MRI in suspected appendicitis

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THESIS SUMMARY
AND FUTURE PERSPECTIVES
THESIS SUMMARY

This thesis focuses on the optimisation of imaging in patients with suspected appendicitis, exploring the use of magnetic resonance imaging (MRI). It comprises the results of the OPTIMAP study (OPTimisation of IMaging APpendicitis) and the RADIANCE study (Research in Acute appendicitis and mAGnetic resonANCE imaging).

In Chapter 1 we describe the design and rationale of the OPTIMAP study. MRI is an unexplored modality in patients with suspected appendicitis. We hypothesized that MRI, if sufficiently accurate, could replace CT and obviate the risk of contrast allergy and cancer induction caused by exposure to contrast medium and ionizing radiation. We designed a multicenter diagnostic accuracy study that included 230 adults with suspected appendicitis in the emergency department of six hospitals. All patients underwent ultrasound, CT (in case of negative or inconclusive ultrasound results) and MRI within two hours of presentation. A final diagnosis was assigned by an expert panel, based on all available information including 3-months follow-up, and used as the clinical reference standard in estimating accuracy.

Previous to the start of the OPTIMAP study, inexperienced readers were trained to evaluate acute appendicitis on MRI. The results are reported in Chapter 2. Nine radiologists and eight radiological residents were trained with a set of 100 abdominal MRI’s of patients with suspected appendicitis and received direct feedback. Between the first and last 25 cases they were able to improve their average sensitivity in detecting acute appendicitis from 82% to 92% ($p = 0.003$) at specificities of 82% and 88% ($p = 0.10$). Evaluation of diffusion weighted images in addition to conventional sequences (HASTE and True FISP) significantly increased MRI sensitivity for acute appendicitis. Radiologists and residents performed equally well in the evaluation of acute appendicitis in abdominal MRI after training. Reading times of radiologists and residents in reading MRI for acute appendicitis decreased significantly after training. We concluded that MRI training with direct feedback improves the diagnostic accuracy of inexperienced readers in the evaluation of acute appendicitis in abdominal MRI.

In Chapter 3 we compare imaging strategies with ultrasound, CT and MRI in 230 adult patients with suspected appendicitis, who were included in the OPTIMAP study. This fully paired diagnostic accuracy study showed that MRI based strategies have a diagnostic accuracy that is equivalent to that of a conditional CT strategy in patients with suspected acute appendicitis. MRI was shown to have a sensitivity of 97% (95% confidence interval 92-99%) at a specificity of 93% (95% confidence interval 87-97%) for acute appendicitis. A strategy with conditional MRI after negative or inconclusive US had a sensitivity of 98% (95% CI: 94-100%) and a specificity of 88% (81-93%). The reference strategy with conditional CT after negative or inconclusive ultrasound had a sensitivity of 97% (95% CI: 93-99%) at a specificity of 91% (95% CI: 84-95%). The accuracy of conditional or immediate MRI is similar to that of conditional CT in patients with suspected appendicitis. We concluded that MRI can replace CT in the diagnostic work-up of suspected acute appendicitis without compromising diagnostic accuracy.

We compared the results of expert reading in the 223 MRI’s performed in the OPTIMAP study to the reading of radiologists with less experience in Chapter 4. The estimated sensitivity of MRI for acute appendicitis, when read by non-expert radiologists, trained with 100
abdominal MRI’s, was 89%. This was significantly lower than the sensitivity of the experts: 97% ($p = 0.01$). Non-expert radiologists had a significantly lower sensitivity for ‘all urgent diagnoses’ compared to expert reading (84% versus 95%, $p < 0.001$). Although their diagnostic accuracy was lower compared to expert reading, a good agreement between non-expert radiologists and expert reading was observed. Non-expert radiologists agreed with expert reading on acute appendicitis in 89% of MRI’s in patients with suspected appendicitis, with a kappa value of 0.78. The observed agreement for ‘all urgent diagnoses’ between non-expert radiologists and expert reading was 83%, with a kappa value of 0.63. From this we concluded that non-expert radiologists reached good agreement with expert reading on urgent diagnoses in MRI for suspected appendicitis, although their sensitivity was significantly lower.

In Chapter 5 we identified MRI features associated with appendicitis based on expert reading of the 223 MRI’s of the OPTIMAP study. The following features were positively associated with appendicitis in MRI: an enlarged appendix (>7mm), peri-appendiceal fat infiltration, peri-appendiceal fluid, appendicolith, destruction of the appendiceal wall, absence of gas in the appendix, restricted diffusion of the appendiceal wall, the appendiceal lumen and focal fluid collections. MRI features that were significantly associated with acute appendicitis after multivariable logistic regression analysis were: an enlarged appendix (>7mm), peri-appendiceal fat infiltration and restricted diffusion of the appendiceal wall. Presence of these three features in a MRI examination leads to an appendicitis probability of 96%, whereas absence of these features almost rules appendicitis out (2%). Incorporating these three features in the evaluation of abdominal MRI in daily practice can help radiologists to increase their performance in diagnosing acute appendicitis.

Discrimination between simple and perforated appendicitis is relevant for triage and timing of emergency interventions and the success of conservative (antibiotic) treatment of simple acute appendicitis. In Chapter 6 we evaluated the diagnostic accuracy of MRI in detecting perforated appendicitis, and compared it to ultrasound with conditional CT, in patients with suspected appendicitis included in the OPTIMAP study. MRI was unable to accurately discriminate between simple and perforated appendicitis. It performed similarly poor compared to the conditional CT protocol. MRI would miss 43% of patients with perforated appendicitis; the conditional CT protocol would miss 52%. Although the investigated imaging strategies can adequately detect appendicitis, the accuracy of discrimination between simple and perforated appendicitis is unsatisfactory.

In Chapter 7 a simple clinical decision model to rule out appendicitis was developed in patients with negative or equivocal ultrasound results. It was developed in 422 patients with suspected appendicitis (OPTIMA study) and validated in 211 others (OPTIMAP study). The clinical decision rule selected patients for discharge and re-evaluation next day if less than two of the following predictors were present: male gender, migration of pain to the right lower quadrant, vomiting and white blood cell count above $12.0 \times 10^9/L$. This decision rule significantly reduced the probability of appendicitis in a large subgroup of patients with negative or inconclusive ultrasound results. This could assist in lowering the number of imaging investigations in patients with suspected appendicitis without compromising safety.

The results of the RADIANCE study (Research in Acute appendicitis and mAgnetic resonaNCE imaging) are described in Chapter 8. In this comparative single center diagnostic
accuracy study three imaging strategies were compared in 104 children with suspected appendicitis: (1) ultrasound only, (2) conditional MRI after negative or inconclusive ultrasound, and (3) MRI only. MRI only and conditional MRI after negative or inconclusive ultrasound had a higher sensitivity than ultrasound only in children with suspected acute appendicitis, while specificity was comparable. The positive predictive value of ultrasound was comparable to that of MRI, so a strategy wherein ultrasound is the first step, followed by MRI in case of negative or inconclusive findings, seems attractive in children. The tolerance of ultrasound and MRI was comparable and there was no significant difference in preference for either technique.

FUTURE PERSPECTIVES

Implementation
The findings described in this thesis support a wider adoption of MRI for the evaluation of patients with clinically suspected appendicitis. The major benefit of MRI compared to CT is that patients are not exposed to ionizing radiation and iodinated contrast medium. The use of low-dose CT protocols has been investigated in recent studies, but such an imaging strategy does not rule out the risks of ionizing radiation completely. As the availability of and expertise with MRI increases, implementation of this examination in the diagnostic work-up of patients with suspected appendicitis can be considered in more and more hospitals. The choice between diagnostic modalities is now based on local logistics, availability, experience and preference of the radiologists, costs, risks of radiation exposure, contrast induced nephropathy and allergy. Clinicians and radiologists can be reluctant to replace existing protocols for a new imaging strategy including MRI. MR images of the acute abdomen are considered difficult to interpret by both radiologists and surgeons. Another hindrance is that in most hospitals, the operational availability of MRI within and outside office hours seems insufficient to perform MRI in the diagnostic work-up of patients with clinically suspected appendicitis. However, introduction of MRI was possible in the participating hospitals of the OPTIMAP study. Some practical recommendations to facilitate the introduction of MRI were applied: adding emergency slots to the MRI planning that can be filled with urgent investigations, to increase availability during office hours, involving radiographers in the implementation of MRI to create support in the radiological department, and teaching this examination to all radiographers to increase availability after hours. The protocol of an MRI abdomen is relatively simple and the controlling of the equipment is made easier with each new generation of MRI scanners.

Further research
The OPTIMAP study did not compare the effects between different imaging strategies on patient outcomes directly, because patients were all managed based on the results of ultrasound and CT. This could be investigated in a study that randomly allocates patients to CT or MRI after inconclusive or negative ultrasound. However, such a study would also require a large sample size, because the results of MRI were concordant with that of the conditional CT strategy in most cases.

The accuracy for several urgent diagnoses other than appendicitis was high in the OPTIMAP study. Because the OPTIMAP study included only patients with suspected appendicitis a
limited number of patients with urgent diagnoses other than appendicitis was available. As a consequence, we were unable to estimate the accuracy of these diagnoses with sufficient precision. Because of the absence of ionizing radiation, an imaging strategy with MRI can be especially profitable in all children and young adults with acute abdominal pain. It would be contributive to further study the role of MRI in patients with acute abdominal pain in general and not only those suspected of appendicitis. A study with a design similar to that of the OPTIMAP study (with MRI besides ultrasound and CT) in consecutive patients with acute abdominal pain would give a better assessment of the accuracy of MRI for various acute abdominal pathology such as diverticulitis, cholecystitis, urological and gynecological disorders. Such a project would require a large number of patients.

The accuracy of MRI and other imaging modalities are insufficient to reliably discriminate between perforated and simple appendicitis, as was shown in Chapter 6 of this thesis. This implicates that adequate selection of patients with simple appendicitis for possible conservative therapy is likely to fail. Even though perforated appendicitis can also be treated non-operatively, the complication rate is to be higher than in simple appendicitis, and appendectomy is the standard treatment at present. Further studies should focus on the exploration of the combination of predictive clinical and imaging features that allow improvement in patient selection for antibiotic treatment. The effectiveness and safety of antibiotic treatment in simple appendicitis, if accurately identified, needs to be determined in new randomized studies.

An important topic that was not included in this thesis is a full economic evaluation of the proposed imaging strategies. Previous studies have already shown that the application of diagnostic imaging, with ultrasound and CT, in selected patients with suspected acute appendicitis is cost-effective. These analyses need to be extended to imaging strategies including MRI. The estimates for this economic evaluation could be based on a well-designed empirical study, taking into account not only the costs of the imaging modalities, but also costs of missed diagnoses, unnecessary surgical explorations, costs associated with CT cancer induction and radiation induced death, as well as the effects on patient outcome.

Although the research reported in this thesis has shown that MRI has a high diagnostic accuracy for suspected appendicitis in adults and children, confirming its potential to replace CT, a full and quantitative description of the benefits, effectiveness and clinical utility of MRI based strategies will only become apparent from such comprehensive comparative evaluations.