DOI: 10.1093/jnci/djp514
Advance Access publication on February 1, 2010.

ARTICLE

Detection of Lymph Node Metastases by Gadolinium-Enhanced Magnetic Resonance Imaging: Systematic Review and Meta-analysis

Wenche M. Klerkx, Leon Bax, Wouter B. Veldhuis, A. Peter M. Heintz, Willem PThM. Mali, Petra H. M. Peeters, Karel G. M. Moons

Manuscript received February 4, 2009; revised November 12, 2009; accepted December 15, 2009.

Correspondence to: Wenche M. Klerkx, MD, PhD, Department of Gynecology and Obstetrics (F05.132), University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands (e-mail: w.klerkx@umcutrecht.nl).

Background Gadolinium-based contrast agents are used with magnetic resonance imaging (MRI) to highlight tumor vascularity in organs. They are also widely used for primary tumor visualization. We conducted a systematic review and meta-analysis of the existing evidence of the accuracy of gadolinium-enhanced MRI for staging lymph node metastases.

Methods We systematically searched the MEDLINE, Cochrane, CANCERLIT, and EMBASE databases for studies published in English or German from January 1, 1988, to January 1, 2008, that assessed the diagnostic accuracy of gadolinium-enhanced MRI in the evaluation of lymphatic metastases compared with histopathologic examination as the reference test. Based on a priori–defined clinical considerations, we studied three subgroups of studies: those that used a single malignancy criterion and those that used multiple malignancy criteria with or without contrast highlighting. Summaries of MRI sensitivity and specificity for detecting lymph node metastases were calculated using a bivariate regression model. All statistical tests were two-sided.

Results The literature search yielded 43 full-text papers that were considered for inclusion in the meta-analysis. We performed quantitative pooled analyses on the 32 studies that provided data on patient-level diagnosis. The weighted estimates of sensitivity and specificity for all studies combined were 0.72 (95% confidence interval [CI] = 0.66 to 0.79) and 0.87 (95% CI = 0.82 to 0.91). Estimates of sensitivity and specificity were essentially unchanged for studies that used a single malignancy criterion (0.71 [95% CI = 0.61 to 0.79] and 0.88 [95% CI = 0.80 to 0.93], respectively; n = 11 studies) or multiple malignancy criteria without contrast enhancement (0.70 [95% CI = 0.58 to 0.79] and 0.86 [95% CI = 0.68 to 0.94], respectively; n = 6 studies). The sensitivity increased to 0.84 (95% CI = 0.70 to 0.92), with a specificity of 0.82 (95% CI = 0.72 to 0.89) for the nine studies that incorporated contrast enhancement in their multiple malignancy criteria. Six studies did not define the malignancy criteria they used.

Conclusions The overall accuracy of gadolinium-enhanced magnetic resonance imaging for the detection of nodal metastases is moderate. Incorporating contrast enhancement in the malignancy criteria substantially improves the accuracy of this diagnostic test.

J Natl Cancer Inst 2010;102:244–253

Lymphatic metastasis is an important prognostic factor in malignancies. Most tumors are classified according to the TNM staging system, and treatment and prognosis are modified when lymph node metastases are present. Lymph node staging by physical examination is not accurate in discriminating metastatic from benign lymph nodes. Even in superficial areas such as the cervical and inguinal regions, a physical evaluation of lymph nodes cannot reliably detect metastases (1,2). The best method and current reference standard for staging lymph node metastases is histopathologic examination. However, this is an invasive surgical procedure in which complications and morbidity may occur. Noninvasive imaging tools, such as computed tomography and magnetic resonance imaging (MRI), are available as methods to enhance the diagnostic evaluation of lymph nodes. However, conventional MRI and computed tomography mainly evaluate the size of lymph nodes. Although it had been assumed that the use of lymph node characteristics, such as homogeneity, margins, and shape, as diagnostic criteria would improve the ability of MRI to discriminate between benign and metastatic lymph nodes, several studies (3–5) showed that the use of these morphological characteristics did not improve the accuracy of conventional MRI.

Contrast-enhanced MRI has been proposed as a tool for improving the diagnostic accuracy of nodal metastases detection (6). One of the contrast agents used with enhanced MRI is ultrasmall superparamagnetic iron oxide (USPIO) particles. A meta-analysis of the diagnostic precision of USPIO-enhanced MRI for detection of lymph node metastasis showed an overall sensitivity of 0.88 (95% confidence interval [CI] = 0.85 to 0.91) and specificity of 0.96 (95% CI = 0.95 to 0.97) (6). However, this staging method also has a number of disadvantages, including the need for slow infusion of the contrast agent 24 hours before imaging to minimize hypersensitivity-related side effects (7,8). Moreover, interpretation of the magnetic resonance images is not a trivial task (9). Consequently, the USPIO contrast agent has not yet been registered at the European Medicines Agency nor has it been approved by the US Food and Drug Administration.

It is thought that the lymph node prepares for metastatic cell implantation by reorganizing lymphatic and vascular structures and, as a consequence, new blood vessels develop within and around lymph nodes (10). The administration of an intravenous contrast agent, such as gadolinium, can reveal these surrounding blood vessels and demonstrate additional morphological characteristics of tumor tissue (11–13). Although gadolinium should be used with care in patients with nephropathy, it is generally accepted as a safe contrast agent when compared with USPIO (14,15). As such, it has been used extensively to visualize a variety of tumors with increased angiogenesis and blood flow [eg, (16)].

The number of studies that have evaluated the accuracy of gadolinium-enhanced MRI to detect nodal metastases compared with that of histopathologic examination has increased sharply in the last decade to more than 30 (3,4). However, to our knowledge, a systematic review of all of these studies has not yet been undertaken. The purpose of this study was to quantitatively summarize, by means of a meta-analysis, all existing evidence in the literature on the diagnostic accuracy of MRI with intravenously administered gadolinium to detect metastatic lymph nodes in any cancer.

CONTEXT AND CAVEATS

Prior knowledge

Magnetic resonance imaging with gadolinium-based contrast agents is widely used to visualize primary tumors and to highlight tumor vascularity.

Study design

A systematic review and meta-analysis of studies that assessed the diagnostic accuracy of gadolinium-enhanced magnetic resonance imaging in the evaluation of lymphatic metastases compared with histopathologic examination as the reference test.

Contribution

The overall accuracy of gadolinium-enhanced magnetic resonance imaging for the detection of nodal metastases is moderate. Incorporating contrast enhancement in the malignancy criteria substantially improves the accuracy of this diagnostic test.

Implications

Contrast highlighting of lymph nodes should be included as a malignancy criterion when gadolinium contrast agent is used for primary tumor visualization.

Limitations

Not all of the included studies reported diagnostic study quality, which precluded formal analyses based on the quality assessment items. A regression test for small-study effects was statistically significant, indicating that the retrieved studies had results that may not be representative of the full range of evidence that has been produced (publication bias). In the overall analyses of the diagnostic accuracy of gadolinium-enhanced magnetic resonance imaging for the detection of lymph node metastases, studies were pooled without regard to the primary tumor site.

From the Editors

Methods

Search Strategy

We performed a comprehensive search of English- and German-language literature to identify articles that examined the diagnostic accuracy of gadolinium-enhanced MRI (as an index test) in the evaluation of lymph node metastases using histopathology as the reference standard. We searched the MEDLINE, Cochrane, CANCERLIT, and EMBASE databases for studies published from January 1, 1988, to January 1, 2008, with the medical subject headings (MeSH) terms "lymph nodes" OR "lymphatic metastasis" and with "lymph node" or "lymph nodes" and "gado* OR gd" as text words. We explicitly included no terms related to the type of cancer because our aim was to analyze the accuracy of gadolinium to detect lymphatic metastases regardless of the location or type of the primary tumor. We identified additional references by cross-checking bibliographies of retrieved full-text papers.

Study Selection and Data Extraction

We included studies that met all of the following inclusion criteria: 1) a minimal sample size of 10 patients with histologically proven primary carcinoma; 2) evaluation of gadolinium-enhanced MRI compared with histopathology of lymph nodes obtained by surgery, autopsy, or biopsy as the reference standard; and 3) sufficient data to (re)construct a 2 × 2 contingency table such that the cells in the table could be labeled as true positive, false positive, true negative, and false negative. We excluded studies that included healthy volunteers only or patients with nonlymphatic metastases, and studies having possible overlap with the selected studies (ie, studies from the same study group, institution, and period of inclusion).

The selection of studies for this meta-analysis was done in two consecutive phases: assessment of the title and abstract by one reviewer (W. M. Klerkx) and assessment of the full article by two independent reviewers (W. M. Klerkx and W. B. Veldhuis). Discrepancies between the two reviewers were resolved having additional reviewers (P. H. M. Peeters and/or K. G. M. Moons) assess the full article, and the decision about whether to include the article was made by consensus. The two original reviewers independently extracted relevant data from the articles that were selected for inclusion in the meta-analysis by using a standard score form that included the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria (17).

For the meta-analysis of diagnostic accuracy data, the two reviewers extracted the numbers of true positives, false positives, true

negatives, and false negatives from each study. When diagnostic data in the article were only presented at the level of the lymph node region, site, or tumor diagnosis, we requested patient-level data from the authors of the study. In addition to the QUADAS criteria and the contents of the 2 × 2 table, we also recorded following information: overall study characteristics (including the first author, country, language, and date of publication); patient characteristics (including mean age at time of study inclusion, site of the primary tumor, stage of disease, and sex ratio); and characteristics regarding the MRI scan and evaluation (including magnetic field strength; type, dosage, and administration route of the gadolinium contrast agent; the number of reviewers and whether they were blinded to each others results; the type and number of malignancy criteria; and whether the malignancy criteria were defined before or after analysis). We classified malignancy criteria according to the definition that was used to indicate a metastatic lymph node. Subsequently, we grouped the studies according to their malignancy criteria as follows: Studies that had a single malignancy criterion (ie, studies that used the size of the lymph node to indicate a metastasis), studies that had multiple malignancy criteria but excluded gadolinium enhancement in the malignancy criteria, and studies that evaluated lymph node metastases by multiple malignancy criteria including gadolinium enhancement. We also documented reference standard characteristics, including the method of lymph node harvesting, histopathologic staining, and sectioning of the histological material.

When raw data were presented in 3 × 3 or 4 × 4 tables (eg, when the lymph node stage was defined as N0 [no metastases], N1 [metastasis in one lymph node], N2 [metastases in two lymph nodes], or N3 [metastases in distant lymphatic draining region]), we reconstructed 2 × 2 tables by considering N1 and higher stages as metastasis-positive lymph nodes and N0 as metastasis-negative lymph nodes, as has been done in most other individual studies [eg, (18)]. Two articles (3,19) presented raw data for several malignancy criteria. We consistently used the data with the highest sensitivity and performed a sensitivity analysis in which we used the data with the lowest sensitivity instead of the data with the highest sensitivity.

Data Preparation and Statistical Analysis

We used forest plots to assess the precision with which sensitivity and specificity had been measured in each study and to evaluate heterogeneity across studies. We then used a bivariate random-effects approach to obtain weighted overall estimates of the sensitivity and specificity of gadolinium-enhanced MRI in detecting lymph node metastasis (20,21). This approach assumes a bivariate distribution for the logit-transformed values of paired sensitivity and specificity. Overall sensitivity and specificity and their 95% confidence intervals were calculated based on the binominal distributions of the true positives and true negatives. Besides accounting for study size, the bivariate model adjusts for the negative correlation between the sensitivity and the specificity of the index test. Univariate models analyze the sensitivity and specificity independently and do not take into account that between-study differences may be because of threshold differences in malignancy criteria. A bivariate approach can model this dependency explicitly. An additional advantage of using the bivariate model is that the bivariate nature of the original data can be maintained throughout the analysis, allowing the generation of summary estimates of sensitivity and specificity. A summary receiver operating characteristic curve was constructed as a way to summarize the true- and false-positive rates from different diagnostic studies.

To formally quantify the extent of between-study variation (ie, heterogeneity), we calculated the Q and I^2 statistics (22). The I^2 statistic describes the proportion of total variation in study estimates that is because of heterogeneity, which ideally would be 0%. We anticipated that there would be substantial clinical heterogeneity and between-study variation in reported pairs of sensitivity and specificity, particularly because of differences how malignancy was defined on the magnetic resonance images. Hence, we estimated the overall accuracy of the index test across the three a priori–defined subgroups of studies based on the number and type of criteria used to determine that the lymph nodes shown on the magnetic resonance images were malignant (ie, studies that used a single criterion, studies that used multiple criteria without incorporating contrast highlighting, and studies that used multiple criteria including contrast highlighting). These three subgroups were chosen because they would allow clinicians to determine whether or not to take contrast enhancement into account as a malignancy criterion.

In addition to this primary subgroup analysis, we also investigated the effect of potential sources of heterogeneity on the diagnostic accuracy of gadolinium-enhanced MRI by including covariates in the bivariate model. Because the number of studies was too small to perform such analyses without sufficient protection for type I errors, we tested the covariates one at a time and, thus, consider this to be an exploratory analysis and the results as hypothesis generating. The covariates included in this analysis were lymph node region (upper abdomen, regional rectum, pelvis, pelvis and para-aortic, axilla, or other); prevalence of lymphatic metastases (<25%, 25%–50%, or >50%; these cut points were chosen a priori to provide a relatively simple interpretation for clinicians); language (German or English); complete vs incomplete outcome verification; and whether reviewers of the index test were blinded to the results of the reference test and vice versa.

We assessed whether the retrieved studies had results that were not representative of the full range of evidence that has been produced (publication bias) by means of a regression test of the natural logarithm of the diagnostic odds ratio on the inverse of the effective sample size (23). The regression test will be statistically significant if small-study effects cause asymmetry. We present these results as exploratory because this approach is known to be unreliable in datasets with substantial between-study variation and when thresholds favor sensitivity over specificity or vice versa (23,24).

Statistical analyses were conducted using STATA 10.0 (StataCorp LP, College Station, TX), notably the midas (25) and metandi (26) commands, MetaDisc (27), and MIX (28) software. All statistical tests were two-sided, and statistical significance was defined as a P value less than .05.

Results

Literature Search and Study Selection

The literature search identified 1089 potentially relevant titles (Figure 1). We excluded 926 titles because the study investigated

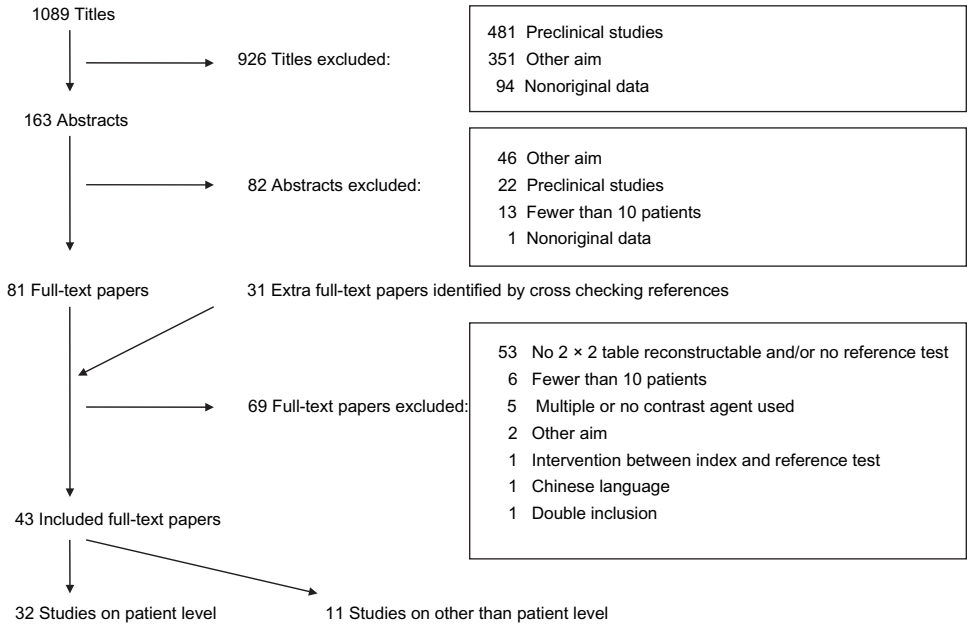

Figure 1. Flow chart of the systematic literature search.

an infectious disease or other nonmalignant diseases, the study subjects were not human, or the study examined the technical aspects of the imaging device rather than its diagnostic accuracy. Eighty-one articles were selected for full-text review, and, after cross-checking the reference lists, 31 additional full-text papers were selected. Fifteen of these 31 articles were included in the analyses. The final number of studies considered for inclusion in the meta-analysis was 43 (Figure 1).

Data Extraction and Quality Assessment

Of the 43 studies considered for inclusion in the meta-analysis, 32 studies (3–5,19,29–56) reported patient-level diagnostic data (Figure 1 and Table 1). Eleven studies (57–67) were not included in the meta-analysis because they reported diagnostic data at the level of the lymph node, anatomic location of the lymph node, side of body (left or right), or tumor (Supplementary Table 1, available online) and therefore could not be compared with those that presented diagnosis data at the patient level. The total number of patients included in the 32 studies was 1402 (range = 10–217 patients), and the mean age at diagnosis was 58.3 years. Eight studies (30,37,38,42,47,50,51,54) described patients with colon and/or rectal cancer, five studies (5,33,40,43,53) presented cervical cancer patients, and four studies (3,4,46,56) included breast cancer patients. The remaining studies described lymph node staging using gadolinium contrast agent in patients with lung (32), head and neck (39), esophageal (36), pancreatic (29,31,49), renal cell (41,44), urinary bladder (48), gall bladder (35), endometrial (19,45), ovarian (52), and gastric (34) cancers.

We assessed the quality of the 32 studies according to the 13-item QUADAS assessment tool (Figure 2 and Supplementary Table 2, available online). Three of the 13 items could be scored in all included articles: completeness of verification via a reference standard of diagnosis (item 5), reporting of uninterpretable results (item 12), and explanation of withdrawals from the study (item 13). Differential verification bias was present in 35% of the studies. Also, blinding to index and reference test results was poorly reported by 90% and 38% of the studies, respectively, as was the presence of uninterpretable test results (81%). Three other QUADAS items were reported in less than 50% of the included studies, namely the availability of clinical data that would be available in clinical practice when using the index test (25%), the time period between the index test and the reference test (41%), and whether patients received the same reference test regardless of the index test result (47%).

Meta-analysis

The overall sensitivity of all 32 studies estimated from the bivariate model was 0.72 (95% CI = 0.66 to 0.79), and the specificity was 0.87 (95% CI = 0.82 to 0.91). There was substantial heterogeneity across studies for sensitivity (I^2 = 62.4) and specificity (I^2 = 84.2) (Figure 3).

For the 11 studies that used a single criterion for metastasis, the sensitivity was 0.71 (95% CI = 0.61 to 0.79) and the specificity was 0.88 (95% = 0.80 to 0.93) (Table 2). There was substantially less heterogeneity across these studies for sensitivity (I^2 = 8.4) and specificity (I^2 = 50.3). The area under the summary receiver operating characteristic curve for the 11 studies that used a single malignancy criterion was 0.84 (95% CI = 0.80 to 0.87) (Figure 4). The estimates of sensitivity and specificity were essentially unchanged for studies that used multiple malignancy criteria without contrast enhancement (0.70 [95% CI = 0.58 to 0.79] and 0.86 [95% CI = 0.68 to 0.94]). For the nine studies that used multiple malignancy criteria with contrast enhancement, the sensitivity increased to 0.84 (95% CI = 0.70 to 0.92) and the specificity was 0.82 (95% CI = 0.72 to 0.89), with substantial heterogeneity across these studies for sensitivity (I^2 = 49.5) and specificity (I^2 = 67.2) (Table 2). The area under the summary receiver operating characteristic curve for these nine studies was 0.90 (95% CI = 0.87 to 0.92) (Figure 4). Six

Table 1. Population and study characteristics of the 32 studies included in the meta-analysis*

First author, year (reference)	Country	Language	No. of patients	Mean age at diagnosis, y	Tumor type or site	Prevalence of lymphatic metastases	Subgroup malignancy criterion†	Sensitivity (95% CI)	Specificity (95% CI)
Bley, 2005 (29)	Germany	English	19	62.8	Pancreas	0.53	1	0.70 (0.35 to 0.93)	0.67 (0.30 to 0.93)
Drew, 1999 (30)	United Kingdom	English	29	NS	Rectum	0.41	3	0.58 (0.28 to 0.85)	0.71 (0.44 to 0.90)
Gaa, 1999 (31)	Germany	German	46	NS	Pancreas	0.52	1	0.75 (0.53 to 0.90)	0.86 (0.65 to 0.97)
Hasegawa, 2003 (32)	Japan	English	30	63.8	Lung	0.40	3	0.92 (0.62 to 1.00)	0.78 (0.52 to 0.94)
Heuck, 1997 (33)	Germany	German	42	45.3	Cervix	0.43	1	0.89 (0.65 to 0.99)	0.92 (0.73 to 0.99)
Kang, 2000 (34)	South Korea	English	46	54	Gastric	0.30	3	0.64 (0.35 to 0.87)	0.91(0.75 to 0.98)
Kaza, 2006 (35)	India	English	15	52	Gall bladder	0.33	—	0.60 (0.15 to 0.95)	0.90 (0.56 to 1.00)
Krupski, 2002 (36)	Germany	German	15	62.7	Esophagus	0.40	3	1.00 (0.54 to 1.00)	0.78 (0.40 to 0.97)
Kvistad, 2000 (3)	Norway	English	65	59.4	Breast	0.37	2	0.63 (0.41 to 0.81)	0.80 (0.65 to 91)
Low, 2003 (37)	United States	English	48	65	Colorectal	0.46	2	0.68 (0.45 to 0.86)	0.96 (0.80 to 1.00)
Wallengren, 1996 (38)	Sweden	English	10	69	Rectum	0.30	—	0.67 (0.09 to 0.99)	1.00 (59 to 1.00)
Einspieler, 1991 (39)	Austria	English	11	55	Head and neck	0.55	1	0.83 (0.36 to 1.00)	0.60 (0.15 to 0.95)
Hawighorst, 1998 (40)	Germany	English	33	55	Cervix	0.58	1	0.68 (0.43 to 0.87)	0.79 (0.49 to 0.95)
Hallscheidt, 1998 (41)	Germany	German	32	60	Renal cell	0.25	—	0.88 (0.47 to 1.00)	0.96 (0.79 to 1.00)
Kim, 2000 (42)	South Korea	English	217	NS	Rectum	0.49	2	0.85 (0.77 to 0.91)	0.41 (0.32 to 0.51)
Luciani, 2004 (4)	France	English	16	56.2	Breast	0.50	3	0.88 (0.47 to 1.00)	0.88 (0.47 to 1.00)
Sheu, 2001 (43)	Taiwan	English	41	56.6	Cervix	0.27	1	0.82 (0.48 to 0.98)	0.87 (0.69 to 0.96)
Vorreuther, 1990 (44)	Germany	German	36	NS	Renal cell	0.11	—	1.00 (0.40 to 1.00)	0.97 (0.84 to 1.00)
Manfredi, 2004 (45)	Italy	English	21	58.8	Endometrial	0.10	1	0.50 (0.01 to 0.99)	0.95 (0.74 to 1.00)
Murray, 2002 (46)	United Kingdom	English	47	63	Breast	0.21	3	1.00 (0.69 to 1.00)	0.54 (0.37 to 0.71)
Okizuka, 1996 (47)	Japan	English	32	65	Rectum	0.47	2	0.67 (0.38 to 0.88)	0.82 (0.57 to 0.96)
Oellinger, 2000 (5)	Germany	English	32	46.3	Cervix	0.41	2	0.38 (0.14 to 0.68)	0.89 (0.67 to 0.99)
Rockall, 2007 (19)	United Kingdom	English	50	61	Endometrial	0.18	1	0.44 (0.14 to 0.79)	0.98 (0.87 to 1.00)
Barentsz, 1996 (48)	The Netherlands	English	57	61	Urinary bladder	0.25	2	0.86 (0.57 to 0.98)	0.95 (0.84 to 0.99)
Ramsay, 2004 (49)	Australia	English	16	57	Pancreas	0.44	—	0.29 (0.04 to 0.71)	0.78 (0.40 to 0.97)
Hünerbein, 2000 (50)	Germany	English	27	65	Rectum	0.15	3	0.75 (0.19 to 0.99)	0.96 (0.78 to 1.00)
Matsuoka, 2003 (51)	Japan	English	19	62	Rectum	0.20	1	0.50 (0.01 to 0.99)	1.00 (0.63 to 1.00)
Tempany, 2000 (52)	United States	English	171	57	Ovarian	0.08	—	0.38 (0.14 to 0.68)	0.84 (0.77 to 0.89)
Thurnher, 1991 (53)	Switzerland	German	21	55	Cervix	0.43	3	0.67 (0.30 to 0.93)	0.92 (0.62 to 1.00)
Matsuoka, 2004 (54)	Japan	English	54	NS	Rectum	0.44	1	0.75 (0.53 to 0.90)	0.73 (0.54 to 0.88)
Medl, 1995 (55)	Austria	English	29	NS	Ovarian	0.41	1	0.50 (0.21 to 0.79)	0.94 (0.71 to 1.00)
Mumtaz, 1997 (56)	United Kingdom	English	75	49	Breast	0.53	3	0.90 (0.76 to 0.97)	0.83 (0.66 to 0.93)

* NS = not specified.

† 1 = studies that used a single malignancy criterion; 2 = studies that used multiple malignancy criteria without using contrast highlighting in their malignancy criteria; 3 = studies that used multiple malignancy criteria with contrast highlighting in their malignancy criteria; — = studies that did not specify the malignancy criterion used.

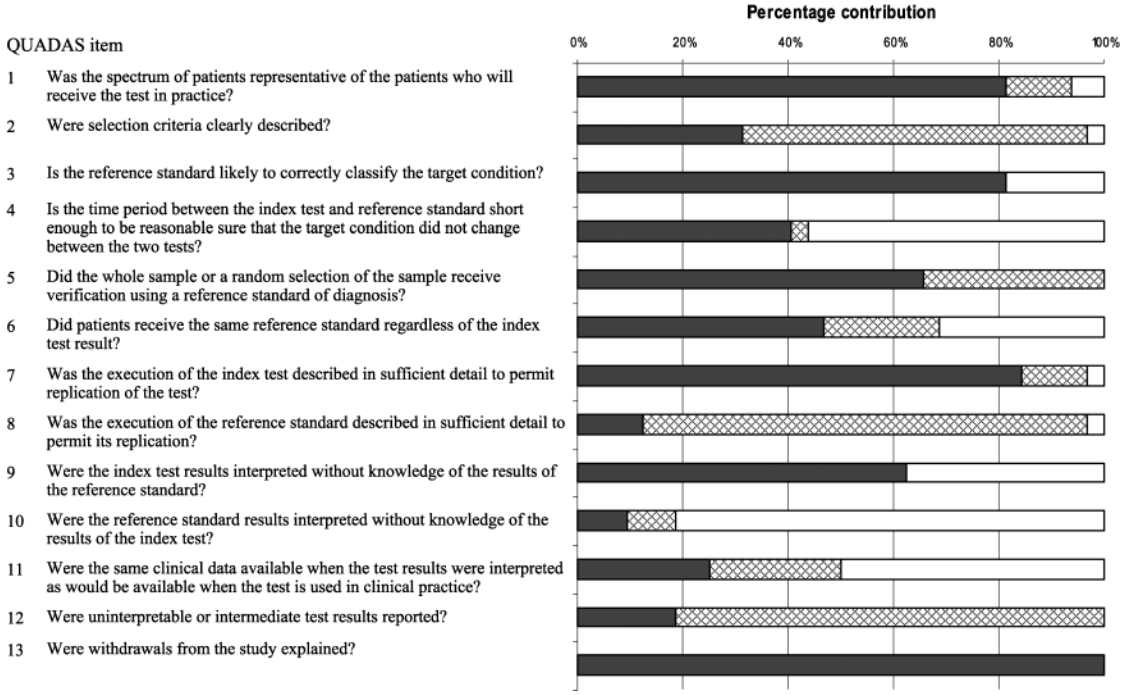

Figure 2. Scoring of the 32 studies that provided data on patient-level diagnosis for 13 relevant items included in the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria. The **black bars** indicate yes, **hatched bars** indicate no, and **white bars** indicate that the QUADAS item was not specified.

studies did not present their malignancy criterion and were therefore not included in this subgroup analysis.

Regarding the other covariates, five studies combined paraaortic and pelvic lymph node evaluation, which resulted in a lower estimate for sensitivity than the pooled sensitivity of the five studies that evaluated pelvic lymph nodes only (0.43 [95% CI = 0.30 to 0.57] vs 0.79 [95% CI = 0.67 to 0.88]). The sensitivity of gadolinium-enhanced MRI increased with increasing prevalence of disease, whereas the specificity declined (Table 2). In general, the sensitivity of gadolinium-enhanced MRI tended to be higher when no differential or partial verification was present. German-language studies had higher diagnostic accuracy estimates (sensitivity and specificity) than English-language studies (Table 2).

The regression test of the natural logarithm of the diagnostic odds ratio on the inverse of the effective sample size was statistically significant ($P = .04$). Figure 5 illustrates this test graphically, with the diagnostic odds ratio on the vertical axis and the inverse of the effective sample size on the horizontal axis. An intercept that is statistically significantly different from zero indicates the presence of small-study effects, that is, the tendency that smaller studies have higher diagnostic odds ratios than bigger studies. However, because in a diagnostic setting, there are many explanations other than publication bias for small-study effects, the borderline statistical significance should be interpreted with caution. According to the result of the regression test, however, publication bias cannot be ruled out.

Discussion

In this systematic review and meta-analysis, we investigated the diagnostic accuracy of gadolinium-enhanced MRI for the detection of lymph node metastases. Histopathologic examination of the lymph nodes was used as the reference test. We considered 43 studies for inclusion in the meta-analysis and quantified the pooled sensitivities and specificities of the 32 studies that provided data suitable for the meta-analysis. We found an overall pooled sensitivity of 0.72, with a specificity of 0.87. However, substantial between-study heterogeneity was present, particularly with regard to variation in the type and number of malignancy criteria that were used to stage the lymph nodes. In anticipation of this between-study heterogeneity, we defined a priori three subgroups of studies for analysis: those that used a single malignancy criterion, those that used multiple malignancy criteria (without including contrast enhancement), and those that used multiple malignancy criteria and included contrast enhancement. When multiple malignancy criteria were used together with contrast enhancement (ie, the third subgroup), the sensitivity of contrast-enhanced MRI in staging lymph node metastasis was 0.84, with a specificity of 0.82. A previous meta-analysis showed that the use of USPIO particles as a lymphotropic intravenous contrast agent to stage lymphatic metastases increased the diagnostic performance of MRI (6). However, USPIO administration has some clinical and logistical disadvantages (7–9). Another approach for lymph node imaging is positron emission tomography, which evaluates tissue functionality. The major limitation of positron emission tomography is its low spatial resolution. Although newly developed methods for conducting positron emission tomography and computed tomography have increased the resolution to 5 mm, small metastases are still being missed (18). Gadolinium-enhanced MRI does not have the limitations of either of these modalities. Imaging can be performed directly after gadolinium administration. Furthermore, gadolinium is approved for use in

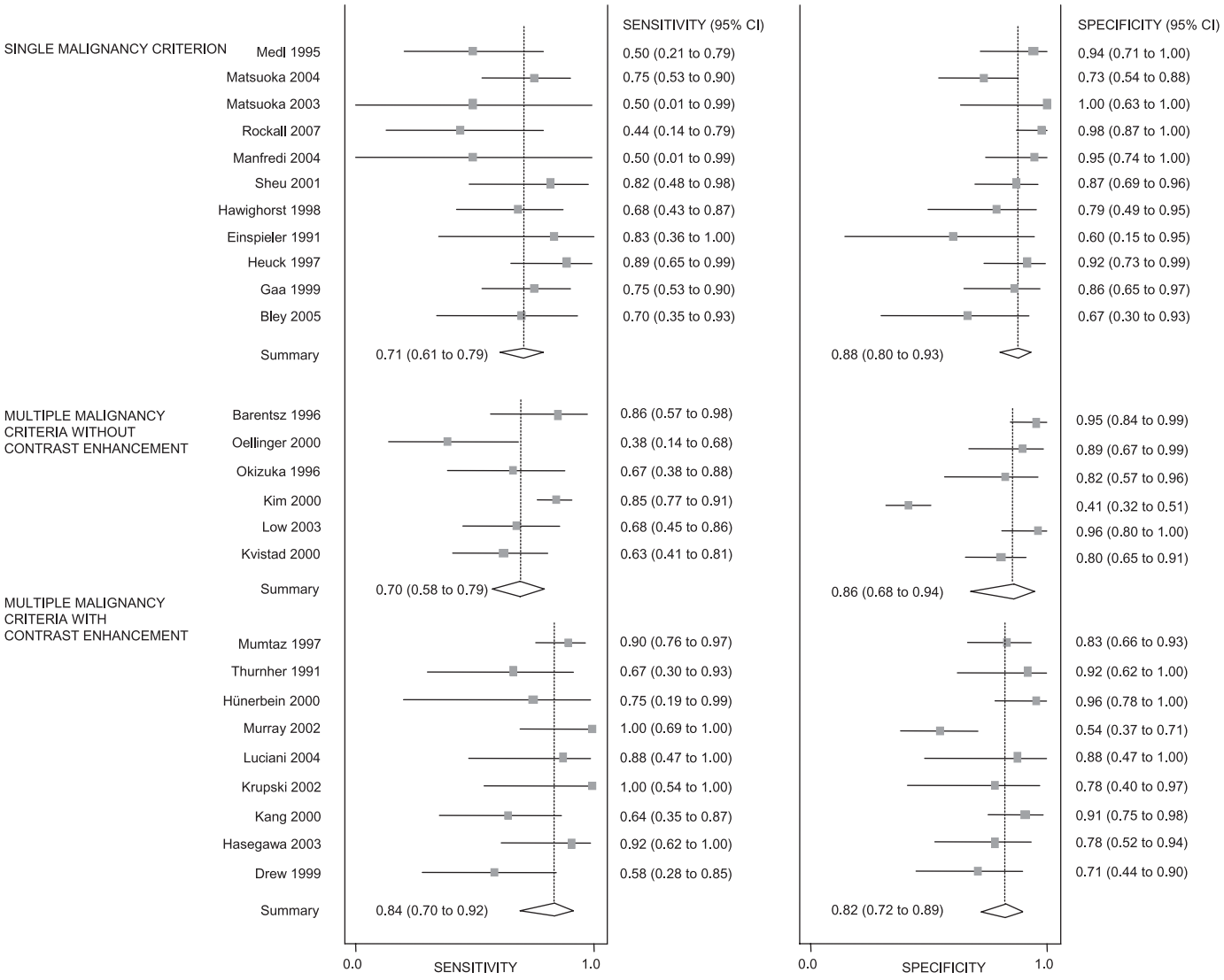

Figure 3. Forest plots of the sensitivity and specificity of magnetic resonance imaging in detecting lymphatic metastasis according to the type of malignancy criterion. The **squares** represent the estimated sensitivity and specificity, and the **horizontal lines** represent 95% confidence intervals, per included study. The **diamonds** represent the pooled sensitivities and specificities for the three subgroups of malignancy criteria.

Europe and the United States and is also commonly used for primary tumor visualization, requiring no need to administer additional contrast agents with potentially adverse effects. However, further research is needed to investigate the value of adding gadolinium-enhanced MRI to inexpensive and noninvasive diagnostic approaches.

This study has several limitations. First, we found that there was a considerable lack of reporting of diagnostic study quality items, particularly those involving the blinding of reviewers of the reference test to the index test and vice versa, the availability of clinical data when interpreting the index test, the length of time between the index test and the reference test, and on whether patients received the same reference test regardless of the index test result (QUADAS items 9, 10, 11, 4, and 6, respectively). This lack of reporting of diagnostic study quality items limited the information provided by our quality assessment and prevented us from conducting formal analyses based on the quality assessment items.

Second, for practical reasons, we included only studies that were written in German or English. We therefore may have missed relevant studies that were published in other languages, possibly introducing publication bias. The regression test for publication bias (or rather, for small-study effects) was indeed statistically significant, although this result only indicates that effects in small studies may be different from effects in larger studies. The regression test is sensitive to selective threshold effects that are likely to play a role in diagnostic datasets such as the one used in this study (23), and we therefore cannot attribute the small-study effects directly to publication-related factors.

Third, there are numerous contrast agents, doses, and administration routes of contrast agents used in MRI. We could not perform separate subgroup analyses because the majority of included studies (at least 27 of the 32 studies, Table 1) used gadolinium-diethylenetriamine penta-acetic acid as an intravenous contrast agent at a dosage of 0.1 mmol/kg body weight.

Table 2. Average sensitivity and specificity across the a priori–defined subgroups*

Study characteristic	No. of studies	Sensitivity (95% CI)	Specificity (95% CI)
Malignancy criterion†			
Single criterion	11	0.71 (0.61 to 0.79)	0.88 (0.80 to 0.93)
Multiple criteria without contrast enhancement	6	0.70 (0.58 to 0.79)	0.86 (0.68 to 0.94)
Multiple criteria with contrast enhancement	9	0.84 (0.70 to 0.92)	0.82 (0.72 to 0.89)
Partial verification			
No	15	0.75 (0.68 to 0.81)	0.83 (0.73 to 0.90)
Yes, partly, or not specified	17	0.68 (0.58 to 0.77)	0.89 (0.84 to 0.92)
Differential verification			
No	26	0.75 (0.67 to 0.81)	0.87 (0.81 to 0.92)
Yes, partly, or not specified	6	0.62 (0.47 to 0.75)	0.84 (0.78 to 0.88)
Blinding: index test to reference test			
Yes	20	0.74 (0.64 to 0.82)	0.87 (0.81 to 0.91)
No	0	ND	ND
Not specified	12	0.69 (0.59 to 0.78)	0.87 (0.76 to 0.94)
Blinding: reference test to index test			
Yes	3	ND	ND
No	3	ND	ND
Not specified	26	0.76 (0.69 to 0.82)	0.86 (0.80 to 0.91)
Lymph node regions‡			
Upper abdomen	7	0.71 (0.55 to 0.83)	0.89 (0.81 to 0.94)
Pelvic and para-aortic	5	0.43 (0.30 to 0.57)	0.92 (0.82 to 0.96)
Pelvic	5	0.79 (0.67 to 0.88)	0.90 (0.83 to 0.95)
Axilla	4	0.90 (0.62 to 0.98)	0.75 (0.61 to 0.85)
Regional rectum	8	0.71 (0.59 to 0.81)	0.87 (0.68 to 0.95)
Language			
German	6	0.83 (0.70 to 0.91)	0.92 (0.85 to 0.96)
English	26	0.69 (0.61 to 0.76)	0.85 (0.79 to 090)
Prevalence, %			
>50	5	0.79 (0.68 to 0.87)	0.80 (0.69 to 0.87)
>25–50	20	0.72 (0.64 to 0.79)	0.87 (0.80 to 0.91)
≤25	7	0.70 (0.37 to 0.90)	0.93 (0.79 to 0.98)

* CI = confidence interval; ND = not done.

† Six studies did not specify their malignancy criterion.

‡ Studies including lymph nodes located in the head and neck region or in the mediastinum were not taken into account in this subgroup analysis because no bivariate analysis could be performed on fewer than four studies.

Finally, in the overall analyses of the diagnostic accuracy of gadolinium-enhanced MRI for the detection of lymph node metastases, we pooled the studies irrespective of the primary tumor site, which was the same approach used by Will et al. (6) in a meta-analysis of the diagnostic precision of nanoparticle-enhanced MRI for lymph node metastases. Lymph node metastases derived from primary tumors may, to some extent, differ in their biological properties because of differences in the primary tumors. However, we believed that gadolinium-enhanced imaging of lymph node metastasis is equally effective over all body regions. Because our endpoint was the detection of lymph node metastases rather than evaluation of the primary tumor characteristics, we assumed that the primary tumor was less relevant to the actual performance of gadolinium-enhanced MRI in lymph node staging. Nevertheless, we also performed a subgroup analyses according to the anatomic region in which the harvested lymph nodes were located. Results of several regions were pooled (Table 2), and we found that different body regions showed differences with regard to the diagnostic performance of MRI. However, we do not believe that these differences are because of biological properties of the primary tumors but rather

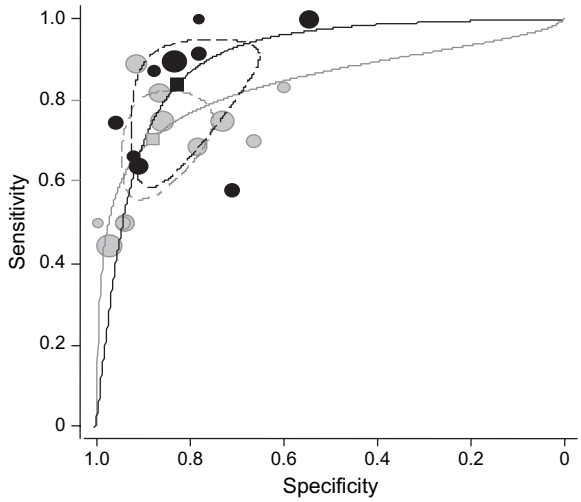

Figure 4. Summary receiver operating characteristic (ROC) curves from the bivariate analysis with 95% confidence region for nine studies that included contrast enhancement in their malignancy criteria and 11 studies that used a single malignancy criterion. **Black circles** represent studies that included contrast enhancement in their malignancy criteria. The **gray circles** represent studies that used a single malignancy criterion. The **size of the circles** indicates the weight of each study (ie, the number of patients included in the study). The **black and gray squares** represent the mean natural logarithm of the diagnostic odds ratios, and the **dotted black and gray lines** represent the corresponding 95% confidence intervals. Sensitivity is set on the *y*-axis, specificity on the *x*-axis. The **solid black and gray lines** represent the summary ROC curves.

to MRI quality aspects (eg, bowel movement disturbs magnetic resonance images more when evaluating regional rectal lymph nodes than when evaluating lymph nodes located in the axilla). Summarizing the diagnostic accuracy across cancer-specific sites was not possible because of the small number of studies per primary tumor.

In conclusion, the results of this meta-analysis suggest that contrast highlighting of lymph nodes should be included as a malignancy criterion when gadolinium contrast agent is used for primary tumor visualization. We further advocate the use of uniform malignancy criteria, including contrast enhancement, for standardization of future evaluations. Gadolinium enhancement by itself

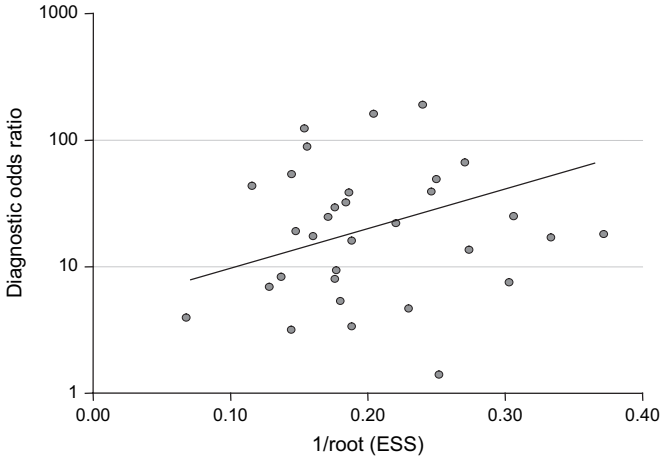

Figure 5. Funnel plot of the diagnostic odds ratio plotted on the *y*-axis against the reciprocal of effective sample size (ESS) plotted on the *x*-axis. The regression line is used as a measure of asymmetry. The **circles** represent the 32 included studies.

does not have the diagnostic accuracy to replace histopathologic examination of lymph nodes; however, it can help identify suspicious lymph nodes that should be surgically collected for histopathologic examination.

References

1. Haberal I, Celik H, Gocmen H, Akmansu H, Yoruk M, Ozeri C. Which is important in the evaluation of metastatic lymph nodes in head and neck cancer: palpation, ultrasonography, or computed tomography? *Otolaryngol Head Neck Surg.* 2004;130(2):197–201.
2. Singh K, Orakwue CO, Honest H, Balogun M, Lopez C, Luesley DM. Accuracy of magnetic resonance imaging of inguinal femoral lymph nodes in vulvar cancer. *Int J Gynecol Cancer.* 2006;16(3):1179–1183.
3. Kvistadt KA, Rydland J, Smethurst HB, Lundgren S, Fjosne HE, Haraldseth O. Axillary lymph node metastases in breast cancer: preoperative detection with dynamic contrast-enhanced MRI. *Eur Radiol.* 2000;10(9):1464–1471.
4. Luciani A, Dao TH, Lapeyre M, et al. Simultaneous bilateral breast and high-resolution axillary MRI of patients with breast cancer: preliminary results. *AJR Am J Roentgenol.* 2004;182(4):1059–1067.
5. Oellinger JJ, Blohmer JU, Michniewicz K, et al. Preoperative staging of cervical cancer: comparison of magnetic resonance imaging (MRI) and computed tomography (CT) with histologic results. *Zentralbl Gynakol.* 2000;122(2):82–91.
6. Will O, Purkayastha S, Chan C, et al. Diagnostic precision of nanoparticle-enhanced MRI for lymph-node metastases: a meta-analysis. *Lancet Oncol.* 2006;7(1):52–60.
7. Anzai Y, Piccoli CW, Outwater EK, et al. Evaluation of neck and body metastases to nodes with ferumoxtran 10-enhanced MR imaging: phase III safety and efficacy study. *Radiology.* 2003;228(3):777–788.
8. Sharma R, Saini S, Ros PR, et al. Safety profile of ultrasmall superparamagnetic iron oxide ferumoxtran-10: phase II clinical trial data. *J Magn Reson Imaging.* 1999;9(2):291–294.
9. Heesakkers RA, Hovels AM, Jager GJ, et al. MRI with a lymph-node-specific contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study. *Lancet Oncol.* 2008;9(9):850–856.
10. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. *Nat Rev Cancer.* 2003;3(6):453–458.
11. Lin SP, Brown JJ. MR contrast agents: physical and pharmacologic basics. *J Magn Reson Imaging.* 2007;25(5):884–899.
12. Degani H, Chetrit-Dadiani M, Bogin L, Furman-Haran E. Magnetic resonance imaging of tumor vasculature. *Thromb Haemost.* 2003;89(1):25–33.
13. Nunes LW, Schnall MD, Siegelman ES, et al. Diagnostic performance characteristics of architectural features revealed by high spatial-resolution MR imaging of the breast. *AJR Am J Roentgenol.* 1997;169(2):409–415.
14. Ersoy H, Rybicki FJ. Biochemical safety profiles of gadolinium-based extracellular contrast agents and nephrogenic systemic fibrosis. *J Magn Reson Imaging.* 2007;26(5):1190–1197.
15. Goyen M, Debatin JF. Gadopentetate dimeglumine-enhanced three-dimensional MR-angiography: dosing, safety, and efficacy. *J Magn Reson Imaging.* 2004;19(3):261–273.
16. Peters NH, Borel Rinkes I, Zuithoff NP, Mali WP, Moons KG, Peters PH. Meta-analysis of MR imaging in the diagnosis of breast lesions. *Radiology.* 2008;246(1):116–124.
17. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol.* 2003;3:25.
18. Kyzas PA, Evangelou E, axa-Kyza D, Ioannidis JP. 18F-Fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. *J Natl Cancer Inst.* 2008;100(10):712–720.
19. Rockall AG, Meroni M, Song S, et al. Evaluation of endometrial carcinoma on magnetic resonance imaging. *Int J Gynecol Cancer.* 2007;17(1):188–196.
20. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a general linear mixed model approach. *J Clin Epidemiol.* 2006;59(12):1331–1332.
21. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol.* 2005;58(10):982–990.
22. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539–1558.
23. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol.* 2005;58(9):882–893.
24. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol.* 2000;53(11):1119–1129.
25. Dwamena BA. *Midas: Computational and Graphical Routines for Meta-analytical Integration of Diagnostic Accuracy Studies in Stata.* Ann Arbor, MI: Division of Nuclear Medicine, Department of Radiology, University of Michigan Medical School; 2007.
26. Harbord RM. *Metandi: Stata Module for Meta-analysis of Diagnostic Accuracy.* Chestnut Hill, MA: Statistical Software Components, Boston College Department of Economics. Revised April 15, 2008. http://ideas.repec.org/c/boc/bocode/s456932.html. Accessed January 27, 2010.
27. Zamora J, Abraira V, Muriel A, Khan KS, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol.* 2006;6:31.
28. Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KGM. Development and validation of MIX: comprehensive free software for meta-analysis of causal research data. *BMC Med Res Methodol.* 2006;6:50.
29. Bley TA, Uhl M, Simon P, et al. Diagnostic accuracy of MRI for preoperative staging of pancreatic carcinoma: tendency for understaging. *In Vivo.* 2005;19(6):983–987.
30. Drew PJ, Farouk R, Turnball LW, Ward SC, Hartley JE, Monson JR. Preoperative magnetic resonance staging of rectal cancer with an endorectal coil and dynamic gadolinium enhancement. *Br J Surg.* 1999;86(2):250–254.
31. Gaa J, Wendl K, Tesdal IK, et al. Combined use of MRI and MR cholangiopancreatography and contrast enhanced dual phase 3-D MR angiography in diagnosis of pancreatic tumors: initial clinical results. *Rofo.* 1999;170(6):528–533.
32. Hasegawa I, Eguchi K, Kohda E, et al. Pulmonary hilar lymph nodes in lung cancer: assessment with 3D-dynamic contrast-enhanced MR imaging. *Eur J Radiol.* 2003;45(2):129–134.
33. Heuck A, Scheidler J, Kimmig R, et al. Lymph node staging in cervix carcinomas: the results of high-resolution magnetic resonance tomography (MRT) with a phased array body coil. *Rofo.* 1997;166(3):210–214.
34. Kang BC, Kim JH, Kim KW, et al. Value of the dynamic and delayed MR sequence with Gd-DTPA in the T-staging of stomach cancer: correlation with histopathology. *Abdom Imaging.* 2000;25(1):14–24.
35. Kaza RK, Gulati M, Wig JD, Chawla YK. Evaluation of gall bladder carcinoma with dynamic magnetic resonance imaging and magnetic resonance cholangiopancreatography. *Australas Radiol.* 2006;50(3):212–217.
36. Krupski G, Lorenzen J, Gawad K, Nicolas V, Izbicki JR, Adam G. MRI-based N-staging is esophageal cancer. *Rofo.* 2002;174(10):1269–1273.
37. Low RN, McCue M, Barone R, Saleh F, Song T. MR staging of primary colorectal carcinoma: comparison with surgical and histopathological findings. *Abdom Imaging.* 2003;28(6):784–793.
38. Wallengren NO, Holtas S, Yndren-Sandberg A. Preoperative staging of rectal carcinoma using double-contrast MR imaging. Technical aspects and early clinical experiences. *Acta Radiol.* 1996;37(5):791–798.
39. Einspieler R, Ebner F, Posawetz W, Ranner G, Fluckiger F, Lammer J. MR-imaging with Gd-DTPA in carcinomas of tongue, oro- and hypopharynx. *Eur J Radiol.* 1991;13(1):21–26.
40. Hawighorst H, Schoenberg SO, Knapstein PG, et al. Staging of invasive cervical carcinoma and of pelvic lymph nodes by high resolution MRI with phased-array coil in comparison with pathological findings. *J Comput Assist Tomogr.* 1998;22(1):75–81.
41. Hallscheidt P, Stolte E, Roeren T, Pomer S, Drehmer I, Kauffmann GW. The staging of renal-cell carcinomas in MRT and CT—a prospective histologically controlled study. *Rofo.* 1998;168(2):165–170.

42. Kim NK, Kim MJ, Park JK, Park SI, Min JS. Preoperative staging of rectal cancer with MRI: accuracy and clinical usefulness. *Ann Surg Oncol.* 2000;7(10):732–737.
43. Sheu MH, Chang CY, Wang JH, Yen MS. Preoperative staging of cervical carcinoma with MR imaging: a reappraisal of diagnostic accuracy and pitfalls. *Eur Radiol.* 2001;11(9):1828–1833.
44. Vorreuther R, Krestin GP, Franzen W, Engelking R, Friedmann G. Clinical value of new rapid nuclear magnetic resonance tomography in preoperative assessment of hypernephroma. A prospective comparative study of CT and MR. *Urologe A.* 1990;29(1):39–42.
45. Manfredi R, Mink P, Maresca G, et al. Local-regional staging of endometrial carcinoma: role of MR imaging in surgical planning. *Radiology.* 2004; 231(2):372–378.
46. Murray AD, Staff RT, Redpath TW, et al. Dynamic contrast enhanced MRI of the axilla in women with breast cancer: comparison with pathology of excised nodes. *Br J Radiol.* 2002;75(891):220–228.
47. Okizuka H, Sugimura K, Yoshizako T, Kaji Y, Wada A. Rectal carcinoma: prospective comparison of conventional and gadopentetate dimeglumine enhanced fat-suppressed MR imaging. *J Magn Reson Imaging.* 1996;6(3): 465–471.
48. Barentsz JO, Jager GJ, van Vierzen PB, et al. Staging urinary bladder cancer after transurethral biopsy: value of fast dynamic contrast-enhanced MR imaging. *Radiology.* 1996;201(1):185–193.
49. Ramsay D, Marshall M, Song S, et al. Identification and staging of pancreatic tumours using computed tomography, endoscopic ultrasound and mangafodipir trisodium-enhanced magnetic resonance imaging. *Australas Radiol.* 2004;48(2):154–161.
50. Hünerbein M, Pegios W, Rau B, Vogl TJ, Felix R, Schlag PM. Prospective comparison of endorectal ultrasound, three-dimensional endorectal ultrasound, and endorectal MRI in the preoperative evaluation of rectal tumors. Preliminary results. *Surg Endosc.* 2000;14(11):1005–1009.
51. Matsuoka H, Nakamura A, Masaki T, et al. Comparison between endorectal coil and pelvic phased-array coil magnetic resonance imaging in patients with anorectal tumor. *Am J Surg.* 2003;185(4):328–332.
52. Tempany CM, Zou KH, Silverman SG, Brown DL, Kurtz AB, McNeil BJ. Staging of advanced ovarian cancer: comparison of imaging modalities—report from the Radiological Diagnostic Oncology Group. *Radiology.* 2000;215(3):761–767.
53. Thurnher S, McPhillips M, von Schulthess GK, Marincek B. Cervical carcinoma staging with magnetic resonance tomography: the use of gadolinium-DOTA with 31 patients. *Rofo.* 1991;154(6):643–649.
54. Matsuoka H, Masaki T, Sugiyama M, et al. Gadolinium enhanced endorectal coil and air enema magnetic resonance imaging as a useful tool in the preoperative examination of patients with rectal carcinoma. *Hepatogastroenterology.* 2004;51(55):131–135.
55. Medl M, Kulenkampff KJ, Stiskal M, Peters-Engl C, Leodolter S, Czembirek H. Magnetic resonance imaging in the preoperative evaluation of suspected ovarian masses. *Anticancer Res.* 1995;15(3): 1123–1125.
56. Mumtaz H, Hall-Craggs MA, Davidson T, et al. Staging of symptomatic primary breast cancer with MR imaging. *AJR Am J Roentgenol.* 1997; 169(2):417–424.
57. Krestin GP, Gross-Fengels W, Marincek B. The importance of magnetic resonance tomography in the diagnosis and staging of renal cell carcinoma. *Radiologe.* 1992;32(3):121–126.
58. Choi SH, Kim SH, Choi HJ, Park BK, Lee HJ. Preoperative magnetic resonance imaging staging of uterine cervical carcinoma: results of prospective study. *J Comput Assist Tomogr.* 2004;28(5):620–627.
59. van den Brekel MW, Castelijns JA, Croll GA, et al. Magnetic resonance imaging vs palpation of cervical lymph node metastasis. *Arch Otolaryngol Head Neck Surg.* 1991;117(6):663–673.
60. Kim SH, Kim SC, Choi BI, Han MC. Uterine cervical carcinoma: evaluation of pelvic lymph node metastasis with MR imaging. *Radiology.* 1994; 190(3):807–811.
61. Wide JM, White DW, Woolgar JA, Brown JS, Vaughan ED, Lewis-Jones HG. Magnetic resonance imaging in the assessment of cervical nodal metastasis in oral squamous cell carcinoma. *Clin Radiol.* 1999;54(2):90–94.
62. Steinkamp HJ, Heim T, Schubeus P, Schorner W, Felix R. The magnetic resonance tomographic differential diagnosis between reactively enlarged lymph nodes and cervical lymph node metastases. *Rofo.* 1992;157(4): 406–413.
63. Yang WT, Lam WW, Yu MY, Cheung TH, Metreweli C. Comparison of dynamic helical CT and dynamic MR imaging in the evaluation of pelvic lymph nodes in cervical carcinoma. *AJR Am J Roentgenol.* 2000;175(3): 759–766.
64. Kato M, Saji S, Kanematsu M, et al. Detection of lymph-node metastases in patients with gastric carcinoma: comparison of three MR imaging pulse sequences. *Abdom Imaging.* 2000;25(1):25–29.
65. Takashima S, Sone S, Takayama F, et al. Papillary thyroid carcinoma: MR diagnosis of lymph node metastasis. *AJNR Am J Neuroradiol.* 1998; 19(3):509–513.
66. Wang Q, Takashima S, Fukuda H, Takayama F, Kobayashi S, Sone S. Detection of medullary thyroid carcinoma and regional lymph node metastases by magnetic resonance imaging. *Arch Otolaryngol Head Neck Surg.* 1999;125(8):842–848.
67. Crisci R, Di CE, Lupattelli L, Coloni GF. MR study of N2 disease in lung cancer: contrast-enhanced method using gadolinium-DTPA. *Eur J Cardiothorac Surg.* 1997;11(2):214–217.

Funding

The authors received no external funding for this study.

Notes

W. M. Klerkx, P. H. M. Peeters, K. G. M. Moons, and L. Bax participated in the conception and design of the study. W. M. Klerkx, W. B. Veldhuis, L. Bax, K. G. M. Moons, and P. H. M. Peeters participated in the extraction, interpretation, and statistical analysis of the data. W. M. Klerkx, P. H. M. Peeters, K. G. M. Moons, L. Bax, W. PThM. Mali, A. P. M. Heintz, and W. B. Veldhuis participated in revising the manuscript critically for important intellectual content. W. M. Klerkx, L. Bax, A. P. M. Heintz, W. PThM. Mali, and P. H. M. Peeters provided administrative support. All authors approved the final version. This study was a literature-based study and as such no ethical approval was required. None of the authors report conflicts of interest in terms of financial and personal relationships with people or organizations that could inappropriately influence this work. All authors had access to the raw (study level) data. The authors take responsibility for all aspects of the study, including design, data acquisition, analysis, interpretation, and drafting of the article. The corresponding author had the final responsibility to submit the manuscript for publication.

Affiliations of authors: Department of Gynecology and Obstetrics (WMK, APMH), Department of Radiology (WBV, WPThMM) and Julius Center for Health Sciences and Primary Care (LB, PHMP, KGMM), University Medical Center Utrecht, Utrecht, the Netherlands; Kitasato Clinical Research Center, Kitasato University, Sagamihara, Japan (LB).