknown. Further, uncertainty exists about the exact manner of how these imaging methods should be used for radiotherapy treatment planning.

## Outline of the thesis

This thesis aims to determine how MRL can be used to improve lymph node irradiation in prostate cancer patients. MRL findings were studied in detail to improve general knowledge about lymph node metastases in prostate cancer patients. Further, an view on the future use of MRL for customized radiotherapy was developed.

First, MRL findings in primary prostate cancer patients are described. As mentioned before, the pattern of spread of lymph node metastases in these patients has not been optimally investigated to date. In **chapter 2**, the geographical distribution of positive lymph nodes on MRL in 60 primary prostate cancer patients is described. This was compared to the clinical target volume for WPRT as defined by the RTOG (RTOG-CTV) to determine the risk of geographical miss when applying this CTV.

**Chapters 3** and **4** concern patients with a biochemical recurrence after prostatectomy. In **chapter 3** the occurrence of nodal metastases on MRL is described. Further, a relation between the Stephenson nomogram and MRL result is investigated. The goal of this latter item was to determine whether the Stephenson nomogram can be used to identify patients with a high risk of lymph node involvement, that might benefit from lymph node irradiation.
As there is no literature describing the pattern of lymph node spread in patients with a biochemical recurrence after prostatectomy, it is unknown what the adequate target volume for lymph node irradiation is in these patients. To gather knowledge on this subject, the geographical distribution of MRL-positive lymph nodes in this patient group was studied. The results are described in **chapter 4**. Again, a comparison between MRL findings and the RTOG-CTV was made to determine the risk of geographical miss when applying this CTV.

Subsequently, in **chapter 5** it is shown how MRL can be used as a basis for customized treatment planning. In four primary prostate cancer patients the MRL-positive non-enlarged lymph nodes were registered on a CT for radiotherapy planning. The target volume for elective irradiation of lymph node regions was individualized based on MRL. For each patient, an IMRT plan was created. An elective dose to the lymph node regions and a boost dose to the prostate as well as to the MRL-positive lymph nodes was prescribed while restricting dose to the organs at risk.

To investigated whether the above-mentioned treatment might be a curative option for MRL-positive patients, follow-up data of prostate cancer patients that underwent an MRL in

our institute were collected, in order to obtain data about their prognosis. **Chapter 6** presents the results. It is investigated whether there are subgroups within the MRL positive group with a better prognosis, in whom a window of opportunity for cure exists.

In the general discussion in **chapter 7** an overview is given of the available evidence in the international literature with regard to WPRT and imaging methods for the detection of lymph node metastases in prostate cancer patients. Furthermore, it is discussed how modern imaging techniques can be implemented into lymph node irradiation, to create an individualized selective high-precision treatment.

A summary of the thesis is given in **chapter 8,** and a summary in Dutch in **chapter 9.**

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# 2

# Geographical distribution of lymph node metastases on MR lymphography in prostate cancer patients

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## Abstract

*Purpose:* To investigate the pattern of lymph node spread on magnetic resonance lymphography (MRL) in prostate cancer patients and compare this pattern to the clinical target volume for elective pelvis irradiation as defined by the radiation therapy oncology group (RTOG-CTV).

*Methods and materials:* The charts of 60 intermediate and high risk prostate cancer patients with non-enlarged positive lymph nodes on MRL were reviewed. Positive lymph nodes were assigned to a lymph node region according to the guidelines for delineation of the RTOG-CTV. Five lymph node regions outside this RTOG-CTV were defined: the para-aortal, proximal common iliac, pararectal, paravesical and inguinal region.

*Results:* Fifty-three percent of the patients had an MRL-positive lymph node in a lymph node region outside the RTOG-CTV. The most frequently involved aberrant sites were the proximal common iliac, the pararectal and para-aortal region, which were affected in 30%, 25% and 18% respectively.

*Conclusion***:** More than half of the patients had an MRL-positive lymph node outside the RTOG-CTV. To reduce geographical miss while minimizing toxicity of radiotherapy, image based definition of an individual target volume seems to be necessary.

## Introduction

Whole pelvis radiotherapy (WPRT) might be of benefit in a selected group of patients with prostate cancer (1). To support the use of intensity modulated radiotherapy (IMRT) for WPRT and to stimulate the use of a uniform target volume, the radiation therapy and oncology group (RTOG) set up a consensus meeting to define a clinical target volume (CTV). In the absence of studies describing the pattern of regional failure and because of the low accuracy of computed tomography (CT) and magnetic resonance imaging (MRI) for the detection of lymph node metastases in prostate cancer (2), this target volume was for the greater part based on data of extended pelvic lymph node dissection and traditional lymphography (3).

The development of new imaging methods, such as the sentinel node procedure and MR lymphography (MRL), has created the opportunity to map the lymph drainage pattern of the prostate more accurately (1). MRL is a technique that uses the contrast agent ferumoxtran-10 to enhance MRI. This method has a sensitivity of 80-100% and a specificity of 87-99% for the detection of involved lymph nodes in prostate cancer (4, 5).

A sentinel node mapping study reported that more than half of the patients had a sentinel node outside the standard CTV for WPRT (6), harboring a great potential risk for geographical miss. The presence of involved lymph nodes in higher echelons than the sentinel nodes, which can be determined with MRL, may even increase this risk.

Inspired by these findings, the present study was performed to map the pattern of lymph node involvement on MRL in prostate cancer patients who were candidates for curative local treatment. This pattern was compared to the RTOG-CTV for WPRT, to determine the risk of geographical miss.

## Methods and Materials

*Patient selection*
Between April 2003 and March 2010 339 patients with a histopathologically proven intermediate to high-risk prostate adenocarcinoma (serum prostate-specific antigen level >10 ng/mL, Gleason score >6, or ≥T3 clinical stage) were scanned with MRL prior to local treatment in three Dutch hospitals. All patients had had a CT or MRI of the pelvis without enlarged lymph nodes, and a negative bone scan.

Sixty-three patients (19%) had a positive MRL. Two patients were excluded from further analysis because of a medical condition that might interfere with the true pattern of lymph node involvement from their prostate cancer: one patient had a synchronous presentation with bladder cancer and the other had had previous pelvis irradiation for rectal cancer. Further, one chart could not be retrieved. The charts of the remaining 60 patients were reviewed.

The study was approved by the Institutional Review Boards of all participating hospitals and all patients provided informed consent.

*MRL scanning procedure*
MRI images were obtained on a 1.5T system (Sonata/Symphony, Siemens, Erlangen, Germany; Gyroscan/Intera, Philips, Eindhoven, Netherlands; or Horizon, GE Medical Systems, Milwaukee, WI, USA) before February 2004 (8 patients) and on a 3T system (TrioTim, Siemens, Erlangen, Germany; Gyroscan/Intera, Philips, Eindhoven, Netherlands) after February 2004 (52 patients). Pelvic phased array coils were used. Patients were placed in the supine position with a knee fix. Images were acquired from the entire pelvis and abdomen. To suppress bowel peristalsis, Buscopan i.m. and i.v., and Glucagon i.m. were administered before scanning. Heesakkers *et al.* previously described the scanning protocol (4).

Twenty-four to 36 hours before MRI, Ferumoxtran-10 (Sinerem®, Guerbet, Paris, France) was injected intravenously. This contrast medium contains ultrasmall superparamagnetic particles of iron oxide. After extravasation, these are transported to the lymph nodes by macrophages. Iron particles give a low signal intensity on a T2*-weighted MRI image. Metastases in the lymph nodes block accumulation of the iron particles. The signal intensity of pathological nodes will therefore remain high on a T2*-weighted MRI image, while the signal intensity of normal lymph nodes becomes low (4, 7).

When a lymph node completely or partially showed high signal intensity on a T2*-weighted image, it was considered malignant (4). The MRL images were analyzed by two experts in consensus reading.

*Analysis of the pattern of lymph node spread*
MRL-positive lymph nodes were assigned to a lymph node region, according to the RTOG description of the CTV for WPRT (RTOG-CTV) (3). Lymph node regions included in these guidelines are the internal and external iliac regions, the obturator region and the presacral region. The common iliac region is included only from the L5/S1 interspace down. This will be referred to as the distal common iliac region.
Five regions outside the RTOG-CTV were defined: the proximal common iliac region, the para-aortic, paravesical, pararectal region and the inguinal region. The proximal common iliac region was defined as the area around the common iliac vessels from the L5/S1 interspace up. The para-aortic region comprised the area of the aorta and vena cava with a transverse margin of 1.5 cm (8). The pararectal lymph node region was defined as the mesorectum, adjacent to the presacral, obturator, external and internal iliac lymph node regions (9). The para-vesical region was defined as the area around the bladder, adjacent to the pararectal, external iliac and obturator region, and to the abdominal wall and pubic bone ventrally (9). The inguinal region comprised the area around the inguinal vessels from the femoral heads downwards (9).
The para-aortic, proximal common iliac, pararectal, paravesical and inguinal regions will be referred to as aberrant lymph node regions.

The geographical distribution of positive nodes was determined for the whole group of patients and separately for the patient group that received hormonal treatment at the time of MRL and the group that did not. For each lymph node region, the occurrence of positive nodes was compared between the two latter groups.

*Analysis of risk factors for aberrant lymph drainage*
To establish whether involvement of the aberrant lymph node regions can be predicted, it was analyzed whether risk factors for aberrant lymph drainage could be identified. For this analysis, the association between known prognostic factors and the presence of positive lymph nodes in the aberrant lymph node regions was determined. These factors were: PSA at the time of MRL, clinical T-stage and Gleason score at biopsy (10). For PSA at the time of MRL, only patients who did not receive hormonal treatment at that time were included for analysis, because of the influence of hormonal treatment on PSA value.

*Statistics*
For statistical testing SPSS 16.0.01 (SPSS Inc. 1989-2007) was used and a $p \leq 0.05$ was a priori deemed significant.
The significance of differences between the groups of patients that did and did not receive hormonal treatment at the time of MRL in the occurrence of positive nodes in each lymph node region was determined using the Pearson Chi Square test.
The Kolmogorov-Smirnov test showed an abnormal distribution for PSA at the time of diagnosis. Therefore, the Mann-Whitney U test was used to determine the significance of a possible association.
Correlation between ordinal variables and the presence of positive lymph node metastases in the aberrant regions was determined using the Spearman correlation.

## Results

*The pattern of lymph node spread*
The characteristics of the 60 patients with a positive MRL are shown in table 1. Figure 1 shows an example of T2* MRL images with positive lymph nodes.

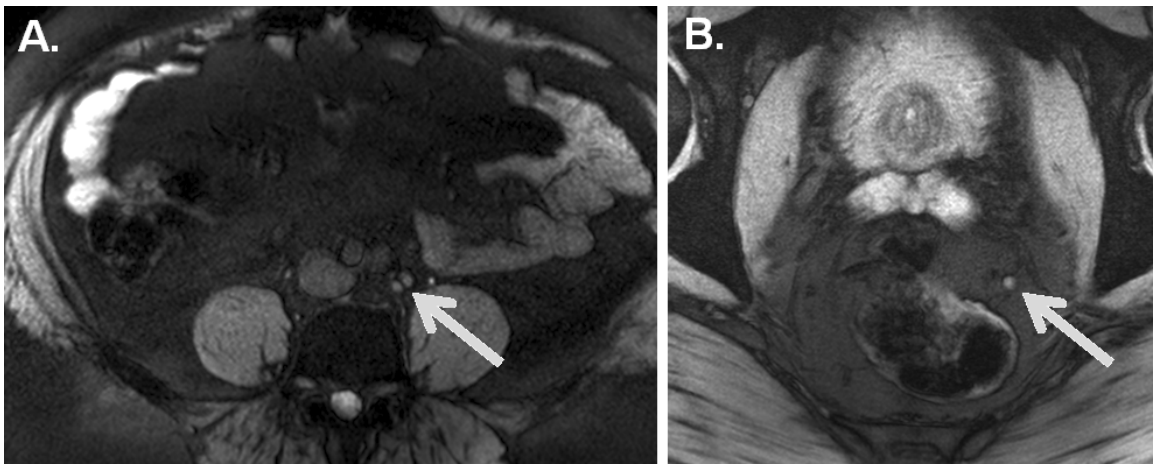


**Fig. 1.** Example of T2* MRL images with positive lymph nodes
A. Axial T2* MRL image showing 2 small round positive lymph nodes in the para-aortal region (arrow).
B. Axial T2* MRL image showing a small positive lymph node in the para-rectal region (arrow).

**Table 1. Patient characteristics**

| Characteristic | Median (range) |
|---|---|
| Age (years) | 64 (45-78) |
| PSA (ng/ml) | 19.4 (2.2-954.0) |
| | **N (%)** |
| Gleason score | |
| 5 | 3 (5%) |
| 6 | 13 (22%) |
| 7 | 20 (33%) |
| 8 | 17 (28%) |
| 9 | 5 (8%) |
| 10 | 2 (3%) |
| Clinical T-stage | |
| Unknown | 2 (3%) |
| 1 | 4 (7%) |
| 2 | 31 (52%) |
| 3 | 22 (37%) |
| 4 | 1 (2%) |
| Hormonal treatment at time of MRL | |
| Yes | 29 (48%) |
| No | 31 (52%) |

*Abbreviations:* PSA= prostate specific antigen

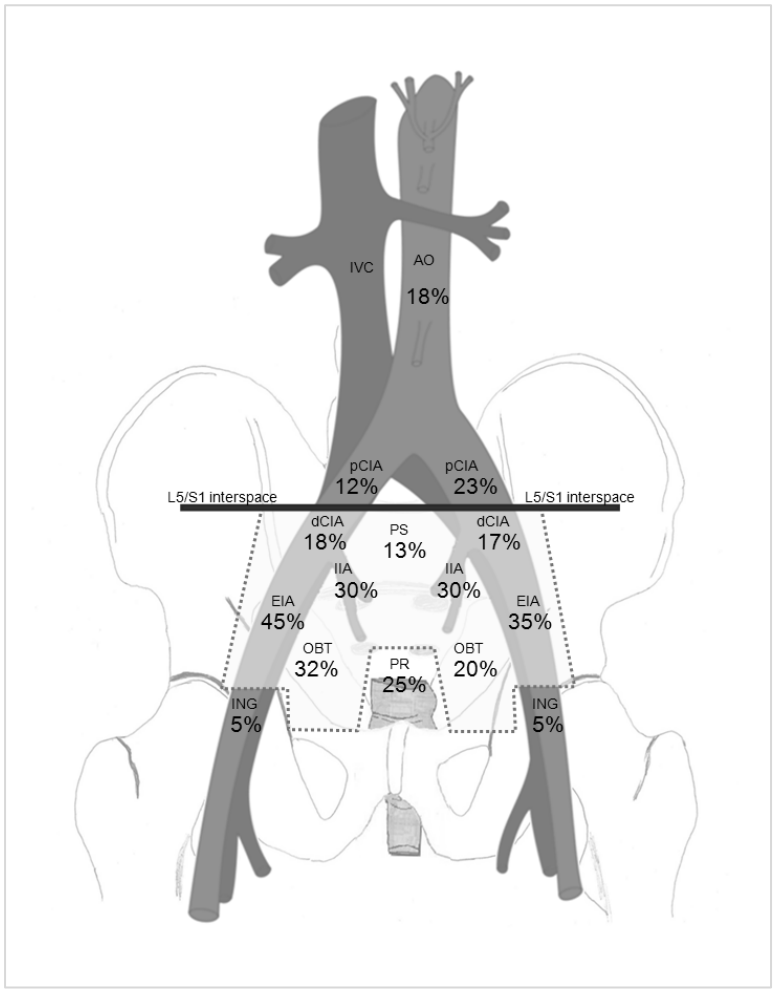


**Fig. 2.** Schematic distribution of positive lymph nodes in all 47 patients.
Numbers represent the percentage of patients with at least one positive lymph node in that lymph node region. The clinical target volume for elective pelvic irradiation in prostate cancer as described by the Radiation Therapy Oncology Group is schematically displayed by the dotted line. The L5/S1 interspace represents the border between the proximal and distal common iliac region. Five percent of the patients had a positive lymph node in the paravesical region (not shown).
*Abbreviations:* IVC = inferior vena cava; AO = aorta; pCIA = proximal common iliac artery; dCIA = distal common iliac artery; EIA = external iliac artery; IIA = internal iliac artery; OBT = obturator region; PS = presacral region; PR = pararectal region

The distribution of the MRL-positive lymph nodes is shown in figure 2. Five percent of the patients had a positive lymph node in the paravesical region (not shown). Thirty percent had positive lymph nodes in either the left or right proximal common iliac artery and 8% in either the left or right inguinal region. In total 53% of the patients had at least one positive lymph node outside the RTOG-CTV. There were no significant differences in the geographical distribution of positive nodes between patients that did and did not receive hormonal treatment at the time of MRL.

*Analysis of risk factors for aberrant lymph drainage*
Patients with positive lymph nodes in the proximal common iliac region had a significantly higher PSA at the time of MRL than patients without positive lymph nodes in this region (23.6 ng/ml vs 13.4 ng/ml; p=0.01). Gleason score was significantly correlated to the presence of positive lymph nodes in the pararectal region (Spearman correlation coefficient 0.48, p=0.01). T-stage was not correlated to the presence of positive lymph nodes in any of the aberrant lymph node regions.

## Discussion

The ambiguous results of the two most recent randomized trials, performed by the RTOG and the groupe d'études des tumeurs uro-génitales (GETUG), have initiated debate about the role of elective WPRT for patients with clinically localized prostate cancer (1). The results of the RTOG 94-13 suggest that there is a benefit for WPRT as compared to irradiation of only the prostate, whereas in the GETUG-01 trial this benefit was not seen (1). This difference might be explained by the fact that in the RTOG 94-13 only patients with a risk of lymph node involvement of >15% were included, while in the GETUG-01 all prostate cancer patients were eligible. Further, in the GETUG-01 study, substantial geographical miss might have occurred in the WPRT group, because a smaller irradiation field was used, which has been shown to be less effective (1).
Definition of an adequate target volume for lymph node irradiation has become even more important with the development of more conformal radiotherapy techniques as IMRT. This was reason for the RTOG to set up a consensus meeting to develop a delineation guideline. However, the definition of a CTV for lymph node irradiation is not unambiguous in prostate cancer. Whereas for other pelvic malignancies the pattern of regional recurrences has been investigated and has been used to determine the appropriate irradiation field, for prostate cancer, these data lack (6). This might be due to the fact that a recurrence is generally detected first as a PSA relapse. Hormonal treatment is then often started, before a regional relapse can be detected with conventional imaging methods as MRI or CT, which have a low sensitivity for detecting lymph node metastases (2).
Further, at the time of the definition of the RTOG-CTV, only scarce data were available on the distribution of pathological lymph nodes in prostate cancer as visualized by newer, more accurate imaging methods, such as MRL, the sentinel node procedure, and positron emission tomography combined with CT (PET/CT). The RTOG-CTV was therefore for the greater part based on data obtained at extended pelvic lymph node dissection and traditional lymphography (3).

There are, however, difficulties in translating the surgical data to a radiotherapy target volume. First, there is a difference in nomenclature of the lymph node regions. Second, even at extended lymph node dissection not all lymph nodes in the pelvis are removed, e.g. the pararectal lymph nodes. Also, the para-aortal region is not commonly resected (6). Traditional bipedal lymphography also has important shortcomings for the definition of a target volume. It mainly visualizes the external and common iliac and para-aortal lymph

nodes (12). Further, the data are difficult to translate to a CT-based target volume, because traditional lymphography only shows the lymph nodes in relation to the bony anatomy.

MRL has a much higher accuracy for the detection of lymph node metastases than conventional imaging methods (4). At this moment, however, the contrast agent ferumoxtran-10 is unavailable for clinical use, and therefore MRL cannot be performed with this contrast agent.
Lymph node status can also be determined accurately with the sentinel node procedure (13), but this is an invasive procedure. An alternative non-invasive imaging method for MRL is choline PET/CT (14). However, reported sensitivity of this imaging modality varies from 0-100% (15). An important limitation of PET/CT is its threshold of 5-6mm for the detection of lymph node metastases, especially in early generation scanners. Another frequently used imaging technique is prostate-specific membrane antigen (PSMA) targeted imaging. For the detection of nodal metastases its sensitivity ranges from 17-75% (16). The first clinical agent for PSMA targeting was $^{111}$In-capromab. A disadvantage of this monoclonal antibody is that it is a large molecule with slow target recognition and poor penetration. Techniques using small molecules such as ($^{123}$I)MIP-1072 and ($^{123}$I)MIP-1095 to target PSMA are currently under investigation (17). Also the diagnostic value of diffusion-weighted MRI (18), and of MRL using an alternative contrast agent ferumoxytol are being investigated. So far, none of these techniques has shown to be as accurate as ferumoxtran-10 MRL, underlining the need for its come-back.

To our knowledge, no detailed mapping studies have been performed using PET/CT or PSMA targeted imaging. Several studies using the sentinel node procedure and MRL *have* investigated the pattern of lymph drainage in relation to the area of lymph node dissection (6,19,20). These studies showed that more than half of the sentinel nodes was localized outside the routine pelvic lymph node dissection area (19), and nearly half of the patients had MRL-positive lymph nodes exclusively outside this region (20).
More recently, Ganswindt *et al.* were the first to compare the distribution of sentinel nodes, as visualized by single photon emission computed tomography (SPECT), to a CTV for WPRT. They found a sentinel node outside this CTV in 65.5% of the patients. These results are in line with the results of the present study. The present study shows that 53% of locally untreated patients has MRL-involved lymph nodes outside the RTOG-CTV for WPRT.
These findings suggest that when applying the RTOG-CTV, there is a substantial risk of geographical miss. Recently, it was shown that in patients with a PSA recurrence after prostatectomy, drainage to lymph node regions outside the RTOG-CTV occurred even more frequently (21).
The most frequently involved aberrant lymph node regions in the present study were the para-aortal, proximal common iliac and pararectal region. In the study by Ganswindt et al the 'ventral part' of the external iliac region and the perirectal region were the most frequent 'outside CTV' regions where sentinel nodes were found. Shih et al. were the first to map MRL-positive lymph nodes in 10 primary prostate cancer patients (8). Important 'outside standard CTV regions' with positive lymph nodes were the para-aortal and perirectal regions. Further comparison with the results of both studies is unfortunately impossible, as Ganswindt and Shih et al counted the number of positive nodes per region,

and in the present study the number of patients with a positive node per region was determined.

To determine whether it can be predicted which aberrant lymph node regions should be included in certain patients, we sought for risk factors for the presence of positive lymph nodes in aberrant regions. The risk of positive pararectal lymph nodes increased with increasing Gleason score. We identified a high PSA value to be associated to the presence of lymph node metastases in the proximal common iliac region. It might be argued that in patients with a high PSA value this region should be included in the CTV, and that in patients with a high Gleason score the pararectal region should be included.

However, to avoid overtreatment in part of the patients, with the likelihood of an increase in toxicity, image based irradiation of the pelvic lymph nodes would be preferred. Using a more accurate method to determine lymph node status could also improve patient selection for lymph node irradiation.
Ganswindt *et al.* proposed to extend the standard target volume to include all sentinel nodes as visualized by SPECT (22). This would result in a reduction of geographical miss, while avoiding overtreatment. The advantage of using MRL would however be twofold: MRL gives a very good indication of whether lymph nodes are involved or not, and lymph nodes in higher echelons than the sentinel nodes can be imaged. This could reduce geographical miss even further and gives the opportunity to boost positive nodes. As dose escalation has shown to improve outcome for radiotherapy of the prostate (23,24), increasing the dose to metastatic lymph nodes might also contribute to a better outcome. MRL-guided IMRT of pelvic lymph node regions with a boost to the MRL-positive lymph nodes in conjunction with irradiation of the prostate is theoretically feasible (25). Whether this approach indeed improves outcome needs to be investigated.

A limitation of the present study is that the MRL-positive lymph nodes were not histopathologically confirmed. Previous pathologic validation studies have, however, demonstrated a very high sensitivity (80-100%) and specificity (87-99%) of MRL (4,5). The pattern of lymph node involvement found on MRL in the present study is therefore likely to be a very close approximation of the true pattern of lymph node involvement.
A second limitation of the study is that part of the patients already received hormonal treatment at the time of MRL. This might have influenced our results, because theoretically, lymph node metastases might decrease in size due to hormonal treatment and they might become too small to detect even with MRL. Our finding that 53% of the patients had positive aberrant lymph nodes might therefore be an underestimation.

## Conclusion

In the current study 53% of the patients had at least one MRL-positive lymph node outside the RTOG-CTV for WPRT. The most frequently involved aberrant lymph node regions were the pararectal, para-aortal and proximal common iliac region. These results show that when applying the RTOG-CTV, geographical miss is likely to occur. This underlines the need to use

an accurate imaging method for the detection of lymph node metastases, such as MRL, for the delineation of the CTV for lymph node irradiation.

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# 3

# Magnetic resonance lymphography findings in patients with a biochemical recurrence after prostatectomy and the relation with the Stephenson nomogram

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## Abstract

*Purpose:* To estimate the occurrence of positive lymph nodes on magnetic resonance lymphography (MRL) in patients with a prostate-specific antigen (PSA) recurrence after prostatectomy and to investigate the relation between score on the Stephenson nomogram and lymph node involvement on MRL.

*Methods and Materials*: Sixty-five candidates for salvage radiation therapy were referred for an MRL to determine their lymph node status. Clinical and histopathologic features were recorded. For 49 patients, data were complete to calculate the Stephenson nomogram score. Receiver operating characteristic (ROC) analysis was performed to determine how well this nomogram related to the MRL result. Analysis was done for the whole group and separately for patients with a PSA <1.0 ng/mL to determine the situation in candidates for early salvage radiation therapy, and for patients without pathologic lymph nodes at initial lymph node dissection.

*Results:* MRL detected positive lymph nodes in 47 patients. ROC analysis for the Stephenson nomogram yielded an area under the curve (AUC) of 0.78 (95% confidence interval, 0.61-0.93). Of 29 patients with a PSA <1.0 ng/mL, 18 had a positive MRL. Of 37 patients without lymph node involvement at initial lymph node dissection, 25 had a positive MRL. ROC analysis for the Stephenson nomogram showed AUCs of 0.84 and 0.74, respectively, for these latter groups.

*Conclusion:* MRL detected positive lymph nodes in 72% of candidates for salvage radiation therapy, in 62% of candidates for early salvage radiation therapy, and in 68% of initially node-negative patients. The Stephenson nomogram showed a good correlation with the MRL result and may thus be useful for identifying patients with a PSA recurrence who are at high risk for lymph node involvement.

## Introduction

After prostatectomy, approximately 25% of patients with prostate cancer develop recurrent disease, presenting as a rise in prostate-specific antigen (PSA) (1). This PSA rise can reflect a local recurrence, in which case salvage radiation therapy of the prostate bed may be a curative treatment option (2), but it can also reflect lymph node or distant metastases.

Little is known about the incidence of lymph node metastases in these patients because accurate determination of lymph node status at this time is difficult. The sensitivity of commonly used imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) for detection of lymph node metastases is low (3). Furthermore, pelvic lymph node dissection is not performed before salvage radiation therapy because there is no evidence of its value for determining lymph node status in these patients (4).
As a result, patient selection for salvage radiation therapy of the prostate bed is suboptimal. This may explain why success rates have historically been poor (5). To improve patient selection, Stephenson et al developed a nomogram that predicts the chance of success after salvage radiation therapy (5). This nomogram is often assumed to distinguish local from distant recurrence, because treatment is most likely to fail in the latter group of patients (6). As a PSA recurrence after prostatectomy occurs without evidence of distant metastases in the majority of patients (7), a significant number of patients who experience failure despite salvage radiation therapy of the prostate bed may be those with occult lymph node metastases. Retrospective studies suggest that whole pelvis salvage radiation therapy might be of benefit for patients with minimal lymph node involvement (8, 9). This makes a reliable tool for assessment of lymph node status in the workup for salvage radiation therapy even more indispensable.
Recently, magnetic resonance lymphography (MRL) has been developed. This technique uses the contrast agent ferumoxtran-10 to enhance MRI (10). It reliably detects lymph node metastases, even in nonenlarged nodes (10, 11).

We hypothesized that the most important reason for failure after salvage radiation therapy is lymph node involvement. If so, the Stephenson nomogram would in fact predict the chance of lymph node involvement, and MRL imaging and the nomogram would demonstrate a good correlation. The nomogram might then be useful for patient selection for pelvic nodal treatment. The purpose of the present study was to estimate the occurrence of positive lymph nodes based on MRL in patients with biochemical recurrence after prostatectomy, and to determine whether the Stephenson nomogram score is related to the presence of lymph node involvement on MRL.

## Methods and Materials

*Patient selection*
From February 2005 to March 2010, 71 patients with prostate cancer who had a PSA recurrence after radical prostatectomy were referred to our institute for MRL to determine

their lymph node status. All patients had a PSA level of ≥0.2 ng/mL at least 6 weeks postoperatively, followed by at least 1 higher value, or a single PSA level of ≥0.5 ng/mL (5).

To investigate the occurrence of lymph node metastases in patients eligible for salvage radiation therapy, patients with a PSA >10 ng/mL were required to have had a bone scan and CT or MRI of the abdomen within the 6 months before MRL without evidence of bony or lymph node metastases. Six patients with a PSA>10 ng/mL were excluded because they did not meet this latter criterium leaving 65 patients eligible for analysis. All patients provided informed consent for undergoing MRL and for use of the obtained data for research purposes.

*Scanning procedure and image analysis*
The MRI images were obtained on a 3T imaging system (TrioTim, Siemens, Erlangen, Germany; Gyroscan/Intera, Philips, Eindhoven, Netherlands) by use of pelvic phased array coils. Patients were placed in the supine position with a knee fix. Images were acquired from the entire pelvis and abdomen. Buscopan was given intramuscularly and intravenously and glucagon was given intramuscularly before scanning to suppress bowel peristalsis. Heesakkers et al previously described the scanning protocol (10).

Ferumoxtran-10 (Sinerem, Guerbet, Paris, France) was injected intravenously 24-36 hours before MRI. It consists of ultrasmall superparamagnetic particles of iron oxide that are transported to the lymph nodes by macrophages after extravasation. These particles give a low signal intensity on the T2*-weighted MR image. Metastases in the lymph nodes block accumulation of the iron particles. The signal intensity of pathologic nodes will therefore remain high on a T2*-weighted MR image, whereas the signal intensity of normal lymph nodes becomes low (10).

All MRL images were analyzed by 2 experts in consensus reading. A lymph node was regarded pathologic when it completely or partially showed a high signal intensity on a T2*-weighted MR image. Patients with at least 1 positive lymph node were classified as MRL positive; patients with only negative lymph nodes were classified as MRL negative.

*The Stephenson nomogram*
The Stephenson nomogram consists of variables that have been demonstrated to have prognostic value (5): preprostatectomy PSA, Gleason score (4-6, 7, or 8-10), presence of seminal vesicle involvement or extracapsular extension (yes or no), resection margin status (positive or negative), presence of lymph node metastases at pelvic lymph node dissection (yes or no), status of postprostatectomy PSA (detectable or undetectable), preradiotherapy PSA (for the current study: pre-MRL PSA), PSA doubling time, neoadjuvant androgen deprivation therapy (yes or no), and radiation dose. For each variable a number of points is applied depending on its value. Adding up these points results in a total score, which corresponds to a certain 6-year progression-free probability after salvage radiation therapy directed at the prostate bed. The higher the score, the higher the chance of treatment failure.

*Relation between MRL result and the Stephenson nomogram*
For statistical testing, SPSS 16.0.01 (SPSS Inc 1989-2007) was used. The total Stephenson nomogram score was calculated by applying 0 points for neoadjuvant androgen-deprivation therapy and radiation dose because patients had not yet been treated for their PSA recurrence at the time of MRL. For pre-MRL PSA, only the PSA values of patients who did not receive hormonal treatment after prostatectomy in the 2 years before the MRL were included, because of the effect of hormonal treatment on PSA.
The Stephenson nomogram score did not have a normal distribution according to the Kolmogorov-Smirnov test; therefore, the Mann-Whitney U test was used to determine the significance of differences between groups.
Receiver operating characteristic (ROC) analysis was performed to determine how well the score on this nomogram related to the MRL result.

*Subgroup analysis*
The analyses were performed separately for patients with a PSA <1.0 ng/mL at the time of MRL who were candidates for early salvage radiation therapy (2) and for patients without lymph node involvement at initial lymph node dissection.

## Results

The patient characteristics are shown in Table 1 for the whole group of 65 patients and for the subgroups of patients with a positive MRL and a negative MRL. Forty-seven patients (72%) had a positive MRL. MRL detected 275 positive lymph nodes, of which 269 had a diameter ≤1 cm.
For 16 patients, the Stephenson nomogram score could not be calculated because of missing data. Of the remaining 49 patients, 33 (67%) had a positive MRL. Figure 1 shows an example of a negative MRL in a patient with a nomogram score of 87 points and a positive MRL in a patient with a score of 267 points.
The Stephenson nomogram score was significantly higher in the group with lymph node involvement (median 174 vs 118 points; P=.002). The ROC analysis for number of points on the Stephenson nomogram is shown in Figure 2. The AUC was 0.78. The curve differed significantly from the reference line (95% confidence interval [CI], 0.61-0.93).

**Subgroup analysis**
*Patients with a PSA <1.0 ng/mL at the time of MRL*
There were 29 patients with a PSA <1.0 ng/mL, 18 of whom had a positive MRL (62%). For 24 patients, data were complete to enable calculation of the Stephenson nomogram score. Of these patients, 14 (58%) had a positive MRL. A positive MRL was associated with a higher Stephenson nomogram score (median 168 vs 114 points; P=.005). The ROC curve with an AUC of 0.84 differed significantly from the reference line (95% CI, 0.67-1.0).

**Table 1. Patient characteristics**

| Characteristic | Median (range) | | |
|---|---|---|---|
| | All patients (n=65) | MRL+ (n=47) | MRL- (n=18) |
| Age (years) | 65 (45-80) | 65 (45-80) | 64 (51-77) |
| Pre-prostatectomy PSA (ng/ml) | 9.3 (1.1-92.5) | 11.1 (2.3-92.5) | 7.5 (1.1-25.8) |
| Pre-MRL PSA (ng/ml) | 0.9 (0.1-34.0) | 0.9 (0.2-8.5) | 0.5 (0.1-7.4) |
| PSA doubling time (months) | 5.8 (0.6-114.5) | 4.2 (0.6-67.1) | 11.6 (1.2-114.5) |
| | N (%) | N | |
| | All patients (n=65) | MRL+ (n=47) | MRL- (n=18) |
| Gleason score* | | | |
| unknown | 1 (2) | 1 | - |
| 5 | 1 (2 | - | 1 |
| 6 | 6 (9) | 2 | 4 |
| 7 | 32 (49) | 23 | 9 |
| 8 | 10 (15) | 8 | 2 |
| 9 | 15 (23) | 13 | 2 |
| Pathological T-stage | | | |
| Unknown | 1 (2) | 1 | - |
| 1c | 1 (2) | 1 | - |
| 2a | 1 (2) | 1 | - |
| 2b | 6 (9) | 2 | 4 |
| 2c | 10 (15) | 5 | 5 |
| 3a | 23 (35) | 15 | 8 |
| 3b | 21 (32) | 20 | 1 |
| 4 | 2 (3) | 2 | - |
| Lymph node metastases at PLND | | | |
| Unknown | 1 (2) | 1 | - |
| No PLND performed | 10 (15) | 7 | 3 |
| Yes | 17 (26) | 14 | 3 |
| No | 37 (57) | 25 | 12 |
| Positive resection margin | | | |
| Unknown | 6 (9) | 5 | 1 |
| Yes | 19 (29) | 14 | 5 |
| No | 40 (61) | 28 | 12 |
| Extracapsular extension | | | |
| Unknown | 4 (6) | 4 | - |
| Yes | 37 (57) | 29 | 8 |
| No | 24 (37) | 14 | 10 |
| Seminal vesicle invasion | | | |
| Unknown | 1 (2) | 1 | - |
| Yes | 22 (34) | 21 | 1 |
| No | 42 (65) | 25 | 17 |
| PSA detectable postoperative | | | |
| Yes | 28 (43) | 23 | 5 |
| No | 37 (57) | 24 | 13 |
| Hormonal treatment | | | |
| None | 42 (65) | 30 | 12 |
| Before RP | 2 (3) | 1 | 1 |
| After RP | 18 (28) | 14 | 4 |
| Before and after RP | 3 (5) | 2 | 1 |

*Abbreviations*: MRL=Magnetic Resonance Lymphography; MRL+=group of patients with positive MRL; MRL-=group of patients with negative MRL; PLND= Pelvic Lymph Node Dissection; RP= Radical Prostatectomy

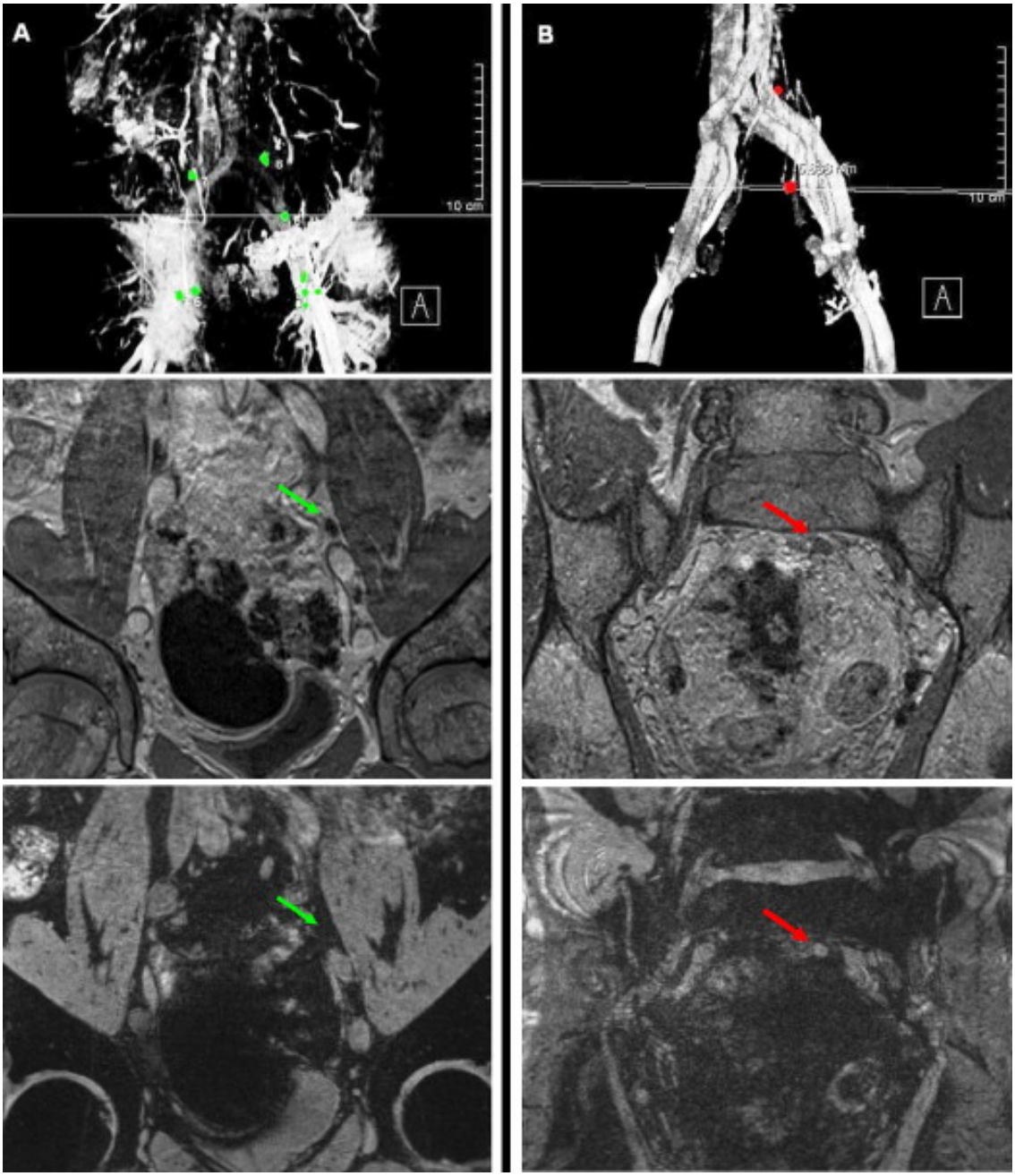


**Fig. 1.** (A) Example of a negative magnetic resonance lymphography in a patient with a score on the Stephenson nomogram of 87 points. (B) Example of a positive magnetic resonance lymphography in a patient with a score on the Stephenson nomogram of 267 points. Above, Lymph nodes mapped in relation to the vessels. The negative lymph nodes are marked green, the positive red. Center, T1-weighted images, showing good visualization of lymph nodes (arrows). Below, The same lymph nodes on a T2*- weighted image. In (**A)** the lymph node is now indistinguishable from the surrounding adipose tissue because it has a low signal intensity owing to accumulation of the iron oxide particles, which identifies the lymph node as negative. The lymph node in (**B)** has a high signal intensity on this T2*-weighted image, which means that accumulation of the iron oxide particles has been blocked and the lymph node is positive.

*Patients without lymph node involvement at initial lymph node dissection*
There were 37 patients without pathologic lymph nodes at initial lymph node dissection, of whom 25 had a positive MRL (68%). For 29 patients, the Stephenson nomogram score could be calculated; of those, 18 (62%) had a positive MRL. MRL-positive patients had a significantly higher Stephenson nomogram score than did MRL-negative patients (median 174 vs 114 points; P=.04). ROC analysis showed a curve with an AUC of 0.74, which differed significantly from the reference line (95% CI, 0.51-0.96).

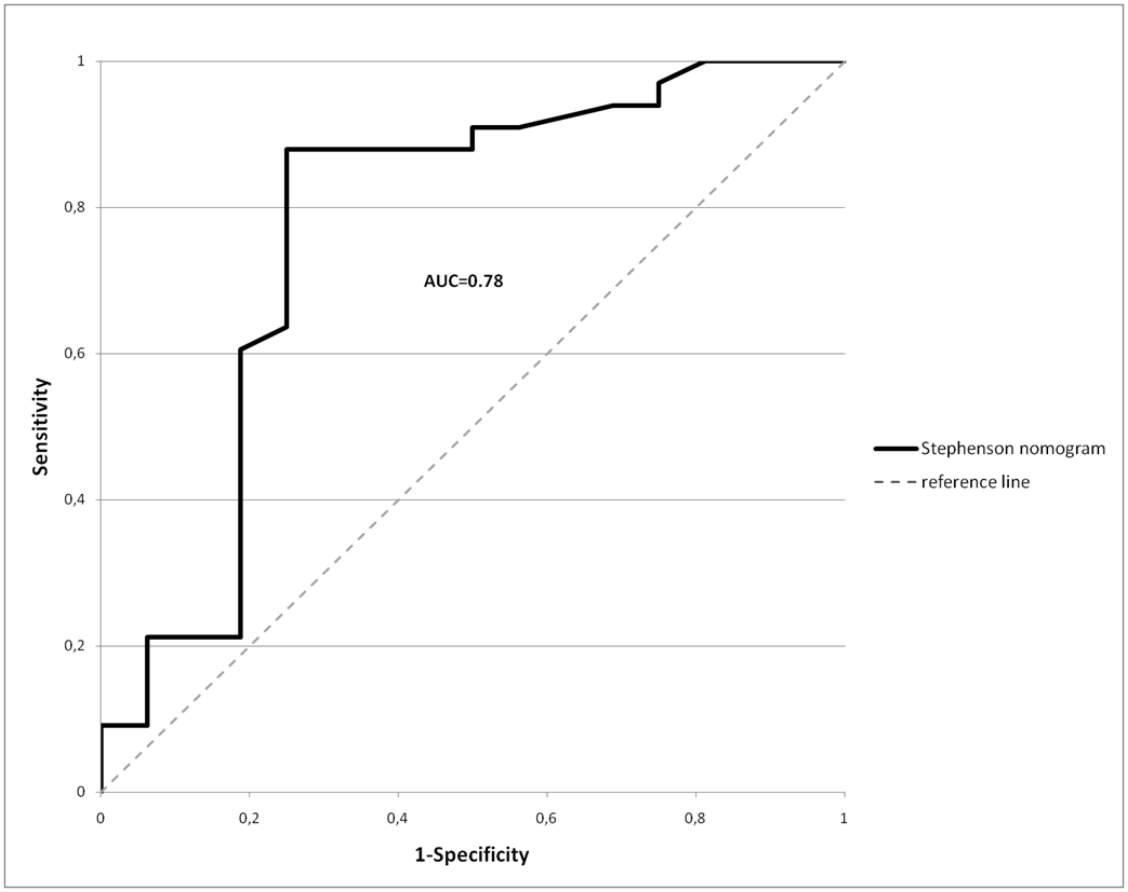


**Fig. 2.** Receiver operating characteristic curve showing the relation between score on the Stephenson nomogram and magnetic resonance lymphography result for the whole patient group.
*Abbreviation:* AUC = area under the curve.

## Discussion

In the present study, 72% of the patients who were candidates for salvage radiation therapy had a positive MRL. For candidates for early salvage radiation therapy with a PSA level <1.0 ng/mL, this was 62%; for patients without lymph node involvement at initial lymph node dissection, this was 68%. This means that many patients in the current study might not be ideal candidates for salvage radiation therapy directed only at the prostate bed.

Little has been described about the incidence of lymph node involvement in patients with a PSA recurrence. Pelvic lymph node dissection has delivered knowledge about the incidence of lymph node metastases in previously untreated patients. But because there is no evidence of its value to determine lymph node status in patients with a recurrence after prostatectomy, it is usually not performed in this setting (4). CT and MRI are likely to underestimate the incidence because they have a low sensitivity for the detection of lymph node metastases (3). In most of the MRL-positive patients in the present study, CT and MRI was or would have been negative, because only 6 of the 275 MRL-positive lymph nodes had a diameter of more than 1 cm.

Newer imaging methods with a better sensitivity for the detection of lymph node metastases are PET/CT and MRL.

The role of 18F-choline and 11C-choline PET/CT for detection of the site of recurrence among patients with a PSA relapse after prostatectomy has been investigated in recent years. The percentage of patients with positive lymph nodes in these studies is highly variable, as was the sensitivity for the detection of the site of recurrence. Sensitivity is especially low in patients with a PSA <1.0-1.5 ng/mL (1). This might be explained by the fact that tumor load is low in patients with a low PSA value (12). Tumor deposits of a few millimeters can be missed with PET/CT because it has a spatial resolution of 5-6 mm (1).

MRL has better spatial resolution (1 mm) (13) and is likely to be more sensitive for the detection of small lymph node metastases. To our knowledge, only one study, that by Ross et al, has published data on the incidence of positive lymph nodes on MRL in the salvage setting (14). Positive lymph nodes were detected in 6 of 26 patients (23%). This percentage is much lower than that in the present study. This can be explained by the fact that in the present study more patients had characteristics predictive of worse outcome (5). In the current patient group, Gleason score and median PSA at the time of MRL were higher, seminal vesicle involvement was more frequent, resection margin positivity occurred less frequent, and median PSA doubling time was shorter. Furthermore, whereas Ross et al did not include patients who had lymph node metastases initially at pelvic lymph node dissection, we did. If the present study had been limited to patients without lymph node involvement at initial presentation, one factor contributing to the prognostic value of the Stephenson nomogram –pathologic nodal status at initial presentation– would have been eliminated. This would have caused a false result in the assessment of the relation between MRL result and the Stephenson nomogram. Therefore, the analyses were performed for the whole group, with a subgroup analysis for initially node-negative patients. In these initially node-negative patients, the occurrence of a positive MRL was 68%, which is only slightly lower than for the whole group (72%).

To improve patient selection for salvage radiation therapy and thereby possibly improve the outcome, the Stephenson nomogram has been developed (5). It is based on a retrospective chart review of patients treated with salvage radiation therapy of the prostate bed and predicts the chance of success after radiation therapy (5). To our knowledge, the present study is the first to show that the score on the Stephenson nomogram is related to the

presence of lymph node involvement at the time of PSA recurrence as determined with MRL. This indicates that the Stephenson nomogram could be useful for identifying patients at risk for lymph node involvement.

Our results have to be interpreted with caution, given that a major limitation of the present study is that no histopathologic data were available from the lymph nodes found positive by MRL. Pathologic validation studies in previously untreated patients, however, have shown a sensitivity of 80%-100% and a specificity of 87%-99% (10, 11). Positive predictive value is dependent on the incidence of lymph node involvement in the group that is investigated. In unselected patients, it has been reported to be 70% (10), but in patient groups with a high incidence of lymph node involvement, it has been shown to be as high as 95% (11).
Our study group consisted of patients with a high risk of lymph node involvement, and positive predictive value most likely is in the higher range. Furthermore, a higher field strength (3T) is currently used, which has been described to improve the image quality (15). The occurrence of MRL-positive lymph nodes in the present study group is therefore likely to be a close estimate of the true incidence of pathologically involved lymph nodes. But, due to the retrospective design of the present study and our center being a tertiary referral center, selection bias is likely to have occurred, and the true incidence of lymph node involvement in patients eligible for salvage radiation therapy might be lower.

MRL may play a role in decision making about salvage radiation therapy. It has been shown to have a negative predictive value of up to 100% (10, 11). MRL could therefore be useful in the selection of only those biochemically recurrent patients without lymph node involvement for salvage radiation therapy of the prostate bed. Lymph node-positive patients would then be spared from salvage radiation therapy and its morbidity.
The optimal treatment for these latter patients is unknown. The data suggest that patients with only limited lymph node involvement form a unique subgroup with a better outcome (16), who might be cured with locoregional surgical treatment (17) or radiation therapy (18,19). Because MRL can detect lymph node involvement at an early stage, locoregional radiation therapy might be an option for a part of the MRL-positive patients. This is supported by the fact that retrospective studies have described a benefit for whole pelvis radiation therapy compared with radiation therapy of only the prostate bed for patients with a high risk of lymph node involvement (8, 9). The results of the Radiation Therapy Oncology Group 0534 phase III trial, which compares these treatments, will have to be awaited for sufficient evidence.
If pelvic salvage radiation therapy will prove to have benefit, MRL may also be of use here. Because it visualizes the localization of the lymph node metastases, geographic miss can be reduced. This may be a greater cause of treatment failure than previously thought, as was recently shown by a study on the distribution of sentinel nodes in treatment-naïve patients. In this study, 65.6% of the patients had a sentinel node outside their conventional target volume for pelvic irradiation (20). Also, a boost dose may be delivered to those lymph nodes that are identified by MRL to contain metastases (21). It might therefore be considered, when MRL is available, to perform MRL before pelvic salvage radiation therapy in patients who are at risk of lymph node involvement.

## Conclusion

The present study showed MRL-positive lymph nodes in 72% of the patients with a biochemical recurrence after prostatectomy. For patients with a PSA <1.0 ng/mL at the time of MRL, this was 62%. For initially node-negative patients, this was 68%. These patients are unlikely to be cured with radiation therapy of only the prostate bed. The Stephenson nomogram score was related to the MRL result. The nomogram may therefore be used to identify patients at risk for lymph node involvement who may benefit from nodal treatment.

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# 4

# High occurrence of aberrant lymph node spread on magnetic resonance lymphography in prostate cancer patients with a biochemical recurrence after radical prostatectomy

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## Abstract

*Purpose:* To investigate the pattern of lymph node spread in prostate cancer patients with a biochemical recurrence after radical prostatectomy, eligible for salvage radiotherapy; and to determine whether the clinical target volume (CTV) for elective pelvic irradiation in the primary setting can be applied in the salvage setting for patients with (a high risk of) lymph node metastases.

*Methods and Materials:* The charts of 47 prostate cancer patients with PSA recurrence after prostatectomy who had positive lymph nodes on magnetic resonance lymphography (MRL) were reviewed. Positive lymph nodes were assigned to a lymph node region according to the guidelines of the Radiation Therapy Oncology Group (RTOG) for delineation of the CTV for pelvic irradiation (RTOG-CTV). We defined four lymph node regions for positive nodes outside this RTOG-CTV: the para-aortal, proximal common iliac, pararectal, and paravesical regions. They were referred to as aberrant lymph node regions. For each patient, clinical and pathologic features were recorded, and their association with aberrant lymph drainage was investigated. The distribution of positive lymph nodes was analyzed separately for patients with a prostate-specific antigen (PSA) <1.0 ng/mL.

*Results:* MRL detected positive aberrant lymph nodes in 37 patients (79%). In 20 patients (43%) a positive lymph node was found in the pararectal region. Higher PSA at the time of MRL was associated with the presence of positive lymph nodes in the para-aortal region (2.49 vs. 0.82 ng/mL; $p = 0.007$) and in the proximal common iliac region (1.95 vs. 0.59 ng/mL; $p = 0.009$). There were 18 patients with a PSA <1.0 ng/mL. Ten of these patients (61%) had at least one aberrant positive lymph node.

*Conclusion:* Seventy-nine percent of the PSA-recurrent patients had at least one aberrant positive lymph node. Application of the standard RTOG-CTV for pelvic irradiation in the salvage setting therefore seems to be inappropriate.

## Introduction

Approximately 25% of patients with prostate cancer treated with prostatectomy will have recurrent disease, initially presenting as a rise of the prostate-specific antigen (PSA) (1). Salvage radiotherapy is a treatment option in case of a PSA recurrence (2). Recommendations generally are to only irradiate the prostate bed (3). However, the results of this treatment leave room for improvement (4, 5). This might partially be due to already-present occult lymph node involvement in a subset of patients (6). These patients will not be cured by irradiation of only the prostate bed, but some might benefit from pelvic lymph node irradiation, as was recently shown in a retrospective study. For patients with a high risk of lymph node involvement, a benefit for whole-pelvic radiotherapy (WPRT) with standard irradiation fields compared with irradiation of the prostate bed alone was reported (7). However, even with WPRT the 5-year biochemical-free survival was still only 47%. We hypothesized that this might partly be due to geographic miss because of a deviant pattern of lymph node spread after prostatectomy. This phenomenon has previously been described in patients treated for breast cancer (8-10).

Little is known about the pattern of lymph node spread in PSA-recurrent patients, because of the limited sensitivity of commonly used imaging methods like CT and MRI for the detection of lymph node metastases (11). Furthermore, whereas pelvic lymph node dissection has yielded information about the distribution of pathologic lymph nodes in primary prostate cancer patients, it is not performed before salvage radiotherapy (12). It is therefore unknown whether the standard clinical target volume (CTV) as described by the Radiation Therapy Oncology Group (RTOG) for elective pelvis irradiation in primary prostate cancer patients can also be applied in the salvage setting.
With the development of MR lymphography (MRL), a technique that uses the contrast agent ferumoxtran-10 to enhance MRI, noninvasive detection of lymph node metastases in prostate cancer patients has become highly sensitive and specific (13, 14). This method can therefore provide reliable information on the distribution of pathologic lymph nodes.

In the present study MRL was used to map the pattern of lymph node involvement in patients with a PSA recurrence after prostatectomy who were eligible for salvage radiotherapy. It was investigated whether the CTV for elective pelvis irradiation in the primary setting as defined by RTOG (15) could also be applied in the salvage setting for patients with (a high risk of) lymph node metastases.

## Methods and Materials

*Patient selection*
Between February 2005 and March 2010, an MRL was performed at our institute in 65 patients with a PSA recurrence after prostatectomy, who were eligible for salvage radiotherapy of the prostate bed. All patients had a PSA level of 0.2 ng/mL at least 6 weeks postoperatively followed by at least one higher value, or a single PSA value of 0.5 ng/mL or higher (6). Patients with a PSA >10 ng/mL had had a bone scan and a CT or MRI of the

abdomen within the 6 months before the MRL without evidence of bony or lymph node metastases. MRL detected positive lymph nodes in 47 patients. Their charts were reviewed. All patients provided informed consent.

*MRL scanning procedure*
The lymph-node-specific contrast agent ferumoxtran-10 (Sinerem; Guerbet, Paris, France) was injected i.v. 24–36 h before MRI. It contains ultrasmall superparamagnetic particles of iron oxide that are transported to the lymph nodes by macrophages after extravasation. The iron particles give a low signal intensity on a T2∗-weighted MRI image. Metastases in the lymph nodes block accumulation of the iron particles. The signal intensity of pathologic nodes will therefore remain high on a T2∗-weighted MRI image, whereas the signal intensity of normal lymph nodes becomes low (13, 16).
Magnetic resonance images were obtained on a 3T imaging systems (TrioTim (Siemens, Erlangen, Germany)); Gyroscan/Intera (Philips, Eindhoven, The Netherlands)) by use of pelvic phased array coils. Patients were placed in the supine position with a knee fix. Images were acquired from the entire pelvis and abdomen. Buscopan i.m. and i.v. and glucagon i.m. were administered before scanning to suppress bowel peristalsis. Heesakkers *et al.*(13) previously described the scanning protocol.

*Image analysis*
All MRL images were analyzed by an experienced radiologist. Lymph nodes were considered malignant when they completely or partially showed high signal intensity on a T2∗-weighted image (13).

*Analysis of the pattern of lymph node spread*
All positive lymph nodes were assigned to a lymph node region. This was done according to the RTOG description of the CTV for elective pelvis irradiation in the primary setting (15), which will be referred to as the RTOG-CTV. Lymph node regions included in these guidelines are the internal and external iliac regions, the obturator region, and the presacral region. The common iliac region is included only from the L5/S1 interspace down. Therefore, this region was divided into a proximal and a distal part, separated by the L5/S1 interspace. Other regions not included in the RTOG-CTV are the para-aortal, paravesical, and pararectal region. The para-aortal region comprised the area of the aorta and vena cava with a margin of 1.5 cm (17). The pararectal lymph node region was defined as the mesorectum, adjacent to the presacral, obturator, and internal iliac lymph node regions (18). The paravesical region was defined as the area around the bladder, adjacent to the pararectal, external iliac, and obturator region, and to the abdominal wall and pubic bone ventrally (18).
The para-aortal, proximal common iliac, pararectal, and paravesical regions will be referred to as aberrant lymph node regions.

*Analysis of risk factors for aberrant lymph drainage*
This analysis was performed to determine whether involvement of the aberrant lymph node regions can be predicted, so that the need for inclusion of these regions in a CTV for pelvic irradiation could be determined on an individual basis.

For statistical testing SPSS 16.0.01 (SPSS, Chicago, IL) was used, and $p < 0.05$ was *a priori* deemed significant. Known factors predicting the outcome after salvage radiotherapy were used in this analysis (6): initial PSA level, PSA level at the time of MRL, PSA doubling time, Gleason score, presence of extracapsular extension and seminal vesicle involvement, status of the lymph nodes at pelvic lymph node dissection (PLND), and postoperative PSA level. The PSA level at the time of MRL was only included in the analysis if patients had not used hormonal treatment after prostatectomy in the 2 years before MRL, because of its influence on PSA value. Further, it was analyzed whether hormonal treatment and PLND were risk factors for aberrant lymph drainage.
For continuous variables normality of distributions was verified with the Kolmogorov-Smirnov test. Because there were no variables with a normal distribution, nonparametric tests were used. The Mann-Whitney *U* test was used to determine the significance of possible associations. To identify confounding factors, the correlation between variables was determined using the Spearman rank correlation test.
Association between discrete variables and the presence of positive lymph nodes in the aberrant regions was determined using Pearson $\chi^2$ testing.
Multivariate analysis was done with binary logistic regression. Factors that were significantly associated with aberrant lymph drainage in univariate analysis and possible confounding factors were included in this analysis. Normal distribution was obtained by converting the variables to a logarithmic scale.

*Pattern of lymph node spread in patients with a PSA level <1.0 ng/mL at the time of MRL*
Patients treated with early salvage radiotherapy have a better outcome (2, 4). Therefore, the lymph node spread pattern in patients with a PSA <1.0 ng/mL at the time of MRL was analyzed separately. Patients that used hormonal treatment in the 2 years before the MRL were excluded from this analysis, because of its possible interference with PSA serum level.

## Results

*Pattern of lymph node involvement*
There were 47 prostate cancer patients with a biochemical recurrence after prostatectomy that had a positive MRL. Their characteristics are shown in Table 1. The total number of positive lymph nodes was 275. Only 6 of these nodes had a diameter of >1 cm. Median number of MRL-positive lymph nodes per patients was 4 (range, 1–40), and the median number of positive lymph node regions was three (range, one to nine). The distribution of the positive lymph nodes is shown in Figure 1. The numbers in this figure represent the percentage of patients with at least one positive lymph node in that particular lymph node region. The RTOG-CTV (15) is schematically displayed in the figures by the dotted contour. In total 37 patients (79%) had at least one positive lymph node in one of the aberrant lymph node regions. Twenty-two patients (47%) had a positive lymph node in either the left or right proximal common iliac region and 11 patients (23%) in the para-aortal region. In 20 patients (43%) a positive lymph node was found in the pararectal region. Two patients had a positive lymph node in the paravesical region.

**Table 1. Patient characteristics**

| Characteristic | Median (range) |
|---|---|
| Age (years) | 65 (45-80) |
| Initial PSA (ng/ml) | 11.05 (2.30-92.50) |
| PSA at the time of MRL (ng/ml) | 0.92 (0.23-34.00) |
| PSA doubling time (months) | 4.23 (0.59-67.10) |
| | **N (%)** |
| Gleason score | |
| unknown | 1 (2.1) |
| 6 | 2 (4.3) |
| 7 | 23 (48.9) |
| 8 | 8 (17.0) |
| 9 | 13 (27.7) |
| Pathological T-stage | |
| Unknown | 1 (2.1) |
| 1c | 1 (2.1) |
| 2a | 1 (1.5) |
| 2b | 2 (9.2) |
| 2c | 5 (15.4) |
| 3a | 15 (35.4) |
| 3b | 20 (32.3) |
| 4 | 2 (4.3) |
| Lymph node metastases at PLND | |
| Unknown | 1 (2.1) |
| No PLND performed | 7 (14.9) |
| Yes | 14 (29.8) |
| No | 25 (53.2) |
| Positive resection margin | |
| Unknown | 5 (10.6) |
| Yes | 14 (29.8) |
| No | 28 (59.6) |
| Extracapsular extension | |
| Unknown | 4 (8.5) |
| Yes | 29 (61.7) |
| No | 14 (29.8) |
| Seminal vesicle invasion | |
| Unknown | 1 (2.1) |
| Yes | 21 (44.7) |
| No | 25 (53.2) |
| PSA detectable postoperative | |
| Yes | 23 (48.9) |
| No | 24 (51.1) |
| Hormonal treatment | |
| None | 30 (63.8) |
| Before RP | 1 (2.1) |
| After RP | 14 (29.8) |
| Before and after RP | 2 (4.3) |

*Abbreviations:* PSA = prostate-specific antigen; MRL = magnetic resonance lymphography; PLND = pelvic lymph node dissection; RP = radical prostatectomy.

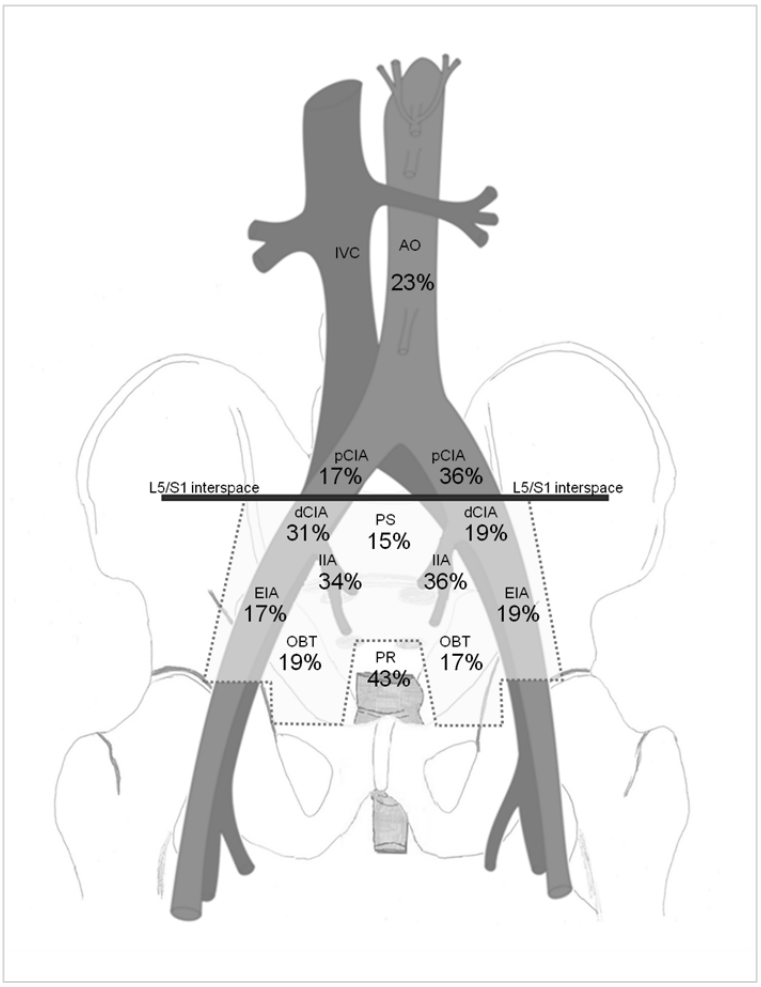


**Fig. 1.** Schematic distribution of positive lymph nodes in all 47 patients.
Numbers represent the percentage of patients with at least one positive lymph node in that lymph node region. The clinical target volume for elective pelvic irradiation in prostate cancer as described by the Radiation Therapy Oncology Group is schematically displayed by the dotted line. The L5/S1 interspace represents the border between the proximal and distal common iliac region. Two patients had a positive lymph node in the paravesical region (not shown).
*Abbreviations:* IVC = inferior vena cava; AO = aorta; pCIA = proximal common iliac artery; dCIA = distal common iliac artery; EIA = external iliac artery; IIA = internal iliac artery; OBT = obturator region; PS = presacral region; PR = pararectal region

*Analysis of risk factors for aberrant lymph drainage*

This analysis was not done for the paravesical region, because only 2 patients had a positive lymph node in this area. No risk factors could be identified for the presence of positive lymph nodes in the pararectal region.

Table 2 summarizes the factors significantly associated with the presence of positive lymph nodes in the para-aortal and proximal common iliac regions. PSA at the time of MRL was significantly higher in the groups of patients with positive lymph nodes in either region. The PSA doubling time was significantly longer in the group with positive para-aortal nodes.

Because this was unexpected, we searched for confounding factors and found a significant correlation between the time between biochemical recurrence and MRL and PSA doubling time (Spearman's ρ coefficient 0.40, $p = 0.002$).
Multivariate analysis was performed for association with the presence of para-aortal lymph node metastases. When including PSA doubling time, time between biochemical recurrence and MRL, and PSA at the time of MRL in this analysis, only PSA at the time of MRL remained significant.

**Table 2. Factors associated with the presence of positive lymph nodes in the para-aortal and proximal common iliac region**

| Factor | PA+ | PA- | Univariate p-value | Multivariate p-value* | pCI+ | pCI- | Univariate p-value |
|---|---|---|---|---|---|---|---|
| PSA at the time of MRL (ng/ml; median) | 2.49 | 0.82 | 0.007 | 0.044 | 1.95 | 0.59 | 0.009 |
| PSA doubling time (months; median) | 7.02 | 3.19 | 0.043 | *NS* | 3.86 | 4.23 | *NS* |

* For multivariate analysis, time between PSA recurrence and MRL, PSA at the time of MRL and PSA doubling time were included.
*Abbreviations:* PA+=group with positive para-aortal lymph nodes; PA-=group without positive para-aortal lymph nodes; pCI+=group with positive proximal common iliac lymph nodes; pCI-=group without positive proximal common iliac lymph nodes; MRL=magnetic resonance lymphography; *NS*=not significant

*Pattern of lymph node spread in patients with a PSA level <1.0 ng/mL at the time of MRL*
Eighteen of the 47 patients had a PSA <1.0 ng/mL. Figure 2 shows the distribution of the positive lymph nodes in these patients. Eleven patients (61%) had at least one positive lymph node in at least one of the aberrant regions. Five patients (28%) had a positive lymph node in either the left or right proximal common iliac artery and 3 patients (17%) in the para-aortal region. In 7 patients (39%) a positive lymph node was found in the pararectal region. One patient had a positive lymph node in the paravesical region.

## Discussion

Common recommendation for salvage radiotherapy in the case of a PSA recurrence is to only irradiate the prostate bed, because prospective studies on the role of pelvic radiotherapy in the salvage setting are lacking (3). This treatment, however, will not suffice for patients who already have (occult) lymph node involvement at this time. Recent studies using positron emission tomography (PET) and MRL to image lymph node metastases in PSA-recurrent patients report an incidence of positive lymph nodes of up to 30% (19-21). Retrospective studies suggest that these patients might benefit from lymph node irradiation in addition to irradiation of the prostate bed. For high-risk patients, Moghanaki *et al.*(22) found an improved biochemical complete response rate with WPRT compared with radiotherapy of only the prostate bed. Spiotto *et al.*(7) found an improvement in outcome for WPRT with standard irradiation fields compared with irradiation of only the prostate bed, also for patients with a high risk of lymph node involvement. Five-year biochemical-free survival was,

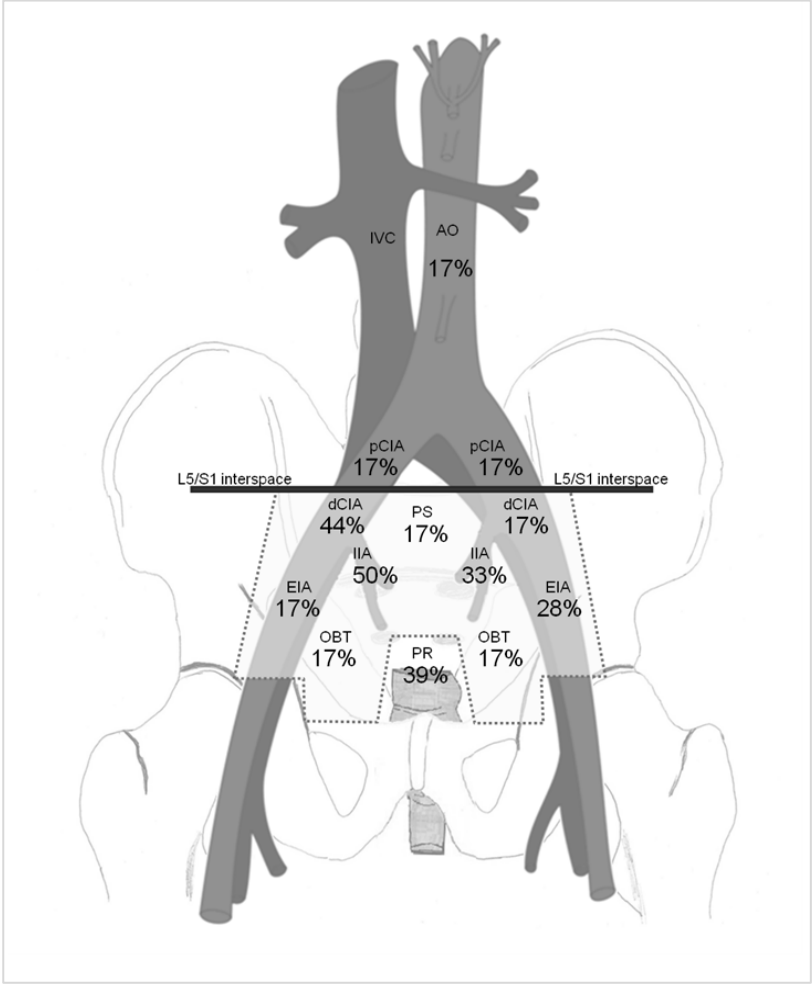


**Fig. 2.** Schematic distribution of positive lymph nodes in 18 patients with a PSA <1.0 ng/mL.
The clinical target volume for elective pelvic irradiation in prostate cancer as described by the Radiation Therapy Oncology Group is displayed by the dotted line. One patient had a positive lymph node in the paravesical region (not shown). Abbreviations as in Fig. 1.

however, still only 47%. The results of the present study suggest that this might partially be due to geographic miss. The optimal target volume for lymph node irradiation may be different from that in the primary setting, because previous treatment might influence the pattern of lymph node spread (8-10, 23).

For elective pelvic irradiation in primary radiotherapy, RTOG developed a guideline for delineation of the CTV (15). This guideline was based on findings of traditional and MR lymphography, data of extended lymph node dissection, and the sentinel node procedure, mostly in treatment-naïve patients (15). Little has been described in the literature regarding the pattern of lymph node spread in patients with a PSA recurrence after prostatectomy. This is because commonly used imaging methods like CT and MRI are insufficiently sensitive for the detection of pathologic lymph nodes (11, 24). Pelvic lymph node dissection, which has yielded information on the distribution of pathologic lymph nodes in previously

untreated patients, is not performed before salvage radiotherapy (12). Studies using PET/CT in PSA-recurrent patients after prostatectomy do not report on the distribution of the positive lymph nodes (21, 25), other than “pelvic or retroperitoneal” in one case (20).

In the present study, MRL was used to determine the pattern of lymph node spread. Magnetic resonance lymphography is a reliable method for the detection of lymph node metastases. In untreated prostate cancer patients it has a sensitivity of 80–100% and specificity of 87–99% (13, 14). To our knowledge, this is the first large investigation on the distribution of pathologic lymph nodes in patients with a PSA recurrence after prostatectomy. It was shown that aberrant lymph drainage indeed occurs frequently in these patients. No less than 79% of all MRL-positive patients had at least one aberrant positive lymph node. For patients with a PSA <1.0 ng/mL this was 61%. These results are in line with the results of a small pilot study using MRL to detect occult lymph node metastases in patients with a PSA recurrence after prostatectomy. Aberrant positive lymph nodes were found in 3 of 6 MRL-positive patients (19).
The present results suggest that in the majority of patients with recurrent disease, use of the RTOG guideline for elective pelvic irradiation would lead to geographic miss and subsequent failure of treatment. Copying the RTOG guidelines for use in the salvage setting therefore seems to be inappropriate. This will have implications for ongoing and future research on the role of pelvic radiotherapy in the salvage setting.

In treatment-naïve prostate cancer patients, aberrant lymph drainage may, however, also be a greater problem than previously thought. Ganswindt *et al.*(26) recently published a single photon emission computed tomography–derived anatomic atlas for treatment-naïve prostate cancer patients (26). They report that 65.6% of the patients had a sentinel node localization that would not be adequately covered with their conventional target volume.

Reducing geographic miss might substantially improve the results of salvage WPRT. This could be achieved by extending the target volume to include all the aberrant lymph node regions. This would, however, lead to an increase in toxicity. It was therefore investigated whether involvement of the aberrant lymph node regions could be predicted, to determine in which patients inclusion of the aberrant lymph node regions would be necessary. No less than 43% of the patients had a positive lymph node in the pararectal region, but no predictive factors for involvement of this site could be identified. Therefore, this region should either always be included in the elective CTV, or, preferably, MRL should be performed in all cases to determine the need for coverage of the pararectal region.
A higher PSA level at the time of MRL was associated with the presence of positive para-aortal lymph nodes and of positive lymph nodes in the proximal common iliac region. Surprisingly, in univariate analysis a longer PSA doubling time was associated with positive lymph nodes in the para-aortal region. Time between biochemical recurrence and MRL, however, positively correlated with PSA doubling time. This might explain why patients with para-aortal positive lymph nodes had a longer PSA doubling time: they have had more time to develop metastases higher up. In multivariate analysis, only PSA at the time of MRL remained significantly associated with the presence of positive para-aortal lymph nodes. Patients with para-aortal lymph node metastases might have metastases higher up than

scanned with MRL and are likely to be at higher risk for developing distant metastases. In both cases, radiotherapy would no longer be curative. These patients would therefore not be good candidates for local treatment. Thus, if lymph node irradiation is considered, it should only be given to recurrent patients who present with low PSA levels with relatively low risk of extrapelvic disease. Nonetheless, of the patients with a PSA <1.0 ng/ml/mL, 17% still had positive para-aortal lymph nodes. Therefore, ideally, an MRL should be performed in all patients that who are candidates for salvage radiotherapy, to optimize patient selection for lymph node irradiation.

The use of MRL might improve the results of lymph node irradiation in the salvage setting in several ways. As mentioned, MRL can aid patient selection, and MRL-guided delineation of the CTV can reduce geographic miss, while minimizing toxicity for the individual patient. The information provided by MRL would also give the opportunity to boost positive lymph nodes. Dose escalation has been shown to improve outcome for radiotherapy of the prostate, as well as of the prostate bed in the salvage setting (27-29). Increasing the dose to relatively small metastatic lymph nodes might further contribute to outcome. Recently, it was shown that MRL-guided irradiation of pelvic lymph node regions with a boost to the MRL-positive lymph nodes in conjunction with irradiation of the prostate is theoretically feasible (30). This approach could also be applied in the setting of salvage radiotherapy.

A major limitation of the present study is that in most patients no biopsy or lymph node dissection was performed, to pathologically confirm the presence of metastases in the lymph nodes identified as positive by MRL. However, pathologic validation studies in treatment-naïve patients have been performed, demonstrating very high accuracy of MRL (13, 14). There are no strong arguments why the same would not apply in the recurrent situation.

## Conclusion

In the present study 79% of the patients with a PSA recurrence after prostatectomy had positive lymph nodes in at least one of four regions (para-aortal, proximal common iliac, paravesical, and pararectal regions) not included in the RTOG-CTV for elective pelvic irradiation (15). For patients with a PSA <1.0 ng/mL this was 61%. Applying this RTOG-CTV in the salvage setting would therefore lead to geographic miss in the majority of patients. Use of MRL to guide salvage radiotherapy will reduce geographic miss and gives the opportunity to boost lymph node metastases, which could lead to an improvement in outcome.

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# 5

# Magnetic resonance lymphography–guided selective high-dose lymph node irradiation in prostate cancer

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## Abstract

*Purpose:* To demonstrate the feasibility of magnetic resonance lymphography (MRL) –guided delineation of a boost volume and an elective target volume for pelvic lymph node irradiation in patients with prostate cancer.
The feasibility of irradiating these volumes with a high-dose boost to the MRL-positive lymph nodes in conjunction with irradiation of the prostate using intensity-modulated radiotherapy (IMRT) was also investigated.

*Methods and Materials*: In 4 prostate cancer patients with a high risk of lymph node involvement but no enlarged lymph nodes on CT and/or MRI, MRL detected pathological lymph nodes in the pelvis. These lymph nodes were identified and delineated on a radiotherapy planning CT to create a boost volume. Based on the location of the MRL-positive lymph nodes, the standard elective pelvic target volume was individualized. An IMRT plan with a simultaneous integrated boost (SIB) was created with dose prescriptions of 42 Gy to the pelvic target volume, a boost to 60 Gy to the MRL-positive lymph nodes, and 72 Gy to the prostate.

*Results:* All MRL-positive lymph nodes could be identified on the planning CT. This information could be used to delineate a boost volume and to individualize the pelvic target volume for elective irradiation. IMRT planning delivered highly acceptable radiotherapy plans with regard to the prescribed dose levels and the dose to the organs at risk (OARs).

*Conclusion*: MRL can be used to select patients with limited lymph node involvement for pelvic radiotherapy. MRL-guided delineation of a boost volume and an elective pelvic target volume for selective high-dose lymph node irradiation with IMRT is feasible. Whether this approach will result in improved outcome for these patients needs to be investigated in further clinical studies.

## Introduction

Controversy exists about the optimal treatment for patients with prostate cancer with (a high risk of) lymph node metastases in the pelvis. Besides lymphadenectomy and hormonal therapy, one of the treatment options is whole-pelvis irradiation. Two randomized trials on the effect of pelvic radiotherapy do not show a benefit for elective irradiation of the whole pelvis compared with irradiation of the prostate only (1, 2). Results of nonrandomized studies on this subject are contradictory (3–7). However, several retrospective studies investigating the impact of pelvic lymph node dissection on prognosis suggest that patients with limited pelvic lymph node involvement could be cured by this regional treatment (8, 9). This indicates that pelvic radiotherapy might also be curative in selected cases.
There are several possible explanations for the disappointing results of the above-mentioned studies. Most studies use the Nodal Risk Formula (NRF) (10) for patient inclusion. This formula only estimates the risk of nodal involvement and does not give information on the localization of pathological nodes. This means that patients without nodal involvement or with nodal involvement outside the standard pelvic target volume (11–13), for example in the para-aortal or para-rectal region (13, 14), could have been included. These patients will obviously not benefit from standard pelvic irradiation.
Furthermore, in localized prostate cancer, dose escalation has shown to improve outcome (15, 16). This may also apply for lymph node metastases and the dose administered in these studies, usually 45 to 50 Gy, might not have been sufficient.

With the development of MRI enhanced with a lymph-node–specific contrast medium called ferumoxtran-10, reliable noninvasive detection of lymph node metastases even in nonenlarged lymph nodes has become possible. This method is frequently referred to as magnetic resonance lymphography (MRL). It has a sensitivity of 80% to 100% and a specificity of 87% to 99% (17–20) and is more reliable than the NRF in predicting lymph node involvement in prostate cancer patients (21). Furthermore, MRL visualizes the pathological lymph nodes, which offers the opportunity to boost these nodes and to adjust the elective nodal target volume to prevent geographical miss.

To date, the use of MRL for selective high-dose lymph node irradiation has not been described. The purpose of this study was to investigate the feasibility of using MRL to delineate a boost volume and an individualized target volume for elective pelvic lymph node irradiation in a group of prostate cancer patients without enlarged lymph nodes on CT and/or MRI. Further, the feasibility of irradiating this individualized pelvic target volume and of boosting the MRL-positive lymph nodes in conjunction with irradiation of the prostate using intensity-modulated radiotherapy (IMRT) was investigated.

## Methods and materials

*Patient selection*
For this pilot study an MRL was performed in 11 patients with histologically proven adenocarcinoma of the prostate who had been referred for curative prostate radiotherapy.

All patients had a risk of lymph node involvement of at least 15% according to the NRF, no evidence of enlarged lymph nodes on CT and/or MRI (performed during workup for radiotherapy), and a negative bone scan. Two patients with a negative MRL were treated with curative prostate radiotherapy, and 9 patients with a positive MRL received hormonal therapy as is common practice in our hospital for these patients. Three of these 9 patients had positive lymph nodes proximal to the bifurcation of the common iliac artery. They were excluded from the present in planning study to prevent too large irradiation volumes. Two patients who had had a diagnostic lymph node dissection before CT were also excluded. Finally, 4 patients were enrolled in this study, after informed consent was given.

*Ferumoxtran-10*

Ferumoxtran-10 (Sinerem; Guerbet, Paris, France) is a contrast agent consisting of ultrasmall superparamagnetic particles of iron oxide. After intravenous injection, the iron oxide particles extravasate and are enclosed by macrophages, which are transported to the lymph nodes. The iron particles give a low signal intensity on a T2*-weighted MRI image. If a lymph node contains a metastasis, this (part of the) lymph node cannot be filled with macrophages loaded with iron oxide particles, and the signal intensity on a T2*-weighted MRI image will remain high (17, 22).

*Scanning procedures*

The CT scan for radiotherapy planning was obtained with 1-mm slice thickness with a multislice CT scanner (Brilliance Big Bore CT; Philips Medical Systems, Bothell, WA). Patients underwent scanning in the supine position with a knee fix and a full bladder. Before scanning, an endorectal balloon was inserted. MRI images were obtained on 3T imaging systems (TrioTim, Siemens, Erlangen, Germany; Gyroscan/Intera, Philips, Eindhoven, the Netherlands) by use of pelvic phased array coils. MRI images were acquired from the entire pelvis and abdomen in the supine position with a knee fix, 24 to 36 h after intravenous infusion of ferumoxtran-10 (Sinerem, Guerbet, France). To improve registration of the CT and MRL images, MRL was also performed with an endorectal balloon. Before the MR examination Buscopan i.m. and i.v. and Glucagon i.m. were administered to suppress bowel peristalsis. The scanning protocol was described previously by Heesakkers et al. (17).

The MRL was performed within 1 week before the planning CT. The MRL images were analyzed by a dedicated radiologist. Lymph nodes were considered malignant if they completely or partially showed a high signal intensity on a T2*-weighted image, as has been previously described by Heesakkers et al. (17).

*Delineation*

A radiologist and a radiation oncologist manually registrated the CT scan and the MRL based on bony anatomy combined with vascular anatomy. This facilitated the recognition of MRL-positive lymph nodes on the CT scan. The actual delineation of the pathological lymph nodes was performed on the CT scan.

The gross tumor volume for nodal boost irradiation ($GTV_{lnn}$) consisted of all MRL-positive lymph nodes. No margin was applied to obtain the clinical target volume ($CTV_{lnn}$). Each pathological lymph node was classified according to location and closest vessel as: external iliacal, internal iliacal, presacral, para-rectal, or obturator.

Subsequently, the radiation oncologist delineated the lymph node regions for elective irradiation to an intermediate dose. This delineation was done according to the Radiation Therapy Oncology Group (RTOG) consensus guidelines (12). To keep toxicity as low as possible, only lymph node regions containing metastases on the MRL were delineated. The obturator area was delineated in all patients, as lymph drainage paths to all lymph node regions run through this area (23). The mesorectal region was contoured in case of MRL-positive para-rectal lymph nodes, by covering the entire mesorectal space on the side of the lymph node metastasis as proposed by Taylor et al. (24). The cranial border of each region was defined by the pathological lymph node itself. All delineated lymph node regions together, to be irradiated to an elective dose, were named $CTV_e$.
The prostate and the base of the seminal vesicles were contoured and named the $CTV_p$.

**Table 1. IMRT planning objectives and weight factors**

| ROI | Objective | Dose level (Gy) | Volume (%) | Weight factor |
|---|---|---|---|---|
| **$PTV_{lnn}$** | Max dose | 62 | | 5 |
| **$PTV_{lnn}$** | Uniform dose | 60 | | 10 |
| **$PTV_{lnn}$** | Min dose | 59 | | Constraint |
| **$PTV_e$** | Max dose | 46 | | 5 |
| **$PTV_e$** | Uniform dose | 42 | | 10 |
| **$PTV_e$** | Min dose | 41 | | Constraint |
| **$PTV_p$** | Max dose | 73 | | 50 |
| **$PTV_p$** | Uniform dose | 72 | | 30 |
| **$PTV_p$** | Min dose | 71 | | Constraint |
| **Rectal wall** | Max DVH | 30 | 8 | 10 |
| **Rectal wall** | Max DVH | 36 | 5 | 10 |
| **Rectal wall** | Max DVH | 52 | 4 | 20 |
| **Rectal wall** | Max dose | 64 | | 10 |
| **Anal wall** | Max DVH | 43 | 4 | 1 |
| **Anal wall** | Max DVH | 34 | 8 | 1 |
| **Anal wall** | Max DVH | 25 | 13 | 1 |
| **Anal wall** | Max DVH | 16 | 20 | 1 |
| **Anal wall** | Max dose | 54 | | 1 |
| **Bladder** | Max DVH | 42 | 20 | 10 |
| **Bladder** | Max DVH | 57 | 5 | 10 |
| **Left femur** | Max dose | 35 | | 1 |
| **Right femur** | Max dose | 35 | | 1 |

*Abbreviations:* $PTV_{lnn}$=Boost volume for the MRL-positive lymph nodes; $PTV_e$=PTV for elective irradiation of lymph node regions; $PTV_p$=PTV for prostate and seminal vesicles; ROI=region of interest; Max dose=maximum allowable dose; Min dose=minimum allowable dose; DVH=Dose Volume Histogram; Max DVH=maximum allowable dose to a certain volume

A margin of 0.5 cm was added to the $CTV_{lnn}$, the $CTV_e$ and the $CTV_p$ to obtain the planning target volumes ($PTV_{lnn}$, $PTV_e$, and $PTV_p$).
The following organs at risk (OARs) were delineated: femoral heads, rectal wall, anal wall sigmoid, small bowel, and bladder.

*Dose prescription and planning procedure*
Planning was done with a step-and-shoot IMRT technique with a simultaneous integrated boost (SIB) using the Pinnacle3 treatment planning system v.9 (Philips Medical Systems, Andover, MA) and the inverse planning module Direct Machine Parameter Optimization (DMPO). The nodal boost dose prescription was 60 Gy in 2-Gy fractions to the $PTV_{lnn}$. An elective dose of 42 Gy in 1.4-Gy fractions was prescribed to the $PTV_e$ and a dose of 72 Gy in 2.4-Gy fractions was prescribed to the $PTV_p$.
The IMRT plans consisted of 19 coplanar, nonopposing, 10-MV photon energy beams with a total maximum of 130 segments. Dose–volume histogram constraint for the PTVs was to cover 99% of the volume with at least 95% of the prescription dose. The constraints to the OARs were according to the RTOG consensus guidelines (12). The IMRT planning objectives for the PTVs and OARs are shown in Table 1.

## Results

According to the NRF (risk of lymph node involvement =2/3PSA + ((Gleason score-6) x 10)

**Table 2. Patient characteristics**

| Patient | T-stage | PSA | Gleason score | Risk of LN involvement according to NRF | No. of MRL-positive LNN | Location of MRL-positive LNN | LN regions included in $CTV_e$ |
|---|---|---|---|---|---|---|---|
| **1** | cT2b | 23.6 | 4+3+7 | 25.7% | 2 | Left external iliac region | Left obturator and external iliac region |
| **2** | cT3a | 18.4 | 4+3=7 | 22.3% | 6 | Right external iliac region, left internal iliac region, right pararectal region | Right and left obturator region, right external iliac region, left internal iliac region, right pararectal region |
| **3** | cT3b | 32.0 | 4+3=7 | 31.3% | 12 | Right and left internal iliac region, right and left external iliac region | Right and left obturator, internal iliac and external iliac region |
| **4** | cT3b | 33.0 | 4+3=7 | 32.0% | 4 | Right internal and external iliac region | Right obturator, internal and external iliac region |

*Abbreviations:* LN=lymph node; LNN=lymph nodes; NRF= Nodal Risk formula; MRL=Magnetic Resoncance Lymphography; No.=Number; $CTV_e$=CTV for elective irradiation of lymph node regions

(10), the 4 investigated patients had an average risk of metastases to the lymph nodes of 27.8%. Table 2 lists the patient characteristics.
Two positive lymph nodes were found in the obturator area, seven in the external and 14 in the internal iliac region, and none in the presacral region. One pathological lymph node was found outside the elective lymph node volume as described by Lawton et al. in the RTOG consensus guidelines (12). This lymph node was located in the para-rectal region.
For all positive lymph nodes on MRL, an anatomical substrate could be found on the CT scan. The average volume of the positive lymph nodes was 0.17 cm3 (range, 0.05–0.49 cm3).

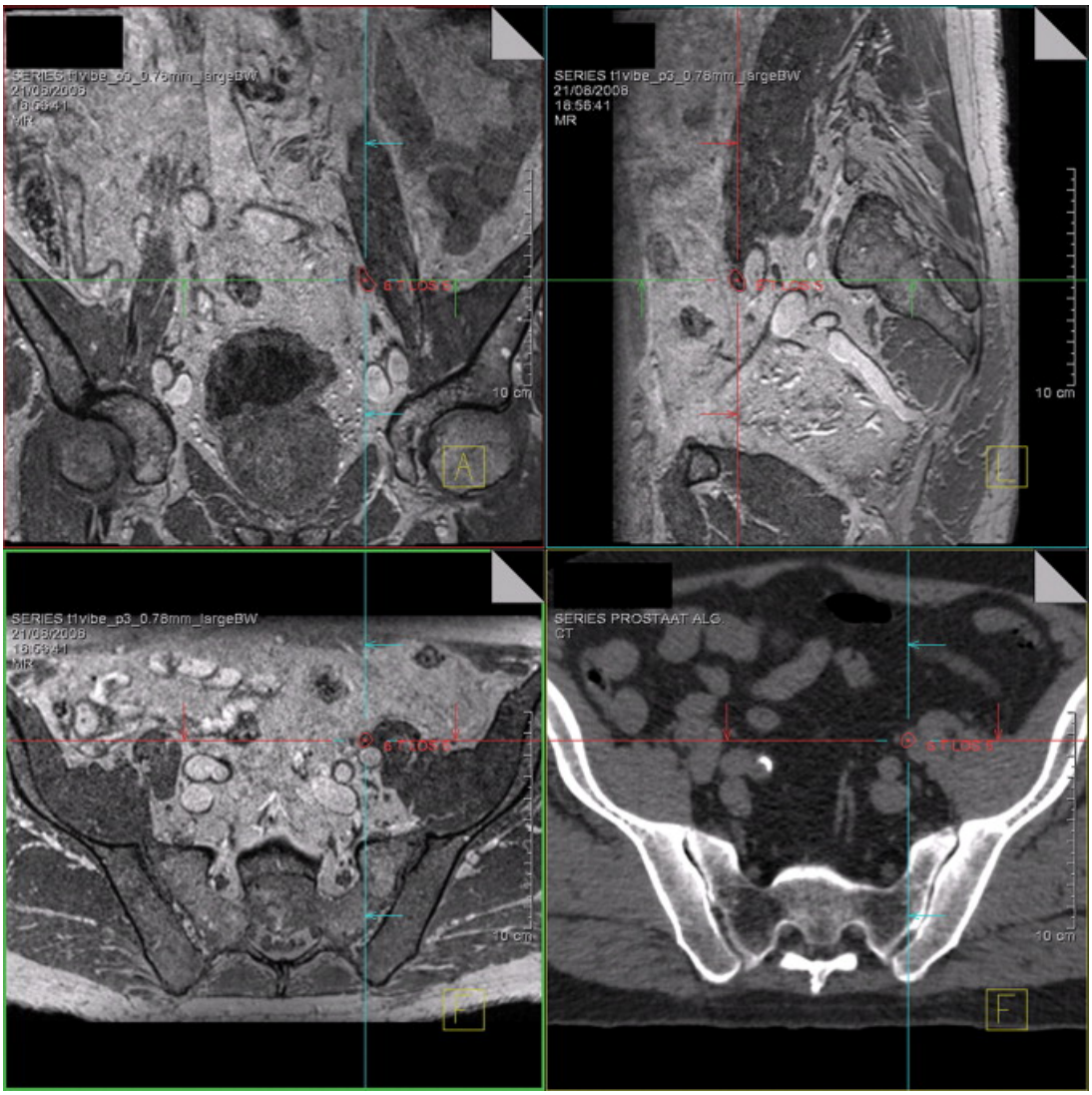


**Fig. 1.** Fusion of magnetic resonance lymphography (MRL) (upper right and left and lower left) and CT scan (lower right) for Patient 1 in Table 2.With help of the MRL, the visible lesion on the CT scan could be identified as a pathological lymph node.

An example of a comprehensive MRL-based lymph node delineation and radiotherapy planning is shown in Figures 1 to 3 for Patient 1 in Table 2. This 78-year-old man presented

with a cT2b adenocarcinoma of the prostate, with a PSA of 23.6 ng/ml and a Gleason score of 4 + 3 = 7. The MRL showed two pathological lymph nodes, both located in the left external iliac region. Figure 1 shows an MRL image in three dimensions of this patient, with one of the positive lymph nodes delineated red. In the lower right corner of the figure, the same lymph node is shown on the CT scan. This example shows that the MRL-positive lymph nodes could be identified on the planning CT scan. Figure 2 shows the subsequent delineation of this lymph node (red) and the $PTV_{lnn}$ (yellow), $PTV_e$ (blue), and $PTV_p$ (orange) on the CT scan.

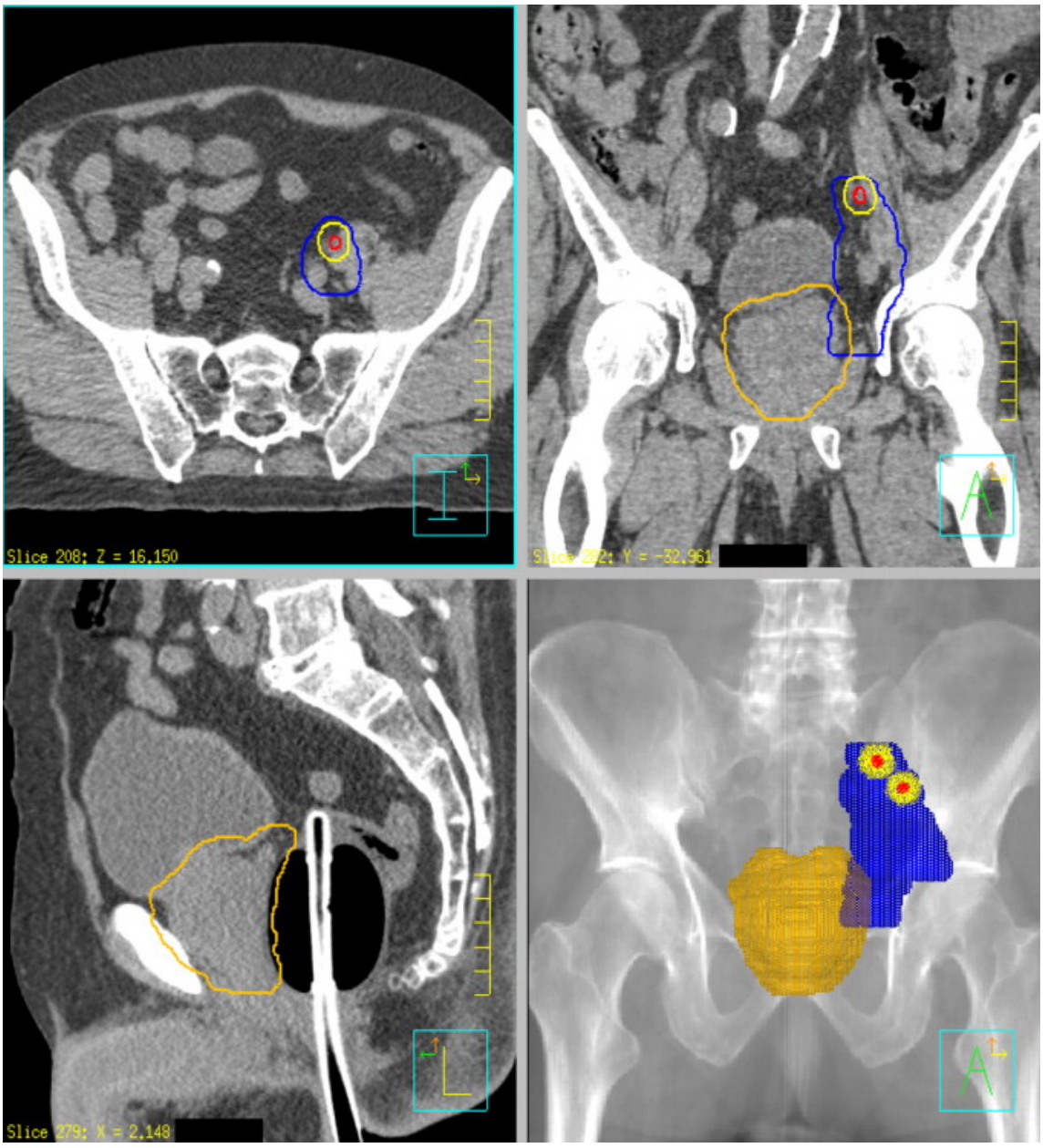


**Fig. 2.** After identification of the pathological lymph nodes, the lymph nodes were delineated on the CT scan. These are shown in red. The $PTV_{lnn}$ is delineated in yellow, the $PTV_e$ in blue, and the $PTV_p$ in orange.

For this patient, an IMRT plan with a SIB was calculated. The dose distribution is shown in Figure 3.

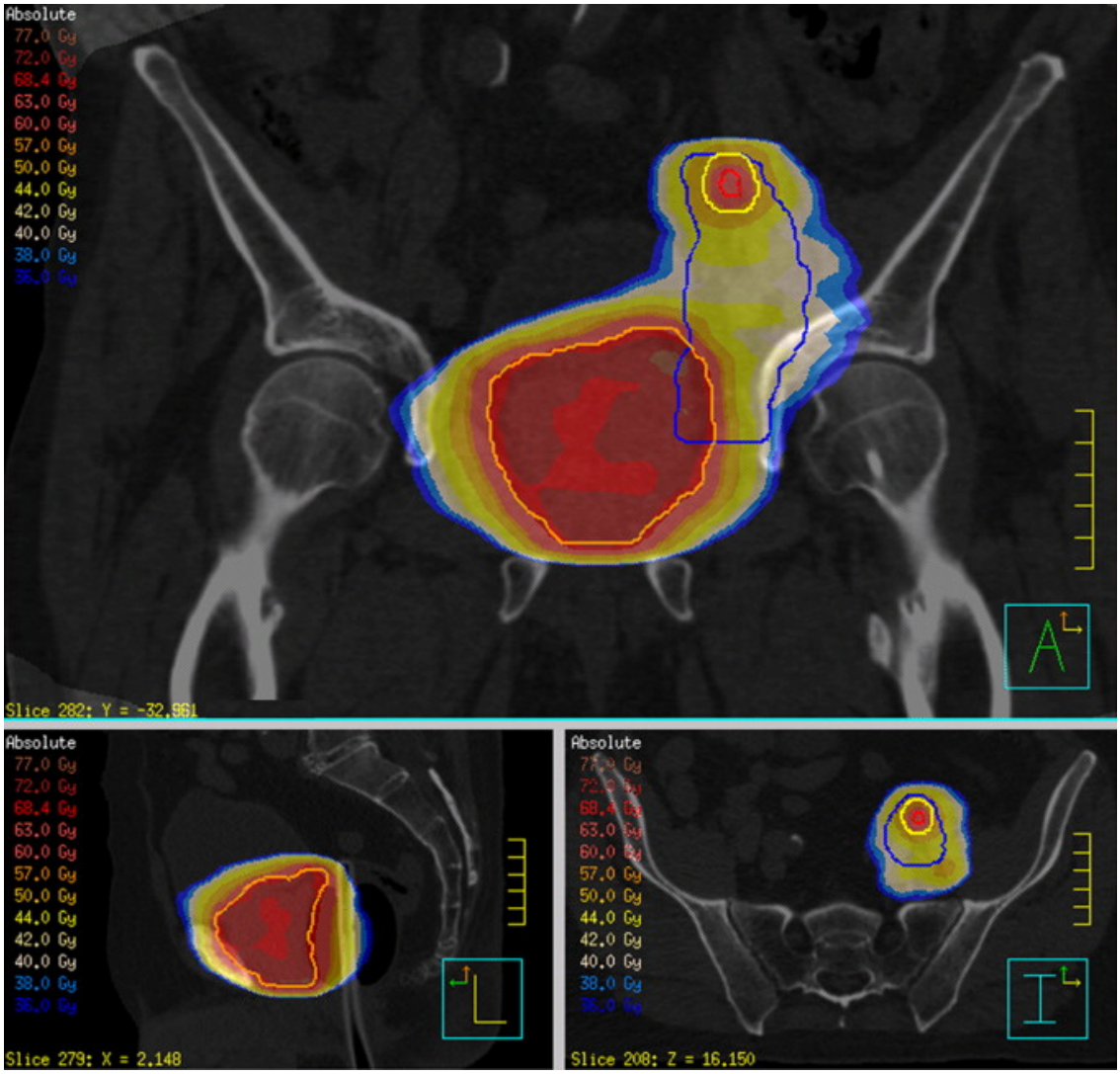


**Fig. 3.** Dose distribution of the intensity-modulated radiotherapy (IMRT) plan for Patient 1 in Table 2.

IMRT planning delivered highly acceptable radiotherapy plans for all 4 patients. For all patients, the dose–volume histogram constraints for the three PTVs were reached. Table 3 and Table 4 show the planning results for the PTVs and OARs. For the third patient, the maximum allowable dose to the small bowel was exceeded because of localization of the small bowel directly adjacent to the $PTV_{Inn}$. In this patient, 1.1 cc of the small bowel received a dose of more than 52 Gy. This was accepted because the small bowel is a moving organ, and it is to be expected that every day a different part of the small bowel lies in this high-dose area.

**Table 3. Planning results for the PTVs**

| Patient | $V_{95\%}$ $PTV_{Inn}$ | Mean dose $PTV_{Inn}$ (Gy) | $V_{95\%}$ $PTV_e$ | Mean dose $PTV_e$ (Gy) | $V_{95\%}$ $PTV_p$ | Mean dose $PTV_p$ (Gy) |
|---|---|---|---|---|---|---|
| 1 | 99.2% | 60.2 | 99.6% | 46.4 | 99.0% | 73.8 |
| 2 | 99.1% | 61.4 | 99.6% | 46.5 | 99.0% | 73.8 |
| 3 | 99.0% | 61.1 | 99.9% | 48.3 | 99.5% | 74.0 |
| 4 | 99.6% | 59.7 | 99.7% | 46.1 | 99.1% | 72.8 |

*Abbreviations:* $V_{95\%}$=Volume receiving 95% of the prescribed dose; $PTV_{Inn}$=Boost volume for the MRL-positive lymph nodes; $PTV_e$=PTV for elective irradiation of lymph node regions; $PTV_p$=PTV for prostate and seminal vesicles

**Table 4. Planning results for the OARs**

| Patient | $V_{55Gy}$ bladder | $V_{70Gy}$ bladder | Maximum dose to small bowel (Gy) | $V_{50Gy}$ rectal wall | $V_{70Gy}$ rectal wall | $V_{50Gy}$ sigmoid | $V_{70Gy}$ sigmoid | $V_{50Gy}$ femoral head right | $V_{50Gy}$ femoral head left |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 13.3% | 4.1% | 43.9 | 28.7% | 17.9% | 0.4% | 0.0% | 0.0% | 0.0% |
| 2 | 10.2% | 3.3% | 50.3 | 29.5% | 14.5% | 0.6% | 0.0% | 0.0% | 0.0% |
| 3 | 16.9% | 4.9% | 58.7 | 26.0% | 12.8% | 0.0% | 0.0% | 0.0% | 0.0% |
| 4 | 14.9% | 3.7% | 48.9 | 28.9% | 14.6% | 0.6% | 0.0% | 0.0% | 0.0% |

*Abbreviation: $V_{dose}$=Volume receiving that certain dose*

## Discussion

In this study, MRL was used to select patients with prostate cancer without enlarged lymph nodes on CT and/or MRI for pelvic irradiation. All MRL-positive lymph nodes could be identified on a CT scan for radiotherapy planning and could then be used to define a target volume for a high-dose boost and to individualize the pelvic target volume for elective irradiation. With IMRT, it is feasible to irradiate this individualized pelvic target volume and boost the MRL-positive lymph nodes to a dose of 60 Gy in conjunction with irradiation of the prostate.

So far, there is no solid evidence that elective whole-pelvis irradiation without a boost is of benefit in patients with prostate cancer with (a high risk of) lymph node involvement. Initial results of the prospective RTOG 94-13 trial, reported in 2003, were promising (25). Whole-pelvis radiotherapy was found to improve progression-free survival as compared with prostate-only radiotherapy. However, after a median follow-up of 7 years, this improvement was no longer seen (1). A second prospective study carried out by the Groupe d'Etude des Tumeurs Uro-Génitales (GETUG) also showed no benefit for whole-pelvis irradiation in terms of overall and progression-free survival (2). Several retrospective nonrandomized studies have reported contradicting results (3-7).

There are several possible explanations for the disappointing results of the above-mentioned studies. First, in most studies, patient selection was based on an estimated risk of lymph node involvement using the NRF. The RTOG study (1, 25) included patients who had a risk of 15% or more of lymph node involvement. In the GETUG trial (2), patients with an even lower risk were included. This means that most patients in these trials would not have developed lymph node metastases even without pelvic treatment.
A second possible explanation is that these trials might have included patients with lymph node metastases to regions outside the standard elective pelvic radiation field. These patients will obviously not benefit from pelvic irradiation with standard pelvic radiation fields. This includes patients with metastases to the para-aortal lymph nodes, and also patients with involved lymph nodes in the para-rectal area. Several studies on the sentinel node procedure in prostate cancer have shown that the latter region was not an unusual place for the sentinel node to be found (13, 14).
A third possible limitation of the above-mentioned trials is the irradiation dose of 45 to 50 Gy that was used. Trials on dose escalation in prostate-only radiotherapy have shown an improvement in freedom from failure with increasing dose up to 78 Gy (15, 16). This might imply that, also for eradication of lymph node metastases in prostate cancer, a higher dose is needed. Besides this, the rationale for boosting pathological lymph nodes is that this might be comparable to surgically removing them by pelvic lymph node dissection (PLND). Several retrospective studies suggest that outcome might be improved with PLND (26), especially for patients with limited lymph node involvement (8-9). These patients might also benefit from pelvic irradiation with a boost to the pathological lymph nodes.

Use of MRL could help to overcome the above-mentioned limitations of the trials performed so far on whole-pelvis radiotherapy. First, it is a more reliable method than the NRF to predict lymph node involvement (21). Sensitivity and specificity of MRL in detecting lymph node metastases have been reported to be as high as 80% to 100% and 87% to 99%, respectively, with a negative predictive value of 88% to 100% (17-20). Using MRL to select patients for pelvic irradiation therefore considerably reduces the risk of including patients without lymph node metastases and of excluding patients with lymph node metastases. Besides MRL, $^{11}$C-choline PET might be another useful tool for patient selection. Patient-to-patient sensitivity and specificity have been reported to be 80% and 96%, respectively (27), with a node-to-node sensitivity and specificity of 64% and 90%, respectively (28).
The second advantage of MRL is that it visualizes the pathological lymph nodes. This quality makes it even more valuable for patient selection, as patients with metastases to para-aortal lymph nodes can be excluded for pelvic radiotherapy. In this study, we have shown that pathological lymph nodes visualized by MRL can also be detected on a CT scan for radiotherapy planning. This offers the opportunity to individualize the elective pelvic target volume, which the highly variable lymphatic drainage in prostate cancer necessitates to prevent geographical miss. Ganswindt *et al.* proposed to individualize the target volume for pelvic irradiation based on individual sentinel node drainage patterns visualized by SPECT functional imaging, mostly by extending the standard radiation fields to include the sentinel node (13). MRL detects pathological lymph nodes with a high sensitivity and specificity on a node-to-node and a region-to-region basis (17, 18). Using MRL therefore makes individualization to a higher level possible. We decided to include only the lymph drainage

paths that we knew had been migrated by malignant cells in the $CTV_e$, i.e., the lymph node regions in which an MRL-positive lymph node was found. We regarded these regions as high-risk regions for micrometastases, possibly missed by MRL. This creates individualized image guided elective nodal target volumes based on individual lymph drainage patterns. In this manner, treatment toxicity can be kept as low as possible while reducing the risk of geographical miss.
Finally, because we have found that MRL-positive lymph nodes can be detected on the CT scan for radiotherapy, one can delineate a boost volume within the elective pelvic target volume. The development of IMRT has led to more conformal treatment plans and a reduction in the dose delivered to the OARs (29), making dose escalation possible. We have found that with IMRT it is feasible to boost the pathological lymph nodes to a dose of 60 Gy, without grossly exceeding the dose constraints to the OARs as defined by the RTOG (12). In 1 patient, 1.1 cc of the small bowel received a maximum dose of more than 52 Gy because of its close proximity to the $PTV_{lnn}$. We accepted this, because the small bowel is a moving organ and we expected that, at every fraction, a different part would lie in this high-dose region.

This feasibility study was limited to 4 patients. Our approach was feasible in these 4 patients with different patterns of lymph node involvement. However, it is possible that patterns of lymph node involvement exist in which this approach would not be feasible.
With better patient selection using MRL, with individualization of the elective pelvic nodal target volume to reduce toxicity and to prevent geographical miss, and by boosting MRL-positive lymph nodes we expect to improve the outcome in patients with prostate cancer with small pathological lymph nodes in the pelvis. However, whether the approach presented here will indeed improve prognosis in patients with lymph node metastases of prostate cancer remains a matter for further investigation.
First, it is unclear whether it is appropriate to include only the lymph node regions containing a pathological lymph node in the elective pelvic target volume. The MRI has a resolution of 1 mm, and therefore micrometastases might be missed (20). Although it is likely it is uncertain whether these possible micrometastases are always in the same lymph node region as the MRL-positive lymph nodes. More research is needed on lymph drainage patterns related to for example T-stage and localization of the dominant intraprostatic lesion and on the localization of false-negative MRL lymph nodes in relation to the MRL-positive lymph nodes before this proposal can be implemented.
Second, it is possible that our boost dose of 60 Gy might not be high enough. However, the small bowel was dose limiting for the $PTV_{lnn}$ in our study because of its location near and sometimes adjacent to this PTV. The small bowel dose constraint as proposed by the RTOG was already slightly exceeded in 1 patient. The only way to increase dose to the pathological lymph nodes is to accept a dose >52 Gy to part of the small bowel. This was done by Fonteyne *et al.*(30). They accepted a maximal dose to the small bowel of 70 Gy and boosted pathologically enlarged lymph nodes on CT scan to a dose of 70 to 80 Gy. They reported no Grade 2 or greater upper GI toxicity. With a median follow-up of 3 months, results on late toxicity have not yet been published, and neither have results on outcomes in these patients. We must await these reports before elevating nodal dose above our proposed 60 Gy.

We expect toxicity to be acceptable with our proposed treatment, as the dose constraints to the OARs as proposed by the RTOG (12) were not exceeded, except for the constraint to the small bowel in 1 patient as mentioned earlier. In addition, an endorectal balloon was inserted to reduce late ano-rectal toxicity (31).

## Conclusion

In this study, it was shown that it is feasible to use MRL for patient selection for pelvic irradiation, and that MRL-positive lymph nodes can be localized on the CT scan. Based on the MRL, an individualized target volume for elective pelvic irradiation and a volume for a high-dose boost to the pathological lymph nodes can be defined. With IMRT, it is feasible to create treatment plans for irradiating this individual elective lymph node target volume and to simultaneously boost the MRL-positive lymph nodes to a dose of 60 Gy in conjunction with irradiation of the prostate. More research is needed, however, to determine the validity and effectiveness of this approach.

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# 6

# Prognosis of prostate cancer patients with lymph node involvement on MR lymphography: who might be cured?

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## Abstract

*Purpose:* To investigate the prognosis of prostate cancer patients with non-enlarged metastatic lymph nodes on MR lymphography (MRL) and to identify a subgroup of MRL-positive patients who might be candidates for curative treatment.

*Methods and materials:* The charts of 138 prostate cancer patients without enlarged lymph nodes on CT, in whom a pre-treatment MRL was performed were reviewed. Endpoints were distant metastases-free survival and overall survival. Relation between the following factors and outcome were investigated: T-stage, PSA value at diagnosis, Gleason score, diameter (short axis and long axis) of the largest MRL-positive lymph node, number of MRL-positive lymph nodes, the presence of extra-pelvic nodal disease, and the extent of resection of the positive lymph nodes. Kaplan-Meier analysis was performed to estimate the survival functions.

*Results:* Of the 138 patients, 24 (17%) had a positive MRL. Patients with a short axis of the largest positive lymph node of ≤8 mm had a significantly better 5-year distant metastases-free (79% vs 16%) and overall survival (81% vs 36%) than patients with larger positive lymph nodes. This also accounted for patients with a largest long axis of ≤10 mm (71% vs 20% and 73% vs 40%, respectively). Outcome was also better in patients in whom all positive lymph nodes had been resected.

*Conclusion:* A selection of MRL-positive patients with a good prognosis could be identified, consisting of patients with small positive lymph nodes. In these patients, cure might be pursued.

## Introduction

Lymph node metastases in prostate cancer patients can only be detected with conventional imaging methods as computed tomography (CT) or magnetic resonance imaging (MRI) when nodal enlargement exists, which does not occur until late in the disease process (1). Nodal involvement is therefore generally detected through a lymph node dissection. Patients with nodal involvement are historically considered to be incurable (2). However, several studies have shown that their prognosis is highly variable (3,4). Patients with a low nodal metastastic tumor burden have a favorable outcome after prostatectomy and lymph node dissection. They can remain disease-free for many years (2).

The development of new imaging methods, such as MR lymphography (MRL), has created the opportunity to detect lymph node metastases at an early stage, in non-enlarged lymph nodes (5). MRL is a technique that uses the contrast agent ferumoxtran-10 to enhance MRI. This method has a sensitivity of 80-100% and a specificity of 87-99% for the detection of involved lymph nodes in prostate cancer (6,7).

Patients in whom lymph node metastases are diagnosed non-invasively at an early stage, before enlargement of the lymph node occurs, form a new category, with an unknown prognosis. Their outcome might be comparable to that of patients with clinically occult metastases detected by pelvic lymph node dissection.

With this new category of node-positive patients, a treatment dilemma has arisen. Should we pursue cure with surgery or locoregional radiotherapy, and if yes, how should we select those patients that are most likely to benefit? To address this issue, it is necessary to obtain more data are about the course of the disease in these patients.

The purpose of the present study was to investigate the prognosis of CT-negative patients with positive lymph nodes on MRL and to identify a subgroup of MRL positive patients with a good prognosis, who might be candidates for curative treatment.

## Methods and Materials

*Patient selection*
Between January 2003 and May 2005, 150 patients with a histopathologically proven intermediate to high-risk prostate cancer (serum prostate-specific antigen level >10 ng/mL, Gleason score >6, or T3 clinical stage), with lymph nodes with a maximum diameter of 1.5 cm on CT, underwent an MRL prior to local treatment in our institute in the context of a pathological validation study. In all patients, histopathological evidence was obtained, either by pelvic lymph node dissection that was in some cases extended based on MRL, or by CT-guided lymph node biopsy. Twelve patients were excluded for the analysis as follow-up data were not available or incomplete. The charts of the remaining 138 patients were reviewed.

*MRL scanning procedure*

MRI images were obtained on a 1.5T system (Sonata/Symphony, Siemens, Erlangen, Germany; Gyroscan/Intera, Philips, Eindhoven, Netherlands; or Horizon, GE Medical Systems, Milwaukee, WI, USA) with pelvic phased array coils. To suppress bowel peristalsis, Buscopan i.m. and i.v., and Glucagon i.m. were administered before scanning. Patients were placed in the supine position with a knee fix. Images were acquired from the entire pelvis and abdomen. Heesakkers et al. previously described the scanning protocol in detail (6).

Twenty-four to 36 hours before MRI, Ferumoxtran-10 (Sinerem®, Guerbet, Paris, France) was injected intravenously. This contrast medium contains ultrasmall superparamagnetic particles of iron oxide. These particles extravasate, and are transported to the lymph nodes by macrophages. Iron particles give a low signal intensity on a T2*-weighted MRI image. Metastases in the lymph nodes block accumulation of the iron particles. The signal intensity of pathological nodes will therefore remain high on a T2*-weighted MRI image, while the signal intensity of normal lymph nodes becomes low (6,8).

Lymph nodes were considered malignant when they completely or partially showed high signal intensity on a T2*-weighted image (6). All MRL images were analyzed by an experienced radiologist.

*Treatment and follow-up after MRL*

After MRL, patients were treated for their disease, according to the result of the histopathological examination. MRL patients that were histopathologically node-negative were locally treated with prostatectomy or local radiotherapy, patients that were node-positive received hormonal treatment. Follow-up took place every 3-6 months, for a minimum of 5 years. At every visit, a PSA value was determined. A CT, MRI or bone scan was performed at the physician's discretion. In case of a recurrence patients were treated depending on the site of recurrence.

*Endpoints and statistical analysis*

For statistical testing SPSS 16.0.01 (SPSS Inc. 1989-2007) was used and a $p<0.05$ was a priori deemed significant.

Endpoints of the present study, that were determined for patients with and without lymph node involvement on MRL, were: distant metastases-free survival (DMFS) and overall survival (OS). Survival rates were estimated with the Kaplan-Meier method, and the unstratified log-rank statistical analysis was used to test for differences.

*Patients with a positive MRL*

For patients with a positive MRL, the prognostic value of tumor-related factors was investigated using Kaplan-Meier analysis: T-stage, Gleason score (<7, 7 or >7), PSA (≤10 ng/ml, >10 ng/ml).

Next, MRL-related factors were investigated: number of positive lymph nodes, largest diameter of the largest lymph node (mm), short axis diameter of the largest lymph node (mm).

For these factors, ROC analysis was performed to determine their predictive potential and to find the threshold with the highest accuracy. This threshold was used to dichotomize the patients for Kaplan-Meier analysis.
Further, the prognostic value of the presence or absence of positive lymph nodes outside the pelvis was determined. Positive lymph nodes above the L5/S1 interspace were considered to be outside the pelvis.
Last, it was investigated whether patients in whom all MRL-positive lymph nodes had been removed had a better prognosis compared to patients in whom only part of the MRL-positive lymph nodes had been removed. To determine whether all MRL-positive lymph nodes had been removed, a comparison between the surgical report, the pathology report, and the MRL result was made.
Multivariate analysis could not be performed, due to the relatively small number of MRL-positive patients.

## Results

*Total study population*
The characteristics of the 138 patients are shown in table 1.

**Table 1. Patient characteristics**

| **Characteristic** | | **Median (range)** |
|---|---|---|
| *PSA* | | *15.9 (2.8-260.0)* |
| | | **N (%)** |
| *Clinical T-stage* | 1 | 31 (22%) |
| | 2 | 85 (62%) |
| | 3 | 22 (16%) |
| *Gleason score* | unknown | 1 (1%) |
| | 5 | 4 (3%) |
| | 6 | 32 (23%) |
| | 7 | 62 (45%) |
| | 8 | 26 (19%) |
| | 9 | 10 (7%) |
| | 10 | 3 (2%) |
| *MRL Result* | Negative | 114 (83%) |
| | Positive | 24 (17%) |
| *Result PA* | Negative | 122 (88%) |
| | Positive | 16 (12%) |
| *Therapy* | Prostatectomy | 77 (56%) |
| | Radiotherapy with neo-adjuvant hormonal treatment | 47 (34%) |
| | Hormonal therapy | 14 (10%) |

*Abbreviations*: PSA=prostate-specific antigen; MRL=Magnetic Resonance Lymphography; PA=pathology

Twenty-four patients had a positive MRL (17%). In 2 patients with a negative MRL, lymph node involvement was found at histopathological verification. In 10 patients with a positive MRL, histopathological examination was negative.
Median follow-up time for all patients was 73 months (range 4-101 months). Figure 1 shows the Kaplan-Meier survival curves for DMFS (A) and OS (B) for patients with a positive and for patients with a negative MRL. Five-year DMFS was 94% for the MRL negative group, and 49% for the MRL positive group. Five-year OS was 96% and 57% respectively.

*Patients with a positive MRL*
The Kaplan-Meier survival curves for both DMFS and OS did not differ significantly between patients with a PSA ≤10 ng/ml and >10 ng/ml, different clinical T-stages, or different Gleason scores (<7, 7 or >7).

In ROC analysis, the number of positive lymph nodes was not predictive for either endpoint. The short axis of the largest positive lymph node was predictive for the occurrence of distant metastases (area under the curve (AUC) 0.76 with p=0.03). The threshold at which the highest accuracy (75%) was reached was 8 mm. The short and the long axis of the largest lymph node were both predictive of OS (AUC 0.82 with p=0.01; AUC 0.74 with p=0.05 respectively). Thresholds with the best accuracy were 8 mm for the short axis and 10 mm for the long axis diameter of the largest lymph node (accuracy 84% and 76% respectively).

Based on these thresholds, patients were dichotomized. Of the group with a short axis of the largest lymph node of ≤8mm, only 1 patient had a long axis of the largest lymph node of >10mm. Vice versa, of the patients with a long axis of the largest lymph node of ≤10mm, also only 1 patient had a lymph node with short axis of >8mm.

Figure 2 shows the corresponding survival curves. DMFS and OS were significantly better for patients in whom the short axis of the largest positive lymph node was ≤8 mm. Five-year DMFS was 79% versus 16% for the group with a longer short axis. Five-year OS was 81% and 36%, respectively. Similar results were obtained after dichotomization by the long axis size. Five-year DMFS was 71% and 20% respectively, 5-year OS 73% and 40% respectively.

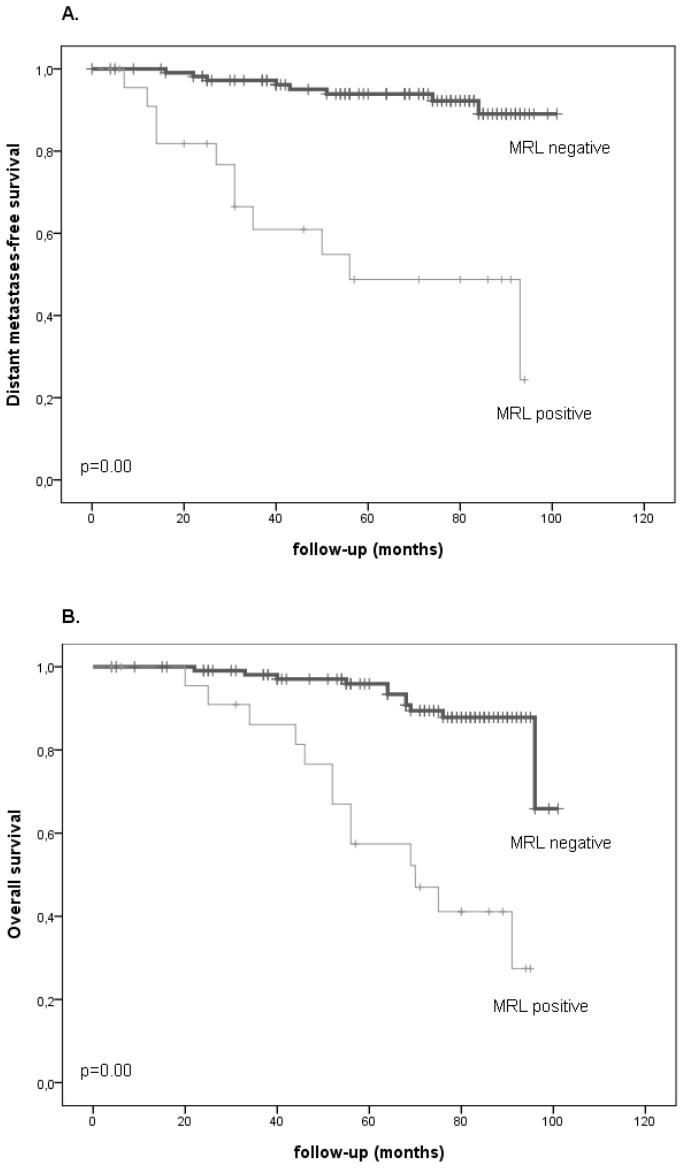


**Fig. 1.** *Survival curves for MRL negative vs MRL positive patients.*
A. Distant metastases-free survival. B. Overall survival

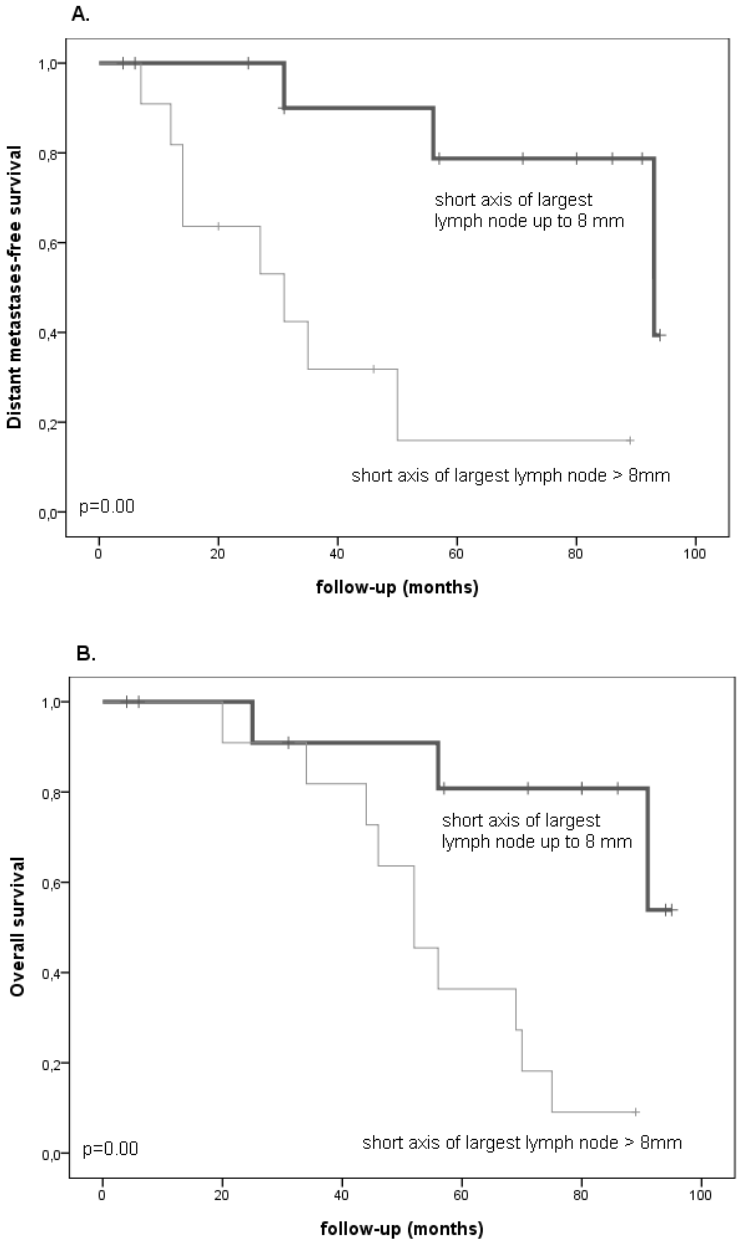


**Fig. 2.** *Survival curves for subgroups of the MRL positive patients with different MRL related factors.*
Patients with a short axis of the largest lymph node of ≤8 mm vs patients with a short axis of the largest lymph node of >8 mm. A. Distant metastases-free survival. B. Overall survival.

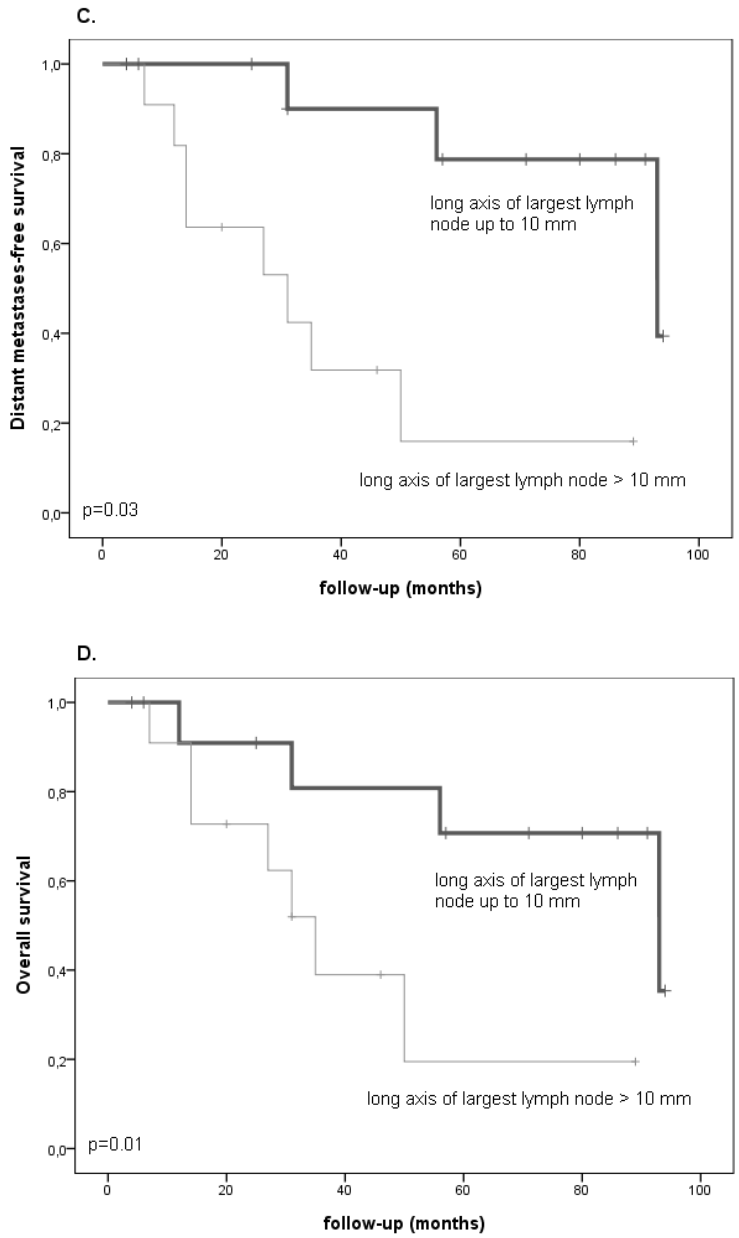


**Fig. 2. (continued)** *Survival curves for subgroups of the MRL positive patients with different MRL related factors.*
Patients with a long axis of the largest lymph node of ≤10 mm vs patients with a long axis of the largest lymph node of >10 mm. C. Distant metastases-free survival. D. Overall survival.

There were 7 patients with extra-pelvic nodal disease. Their distant metastases-free and overall survival did not significantly differ from those of patients with nodal disease limited to the pelvis.

In eight patients all MRL positive lymph nodes had been removed. These patients had a significantly better 5-year DMFS (80%) than patients in whom only part of the positive lymph nodes had been removed (35%l p=0.04). OS did not differ between the groups.

## Discussion

The presence of lymph node metastases in prostate cancer is a poor prognostic sign (1), and patients with lymph node metastases generally are considered incurable (1, 2). The present study shows that patients with a negative MRL indeed have a far better outcome than MRL-positive patients. However, within the group of MRL-positive patients, a subgroup could be defined with a better prognosis, consisting of patients with only small nodal metastases. In these patients cure might be pursued, for example by locoregional radiotherapy or resection of the positive nodes.

CT and MRI have a very low sensitivity for the detection of lymph node metastases in prostate cancer (3). The presence of lymph node metastases is therefore usually detected at pelvic lymph node dissection. However, the development of more accurate imaging methods has created the opportunity to detect lymph node involvement at an early stage, in a non-invasive manner. MRL is a very accurate imaging method, with a sensitivity of 85-100%, which can detect lymph node metastases even in non-enlarged lymph nodes (4, 5).
Thus a new category of patients emerges, whose prognosis and the treatment from which they benefit require further investigation. The present study aimed to take the first steps in describing this group of patients.

MRL-positive patients had a significantly worse prognosis compared to MRL-negative patients. Five-year OS was 57%, which is comparable to the survival of lymph node positive patients treated with androgen suppression therapy alone in other reports (6). However, patients with small MRL positive lymph nodes (a short axis of the largest positive lymph node of ≤8 mm or a long axis of ≤10 mm), had a 5-year DMFS and OS of more than 70%. This is comparable to the prognosis of high-risk node-negative patients treated with radiotherapy (7, 8).

These findings reinforce the results from previous studies investigating outcome after prostatectomy and lymph node dissection. These retrospective studies have shown that patients with limited lymph node involvement have a far better outcome compared to patients with more extensive lymph node involvement (1, 2). The number of positive lymph nodes (2, 9) and the size of the largest positive lymph node (1) were prognostic factors. Disease-specific survival was 99% at 5 years for patients with a single lymph node metastasis (2), 84% at 15 years for patients with up to 2 positive lymph nodes (9), and over 80% at 5 years for patients in whom the largest positive lymph node was ≤ 10 mm. Five-year recurrence-free survival of the latter group was around 40% (1).

Although patients with limited lymph node involvement seem to have a better outcome compared to patients with more extensive nodal disease, the question remains: can they be cured? The answer may be 'yes' for at least part of the MRL-positive patients. The finding of the present study that DMFS is high for patients with limited nodal involvement, indicate a window of opportunity for cure with locoregional treatment, before distant metastases develop. This was also found by Leibel et al, who described the outcome in patients with nodal disease treated with pelvic lymphadenectomy and brachytherapy (10). N1 (single lymph node metastasis <2 cm) patients had a better DMFS than N2 (multiple lymph node metastases or single lymph node metastasis >2 cm but <5 cm) patients. This is further supported by the results of the above mentioned studies (1, 2, 9). Our finding that patients in whom all MRL-positive lymph nodes had been removed at pelvic lymph node dissection had a very high 5-year DMFS of 80%, further substantiate this. This is also in line with the findings of several retrospective studies indicating that the larger the extent of a lymph node dissection, and thus the higher the chance of removal of all nodal disease, the better the prognosis (11, 12).

Preferably, only lymph node positive patients without distant micrometastases would be selected for locoregional treatment. The findings of the present study that patients with small MRL-positive lymph nodes less often and less early develop clinically apparent distant metastases, can guide MRL-based patient selection for a potentially curative locoregional treatment. When selecting node positive patients for locoregional treatment with MRL, the size of the short axis of the largest lymph node should be the main selection criterion, as there was significant overlap between the group with a short axis of the largest MRL-positive lymph node of ≤8 mm and the group with a long axis of ≤10 mm, with the short axis being a stronger prognostic factor at ROC analysis.

MRL can yield important progress in locoregional treatment for node positive patients. First, geographical miss of positive lymph nodes can be reduced. Studies using the sentinel node procedure or MRL to map the pattern of lymph drainage in prostate cancer patients, have shown that this is a larger problem than was previously thought. Positive lymph nodes and sentinel nodes were found outside the area of routine lymph node dissection (13), as well as outside the standard target volume for elective pelvis irradiation in more than half of the patients ((14), (15)). The possibility to target pathological lymph nodes more accurate, will increase the effectiveness of locoregional treatment in these patients.
Further, for radiotherapy, the use of MRL gives the opportunity to boost the positive lymph nodes. This has shown to be theoretically feasible, using an intensity modulated radiotherapy technique (16). Dose escalation to the prostate has shown to improve outcome (17), and this may also account for the involved lymph nodes.

A limitation of the present study is the small number of MRL-positive patients. The findings of this study should therefore be interpreted as a first step towards identification of MRL-positive patients with a good prognosis in whom cure might be feasible.
A second limitation is that histopathological examination was negative in 10 of 24 MRL-positive patients. In 4 of these patients, however, the tissue sampling was not representative, because the MRL-positive lymph nodes were not removed, as was shown by

a repeated MRL within 3 months after the initial MRL. We elected to include all MRL-positive patients for analysis. This because the aim of the present study was to find prognostic factors based on MRL without subsequent histopathological confirmation. This might have influenced our results, certainly as the histopathologically negative patients received a different (curative) treatment. As the group was too small for multivariate analysis, the influence of this factor on outcome relative to that of the prognostic factors found in our study could unfortunately not be investigated.

## Conclusion

Whereas lymph node involvement on MRL was a poor prognostic factor, a subgroup of MRL-positive patients with a relatively good prognosis could be identified. Patients with a short axis of the largest lymph node ≤8mm or a long axis ≤10mm had a good outcome, comparable to that of high-risk node-negative prostate cancer patients. These seem to be the patients in whom cure might be pursued. Patients in whom all MRL-positive lymph nodes had been resected, had a better prognosis than patients in whom part of the nodal disease was left in situ. This encourages the application of a locoregional curative treatment in these patients.

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# 7

## General Discussion

## *Future perspectives for lymph node irradiation in prostate cancer: towards an image-based individualized treatment*

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## Abstract

Controversy exists about the benefit of elective lymph node irradiation, often referred to as whole pelvis radiotherapy (WPRT), compared to prostate-only radiotherapy (PORT) for intermediate- and high-risk prostate cancer. In the PSA era, two large randomized trials comparing WPRT with PORT have been performed, as well as multiple retrospective studies, showing contradicting results. Data on the use of WPRT in patients with a biochemical recurrence after prostatectomy are scarce. As a consequence, the practice of WPRT varies largely worldwide. Recently, more accurate imaging methods for the detection of lymph node metastases in prostate cancer patients have been developed, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), diffusion weighted magnetic resonance imaging (DWI) and magnetic resonance lymphography (MRL). The use of these imaging methods might improve nodal irradiation. They can be used for patient selection, but also for determining the target volume to reduce geographical miss. Further, they enable dose escalation to involved lymph nodes. This article reviews these new image modalities and their potential impact on the treatment of prostate cancer.

## Introduction

Elective lymph node irradiation in prostate cancer, often referred to as whole pelvis radiotherapy (WPRT), is controversial. Trials investigating the benefit of WPRT as compared to prostate-only radiotherapy (PORT) have shown contradictory results (1-12). Little is known about the benefit of WPRT in the salvage setting. As a result, the application of WPRT is highly variable worldwide. The development of more accurate imaging methods for the detection of lymph node metastases in prostate cancer patients has opened doors not only towards improvement of patient selection for lymph node irradiation, but also towards improvement of the radiation treatment itself.

In this review, the available evidence for WPRT will be discussed and an outline will be provided how and why modern imaging methods might be used in the future to potentially improve the outcome after lymph node irradiation.

## Materials and methods

A systematic literature review was performed, based on database searches in PubMed/MEDLINE. Terms used for the search of articles on WPRT were ‘lymph node’, ‘pelvis’, ‘nodal metastases’ and synonyms, combined with ‘irradiation’ or ‘radiotherapy’ AND with ‘prostate’ or ‘prostate cancer’ or synonyms. Both full-text articles as well as abstracts were included from 1980 up to August 2012. The terms used for the search for articles on imaging methods for pathological lymph nodes in prostate cancer patients were: ‘lymph node’ or ‘nodal metastases‘ or synonyms, combined with ‘radiodiagnostic imaging’ or synonyms, combined with ‘prostate’ or ‘prostate cancer’ or synonyms and combined with terms describing the different imaging methods discussed below. Studies were included from 2000 up to August 2012, with the exception of articles on the use of prostate-specific membrane antigen targeted imaging for the detection of nodal metastases, where few articles were found in this timeslot. For this subject, articles were included from 1995 on.

The reference lists of identified papers were searched for further leads. Only papers in English were included.

## Whole pelvis radiotherapy in primary prostate cancer patients

Most trials on WPRT have been performed in primary prostate cancer patients. In table 1 an overview of published trials is given.

**Table 1. Overview of studies comparing whole pelvis irradiation to irradiation of only the prostate**

| First author (reference) | Study design | Patients | Method of assessing lymph node status | Key findings |
|---|---|---|---|---|
| Asbell (12) | Prospective randomized controlled trial in pre-PSA era, comparing WPRT to PORT | 445 patients with stage A2-B prostate cancer; clinically node-negative | Clinical (lymphangiogram) and/or pathological (biopsy) | No benefit of WPRT |
| Mantini (15) | Retrospective chart review, comparing WPRT with PORT both followed by long-term ADT (>1 year) | 358 high-risk patients | Clinical (CT or MRI of the abdomen and pelvis) | Benefit of WPRT for patients with a >30% risk of LNI; 4-year biochemical DFS 88% vs 70%. |
| Aizer (6) | Retrospective chart review, comparing WPRT with PORT; 94% also received ADT | 277 patients with a risk of LNI ≥15% | Clinical (CT of the pelvis) | 4-year PFS significantly better in WPRT group (86% vs 69%) |
| Seaward (3) | Retrospective chart review, comparing WPRT with PORT; 39% also received ADT | 201 patients with a risk of LNI ≥15% | Clinical | Benefit for WPRT; median PFS = 34.3 months vs. 21.0 months. |
| Pan (10) | Retrospective chart review, comparing WPRT with PORT; 21% also received neo-adjuvant ADT | 1281 patients with any risk of LNI | Clinical | Benefit for WPRT, most pronounced in group with intermediate risk (5-15%) of LNI; 2-year freedom from BR 90% vs 81%. |
| Milecki (11) | Non-randomized comparison study, comparing WPRT with PORT both preceded by ADT | 162 high-risk patients | Clinical (CT) | Benefit for WPRT; 5-year biochemical PFS 52% vs 40%. |
| Vargas (5) | Retrospective chart review, comparing WPRT with PORT; 51% also received neo-adjuvant ADT | 596 patients with a risk of LNI >15% | Clinical (CT of the abdomen and pelvis) | No benefit for WPRT. |
| Jacob (14) | Retrospective chart review, comparing WPRT with PORT; 17% also received short-term ADT | 460 patients with a risk of LNI ≥15% | Clinical | No benefit for WPRT. |

| | | | | |
|---|---|---|---|---|
| Pommier (4) | Prospective randomized controlled trial (GETUG-01); randomization between WPRT and PORT | 444 cT1b-3c N0 M0 prostate cancer patients with any risk of LNI | Clinical (CT of the pelvis) | No benefit for WPRT, also not in subgroup of high-risk patients; 5-year PFS 66% vs 65%. |
| Roach (1)/ Lawton (2) | Prospective randomized controlled trial (RTOG 9413); randomization between 4 treatment arms: WPRT or PORT; either with adjuvant or neo-adjuvant and concurrent ADT | 1292 patients with a risk of LNI ≥15% | Clinical | Benefit for WPRT, but only in the subgroup that received neo-adjuvant ADT. 4-year PFS 60% vs 44-50% in the other 3 subgroups; benefit disappeared after median follow-up of 7 years. |

*Abbreviations:* PSA=prostate-specific antigen; WPRT=whole pelvis radiotherapy; PORT=prostate-only radiotherapy; ADT=androgen depression therapy; DFS=disease-free survival; LNI=lymph node involvement; PFS=progression-free survival; BR=biochemical recurrence

Trials performed before PSA-measurement was commonly available, had the disadvantage of suboptimal follow-up and patient selection. The first major prospective study, conducted in the pre-PSA era, was RTOG 7706 (12, 13). Four hundred and forty-five patients with stage A2-B adenocarcinoma of the prostate were included in this trial. It did not demonstrate a benefit of WPRT compared to PORT.

During the PSA era, multiple retrospective (3, 5, 6, 10, 11, 14, 15) and two large prospective randomized trials (1, 2, 4) have been performed. Most of these studies did not include all prostate cancer patients, but only patients with a substantial risk of lymph node involvement (LNI). This risk was determined either with the Partin tables, based on clinical tumor stage, Gleason score and PSA level (16); or with the Roach formula, which is derived from these tables: 2/3 PSA+ [(Gleason-6) x 10] (17).
Most retrospective studies reported a benefit for WPRT. Mantini et al. reviewed the charts of 358 patients with high risk prostate cancer (15). Four-year biochemical disease-free survival was better for the WPRT group, but only for the patients with a risk of LNI of >30% according to the Roach formula. Aizer et al. (6) and Seaward et al. (3) included only patients with a ≥15% risk of LNI. Both studies also found a benefit for WPRT. A fourth study, by Pan et al. (10), observed a benefit in freedom from biochemical recurrence for WPRT for all prostate cancer patients, but most pronounced in the group with an intermediate risk of LNI. In a prospective non-randomized comparison study performed by Milecki et al. (11), high risk prostate cancer patients receiving WPRT had a better 5-year biochemical progression-free survival than patients treated with PORT.
In contrast, Vargas et al.(5) and Jacob et al. (14), reported that in patients with a risk of LNI ≥15%, outcome was not determined by the choice for WPRT or PORT.

The Groupe d'Etude des Tumeurs Uro-Génitales (GETUG-01) performed a randomized trial in patients with any risk of lymph node involvement. There was no difference in progression-free survival between PORT and WPRT (4).
The second randomized trial was performed by the Radiation Therapy Oncology Group (RTOG 9413) (1, 2). Only patients with a risk of LNI of ≥15% according to the Roach formula were included. Patients were randomized between four treatment arms: neo-adjuvant and concurrent hormonal therapy with PORT or WPRT; and PORT or WPRT with adjuvant androgen deprivation therapy. When comparing PORT with WPRT, patients in the latter group had a better progression-free survival. When comparing all four treatment arms, the group of patients that received neo-adjuvant and concurrent hormonal therapy with WPRT had a significantly better progression-free survival compared to the other three arms. In an update of the trial after a median follow-up of 7 years (2), the difference in progression-free survival between WPRT and PORT disappeared, however.

Altogether, these data indicate that there is no benefit of WPRT for patients with a risk of <15% of LNI. For patients with a higher risk of nodal involvement there is also no clear benefit of WPRT in the two prospective randomized trials. Moreover, high risk patients are currently often treated with long-term androgen depression therapy, and there is certainly no evidence of a benefit of WPRT in this scenario. Therefore, we do not consider WPRT standard of care at present.

## Whole pelvis radiotherapy in patients with a PSA recurrence after prostatectomy

Only three retrospective analyses have compared WPRT to irradiation of only the prostate bed in patients with a biochemical recurrence after prostatectomy (18, 19). Table 2 provides an overview of these studies. The first report was by Kim et al. (20). A trend towards better PSA control was seen in the group receiving WPRT, especially for patients with adverse histopathologic factors (LNI at initial lymph node dissection, positive surgical margins, seminal vesicle involvement, extracapsular extension, perineural invasion). Statistical significance was not reached in this small group of 46 patients. In a study by Spiotto et al. (19), biochemical recurrence-free survival was significantly better in the WPRT group, but only in the high-risk group (Gleason score >8, a preoperative PSA >20 ng/mL, seminal vesicle or prostate capsule involvement, or LNI at lymph node dissection). Moghanaki et al. (18) also observed a benefit for WPRT, again only for patients who were considered to be at high risk for LNI (preoperative PSA ≥20, Gleason 8-10, seminal vesicle involvement, extracapsular extension, LNI at lymph node dissection, or peak postoperative PSA ≥2.0).
These retrospective studies show promising results for WPRT in patients with a biochemical recurrence. Currently, the randomized controlled RTOG 0534 trial is prospectively investigating the benefit of WPRT in the salvage setting. The results of this trial will have to be awaited, before this treatment can be implemented in clinical practice.

**Table 2. Overview of studies comparing whole pelvis irradiation to irradiation of only the prostate bed in the salvage setting**

| First author | Study design | Patients | Key findings |
|---|---|---|---|
| Kim (20) | Retrospective chart review, comparing WPRT to PBORT; none of the patients received ADT | 46 patients with a BR after prostatectomy | Trend towards better PSA control in WPRT group; 10-year biochemical DFS 52% vs 47%. |
| Spiotto (19) | Retrospective chart review, comparing WPRT to PBORT; 54% of the patients received short-term neo-adjuvant and concurrent ADT | 160 patients; 13% adjuvant radiotherapy, 87% salvage radiotherapy | Benefit for WPRT; 5-year BR-free survival 53% vs 36%; in subgroup analysis benefit for WPRT only in high-risk group |
| Moghanaki (18) | Retrospective chart review, comparing WPRT to PBORT; 21% received adjuvant ADT | 324 patients with BR after prostatectomy | bCR significantly better in WPRT group (95% CI: 82-93% vs. 67-80%) |

*Abbreviations:* WPRT=whole pelvis radiotherapy; PBORT=prostate bed-only radiotherapy; ADT=androgen depression therapy; PSA=prostate-specific antigen; DFS=disease-free survival; BR=biochemical recurrence; bCR=biochemical complete response

## The WPRT concept

The classical WPRT concept of large standard irradiation fields for all patients with a relatively high risk of lymph node involvement has developed out of a lack of accurate imaging for the detection of nodal metastases in prostate cancer patients. Contemporary imaging methods and evolving improvements will aid in modernizing nodal irradiation and thereby potentially improve outcome. In the next part of this review, we describe currently used and emerging imaging methods and how they can play a future role in the improvement of nodal irradiation.

## Imaging methods for the detection of lymph node metastases in prostate cancer patients

### *Conventional imaging methods*

*Computed tomography (CT) and magnetic resonance imaging (MRI)*

For both CT and MRI, the decision of whether a lymph node is involved or not, is mainly based on its size, and to a lesser extent on its shape. Generally a lymph node with a short axis of greater than 1 cm is regarded pathological (21). The threshold at which a lymph node is deemed enlarged, however, is debatable and varies from 0.5 cm to 2.0 cm (22). In some reports, round or asymmetric lymph nodes are regarded pathological at a smaller size than oval lymph nodes (23, 24). Further, in metastatic lymph nodes an irregular border, heterogeneity in signal intensity on a T2 MRI sequence, central necrosis and loss of the fatty hilus can be seen (25). Reported diagnostic performance of CT and MRI varies largely, with sensitivity ranging from 9-94% and 6-83% respectively. Specificity ranges from 59% to 99%

for CT and from 65% to 99% for MRI (22). A meta-analysis found a pooled sensitivity of 42% for CT and 39% for MRI. The pooled specificity was better with a value of 82% for both methods (22). The poor sensitivity can be explained by the fact that both imaging methods use a size criterion for the determination of LNI. Disease smaller than the threshold will not be detected with CT or MRI. Nodal enlargement does not occur until late in the disease process (26). Conventional CT and MRI therefore have limited value for determining lymph node status in prostate cancer patients.

### *Emerging imaging techniques*

*Positron emission tomography (PET)*

PET is a molecular imaging modality, and is often combined with CT in a hybrid PET/CT scanner to provide both molecular and anatomical data in a single imaging session (27).
PET uses an intravenously injected tracer that is incorporated by tumor cells, labeled with a positron emitting isotope. The positron emission yields a pair of 511 keV gamma photons, which can be detected by the PET-scanner and reconstructed into a three-dimensional image. The most commonly used tracer is $^{18}$F-deoxyglucose (FDG). This tracer seems to accumulate mainly in aggressive lesions and not in less aggressive or indolent lesions (28). It is of limited value for lymph node staging, because evaluation of pelvic lymph nodes is hampered by tracer activity in the bladder (29). Better results have been obtained using chorine, either labeled with $^{11}$C or $^{18}$F (27, 30). Choline is a substrate for the synthesis of phosphatidylcholine, which is the major phospholipid in the cell membrane. In prostate cancer cells, choline kinase activity is upregulated (27).

Several validation studies including between 20 and 111 patients, have investigated the diagnostic performance of choline PET/CT (31-36). Table 3 gives an overview. Sensitivity of $^{18}$F-choline-PET/CT ranges from 0-100%, specificity from 80-100% (32, 34-36). The large differences in reported sensitivity, might be due to differences in patient selection, experience of the nuclear physicist and differences in the reference methods for validation. The largest study by Beheshti et al (32) is likely to reflect the 'true' sensitivity closest. It comprised 130 patients, and a lymph node dissection was performed in all PET/CT negative patients. Sensitivity was 45%, which is not much higher than conventional CT and MRI. For $^{11}$C-choline-PET/CT, sensitivity has been reported from 42.9-80%, specificity is again higher with values of 96-100% (31, 37, 38). An important limitation of PET/CT is its threshold of 5-6mm for the detection of lymph node metastases, especially in early generation scanners (39).

**Table 3. Overview of studies investigating the use of choline positron emission tomography for the detection of lymph node metastases in treatment-naïve prostate cancer patients**

| First author (reference) | Tracer | Patient characteristics | Criteria for positivity of lymph node | Verification method | Sensitivity/ Specificity (patient based) |
|---|---|---|---|---|---|
| Beheshti (32) | $^{18}$F-choline PET with CT | 130 intermediate-high risk patients | CT: short axis > 10 mm, absence of fatty hilus, contrast enhancement, round configuration. PET: Uptake above background | 22 patients with PET+ nodes : lymph node dissection (N=7) patients, follow-up with PSA (N=15) patients; 108 patients without PET+ nodes: lymph node dissection | 45%/96% (66%/96% for patients with a pathological node ≥5 mm) |
| Steuber (33) | $^{18}$F-choline PET with CT | 20 patients with risk of LNI >20% | CT: short axis >10 mm<br>PET: Uptake above background | Lymph node dissection in all patients | 0%/100% |
| Poulsen (34) | $^{18}$F-choline | 25 intermediate-high risk patients, negative bone scan | CT: not stated;<br>PET: Uptake above background | Lymph node dissection in all patients | 100%/95% |
| Hacker (35) | $^{18}$F-choline PET with CT | 20 intermediate-high risk patients with negative bone scan | CT: no fatty hilus, round configuration, diameter > 10 mm and/or contrast enhancement;<br>PET: Uptake above background | Lymph node dissection in all patients | 10%/80% |
| Husarik (36) | $^{18}$F-choline PET with CT | 43 patients, not otherwise specified | CT: not stated;<br>PET: Uptake above background | Follow-up (N=18) patients, lymph node dissection (N=23), targeted lymphadenctomy (N=2) | Sensitivity/ specificity based on patients with histopathologic confirmation 33%/100% |
| Jong, de (31) | $^{11}$C-choline PET, no CT | 66 patients; T4 tumor or distant metastases excluded | PET: Uptake above background | In patients with total Gleason score 6 and PSA <15 ng/ml and inoperable patients only follow-up with PSA (N=23); pelvic lymph node dissection (N=43) | 80%/96% |

| | | | | | |
|---|---|---|---|---|---|
| Schiavina (37) | $^{11}$C-choline PET with CT | 57 intermediate-high risk patients, negative bone scan | Only based on PET images; uptake above background | Lymph node dissection in all patients | 60.0%/97.6% |
| Budiharto (38) | $^{11}$C-choline PET with CT | 36 patients, risk of LNI 10-35% , negative CT of abdomen and negative bone scan | CT: not stated; PET: uptake above background | Lymph node dissection in all patients | 42.9%/81.8% |

*Abbreviations:* PET: positron emission tomography; CT: computed tomography; PET+= positive on positron emission tomography; LNI=lymph node involvement

There are only a few studies on the use of PET/CT for nodal staging in patients with a biochemical recurrence. Scattoni et al. (40) selected 25 patients with a biochemical recurrence that either had a positive $^{11}$C-choline-PET and/or CT. The 4 PET negative patients were also negative at histopathological examination, and in 19/21 PET positive patients histopathological examination did show evidence of LNI. Schilling et al. (41) reviewed the charts of 10 patients who underwent lymph node dissection because of a positive $^{11}$C-choline-PET, performed because of a biochemical recurrence. In 3/10 patients histopathological examination showed no evidence of LNI.
An important limitation of choline-PET/CT in patients with a biochemical recurrence, is the low detection rate in patients with a marginally increased PSA (39, 42). This is probably due to low tumor load in these patients in combination with a resolution of PET/CT of 5-6mm (39).
The routine use of choline-PET/CT for nodal staging in prostate cancer patients is currently not recommended, because of the lack of large prospective trials, and the wide range of reported sensitivity (27).

*Single photon emission tomography and the sentinel node procedure*

The sentinel node concept is based on the hypothesis that there are one or more lymph nodes first receiving lymph drainage from the tumor, the so-called sentinel nodes. The status of these nodes would accurately predict the presence or absence of lymph node metastases (43).
A radioactive tracer, usually $^{99m}$Tc-nanocolloid, is injected into the prostate. Lymphatic drainage results in transport of this tracer to the lymph nodes. These nodes can be visualized with a gamma camera, which delivers 3D images when single photon emission computed tomography (SPECT) is performed. During surgery the emitted photons can be detected with a hand-held gamma probe and subsequently the sentinel nodes can be removed (43, 44).
Several studies have validated this method in 100 to over 600 patients (43-46) and show that, with the correct dose of $^{99m}$Tc-nanocolloid, the sentinel node can be identified in >90-

95% of the patients during surgery (44-46). In patients with a successful sentinel node procedure, the number of false-negatives is very low, resulting in a sensitivity of >95% (43-46).
A new development is the combination of SPECT and CT imaging in a single hybrid camera. Besides better anatomical information on the localization of the lymph nodes, this increases the success rate of the procedure because of better discrimination of sentinel nodes near the high activity of the injection site where they may otherwise be missed (47). Similarly, SPECT can be combined with MRI by applying software image fusion (48).
These promising results and the fact that it is less invasive than the golden standard- a pelvic lymph node dissection, seem to justify a warm welcome for the sentinel node procedure into clinical practice. Despite this, it has not been widely implemented for prostate cancer, possibly because of unfamiliarity with this technique.

*Prostate-specific membrane antigen (PSMA)-targeted imaging*

Another molecular imaging method is the targeting of prostate-specific membrane antigen (PSMA) with radiolabeled antibodies to create a SPECT image. This antigen is expressed in prostate adenocarcinoma, but also in benign prostatic tissue, the small intestine, salivary glands, and renal tubular tissue, albeit 100-1000 fold less. (49). The first clinical radiopharmaceutical for targeting PSMA was $^{111}$In-capromab, a murine antibody labeled with Indium-111. Reported sensitivity of this so-called ProstaScint for the detection of lymph node metastases is 62-75%, with a small study of 22 patients reporting a sensitivity of only 17%. Reported specificity is 72-97% (50-53). Table 4 gives an overview of the various studies.

**Table 4. Overview of studies investigating the use of prostate-specific membrane antigen (PSMA)-targeted imaging using 111In-capromab pendetide for the detection of lymph node metastases in treatment-naïve prostate cancer patients**

| First author (reference) | Patients | Criteria for positivity of lymph node | Verification method | Sensitivity/ Specificity (patient based) |
|---|---|---|---|---|
| Manyak (50) | 152 intermediate –high risk patients; negative MR or CT of pelvis, negative bone scan and chest X-ray | Not stated | Lymph node dissection | 62%/72% |
| Hinkle (51) | 51 high risk patients | Not stated | Lymph node dissection | 75%/86% |
| Polascik (52) | 198 high risk patients, negative chest X-ray, bone scan and CT/MRI of pelvis | Not stated | Lymph node dissection | 67%/80% |
| Ponsky (53) | 22 patients, negative CT of abdomen and negative bone scan | Not stated | Lymph node dissection | 17%/90% |

Although the larger studies show that ProstaScint is much more accurate than CT and MRI, its accuracy does not seem to be high enough to base treatment decisions on concerning nodal status.
Accuracy seems to improve when the SPECT image is fused with CT or MRI, but this has not been validated for the detection of lymph node metastases (54-56). A disadvantage of $^{111}$In-capromab, which targets the intracellular domain of PSMA, is that it is a large molecule with poor penetration. Currently, new small molecules labeled with Iodine-123 which target PSMA are being investigated, such as [$^{123}$I]MIP-1072 and [$^{123}$I]MIP-1095 (49, 57). Figure 1 shows an example of PSMA-targeted SPECT image with MIP1404 radiolabeled with Tc-99m. Also, new (prostate) cancer cell-specific targets are under investigation, such as gastrin-releasing peptide receptors, which can be targeted with bombesin analogues (58, 59).

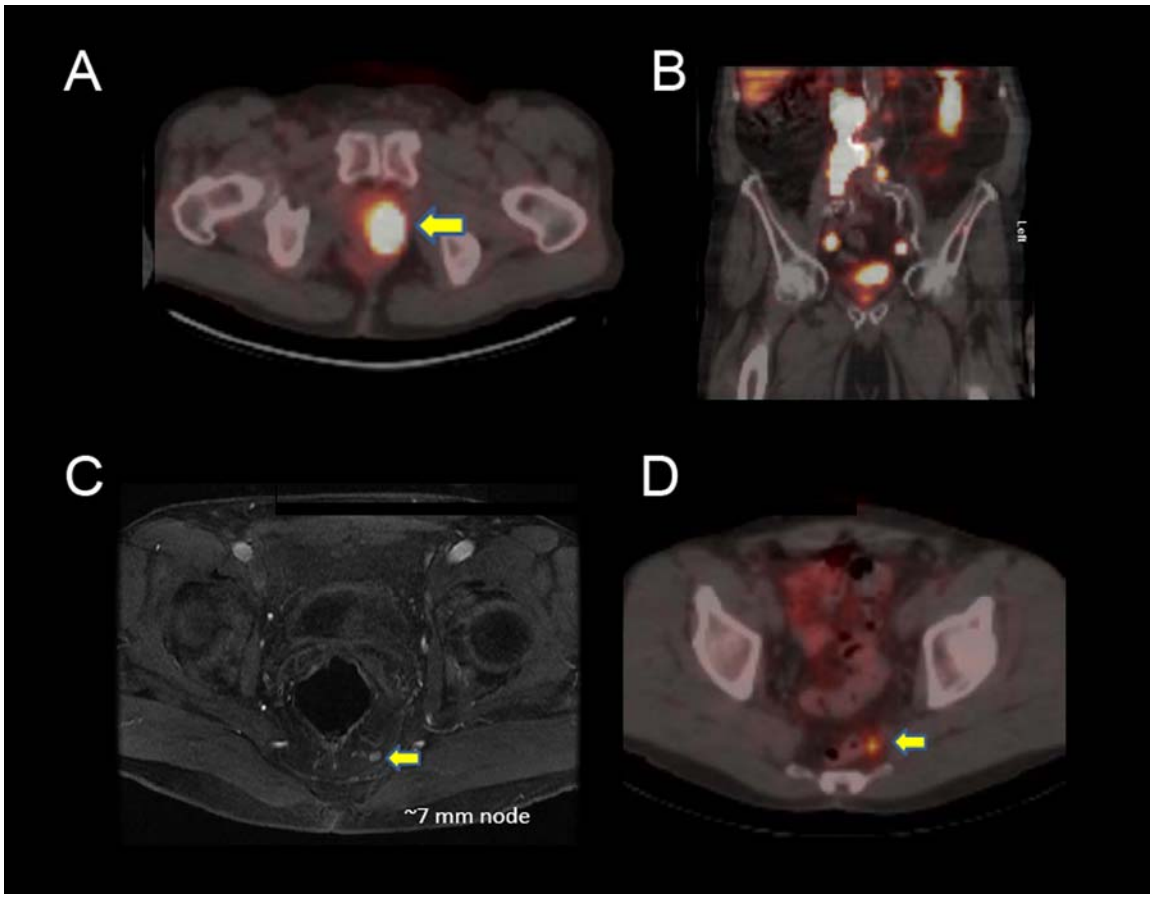


***Fig. 1.*** *Targeting prostate cancer with the small molecule MIP1404 radiolabeled with Tc-99m*
MIP1404 binds to the glutamate carboxy peptidase domain of PSMA and is subsequently internalized into prostate cancer cells.
A. Targeting of primary prostate carcinoma in the left lobe of the prostate (transverse SPECT/CT).
B. Targeting of extensive para-iliac and para-aortic lymph node metastases (coronal SPECT/CT)
C/D. Small (7mm) metastatic pararectal lymph node on MRI (C) showing Tc-99m-MIP1404 targeting on SPECT/CT (D)

*Diffusion weighted MRI (DWI)*

DWI derives its contrast from differences in random motion between intracellular and extracellular protons. Extracellular protons diffuse more freely than intracellular protons. A magnetic field gradient pulse is applied, followed by a gradient pulse that is equal in strength but opposite in polarity. If protons would not move, after the second pulse, the net phase shift would be zero at the time of echo. However, as protons move, the phase shifts will be randomly distributed, which causes a signal loss. The degree of signal loss is a measure for the magnitude of motion of the protons, which is quantified by the so-called apparent diffusion coefficient (ADC). This value can be calculated pixel-by-pixel, forming an ADC map. For measuring diffusion a long echo time is needed, and therefore DWI images are heavily T2-weighted. In areas with a high degree of cellularity, e.g. a lymph node containing a metastasis, the motion of the protons will be limited and the ADC value will be low. This translates to a high signal intensity (60).
For the detection of lymph node metastases in prostate cancer patients this method has not been extensively evaluated. Eiber et al. (61) performed DWI in 29 prostate cancer patients. The reference method was lymph node dissection in 10 patients, follow-up imaging in 6 patients, and PSA follow-up in the other 13 patients. They found a significant difference in ADC value between benign and malignant lymph nodes. With a cut-off value for ADC of 1.30 $\times 10^{-3}$ $mm^2/s$, sensitivity was 86% and specificity 85%. Budiharto et al. (38) performed a DWI in 36 patients before prostatectomy with extended pelvic LN dissection. Sensitivity was 19%, probably due to the fact that they used a more sensitive reference method, and because they excluded patients with enlarged lymph nodes on CT.
Due to low sensitivity in the latter study and the lack of properly designed large clinical studies, DWI is currently not recommended for lymph node staging in prostate cancer. The combination of DWI with other MRI sequences, i.e. multiparametric MRI, has yielded improvements for the assessment of the primary prostate tumor (62) and might also provide better perspectives for the detection of nodal metastases.

*MR Lymphography (MRL)*

Another new imaging technique for the detection of lymph node metastases is MRL, which uses the intravenously injected lymph-node-specific contrast agent ferumoxtran-10 to enhance MRI. This contrast agent consists of ultrasmall superparamagnetic particles of iron oxide that are transported to the lymph nodes by macrophages after extravasation. The iron particles give a low signal intensity on a T2*-weighted MR image. Metastases in the lymph nodes block accumulation of the iron particles. The signal intensity of pathological nodes will therefore remain high on a T2*-weighted MR image, while the signal intensity of normal lymph nodes becomes low (63, 64). Figure 2 shows an example of a positive MRL.
MRL has been validated for prostate cancer in several studies, based on histopathological verification with lymph node dissection in most patients, and with CT-guided biopsy in some patients with easy-to- reach large nodes. These studies have shown a sensitivity of 80-100% and a specificity of 87-99% (63, 65). Because MRI has a high resolution, metastases in small, morphologically normal lymph nodes (<5 mm) can be detected (65).

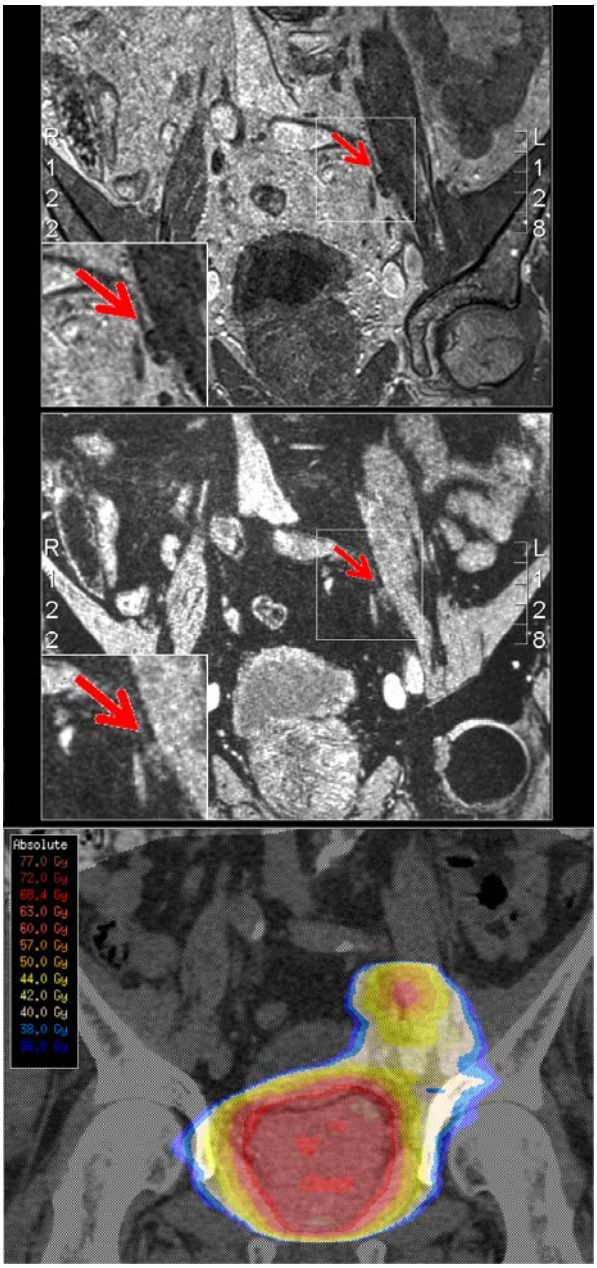


**Fig. 2.** *Example of a positive MRL with an MRL-based irradiation plan*
Upper panel: T1 MRI image, which provides good visualization of non-enlarged lymph nodes (arrow). The lymph node in this image has a short axis of 3 mm.
Middle panel: T2* MRI image. Ferumoxtran-10, an intravenously injected contrast agent containing ultrasmall particles of iron oxide, has been injected 24-36 hours before the MRI was performed. The iron oxide particles are transported to the lymph nodes by macrophages. A negative lymph node would have been filled with these particles, and as a result would have had a low signal intensity, becoming indistinguishable from the fatty tissue. The lymph node in the figure has a high signal intensity. This is the case in pathological lymph nodes, where accumulation of iron oxide particles has been blocked by metastasis formation.
Lower panel: Example of a radiotherapy plan based on this MRL, with a boost to the pathological lymph node (colour shade indicates dose gradient from low (blue) to high (red)).

With this technique, pathological lymph nodes can be detected at a very early stage. Data suggest that patients with only limited nodal involvement have a favorable outcome, and might be candidates for curative treatment (66, 67). This is an advantage of this technique, compared to PET/CT (68). However, metastases in lymph nodes <5 mm are frequently missed(69) and therefore sensitivity decreases for smaller lymph nodes, to as low as 41% for lymph nodes <5mm (65).

Little is known about the accuracy of MRL in patients with a biochemical recurrence. Ross et al. (70) performed MRL in 26 of these patients, of which 6 patients had a positive MRL. Unfortunately, in only 1 patient a CT-guided biopsy with sufficient material for histopathological verification could be obtained compared to MRL alone.
Thoeny et al. (71) investigated the accuracy of the combination of MRL and DWI in 21 patients with bladder or prostate cancer. This combination substantially decreased the time needed for analysis of the images, but it did not increase accuracy.
This very promising technique, which is also favorable in terms of cost-effectiveness compared to CT followed by pelvic lymph node dissection (72), might have been introduced into clinical practice, be it that ferumoxtran-10 is currently unavailable. The alternative contrast agent ferumoxytol, is under investigation, but seems to be less promising than ferumoxtran-10 MRL, underlining the need for the re-introduction of the latter.

## Limitations of present-day whole pelvis radiotherapy and the role of new imaging techniques

### *Patient selection*

Patient selection for WPRT is difficult. Preferably, only patients with microscopic or minimal macroscopic LNI should be selected. A lymph node dissection is currently the gold standard, but has the disadvantage of being an invasive technique. Also, many patients only have positive lymph nodes outside the routine dissection area, limiting its sensitivity (73). Therefore, in current practice as well is in most studies on WPRT the risk of LNI is estimated with the Partin tables (16) or with the Roach formula (17). In general, patients with a risk of LNI ≥15% were included. This leads to significant overtreatment (74), as up to 85% of the patients will not have LNI and will not benefit from WPRT.

In patients with a biochemical recurrence, patient selection is even more difficult. Little is known about the incidence of LNI in these patients. In previously untreated prostate cancer patients, knowledge on the incidence of lymph node metastases has been gathered from data of pelvic lymph node dissections. In patients with a biochemical recurrence, however, a pelvic lymph node dissection is usually not performed, as there is no evidence for its value for determining lymph node status in this setting (75). As a result, the risk of LNI for individual patients cannot be properly estimated, which impedes patient selection.
Studies using choline-PET/CT or MRL in patients with a biochemical recurrence report LNI in 9-72% (70, 76-79). This highly variable percentage is probably due to differences in sensitivity of the imaging methods, and differences in patient characteristics between

studies. Larger, prospective studies using new imaging modalities are needed to determine the true incidence of LNI in these patients and to define risk groups.

The use of accurate imaging will benefit individual patients. It creates the opportunity of better patient selection for local treatment, without having to perform a lymph node dissection (63). However, it will also create a dilemma on the therapeutic consequences. The optimal treatment for patients with minimal LNI that can be visualized only with these newer imaging techniques, is unclear. Currently, node-positive disease is generally regarded incurable. However, there are data that patients with limited nodal involvement might be cured (66, 67) and that the addition of radiotherapy to hormonal treatment significantly improves the outcome (80). With access to new imaging modalities that enable detection of metastatic disease at the millimeter level in non-enlarged lymph nodes, there is now the challenge to explore whether radiotherapy can offer cure for this category of prostate cancer patients.

***The target volume***

The delineation of an adequate target volume is of particular importance when using modern radiotherapy techniques as intensity modulated radiotherapy (IMRT) or rapid arc/volumetric modulated arc therapy (VMAT). With these techniques very conformal treatment plans can be created with the risk of missing the target if not accurately delineated. Currently used target volumes and irradiation fields for prostate cancer as, for example defined by the RTOG are mainly based on extended pelvic lymph node dissection and limited data of traditional lymphography (81). Both pelvic lymph node dissection and traditional lymphography do however not assess all possibly involved lymph node regions. Even at extended pelvic lymph node dissection, pararectal and para-aortal lymph nodes are not resected (82). Traditional lymphography mainly visualizes the para-aortal, external and common iliac lymph node regions (83).

New imaging methods do visualize all potentially involved lymph node regions. These methods have shown a substantial risk of geographical miss when applying the standard target volume for WPRT. Ganswindt et al. recently published a SPECT-derived anatomical atlas showing the distribution of sentinel nodes in primary prostate cancer patients. They found that over 65% of the patients had a sentinel node outside the target volume for WPRT (82). Similar results were obtained in a lymph node mapping study using MRL(84). In patients with a PSA recurrence after prostatectomy, the risk of geographical miss seems to be even higher. We recently mapped the pattern of lymph node spread using MRL and found that 79% of these patients had an MRL-positive lymph node outside the CTV as defined by the RTOG (85). This might be due to the fact that lymph drainage may change after surgery, as has been previously described in breast cancer patients (86, 87). The most frequently involved lymph node regions outside standard target volumes are the pararectal and the proximal common iliac region (82, 85).
To reduce the risk of geographical miss, the standard CTV could be extended to include all additional regions. This will, however, increase toxicity. An alternative could be to determine

a customized CTV for each individual patient based on high accuracy imaging. One approach would be to use the standard CTV and include additional lymph node regions only when involved as indicated by accurate imaging or when SPECT with Tc-99m-nanocolloids shows lymphatic drainage to that region. Another approach would be to only include involved lymph node regions in the elective target volume. A third option would be to only irradiate the involved nodes without irradiating an elective volume or with a significant reduction of dose to the elective volume. This new treatment philosophy is now implemented in the treatment of lymphoma (88)and lung cancer (89), where systemic treatment is thought to eliminate the subclinical disease. This approach may also be considered for other tumor types including prostate cancer. However, one has to bear in mind that even with the most sophisticated imaging techniques, some pathological nodes can be missed and not all positive nodes will indeed be pathologically malignant. Which is the optimal approach should be the subject of future clinical investigations.

***Radiation dose and fractionation***

Escalation of the radiation dose to the prostate has shown to improve outcome (90, 91). The prospective randomized trials assessing the value of WPRT were initiated before this evidence appeared in the literature. As a consequence, the patients in both randomized trials (2, 4), including the high-risk patients, were treated with a dose of 70 Gy or less to the prostate. This puts all patients at a relatively high risk of a local recurrence, which is detected as a biochemical recurrence, masking a possible benefit of WPRT.

The proven benefit of dose escalation to the prostate might also have consequences for WPRT. Dose escalation to involved lymph nodes might also be necessary for adequate eradication. With this hypothesis, Adkison et al. (92) set up a phase I trial with 53 patients, in which the elective dose to the lymph nodes was increased to 56 Gy in 2-Gy fractions with a simultaneous integrated hypofractionated boost to the prostate to a dose of 70 Gy. At a median follow-up of 25.4 months, none of the patients had evidence of nodal failure within the pelvis. Three patients had developed para-aortal nodal failure, of whom one was clinically node positive before treatment. Six patients developed distant metastases. With no acute grade 3 or higher acute toxicity, late grade 3 genitourinary toxicity in only one patient and no late grade 3 gastrointestinal toxicity, the feasibility of this regimen was demonstrated.

With the development of IMRT and VMAT, dose escalation to involved lymph nodes has become possible. Imaging must form the basis of these treatment plans. Fonteyne et al. escalated the dose to CT-positive lymph nodes using VMAT in 31 prostate cancer patients (93). A median dose of 78 Gy in 25 fractions was prescribed to the planning target volume of the prostate and positive lymph nodes, and a median dose of 45 Gy in 25 fractions to the elective lymph node regions. Acute grade 3 gastrointestinal toxicity was not seen and acute grade 3 genitourinary toxicity was observed in 2 patients. Data on late toxicity and outcome will have to be awaited, as the median follow-up was only 3 months.

The group of Würschmidt (94) applied choline PET-based treatment plans for 26 patients with primary or recurrent prostate cancer, of whom 20 had positive lymph nodes. A median dose of 66.6 Gy was given to PET positive lymph nodes, 45-50.4 Gy to the elective lymph

node regions and a median dose of 60-66.6 Gy to the prostate bed in post-prostatectomy cases or 75.6 Gy to the prostate for primary treatment. Median follow-up time was 28 months. Three-year biochemical relapse-free survival was 83% for primary and 49% for recurrent patients. No acute or late grade 3 toxicity was reported.
MRL can also be used as a basis for treatment plans. A planning study showed that MRL-based IMRT with a boost of 60 Gy to non-enlarged positive lymph nodes was theoretically feasible in conjunction with irradiation of the prostate, with acceptable dose to the organs at risk (95). Figure 2 shows an example of an MRL-based IMRT plan.
Further, with increasing evidence that the alpha/beta ratio of prostate adenocarcinoma is low (96), hypofractionation may also be of benefit. This is currently under investigation for irradiation of the prostate, and may also have consequences for the irradiation of nodal disease. This may develop into stereotactic radiotherapy to the pathological lymph nodes, which has shown to be a feasible approach (97). Currently, the NCT01558427 phase II trial is ongoing, investigating the benefit of either surgical excision or stereotactic radiotherapy of pathological lymph nodes or distant metastases (with a total maximum of 3) in patients with a biochemical recurrence.

## Conclusions

Classical WPRT is sub optimal, because of limitations in patient selection, target volume definition and radiation dose. New imaging methods with a higher accuracy for the detection of lymph node metastases, such as PET/CT, SPECT/the sentinel node procedure, diffusion weighted MRI and MR lymphography, create the opportunity to improve treatment. With these methods, patients that are most likely to profit from nodal irradiation can be selected. However, most new imaging techniques still need solid validation. Also, even with the most sophisticated techniques, false-positive and false-negative findings will always remain.
We envisage the abandonment of the classical WPRT concept and the introduction of individualized image-based radiotherapy planning with customized target volume definition and dose-escalation to minimally involved lymph nodes. The reduction of geographical miss and improved control of regional metastatic disease will likely increase the effectiveness of lymph node irradiation and ultimately treatment outcome.

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# 8

# Summary and Conclusions

## Summary

The development of accurate imaging methods for the detection of lymph node metastases in prostate cancer, such as magnetic resonance lymphography (MRL), has created the opportunity to increase knowledge about lymph node involvement and to potentially improve treatment. In this thesis MRL findings were studied in detail in order to obtain data on the incidence and pattern of spread of lymph node metastases in prostate cancer patients. Further, a vision on the application of MRL for lymph node irradiation in individual patients was developed.

In primary prostate cancer patients the pattern of spread of lymph node metastases has been sub optimally investigated. Data mainly come from the findings obtained at pelvic lymph node dissection, which does not address all potentially involved lymph node regions. In **Chapter 2** the pattern of spread of MRL-positive lymph nodes is investigated in 60 primary prostate cancer patients. This pattern was compared to the clinical target volume (CTV) for elective lymph node irradiation as defined by the radiation therapy oncology group (RTOG), which aims to encompass all subclinical nodal metastases in the majority of the patients. The results show that 53% of the patients had an MRL-positive lymph node outside this CTV. This means that in more than half of the patients geographical miss would occur when applying this CTV. The most important involved regions outside this CTV were the pararectal, proximal common iliac and para-aortal regions, which were affected in 30%, 25% and 18% respectively. To reduce the risk of geographical miss, the CTV should be extended to include these regions, but preferably, to minimize toxicity, the need for inclusion of these regions should be determined with accurate imaging.

In patients with a biochemical recurrence after prostatectomy, data on both the incidence and the pattern of spread of lymph node metastases are very limited. This is because a lymph node dissection is usually not performed in these patients. In our institute, 65 patients with a biochemical recurrence who were eligible for salvage radiotherapy, underwent an MRL. In **chapters 3** and **4** the MRL findings regarding the incidence and the pattern of spread of nodal metastases in these patients are described. Forty-seven of these 65 patients (72%) had a positive MRL. Of the patients with a PSA <1.0 ng/mL, 62% had a positive MRL. Among patients without lymph node involvement at initial lymph node dissection this was 68%. Although a selection bias towards unfavorable cases might have occurred due to the retrospective design of the study and the patient referral patterns in our clinic, these results show that a large proportion of patients with a biochemical recurrence after prostatectomy is likely to have nodal disease, being unfit candidates for salvage radiotherapy directed only at the prostate bed.
Currently, the Stephenson nomogram is being used to select patients for this latter treatment. This nomogram predicts the chance of success, based on clinical and histopathological parameters. The results of **chapter 3** show that the score on this nomogram is related to the risk of lymph node involvement and might therefore be used to select patients for nodal treatment, analogous to the Partin tables and the Roach formula for primary prostate cancer patients. Nodal irradiation may be of benefit in these patients as

has been shown by retrospective trials. Currently, this matter is under prospective investigation in the randomized RTOG 0534 phase III trial.
**Chapter 4** describes the pattern of spread of MRL-positive lymph nodes in the 47 MRL-positive patients with a biochemical recurrence after prostatectomy. In 37 patients (79%), at least one positive lymph node was localized outside the CTV for elective nodal irradiation as described by the RTOG. Again, the pararectal region was the most frequently involved region outside this CTV. Forty-three percent of the patients had a positive lymph node in this region. These results show that aberrant lymph drainage is even more frequent in this category of patients. This might be caused by the previous prostatectomy. To reduce geographical miss, the CTV should therefore be extended to include the most frequently involved lymph node regions, preferably based on accurate imaging.

Subsequently, in **chapter 5** it is shown how MRL might be used as a basis for individual treatment plans. For four primary prostate cancer patients an MRL-based radiotherapy treatment plan was created. The non-enlarged MRL-positive lymph nodes could be identified on the CT for radiotherapy planning. A customized target volume for elective irradiation of lymph node regions was designed based on MRL. For each patient, an intensity modulated radiotherapy (IMRT) plan was created. An elective dose to the lymph node regions (42 Gy in 30 fractions) and a boost dose to the prostate (72 Gy in 30 fractions) as well as to the MRL-positive lymph nodes (60 Gy in 30 fractions) was prescribed. Excellent coverage of the target volumes could be achieved, with acceptable dose to the organs at risk. The small bowel appeared to be the dose limiting structure. The RTOG guideline sets the maximum dose constraint on 52 Gy. This could not be achieved for one patient in whom the small bowel was adjacent to an MRL-positive lymph node. A volume of 1.1cc of the small bowel received a dose of >52 Gy. This was accepted, because of the small volume and because the bowel is a moving organ and it is to be expected that at every fraction, a different part would lie in this high-dose region.

Whereas the use of modern imaging methods for nodal irradiation in prostate cancer patients creates many new possibilities, it also faces us with new uncertainties. Patients with non-enlarged pathological lymph nodes that are visualized by modern imaging techniques are a new category of patients, whose prognosis and the treatment from which they benefit the most are unknown. In **chapter 6** the prognosis of patients with non- or marginally enlarged MRL-positive lymph nodes is described, in order to take the first step to shed light on this issue. It shows that whereas MRL-positive patients have a poorer prognosis than MRL-negative patients, a subgroup within the MRL positive group could be identified with a relatively favorable prognosis. Patients with a short axis of the largest positive lymph node of ≤8 mm had a significantly better 5-year distant metastases-free (79% vs 16%) and overall survival (81% vs 36%) than patients with larger positive lymph nodes. This also accounted for patients with a largest long axis of ≤10 mm (71% vs 20% and 73% vs 40%, respectively). This outcome is comparable to that of node-negative high-risk prostate cancer patients. Whereas this study comprised only 24 MRL-positive patients and has a retrospective design, these results do imply that there is a window of opportunity for cure in these patients. The treatment as proposed in **chapter 5** might be an option for them. However, this remains to be investigated in a prospective clinical trial.

Finally, **Chapter 7** provides an overview of the currently available evidence in the international literature with regard to elective lymph node irradiation, often referred to as whole pelvis irradiation (WPRT). It further describes the limitations of present-day WPRT and argues how modern imaging techniques can play a role in overcoming these limitations.
For primary prostate cancer patients, most retrospective studies that compare WPRT to prostate-only radiotherapy (PORT) find a benefit for WPRT, especially in patients with high-risk disease. Two randomized trials show contradicting results, with widely varying treatment protocols throughout the world as a result. For patients with a biochemical recurrence after prostatectomy the only 3 retrospective trials available see a benefit for WPRT, again mainly for high-risk patients. The phase-III RTOG 0534 trial is currently prospectively comparing these treatments.
Computed tomography (CT) and magnetic resonance imaging (MRI) have limited value in the detection of lymph node metastases in prostate cancer patients. Modern and emerging imaging methods as choline-positron emission tomography/CT (PET/CT), prostate-specific membrane antigen (PSMA)-targeted imaging, single photon emission computed tomography (SPECT), diffusion-weighted MRI and especially the sentinel node procedure and MRL show more promising results. These imaging methods are likely to initiate a development from elective nodal irradiation towards selective nodal irradiation. They could be used to select patients for nodal treatment accurately and they can be helpful in reducing the risk of geographical miss. Also, they create the opportunity to boost pathological lymph nodes. Thus, if modern imaging techniques are implemented into lymph node irradiation, this opens the door to the creation of individualized selective high-precision treatment plans.

In conclusion, the MRL findings described in this thesis provided data about the pattern of spread of lymph node metastases in both primary and recurrent prostate cancer patients, showing that the current standard CTV does not adequately cover all lymph node regions with a high risk of involvement. Further, a high incidence of subcentimeter nodal involvement was found in patients with a biochemical recurrence after prostatectomy. This implies that salvage radiotherapy directed only at the prostate bed is an inadequate treatment for many of these patients. Nodal irradiation might be an option for a subset of these patients. The Stephenson nomogram might be used to select patients in this context.

With the development of new imaging techniques the limitations of elective lymph node irradiation have become more clear than ever. We therefore envisage the abandonment of elective nodal irradiation and a development towards selective nodal irradiation, with the use of modern imaging techniques to create high-precision treatment plans. Here lies an important role for MRL. We have shown that MRL-based radiotherapy with an elective dose to an individually defined nodal target volume and a boost to the positive lymph nodes and the prostate is theoretically feasible. This might be a treatment option especially for MRL-positive patients with only small positive lymph nodes, as they seem to have the widest window of opportunity for cure before distant metastases develop. Clinical trials are, however, needed, to draw definite conclusions.

# 9

**Summary in Dutch (Nederlandse samenvatting)**
**Dankwoord**
**Curriculum Vitae**
**List of Publications**

## Summary in Dutch (Nederlandse Samenvatting)

Prostaatkanker is de meest voorkomende maligniteit bij mannen boven de 45 jaar. In 2010 werd bij ruim 10.000 mannen in Nederland prostaatkanker vastgesteld (1). De meest frequent toegepaste therapieën zijn prostatectomie en radiotherapie (2).

Bij patiënten met lokaal gevorderde ziekte bestaat een aanzienlijk risico op lymfkliermetastasen (3). Een belangrijke beperking in de behandeling van patiënten met prostaatkanker is dat er lange tijd geen goede niet-invasieve manier was om de lymfklierstatus vast te stellen. Deze is van groot belang voor de prognose en de keuze van behandeling. Computed tomography (CT) en magnetic resonance imaging (MRI) hebben een erg lage sensitiviteit voor de detectie van lymfkliermetastasen, omdat zij deze pas kunnen detecteren wanneer vergroting van een lymfklier ontstaat, hetgeen meestal in een laat stadium van de ziekte pas gebeurt (4). Daarom wordt gebruik gemaakt van predictieve modellen, zoals de Partin tabellen (3) en de Roach formule (5), om de kans op lymfkliermetastasen in te schatten aan de hand van klinisch T-stadium, prostaat-specifiek antigeen (PSA) en Gleason score. Bij patiënten met een substantieel risico op kliermetastasen kan dan een lymfklierdissectie gedaan worden om vast te stellen of sprake is van lymfkliermetastasen. Dit is echter wel een invasieve procedure, met een niet te verwaarlozen morbiditeit en hoge kosten (6).

De Partin tabellen en de Roach formule kunnen ook worden gebruikt om patiënten te selecteren voor een lymfklierbestraling. Bij veel solide tumoren is dit een standaard onderdeel van de radiotherapie behandeling, vooral als sprake is van lokaal gevorderde ziekte (2). Echter, bij prostaatkanker, is lymfklierbestraling, ook wel totale bekkenbestraling (TBB) genoemd wanneer dit gecombineerd wordt met prostaatbestraling, controversieel. Dit komt doordat de resultaten van studies die TBB hebben vergeleken met bestraling van alleen de prostaat tegenstrijdig zijn (7-18).

Van de patiënten die behandeld zijn met een prostatectomie, ontwikkelt ongeveer 25% een recidief, dat zich over het algemeen initieel presenteert als een stijging van het prostaat-specifiek antigeen (PSA) (19). Voor deze patiënten is salvage radiotherapie een therapeutische optie. Hierbij wordt over het algemeen alleen het prostaatbed bestraald, omdat bij deze groep patiënten erg weinig bekend is over lymfkliermetastasering en lymfklierbestraling. Deze behandeling kan dan ook alleen curatief zijn indien een patiënt een geïsoleerd lokaal recidief heeft. Verder worden de beste resultaten behaald als patiënten deze bestralingsbehandeling ondergaan op het moment dat zij een laag PSA hebben (20). Bij lage PSA waarden is de hoeveelheid tumorcellen laag, en is beeldvorming niet accuraat genoeg om deze ziekte te detecteren (4, 21, 22). De precieze plaats van het recidief –lokaal, regionaal of distaal- kan op dat moment meestal dan ook niet worden vastgesteld. Om deze reden wordt het besluit tot het al dan niet toepassen van salvage radiotherapie bij individuele patiënten meestal gebaseerd op het Stephenson nomogram (23). Dit nomogram voorspelt de kans op succes na deze behandeling, en is gebaseerd op klinische en histopathologische kenmerken.

Recent zijn er beeldvormende technieken ontwikkeld die lymfkliermetastasen met een grotere accuraatheid kunnen detecteren, zelfs in niet-vergrote lymfklieren. De misschien wel meest veelbelovende techniek is magnetic resonance lymphography (MRL) (24).
MRL is een MRI techniek waarbij gebruik wordt gemaakt van het contrastmiddel ferumoxtran-10, dat kleine deeltjes ijzeroxide bevat, de zogenaamde ultrasmall superparamagnetic particles of iron oxide (USPIO). Deze deeltjes extravaseren, en worden vervolgens door macrofagen naar de lymfklieren getransporteerd. Normale klieren worden helemaal opgevuld met deze ijzeroxide deeltjes, waardoor ze een lage signaalintensiteit hebben op een T2* MRI beeld. In pathologische lymfklieren wordt de accumulatie van de ijzeroxide deeltjes geblokkeerd door de metastase. Deze lymfklieren behouden dan ook een hoge signaalintensiteit op een T2* beeld. Deze techniek heeft een sensitiviteit van 80-100% en een specificiteit van 87-99% voor het detecteren van lymfkliermetastasen bij prostaatkanker (24).

Nieuwe beeldvormende technieken kunnen bijdragen aan de kennis over lymfkliermetastasering bij patiënten met prostaatkanker. Het patroon van lymfkliermetastasering is nog onvoldoende in kaart gebracht, omdat conventionele beeldvorming onvoldoende betrouwbaar is en bij lymfklierdissectie niet alle mogelijk bedreigde klierregio's worden onderzocht.

Bij patiënten met een recidief na prostatectomie wordt over het algemeen geen lymfklierdissectie gedaan. Bij deze categorie patiënten is dan ook nauwelijks iets bekend over de incidentie of het patroon van lymfkliermetastasering. En dat terwijl de voorafgaande chirurgie de lymfdrainage veranderd kan hebben, zoals ook bij bijvoorbeeld patiënten met borstkanker beschreven is (25). Het is van belang hierover meer te weten om het juiste doelvolume voor electieve bestraling te kunnen bepalen. Met nieuwe beeldvormende technieken kan hierover meer informatie verkregen worden om zo de TBB behandeling in het algemeen te verbeteren, bijvoorbeeld doordat hiermee een accurater doelvolume gedefinieerd kan worden.

Het gebruik van goede beeldvorming in de dagelijkse praktijk kan bovendien voordeel opleveren voor individuele patiënten. Patiënten zonder positieve klieren kan een lymfklierdissectie bespaard worden. Daarnaast ontstaat de mogelijkheid om patiënten met minimale lymfkliermetastasering te behandelen met een klierbestraling volgens individuele beeld-gestuurde bestralingsplannen met een boost op de pathologische klieren. Deze laatste mogelijkheid heeft echter ook voor veel nieuwe vragen gezorgd. Het is nog onduidelijk wat de prognose en juiste behandeling is voor patiënten met niet-vergrote pathologische lymfklieren die zichtbaar gemaakt kunnen worden met nieuwe beeldvormende technieken. Ook is het onduidelijk hoe moderne beeldvorming precies gebruikt moet worden voor het maken van individuele bestralingsplannen.

In dit proefschrift wordt een aantal studies besproken, waarin MRL bevindingen werden bestudeerd om informatie te verkrijgen over de incidentie en het patroon van

lymfkliermetastasering bij patiënten met prostaatkanker. Ook wordt een voorstel voor het gebruik van MRL voor lymfklierbestraling bij individuele patiënten besproken.

In **hoofdstuk 2** wordt het patroon van verspreiding van MRL-positieve lymfklieren bij 60 patiënten met prostaatkanker beschreven. Dit patroon wordt vergeleken met het doelvolume (clinical target volume (CTV)) voor electieve lymfklierbestraling zoals dat werd beschreven door de Radiation Therapy Oncology Group (RTOG). Dit RTOG-CTV zou uiteraard alle subklinische lymfkliermetastasen moeten omvatten bij de meerderheid van de patiënten. Maarliefst 53% van de patiënten had een MRL-positieve klier buiten dit RTOG-CTV. Dit betekent dat bij meer dan de helft van de patiënten (een deel van) het doelwit gemist zou worden bij bestraling gericht op dit CTV. De meest frequent aangedane regio's buiten het RTOG-CTV waren de pararectale regio, het gebied rond de proximale iliaca communis en de para-aortale regio. Deze waren aangedaan bij respectievelijk 30%, 25% and 18% van de patiënten. Om de kans op het missen van ziekte te verminderen, zou het standaard CTV uitgebreid moeten worden naar deze regio's. Dit zou echter de toxiciteit van de behandeling doen toenemen. Bij voorkeur zou inclusie van deze regio's dan ook gebaseerd moeten worden op accurate beeldvorming.

**Hoofdstuk 3** en **4** behandelen de bevindingen bij 65 patiënten met een biochemisch recidief na prostatectomie die een MRL ondergingen in het UMC St. Radboud, voorafgaand aan salvage radiotherapie. De resultaten van **hoofdstuk 3** laten zien dat 47 van deze 65 patiënten (72%) een positieve MRL hadden. Van de 28 patiënten met een PSA <1.0 ng/ml hadden er 18 een positieve MRL. En van 37 patiënten die geen lymfkliermetastasen hadden bij de lymfklierdissectie die initieel bij diagnose werd uitgevoerd, hadden er 25 een positieve MRL. Hoewel onze groep bestond uit relatief veel patiënten met prognostisch slechte tumor karakteristieken, mogelijk ten gevolge van selectie bias door het retrospectieve karakter van de studie, wijzen deze resultaten uit dat een groot deel van de patiënten niet gebaat is bij salvage radiotherapie van alleen het prostaatbed.
De resultaten in hoofdstuk 3 laten verder zien dat de score volgens het Stephenson nomogram gerelateerd is aan de kans op lymfkliermetastasen bij deze patiënten. Dit nomogram zou dus gebruikt kunnen worden om patiënten te selecteren voor een klierbehandeling, analoog aan de Partin tabellen bij primaire prostaatkanker patiënten. Zoals 3 retrospectieve studies laten zien, zou lymfklierbestraling bij deze patiënten van voordeel kunnen zijn. Dit moet echter nog bevestigd worden in de prospectief gerandomiseerde RTOG 0534 fase-III studie, die op dit moment loopt.
**Hoofdstuk 4** beschrijft het patroon van verspreiding van MRL-positieve klieren bij de 47 MRL-positieve patiënten. Bij 37 patiënten (79%) was tenminste 1 MRL-positieve klier gelegen buiten het RTOG-CTV. Van de klierregio's buiten dit CTV was de pararectale regio opnieuw het meest frequent aangedaan, namelijk bij 43% van de patiënten. Aberrante drainage lijkt bij deze categorie patiënten dus nog vaker voor te komen dan bij primaire prostaatkanker patiënten, mogelijk door de voorafgaande prostatectomie. Ook bij deze patiënten zou het standaard CTV dus ofwel uitgebreid moeten worden naar de meest frequent betrokken regio's, of zou het doelvolume individueel bepaald moeten worden op basis van accurate beeldvorming.

In **hoofdstuk 5** wordt bij 4 primaire prostaatkanker patiënten getoond hoe MRL gebruikt zou kunnen worden als basis voor individuele bestralingsplannen. Alle niet-vergrote MRL-positieve klieren konden op de radiotherapie planningsCT geïdentificeerd worden. Het doelvolume voor electieve bestraling van klierregio's werd geïndividualiseerd aan de hand van de MRL. Voor elke patiënt werd een intensity modulated radiotherapy (IMRT) plan gemaakt. Er werd een electieve dosis van 42 Gy op de lymfklierregio's voorgeschreven, en een boost dosis op de prostaat en de positieve lymfklieren van 72 respectievelijk 60 Gy, allen in 30 fracties. Er kon een uitstekende coverage bereikt worden van de doelvolumes, met een acceptabele dosis op de omliggende organen. De dunne darm bleek dosis-limiterend te zijn. In de RTOG richtlijn is de maximum dosis op de dunne darm gesteld op 52 Gy. Voor 1 patient kon deze beperking niet worden gehaald, omdat de dunne darm tegen een positieve klier aan lag. Bij deze patient zou 1.1cc van de dunne darm een dosis van >52 Gy krijgen. Dit werd geaccepteerd, vanwege het kleine volume en omdat de darm een bewegend orgaan is, en het verwacht mag worden dat er elke dag een ander deel van de darm in het hoge-dosis gebied ligt.

Het is uiteraard de vraag of bovenstaande behandeling effectief zal zijn en of zij ook curatief kan zijn. Tot op heden worden patiënten met lymfkliermetastasen namelijk vaak beschouwd als hebbende afstandsmetastasen en krijgen zij een palliatieve behandeling. Echter, patiënten met niet-vergrote positieve klieren op moderne beeldvorming zijn eigenlijk een nieuwe groep patiënten, bij wie er nieuwe behandelmogelijkheden ontstaan en van wie de prognose onbekend is. Om over de prognose wat meer duidelijkheid over te krijgen, werd het ziektebeloop bekeken van dergelijke patiënten die in het UMC St. Radboud een MRL kregen. In **hoofdstuk 6** worden de resultaten beschreven. MRL-positieve patienten hadden inderdaad een slechtere prognose dan MRL-negatieve patiënten. Echter, binnen de MRL-positieve groep was er een subgroep te definiëren met een relatief gunstige prognose, vergelijkbaar met die van high-risk patiënten zonder kliermetastasen. Patiënten bij wie de korte as van de grootste positieve klier ≤8mm was, hadden een significant betere 5-jaars afstandmetastase-vrije overleving (79% vs 16%) en totale overleving (81% vs 36%) dan patiënten met grotere positieve klieren. Hetzelfde gold voor patiënten bij wie de lange as van de grootste positieve klier niet groter was dan 10 mm. Hoewel in deze studie de follow-up resultaten van slechts 24 MRL-positieve patiënten bekeken konden worden, is dit toch een eerste stap om patiënten te identificeren bij wie curatie nog mogelijk zou kunnen zijn. De behandeling beschreven in **hoofdstuk 5** zou in theorie voor hen een optie kunnen zijn. Dit moet uiteraard nog onderzocht worden in klinische studies.

De general discussion in **hoofdstuk 7** geeft tot slot een overzicht van de internationale literatuur over TBB, en behandelt moderne technieken voor het afbeelden van lymfkliermetastasen bij prostaatkanker. Bovendien geeft het aan hoe moderne beeldvormende technieken in de toekomst een rol kunnen spelen bij de bestraling van lymfkliermetastasen.
De meeste retrospectieve studies die TBB vergeleken hebben met bestraling van alleen de prostaat, zien een voordeel van TBB, met name bij hoog-risico patiënten. De twee prospectief gerandomiseerde studies laten echter tegenstrijdige resultaten zien. Voor patiënten met een biochemisch recidief na prostatectomie zijn er slechts 3 retrospectieve

studies gedaan die TBB hebben vergeleken met bestraling van alleen het prostaatbed. Deze resultaten suggereren een voordeel voor TBB, opnieuw met name voor hoog-risico patiënten. Zoals hierboven reeds genoemd, wordt deze kwestie momenteel onderzocht in de prospectief gerandomiseerde RTOG 0534 studie.
Moderne en opkomende beeldvormende technieken, zoals choline-positron emission tomography (PET)/CT, single photon emission computed tomography (SPECT)/sentinel node procedure, prostaat-specifiek membraan antigeen (PSMA)-targeted imaging, diffusion-weighted MRI en MRL zijn veelbelovende technieken voor het afbeelden van lymfkliermetastasen bij prostaatkanker. Met het gebruik van deze technieken kan lymfklierbestraling verbeterd worden. Zo zouden ze gebruikt kunnen worden voor een betere patiënten selectie. Ook kunnen ze gebruikt worden bij het definiëren van het doelvolume, zodat het risico op het missen van ziekte met radiotherapie gereduceerd wordt. Daarnaast geven ze de mogelijkheid tot het boosten van pathologische lymfklieren. Op deze manier kunnen geïndividualiseerde bestralingsplannen gemaakt worden. Deze ontwikkelingen zouden kunnen leiden tot het verlaten van het concept van electieve lymfklierbestraling, en het verder ontwikkelen van selectieve klierbestraling. Of dit ook tot betere resultaten zal leiden, zal in klinische studies onderzocht moeten worden.

Concluderend laten de MRL bevindingen in dit proefschrift zien dat het huidige CTV voor lymfklierbestraling niet alle lymfkliergebieden die een hoog risico hebben om aangedaan te zijn omvat. Dit geldt voor primaire prostaatkanker patiënten, maar nog meer voor patiënten met een biochemisch recidief na prostatectomie. Verder is getoond dat er bij deze laatste groep patiënten een hoog risico op ‘subcentimeter’ lymfkliermetastasen lijkt te bestaan. Bestralen van alleen het prostaatbed zal bij deze patiënten geen curatieve optie zijn, maar mogelijk is lymfklierbestraling bij een deel van deze patiënten wel van voordeel. Het Stephenson nomogram zou gebruikt kunnen worden om patiënten te selecteren voor deze behandeling.

De ontwikkeling van betere moderne beeldvormende technieken voor het opsporen van lymfkliermetastasen heeft de beperkingen van electieve klierbestraling blootgelegd. Het ligt dan ook in de lijn der verwachting dat het concept van electieve klierbestraling verlaten zal worden, en dat selectieve klierbestraling, met het gebruik van moderne beeldvormende technieken, verder doorontwikkeld zal gaan worden. In dit proefschrift hebben we laten zien dat MRL hierbij een belangrijke rol zou kunnen gaan spelen. Op MRL gebaseerde radiotherapie met een electieve dosis op een individueel bepaald doelvolume en een boost op de positieve lymfklieren en de prostaat is theoretisch mogelijk. Dit zou een behandeloptie kunnen zijn voor patiënten met alleen zeer kleine positieve lymfklieren, omdat het bij hen een lange tijd duurt voordat er afstandsmetastasen ontstaan en zij daarom een kans op curatie lijken te hebben. Klinische studies zijn echter nodig, om hierover definitief conclusies te kunnen trekken.

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## Curriculum Vitae

Hendrika (Hanneke) Josephia Maria Meijer werd geboren op 15 juni 1983, te Boxmeer. Zij groeide op in het kleine dorpje St. Hubert, in Noord-Brabant. De middelbare school doorliep zij op het Elzendaalcollege in haar geboorteplaats. Hier behaalde zij in 2001 haar VWO-diploma (cum laude), waarbij zij ook de Natuurkundeprijs van OMO (Ons Middelbaar Onderwijs) kreeg. Zij koos ervoor om Geneeskunde te gaan studeren aan de Katholieke Universiteit Nijmegen, inmiddels omgedoopt tot Radboud Universiteit Nijmegen. In 2007 rondde zij deze studie af.

Na korte tijd gewerkt te hebben op de afdeling neurologie in het Catharina Ziekenhuis in Eindhoven, solliciteerde zij begin 2008 op een ANIOS vacature in het UMC St. Radboud te Nijmegen op het vakgebied van haar speciale interesse: radiotherapie. Zij startte in april 2008 en werd tevens kliniekvertegenwoordiger van het UMC St. Radboud binnen de NVRO. In januari 2009 begon zij aan haar opleiding tot radiotherapeut-oncoloog in hetzelfde instituut. Onder leiding van prof. dr. J.H.A.M. Kaanders, prof. dr. J.O. Barentsz en dr. E.N.J.Th. van Lin begon zij in 2010 aan haar PhD project, dat uiteindelijk heeft geresulteerd in dit proefschrift. In 2012 werd haar werk bekroond met een Best Poster Award van de European Society for Radiotherapy and Oncology (ESTRO).

Momenteel is Hanneke werkzaam in het UMC St. Radboud. Zij hoopt in december 2014 haar opleiding tot radiotherapeut-oncoloog af te ronden.

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