Diagnostic performance of USPIO-enhanced MRI for lymph-node metastases in different body regions: a meta-analysis
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CRD summary
This review concluded that ultra-small superparamagnetic iron oxide contrast-enhanced (USPIO-enhanced) magnetic resonance imaging (MRI) had better diagnostic performance than non-enhanced MRI, and had high sensitivity and specificity for the detection of lymph-node metastases. These conclusions reflect the data presented and are likely to be reliable, despite some limitations in the methods of analysis.

Authors' objectives
To assess the performance of USPIO-enhanced MRI for the detection of lymph-node metastases in different regions of the body.

Searching
PubMed and EMBASE were searched without restrictions to April 2009. Search terms were reported. The bibliographies of included studies and review articles were screened for additional studies.

Study selection
Studies of USPIO-enhanced MRI for the detection of lymph-node metastases, which used pathological examination as the reference standard, were eligible for inclusion.

Studies were published between 1994 and 2008. Where reported, the median age of study participants ranged from 35 to 75 years. Most included studies used 1.5T MRI, a contrast agent dose of 2.6mg Fe/kg and imaged between 24 and 36 hours post-contrast. The area imaged varied between studies and included: pelvis; head and neck; thorax; axilla; neck and body; body; abdomen; and abdomen and pelvis. Participants had various primary tumours, such as head and neck cancer, breast cancer and prostate cancer.

Two reviewers assessed studies for inclusion and any disagreements were resolved by discussion.

Assessment of study quality
The methodological quality was assessed using the 14-item Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool and the 25-item Standards for Reporting of Diagnostic Accuracy (STARD) statement. Both assessments were reported as an overall score (maximum 14 QUADAS and 25 STARD).

Two reviewers independently assessed study quality and any disagreements were resolved by discussion.

Data extraction
Data were extracted to calculate per lymph-node and per patient sensitivity and specificity of USPIO-enhanced MRI for the detection of metastases, with 95% confidence intervals (CIs), for each included study. Data were also extracted for non-enhanced MRI and for post-contrast MRI alone.

Two reviewers independently extracted data and any disagreements were resolved by discussion.

Methods of synthesis
Pooled estimates of the per lymph-node and per patient sensitivity, specificity and diagnostic odds ratio (DOR) of USPIO-enhanced MRI, with 95% confidence intervals, were calculated using a random-effects model. Pooled estimates of sensitivity and specificity were also calculated for non-enhanced MRI and for post-contrast MRI alone. Summary receiver operator characteristic (SROC) curves were generated using the Moses and Littenberg model.

Between-study heterogeneity was assessed using $X^2$ and $I^2$. Regression analysis was used to investigate the effects of potential sources of heterogeneity on test performance. Univariate analyses were conducted for quality score, whether more than 100 nodes were assessed, 1.5T MRI scanners, USPIO dose and year of publication. Explanatory variables
(p<0.05) were entered in a multivariable regression model, which used a backwards stepwise algorithm. The following subgroup analyses were also performed: studies with a QUADAS score of 11 or greater; studies that used 1.5T MRI; studies that used 1.7 or 2.6mg/kg contrast agent; studies that assessed more than 100 nodes; studies that analysed different body regions (such as, head and neck, pelvis, axilla); studies that were published after 2004.

Results of the review

Thirty four studies, with a total of 1,342 patients and 6,019 lymph nodes, were included in the review. QUADAS scores ranged from 7 to 13 and STARD scores ranged from 11 to 2.

The pooled, per lymph-node, estimate of the sensitivity of USPIO-enhanced MRI for the detection of metastases was 90% (95% CI 88 to 91%) and specificity was 96% (95% CI 95 to 97%) with 30 studies. The P value for sensitivity was 62.1% and specificity was 89.9%. The pooled DOR was 162.28 (95% CI 91.82 to 286.81).

The pooled, per patient, estimate of the sensitivity of USPIO-enhanced MRI for the detection of metastases was 89% (95% CI 84 to 92%) and specificity was 89% (95% CI 86 to 91%) with 14 studies. The P value for sensitivity was 66.7% and specificity was 69.4. The pooled DOR was 36.11 (95% CI 15.89 to 82.06).

The pooled estimate of the sensitivity of non-enhanced MRI for lymph-node metastases was 39% (95% CI 34 to 43%) and specificity was 90% (95% CI 89 to 91%). The P value for sensitivity was 82.1% and specificity was 93.6%. The pooled DOR was 5.81 (95% CI 3.64 to 9.82).

The pooled estimate of sensitivity of post-contrast MRI alone for the detection of lymph node metastases was 85% (95% CI 81 to 88%) and specificity was 93% (95% CI 91 to 95%). The P value for sensitivity as 80.0% and specificity was 60.4%. The pooled DOR was 76.92 (95% CI 34.21 to 172.93).

Multivariable regression analysis indicated that study quality and number of nodes assessed were associated with increased DOR, and contrast-agent dose was associated with decreased DOR. The results of all subgroup analyses were also reported.

Authors’ conclusions

Ultra-small superparamagnetic iron oxide contrast-enhanced (USPIO-enhanced) magnetic resonance imaging-enhanced (MRI) had better diagnostic performance than conventional MRI, and had high sensitivity and specificity for the detection of lymph-node metastases.

CRD commentary

The article provided a clearly stated objective and defined inclusion criteria for the index test, reference standard and target condition. All included studies were published in English, but language of publication did not appear to have been inclusion/exclusion criteria and searches were reported as unrestricted. Measures to minimise error and/or bias were applied throughout the review process. The methodological quality of included studies was assessed, but this assessment used STARD in addition to the QUADAS tool; STARD was a guideline for the reporting of tests accuracy studies and was not intended for use as a quality assessment tool. In addition, both assessments were reported as overall scores, a practice which reduced the informative value of the assessment and was not recommended.

The effect of methodological quality on test performance was assessed using regression analyses, but the nature of the quality variable (for example whether a threshold was used to define higher quality studies) and the direction of the effect (such as whether higher or lower quality scores associated with increasing DOR) were not clear. The meta-analytic methods were broadly appropriate, but the validity of using a simple random-effects model to generate pooled estimates of sensitivity and specificity from heterogeneous data was questionable. The use of bivariate of hierarchical SROC models is now widely recommended for the generation of both SROC curves and summary measures. Despite some limitations in the methods of analysis, the authors’ conclusions reflect the data presented and are likely to be reliable.

Implications of the review for practice and research

Practice: The authors did not specify any recommendations for clinical practice.

Research: The authors stated that future studies should include a direct comparison between dual positron emission
tomography with computed tomography and USPIO-enhanced MRI. They further stated that comparative studies were necessary to demonstrate a possible benefit of USPIO-enhanced MRI for diagnosing lymph-node metastases, staging and treatment. Further recommendations were comparison of diagnostic performance of 1.5 and 3.0T MRI and cost-effectiveness analyses.

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