MRI in suspected appendicitis
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INTRODUCTION AND OUTLINE OF THESIS
INTRODUCTION

Clinical diagnosis of acute appendicitis

A classical presentation of acute appendicitis includes pain migration to the right lower abdomen, abdominal rigidity and elevated inflammatory parameters. The combination of these clinical features is very predictive in young males (positive predictive value of 100%). However, such a presentation is rare. It is only present in 6% of all patients with suspected appendicitis, and the diagnosis of appendicitis is more difficult in the majority of patients.

In the past only clinical evaluation was used to evaluate patients with suspected appendicitis, but this is imperfect. The threshold to refer for an appendectomy was low, since a missed appendicitis, and the associated perforation risk, were considered to be more harmful than a negative appendectomy. As a consequence, negative appendectomy rates up to 40% have been reported in the past. Yet unnecessary surgical exploration is not without downsides. It carries an increased risk of mortality, of prolonged hospital stay, and of wound infections.

Based on clinical evaluation only, one misses approximately twelve percent of patients with appendicitis. Such a missed diagnosis results in a treatment delay, and an increased risk of perforation. Perforated appendicitis is associated with higher mortality and morbidity rates. For both these reasons – negative appendectomy rates and missed appendicitis cases – imaging has become widely used in first world countries to aid the clinical evaluation of acute abdominal pain.

Ultrasound

Ultrasound was introduced as one of the first modalities to evaluate patients with suspected appendicitis. Puylaert et al. described the graded compression technique to detect appendicitis in 1986. With this technique the transducer is gently pushed into the indicated painful location of the abdomen. Overlying bowel structures that block the ultrasound are displaced or compressed so that the appendix can be visualized.

A normal appendix can be visualized with ultrasound at the base of the cecum, as a blind-ended compressible tubular structure (A) with a wall of 2 mm or below and a diameter ≤ 6-7 mm. In case of appendicitis a non-compressible, enlarged, blind ending structure is visualized (B,C).
The following features indicate an inflamed appendix in ultrasound: transducer tenderness, a diameter over 6mm, non-compressibility, presence of an appendicolith, peri-appendiceal fat infiltration, peri-appendiceal free fluid and increased flow in Doppler. The combination of transducer tenderness, a thickened appendix and peri-appendiceal fat infiltration had the highest probability of appendicitis in a study by van Randen et al.

The main advantage of an ultrasound examination is that it is widely available, relatively inexpensive, and safe. Several meta-analyses have been performed to estimate the accuracy of ultrasound; the most recent of these reported a sensitivity of 78% and a specificity of 83%.

Low sensitivity is the main disadvantage of ultrasound; there are many missed cases because a negative or inconclusive ultrasound does not rule out appendicitis entirely. Sometimes the appendix cannot be visualized due to overlying gas in a distended bowel, the surplus of subcutis of obese patients, or the position of the appendix. In some cases a perforated appendix can be misinterpreted as an healthy appendix due to decompression of the perforated lumen. Another disadvantage is that ultrasound is operator dependent.

**Computed tomography**

A more accurate modality is computed tomography (CT). This modality is now widely used for the diagnosis of appendicitis, especially in the United States. A standard protocol as recommended by most guidelines is one with intravenous contrast material, thin slices of 3 mm and coverage of the entire abdomen (because of the variability of position of the appendix, but also to diagnose alternative diagnoses). Most CT scan protocols have a radiation dose of approximately 8-10 mSv per abdominal scan. Recent studies report promising results on the diagnostic accuracy acute abdominal conditions of scan protocols at lower radiation levels.

Classic CT findings strongly associated with appendicitis are a completely visualized appendix, a thickened appendix, peri-appendiceal fat infiltration or fat stranding, presence of an appendicolith and appendiceal enhancement. Presence of only two of these features would give a probability for appendicitis of 89%. Absence of these features almost rules appendicitis out.
The main advantage of CT is its high diagnostic accuracy for appendicitis and other diagnoses. A recent meta-analysis estimated CT sensitivity at 91%, with a specificity of 90%, an accuracy considerably higher than that of ultrasound. A major disadvantage of CT is cancer risk associated with ionizing radiation. This negative effect of CT was suggested by Brenner in 2001, based on calculations of survivors of the atomic bombings in Hiroshima and Nagasaki. The estimated lifetime cancer risk due to ionizing radiation is age dependent; An abdominal CT in a 25 year old patient would cause cancer in one out of 900 patients and fatal cancer in one out of 1800 patients. This cancer risk decreases with age, but the exact risk of inducing malignancies from ionizing radiation remains a matter of debate. Some argue that the results of exposure to doses of more than 100mSv in the Japanese atomic bomb survivors cannot be simply extrapolated to patients undergoing CT. Despite this debate, one can say that it is probable that excessive exposure to ionizing radiation leads to an increased risk of malignancies. There is also a growing public awareness about this issue, which puts pressure on radiologists and medical physicists, encouraging them to reduce CT radiation exposure whenever possible, and to explore alternatives. A reduction of the radiation can be achieved by selective use of CT, or by using a lower radiation dose. There are also risks associated with the iodine contrast material that is used intravenously in the standard CT protocol. It has been associated with nephrotoxicity and allergic reactions.

Current imaging strategy

The combination of a careful medical history and physical examination is the cornerstone of diagnosing acute appendicitis. Imaging can improve diagnostic accuracy in patients in whom acute appendicitis is suspected after clinical evaluation. Several studies, including two randomised controlled trials, have shown that routine imaging has a positive effect on patient outcomes in patients with suspected appendicitis, compared to selective use of imaging. Despite these findings, some members of the surgical community remain reluctant to add imaging as a standard element to the clinical evaluation of patients with suspected appendicitis.

Ultrasound misses too many patients with appendicitis, CT is more expensive and uses ionizing radiation. A number of single and multi-modality imaging strategies were compared in the OPTIMA study, in which more than 1000 patients with acute abdominal pain underwent an abdominal X-ray, ultrasound and CT. A strategy with initial ultrasound in all patients, and additional CT in case of a negative or inconclusive ultrasound, resulted in the highest sensitivity in detecting urgent conditions, while reducing ionizing radiation exposure compared to using the

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In a 49-year-old male suspected for appendicitis CT, after intravenously administered contrast medium, shows a thickened appendix (arrow) with a thickened appendiceal wall and infiltration of the adjacent fat. Appendicitis was proven at surgery and histopathology.
most accurate modality, CT, in all.\textsuperscript{23} These findings are supported by similarly favourable accuracy results in patients with suspected appendicitis in other analyses.\textsuperscript{26,28} The available evidence provided the basis for the recommendations in the current Dutch guideline for the diagnosis of acute appendicitis\textsuperscript{41}. This guideline specifies routine imaging in all patients with suspected appendicitis: ultrasound initially, and additional CT in case of inconclusive or negative findings.\textsuperscript{41}

**Magnetic resonance imaging**

Magnetic resonance imaging (MRI) is a relatively new modality in the evaluation of patients with acute abdominal pain. In recent years MRI scanners became faster and more precise, and this technique became available for patients in the emergency setting. The main advantage of MRI is the lack of ionizing radiation exposure. The high intrinsic contrast resolution of MRI is another advantage, as intravenous contrast medium is not required. So far, most radiologists have little experience with the interpretation of MR images for acute appendicitis and are more comfortable with the interpretation of CT, which could limit the dissemination. Other limitations for using MRI more often in suspected acute appendicitis are its limited availability after office hours, and high examination costs. Yet, with the expanding availability of MRI and shorter examination times costs will probably drop. MRI examination is contraindicated in case of claustrophobia, presence of a pacemaker or metallic foreign bodies. In the current Dutch guideline for the diagnosis of acute appendicitis MRI can be considered in the diagnostic work-up for pregnant women after equivocal ultrasound results.\textsuperscript{41}

**MRI protocol**

The expected abnormalities in patients with suspected appendicitis are the presence of an enlarged appendix, thickening and edema of the appendiceal wall, fat infiltration of the adjacent fatty tissue and free fluid or pus in the abdomen. In T2-weighted sequences with and without fat saturation it is possible to evaluate the anatomical structures, and to observe pathological alterations. To avoid artifacts, due to peristalsis and respiration, fast T2 sequences such as single shot sequences (HASTE / SSFSE) are suitable. Alternatively, gradient T2 weighted series can be used (TrueFISP / Balanced FFE). It is preferred to acquire the images in the coronal and axial plane, and optionally in sagittal plane.

Diffusion weighted imaging (DWI) can be added to the protocol to locate infectious alterations to the abdominal structures. DWI is not dependent on the image of anatomical structures, but of thermo-dynamic movement of water molecules.\textsuperscript{50}

The ‘apparent diffusion coefficient’ (ADC) is a measure for the net transfer of water molecules in tissue, and is therefore not dependent on T1 or T2 effects. The ADC-map is calculated for each voxel in the DWI and displayed as a separate image.

In case of an (abdominal) infection the diffusion of water molecules is restricted which causes a (1) high intensity signal in diffusion weighted images and a (2) low intensity signal in the ADC map. With the ADC map readers can differentiate between artifacts (e.g. T2 shine-through effects; high signal intensity in DWI, high signal intensity in ADC-map) and real lesions (high signal intensity in DWI, low signal intensity in ADC).

DWI is a technique that has not been widely applied in the evaluation of acute abdominal pain, but can help radiologist to identify an inflamed appendix\textsuperscript{52};
The role of MRI

The increased availability of MRI, the shorter scan protocols and efforts to reduce ionizing radiation and iodine contrast exposure have led to an exploration of the role MRI could play in the workup of patients with acute abdominal pain. A limited number of studies on the diagnostic accuracy of MRI in detecting acute appendicitis have been published so far. Overall, these showed promising results. The available studies have primarily included selected patients – often pregnant women – with a spectrum and prevalence of disease that differ from that of the general population. A few studies on the accuracy of MRI in detecting appendicitis in patients from the general population are available. These studies were monocentric, limited
in sample size and reported varying results on sensitivity (83 to 100%) and specificity (50 to 99%) for acute appendicitis.

If MRI was proven to be sufficiently accurate, it could be introduced in the diagnostic pathway of all patients with suspected appendicitis, increasing diagnostic accuracy and improving clinical outcomes, without the risk of radiation induced cancer or iodinated contrast medium-related drawbacks. In the research reported in this thesis several aspects for the optimization of imaging of patients with suspected appendicitis at the emergency department were evaluated. At the core of this thesis is the OPTIMAP project (OPTimization of IMaging patients suspected of having APpendicitis) in which 230 patients with suspected acute appendicitis underwent ultrasound with conditional CT and MRI. A number of additional research projects evaluated a number of other questions regarding the use of MRI in suspected appendicitis.
OUTLINE OF THIS THESIS

In Chapter 1 the study protocol and rationale of the OPTIMAP study are described. This study was designed to evaluate MRI in patients with suspected acute appendicitis at the emergency department, and to compare it to the currently used imaging strategy, with initial ultrasound and additional, conditional computed tomography in case of a negative or inconclusive ultrasound.

Before the start of the OPTIMAP study radiologists and radiological residents of the participating hospitals were trained to interpret abdominal MR images with additional DWI for appendicitis. Seventeen readers evaluated 100 MRI scans of patients with suspected appendicitis, recorded their findings and reviewed the reference standard and details of expert reading after each case. Results of their learning curve are described in Chapter 2.

In the study reported in Chapter 3 the accuracy of imaging strategies with MRI in detecting appendicitis was compared to that of the current reference strategy, with ultrasound and conditional CT in case of a negative or inconclusive ultrasound. In this chapter we also describe differences in accuracy between men and women.

The MRI scans in the OPTIMAP study were evaluated by a panel of experts in consensus and by trained radiologists in clinical practice. Interobserver agreement and differences in accuracy were evaluated, and the corresponding study is reported in Chapter 4. In this chapter we also discuss the accuracy of MRI for urgent diagnoses other than acute appendicitis in both groups of readers. In Chapter 5 we report MRI features that are associated with acute appendicitis and calculate the predictive value per combination of the features that were significantly associated with acute appendicitis.

Most imaging modalities cannot accurately identify the presence of a perforated appendicitis. This distinction will become more of clinical importance in the light of the trials that investigate whether simple appendicitis can be treated non-operatively with antibiotics. We assessed if MRI can improve the preoperative identification of perforated appendicitis in patients with suspected appendicitis included in the OPTIMAP study. We report on accuracy of MRI for perforated appendicitis in Chapter 6.

In the OPTIMAP study almost half of the patients underwent additional CT after a negative or inconclusive ultrasound. In an additional project, described in Chapter 7, we assessed if we could identify a group of patients with a simple prediction rule, based on a set of clinical features, that rules out appendicitis in patients with suspected appendicitis and inconclusive or negative US findings.

In Chapter 8 the results of the RADIANCE study are reported: Research in Acute appendicitis and magnetic resonance imaging. In this comparative 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. The findings of this thesis are summarized and discussed in the last chapter, in which we also present perspectives for future research.
REFERENCES

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