The value of MR lymphography in the detection of lymph node metastases in patients with prostate cancer

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1 Introduction

Epidemiology and burden of illness

Prostate cancer is the most common cancer in men and the second most common cause of death among malignancies afflicting men. In The Netherlands 7902 men were diagnosed with prostate cancer in 2003. In total 2349 patients died of prostate cancer in 2003. [1]

The incidence of prostate cancer is increasing as a result of ageing of the population and the widespread use of prostate specific antigen (PSA) testing.

Prostate cancer affects health related quality of life and life expectancy depending on the stage of the disease and whether appropriate treatment is given to the patient. [2,3]

The health care cost to Dutch society related to prostate cancer is approximately 31.6 million Euros, which is 0.10% of total health care costs in the Netherlands. [4]

Treatment options in patients with clinically localized prostate cancer

When prostate cancer is diagnosed, clinical staging is performed to determine the optimal therapeutic actions. When the probability of organ-confined prostate cancer is high, the use of local therapy such as radical prostatectomy (RP) or radiation therapy (RT) is associated with a significant likelihood of cure. Active surveillance is also considered a valuable strategy for these patients. This results in good outcomes in terms of survival and quality of life. The life expectancy of a 60 year old man having undergone radical prostatectomy is estimated to be 11 years on average. After radiotherapy the life expectancy of a 60 year old man is 10 years. [2,3]

However, once prostate cancer spreads to the lymphatic tissue, the patient's status is changed to one of systemic disease and the opportunity for cure with a local therapy is extremely limited or no longer present. Patients with a single microscopic node have a pattern of progression and cancer specific mortality similar to patients with more extensive nodal metastases and markedly worse than patients with negative nodes.[5]

A patient with positive pelvic lymph nodes requires systemic therapy, usually in the form of hormone therapy. Life expectancy in this case is 8 years for a 60 year old man.

Thus, the treatment options and strategy to be chosen for a patient depends on the nodal stage of the disease.

CHAPTER 1

Introduction

Current practice in lymph node staging

Currently, the recommended procedure to assess the risk of lymph node involvement in prostate cancer patients involves the use of predictive models employing nomograms, algorithms or neural nets such as those of Partin et al (2001), Narayan et al (1995), and Bluestein et al (1994).[6,7,8]

PSA, Gleason score and clinical stage are used in these risk assessment tools. Utilizing combined variable analysis these tools provide statistically more significant information.[9,10]

Patients having a low risk for lymph node metastases (< 5%) usually receive curative treatment and do not undergo radiological lymph node staging or a diagnostic lymph node dissection, whereas patients with higher risk undergo additional staging.[7]

A number of nodal staging methods are used in patients having an intermediate or high risk (>5%) for lymph node involvement. A pelvic lymph node dissection (PLND) is considered the most reliable staging modality and is the most widely used method to document nodal involvement. However, this is both invasive and expensive.[11] However, in PLND usually only the obturator fossa area is examined to minimize the risk of unnecessary complications. This often results in false negative results.

Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) are non-invasive procedures that are also commonly used for nodal staging. A negative result with either test should be verified by means of a PLND, since the probability of lymph node metastases after a negative result is higher than 5%. Alternatively, in case of a positive imaging result, a CT guided biopsy of the lymph nodes may provide a decisive answer. Nodal biopsy is not a highly sensitive staging procedure and a false negative rate of 40% has been reported by Jager et al. (1996)[12] In case of an indecisive or negative result using biopsy, a PLND is performed.

MR lymphography in the detection of lymph node metastases

Recently, high resolution MRI using a lymph node specific contrast agent has been used as a nodal staging method in prostate cancer.[13,14] This technique is called MR-lymphography (MRL). The contrast agent used with this technique consists of Ultrasmall Super Paramagnetic Iron Oxide (USPIO) particles. When these particles are injected intravenously, they are transported by macrophages to only normal lymph node tissue as macrophage activity is absent in metastatic tissue. The iron containing particles cause alterations in magnetic properties resulting in changed signal intensity detectable by MRI.[13,14] Therefore, normal functioning lymph nodes appear black on MRI 24-36 hours after administration of USPIO. In metastatic nodes, however, the signal intensity remains unchanged due to the absence of iron particles.[13,14] (Figure 1) One of the possible advantages of MRL over PLND is that in using MRL, the lymph nodes in the whole pelvic area can be examined instead of only the obturator fossa.

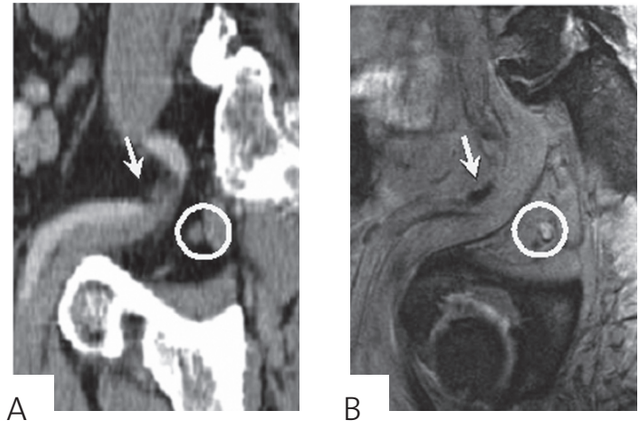

Figure 1. *Normal node and small positivenode in a 60 year old male with prostate cancer. A. CT scan in obturator plane shows 2 nodes of normal size (circle 7 mm; arrow 4 mm). B. On post ferumoxtran-10 T2*-weighted MEDIC MR image (=MRL image) one node is black due to iron accumulation in macrophages in normal node tissue (arrow). The other node is white due to replacement of normal node tissue (macrphages) by metastases (circle). On histopathology, the black node was normal and the white one was metastatic.*

Harisinghani & Barentsz et al (2003) published a study that presented a negative predictive value and a sensitivity of 100% for MRL.[13] These results suggest that a negative MRL obviates the need for lymphnode dissection.[7]

This requires a paradigm shift, while CT and MRI without a lymph node specific contrast agent are focused on identifying metastatic nodes, and obviating the need for PLND in a small number of patients in whom the diagnosis can be established by FNAB, MRL obviates the need for PLND in all patients with a negative result.

Evaluation of diagnostic technology

In the literature several different levels are distinguished to evaluate new diagnostic technology.[15,16] (See figure 2) The first level is technical efficacy. In the development of a test it is important to define the technical parameters that give the best diagnostic accuracy. For example in MRI it is important to determine the optimal sequences and echo time. The second level is diagnostic efficacy. At this level one attempts to answer the question "How well does this test distinguish disease from the non diseased state?". Evaluation of the third level, diagnosis, provides information on whether the results of the new technology alter the diagnosis of the patient or provides more diagnostic certainty. Consequentially it is important to evaluate whether the results of the test are helpful in patient treatment planning. (Level 4). The fifth level focuses on patient health outcomes. In this level information is obtained on whether the new technology improves the patient's health. The final and sixth level focuses on societal value of the new test, by looking at the cost-effectiveness from a societal perspective. [15,16]

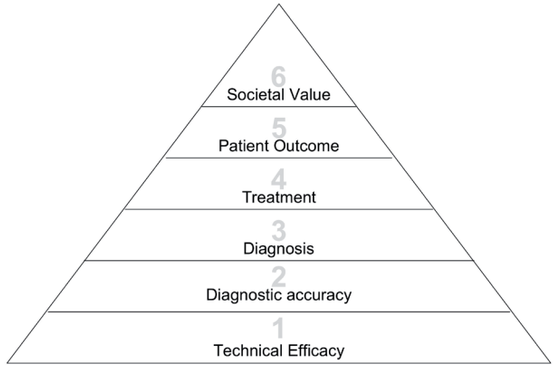

Figure 2. *The hierarchical levels of evaluating diagnostic technology [15,16]*

Regarding MRL in prostate cancer, evaluation of the first level has been established by Harisinghani et al.[13,14] Technical evaluation consists of the description of optimal MRI parameters, characteristics of the contrast agent and preliminary observations of MRL.[14] Promising results press for evaluation of the other levels in order to be able to implement this new diagnostic technology. According to the above mentioned framework for clinical evaluation of diagnostic technologies, in this thesis the focus will be on diagnostic evaluation from the second level up to the sixth level.

Economic evaluations in health care

Besides completing the evaluation hierarchy of diagnostic technology, cost-effectiveness analyses are becoming increasingly important for decision making regarding the reimbursement of health care technology. The discussions on the health care budget, increasing insurance premiums, and related to these the question 'what is acceptable health care' are presently important policy issues. Cost-effectiveness analyses contribute to rationalizing health care policy. [17]

As in many countries, in the Netherlands the growing tension between the rising demand for health care and political pressure to contain its costs has led policy makers to recommend that new health care technology should not be incorporated into standard practice without evaluation of its added value compared to current practice. Therefore the need arose to assess new technology in terms of their costs and benefits in order to come to a decision on registration, reimbursement and pricing.[18]

Economic evaluations have now been performed for many different technologies, including both therapeutical technologies and diagnostic technologies, although to date the methodological quality of economic evaluation of diagnostic technologies is limited [19].

Aim of this thesis

The aim of this thesis is to estimate whether MRL is an alternative for CT and PLND in the detection of lymph node metastases in patients with prostate cancer

This evaluation will be based on the above described criteria of:

- diagnostic accuracy,
- diagnosis,
- treatment,
- patient outcome,
- societal value (cost effectiveness),

This was performed in the framework of a multi center study on the use of MRL in detecting lymph node metastases in patients with prostate cancer.

Outline of this thesis:

Chapter 2 provides information on the state of affairs in radiological imaging in detecting lymph node metastases before the introduction of MR lymphography using a meta-analysis.

In chapter 3 the diagnostic accuracy of MRL is described. MRL was compared with CT in detecting lymph node metastases using histopathology of nodal tissue as a reference standard.

Chapter 4 describes a regression analysis based on data from patients in the multicenter study to determine whether staging by MRL substantially improves the diagnostic certainty compared to the current staging strategy.

The impact of the results of MRL on the therapeutic and diagnostic choices of urologists is described in Chapter 5. In an explorative study the weight of results of MRL in decisions regarding the patient management process are estimated.

Chapter 6 describes a pilot cost-analysis of three diagnostic strategies for patients with prostate cancer and a high or intermediate risk of lymph node metastases.

Chapter 7 deals with the core questions of this thesis, which are aimed at gaining insight into the cost-utility of MR with a lymph node specific contrast agent compared to PLND and CT.

In Chapter 8 the main findings and limitations of the thesis are discussed and the results put into perspective.

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CHAPTER 2

2

The Diagnostic Accuracy of CT and MRI in the Staging of Pelvic Lymph Nodes in Patients with Prostate Cancer. A Meta-Analysis.

Abstract:

Objectives: To compare the diagnostic accuracy of CT and MRI in the diagnosis of lymph node metastases in prostate cancer.

Methods: After a comprehensive literature search, studies were included that allowed construction of contingency tables for detection of lymph node metastases by CT or MRI. In addition, a summary ROC analysis was performed.

Results: A total of 25 studies were included. For CT, pooled sensitivity(+) was 0.42 (0.26-0.56 95% CI) and pooled specificity was 0.82 (0.80-0.83 95% CI). For MRI, the pooled sensitivity was 0.39 (0.22-0.56 95% CI) and pooled specificity was 0.82 (0.79-0.83 95% CI). The differences in performance of CT and MRI were not statistically significant.

Conclusion: CT and MRI demonstrate an equally poor performance in the detection of lymph node metastases from prostate cancer. Reliance on either CT or MRI will misrepresent the patient's true status regarding nodal metastases and thus misdirect the therapeutic strategies offered to the patient.

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Introduction:

Prostate cancer is the most common cancer in men and the second most common cause of death among malignancies afflicting men. In circumstances where metastatic disease does not appear to be present and the probability of organ-confined prostate cancer is high, the use of local therapy such as radical prostatectomy (RP) or various modalities of radiation therapy (RT) is associated with a significant likelihood of cure. However, once prostate cancer spreads to the lymphatic tissue, the patient's status is changed to one of systemic disease and the opportunity for cure with a local therapy is either markedly diminished or no longer present. Currently, the recommended strategy to assess risk insofar as lymph node involvement involves the use of predictive models using inputs as PSA, Gleason score and clinical stage, such as those of Partin, Narayan, and Bluestein. [1,2,3]

Patients found to have a low risk for lymph node metastases (<5%) usually receive curative treatment and often do not undergo further radiologic imaging or diagnostic lymph node dissection, whereas patients with higher risk should be referred for additional staging.[4,5] A number of nodal staging methods are used in patients having an intermediate or high risk for lymph node involvement. The most reliable method available to document nodal involvement is pelvic lymph node dissection (PLND). However, this is both invasive, expensive, and may be associated with significant morbidity. Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) are non-invasive procedures that are commonly used for nodal staging. A finding of lymph node metastases with either test can be verified by means of PLND. Alternatively, fine needle aspiration biopsy (FNAB) is often used to provide a decisive answer in case of a positive imaging result. Frequently, however, the lymph node is hard to reach because of its anatomic position. In addition, FNAB is not a highly sensitive staging procedure and a high false negative rate of 40% has been reported by Jager et al.[6] In case of an indecisive or negative result using FNAB, an excisional biopsy or PLND is performed.

Overall, the medical literature demonstrated that the specificity of CT and MRI in the detection of lymph node metastases is high. For example, Wolf et al reported a specificity of 97% for CT and MRI in finding lymph node metastases in prostate cancer. In contrast, however, in their report they found a sensitivity of 36%. They concluded that nodal imaging studies should only be recommended for patients having a probability of 45% or higher for lymph node metastases.[7]

The current literature shows a broad range in the diagnostic performance for both CT and MRI. Methodological as well as patient group characteristics appear to cause bias and over- or underestimation of the diagnostic performance of these tests.[8] A meta-analysis of the diagnostic accuracy of presurgical CT or MRI and the criteria used for staging pelvic lymph nodes was undertaken to evaluate the value of these studies in the staging of men with prostate cancer. In addition, we investigated the effect of patient-group characteristics and methodological characteristics on the staging performance of CT and MRI for the diagnosis of lymph node metastases in prostate cancer.

Material and methods:

Data Sources and Study Selection:

A search of the online databases within Medline and the Cochrane library was performed to identify all relevant articles published between 1980 and 2003, thereby taking into account the time of clinical introduction of CT (±1980) and MRI (±1985).
The following search terms were used: prostat*, cancer or carcinoma, neoplasm, lymph* nod* staging, MRI, Magnetic reson*, CT and Computed Tomography. To identify additional relevant articles, reference lists of retrieved articles were checked manually.

Abstracts on articles were checked by 2 authors (A.H. and R.H.)
for the following inclusion criteria:

- The article was published between 1980 and 2004

- The study-population consisted of patients diagnosed with prostate cancer

- Focus of the study was on the accuracy of CT and/or MRI on nodal staging.
Studies on lymphangiography and PET were excluded.

- Histopathological evaluation of the lymph nodes was used as gold standard.

- Information on true positive and negative as well as false positive and negative rates had to be presented or it had to be possible to calculate them from the published data.

If a study did not meet the inclusion criteria, the study was excluded and the reason recorded. Only the first found reason for exclusion was recorded.

Methodological Assessment and Data Extraction:

To assess methodological quality, the following elements for study quality were scored: sample size, publication year, consecutively enrolled patients, prospective study design, reference tests, blind interpretation of test results and a clear description of the test.[8] These characteristics were included because studies with shortcomings in these methodological characteristics may overestimate the accuracy of a diagnostic test, particularly those including non-representative patients or applying different reference standards.[8]

Furthermore, the following data in patient groups were scored: PSA, Gleason score, tumor grade, CT and MRI slice-thickness and criteria for minimal size of a positive lymph node.

For each study the numbers of true positives and negatives as well as false positives and negatives were recorded or calculated. Only data of patients who fulfilled inclusion criteria were included. For this latter reason, the total number of patients in the original report could be greater.

Statistical analysis:

Sensitivity, specificity as well as the diagnostic odds ratio (DOR) were calculated from the data for each study. The DOR is the odds of a positive test result in a patient with lymph node metastases relative to the odds of a positive test result in a patient with no lymph node metastases. Sensitivity and specificity were pooled using a random effects model.[9]

Since sensitivity and specificity are correlated, we also summarized their joint distribution using a summary receiver operating characteristic (sROC) curve.[10] Following guidelines for fitting sROC curves, single number summaries (Q*values) were obtained for both MRI and CT representing the point on the sROC curve where sensitivity and specificity are equal. The maximum Q* value of a perfect test is 1, and the maximum Q* value of a test that has no diagnostic value is 0.5. Testing for differences between CT and MRI was based on the Q*values and their standard errors (SEs).[10,11] Summary likelihood ratios (LR) were calculated. Since a LR of 1 means that the posttest probability is exactly the same as the pretest probability, clinically useful tests should have high positive LR (>5="good in ruling in disease") and low negative LR (<0.2="good in ruling out disease")[12,13]

The posttest odds were calculated by multiplying the likelihood ratios by the pretest odds (Prevalence/1-prevalence). From the posttest odds, the posttest probability was calculated (Probability=odds/(odds+1). This probability represented the probability for a patient with a certain test result to have lymph node metastases.

To determine if certain methodological or clinical characteristics affected diagnostic accuracy, we compared studies that did and did not have these characteristics in subgroup analyses. To make statistical comparisons between groups of studies we compared log odds ratios (OR) by using unpaired t-tests or the Mann-Whitney-U-test, as appropriate.[14]

Results:

Literature search:

The search-strategy produced 181 hits. A total of 157 articles were excluded for reasons displayed in Table 1. Using the bibliographies of the included articles we found an additional 6 useful articles. Finally, 24 articles fulfilled the inclusion criteria. In four, MRI was compared to CT. The data on MRI and CT in these articles were considered separate studies. A total of 10 studies using MRI with data on 628 patients, and 18 studies using CT with data on 1024 patients were included in the meta-analysis.

TABLE 1: *Reasons for Exclusion of Articles*

Reason for exclusion	N
Language	6
No information on prostate cancer patients	21
No information on CT or MRI	81
Reference test is not histopathology	6
No information on sensitivity or specificity	11
No information on lymph node involvement	44
Duplicate publication	6
Total	157

Meta-analysis

The sensitivity, specificity and DOR of the included studies are reported in Table 2. Sensitivity ranged from 5% to 94% for CT and from 6% to 83% for MRI. Specificity ranged from 59% to 99% for CT and from 65% to 99% for MRI. Pooled sensitivity and specificity for CT were 0.42(0.20-0.56 95%CI) and 0.82(0.80-0.83 95%CI), respectively. For MRI the pooled sensitivity and specificity were 0.39(0.19-0.56 95%CI) and 0.82(0.79-0.83 95%CI).

TABLE 2: *Sensitivity, Specificity and Diagnostic Odds Ratio of Included Studies on the Performance of CT and I.*

Authors	Publication year	N	Sensitivity	Specificity	DOR
CT					
Benson [15]	1981	23	50%(1/2)	66%(14/21)	1,93
Golimbu [16]	1981	46	31%(5/17)	92%(27/29)	4,84
Levine [17]	1981	16	94%(7/7)	83%(7/8)	75,00
Morgan [18]	1981	9	36%(2/6)	95%(10/10)	11,67
Giri [19]	1982	12	75%(4/5)	81%(6/7)	13,00
Emory [20]	1983	27	27%(3/12)	97%(15/15)	11,42
Sawczuk [21]	1983	8	25%(1/5)	88%(3/3)	2,33
Weinermann [22]	1983	19	68%(7/10)	75%(7/9)	6,43
Flanigan [23]	1985	35	50%(3/6)	98%(29/29)	0,29
Mukamel [24]	1986	10	50%(0/0)	59%(6/10)	1,44
Biondetti [25]	1987	7	83%(2/2)	92%(5/5)	55,00
Hricak [26]	1987	85	25%(2/9)	99%(76/76)	51,00
Platt [27]	1987	32	8%(0/5)	95%(26/27)	0,07
Engeler [28]	1992	160	5%(2/47)	100%(113/113)	12,47
Van Poppel [29]	1994	285	77%(35/45)	96%(232/240)	92,48
Flanigan [30]	1996	173	27%(3/12)	97%(156/161)	10,48
Rorvik [31]	1998	64	28%(2/8)	97%(44/45)	11,41
Borley [32]	2003	13	5%(0/9)	90%(4/4)	0,47
MRI					
Mukamel [24]	1986	10	25%(0/1)	65%(6/9)	0,62
Biondetti [25]	1987	29	83%(2/2)	97%(16/16)	165,00
Hricak [26]	1987	85	45%(4/9)	99%(76/76)	125,18
Bezzi [33]	1988	51	68%(9/13)	94%(36/38)	30,82
Rifkin [34]	1990	185	6%(1/23)	95%(155/162)	1,38
Kier [35]	1993	27	17%(0/2)	90%(23/25)	1,88
Jager [6]	1996	63	59%(9/15)	97%(47/48)	46,28
Perotti [36]	1996	56	13%(0/3)	90%(48/53)	1,26
Borley [32]	2003	42	29%(3/11)	98%(31/31)	25,94
Harisinghani [37]	2003	80	46%(15/33)	78%(37/47)	2,99

N is the number of patients who fulfilled the inclusion criteria. In the original report N may be larger. Sensitivity and specificity are calculated from these numbers and conventional correction was applied by adding 0.5 to each cell in the 2x2 tables to prevent division by zero. DOR: diagnostic odds ratio

TABLE 3: *Population and Methodological Characteristics of the Included Studies.*

Authors	Publication year	N	Age	PSA	Gleason*	Tumor Stage	Prevalence	Slice Thickness	Threshold of a positive lymph node	Reference test	Consecutive	Prospective	Blind interpretation of test results	Clear description of test	Clear description population
CT															
Benson [15]	1981	23	n.m.	n.m.	n.m.	n.m.	0.09	1.3	0.8	PLND	No	Yes	No	Yes	No
Golimbu [16]	1981	46	n.m.	n.m.	n.m.	A2-D	0.37	1.3	1	PLND	No	Yes	No	Yes	Yes
Levine [17]	1981	16	n.m.	n.m.	n.m.	A-B	0.47	1	1.5	PLND + FNAB	Yes	No	No	Yes	Yes
Morgan [18]	1981	9	n.m.	n.m.	n.m.	n.m.	0.38	0.5	1.5	PLND	No	No	Yes	Yes	No
Giri [19]	1982	12	n.m.	n.m.	n.m.	n.m.	0.42	1.3	n.m.	PLND	No	Yes	No	Yes	No
Emory [20]	1983	27	n.m.	n.m.	n.m.	n.m.	0.44	1.5	2	PLND + FNAB	No	No	No	Yes	No
Sawczuk [21]	1983	8	n.m.	n.m.	n.m.	n.m.	0.63	n.m.	1.2	PLND	No	No	No	No	No
Weinermann [22]	1983	19	n.m.	n.m.	n.m.	n.m.	0.53	1.2	1.2	PLND + FNAB	No	Yes	No	Yes	No
Flanigan [23]	1985	35	n.m.	n.m.	n.m.	A2-Do	0.89	n.m.	1.5	PLND + FNAB	Yes	Yes	No	Yes	Yes
Mukamel [24]	1986	10	n.m.	n.m.	n.m.	n.m.	0	n.m.	n.m.	PLND	Yes	Yes	No	Yes	No
Biondetti [25]	1987	7	68	n.m.	n.m.	B	0.29	1	1.5	PLND	No	Yes	No	Yes	Yes
Hricak [26]	1987	85	n.m.	n.m.	n.m.	n.m.	0.11	1	1.5	PLND	Yes	Yes	Yes	Yes	No
Platt [27]	1987	32	n.m.	n.m.	n.m.	n.m.	0.81	0.8	1.5	PLND	Yes	Yes	No	Yes	No
Engeler [28]	1992	160	67.6	n.m.	n.m.	n.m.	0.29	1	1.5	PLND	No	No	No	Yes	Yes
Van Poppel [29]	1994	285	64	3.5-54	7.1	A-C	0.16	0.8	0.6	PLND + FNAB	Yes	Yes	No	Yes	No
Flanigan [30]	1996	173	n.m.	n.m.	n.m.	n.m.	0.07	n.m.	0.5	PLND + FNAB	Yes	No	Yes	No	No
Rorvik [31]	1998	64	63	n.m.	n.m.	n.m.	0.15	1	1	PLND + FNAB	No	Yes	No	Yes	Yes
Borley [32]	2003	13	64.3	38,8	n.m.	T1-T3	0.69	1	1	PLND	No	No	No	Yes	Yes
MRI															
Mukamel [24]	1986	10	n.m.	n.m.	n.m.	n.m.	0.1	n.m.	n.m.	PLND	Yes	Yes	No	Yes	No
Biondetti [25]	1987	29	68	n.m.	n.m.	B	0.11	1	1.5	PLND	No	Yes	No	yes	Yes
Hricak [26]	1987	85	n.m.	n.m.	n.m.	n.m.	0.11	0.7	1.5	PLND	Yes	Yes	Yes	Yes	No
Bezzi [33]	1988	51	67	n.m.	n.m.	n.m.	0.25	0.5	1	PLND + FNAB	No	No	No	Yes	Yes
Rifkin [34]	1990	185	60.8	n.m.	n.m.	n.m.	0.12	1	1	PLND	No	Yes	No	Yes	Yes
Kier [35]	1993	27	64	8.0-57	n.m.	n.m.	0.07	0.5	1.5	PLND	No	Yes	No	Yes	Yes
Jager [6]	1996	63	64	8.2	n.m.	n.m.	0.24	1	0.8	PLND + FNAB	Yes	Yes	No	Yes	Yes
Perotti [36]	1996	56	43-71	0.8-67.6	n.m.	n.m.	0.05	0.4	1	PLND	No	Yes	No	Yes	Yes
Borley [32]	2003	42	64.3	38.8	n.m.	T1-T3	0.26	1	1	PLND	No	Yes	No	Yes	Yes
Harisinghani [37]	2003	80	64	21	7	n.m.	0.41	0.7	1	PLND + FNAB	No	Yes	No	Yes	Yes

n.m. : not mentioned in the article

The population and methodological characteristics are displayed in Table 3. In only one study was the patient population described in detail.29The Gleason-score and average PSA were mentioned in 10 out of 28 studies. The sROC curve is presented in Figure I. For CT, a Q* value of 0.77(0.69-0.83 95%CI) was found. A Q* value of 0.77(0.73-0.80 95%CI) was found for MRI.

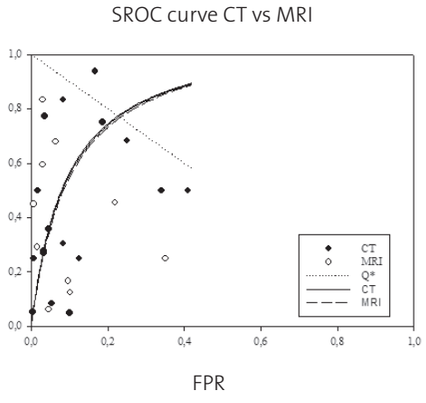

Figure 1. *Summary ROC curve for CT compared to MRI*

TPR: True positive rate (sensivity)
FPR: False positieve rate (1-specificity)
Q represents the line on which sensitivity and specitficity are equal. The difference in Q* values between MRI and CT did not reach statistical significance*

Overall, summary likelihood ratios and posttest probabilities are presented in Table 4. Since "1" is included in the confidence interval of the negative likelihood ratios, the post-test probability is no different from the pretest probability. The average prevalence of lymph node metastases in studies included in this analysis was 0.17 for CT and 0.30 for MRI. When these numbers were used as pretest probabilities the post-test probabilities of a positive test were 0.31(0.23-0.40 95%CI) for CT, and 0.47 (0.30-0.58 95%CI) for MRI. The post-test probabilities for a negative test were 0.12 (0.10-0.16 95%CI) for CT and 0.23(0.18-0.29 95%CI) for MRI. Since only 10 out of 28 studies reported information on Gleason score and PSA, no subgroup-analysis was done for high-risk patients versus low-risk patients due to this lack of information.

TABLE 4: *Summary Likelihood Ratios and the Positive and Negative Post-test Probabilities of Each Test.*

Test	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	Posttest probabilities	
			Positive test	Negative test
CT	2.33 (0.95-3.29)	0.70 (0,53-1.00)	0.32 (0.23-0.40)	0.12 (0.10-0.16)
MRI	2.16 (0.89-3.29)	0.74 (0.53-1.02)	0.47 (0.30-0.58)	0.24 (0.22-0.41)

The summary logORs for CT and MRI are displayed in Figure 2.
For the criteria suggested by Lijmer there was no significant difference between studies with or without these characteristics. However, diagnostic accuracy of CT was better in 5 studies that had a sample size of more than 50 patients. (p=0.03) The summary log OR of the studies with sample size of more than 50 patients was 3.3 (2.12–4.48 95%CI). For other characteristics used in subgroupanalysis there was no significant difference in estimates between studies with or without the corresponding feature. Since data collection in all studies on MRI was prospective and interpretation of the test results was not blinded, subgroup comparison for these characteristics was not possible. No significant differences were found between studies on MRI with or without the other methodological and population characteristics.

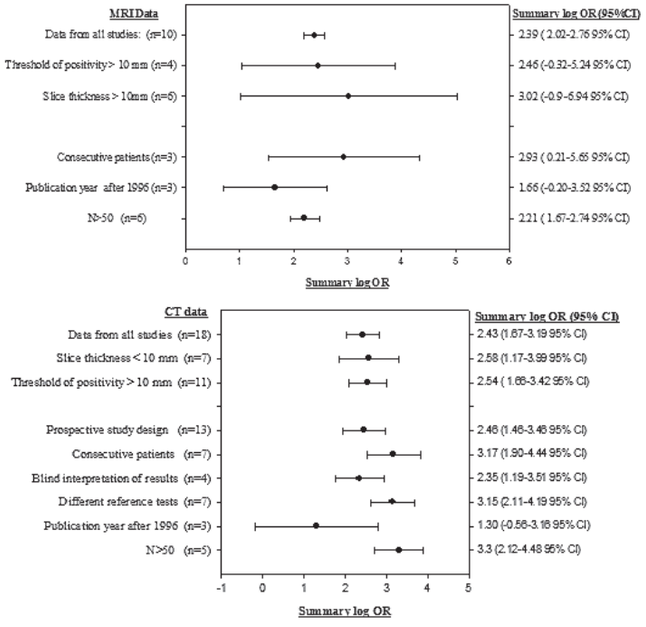

Figure 2. *Summary log ORs of studies on MRI (top) and CT (bottom).*

In all studies concerning MRI the test results were interpreted blindly and a sufficient description of the test was given. A significant difference was found for studies with N>50.

In all studies concerning MRI the test results were interpreted blindly and a sufficient description of the test was given. A significant difference was found for studies with N>50

Discussion:

Based on calculations of relevant data available in the current published literature, results indicate that CT and MRI perform similarly in the detection of pelvic lymph node metastases from prostate cancer. The likelihood ratios on CT and MRI indicate that a positive or negative result does not give relevant information on the lymph node status of the patient, since 1 is in the confidence interval. With post-test probabilities of 12%, a negative result of CT gives an indication towards the absence of nodal metastases, but not strong enough to forego additional lymph node staging by PLND. Mean prevalence of lymph node metastases in studies included was used as pretest probability in the calculation of the post-test probability. The post-test probabilities of a positive test increased slightly and post-test probabilities of a negative test decreased minimally compared to the pretest probability.

Urologists, in general, accept a probability of lymph node metastases of less than 5% to recommend curative treatment such as radical prostatectomy; additional nodal staging is not suggested in this context. Our results show that the performance of CT and MRI does not add significant information in our assessment of lymph node metastases. Both tests are too insensitive in their ability to detect nodal malignancy and should not be used in their current form. The preliminary results of new techniques, e.g. high resolution MRI utilizing an intravenous contrast agent consisting of ultra-small super paramagnetic iron oxide (USPIO) approach probability levels that are acceptable by urologists. [37,38]

When using CT or MRI, the decision that nodal involvement is present rests solely on whether there is enlargement of the investigated lymph nodes. The centimeter threshold used to decide whether a lymph node is metastatic varies in literature. In studies included in this meta-analysis, this threshold varied from 0.5 cm to 2 cm. A threshold of 1 cm in the short-axis nodal diameter for oval nodes and 0.8 cm for round nodes has been recommended as criteria for diagnosis of lymph node metastases.[6] The results show that despite a trend towards a better diagnostic performance in studies that use a threshold below 1 cm, no significant effect on diagnostic performance employing CT or MRI was found.

Only 10 of 28 studies included in this analysis provided information on the average PSA or Gleason score. Because of lack of information on these patient characteristics, it was not possible to compare results of nomograms projecting the risk of lymph node metastases with diagnostic performance of CT or MRI.

As indicated in our methods section, Lijmer et al suggested a number of methodological

aspects that may cause bias and consequently have an effect on diagnostic performance of a test.[8] We applied these criteria in this analysis and found no significant effect on diagnostic performance using CT or MRI. Studies with a sample size smaller than 50 yielded a significant underestimation of diagnostic performance of CT as confirmed by Lijmer et al.[8] In MRI, a similar trend was found, but this was not significantly different.

A specific design for meta-analysis of diagnostic tests has not been firmly established. Pooling of results across studies, or averaging sensitivity and specificity, may cause underestimation of test performance, because the relationship between sensitivity and specificity is not linear.[9,40] To address this problem, sROC analysis was used in this meta-analysis. sROC analysis corrects for variation due to differences in test thresholds in the original studies.[9,10,12,14,40]

The present study had the following limitations. First, some of the studies included in the meta-analysis were subsets from a larger study since only a limited number of patients fulfilled the inclusion criteria. This results in a smaller sample size and therefore potentially an underestimation of the diagnostic performance. In addition, the mandatory correction for zero entries by adding 0.5 to each cell had a rather large effect on studies with small sample sizes. A final limitation of this study is the possibility of publication bias. We did not attempt to search for unpublished studies. Conclusions of published studies on CT and MRI in the staging of lymph node metastases may be overly optimistic, since studies with favorable results are more likely to be submitted and published.

The impact on health providers, therapeutic impact and patient outcome were not evaluated in this study. But as these imaging techniques are widely and commonly used, they have a huge negative impact on health care costs involving an annual expenditure of hundreds of millions of dollars.[41] Moreover, subsequent misguidance involving treatment decisions based on conclusions from these imaging studies further compound this negative impact on healthcare funds.

Results from this meta-analysis indicate that both CT and MRI perform equally poorly in the detection of lymph node metastases from prostate cancer. Because of low post-test probabilities of a positive test, an assessment of lymph node involvement should not be done using CT or MRI. Reliance on CT or MRI will misrepresent the patient's true status insofar as lymph node metastases are concerned and misdirect the therapeutic strategies offered to the patient.

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CHAPTER 3

3 MRI with a lymph node specific contrast agent (Ferumoxtran-10): an alternative for Multi Detector CT-scanning and lymph node dissection in patients with prostate cancer?

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Submitted to Radiology

Abstract

Purpose: Determine the diagnostic accuracy of Magnetic Resonance Lymphography (MRL) compared to multi detector CT (MDCT) in a large patient population. Test the hypothesis that a negative MRL result obviates the need for a PLND. In addition this multicenter trial provides an opportunity to observe whether this technique can be easily implemented in the clinical setting without prior experience.

Patients and methods. Prospective cohort study of 375 consecutive prostate cancer patients, with an intermediate or high risk of having lymph node metastases. Study was conducted in 11 hospitals in the Netherlands between April 2003 and April 2005. All patients were examined by MDCT and MRL and underwent PLND or FNAB. Imaging results were correlated with histopathology. Results were compared between experienced and less experienced hospitals.

Results: Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of MDCT and MRL respectively were 34% and 82%, 97% and 93%, 88% and 96%, 66% and 69%. The accrual distribution was skewed, as 3 hospitals included 295 of all patients. Compared to the other centers their results were better. It appears that due to a good multidisciplinary collaboration the implementation of MRL was easier in these hospitals and has a positive effect on the results.

Conclusions: The diagnostic accuracy of MRL is significantly higher than MDCT regarding the detection of lymph node metastases. The post test probability of having lymph node metastases is low enough to omit a PLND after a negative MRL. MDCT is of limited use in lymph node staging due to low sensitivity. Finally, the MRL technique could be easily implemented if good multi-disciplinary collaboration exists, and adequate MRI-capacity is present.

Introduction

If pelvic lymph node metastasis in a patient with prostate cancer are present, curative treatment by radical prostatectomy or radiotherapy is no longer the best option[1]. To detect lymph node metastases patients may undergo non-invasive imaging like Computed Tomography (CT) and Magnetic Resonance Imaging (MR imaging). Because the sensitivity of these techniques is about 30% , which is too low to rule out the presence of lymph node metastases in case of a negative result, a pelvic lymph node dissection (PLND) will be performed [2]. The role of additional imaging is to establish the diagnosis of metastases with Fine Needle Aspiration Biopsy (FNAB) and thus obviates the need for PLND. This is in approximately 5- 10% of patients being imaged. Therefore many urologists perform a PLND without imaging.

It has been generally accepted, that a PLND can be omitted if the *a-priori* risk of lymph node involvement is less than 5%. [3-6]. Patients with a serum PSA > 10 or a Gleason score > 6 or a T3 tumour at DRE, have an *a-priori* risk of lymph node involvement up to 65%. [7,8] In these patients a diagnostic PLND is routinely performed.

With the introduction of Multi Detector MDCT, and the introduction of lymph node specific MR intra-venous contrast agent (ultra small particle of iron oxide (USPIO = Ferumoxtran-10) the diagnostic potentials of both imaging techniques have improved. The latter technique will be referred as Magnetic Resonance Lymphangiography (MRL). Initial studies demonstrated a high negative predictive value (NPV) of MRL in ruling out lymph node metastases. [9-13] Harisinghani et al. reported a high sensitivity, (91%), specificity and NPV (98%). With these results the post test risk of lymph node involvement is less than 5% and a PLND could be omitted. The study was, however, performed in a limited number of patients in two academic centers where extensive experience with this technique existed. [12]

The purpose of this multi-center study is first to determine the clinical effectiveness of MRL compared to MDCT with respect to the detection of lymph node metastases, secondly to test the hypothesis that a negative MRL result can obviate the need for a pelvic lymph node dissection. In addition, this multicenter trial provides an opportunity to observe whether this technique can be easily implemented in the clinical setting without prior experience.

Material & Methods

Patients

In a prospective multi center cohort study, from April 2003 to April 2005, 375 patients with biopsy proven prostate cancer were enrolled. All patients had a serum PSA level >10 ng/ml or a Gleason score > 6 or a T3 tumour on DRE. The mean age of the patients was 67y (range 46-83y) the mean serum PSA 25.7 ng/ml (range: 2.3-260 ng/ml) and the median Gleason sum was 7 (range 3-10). Institutional Review Board approval was obtained for all centers. All patients signed a written informed consent.

The study was conducted in 4 university medical centers: Radboud University Medical Center (RU) n=106, University Medical Center Amsterdam (UMCA) n=16, University Medical Center Maastricht (UMCM) n=9, Erasmus Medical Center (EMC) n=3, and 7 community hospitals: Catharina Hospital Eindhoven (CZE) n=110, Hospital Zeeuws-Vlaanderen (ZZV) n=31, Antoni van Leeuwenhoek Hospital (NKI) n=19, Rode Kruis Hospital (RKZ) n=15, Rijnstate Hospital Arnhem (Rijn) n=9, Leyenburg Hospital (Ley) n=9, and Canisius Wilhelmina Hospital (CWZ) n=48. Patients from CWZ had imaging at RU.

Interventions:

All patients were scheduled for a pelvic MDCT, MRL and a PLND. The MDCT and MR examinations were performed within one week of each other. A maximum of 8 weeks elapsed between the MRL and the PLND.

For all CT examinations state-of-the-art MDCT scanners were employed. A minimum of a 2 detector scanner was required for inclusion and the slice thickness was 3 mm with 1 mm overlap. Images of the abdomen were obtained after administration of oral and intravenous (150 ml) iodinated non-ionic contrast agent. Patients were scanned form the aortic bifurcation to the pubic symphysis.

MRI images were obtained on 1.5T state of the art imaging systems from one of three commercial vendors (Sonata/Symphony, Siemens, Erlangen, Germany, Gyroscan/Intera, Philips, Eindhoven, The Netherlands, and Horizon, GE Medical Systems, Milwaukee, Wisconsin,USA), with pelvic phased array coils. T2*-weighted gradient echo (GRE) and T1-weighted fast spin echo (FSE) MR images were acquired from the pelvis, extending from the aortic bifurcation to the pubic symphysis, within 24-36 hours after intravenous injection of Ferumoxtran-10. The T1- and T2*- weighted MR images were each acquired in 2 planes, using identical position and resolution parameters, in order to allow comparison. Image planes were a semi-sagital (“obturator”) plane (parallel to the psoas muscle) and axial plane. The T1-weighted images are insensitive, and the T2*-weighted images are

TABLE 1.: *Pulse sequences used to obtain MR images.*

	TR	TE	Bandwidth Hz/pixel	No. acquisitions	Slice thickness	Gap	Matrix	Field of view
Axial T1/PD weighted sequence turbo/fast SE	1800 – 2200 ms	9-12 ms	195	29 slices	5 mm	ffi 10%	230 x 512	225 x 300mm • From aortic bifurcation to pelvic floor • Cranial and caudal inflow presaturation • Spatial pre saturation on anterior abdominal wall
Axial T2* weighted sequence 2D GRE with flow compensation	1400 - 1800 ms	15 ms = 30°	78	29 slices	5 mm	ffi 10%	230 x 512	
Obturator T1/PD weighted sequence turbo/fast SE parasagittal plane along iliac vessel axis	1800 – 2200 ms	9-12 ms	195	2 x 13 slices	3 mm	ffi 10%	230 x 512	
Obturator T2* weighted sequence 2D GRE with flow compensation	1400 – 1800 ms	15 ms = 30°	78	2 x 13 slices	3 mm	0%	230 x 512	

very sensitive to the iron-containing contrast agent. Additionally, a 3D T1-weighted GRE sequence was applied to allow anatomical localization of the lymph nodes in relation to the vessels. The scan protocol is provided in table 1.

Image analysis

All findings were recorded on a specially designed electronic Case Record Form (e-CRF). This e-CRF (Bergson, Eindhoven, The Netherlands) also consisted of a help file to instruct all investigators. In each hospital all images were analyzed "on-site" by a radiologist affiliated with the corresponding hospital, using soft-copy reading at an electronic workstation with multiplanar reconstruction. At the start of the study only the primary investigator (J.B) had substantial (8 years) experience with MRL, the other radiologists had no prior experience. Anonymized MDCT images were read independently from the MRL images in random order. Besides instructions in the e-CRF help file, each radiologist of the individual centers received personal training for reading the MRL images prior to the study. Image quality for the first 10 MRL examinations at each of the participating centers was evaluated by the principal investigator. During the study regular quality control of both MDCT and MRL images was performed.

On MDCT images lymph nodes were classified as malignant if the minimal axial diameter exceeded 10 mm for an oval node and 8 mm for a round lymph node (14). Only positive nodes were reported. On MRI, nodal shape and size as well as the presence of high signal (i.e. fatty areas) within the node were assessed on the iron insensitive T1weighted turbo Spin Echo images.. A "black" area on the corresponding node on the iron sensitive T2*-weighted images was considered to be normal nodal tissue, If a "white" area of a node met the criteria presented in figure 1, then this node was considered to be metastatic, However, if a "white" area on the T2-*weighted image corresponded with a high signal area on the T1-weighted image, it was considered to be a fatty area and not a metastasis (Figure 2).

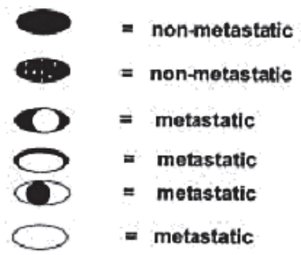

Figure 1.
Classification of lymph nodes as provided by Guerbet

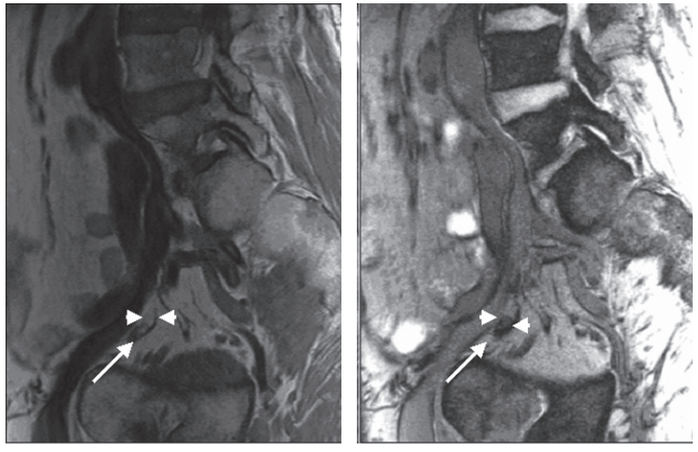

Figure 2.
Left: T1-weighted MR image (insensitive to iron) in obturator plane. Lymph node as a intermediate-low signal (arrows) and the fat high (arrowheads).
Right: T2 weighted MR image after Ferumoxtran-10 contrast. Half of the node has a low signal intensity (arrows) the other half remains white (arrowheads). As that part is also white on the T1 weighted MR image, it is fat and no mastasis.*

Patients were evaluated on a patient-to-patient basis. A patient was called positive when one or more metastatic lymph nodes were found. The location and size of the metastatic nodes on MDCT and MRL were independently recorded on a map embedded within the e-CRF (Figure 3). A merged map which combined the MRL and MDCT results was provided to the surgeon prior to the PLND. The surgeon noted the location of the removed lymph nodes. Finally, lymph node location determined at surgical resection was compared with the Ferumoxtran-10 enhanced scan.

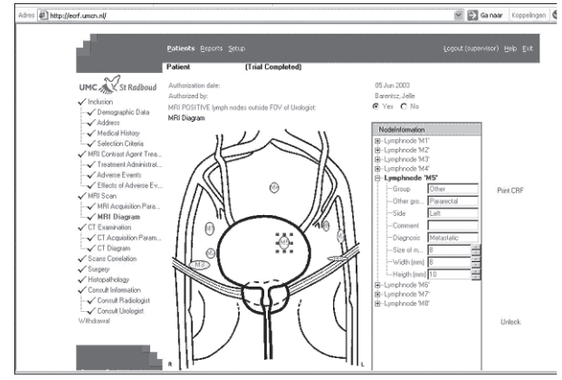

Figure 3.
All lymph nodes were drawn into an electronic database (e-CRF). For each node the size, location and diagnosis was noted in a map. The maps of MRL and MDCT were merged and provided to the surgeon.

Surgery

Open PLND was performed in 140 patients and laparoscopic PLND in 221. In 14 patients a nodal metastasis was proven by FNAB. In these patients PLND was omitted. The PLND consisted of a routine, limited (obturator) lymph node dissection, including resection of the nodes and fibro-fatty tissue along the external iliac vein and along the pelvic side wall, caudal to the femoral canal with the superior border being the bifurcation of the common iliac artery. The posterior border was the obturator nerve. In 15 patients, however, the PLND was more extensive as guided by the findings of the MRL, suggesting that there were positive nodes outside the field of the limited, routine PLND (figures 4-5). All lymphatic tissue was sent for final pathology en bloc on a grid identifying their location [11].

Analysis

Histopathology was the standard of reference, and all results were included in the e-CRF. Sensitivity, specificity, accuracy, NPV, PPV and the 95% confidence interval (95% CI) were calculated for both MRL and MDCT. Additionally, the McNemar test was applied in these two groups, with a confidence level of 95% (a difference with $p < 0.05$ was considered significant.)

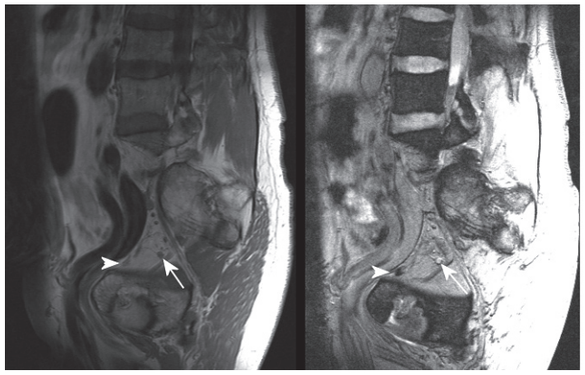

Figure 4.
Post Ferumoxtran-10 MR images in the semi-sagittal plane.
Left: T1 weighted MR image shows round 7 mm lymph node ventral to internal iliac vessels (arrow). This lymph is according to size and shape criteria benign. There is another small lymph node in the obturator fossa (arrowheads).
Right: T2 weighted MR image shows that the lymph node ventral of the iliac vessels (arrow) is white. This node is outside the regular PLND area. Based on the MRL image the PLND was extended and confirmed a malignant node. The node in the obturator fossa (arrowheads) is black due to iron uptake and was benign at histopathology following PLND.*

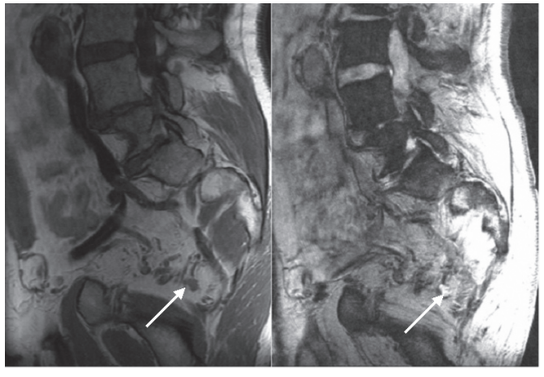

Figure 5.
Post Ferumoxtran-10 MR images
Left: T1 weighted MR image shows round 8 mm lymph node in internal iliac area (arrow).
Right: T2 weighted MR imaga shows, that this lymph node is white, and thus metastatic. This node is outside the regular PLND area. FNAB confirmed metastasis.*

Results

No serious adverse events occurred after Ferumoxtran-10 administration. Six patients (1.6%) reported low back pain during Ferumoxtran-10 infusion. The pain disappeared after the infusion was stopped. When the infusion was resumed after approximately 10 minutes, the pain did not recur. Other adverse events reported were: diarrhoea or abdominal cramps (n=9; 2.4%), itching and urticaria (n=4; 1%), and headache (n=2; 0.5%). No adverse events were reported with the CT contrast agent.

Of all 375 patients, 61 (16.3%) had histologically proven lymph node metastases. Sensitivity, specificity, NPV and PPV of MDCT and MRL respectively were 34% and 82%, 97% and 93%, 88% and 96%, 66% and 69% (see table 2). Sensitivity and NPV of MRL were significantly better compared to MDCT (McNemar p< 0.05).

TABLE 2: *Accuracy values of CT and MRL*

	CT	MRL
Sensitivity (%)	34.4	82.0
Specificity (%)	96.5	92.7
Accuracy (%)	86.4	90.9
Positive predictive value (%)	65.6	68.5
Negative predictive value (%)	**88.3**	**96.4**
Post test probability (%)	11.7	3.6

N=375, Prevalence of positive nodes: 16.3%

MDCT detected positive lymph nodes in 21 cases and MRL in 50 cases. Forty of the 50 positive patients, detected by MRL had had metastases in normal sized lymph nodes (figure 6,next page) The CT and MRL were false negative in 40 and 11 patients respectively and false positive in 11 and 23 patients respectively.

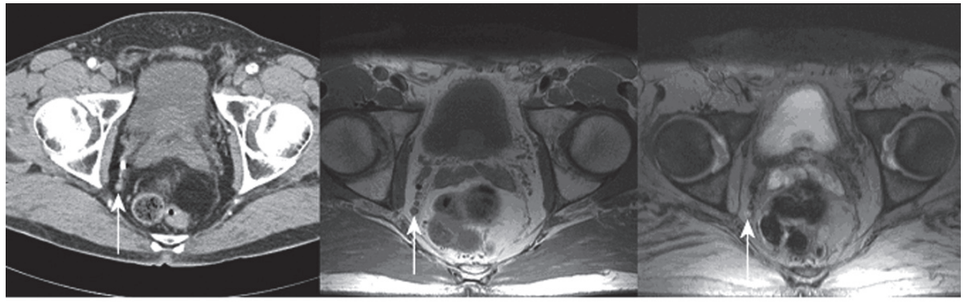

Figure 6.
Axial CT image with IV and oral contrast (left), T1 weighted post Ferumoxtran-10 MR image (middle) and T2 weighted MR post Ferumoxtran-10 image (right) in the same patient. A 6 mm lymph node is present in the internal iliac region (arrow). This node has the high signal intensity on the T2* weighted sequence and was malignant at histopathology.*

The accrual distribution was heavily skewed, as three hospitals (RU and CWZ combined as one) included 295 patients, while the other seven hospitals only included 80 patients. Because the complete cohort remains skewed toward three institutions, the results are not generalizable for all hospitals. A sub analysis of the MRL results of those two groups showed a sensitivity, specificity, NPV and PPV of 90.2%, 93.9%, 75.4% and 97.9% respectively, for the 3 major recruiting centers. The sensitivity, specificity, NPV and PPV of the remaining 7 hospitals were 40.0%, 88.6%, 33.3% and 91.2% respectively (table 3)

TABLE 3: *Results of MRL*

	RU+CWZ, ZZV,CZE	**Remaining 7 hospitals**
N	295	80
Sensitivity (%)	90.2	40.0
Specificity (%)	93.9	88.6
Positive predictive value (%)	75.4	33.3
Negative predictive value (%)	97.9	91.2
Post test probability (%)	2.1	8.8

Discussion

In our study only minor adverse events were seen, the most severe being lumbar pain during infusion. The mechanism behind this pain is still unexplained.[29,30] The same side effects are also reported with other super paramagnetic iron particle agents. Our findings confirm that the safety profile of Ferumoxtran-10 normally is good. [30-32]

This is the largest prospective multi-center study comparing the diagnostic performance of MRL with MDCT using PLND or a positive FNAB as a standard of reference. This study demonstrates that, the sensitivity of MRL is significantly higher than MDCT. Our results show MDCT is of limited use in detecting lymph node metastases in prostate cancer patients, since the sensitivity of MDCT corresponds with the results of Wolf et al.[15] This can be explained by the fact that MDCT relies on nodal size as a diagnostic criterion. [7,8,16-19] Round lymph nodes with a diameter larger than 8 mm and oval nodes with the smallest diameter larger than 10 mm are considered to be metastatic.[14,20,21] Because metastases in prostate cancer are predominantly found in lymph nodes smaller than 8-10 mm, using size and shape criteria result in a sensitivity of 36-40 %. [12] Oyen et al. achieved a sensitivity of 77.8% with only CT staging of lymph nodes, using a lower size threshold, combined with CT-biopsy. These results, however, could not be reproduced by others.[22]

The sensitivity of MRL in this study is in the range of other MRL studies conducted with iron containing nanoparticles .(82%-100%).[11-13,23-26] Harisinghani et al. reported a sensitivity of 100% for MRL on a patient-to-patient basis.[12] This is higher than the 82% found in our study. However, these authors included smaller number of patients. On a node-to-node basis they evaluated 334 lymph nodes and found a sensitivity of 91%.[12] This is still slightly higher than the results of this study. Harisinghani et al used expert readers, whereas this multi-center study was designed to evaluate how the MRL technique would perform when introduced in general practice, where it was read by radiologists who had limited or no prior experience with MRL. The three hospitals which included more than 30 patients showed results comparable to Harisinghani et al. [12]

The inclusion of the patients between the centers was skewed, indicating that in some centers the MRL technique could be implemented more easily than in other centers. The radiologists in the centers with low inclusion did not gain a lot of experience with MRL during the trial, since they included less than 20 patients. This may be an explanation

of their lower sensitivity (40.0%), and NPV (91.2%). These results are only slightly better than the results of MDCT (sensitivity 34.4%, NPV 88.3%). This emphasizes the need of trained and skilled radiologists. There are a lot of factors which influence the inclusion rate in the participating centers. It is likely that extensive multidisciplinary collaboration and adequate MRL-capacity were the critical factors for achieving high inclusion of patients and optimal results on MRL.

The high NPV and sensitivity imply that patients with a negative MRL result have an *a priori* chance of having positive lymph nodes of only 3.6% of patients. It has been generally accepted that a PLND should not be performed, if the a-priori risk of lymph node involvement is less than 5%. [3-6] This implies that in patients with a negative MRL a PLND can be omitted. In this study it would have saved a PLND in 302 (81%) of all included patients. Thus, after a negative MRL an urologist can immediately proceed to the therapy without performing PLND. When a positive lymph node is found, a MRL-guided fine needle aspiration biopsy or MR-guided limited PLND FNAB can be performed.

The main limitation of this study is that this is prone to verification and work-up bias. As described by Bossuyt et al [27], a good diagnostic test should comply with the strict criteria. One of the main criteria is that the reference test should be performed independent of test results. In our study, the local ethical committee did not approve a study design in which the urologist was blinded for the MRL results. The scheme with merged results of CT and MRL was provided before surgery. In addition there is a possibility that the PLND is more extensive in case of a positive MRL result. Some urologists even extended the PLND if a lymph node was found outside the routine dissection area. In this case positive nodes are found, which would probably be missed in a routine PLND (Heesakkers et al, in press). This resulted in an improved therapy, as more metastatic nodes were found.

All results in this study are based on a patient-to-patient evaluation. We chose this strategy for different reasons. First, it is very difficult to perform a node-to-node correlation with histopathology. This problem was also encountered by Sironi et al.[28] Second, as most urologists will not perform a prostatectomy if one positive lymph node is found, the most relevant issue is whether the patient has positive lymph nodes. Thus a patient-to-patient evaluation is the most relevant clinical issue. At the start of this study a region-to-region correlation was intended, but despite extensive effort, e.g. using an e-CRF scheme and a post-operative grid, it was not possible to reliably perform a region-to-region evaluation in all centers. Some urologists followed their department guidelines and performed only a standard PLND. Due to logistical differences between hospitals, it was only in some hospitals possible to perform a region-to-region evaluation.

In conclusion, the diagnostic accuracy of MRL is significantly higher than MDCT regarding the detection of lymph node metastases. The post test probability of having lymph node metastases is low enough (3.6%) to omit a PLND after a negative MRL. MDCT is of limited use in lymph node staging due to low sensitivity. However, training and experience of the radiologist plays an important role. Finally, the MRL technique could be easily implemented if good multi-disciplinary collaboration exists, and adequate MRI-capacity is present.

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CHAPTER 4

4 Effect of MR lymphography on the probability for lymph node involvement in patients with prostate cancer.

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Submitted to European Radiology

Abstract

Objective To estimate the effect of the results of MRL on the probability of lymph node metastases.

Methods A logistic regression analysis was performed with the results of histopathological evaluation of the lymph nodes as dependent variable and the serum level PSA, preoperative Gleason score, DRE results as independent variables. In a second model the results of MRL were added to the regression analysis.

Results A total of 315 patients were included in the analysis. In the first model PSA (P<0.001) and Gleason score (p=0.06) were independently predictive of the risk of positive lymph nodes. These risk factors were no longer significant after including the result of MRL in the model (PSA: p=0.948, Gleason: p=0.857), however, the result of MRL is significant (p<0.001). After a negative result of MRL, the probability of lymph node metastases is less than 3%, regardless of the other risk parameters.

Conclusion The result of MRL has a significant impact on the probability of lymph node involvement. After a negative MRL result the probability of lymph node metastases is <3%, thereby a PLND can be avoided when the MRL shows normal nodes. After a positive MRL result the probability for lymph node metastases is >75% and thus MRL should be followed by additional staging in the form of PLND or CT guided biopsy.

Background

Prostate cancer is one of the most common malignancies in men. When there are no metastases prostate cancer can be cured by radical prostatectomy or radiotherapy. However, the presence of lymph node metastases transforms prostate cancer from a local disease to a systemic disease that can no longer be treated with curative therapy. Currently, the standard procedure to assess risk of lymph node involvement in patients with prostate cancer is the use of models or equations based on serum prostate specific antigen (PSA) and the Gleason score. Patients with low risk for lymph node metastases usually receive curative treatment without imaging or lymph node dissection beforehand, whereas patients with higher risk are referred for additional staging. In the study

of Narayan et al.[1] a logistic regression combining preoperative PSA level and Gleason score determined that a Gleason score of 6 or less and a preoperative PSA level of 10 or less predicted adequately that there was a very low probability of lymph node involvement (2%) and that PLND can be safely avoided in these patients.[1]

A number of nodal staging methods are available for patients with a higher risk of positive lymph nodes. A pelvic lymph node dissection (PLND) is considered the most reliable method available to detect metastases in pelvic lymph nodes. However, PLND has some downsides: it is expensive, invasive and requires hospital admission.[2] Recently, magnetic resonance imaging with a lymph node specific contrast agent (MRL) is suggested as a meaningful staging method for lymph node metastases. A sensitivity of 92.9%, a specificity of 93.8% and a negative predictive value (NPV) of 98.4% in patients with PSA>10 or Gleason>6 is reported. [3,4] It is suggested that after a negative MRL, additional staging by PLND could be foregone because of the high negative predictive value and sensitivity. A PLND should only be performed to confirm a positive result of MRL by histopathology.[3,4] If this is confirmed, MRL could be a useful addition to the process of risk assessment of lymph node involvement.

The aim of this study is to estimate the effect of the results of MRL on the probability of lymph node metastases.

Methods

Patients

A total of 375 patients who were eligible for PLND between January 2002 and July 2005 were identified in a multicenter trial.

Inclusion criteria were PSA >10 ng/ml or Gleason sum >6. Exclusion criteria were a positive bone scintigraphy, previous androgen therapy, or radiotherapy of the pelvic area. Over a three year period, patients were prospectively recruited from the department of urology of nine non-university hospitals and four university hospitals in the Netherlands. The ethical review board of each hospital approved the study and written consent was obtained from all subjects. All participants were subjected to MRL and histopathological evaluation of the lymph nodes by either PLND or CT guided biopsy of an enlarged lymph node. Preoperative serum PSA level and Gleason score were collected prospectively using an electronic case report form.

All prostate biopsy specimens were evaluated using the Gleason system in which the criteria for assigning grade are clearly defined and the gradings are relatively reproducible, permitting inter-institutional comparisons of tumors.[5]

Since this is a multicenter study it is likely that there is a substantial inter-observer variation in the determination of clinical stage. Therefore, we excluded clinical stage from our analysis.

Regression

Information on PSA, Gleason, result of MRL and the result of histopathology of the lymph nodes was used in a logistic regression analysis.

Two models were constructed. In both the result of histopathology of the lymph nodes was the dependent variable and PSA and Gleason were the independent variables. In the second model the result of MRL was added as an independent variable.

Gleason score was coded 1 for grades 5 and 6 and 2 for grades 7 to 10. PSA was coded numerically. Result of MRL was coded 0 for a negative result and 1 for a positive result.

The impact of interaction terms was estimated as well. When regression analysis showed that interactive terms were not significant, they would be excluded from the model.

The analyses were performed in SPSS 12.01 for Windows.

Results

Of the 375 eligible patients, a total of 315 patients were included in the analysis; the data on 60 patients was incomplete due to missing or unreliable information on PSA (n=24) or Gleason (n=36). Positive lymph nodes were detected in 16.5% (52 out of 315). The actual incidence of positive nodes in relation to each of these predictors is displayed in table 1, 2 and 3. A total of 6 out of 256 patients with a negative MRL result had positive lymph nodes. Of the 55 patients with a positive MRL result, 46 had positive lymph nodes. In the regression analysis, interactive terms were not statistically significant and were not included in the model. PSA (P<0.001) and Gleason score (p=0.06) were independently predictive of the risk of positive lymph nodes. Figure 1 demonstrates the increasing risk of lymph node involvement for higher levels of PSA. A patient with Gleason 5-6 and PSA <5 has a probability of 3% of having lymph node metastases, while a patient with Gleason 5-6 and PSA >20 has a probability of 15% of having lymph node metastases. A higher Gleason score also results in a higher risk for lymph node metastases. A patient with Gleason 5-6 and PSA>20 has a probability of 15% for lymph node involvement, while for a patient with Gleason 7-10 this probability is 26%.

After including the result of MRL in the model, the other risk factors are no longer significant. (PSA: p=0.948, Gleason: p=0.857) The result of MRL is significant in the model (p<0.001).

In figure 2 the risk of lymph node involvement after additional staging based on the regression parameters is displayed. After a negative result of MRL, the probability of lymph node metastases is below 3% regardless of the other risk factors. The probability of lymph node metastases after a positive result is greater than 75% regardless of the other risk factors.

TABLE 1: *Patients with positive lymph nodes according to Gleason score and PSA*

Gleason	PSA (ng/ml)							
score	0-4	4.1-6	6.1-8	8.1-10	10.1-15	15.1-20	>20.1	Total (%)
5-6	0/1	0/0	0/0	0/0	3/42	3/21	6/36	12/100 (12)
7-10	2/8	1/20	4/27	4/20	1/39	3/27	24/74	39/215 (18)
Total (%)	2/9(22)	1/20(5)	4/27 (15)	4/20(20)	4/81 (4)	6/48(12)	30/110(27)	52/315 (17)

TABLE 2: *Patients with positive lymph nodes and a negative result of MRL according to Gleason score and PSA*

Gleason	PSA (ng/ml)							
score	0-4	4.1-6	6.1-8	8.1-10	10.1-15	15.1-20	>20.1	Total (%)
5-6	0/1	0/0	0/0	0/0	2/38	0/16	1/30	3/85 (4)
7-10	0/6	0/19	1/23	0/16	0/37	0/24	2/46	3/171 (2)
Total (%)	0/7 (0)	0/19 (0)	1/23 (4)	0/16 (0)	2/75 (3)	0/40 (0)	3/76 (4)	6/256 (2)

TABLE 3: *Patients with positive lymph nodes and a positive result of MRL according to Gleason and PSA*

Gleason	PSA (ng/ml)							
score	0-4	4.1-6	6.1-8	8.1-10	10.1-15	15.1-20	>20.1	Total (%)
5-6	0/0	0/0	0/0	0/0	1/2	3/3	5/6	9/11 (81)
7-10	2/2	1/1	3/4	4/4	1/2	3/3	22/28	36/44 (81)
Total (%)	2/2 (100)	1/1 (100)	3/4 (75)	4/4 (100)	2/4 (50)	6/6 (100)	27/34 (79)	45/55 (81)

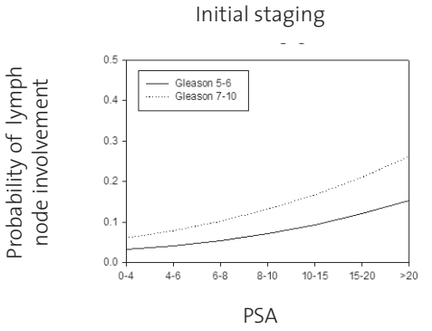

Figure 1. *Risk of lymph node involvement after initial staging*
The increasing risk of lymph node involvement with higher PSA levels for patients with Gleason 5-6 and Gleason 7-10 after initial staging. PSA level is displayed on the x-axis, while in the Y-axis the probability of lymph node is displayed. The two lines represent patients with Gleason score 5-6 and Gleason score 7-10. Results of MRL are not taken into account in this graph.

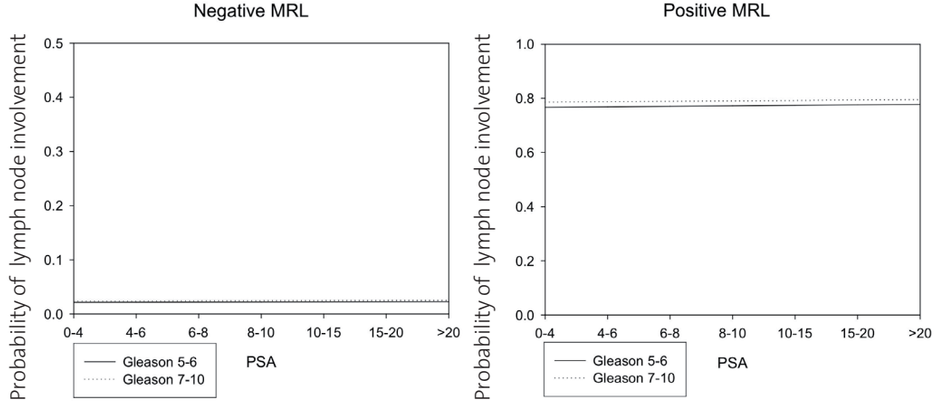

Figure 2. *Risk of lymph node involvement after additional staging by MRL*
The graphs on the left represent the risk of lymph node involvement for patients with Gleason 5-6 and Gleason 7-10 after a negative result of MRL. The graph on the right represent the risk of lymph node involvement for patients with Gleason 5-6 and Gleason 7-10 after a positive result of MRL. The risk of lymph node involvement after a negative result of MRL is below 3% regardless of the other risk factors.

Discussion

In the current study we estimated the effect of the result of MRL on the probability of lymph node involvement in patients with prostate cancer.

After a negative result of MRL the probability of lymph node involvement is below 3% regardless of the other risk factors. This is a probability acceptable for urologists to start curative therapy without additional staging in the form of PLND.[1,6] After a positive MRL additional staging is required by means of histopathological examination of the lymph node tissue.

Partin et al. described a nomogram for prediction of final pathological findings, based on Gleason score, PSA and clinical stage, that is very useful for clinical decision making.[6]

In addition, they described the predictive performance of positive lymph node involvement nomograms. The sensitivity of the nomograms decreases as the probability of lymph node involvement increases. This implicates that the risk of false negatives from the nomograms increases when there is a higher risk of lymph node involvement, indicating the need for additional staging at a risk of lymph node involvement of >3% (sensitivity of nomograms 90%). [6]

Narayan et al. reported similar results.[1] They found Gleason <5 and PSA< 10 to be strong predictors for the absence of lymph node metastases. Patients with a Gleason < 5 and PSA< 10 have a probability of 3% of lymph node metastases and the false negative rate of the combination of Gleason and PSA was 2%. However, additional staging in the form of PLND was still necessary for patients with a higher risk of lymph node metastases.[1]

In the current study we suggest MRL as an additional staging method. After a negative MRL result, Gleason score and PSA are no longer of consequence in the clinical decision making process. This results in cost savings since in 83.6% of the patients with a risk greater than 3%, according to Gleason score and PSA, had a negative MRL. Thus in these patients a staging PLND can safely be avoided. A cost analysis on MRL compared to the current strategy from the health care perspective was presented elsewhere.[7] The latter cost-analysis analysis focused on the diagnostic costs only. Results show that expected costs savings per patient may amount to € 2526 per patient. [7]

In addition, PLND is an invasive procedure that appears to have no therapeutic value. [2,8]

A positive result of MRL must be verified by histopathology. The tissue samples for histopathology can be obtained by CT guided biopsy or PLND.

Our study has some limitations. Firstly, MRL is a relatively new technique not yet commonly applied. Consequently the sample size is rather small, permitting potential underpower. Being a new technique, there is a potential learning curve. Therefore a better result is expected for MRL after some experience with the technique. This may result in minor changes to the outcomes this study, but the conclusions will not alter.

Secondly Partin et al. found that clinical stage was also a valuable predictor for the final pathological state.[6] However, clinical staging based on digital rectal examination is very likely to have interobserver differences. It has been suggested in literature that race, age, comorbidity and other methods for obtaining information on Gleason and PSA should be incorporated in the analysis.[10,11,12] Although these suggestions may improve the prediction of the pathologic stage, they make the use of simple nomograms more cumbersome because of the increased number of variables that have yet to be validated in large cohorts of patients.[6]

Since MRL is positioned as staging method for intermediate or high risk patients, our study did not include low risk patients. However, there were some intermediate or high risk patients included in the analysis with either a high PSA and low Gleason or vice versa. Therefore the probability of lymph node metastases for a low PSA level or low Gleason score is included in the regression. Additionally, within this contemporary cohort, the numbers of biopsies with Gleason scores 2 to 4 are very limited and the probabilities should be interpreted with caution.[6]

This study was intended to estimate the effect of MRL as a nodal staging method for patients with prostate cancer and a high or intermediate risk of nodal metastases. When MRL is implemented in daily practice, the advantages of MRL compared to PLND in staging lymph nodes must be emphasized to urologists involved, since the results of MRL can be very useful in making management decisions for patients with prostate cancer.

In conclusion, the result of MRL has a significant impact on the probability of lymph node involvement. After a negative MRL result PLND can be avoided safely, since the probability of lymph node metastases is <3%. After a positive MRL result the probability for lymph node metastases is >75% and should be followed by additional staging in the form of PLND or CT guided biopsy.

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CHAPTER 5

5 An explorative study on the preferences of uro logists for treatment decisions in patients with prostate cancer after MR Lymphography with lymph node specific contrast agent

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Abstract

Objective: To explore the impact of magnetic resonance lymphography (MRL) on management decisions by urologists for patients with prostate cancer and intermediate or high probability of lymph node metastases. The secondary aim was to estimate if the required paradigm-shift for urologists has taken place in which a negative MRL leads to curative therapy and a positive MRL leads to additional staging by pelvic lymph node dissection (PLND).

Material and methods: Urologists were asked to rate the appropriateness for five optional treatment-modalities in 25 hypothetical case-summaries. The treatment-modalities were: 1) watchful waiting (WW), 2) PLND, 3) prostatectomy, 4) radiotherapy, 5) hormonal therapy. The case-summaries were constructed based on six attributes: 1) patient-age; 2) prostate specific antigen level (PSA); 3) Gleason score; 4) result of digital rectal examination (DRE); 5)outcome of a bone scan; 6)outcome of MRL. Multinomial logistic regression analysis was used to estimate the relative weight of each of the attributes.

Results: In total 17 urologists participated in this study (response-rate:57%). Age and bone scan were the strongest indicators for choosing one of the treatment-options. A positive outcome of MRL significantly decreased the likelihood of WW (OR=0.18 95%CI=0.05-0.63), PLND (OR=0.17 95%CI=0.06-0.45), or prostatectomy (OR=0.10 95%CI=0.02-0.65). In patients with a negative MRL there was a trend towards more prostatectomy's and radiotherapy.

Conclusions: In case of a positive MRL urologists choose significantly less for WW, PLND and prostatectomy as treatment-option over hormone therapy. However, a negative MRL did not affect the treatment decisions. Overall, the paradigm-shift has not taken place, since the evaluation strategy of urologists did not alter based on additional information.

Introduction

Prostate cancer is one of the most common cancers in men.[1] In absence of metastases prostate cancer can be cured by prostatectomy or radiotherapy. However, even one positive lymph node transforms prostate cancer from a local to a systemic disease that can no longer be managed with curative therapy. Currently, the standard procedure to assess risk of lymph node involvement in patients with prostate cancer is the use of models or equations based on serum prostate specific antigen (PSA) and the Gleason score. [2,3,4] Patients with low risk for lymph node metastases usually receive curative treatment without imaging or lymph node dissection beforehand, whereas patients with higher risk are referred for additional staging.

A number of nodal staging methods are available for patients with intermediate or high risk of lymph nodes. A pelvic lymph node dissection (PLND) is considered the most reliable method available to detect metastases in pelvic lymph nodes.[5] However, computed tomography (CT) or magnetic resonance imaging (MRI) is also used for nodal staging. Because the sensitivity and negative predictive value of CT and MRI are rather low a lymph node dissection has to be performed after a negative outcome of a CT or MRI scan. [6,7,8]

Recently, magnetic resonance imaging with a lymph node specific contrast (MRL) is suggested as a meaningful staging method for lymph node metastases. [6] The contrast agent used with this technique consists of Ultrasmall Superparamagnetic Iron Oxide (USPIO) particles. When these particles are injected intravenously, they are transported by macrophages to normal lymph node tissue. Therefore, normal functioning lymph nodes appear black on MRI 24-36 hours after administration of USPIO. In metastatic nodes, however, the signal intensity remains unchanged due to the absence of iron particles.6 Using MRL the lymph nodes in the whole pelvic area can be examined instead of only the obturator fossa. With a posttest probability of less than 5% no additional nodal staging by means of a PLND is considered necessary. This probability was based on PSA, Gleason and clinical stage. Harisinghani et al. (2001) found no lymph node metastases at all after a negative result of MRI on patient-to-patient basis and a 2% probability of lymph node metastases on node-to-node basis.[6] Thus by using MRL in the pre-operative assessment of lymph node metastases a considerable number of PLND can be avoided. However, this requires a paradigm shift for physicians, since the focus is on detecting healthy nodal tissue and ruling out nodal metastases instead of ruling them in. Based on these results we expected urologists to choose for radical prostatectomy or radiotherapy after a negative result of MRL and forego PLND.

The aim of this study was to explore the impact of the outcome of the relatively new MRL on the management decisions made by urologists for patients with prostate cancer. The secondary aim was to estimate if the required paradigm shift for urologists has taken place in which a negative result of MRL leads to curative therapy and a positive result leads to additional staging by PLND or biopsy.

Material and Methods

Study design

In this study three stages were distinguished based on the conjoint analysis methodology.[9,10,11] First, the identification of patient characteristics that play a role in the choice of additional staging or therapy for patients with prostate cancer. For this purpose a literature search was performed. Second, these patient characteristics were used to construct virtual case summaries (Orthoplan, SPSS) that described a patients' condition after initial staging. Urologists were asked to give their preferred treatment choices for this set of case summaries. Third, treatment preferences were analysed and the patient characteristics were weighted for their relative contribution to a specific treatment alternative.

Patient characteristics

The following patient characteristics were identified: 1) patient age; 2) serum prostate specific antigen level (PSA); 3) Gleason score; 4) result of digital rectal examination (DRE); 5) result of a bone scan; 6) result of MRL. These characteristics were selected from literature and were believed to affect the urologist's decision of additional staging or therapy. The levels of the patient characteristics PSA, Gleason and DRE were obtained from the literature. [2,3,4,12] 'Result of a bone scan' had the levels 'positive' or 'negative', where 'positive' stood for a strong indication of bone metastases by whole body scintigraphy. For the patient characteristic 'result of MRL' the level 'No MRL performed' was added in order to estimate the added value of staging by MRL compared to no staging by MRL. The levels of the patient characteristics are presented in table 1.

TABLE 1:
The patient characteristics and levels included in the multinomial regression analysis

Attributes	Levels
Age	60-65, 65-70, 70-75, 75-80
Gleason	2- 6, 7-10
PSA	ffi4, 4<PSAffi10, 10<PSAffi20, PSA>20
DRE	T1-T2, T3-T4
Bone scan	Positive, Negative
MRL	Positive, Negative, No MRL performed

Selection of case summaries

A fractional factorial design was used to capture the main effects in the model using the SPSS Orthoplan procedure. Orthoplan generated 25 case summaries based on the identified patient characteristics and the levels assigned to them. An example of a case summary is presented in figure 1. For each case summary the respondents were asked to express his or her inclination to use the following management alternatives: 1) Watchful waiting; 2) PLND; 3) Radical prostatectomy; 4) Curative radiotherapy; 5) Hormonal therapy.

Patiënt 0201

• Age:	62
• PSA:	30
• DRE:	T1
• Gleason:	9
• Botscan:	-
• MR Lymphography:	+

Please choose which management option you find most appropriate, based on this patient description*

Watchfull waiting	O
Lymph node dissection	O
Radical prostatectomy	O
Radiotherapy	O
Hormonetherapy	O

*check 1 box

Figure 1. *Patient description as presented to the urologists in this study*

Respondents

The case summaries were sent by postal mail to 30 Dutch urologists from large and university hospitals. Each urologist received the 25 case summaries in a random sequence, which was the same for all participants. The urologists were asked whether they were knowledgeable about MRL and whether they had in house MRL facilities. By giving treatment preferences for the cases, urologists implicitly weighted the eligibility criteria that affect the possibility of surgical treatment.

Analysis

Multinomial logistic regression analysis was used to assess the relative weight of each of the patient characteristics in the rating of the case summaries. This is a decompositional method that estimates the structure of preferences of participants given their individual evaluations of the case summaries.[8] The responses of the urologists were used as the dependent variable and the attributes as independent variables.[9] The exponent of the regression coefficient is equal to the odds ratio for treatment choices associated with the attributes from the case summaries. Hormone therapy was used as the reference case in the model (all odds ratios zero by definition). All analyses were performed in SPSS version 12.0.

Results

A total of 17 urologists took part in this study (57% response). They were all knowledgeable about MRL. Nine of them also had in house MRL facilities. Seven of them worked at an academic hospital, while the other ten worked at non-academic hospitals. In figure 2 (next page) the distribution of treatment choices by the urologists for a certain case summary are displayed.

The odds ratios for treatment choices and patient characteristics are depicted in table 2. Watchful waiting is chosen significantly less for patients younger than 65 (OR= 0.10 95% CI = 0.03-0.328) and for patients between 65 and 70 (OR=0.12 95% CI = 0.02-0.60) than for patients over 75. For patients with PSA between 4 and 10 watchful waiting is significantly more likely than hormone therapy compared to patients with PSA over 20. (OR=3.94 95% CI=1.21-12.83). The analysis shows that urologists choose radiotherapy significantly more than hormone therapy for patients with PSA under 4 (OR=7.44 95% CI=1.46-37.77) and patients with PSA between 4 and 10 (OR=8.88 95% CI=1.65-47.68) compared to patients with PSA over 20.

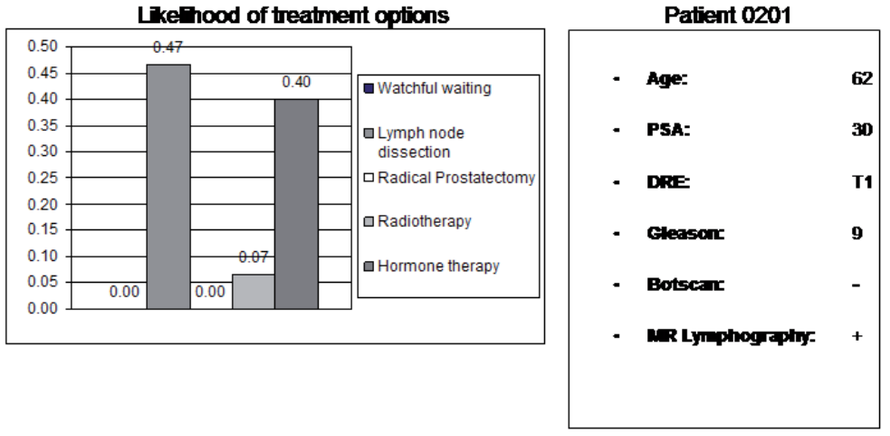

Figure 2. *Likelihood of the treatment options for this patient description.*
On the right the patient characteristics as presented to the urologists are displayed. On the left hand the likelihood of the different treatment options for this patient description are displayed. The most likely choice for this patient is lymph node dissection.

A positive result of MRL significantly decreases the likelihood of receiving watchful waiting (OR=0.18 95% CI = 0.05-0.63), PLND (OR=0.17 95% CI=0.06-0.45), or radical prostatectomy (OR= 0.10 95% CI=0.02-0.65). For patients with a negative result of MRL there is a trend towards more radical prostatectomy's (OR=1.98 95%CI= 0.42-9.30) and radiotherapy (OR=1.60 95% CI=0.34-7.59), but this is not significant.

Furthermore, analysis based on this group of urologists shows that for a patient with a negative result of a bone scan results it is significantly more likely that an urologist will chose watchful waiting (OR=2.67 95% CI =1.05-6.78), PLND (OR=17.95 95% CI=8.27-38.94) or radical prostatectomy (OR= 13.87 95% CI=3.11-61.89). In this group of urologists, a positive bone scan was a strong indicator for radiotherapy over hormone therapy (OR=67.05 95% CI= 15.39-292.07).

A Gleason score of 6 or less significantly increased the likelihood of receiving a radical prostatectomy (OR=5.46 95% CI=1.55-27.27) or radiotherapy (OR= 5.45 95% CI=1.44-20.72).

For patients with a T1 or T2 tumor the odds ratio for watchful waiting was 3.04 (95% CI=1.14-8.10) and for PLND 2.22 (95% CI=1.06-4.64) indicating that urologists chose significantly more for watchful waiting and PLND over radiotherapy. Analysis based on this group of urologists shows that they chose significantly more for watchful waiting (OR=3.04 95% CI=1.14-8.10) or PLND (OR=2.22 95% CI=1.06-4.64).

TABLE 2: *Odds ratios for treatment choices associated with patient characteristics used in the case summaries*

Patient characteristics		Odds ratio's (95% CI)			
		Watchful waiting	Pelvic lymph node dissection	Radical prostatectomy	Radiotherapy
Age	<65	0.10 (0.03-0.33)±	1.17 (0.39-3.50)	1.65 (0.32-8.47)	0.75 (0.20-2.78)
	65<age<70	0.12 (0.02-0.60) ±	1.46 (0.43-4.93)	0.63 (0.07-5.76)	1.62 (0.29-9.12)
	70<age<75	0.48 (0.16-1.46)	1.30 (0.39-4.41)	0.62 (0.06-6.04)	0.38 (0.05-2.80)
	>75*	-	-	-	-
PSA	<4	2.06 (0.45-9.40)	1.87 (0.76-4.58)	3.96 (0.90-17.39)	7.44(1.46-37.77) ±
	4<PSA<10	3.94 (1.21-12.83) ±	2.38 (0.94-6.03)	1.18 (0.17-8.07)	8.88(1.65-47.68) ±
	10<PSA<20	2.28 (0.60-8.58)	2.20 (0.80-6.04)	0.22 (0.03-1.47)	2.80(0.50-15.70)
	>20*	-	-	-	-
MRL	Negative	0.44 (0.12-1.61)	0.48 (0.17-1.312)	1.98 (0.42-9.30)	1.60 (0.34-7.59)
	Positive	0.18 (0.05-0.63) ±	0.17 (0.06-0.47) ±	0.10 (0.02-0.65) ±	0.38 (0.08-1.85)
	No outcome of MRL *	-	-	-	-
Bone scan	Negative	2.67 (1.05-6.78) ±	17.95 (8.27-38.94) ±	13.87 (3.11-61.89) ±	67.05 (15.39-292.07) ±
	Positive*	-	-	-	-
Gleason	2-6	1.70 (0.64-4.52)	0.82 (0.40-1.69)	5.46 (1.55-27.27) ±	5.45(1.44-20.72) ±
	7-10*	-	-	-	-
DRE	T1, T2	3.04 (1.14-8.10) ±	2.22 (1.06-4.64) ±	1.49 (2.46-37.46)	1.49 (0.50-4.43)
	T3, T4*	-	-	-	-

In the analysis shown, hormone therapy is designated as reference case. As a consequence all regression coefficients and OR's for chemotherapy are zero by definition and chemotherapy as treatment option is not displayed. Taking the exponent of the regression coefficients produces the odds ratios or probabilities. These odds ratios show how many times a certain level of a domain affects the treatment decision relative to the other levels of the same domain. For example, watchful waiting shows an OR of 0.10 for patients under 65 years of age, indicating that a patient under 65 years 10 times less likely to be treated with watchful waiting compared to hormone therapy.

* Last level of each attribute is the reference level with a regression coefficient of zero by definition

\- Last level of each attribute is the reference level

± Statistically significant

Discussion

Results show that patients with a negative result of MRL are more likely to receive radical prostatectomy or radiotherapy, however not significantly, while a patient with a positive result of MRL is significantly more likely to undergo hormone therapy. Further, the results indicate that age of the patient and outcome of the bone scan seem to be the most influential attributes on all of the possible choices of treatment.

Wolf et al. (1995) described a sensitivity of 36% and a specificity of 97% for CT and MRI without a lymph node specific contrast agent in finding lymph node metastases in prostate cancer and showed that imaging is only beneficial in patients with a probability for lymph node metastases of 45% under the condition that a positive result of imaging is followed by histopathology.[7] However, imaging can be beneficial when in case of a negative result of verification by histopathology may be foregone. This can be achieved using imaging techniques with a high negative predictive value and sensitivity. With a posttest probability of less than 5% no additional nodal staging by means of a PLND is necessary. Based on the first results we expected urologists to choose for radical prostatectomy or radiotherapy after a negative result of MRL and forego PLND.[6] However, our data show a trend towards more radical prostatectomy and radiotherapy after a negative result of MRL, but these treatment options are not chosen significantly more than hormone therapy compared to no result of MRL. In addition, there is no significant decrease in PLND after a negative result of MRL. A positive result of MRL significantly decreases the likelihood of watchful waiting and radical prostatectomy as expected. However, the likelihood of a PLND after a positive MRL is also significantly decreased. This is surprising since the positive predictive value of MRL is 94.2% and additional staging by histopathology is still considered necessary.[6]

This study has a number of limitations. First, the number of urologists involved is low (n=17, response: 57%). Second, case descriptions can never fully reflect the complexity of real cases, as they lack visual clues and doctor-patient interaction. Third, complaints and co-morbidity of patients were not included in the patient descriptions. However, for diagnostic and treatment decisions a high correlation has been found between decisions made for real patients and case summaries. [13, 14]

MRL is a fairly new staging technique. The other attributes in the model are established indicators for the stage of a patient with prostate cancer. (PSA, Gleason, outcome of a bone scan, DRE, age). Currently, a prospective multicenter trial is in progress to study the accuracy and cost-effectiveness of MRL compared to current staging strategies. The real impact of MRL on management decisions can be assessed after implementation. This study was intended to explore the impact of MRL as a nodal staging method for patients with prostate cancer on the treatment decisions by urologists. When MRL will be implemented in daily practice, the advantages of MRL compared to other imaging (e.g. CT) in staging lymph nodes must be underlined strongly towards urologists involved, since the results of MRL can be very useful in making management decisions for patients with prostate cancer.

In conclusion, this explorative study shows that after a positive result of MRL urologists choose significantly more for hormone therapy than for the other treatment options. A negative result of MRL does not have a decisive impact on the management decisions of urologists. Overall, the paradigm shift has not taken place, since the evaluation strategy of urologists did not alter based on additional diagnostic information.

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CHAPTER 6

6 Cost-analysis of staging methods for lymph nodes in patients with prostate cancer: MRI with a lymph node specific contrast agent compared to pelvic lymph node dissection or CT.

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Abstract:

Objective: The aim of this study was to compare the costs of three strategies in patients with prostate cancer in a specific setting. Firstly a strategy including MRL in which PLND is foregone in case of negative result. The second strategy involves CT followed by a biopsy or PLND. The third strategy consists of PLND without imaging beforehand.
Materials and Methods: A decision analytic model was constructed. This model represented the diagnostic process for patients with prostate cancer and intermediate or high risk for nodal metastases comparing the three strategies on costs. Cost-analysis is done from the health care perspective.
Results: The model indicated that the expected costs for the MRL strategy were €2527. The expected costs for the strategy using CT were €3837 and for PLND €3994. These results show that potential savings performing MRL instead of CT were €1310 and €1467 for PLND.
Sensitivity-analyses show that variation in costs of PLND was most influential on the costs of all strategies. However, the overall savings pattern did not alter.
Conclusion: Average costs of MRL staging in our institution are less than for CT and PLND in staging lymph nodes of patients with prostate cancer and intermediate or high risk for nodal metastases.

Introduction:

Clinically localized prostate cancer can be treated by radical prostatectomy or radiation therapy as these patients have a low risk for recurrence and a normal life expectancy.[1] However, once the tumor has spread into the pelvic lymph nodes, curative therapy is not possible.[2] The standard procedure nowadays to assess lymph node involvement in patients with prostate cancer is the use of models/equations based on pathologic data (T stage, bioptic Gleason PS, iPSA): e.g. Partin's table. Patients with low risk for lymph node metastases usually receive curative treatment without imaging of lymph node dissection beforehand.

A number of nodal staging methods are available for patients with intermediate or high risk of lymph node metastases who are considered candidate for curative therapy. Computed Tomography (CT) is often used for staging pelvic lymph nodes. After a positive result of CT it might be possible to perform an image-guided biopsy to evaluate the lymph nodes. Because the sensitivity and negative predictive value of CT are rather low a lymph node dissection has to be performed after a negative result of a CT scan. [6]

In addition pelvic lymph node dissection (PLND) is often used without imaging beforehand. Although PLND is considered the standard of reference, only the lymph nodes in the obturator region are removed and therefore, metastatic lymph nodes outside this region will be missed (11%). [5]

Recently high resolution MRI using a lymph node specific contrast agent has been suggested as a nodal staging method in prostate cancer.[5,6] This technique is called MR-lymphography (MRL). The contrast agent used with this technique consists of Ultrasmall Superparamagnetic Iron Oxide (USPIO) particles. When these particles are injected intravenously, they are transported by macrophages to normal lymph node tissue. Therefore, normal functioning lymph nodes appear black on MRI 24-36 hours after administration of USPIO. In metastatic nodes, however, the signal intensity remains unchanged due to the absence of iron particles.[5,6] Using MRL the lymph nodes in the whole pelvic area can be examined instead of only the obturator fossa. Recently, Harisinghani & Barentsz. (2003) published a study that presented a negative predictive value and a sensitivity of 100% for MRL on a patient-to-patient basis.[5] Because urologists in general accept that if the a priori chance of having lymph node metastases is lower than 5 or even 10 percent PLND may be avoided in case of a negative MRL.

Lymph node dissection is relatively expensive and requires hospitalization. When PLND could be foregone after a negative MRL the costs of PLND might be saved for the hospital.

The purpose of this study was to compare the costs of the MR lymphography to the costs of PLND and CT in patients with prostate cancer who are considered candidate for curative treatment.

Methods

A decision analytic model was built to describe the diagnostic process of the three alternative staging methods using the software program DATA. (See fig 1) The three staging methods were MRL, CT and PLND. This decision analytic model is not a complete representation of reality, but rather a simplified and highly stylized model of the most important components. To determine the appropriate level of complexity of the model, we considered whether the models captures the issues necessary to fully describe the procedures in our institution by using a consensus panel of 4 radiologists and urologists from our institution. The outcome measure of the model is the expected costs of the diagnostic strategies.

The probabilities attached to the branches of the model were derived from the data reported by Harisinghani & Barentsz[5] and Wolf et al.[7]

The analysis was performed from a health care perspective. This means that the research focused mainly on the activities associated with the medical production processes. Differences in costs between the three alternative staging methods were hypothesized to be found most in the direct consumption of health care. Therefore the study focused on the diagnostic traject only. The input of resources in the diagnostic production process was assessed by collecting volumes of consumed resources and multiplying these by a guideline price of each resource unit (Oostenbrink et al, 2000).[8] If a guideline price was not available self-determined prices were calculated based on the full costing method. Information on prices was obtained from the financial administration of the departments of Radiology and Urology. All prices were indexed to 2001 prices using price index digits for consumption of the Central Bureau of Statistics. Information on volumes of care was obtained from patient records and from expert opinion. Expert opinion was obtained using a consensus panel of 4 radiologists and urologists from our institution.

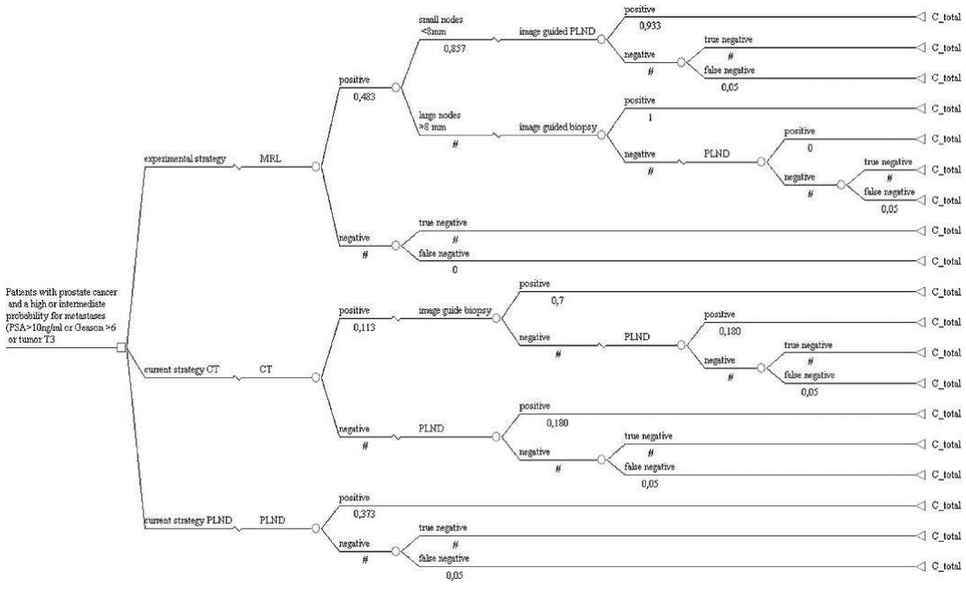

Figure 1. *The decision analytic model.*
The first node represents the decision between the current and experimental strategy (displayed as a square). This node has three branches; the experimental staging method with MRL and the current staging methods CT and PLND. After the decision node, a series of chance nodes (displayed as circles) follow along each arm that represent the probabilities of a positive or negative result on a certain test. Costs are assigned to the endnodes. (displayed as triangles)

Costs were categorized in personnel, material, capacity and overhead. Costs of personnel were calculated using standard time estimates per procedure and multiplying these with a mean wage cost per category of personnel. Capacity costs were calculated using linear depreciation on the historical cost prices. Maintenance costs were taken into account (6% on top of cpacity costs). Overhead costs were assumed an additional 35% on top of the total direct costs as suggested by the guidelines for economic evaluation as described by Oostenbrink et al, 2000. 8 The expected costs of each staging method were calculated by multiplying the health care consumption in each branch by the probabilities attached to that branch. To investigate uncertainty concerning variables in our model one-way sensitivity analyses were performed. Input for sensitivity analysis about the probabilities was obtained from literature. [5,6,7,11,13-16] Duration of hospitalization and of procedures were varied between the minimum and maximum value of the range found in the financial administration and the patient records.

Results:

Table 1 presents the total costs of the staging methods. The costs of the MRL procedure amount to €852,. The major part of these costs consisted of the costs for the contrast agent, which is €413 for each patient. The costs of a CT procedure were €124. An image guided biopsy costs €311 and the costs of a PLND procedure amounted to €3994.

TABLE 1: *The costs of the staging methods divided into costs of personnel, material, capacity, and overhead.*

	MRL (€)	CT (€)	CT guided biopsy (€)	PLND (€)
Personnel	117,07	35,05	99,88	673,48
Material	456,10	30,27	87,61	73,40
Capacity	58,09	26,31	42,61	2211,36
Overhead	220,94	32,07	80,84	1035,38
Total	852,20	123,70	310,64	3993,62

Solving the decision tree showed that the expected costs for the MRL strategy were €2527. The total expected costs for the CT strategy were €3837 and for the PLND strategy €3994. (Fig 1 and Table 2). These results show that the potential savings when the MRL strategy is performed instead of the CT strategy were €1310 and for the PLND strategy €1467 compared to MRL.

TABLE 2: *The expected total costs per patient of each staging method.*

Staging Method	Expected total costs per patient (€)
MRL	2526,74
CT	3836,53
PLND	3993,62

Tables 3, 4 and 5 show the results of the sensitivity analyses for the three staging methods. The range in the costs of the PLND procedure and the probability of a positive MRL had most impact on the expected costs of MRL. For the CT strategy the costs of the PLND procedure and the probability of a positive biopt after a positive CT were the most influential factors. For the PLND strategy the costs of the PLND procedure were the only influential factor for the expected costs of the current strategy PLND. The prioritization of the staging methods was not altered by variation in these variables.

TABLE 3: *Sensitivity analysis for MRL.*

Variable	Base case value	Range used for sensitivity analysis		References	Cost of strategy according to one way sensitivity analysis (€)		Rank
		Low	High		Low	High	
Probabilities							
Probability of a positive MRL	0,483	0,280	0,483	5,6	1822,95	2526,74	2
Probability of small nodes	0,857	0,600	0,900	EO	2069,57	2603,23	3
Probability of a positive biopt after a positive MRL	1	0,240	1	14, 16	2492,41	2559,94	5
Costs:							
Costs of MRL	852,20	656,31	1048,10	FA	2330,85	2722,64	4
Costs of PLND	3993,62	1807,77	7260,05	FA	1621,95	3878,82	1
Costs of image guided biopsy	310,64	298,84	322,43	FA	2525,92	2527,55	6

EO: expert opinion
FA: financial administration
Rank: rank of each variable's influence on cost-effectiveness estimates across the range used for the sensitivity analysis.

TABLE 4: *Sensitivity analysis for CT.*

Variable	Base case value	Range used for sensitivity analysis		References	Cost of strategy according to one way sensitivity analysis		Rank
		Low	High		Low	High	
Probabilities							
Probability of a positive CT	0,113	0,113	0,160	11, 13,14	3719,74	3806,71	3
Probability of a positive biopt after a positive CT	0,700	0,240	0,814	7, 14, 15	3785,08	4044,12	2
Costs							
Costs of CT	123,70	111,90	135,50	FA	3824,73	3848,33	4
Costs of PLND	3993,62	1807,77	7260,05	FA	1823,58	6844,587	1
Costs of image guided biopsy	310,64	298,84	322,43	FA	3835,19	3837,86	5

EO: expert opinion
FA: financial administration
Rank: rank of each variable's influence on cost-effectiveness estimates across the range used for the sensitivity analysis.

TABLE 5: *Sensitivity analysis for PLND.*

Variable		Range used for sensitivity analysis		References	Cost of strategy according to one way sensitivity analysis		Rank
		Low	High		Low	High	
Costs of PLND	3993,62	1807,77	7260,05	FA	1807,77	7260,05	1

FA: Financial administration
Rank: rank of each variable's influence on cost-effectiveness estimates across the range used for the sensitivity analysis.

Discussion

Our results show that MRL was the least expensive staging method. The savings when implementing MRL and consequently substituting the CT and PLND strategies can amount up to €1467. However, it should be noted that these are anticipated savings and not real savings. Some factors influence the total costs of the staging methods. The costs of the PLND procedure were the most influential factor on total costs for all three strategies, but variation of this parameter did not alter prioritization.

The incidence of prostate cancer in the year 2000 in the Netherlands was 6892, and is increasing every year. As data about the distribution of patients with low risk versus intermediate/high-risk for lymph node metastases are not known for the Netherlands, these figures were estimated based on the literature. In 2000 a total of 2756 patients underwent curative prostatectomy or radiotherapy. These patients are derived from the low risk group for nodal metastases, which is 44% according to Crawford, (CR), and from the negative nodal dissections of the intermediate/ high risk group, which is 62.7% according to Wolf. [9]

The total number of patients in the intermediate or high risk group is 1905. When implementing MRL a total of €2.796.008 per year might be saved compared to the current strategies.

Urologists in general accept that if the a priori chance of having lymph node metastases is lower than 5 or even 10 percent PLND may be avoided. When MRL is implemented in the future it is expected that the high negative predictive value found by Harisinghani and Barentsz et al. might be slightly lower, but we estimate that the number of false positives in MRL and PLND is almost equal. (2-5%) [3]

Another positive effect of MRL, which was not taken into account, is the fact that MRL may be of help in finding positive lymph nodes during the lymph node dissection, which increases the number of true positive nodes and decreases operating time.

This study was done from a health care perspective. Considering another perspective, for example the societal, could have altered the outcome. It might be that the private costs of a patient that underwent an invasive procedure could be higher than the costs of a patient that underwent a less or non-invasive procedure like MRL. In addition, when positive, MRL might be used as an indication for the use of image guided biopsy. When suspicious nodes can be proved metastatic by a biopsy, a PLND can also be avoided, which might result in again decreased diagnostic costs.

The cost analysis was performed in our institution. Therefore it should be remarked that procedures and prices in other settings may differ from ours. This might alter the absolute results but unlikely the conclusion that MRL saves money.

Furthermore, the cost-analysis neglected complications from PLND. As the analysis only considered the diagnostic traject, the costs of radical prostatectomy or other options of treatment were not included.

This modelling study was did not include the effect and cost of the number of patients who are treated with alse negative results. Ie., the study was performed using a conservative approach towards costs and effects of MRL.

We now started a prospective multi-center trial, which is focussed on the cost and effects of the different strategies.

In conclusion this study provides a valuable first indication on the economic attractiveness of MRL.

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CHAPTER 7

7 Cost-effectiveness analysis of MRI with a lymph node specific contrast agent for the detection of lymph node metastases in patients with prostate cancer and intermediate or high risk of lymph node metastases.

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Abstract

Purpose: To apply a decision analytic model to determine whether the addition of Magnetic Resonance Lymphangiography (MRL) to the diagnostic workup of patients with intermediate or high probability of lymph node metastases is cost effective from a health care perspective.

The data that were used for the decision analytic model are obtained from an empirical study population of 375 patients.

Materials and Methods: As the input of the decision analytic model was based on prospective patient data from several hospitals, the ethical review board of each hospital approved the study. Written consent was obtained from all patients. To investigate possible differences between strategies that utilize MRL ("MRL strategy") and those that do not (pelvic lymph node dissection "PLND strategy") two outcome-measures were examined and combined in an incremental cost effectiveness ratio (ICER): 'health care resources consumed' ($) and quality adjusted life year (QALY's). Probabilistic sensitivity analysis was performed.

Results: PLND strategy is dominated by the MRL strategy. Probabilistic sensitivity analysis showed that MRL was the dominant strategy in 63% (cost saving and better patient outcome) of the simulations. The probability of MRL being inferior (more expensive and worse patient outcome) is less than 3%

Conclusion: MRL is an efficient strategy in the detection of lymph node metastases of prostate cancer when compared to the PLND strategy.

Introduction

In patients with prostate cancer, pelvic lymph node metastases have a significant impact on the prognosis, as metastasis in a single node can rule out curative treatment. Cross-sectional imaging does not have the desired sensitivity or specificity in identifying metastases.[1,2] Nonetheless, CT is often obtained in patients prior to pelvic lymph node dissection (PLND) or CT guided biopsy in order to stage the pelvic lymph nodes. PLND is currently the only reliable method of assessing lymph node status. It is a highly invasive procedure, with possible complications and it appears to have no therapeutic value. [1] Laparoscopic PLND, although less invasive, nevertheless involves time, hospitalization and equipment related expenditure. [1]

Recently high resolution MRI using a lymph node specific contrast agent (Sinerem®, Guerbet, Paris) has been suggested as a nodal staging method in prostate cancer. Approval is expected end of 2007 for Sinerem. This technique is called MR-lymphography (MRL). The results of a prospective multi-center study comparing MRL to PLND show a negative predictive value of 97% on a patient-to-patient basis, which are in agreement with published data. [2]

Patients with PSA below 10ng/mL and Gleason Score below 6 have a three percent a priori probability of lymph node metastases.[1] Urologists in general choose curative treatment without additional nodal staging when a patient has an estimated prior probability of lymph node metastases of less than five percent.[1]

The decision regarding which staging method is to be preferred in a particular clinical setting should not be based on diagnostic accuracy alone. Costs related to the performance of the tests and costs related to the consequences of the tests also have to be taken into consideration.[3] In addition, it is important to look at other outcomes that are a direct or indirect result of more adequate diagnostics, such as quality adjusted life years (QALY's) gained.

The objective of this study is to apply a decision analytic model to determine whether the addition of Magnetic Resonance Lymphangiography (MRL) to the diagnostic workup of patients with intermediate or high probability of lymph node metastases is cost effective from a health care perspective.

Methods

This work was supported by a financial grant from the Netherlands Organisation for Health Research and Development (ZonMW). The authors had control of the data and the information submitted for publication.

Decision analytic model

The decision analytic model, shown in figure 1, was based mainly on published clinical guidelines used in the department of Urology in the Radboud University Nijmegen Medical Center, and on expert opinion.[4]

Two strategies are displayed in the model. First, the experimental strategy where MRL is followed by PLND or CT guided biopsy in case of a positive result (lymph nodes suspected of metastases). The choice between PLND and CT guided biopsy is based on the size and anatomical position of the suspicious lymph nodes. In case of a negative MRL-result, the patient undergoes curative treatment using either radical prostatectomy or radiotherapy combined with hormone therapy depending on the age and vitality of the patient.[5] In some cases prostatectomy is followed by adjuvant radiotherapy. This usually occurs when the surgical margins of a T3 tumor are positive. [5] When lymph node metastases are confirmed by histopathology, hormone therapy is initiated. The second strategy is the current standard of care wherein abdominal-pelvic CT is followed by histopathological evaluation by either a CT guided biopsy or PLND. Regardless of whether the MRL or the PLND strategy is pursued, the treatment choices that follow the diagnostic phase are the same.

Markov chain analyses were added to the decision tree to evaluate the life expectancy of patients in the model. The Markov chain analyses were added to the endnodes of the decision analytic model resulting in five different situations for which Markov chain analyses were done (table 1). For each Markov chain the structure was the same, but the utilities and transition probabilities depended on the specific combination of true lymph node status and treatment. In each 1-year cycle patients were at risk of dying from natural causes and from prostate cancer. Therefore after the Markov node two states were defined; "cancer" and "death" (figure 2). We assigned utilities to the health state "cancer" and calculated quality adjusted life expectancy by multiplying the time spent by patients in this health states with the corresponding utilities. The diagnostic costs and the cost of primary treatment were defined in the decision tree and no difference is expected in later costs between the strategies. In addition, costs over a longer period were not available. Therefore no costs were assigned to the health states in the Markov chains.

To determine the appropriate level of complexity of the model, we considered whether the model captures the issues necessary to fully describe the procedures in our institution by using a consensus panel of four radiologists and urologists from our institution.

Probabilities used in the decision analytic model

The data that were used for the decision analytic model were derived from an empirical study population of 375 consecutive patients from 13 hospitals in the Netherlands. In this multi-center study, patients with prostate cancer and PSA>10, Gleason >6 or tumor stage T3 were submitted to a diagnostic work-up for detecting pelvic lymph node metastases. Over a three-year period, patients were prospectively recruited from the Department of Urology of nine non-academic hospitals and four academic hospitals. The ethical review board of each hospital approved the study and written consent was obtained from all subjects. All participants were subjected to CT and MRL and histopathological evaluation of the lymph nodes by either PLND or CT guided biopsy. (Figure 1)

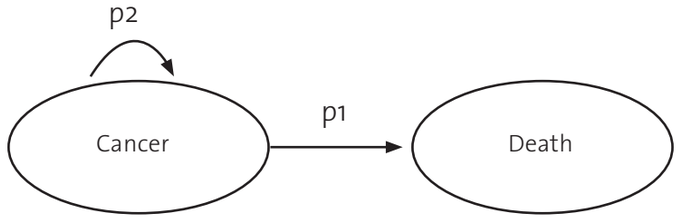

Figure 2. *Influence diagrams of the Markov part of the model*
P1: probability of dying from prostate cancer, based on data from literature and natural mortality rates based on age related survival tables supplied by the Central Bureau of Statistics in the Netherlands. P2= 1-p1

Patients with a diagnosis of lymph node metastases were treated with hormone treatment. Hormone treatment was administered at pharmacological doses in all patients. All patients treated with hormone therapy in this study received adjuvant hormone therapy in the form of medication.

Patients with no lymph node metastases were treated with radiotherapy or radical prostatectomy.[5] Data that the multi-center study could not provide were subtracted from literature. In table 2 the probabilities used in the model are presented.

Figure 1: *The decision analytic model.*
The first node represents the decision between the PLND strategy and the MRL strategy (displayed as a square). After the decision node a series of chance nodes (displayed as circles) follows along each arm that represents the probabilities of a certain event. (For instance a positive or negative result of a certain test) Costs and effects are assigned to the end nodes (displayed as triangles).

TABLE 1:
Results of the multicenter study on diagnostic accuracy of CT and MR lymphography

	Sensitivity	Specificity	NPV	PPV
CT	34.4%	96.5%	88.3%	65.5%
MRI	82.0%	92.7%	96.4%	68.5%

Data presented in this table are based on the complete dataset of 375 patients.[3]

Cost calculation

The cost-analysis was based on a health care perspective. This means that the research focused on the activities associated with the medical production processes. Since the patients of interest in this study are mostly over 65 years of age, analysis from the societal perspective will not have an added value.

The input of resources in the diagnostic and therapeutic process was assessed by collecting volumes of consumed resources during the prospective multi-center study and multiplying these by a Dutch guideline price of each resource unit (Oostenbrink et al, 2000) [6]. If a guideline price was not available prices were calculated based on the full costing method.[6]

TABLE 2: *Input for the decision analytic model*

Variable	**Value**	**Distribution**	**Parameters**
Probabilities			
Probability of a positive MRL	0.19	Beta	N=351 R=65
Probability of large nodes	0.20	Beta	N=65 R=13
Probability of a positive CT guided biopsy	1	Beta	N=13 R=13
Probability of a positive PLND after a negative biopsy		Beta	N= R=
Probability of a positive PLND after a positive MRL	0.66	Beta	N=65 R=43
Probability of a true negative MRL	0.91	Beta	N=286 R=261
Probability of radical prostatectomy after a negative PLND	0.48	Beta	N=282 R=135
Probability of adjuvant radiotherapy after prostatectomy	0.13	Beta	N=135 R=17
Probability of a positive CT guided biopsy after a positive CT	0.35	Beta	N=28 R=10
Probability of a positive PLND after a negative CT	0.10	Beta	N=322 R=32
Probability of a false negative PLND	0.06	Beta	N=286 R=18
Transition probabilities			
Hormonetherapy	0,041	Beta	a=15.944.253 ß=375.133.818
Radiotherapy	0,005	Beta	a=201.58944. ß=595.911
Radical prostatectomy	0,005	Beta	a=248.75049. ß=501.250
Radiotherapy (lymph node metastases)	0,041	Beta	a=16.430.021 ß=380.430.379
Radical prostatectomy (lymph node metastases)	0,037	Beta	a=13.323.612 ß=344.837.988
Costs (€)			
Costs of MRL	829	Gamma	a=300.501/ß= 0.26
Costs of CT	220	Gamma	a=367.95 1/ß=1.48
Costs of CT guided biopsy	323	Gamma	a=25.91 1/ß=0.11
Costs of PLND	4011	Gamma	a =354.231/ß=0.108
Costs of radical prostatectomy	8590	Gamma	a = 319.66 1/ß=0.05
Costs of radiotherapy	697	Gamma	a= 251.98 1/ß=0.37
Costs of hormone therapy	3027	Gamma	a=121.16 1/ß=0.04
Utilities			
Prostatectomy, no lymph node metastases 10 (U_{rp})	0.85	Beta	a=2.10 ß=0.38
Radiotherapy, no lymph node metastases 10 (U_{rt})	0.83	Beta	a= 2.27 ß=0.47
Prostatectomy, lymph node metastases 10	0.92*U_{rp}	-	-
Radiotherapy, lymph node metastases 10	0.85*U_{rt}	-	-
Hormone therapy 10	0,83	-	a=1.41 ß=0.28

To construct the beta distribution for the probabilities the parameters N and R are necessary, where N is the population and R is the number of cases. To construct a gamma distribution, the parameters a and ß are necessary, where a = (mean costs)²/ (standard error)² and 1/ß = 1/(standard error²/ mean costs). To construct a beta distribution for the utilities and the transition probabilities the parameters a and ß are necessary, were a = (mean utility²)*(1-mean utility) / (standard error²) and ß = mean utility*(1-mean utility) / (standard error²) - a

Total costs of the diagnostic and therapeutic processes were based on the inputs: personnel, material, capacity and overhead. Costs of personnel were calculated using standard time estimates per procedure and multiplying these with the appropriate guideline price[6]. Capacity costs were calculated using linear depreciation on the historical investment price. Maintenance costs were taken into account (6% on top of capacity costs). Overhead costs were assumed an additional 35% on top of the total direct costs as suggested by the guidelines for economic evaluation. [6]
Costs were converted from euros to US dollars using a conversion rate of 1.295 (February 7th 2007).

Outcome measure
Effectiveness was measured in terms of life expectancy and quality adjusted life years (QALY's). QALY's are the product of life expectancy and the utility associated with a certain health state. Utilities refer to cardinal preferences that individuals or society have for a particular health state, as measured on a scale between 0 (death) and 1 (perfect health).[7] Survival (life expectancy) and utility values, necessary input for the Markov chain model, were obtained from the literature.[8] Age-related survival tables supplied by the Central Bureau of Statistics in the Netherlands (Statline) were used for average mortality rates not related to a specific disease. [9]
The parameters of the distributions for utilities are displayed in table 3. The utility value of prostatectomy with metastases was calculated by multiplying the utility value of prostatectomy without metastases by 0.92. This is the ratio of the utility value for patients who underwent prostatectomy and the utility value for patients who had metastases.[8] The utility values of radiotherapy with metastases was calculated in the same way. The utilities used in these ratios were expert opinion based point estimates obtained from literature.
The base case analysis evaluated 65 year old men with prostate cancer and intermediate or high probability of lymph node metastases and assumed no co-morbidities. For the Markov model the cancer mortality rate was assumed to be zero after 15 years.

Baseline analysis
Baseline values of the probabilities and costs were determined and incorporated into the decision model using the software program DATA version Pro 2005. (Tree Age software, Williamstown, MA)

Analyzing the decision model, the expected costs per patient and the expected effect per patient were compared between the strategies. Cost-effectiveness ratio's and an incremental cost-effectiveness ratio (ICER) were calculated. The ICER is calculated using all incremental costs (diagnostic and therapeutic) and incremental QALY's.

Sensitivity analysis
To investigate sampling uncertainty concerning variables in our model, probabilistic sensitivity analysis was performed. In a probabilistic sensitivity analysis, sampling uncertainty in most input parameters of the model are considered simultaneously. Distributions are defined for almost all variables in the model. We adopted gamma distributions for the costs. These distributions were derived from the resource use of the patients in the multi-center study. For the probabilities in the model we used beta distributions derived from the results of staging and treatment for the patients in the multi-center study. For utilities a real-numbered Beta distribution was used. The distribution was calculated for each health state in the model, using the mean and the standard deviation. The assumption was made that the utilities for the health states were not fully independent. It was assumed that the health state of prostatectomy with nodal metastases had a lower utility than the health state of prostatectomy without metastases. The same assumption was made for radiotherapy with or without metastases. In addition it was assumed that undergoing hormone therapy had a lower utility than undergoing radical prostatectomy or radiotherapy without nodal metastases. The characteristics of the distributions used are displayed in table 2. The analyses were performed using a first order Monte Carlo simulation to represent sampling uncertainty and superimposed on this was a second order Monte Carlo simulation with 1000 repetitions to represent parameter uncertainty.10 From these simulations a cost-effectiveness acceptability curve was derived.[11] In a Bayesian sense this curve gives an estimate of the proportion of the sampling distribution favoring one strategy over the other given a willingness-to-pay (WTP) for a QALY gained. [12, 13, 14]
This proportion can be identified, by observing the proportion of simulations lying to the south and east of a line, with slope WTP, through the origin of the incremental cost-effectiveness plane. This way it is assumed that the willingness to pay for a unit of a certain effect gained is identical to the willingness to accept (WTA) compensation for loss of a unit of that effect. [14, 15] However, O'Brien et al (2002) show in a meta-analysis that WTA is greater than WTP based on individual preferences.[16] With that in mind we constructed two scenario's of cost-effectiveness acceptability curves from our simula-

tions. The first curve is based on the assumption that WTA=WTP and the second curve is based on the assumption that WTA=infinite. (No loss in effectiveness is accepted)

TABLE 3: *Pathway probabilities in the decision analytic model, life years gained and QALY's for these endpoints as calculated from the decision analytic model.*

Treatment	Lymph node status	Probability in MRL strategy	Probability in PLND strategy	Life years gained	QALY's
Hormonetherapy	Positive	0.136 (0.064-0.243)	0.135 (0.07-0.219)	7.85	6.55
Radiotherapy	Positive	0.015 (0.002-0.055)	0.026 (0.005-0.061)	7.80	6.53
Radical prostatectomy	Positive	0.016 (0.001-0.049)	0.028 (0.005-0.07)	7.66	6.11
Radiotherapy	Negative	0.401 (0.303-0.542)	0.391 (0.288-0.506)	11.50	10.80
Radical prostatectomy	Negative	0.429 (0.307-0.556)	0.419 (0.303-0.542)	10.92	9.96

The QALY's generated per treatment are assumed to be identical for both strategies.

Results

Table 3 presents the probability of getting a certain treatment for each strategy as calculated by the model. The probability of having a prostatectomy or radiotherapy while lymph node metastases are present are slightly higher in the PLND strategy. In Table 3 the resulting QALY's are presented as well. The number of QALY's associated with having lymph node metastases is about the same for all treatments.

Table 4 presents the average costs of the staging methods and treatment for the patients included in the observational study. A lymph node dissection is the most expensive diagnostic procedure ($5280). The cost of MRL is $1074, the major part of these costs consisted of the contrast agent, which is assumed at $535 per patient.

TABLE 4: *Average costs of staging methods and treatment divided into costs of personnel, material, capacity and overhead.*

Category	MRL (€)	CT (€)	CT guided biopsy (€)	PLND (€)	Hormone therapy (€)	Radio -therapy (€)	Prostat -ectomy*(€)
Personnel	123	57	125	539	294	376	817
Material	419	58	80	100	1948	92	123
Capacity	72	48	49	2332	0	48	5423
Overhead	215	57	69	1040	785	181	2227
Total	829	220	323	4011	3027	697	8590

** The average costs of a prostatectomy are based on PLND followed by radical prostatectomy*

Cost-effectiveness

In table 5 the results of the cost-effectiveness analysis are presented.
The expected diagnostic costs per patient per strategy are higher in the PLND strategy due to a higher number of PLND's performed in that strategy.
The expected number of QALY's gained is slightly higher in the MRL strategy.
Since the expected costs of MRL are lower than the costs of PLND and the effects of MRL are higher, the MRL strategy dominates the PLND strategy.

TABLE 5: *Costs, effects, cost-effectiveness and incremental cost-effectiveness of the MRL strategy compared to the PLND strategy*

	MRL	PLND
Expected cost per patient per strategy (€)	6 680	7 558
Expected number of QALY's per strategy*	9.74	9.65
Health care costs per QALY (€)	686	783
Incremental costs per QALY.		Dominated

Sensitivity results

Figure 3 represents the uncertainty surrounding the costs and QALY's of MRL compared to PLND. The simulations spread over all four quadrants of the incremental cost-effectiveness plane. (Figure 3). For a willingness to pay for the gain of a QALY of zero, the probability of MRL being the optimal strategy is 0.908, indicating that in 90.8% of the

simulations cost savings are involved. When the willingness to pay for a QALY increases, the value attributed to the loss of a QALY increases as well, resulting in a decrease of likelihood that MRL is the optimal strategy. Approximately 69.8% of the simulations are to the right of the Y-axis, indicating that there is a 69.8% probability that MRL is diagnostically more effective than PLND.

When it is assumed that loss of QALY's is considered unacceptable, the WTA for a QALY is infinite and all simulations generating ICER's with negative incremental QALY's are excluded leaving about 63% of the simulations that prevail favorable (MRL is both more effective and less costly)[13]. The curve asymptotes to approximately 0.698, since in 69.8% of the sample MRL is more effective than PLND in terms of QALY's. However 2.45% of the sample lies in the inferior quadrant.

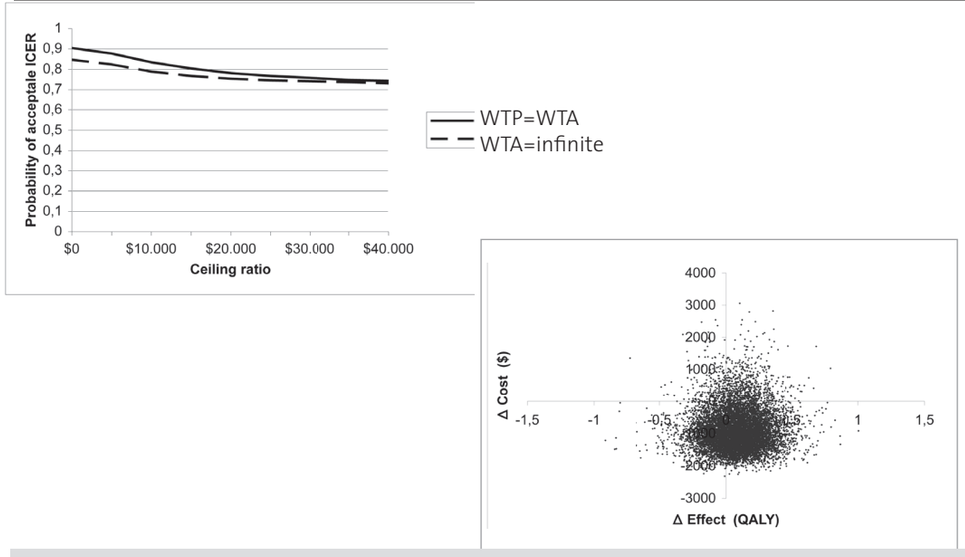

Figure 3. *Cost per QALY*

The graph on the right represents the cost-effectiveness plane of the difference in costs and effects of the MRL strategy compared to the PLND strategy. Each dot represents 1 of 1000 model simulations. The horizontal axis represents the difference in the difference in QALY's between the strategies and the vertical axis represents the difference in costs of the diagnostic and therapeutic process. The graph on the left represents the cost-effectiveness acceptability curve. The vertical axis represents the probability that the incremental cost-effectiveness ratio of the MRL strategy compared to the PLND strategy is acceptable for a range of values of the willingness to pay per QALY.

Discussion

In this study we have compared the cost-effectiveness of a strategy for staging pelvic lymph nodes using MRL to a strategy using PLND from the health care perspective. By performing probabilistic sensitivity analysis it was possible to determine the optimal strategy for a range of values of willingness to pay for a correct diagnosis. The results of the study show that MRL is most likely to be a cost-effective strategy in staging patients with prostate cancer who have an intermediate or high probability of harboring lymph node metastases compared to the PLND-strategy based on their PSA and Gleason score.

The cost savings in the MRL strategy are achieved by eliminating the PLND in 78% of the patients. In addition, in 21% of the patients with a positive MRL a lymph node tissue sample for histopathological examination can be obtained by CT guided biopsy rather than PLND. Finally, a positive MRL can lead to an extended PLND in 80% of patients, since the suspicious node is often located outside the surgical field of view. (obturatori fossa)[4] This results in a more adequate diagnosis of lymph node metastases and therefore more adequate treatment of prostate cancer.

Weinstein et al described guidelines for conducting and reporting modelling studies. Criteria for assessing the quality of models as described in these guidelines fall into three areas: model structure, data used as inputs to models and model validation. In this study we have followed these criteria in the construction, analysis and reporting of the model. [17]

The results in the utility analysis are heavily dependent on the underlying assumption of the analysis that survival is the same for all radical treatments. Conclusive evidence of differences in survival between prostate cancer treatments is difficult to obtain. Most patients survive for many years after their prostate cancer diagnosis and die of other causes. Therefore, trials need to include relatively large numbers of patients followed over many years to be adequately powered to detect survival differences.

The number of QALY's per treatment calculated by our model is comparable to the number of QALY's presented by Hummel et al. [18]

Since a Beta distribution was used for utilities higher than 0.5, the distribution is skewed to the left. Therefore the results are likely to be conservative. In addition, data on the gain in quality of life because of the less invasive diagnostic procedure of MRL are not yet available. The small difference in QALY's between the MRL strategy and PLND strategy is mainly based on the difference in the number of false negative patients. For the calculation of utilities only the utilities of radical prostatectomy and radiotherapy with

no nodal metastases were drawn from distributions. The other utilities were calculated relative to these utilities. This was done from the assumption that these utilities were not independent. The costs of co- morbidity of the patients were not included in this study. The calculation of costs was limited to the first six months after the diagnosis of prostate cancer. Costs over a longer period were not available. In addition, the analysis was performed from a health care perspective. When approached from another perspective, for example the societal perspective, the outcome might be altered. The private costs of a patient who underwent an invasive procedure might be higher than the costs of a patient who underwent a less or non-invasive procedure such as MRL. This study was performed using a conservative approach towards cost and effects of MRL. It should also be noted that these results may not extend to patients with low risk disease in whom PLND is most often not routinely performed.

In conclusion, MRL is an efficient strategy in the detection of lymph node metastases of prostate cancer in intermediate and high risk patients when compared to CT followed by PLND or CT guided biopsy.

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8 General Discussion

This thesis was aimed at evaluating whether MRL is a valuable alternative for CT and PLND in the detection of lymph node metastases in patients with prostate cancer.
This evaluation was based on the following items:

- diagnostic accuracy,
- effect on patient diagnosis,
- treatment,
- patient outcome,
- cost effectiveness (societal value)

Within the scope of this aim, the current state of affairs in radiological staging of lymph nodes in patients with prostate cancer was studied as well as the diagnostic performance of MRL, a new technique in this field. We also explored the impact of this new technique on the risk assessment of lymph node metastases (diagnosis) and on the treatment decisions by urologists. Finally we estimated the value of the new technique from a societal perspective by means of a cost analysis and a cost-effectiveness analysis. In the latter, effectiveness is considered in terms of survival and quality of life. These analyses were performed in the framework of a multi center study on the use of MRL in detecting lymph node metastases in patients with prostate cancer.

In this chapter, the main findings and limitations of the thesis of the research performed will be discussed and the results will be put into perspective.

Main findings

Current state of affairs

The state of affairs in radiological imaging with regard to detecting lymph node metastases before the introduction of MRL is described using a meta-analysis. A post-test probability of a negative result of 12% for CT and 23% for MRI was found indicating that the diagnostic performance of CT and MRI is not sufficient to alter the diagnostic or therapeutic strategy.
Therefore CT and MRI without lymph node specific contrast always require diagnostic follow up by means of PLND or CT guided biopsy. Wolf (1994) showed in a meta-analysis that imaging by CT or MRI is only valuable in patients with a probability of lymph node metastases higher than 45%, under the condition that fine needle aspiration biopsy is

performed.[2] Our results confirm the conclusions of Wolf concerning the limited value of CT and MRI in detecting lymph node metastases.
In addition, from our meta-analysis can be concluded that CT and MRI were none the less still being used in detection of lymph node although the prevalence was below 45%. Moreover, our results show that there is place for a new radiological technique with stronger diagnostic performance.

- *CT and MRI have a post-test probability of a negative result of 12% and 23%, respectively. This indicate, that the diagnostic performance of CT and MRI is not sufficient to alter the diagnostic or therapeutic strategy*
- *There is a place in the staging process for a new radiological technique with stronger diagnostic performance*

Diagnostic accuracy
Following this meta-analysis, the potential use of MRL was explored. The use of MRL requires change in the current paradigm in which imaging is used to detect affected lymph node tissue. MRL focuses predominantly on detecting healthy tissue and following up only suspicious lymphatic tissue by biopsy or PLND. When MRL has a high sensitivity and a negative predictive value (NPV) is present, a patient with a negative result of MRL has a low probability of having lymph node metastases. For low risk patients (< 5% probability of lymph node metastases) curative therapy is justified.
In a multicenter study the diagnostic performance of MRL was compared to the diagnostic performance of Multi-Detector CT (MDCT). All patients underwent a MDCT followed by MRL and finally histopathology of the lymph nodes was examined after patients had a PLND or a CT guided biopsy. The results of MRL show a high sensitivity and NPV (100% and 98%, respectively), indicating that PLND can be foregone after a negative result of MRL. MRL had a specificity and positive predictive value (PPV) of 93% and 69% respectively. For MDCT sensitivity, specificity, NPV and PPV were 34%, 87%, 88% and 66%, respectively.
A study by Harisinghani et al (2003) reported on preliminary results of MRL. A sensitivity and NPV of 100% in 80 patients was reported.[3] However, it was doubtful that these results could be confirmed in daily practice, but it is an indication of the potential of MRL. Therefore, a multi-center study was performed, evaluating the diagnostic performance of MRL compared to that of MDCT. All patients underwent MDCT followed by MRL and finally histopathology of the lymph nodes was examined after patients had a PLND or a CT guided biopsy. The results confirm a high sensitivity and NPV (82% and 96.4%, respectively), indicating that PLND can be foregone after a negative result of MRL.
Bossuyt et al described the Standards for Reporting of Diagnostic Accuracy (STARD).[4] One of these standards is that the reference test should be performed independent of test results. In our multicenter study, due to ethical considerations, the urologist was not blinded for the MRL and MDCT results. The scheme with merged results of MDCT and MRL were provided before surgery. In addition there is a possibility that the PLND will be performed more thoroughly in case of a positive MRL result. Some urologists even extended the lymphadenectomy if lymph node metastases were found on MRL, but fell outside the routine dissection area. Thus, in this case, due to MRL positive nodes are found that would otherwise probably be missed in a regular lymphadenectomy.

- *These results confirm a high sensitivity and NPV of MRL (82% and 96.4%, respectively), indicating that PLND can be foregone after a negative result of MRL.*

Impact on diagnosis
To estimate the impact of MRL on the risk assessment of lymph node metastases, a logistic regression analysis is performed with histopathology of the removed lymph nodes as the independent variable and parameters for the risk assessment as the dependent variables. Currently, the recommended strategy to assess risk insofar as lymph node metastases involves the use of predictive models employing nomograms, algorithms and/or neural nets such as those of Narayan et al(1995), Partin et al (2001), and Bluestein et al (1994).[1,4,5]
These risk assessment tools use inputs such as PSA, Gleason score and clinical stage.
In our study the added value of MRL to accepted nomograms like those of Narayan et al (1995), Partin et al (2001), or Bluestein et al (1994), could be estimated [1,5,6]
Before MRL was added to the logistic regression model, the results in terms of risk prediction were comparable to the above mentioned nomograms. After addition of MRL, the other parameters did not contribute significantly to diagnostic decision making. After a negative MRL the probability of lymph node involvement was below 3% regardless of the other parameters.

These results show that if MRL is added to risk assessment of lymph node metastases, for a large portion of the patients risk assessment for lymph node metastases can be

performed using a minimally invasive procedure. This might lead to a more efficient diagnostic process and a more adequate care for patients with prostate cancer, provided MRL is used appropriately.

- *If MRL is added to risk assessment of lymph node metastases, for a large portion of the patients this assessment can be performed without surgical nodal dissection (PLND)*
- *Provided MRL is used appropriately, this might lead to more efficient diagnostic process and a more adequate care for patients with prostate cancer*

Treatment decisions

Whether the results of MRL have an impact on treatment decisions by urologists is explored in chapter 5. Results show that the positioning of MRL must be strongly emphasized when communicating with the treating urologists, since a negative result of MRL hardly changes the decision process, while a positive result does however have a substantial impact. As this study was an early exploration of the impact of MRL on treatment decisions, when staging by MRL is incorporated into daily practice, outcomes should be measured to determine the actual impact of MRL on treatment decisions. To establish the required paradigm shift, urologists must be well informed on the advantages of the new technique by publication and presentation of the results of MRL. This might be accomplished by close collaboration between urologists and radiologists involved in order to bring about the optimal use of MRL for each patient.

- *The positioning of MRL, that a negative result is highly reliable, must be strongly emphasized when communicating with the treating urologists.*

Societal value (cost-effectiveness)

The societal value of a new technique has many aspects. In this thesis the focus was on the economic impact of the technique. Other aspects of societal value, such as equity and righteousness/justice are not taken into account. [7]

The economic impact of MRL was examined sequentially in two analyses. First a cost-analysis was done assuming equality in diagnostic performance of three strategies; MRL vs. CT followed by PLND vs. PLND alone. This analysis gives a first indication of the economic attractiveness of MRL: it generates cost savings that result from avoiding PLND in 78% of the patients.

Secondly, a cost-effectiveness analysis was performed using the probability of a correct diagnosis and quality adjusted life years (QALY's) as measures of effect. After probabilistic sensitivity analysis, MRL was found cost saving in more than 97.5% of the replications and is more effective than PLND in more than 60% of the replications. Quality adjusted life years were calculated based on utility values and survival of the types of treatment for the included patients. These utility values and survival were obtained from literature. It can be expected that the avoidance of an invasive procedure results in better quality of life. Since in the multicenter study all patients received both MRL and an invasive procedure, the gain in quality of life in patients with a negative result of MRL could not be studied, In addition the duration of this gain in quality of life is uncertain, but no difference in final outcome (survival) is expected. Based on these two analyses we can conclude that MRL is value for money and has an added value from a broad societal perspective.

- *MRL is cost saving in more than 97.5% of the replications, and is more effective than PLND in more than 60%*
- *It can be expected that the use of MRL results in better quality of life*

General implications

The introduction of MRL requires a shift in paradigm, since in this technique the emphasis lies on detecting healthy nodal tissue by identifying black coloured lymph nodes

However, to be able to bring about and support this paradigm shift MRL must show a high sensitivity and NPV. This major advantage of the technique must be emphasized in communications with urologists, since our explorative study shows that the paradigm shift has as yet not taken place.

There are some changes in the field of prostate cancer that might have an effect on the implementation and success of this new technology. Firstly, detection of prostate cancer has improved and therefore prostate cancer is detected in an earlier stage. This results in a decreasing number of patients with intermediate or high risk of lymph node metastases.[8] Secondly, other techniques to detect nodal metastases are developing and improving. Minimally invasive techniques, such as laparoscopic and mini-laparotomy pelvic lymph node dissection, are well described and provide com-parable information to open PLND and show improved patient recovery. [9,10] PET scan is also suggested as a

staging method and is showing favorable results in the detection of metastases. [11] However, there is no evidence that these techniques offer advantages in terms of costs and accuracy, whereas our results show that MRL is value for money.

Future research

In this thesis the value of MRL as a new diagnostic technology in the staging of lymph nodes in patients with prostate cancer is described using a hierarchical approach as described by Guyatt et al.[12] However, the structure used in this study has some limitations. Firstly, the evaluation of diagnostic accuracy is focused on determining pairs of sensitivity and specificity values in comparison to a reference standard (histopathology after PLND or biopsy). However, the reference standard is not flawless in distinguishing between patients with and without lymph node metastases. In a study by Heesakkers et al (2006) it was shown that 40% of the lymph nodes were found outside the field of view of the surgeon in lymph node dissection. [13] This situation may lead to an underestimation of sensitivity and specificity of MRL.

Secondly, Hunink et al (2002) suggest that relevant information will not always lead to implementation of optimal diagnostic imaging technology. Both physicians and patients assume that more imaging studies will lead to better diagnostics. In addition, more tests yielding the same findings increase confidence in the diagnosis. Often implementation of a new technology results in addition to the old technology instead of replacing it. [14, 15] However, the cost-effectiveness of MRL can only be accomplished when it fully replaces MDCT and PLND after a negative result of MRL. An addition of MRL to the current standard of practice would result in a substantial increase of cost. Therefore, more research is needed on the implementation obstacles of MRL. Moreover it is important that the new strategy using MRL is implemented as a replacement of the current strategy.

Thirdly, the connection between more diagnostic imaging information and patient outcomes is difficult to demonstrate because of the multiple intermediate steps. [15]

However, since invasive procedures as PLND can be avoided after MRL, it is expected that there is a clear link between patient outcomes and diagnostic imaging. Therefore, more research is needed on the outcomes of the diagnostic and treatment strategy including MRL. A quality of life gain is expected both from the avoided invasive procedure and from the more adequate staging of prostate cancer.

Finally it is very important to consider outcomes over time. In the multi-center trial a correlation was found between the number of patients who underwent MRL per center and the diagnostic performance of MRL in that center. Centers show optimal performance after at least 20 patients have undergone MRL. This indicates the existence of a learning curve. Therefore it would be interesting to measure outcomes that reflect the learning curve and acceptance over time. [14] A steep learning curve can make quick implementation of the new technique easier.

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9 Summary/Samenvatting

Summary

This thesis reports on the value of MRI with a lymph node specific contrast agent in patients with prostate cancer. In current practice the risk of lymph node metastases is assessed using nomograms in which the combination of the serum PSA level, Gleason score and digital rectal examination result gives a probability of lymph node involvement. High and intermediate risk patients are then referred for additional lymph node staging. This is done by either a pelvic lymph node dissection (PLND) alone or PLND preceded by CT. Recently MR lymphography was suggested as a new staging technique. The contrast agent used with this technique consists of Iron Oxide containing nanoparticles. When these particles are injected intravenously, they are transported by macrophages to normal lymph node tissue. The iron containing particles cause alterations in magnetic properties resulting in changed signal intensity detectable by MRI. Therefore, normal functioning lymph nodes appear black on MRI 24-36 hours after administration of this contrast. In metastatic nodes, however, the signal intensity remains unchanged due to the absence of iron particles. Using the combination of these nanoparticles and MRI –hereafter referred to as MR-Lymphography (MRL)- the lymph nodes in the whole pelvic area can be examined instead of only the routine surgical area (the nodes in the obturator fossa).

In **Chapter 1**, the scope and objective of this thesis are described. It outlines the current thinking on the evaluation of diagnostic technology by presenting the six phases of evaluating new diagnostic technology: technical efficacy, diagnostic accuracy, impact on diagnosis, impact on treatment, patient outcome, and societal value. Within this scope, the objective of this thesis was to gain insight in the value of MRL in the staging process of patients with prostate cancer and an intermediate to high probability of lymph node metastases.

In **Chapter 2** a meta-analysis is described where the performance of the currently used techniques -CT and MRI without contrast- in the detection of lymph node metastases is compared.
A summary receiver operating curve (sROC) was constructed for both staging techniques following guidelines. Single number summaries were calculated as well as summary

CHAPTER 9

Summary/ Samenvatting

likelihood-ratios and post-test probabilities. Methodological characteristics and population characteristics that were believed to influence the performance of MRI and CT were used as covariates in the model. The summary positive likelihood ratios show that a positive result of CT or MRI is not a strong indicator for the presence of metastases in the lymph nodes. A positive likelihood ratio of >5 gives a strong indication of presence of lymph node metastases, and a negative likelihood ratio of <0.2 gives a strong indication of the absence of lymph node metastases. Urologists accept a probability of approximately five percent of lymph node metastases to start curative therapy. The negative post-test probability is, however, much higher, respectively 12% for CT and 23% for MRI. Studies with N<50 had a significant impact on the diagnostic performance of CT. These studies reported a lower performance. The other covariates had no significant influence on the performance of CT or MRI. Thus the performance of CT and MRI without contrast is not good enough to affect the treatment and diagnostic process of the patient. Additional staging in the form of PLND or biopsy is needed to decide on the optimal strategy.

Chapter 3 describes the results of a multi-center study that evaluated the accuracy of MRL compared to CT and MRL. In 13 hospitals in the Netherlands 375 patients received MDCT, MRL and PLND or CT guided biopsy. Patients were consecutively included between April 2002 and April 2005. Data were collected using an electronic standardised case report form (e-CRF). The location and size of the metastatic nodes on MDCT and MRL were independently recorded on a map embedded within this e-CRF. Histopathology was the used as the standard of reference. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) were calculated. The accrual distribution was skewed as three hospitals included 79% of all patients (295). Subgroup analyses showed that results from these three hospitals were better than from the others. For all patients the sensitivity, specificity NPV and PPV for MDCT were 34%, 97%, 88% and 66%, respectively. For MRL the sensitivity, specificity NPV and PPV were 82%, 93%, 97% and 69%, respectively. The high NPV suggests that after a negative result of MRL, PLND can be safely omitted, as the chance that a patient with a negative MRL result has metastasis is only 3%. The diagnostic accuracy of MRL was significantly better indicating that MRL is a good alternative for CT and PLND in the detection of lymph node metastases in patients with prostate cancer.

In **chapter 4** the impact of the addition of MRL to the process of risk assessment of lymph node metastases is described. A logistic regression analysis was performed with the results of histopathological evaluation of the lymph nodes as dependent variable and the serum level PSA, preoperative Gleason score, DRE results as independent variables. In a second model the results of MRL are added to the regression analysis. The first regression model shows similar results to the nomogram of Narayan et al. When PSA level exceeds 15 or Gleason exceeds 6, the risk of lymph node metastases is higher than 5% and additional staging in the form of PLND is needed. When MRL is added to the model, the other variables are no longer significant. A negative result of MRL results in a probability of lymph node metastases below 3% regardless of the value of the other parameters. Therefore in case of a negative result of MRL curative therapy can be started safely. In case of a positive result the probability of lymph node metastases is higher than 70% regardless of the other parameters. This gives a strong indication of the presence of metastases, but additional staging of PLND is necessary to confirm. Results of this study show that MRL is a valuable addition to the staging process. After a negative result of MRL it is justified to forego PLND.

Chapter 5 describes an explorative study, which was performed to assess the impact of MRL on the treatment decisions of urologists for patients with prostate cancer.
Participating urologists were presented with 25 fictitious case summaries of patients in which serum PSA level, preoperative Gleason score, digital rectal examination, results of bone scan and results of MRL were described. Urologists had to make a choice between a number of management options; radical prostatectomy, radiotherapy, hormone therapy, watchful waiting or additional staging by PLND. Multinomial regression analysis was performed to estimate the weight of the attributes. A total of 18 urologists participated in this study. The response rate was 57%.
Based on the positioning of MRL, as described in the previous chapters, it is expected that urologists will chose for curative therapy in the form of prostatectomy or radiotherapy after a negative result of MRL without PLND. Also, after a positive result of MRL additional staging is necessary in the form of PLND to confirm diagnosis by histopathology. However, the participating urologists chose significantly more for hormone therapy after a positive result of MRL, and did not change their treatment when MRL was negative. Thus the results of this first exploration indicate that the positioning of MRL must be strongly emphasized towards urologists for whom MRL can be of use when the technique is implemented.

In **chapter 6** the cost savings are described when the diagnostic strategy using MRL is used for patients with prostate cancer. A decision analytic model is used to describe the events in three possible strategies for the staging of lymph node metastases. The first strategy is MRL followed by PLND or CT guided biopsy in case of suspicious nodes seen on MRL. The second strategy consists of CT followed by CT guided biopsy in case of a positive result.. The final strategy consists of PLND without imaging beforehand.
MRL was the least expensive strategy, since PLND can be avoided in 60% of the patients because of a negative result of MRL. The savings can amount up to €1310 per patient when compared to the strategy using CT and €1467 when compared to the strategy using PLND. In conclusion, this study provides a valuable first indication on the economic attractiveness of MRL.

A cost-effectiveness analysis based on the patients from the multi-center trial is presented in **chapter 7**. The decision analytic model from the cost-analysis of chapter 6 was extended to include treatment of the patients after the diagnostic process. Markov chain analyses were added tot the decision tree to evaluate the life expectancy of patients in the model. Cost-utility analysis was done from the health care perspective. In the multicenter trial (see chapter 4) information on resource use was collected using standardised case record forms. Information on (transition) probabilities was also obtained from this trial. By performing probabilistic sensitivity analysis it was possible to determine the optimal strategy for a range of values of willingness to pay for a quality adjusted life year (QALY).
Results show that in approximately 63% of the simulations used to construct the cost-effectiveness acceptability curves MRL was more effective and less expensive. The probability of MRL being inferior (more expensive and worse patient outcomes) is less than 3%.
In conclusion, MRL is an efficient strategy in the detection of lymph node metastases of prostate cancer in intermediate and high risk patients when compared to CT followed by PLND or CET guided biopsy.

The general discussion (**Chapter 8**) aims at putting the individual studies regarding the value assessment of MRL into a broader perspective.
Given the assessment of the different aspects of the value of MRL, it can be concluded that MRL is a valuable addition to the staging process in patients with prostate cancer and an intermediate or high probability of lymph node metastases.

Samenvatting:

In dit proefschrift wordt de waarde van MRI met een lymfeklierspecifiek contrastmiddel voor patiënten met prostaatkanker beschreven. Voor deze patiënten wordt het risico op lymfekliermetastasen in de huidige praktijk bepaald met behulp van nomogrammen, waarin de combinatie van een antistof tegen prostaatweefsel (PSA), de agressiviteitgraad van het biopt (Gleason-score) en de uitslag van rectaal toucher wordt gebruikt. Bij patiënten met een licht verhoogd of verhoogd risico op uitzaaiingen is aanvullend onderzoek nodig. De meest gebruikelijke methode is lymfeklier dissectie van het kleine bekken (PLND), soms voorafgegaan door computer tomografie (CT). Recent werd MRI met een lymfeklierspecifiek contrastmiddel (MRL) beschreven als nieuwe techniek. Dit contrastmiddel bestaat uit nano-partikelen van ijzeroxide (USPIO). Als dit middel intraveneus wordt ingebracht, wordt het door macrofagen naar gezond lymfeklierweefsel gebracht. Het ijzer veroorzaakt veranderingen in de magnetische eigenschappen van het weefsel, dat resulteert in veranderingen in de signaal-intensiteit op de MRI beelden. Hierdoor zijn 24-36 uur na toediening van het contrast gezonde lymfeklieren zwart op MRI. In lymfekliermetastasen verandert de signaalintensiteit echter niet en blijft het weefsel grijs-wit. Met MRL kan de hele buik worden onderzocht in plaats van alleen een beperkt gebied rond enkele bekkenvaten, zoals bij de PLND onderzocht wordt.

Hoofdstuk 1 is een algemene inleiding op het proefschrift, waarin wordt ingegaan op het ziektebeeld van prostaatkanker en de diagnostiek en behandeling, die daar bij horen. Ook worden de 6 fasen van de waardebepaling van een nieuwe diagnostische techniek beschreven: technische werkzaamheid, diagnostische accuraatheid, impact op diagnose, impact op behandeling, uitkomsten op patiënt niveau en maatschappelijke waarde. Het doel van dit proefschrift is de waarde van MRL als techniek voor de stadiëring van lymfeklieren te onderzoeken op voor wat betreft de laatste 5 aspecten.

Op dit moment zijn CT en MRI de meest gebruikte afbeeldingtechnieken bij het ontdekken van lymfeklier metastasen. In Hoofdstuk 2 wordt een meta-analyse beschreven van de diagnostische accuraatheid van CT en MRI bij het opsporen van lymfeklier metastasen bij patiënten met prostaatkanker. Er is een systematische literatuur zoektocht gedaan, waarbij de gegevens over accuraatheid werden gepoold volgens richtlijnen. Methodologische karakteristieken en eigenschappen van de onderzoekspopulatie, die de accuraatheid van CT en MRI kunnen beïnvloeden, werden meegenomen in het model als covariaten. Likelihood-ratio's en 'summary receiver operating curve' (sROC) zijn

berekend voor beide technieken. Resultaten laten zien dat er geen significant verschil in accuraatheid tussen CT en MRI zit. De positieve likelihood-ratios laten zien dat een positieve uitslag van CT of MRI geen sterke indicatie is voor uitzaaiingen in de lymfeklieren. Uit de negative likelihood-ratios blijkt dat ook een negatieve uitslag van CT of MRI zeer slecht de afwezigheid van lymfeklier uitzaaiingen kan voorspellen. Op grond hiervan moet ook nog een diagnostische PLND gedaan worden, voordat een curatieve therapie gestart kan worden. Studies met N<50 hadden een significante impact op de accuraatheid van CT; deze studies lieten een lagere accuraatheid zien dan studies met N>50. De overige covariaten hadden geen significante impact op de accuraatheid van CT of MRI.
Uit deze meta-analyse kan worden geconcludeerd dat de accuraatheid van CT en MRI zonder lymfeklierspecifiek contrast middel niet hoog genoeg is om het diagnostisch en behandeltraject van de patiënt te veranderen. Aanvullende diagnostiek door PLND of biopt is nodig ongeacht de uitslag van CT of MRI. Deze technieken kunnen dus beter achterwege gelaten worden bij de diagnostiek van lymfeklier uitzaaiingen bij patiënten met prostaatkanker.

De diagnostische accuraatheid van MR Lymphography wordt beschreven in **hoofdstuk 3**. In 13 Nederlandse centra kregen 375 patiënten multidetector-CT (MDCT) en MRL gevolgd door PLND of CT-geleid biopt. Histopathologie van klierweefsel verkregen door PLND of CT-geleid biopt werd gebruikt als de gouden standaard.
Tussen April 2003 en April 2005 zijn de patiënten geïncludeerd. Gegevens werden verzameld door middel van een gestandaardiseerde elektronische case record form (eCRF) waarin ook de locatie van verdachte lymfeklieren zoals gevonden op de MRL of MDCT werden weergegeven. Sensitiviteit, specificiteit, negatief voorspellende waarde (NPV), positief voorspellende waarde (PPV) en positieve en negatieve likelihood-ratios werden berekend voor MDCT en MRL. De inclusie van patiënten was zeer onregelmatig verdeeld over de betrokken ziekenhuizen; drie ziekenhuizen includeerden 79% van alle patiënten (295). Uit subgroepanalyses bleek dat de resultaten van deze ziekenhuizen beter waren dan van de overige centra. Voor de totale groep patiënten waren de sensitiviteit, specificiteit, NPV en PPV van MDCT 34%, 97%, 88% en 66%. Voor MRL was de sensitiviteit, specificiteit, NPV en PPV 82%, 93%, 96% en 69%. De diagnostische accuraatheid van MRL is significant hoger dan MDCT in het opsporen van lymfekliermetastasen. De hoge negatief voorspellende waarde (3%) laat zien dat na een negatieve uitslag op MRL, een PLND veilig achterwege kan worden gelaten.

In **hoofdstuk 4** wordt de invloed van de toevoeging van MRL op de standaard schatting van het risico op lymfekliermetastasen van bestaande nomogrammen beschreven. Een logistische regressie analyse werd uitgevoerd met de uitslag van histopathologisch onderzoek van de lymfeklieren als afhankelijke variabele en PSA, Gleason score als onafhankelijke variabelen. De input voor deze variabelen kwam uit het multicenter onderzoek naar de accuraatheid van MRL. (zie hoofdstuk 3) Op deze manier kon de invloed van PSA en Gleason score op lymfeklieruitzaaiingen worden onderzocht.
Vervolgens werd de uitslag van de MRL toegevoegd in het model om te kijken of de uitslag van MRL de kans op uitzaaiingen veranderd en daarmee een toegevoegde waarde levert aan het stadiërings-proces.
De resultaten van het eerste model komen overeen met de resultaten van de bestaande nomogrammen van Partin en Narayan. Als de PSA boven 15 is en de Gleason score hoger is dan 6, is het risico van lymfeklier metastasen hoger dan 5% en is aanvullende stadiëring in de vorm van PLND nodig. Wanneer MRL wordt toegevoegd aan het regressie model, zijn de andere variabelen niet langer significant. Na een negatief resultaat van MRL is de kans op lymfekliermetastasen lager dan 3% ongeacht de waarde van de andere variabelen. Na een negatieve uitslag van MRI is het inzetten van curatieve therapie, zonder dat een PLND nodig is, gerechtvaardigd.
Na een positieve uitslag is de kans op uitzaaiingen in de lymfeklieren hoger dan 70% ongeacht de andere variabelen. Dit geeft wel een sterke indicatie van de aanwezigheid van uitzaaiingen, maar aanvullende diagnostiek in de vorm van PLND is wel nodig.
Resultaten van deze studie bevestigen dat MRL een waardevolle toevoeging in aan het diagnostische traject voor patiënten

Een verkennende studie naar de impact van MRL op de besluitvorming van de urologen wordt beschreven in **hoofdstuk 5**. Een set van 25 fictieve patiëntbeschrijvingen werd voorgelegd aan de participerende urologen. In deze patiëntbeschrijvingen waren PSA, Gleason score, rectaal toucher, uitslag van een botscan en de uitslag van MRL opgenomen. Urologen moesten vervolgens per patiënt aangeven welke van de volgende mogelijkheden het meest geschikt was: radicale prostatectomie, radiotherapie, hormoontherapie, “watchful waiting” of aanvullende diagnostiek in de vorm van PLND. Om het gewicht van de onderdelen van de patiëntbeschrijving te bepalen werd multinomiale regressie analyse gebruikt.
Aan deze studie deden 18 urologen mee (respons 57%). De uitslag van een botscan had het grootste effect op de beslissing van een uroloog. Een positieve uitslag van MRL had

significant meer keuzes voor hormoontherapie tot gevolg. Een negatieve uitslag van MRL liet een trend zien richting meer keuzes voor radiotherapie en radicale prostatectomie, maar dit was niet significant. Op grond van de accuraatheid van een negatieve MRL uitslag was de verwachting was echter dat na een negatieve uitslag van MRL er meer gekozen zou worden voor curatieve therapie, zonder de inzet van PLND, en dat na een positieve uitslag de uroloog zou kiezen voor aanvullende diagnostiek. Deze verwachting was gebaseerd op de hoge sensitiviteit en negatief voorspellende waarde van MRL.
De resultaten van deze verkennende studie laten zien dat de positionering van MRL en de hoge NPV en sensitiviteit benadrukt moeten worden, omdat anders de MRL verkeerd geïmplementeerd wordt.

In **hoofdstuk 6** worden de kosten van een strategie met MRL vergeleken met de gangbare bestaande uit PLND en CT. Dit wordt gedaan met behulp van een besliskundig model. De kosten worden berekend vanuit een gezondheidszorg perspectief. Dit betekent dat alleen de directe kosten in de gezondheidzorg worden meegenomen.
De kosten zijn opgedeeld in materiele, personele en capaciteitskosten. Uit analyse van het model blijkt dat de MRL strategie kostenbesparend is in vergelijking met de beide andere strategieën. Het volgen van de MRL strategie resulteert in een besparing van €1310 in vergelijking met de PLND strategie en €1467 in vergelijking met de CT strategie.
De besparingen kunnen vooral verklaard worden door het vermijden van de lymfeklierdissectie in geval van een negatieve uitslag van MRL. Deze studie is een eerste indicatie dat MRL vanuit een economisch perspectief een goed alternatief is voor het opsporen van lymfekliermetastasen.

In **hoofdstuk 7** wordt de kosteneffectiviteit van MRL beschreven in vergelijking met PLND al dan niet voorafgegaan door MDCT. Het model, dat gebruikt is in hoofdstuk zes, is uitgebreid met Markov-chains om de levensverwachting van de patiënten te kunnen modelleren.
Er is een kosten-utiliteitsanalyse uitgevoerd vanuit een gezondheidszorg perspectief. Tijdens de multicenter studie beschreven in hoofdstuk 3, is informatie over zorgconsumptie verzameld met gestandaardiseerde case record forms. Informatie voor kansen en transitiekansen in het model zijn ook verkregen uit deze studietrial. Door een probabilistische sensitiviteitsanalyse uit te voeren kon bekeken worden wat de optimale strategie is voor een range van waardes voor “willingness to pay” voor een QALY.

Uit resultaten blijkt dat in 63% van de simulaties MRL effectiever, en goedkoper is dan CT gevolgd door PLND of een biopt. De kans dat MRL inferieur (minder effectief en duurder) is, is kleiner dan 3% . Concluderend: MRL is de optimale strategie voor de detectie van lymfekliermetastasen van prostaatkanker, vergeleken met CT gevolgd door PLND of een CT geleid biopt.

In **hoofdstuk 8** worden de individuele studies in een breder perspectief geplaatst.
Na bestudering van de verschillende aspecten van de waarde van MRL kan worden geconcludeerd dat MRL een waardevolle toevoeging is tot het proces van stadiering in patiënten met prostaatkanker en een middelhoge of hoge kans op lymfekliermetastasen en dat bij een negatieve uitslag van MRL zowel CT als PLND achterwege moet blijven.

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