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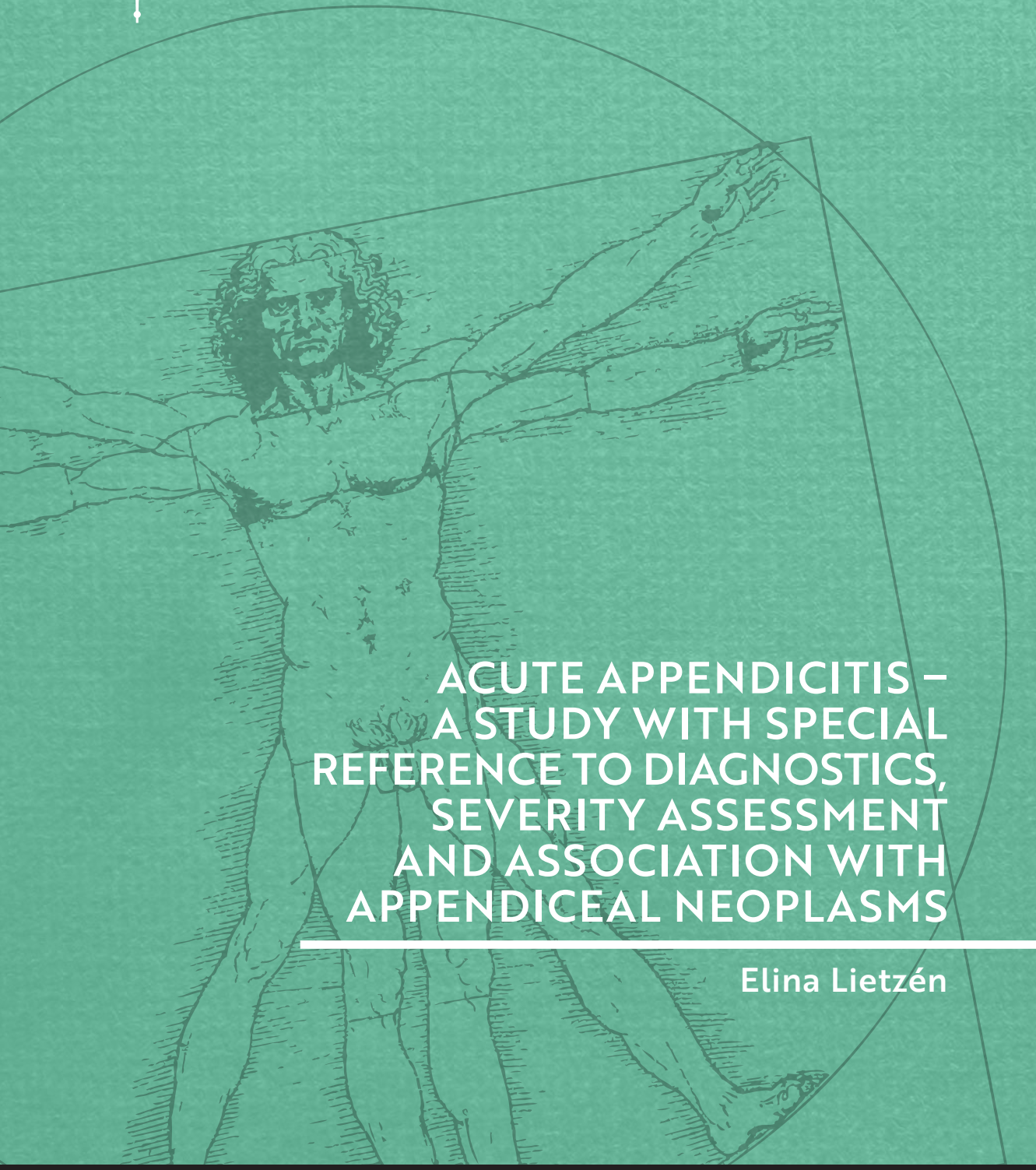

ACUTE APPENDICITIS – A STUDY WITH SPECIAL REFERENCE TO DIAGNOSTICS, SEVERITY ASSESSMENT AND ASSOCIATION WITH APPENDICEAL NEOPLASMS

Elina Lietzén

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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To my mum and dad

ABSTRACT

Elina Lietzén, MD
Acute appendicitis – a study with special reference to diagnostics, severity assessment and association with appendiceal neoplasms

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Acute appendicitis is the most common indication for emergency abdominal surgery. Today, it is generally accepted that acute appendicitis does not invariably progress to perforation. Recent studies have shown that the majority of uncomplicated infections will subside with antibiotics alone. To optimize the treatment for acute appendicitis, accurate diagnostic tools such as computed tomography (CT) are required. As the treatment of uncomplicated acute appendicitis may be changing towards conservative treatment, there has been a rising concern of missing possible appendiceal tumors, found in 0.7-1.7% of appendectomy specimens.

This study was carried out to evaluate the feasibility of clinical history and clinical and laboratory findings in diagnosing acute appendicitis as well as in the differential diagnosis between uncomplicated and complicated acute appendicitis. This study also aimed to assess the accuracy of CT and the role of the experience of the radiologist in the emergency setting in the diagnosis of acute appendicitis. In addition, this study was performed to assess both the incidence of appendiceal tumors among acute appendicitis patients and the possible tumor association with acute appendiceal inflammation.

Both clinical findings and laboratory tests were unable to reliably diagnose acute appendicitis or to assess the severity of inflammation. Contrast enhanced abdominal CT displayed high sensitivity and specificity in diagnosing suspected acute appendicitis and in the differential diagnosis of assessing its severity. The experience of the radiologist did not affect the diagnostic accuracy. The incidence of appendiceal tumors among acute appendicitis was very low but there was a statistically significantly higher tumor risk associated with complicated acute appendicitis. Appendiceal tumors were rarely detected in preoperative imaging and even more rarely in the early stage of the disease. Thus, there is a low risk of missing possible appendiceal tumors related to the non-operative treatment of uncomplicated acute appendicitis.

Keywords: acute appendicitis, uncomplicated appendicitis, complicated appendicitis, CT, appendiceal tumor

TIIVISTELMÄ

LL Elina Lietzén
Akuutti umpilisäketulehdus – tutkimuksia diagnostiikasta, vaikeusasteen määrityksestä ja yhteydestä umpilisäkkeen kasvaimiin

Turun yliopisto, Lääketieteellinen tiedekunta, Kirurgia, Turun kliininen tohtoriohjelma, Gastrokirurgia; Vatsatoimialue, Turun yliopistollinen keskussairaala, Turku, Suomi.

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Akuutti umpilisäketulehdus on yksi yleisimmistä päivystysleikkauksen aiheista. Nykytiedon mukaan umpilisäkkeen tulehdus ei aina johda umpilisäkkeen puhkeamiseen. Viimeaikaisten tutkimusten mukaan iso osa komplisoitumattomista eli lievemmistä akuuteista umpilisäketulehduksista voitaisiin hoitaa yksinomaan antibiooteilla. Optimaalisen hoidon valinnan edellytyksenä on tarkka diagnoosi, johon tarvitaan tietokonetomografiakuvantamista (TT). Komplisoitumattoman umpilisäketulehduksen konservatiivista hoitoa arvioitaessa on otettava huomioon, että osalla umpilisäketulehduspotilaista voidaan todeta poistetussa umpilisäkkeessä sattumalöydöksenä kasvain, esiintyvyys 0.7-1.7 %.

Tämän väitöskirjatyön tarkoituksena oli selvittää kliinisen diagnostiikan osuvuutta sekä umpilisäketulehduksessa että erotusdiagnostiikassa komplisoituneen ja komplisoitumattoman tulehduksen välillä. Tutkimme myös TT:n osuvuutta ja radiologin kokemuksen merkitystä umpilisäketulehduksen diagnostiikassa. Tutkimuksen tarkoituksena oli lisäksi selvittää umpilisäkkeen kasvainten esiintyvyyttä akuutin umpilisäketulehduksen vuoksi leikatuilla sekä kasvainten mahdollista yhteyttä umpilisäkkeen tulehdukseen.

Akuutin umpilisäketulehduksen diagnosoiminen ja tulehduksen vaikeusasteen määritys kliinisten oireiden ja löydösten sekä laboratoriotutkimusten avulla osoittautui epävarmaksi. Varjoainetehosteisella TT-tutkimuksella saavutettiin erinomainen diagnostinen tarkkuus riippumatta radiologin kokemuksesta. Sen sijaan umpilisäkkeen kasvaimet löytyivät kuvantamisella vain harvoin varsinkin taudin alkuvaiheessa. Umpilisäkkeen kasvainten esiintyvyys akuutin umpilisäketulehduksen yhteydessä oli erittäin pieni. Kasvaimen riski oli tilastollisesti merkittävästi suurempi komplisoituneissa akuuteissa umpilisäketulehduksissa. Vaikka komplisoitumattoman akuutin umpilisäketulehduksen konservatiivinen hoito tulevaisuudessa yleistyisi, on umpilisäkkeen kasvaimen hoitamatta jäämisen riski hyvin vähäinen.

Avainsanat: akuutti umpilisäketulehdus, komplisoitumaton umpilisäketulehdus, komplisoitunut umpilisäketulehdus, TT, umpilisäkkeen kasvain

TABLE OF CONTENTS

ABBREVIATIONS

AIR	Appendicitis Inflammatory Response
AUC	Area under curve
CRP	C-reactive protein
CI	confidence intervals
CT	computed tomography
DNI	delta neutrophil index
FCR	Finnish Cancer Registry
FIMEA	Finnish Medicines Agency
HCG	human chorionic gonadotropin
Hgb	blood hemoglobin
HIPEC	hyperthermic intraperitoneal chemotherapy
ICD	International Classification of Disease
IV	intravenous
LAMN	low-grade appendiceal mucinous neoplasm
LR	likelihood ratio
MANEC	mixed adeno-neuroendocrine carcinoma
MRI	magnetic resonance imaging
NAR	negative appendectomy rate
NET	neuroendocrine tumor
NIHW	National Institute for Health and Welfare
NOTES	natural orifice transluminal endoscopic surgery
NSAP	non-specific abdominal pain
OR	Odds ratio
RCT	randomized controlled trial
ROC	receiver operating characteristic
SD	standard deviation
SILS	single-incision laparoscopic surgery

US	ultrasonography
WBC	white blood cell count
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by Roman numerals I-IV.

I. Lietzén E*, Ilves I*, Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, Kauko T, Jartti A, Sand J, Mecklin JP, Grönroos JM. "Clinical and laboratory findings in the diagnosis of right lower quadrant abdominal pain: outcome analysis of the APPAC trial." Clin Chem Lab Med. 2016 Oct 1;54(10):1691-7.

II. Lietzén E, Mällinen J, Grönroos JM, Rautio T, Paajanen H, Nordström P, Aarnio M, Rantanen T, Sand J, Mecklin JP, Jartti A, Virtanen J, Ohtonen P, Salminen P. "Is preoperative distinction between complicated and uncomplicated acute appendicitis feasible without imaging?" Surgery. 2016 Sep;160(3):789-95.

III. Lietzén E, Salminen P, Rinta-Kiikka I, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, Sand J, Mecklin JP, Jartti A, Virtanen J, Ohtonen P, Ånäs N, Grönroos JM. The Accuracy of The Computed Tomography Diagnosis of Acute Appendicitis: Does The Experience of The Radiologist Matter? Scand J Surg. 2018 Mar;107(1):43-47.

IV. Lietzén E, Grönroos JM, Mecklin JP, Leppäniemi A, Nordström P, Rautio T, Rantanen T, Sand J, Paajanen H, Kaljonen A, Salminen P. Appendiceal Neoplasm Risk Associated with Complicated Acute Appendicitis – a Population Based Study. Int J Colorectal Dis. 2018 Sep 22.

*The original publication I has also been used in thesis of Imre Ilves.

1 INTRODUCTION

Acute appendicitis is one of the most common causes of abdominal pain encountered in emergency departments, occurring in 7-12% of the general population (Livingston et al. 2011). Acute appendicitis is also the most common indication for emergency abdominal surgery. Appendectomy has been the standard treatment for acute appendicitis for over a century. Previously, the decision to proceed to appendectomy in a patient with suspected acute appendicitis has been established on the basis of the clinical examination and laboratory findings. However, the clinical diagnosis of acute appendicitis is challenging as every patient does not have a typical clinical presentation and not every typical presentation is acute appendicitis. Today, it is generally accepted that acute appendicitis does not invariably progress to perforation, as complicated and uncomplicated acute appendicitis are known to have different pathophysiologies (Livingston et al. 2007). The treatment paradigm of acute appendicitis may be changing as operative treatment may be unnecessary for the majority of uncomplicated acute appendicitis patients (Salminen et al. 2015, Hansson et al. 2012, Styrud et al. 2006, Vons et al. 2011). Nonetheless, a precise and accurate diagnosis is required in order to optimize and tailor the treatment for acute appendicitis.

In clinical practice, the accuracy of diagnosis without preoperative imaging varies greatly (Berry et al. 1984, Körner et al. 1997, Mariadason et al. 2012, Wagner et al. 2008). So far, no specific biomarkers are available either for the accurate diagnosis of acute appendicitis (Paajanen et al. 2002b, Andersson 2004, Al-Gaithy 2012, Schellekens et al. 2013) or for predicting the presence of an appendicolith or for assessing the severity of inflammation (Shindoh et al. 2011). Acute appendicitis is considered to be complicated when there is an appendicolith, perforation, or periappendicular abscess. Several scoring systems have been created to aid in the clinical diagnosis of acute appendicitis (Alvarado 1986, Andersson et al. 2008, Sammalkorpi et al. 2014). However, none of the scoring systems is able to differentiate between complicated and uncomplicated acute appendicitis (Alvarado 1986, Andersson et al. 2014, de Castro et al. 2012). Over the past decade, clinicians have increasingly relied on preoperative imaging in order to reduce the negative appendectomy rate (NAR) and to decrease surgery related mortality and expenses (Rao et al. 1998, Lahaye et al. 2015, Raja et al. 2010, Sippola et al. 2017). Although imaging examinations have some limitations such as the additional radiation exposure (CT), the lower accuracy rate in adults (ultrasonography, US) and high costs (magnetic resonance imaging, MRI), these techniques are helpful in making an accurate diagnosis. CT has become the gold standard imaging modality for diagnosing acute appendicitis with a sensitivity of up to 95-100% and a positive predictive value of 96% (Boonstra et al.

2015, Kim et al. 2008, Raman et al. 2008). CT also enables a better differential diagnosis between complicated and uncomplicated acute appendicitis (Kim et al. 2018a). The increased use of CT has been shown to decrease the NAR without increase in false-positive or delayed diagnosis (Raja et al. 2010, Rao et al. 1999, Coursey et al. 2010, van Rossem et al. 2016a). The implementation of the Dutch guideline for mandatory imaging preoperatively for all patients with suspected appendicitis, markedly decreased the NAR (from 23% to 6% and from 19% to 5%) between 2008-2011 (Boonstra et al. 2015, Lahaye et al. 2015). In the study of Sammalkorpi et al (2017), the NAR decreased from 18.2% to 8.7% after implementation of the Adult Appendicitis Score algorithm (Sammalkorpi et al. 2017).

With the development of precise diagnostic tools like CT, appendiceal tumors may increasingly be suspected on in the preoperative imaging (Whitley et al. 2009, Pickhardt et al. 2002). However, most of the CT signs related to appendiceal tumors are unspecific and the preoperative diagnosis of an appendiceal tumor on CT can be obscured by signs of acute or secondary inflammation (Whitley et al. 2009). Appendiceal tumors are usually incidental findings, most often detected in the histological evaluation of an inflamed appendix. Appendiceal tumors are rare with varying incidences ranging from 0.7% to 2.5% in several large appendectomy series (Andersson et al. 2007, Murphy et al. 2006, Teixeira et al. 2017, Loftus et al. 2017). Appendiceal tumors are a heterogeneous disease group with a diverse clinical behavior; their pathological classification and terminology have undergone major changes over the last decades (Shaib et al. 2016, Hsu et al. 2013, Brathwaite et al. 2016). The possible tumor association to appendiceal inflammation is unknown. However, there are recent studies reporting an alarming rate of appendiceal tumors detected at interval appendectomy in patients with previous periappendicular abscess (Wright et al. 2015, Furman et al. 2013).

Our aim in study I, was to evaluate whether the patients in whom there was a clinical suspicion of acute appendicitis, but negative CT findings had different clinical or laboratory characteristics from those patients with positive CT diagnosis for acute appendicitis. As the treatment paradigm of acute appendicitis may be changing in the future, a precise and accurate differential diagnosis of uncomplicated and complicated acute appendicitis is required. The goal of study II was to evaluate the feasibility of clinical and laboratory findings in establishing this differential diagnosis without imaging with a special interest in predicting the presence of an appendicolith. In study III with 1321 abdominal CT scans, we conducted a prospective study to investigate the capability and accuracy of the on-call radiologist in diagnosing acute appendicitis using CT. We aimed to assess the accuracy of the CT in the emergency setting and to clarify whether the expe-

rience of the radiologist had any effect on the diagnostic accuracy. With the increased use of preoperative imaging, appendiceal tumors may increasingly be suspected on CT. The aim of the study IV was to evaluate the incidence of these tumors among acute appendicitis patients and to clarify their association with acute inflammation. Our special interest was to evaluate the risk of misdiagnosing appendiceal tumors among uncomplicated acute appendicitis patients as non-operative treatment becomes more popular in the future.

2 REVIEW OF LITERATURE

2.1 Anatomy and function of the appendix

Vermiform appendix is a 2 to 20 cm long blind–ended diverticulum arising from the posteromedial side of the cecum. The blood supply to the appendix derives from the appendicular artery, which originates from the ileocolic artery. The position of the appendix is not consistent, instead it is related to the embryological development and growth of the cecum and appendix from the midgut (Schumpelick et al. 2000, Wakeley 1933). Most commonly (40%), the appendix lies behind the cecum retrocecally, but a long appendix may extend behind the ascending colon and even abut onto the right kidney or the duodenum. The appendix can also be in a subcecal abdominal position, hang down in a pelvic location, or tuck itself behind the terminal ileum retroileally (Schumpelick et al. 2000, Wakeley 1933). While the position of the distal part of the appendix varies, the base of the appendix to the cecum is constant, 1.7 to 2.5 cm below the terminal part of the ileocecal junction, at the junction of the taenia coli. The ultimate location of the appendix is determined by the location of the cecum but its most typical location, called McBurney´s point, is situated approximately one-third of the distance from the right anterior superior iliac spine to the umbilicus. The location can vary in cases of malrotation or maldescent of the cecum and more commonly in pregnant women due to the growth of the uterus (House et al. 2014, Oto et al. 2006, Schumpelick et al. 2000).

Although the appendix was identified in humans more than 400 years ago, its function remained unknown until the 21st century (Laurin et al. 2011). The appendix is a tube-like structure with its lumen lined by the colonic epithelium. The appendix contains an abundance of lymphatic tissue in the submucosa – gut-associated lymphoid tissue (GALT). After biological evidence about the GALT emerged from histological studies more than a century ago, it was proposed that the appendix has some sort of immune function (Berry 1900, Smith et al. 2009). The immune system apparently supports the growth of beneficial (symbiotic) bacteria in the mammalian gut in the form of microbial communities called biofilms (Randal Bollinger et al. 2007). An improved understanding of the interactions between the normal gut flora and the immune system has led to the identification of the appendix as an apparent safe-house for normal gut bacteria (Laurin et al. 2011, Randal Bollinger et al. 2007, Smith et al. 2009). The concentration of biofilms was found to be higher in the appendix than in any other area of the intestine (Randal Bollinger et al. 2007). Based on recently acquired understanding, it is now apparent that the biofilm formation in the appendix enhances the sur-

vival of normal enteric bacteria while impairing the adherence of the pathogenic organisms within the large bowel (Randal Bollinger et al. 2007).

2.2 History of acute appendicitis and appendectomy

The first identification of the appendix in humans is thought to date from 1492, when Leonardo Da Vinci demonstrated the appendix in his drawings. In the 16th century, Vesalius and DaCarpi made the first descriptions of the appendix (Seal 1981, Prystowsky et al. 2005). Lorenz Heister is credited with being the first physician to perform a post-mortem dissection of an appendix at the beginning of the 18th century. He was the first physician, who speculated that the appendix might be the reason for right lower quadrant abdominal inflammation. In the 1800s, appendicitis had several names including peri-cecal inflammation, typhlitis and perityphlitis. The first known appendectomy was performed in 1735 by Claudius Amyand (Prystowsky et al. 2005). Appendectomy was not a routine treatment before the development of general anesthesia in the mid-1800s. Early appendectomy was first described as a treatment for acute appendicitis in 1886 by the pathologist, Reginald Fitz (Fitz 1886). His paper entitled "Perforating inflammation of the vermiform appendix: with special reference to its early diagnosis and treatment" emphasized the importance of an accurate diagnosis and early removal of an inflamed appendix before perforation occurred (Fitz 1886). Fitz was not the first to describe suppuration of the vermiform appendix, but from his perceptive correlation of clinical and pathological features emerged a clear concept of the disease to which he gave the term "appendicitis". The article "The indications for early laparotomy in appendicitis" by Charles McBurney was published in 1891 (McBurney 1891). The typical symptoms and clinical findings of acute appendicitis were described for the first time: acute onset of abdominal pain, fever, tachycardia, guarding, relocation of pain from the whole abdomen to the right iliac fossa and maximal pain localization over the appendix (thereafter known as "McBurney's point") (McBurney 1891, 1889).

Appendectomy had been performed through either a midline or a paramedian incision before McBurney published his article: "The incision made in the abdominal wall in cases of appendicitis, with a description of a new method of operating" (McBurney 1894). This muscle-splitting oblique incision used in appendectomy over the decades became known as the "McBurney's incision, although he was not the first to describe the procedure (Grover et al. 2012, McBurney 1894). After the era of Fitz and McBurney, the appendectomy remained technically rather similar to modern open surgery. In 1980, Kurt Semm performed the first laparoscopic appendectomy (Semm 1983, Semm K 1980). At first, his oper-

ation was severely criticized (Bhattacharya 2007). However over the years, the laparoscopic technique has become more common and is today considered as the gold standard operative treatment for acute appendicitis (Masoomi et al. 2011). The studies of Fitz and McBurney were published 40 years before the discovery of antibiotics. Early appendectomy in the case of appendicitis saved lives by reducing the risk of uncontrolled abdominal infection in the absence of antibiotics. In 1956, Coldrey et al. was the first to report treating acute appendicitis patients with antibiotics; this group described similar results as have been obtained in the more recent trials, but his pioneer study was deliberately ignored and unappreciated (Coldrey 1956). Recently, the nonoperative treatment of uncomplicated acute appendicitis with either antibiotics alone (Salminen et al. 2015, Hansson et al. 2012, Vons et al. 2011, Styrud et al. 2006) or symptomatic therapy, i.e. spontaneous resolution of acute appendicitis, have been areas of intense research activity (Cobben et al. 2000, Migraine et al. 1997, Park et al. 2017).

2.3 Epidemiology of acute appendicitis

Acute appendicitis occurs in 7-12% of the general population and appendectomy is the most common indication for emergency abdominal surgery (Livingston et al. 2011). In Finland, around 8000 appendectomies are performed annually due to acute appendicitis or its suspicion (Finnish National Institute for Health and Welfare). The lifetime incidence of acute appendicitis in Finland is 7%. Approximately 250,000 cases of appendicitis occurred annually in the United States during a study period between 1970 and 1984 (Addiss et al. 1990). The study reported that while the overall incidence of acute appendicitis decreased, the highest incidence of appendicitis occurred in the age group from 10- to 19-years, and men were more likely to develop appendicitis than women (Addiss et al. 1990). The lifetime risk of acute appendicitis for men is 8.6% whereas for women, it is 6.7%. At that time period, the incidence of acute appendicitis was decreasing, however, the incidence has subsequently increased (Buckius et al. 2012). Between 1993 and 2008, the annual rate of acute appendicitis increased from 7.62 to 9.38 per 10,000. The frequencies of acute appendicitis in different age groups are shown in Table 1. The highest frequency of acute appendicitis was still found in the age group from 10- to 19-years, however its occurrence in this group decreased by 4.6% (Buckius et al. 2012). Acute appendicitis has become more common in older patients and in this study, patients between ages 30- and 69-years experienced an increase of acute appendicitis by 6.3% (Buckius et al. 2012). The mean age of acute appendicitis patients has risen from 29.6 to 32.7 years (Buckius et al. 2012).

Table 1 The frequency of acute appendicitis in the United States as percentages between 1993-2008 (Buckius et al. 2012)

	1993-1996	1997-2000	2001-2004	2005-2008
Gender				
Male	59.3	59.0	57.6	56.6
Female	40.7	41.0	42.4	43.4
Age Range				
0-29	**57.9**	**55.0**	**51.7**	**50.9**
0-9	9.1	9.2	8.7	8.6
10-19	27.5	26.0	23.8	22.9
20-29	21.3	19.8	19.2	19.4
30-69	**38.2**	**41.4**	**44.1**	**44.5**
30-39	17.8	17.7	17.2	15.8
40-49	9.7	11.1	12.5	12.6
50-59	6.2	7.8	9.4	10.2
60-69	4.5	4.5	5.0	5.9
70-	**4.0**	**3.8**	**4.2**	**4.7**
70-79	2.9	2.8	3.0	3.2
80-89	1.0	0.9	1.1	1.3
90-	0.1	0.1	0.1	0.2

The incidence of acute appendicitis does not differ significantly in the different Scandinavian countries (Andersson et al. 1994, Körner et al. 1997). However, acute appendicitis seems to be more common in the developed than in developing countries. The incidence of acute appendicitis in developing countries is much lower and also a disparity still exists between the black and white people in Africa in terms of the incidence of acute appendicitis (<1% vs 10%) (Kong et al. 2012, Ferris et al. 2017). Interestingly, the incidence of acute appendicitis is still changing around the world. An epidemiological study from Finland showed that the incidence of appendicitis declined from 14.5 to 9.8 per 10,000 between 1987 and 2008 (Ilves et al. 2014). According to the recent study of Ferris et al, the incidence of acute appendicitis has mostly stabilized during the latter portion of the 20th century in Western countries (Ferris et al. 2017). In the United States, the incidence is 100 per 100,000 person-years with nearly 400,000 diagnoses being made in 2015. In contrast, the incidence is now increasing in the newly industrialized countries of Asia, the Middle East, South America, and Africa and since 2000, the incidences of acute appendicitis in some of these countries have been even higher than in many Western countries (Ferris et al. 2017). A paucity of population-based studies on the incidence of acute appendicitis from developing countries highlights a major gap in the literature and may be one reason for the apparent changes in the trends in the developing countries.

Despite the significant changes in the overall incidence rate of acute appendicitis, the rate of perforated appendicitis has shown different tendencies. Studies on the epidemiology of perforated and non-perforated acute appendicitis have revealed that these conditions display different epidemiological trends (Andersson et al. 1994, Livingston et al. 2007, Livingston et al. 2011). Despite these significant changes in the incidence of acute appendicitis, the rate of perforated appendicitis has undergone only minor changes over the same period. The uncomplicated acute appendicitis rates decreased between 1970 and 1995 and the trend was accounted for almost entirely by the decreasing incidence in the 10–19 year age group (Livingston et al. 2007). Thereafter, an increased incidence occurred in all age groups above 5 years and paralleled increasing rates of CT imaging and laparoscopic surgery on the appendix (Livingston et al. 2007).

The epidemiological patterns of acute appendicitis support the notion that appendicitis is driven by multifactorial environmental triggers. Incidence trends observed in different geographic zones and time frames suggest that the pathogenesis of acute appendicitis is dependent on the industrialization of society. Acute appendicitis is rare where hygiene is poor and diets are high in fiber (Barker et al. 1988). The incidence has increased over time as cleanliness in the Western world has improved and acute appendicitis is more common in populations with a higher socioeconomic status (Livingston et al. 2011). Smoking has also been associated with an increased incidence of acute appendicitis, which may partly explain the rising incidence outside the Western countries (Oldmeadow et al. 2008). Air pollution has also been shown to increase the incidence of acute appendicitis; especially complicated acute appendicitis (Kaplan et al. 2013). There is also a seasonal variation in the incidence of acute appendicitis, summer having the highest and winter the lowest incidence (Ilves et al. 2014). The increased use CT of imaging in the Western world might be one explanation for this increased incidence (Buckius et al. 2012). Consequently, more research is needed to clarify the epidemiological patterns of acute appendicitis, however, it is evident that the etiology is multifactorial.

2.4 Etiology and pathogenesis of acute appendicitis

The most commonly accepted theory of the pathogenesis of acute appendicitis is that it results from the obstruction of the lumen followed by infection (Wangensteen et al. 1939). The obstruction of the lumen may result from a variety of causes: an appendicolith, lymphoid hyperplasia, tumor, parasites and foreign bodies. Mucus accumulates within the obstructed lumen and pressure within the appendix increases. The accumulated mucus is converted into pus by virulent

bacteria. The relative inelasticity of the serosa combined with continued secretion leads to increased pressure within the lumen. This results in obstruction of the lymphatic drainage which causes edema of the appendix, the appearance of mucosal ulcers and diapedesis of bacteria. Continued luminal secretion and increasing edema further elevate the intraluminal and tissue pressure, resulting in venous obstruction and ischemia of the appendix. Bacteria migrate into and through the wall of the appendix leading to acute suppurative appendicitis. As the process continues, venous and arterial thromboses occur in the wall of the appendix, resulting in gangrenous acute appendicitis. Small infarcts occur in the appendiceal wall, permitting leakage of bacteria and contamination of peritoneal cavity. Perforated acute appendicitis is the final stage of disease, where accumulated pus and feces spill through a gangrenous infarct of the appendiceal wall (Yeo C.J. 2012).

This concepts behind the pathogenesis of appendicitis originate from its first description in the detailed histopathological analysis performed by Fitz already in 1886 (Fitz 1886). In establishing the relationship between acute appendicitis and right lower-quadrant sepsis, Fitz noted that the appendix developed mucosal ulcerations that seemed to cause inflammation, gangrene, and eventual perforation. Fitz hypothesized that acute appendicitis would progress inevitably to perforation. However, Fitz also incidentally noted that one-third of patients undergoing autopsy had evidence of prior appendiceal inflammation, suggesting that acute appendicitis often resolved spontaneously without surgery (Fitz 1886). Today, it is generally accepted that acute appendicitis does not invariably progress to perforation, as uncomplicated and complicated acute appendicitis are suggested to have different pathophysiologies and epidemiologies (Livingston et al. 2007, Livingston et al. 2011, Andersson et al. 1994).

As the hypothesis of acute appendicitis pathogenesis is still unclear, the precise etiology of the disease also remains a mystery. Many possible contributing factors were recognized already in 1939 by Wangensteen et al (Wangensteen et al. 1939). However, the role of these factors in the pathogenesis of acute appendicitis still remains undetermined. Appendicolith has been regarded as one of the most common reasons for causing a mechanical obstruction of the appendiceal lumen. In the study of Singh et al (2013) examining adult patients, appendicoliths were found in 13.7% (99/772) of appendicitis specimens and 31.6% (6/19) of negative appendectomies (Singh et al. 2013). In the study of Ramdass et al (2015), appendicoliths were identified in 121 patients of 968 appendectomy specimens with acute appendicitis (12.5%) and in 65 patients of 389 NAR cases (16.7%) (Ramdass et al. 2015). Lymphoid hyperplasia can develop due to an immune reaction and cause acute appendicitis. Furthermore, lymphoid hyperplasia has been found in a histopathologically normal appendix without any infection

and in some reports, this has been even a more common finding in normal than inflamed appendix (Chan et al. 1987, Chang 1981).

Primary appendiceal tumors are rare, usually incidental findings most often detected in the histological evaluation of a removed appendix. The tumor rate has varied from 0.7% to 2.5% of appendectomy specimens in several large appendectomy series (Andersson et al. 2007, Murphy et al. 2006, Teixeira et al. 2017, Loftus et al. 2017). Considering the low overall incidence of appendiceal tumors and the even lower incidence in cases of acute inflammation, these tumors are a relatively rare cause of acute appendicitis.

Specific infections have been linked to acute appendicitis. Some evidence has been found for viral infections as an etiological factor of acute appendicitis (Alder et al. 2010). It has also been speculated that these lymphotrophic enteric viral infections might be the reason for the seasonal variation in incidence of acute appendicitis (Alder et al. 2010). Numerous bacterial infections may be involved in acute appendicitis, with or without involvement of the surrounding bowel. Their initial role in the etiology of acute appendicitis remains unclear, even though bacteria from the appendix may be important pathogens in acute appendicitis and its complications. The possible contributions that any of these organisms might make to the pathogenesis of acute appendicitis remain unclear, but it is known that a mixture of anaerobic and aerobic bacteria that can exist within an inflamed appendix (Lamps 2010). Parasitic infection of the appendix is very rare and even though it can be found globally, its incidence is highest in the tropical countries. Different parasites have been detected during a histopathological evaluation of the appendix, but their role in the pathogenesis of acute appendicitis is unresolved since they are found also in normal appendices (Lamps 2010).

2.5 Classification of acute appendicitis

2.5.1 Uncomplicated acute appendicitis

Acute inflammation of either a part or throughout the entire appendix is defined as acute appendicitis. At the beginning of the disease, the mucosa of the appendix is inflamed and usually ulcerated. Neutrophilic infiltration in the submucosa and muscularis propria has been shown in histopathological analysis. The obstruction of the lymphatic drainage system leads to edema in the appendix, which causes vascular thrombosis. Later, both transmural inflammation and intramural abscesses are typically seen. If this pathological process continues, gangrene of the

appendiceal wall develops due to vascular thrombosis. Transmural inflammation with areas of necrosis and extensive mucosal ulceration are seen in the histopathological analysis of gangrenous acute appendicitis (Carr 2000, Yeo C.J. 2012). Gangrenous acute appendicitis may eventually lead to perforation (Table 2).

Aside from demonstrating the changing epidemiological trends for appendicitis and appendectomy, the findings of Livingston et al (2007) suggest that appendicitis is a more complex and heterogeneous disease than previously thought (Livingston et al. 2007). Given that secular trends for uncomplicated and complicated acute appendicitis radically differ, it seems unlikely that perforated appendicitis is simply the progression of acute appendicitis resulting from delayed treatment. As Livingstone et al (2007, 2011) concluded, uncomplicated and complicated acute appendicitis may be different entities with different natural histories (Livingston et al. 2007, Livingston et al. 2011). The majority, approximately 75 - 80%, of acute appendicitis cases are of an uncomplicated nature (Livingston et al. 2007).

An increasing amount of evidence suggests that even the spontaneous resolution of appendiceal inflammation may be common. The estimated incidence of spontaneously resolving appendicitis has been reported to be around 8%, but the true incidence is unknown (Cobben et al. 2000, Park et al. 2017, Rice 1964). There are several studies showing that the increased frequency of appendectomy is associated with more acute appendicitis cases being diagnosed, especially uncomplicated appendicitis (Andersson et al. 1994, Howie 1964, Decadt et al. 1999, Andersson 2007). The incidence of complicated acute appendicitis has remained unaltered regardless of the amount of surgical interventions (Andersson et al. 1994). These results suggest that a significant number of patients with appendicitis may resolve while undiagnosed as a restrained attitude to surgical intervention has resulted in fewer diagnoses of acute appendicitis. There is also evidence that the more frequent use of CT may lead to an increased detection and unnecessary overtreatment of otherwise spontaneously resolving appendicitis (Rao et al. 1999, Andersson 2008). In the study of Rao et al (1999), there were 5.6 operations for uncomplicated acute appendicitis per month prior to the introduction of CT, whereas the number increased to 13.8 after the use of CT (Rao et al. 1999). The number of operations for complicated acute appendicitis per month remained unchanged prior to and in the post CT era (Rao et al. 1999).

2.5.2 Complicated acute appendicitis

Approximately 25% of acute appendicitis cases present as complicated (Livingston et al. 2011). Acute appendicitis is histopathologically considered complicated when there is gangrena, perforation or periappendicular abscess (Table 2). Perforated acute appendicitis is the final stage of the disease, where accumulated pus and feces spill through a gangrenous infarct of the appendiceal wall. The pathogenesis behind the fact that only a part of acute appendicitis events proceed to perforation is still unknown. The average rate of perforation at presentation has been reported as being under 20% (Livingston et al. 2007, Livingston et al. 2011, Andersson et al. 2007, Young et al. 2018, Drake et al. 2014). Historically, it has been stated as a fact that the delay in care is a major risk factor for perforation (Yeo C.J. 2012). Nevertheless, several studies have shown that there is a relationship between perforation and the pre-hospital delay, whereas there is no association with the in-hospital delay (Temple et al. 1995, Drake et al. 2014, Andersson 2007, Kim et al. 2018b, van Dijk et al. 2018). However, there seems to be a subgroup of acute appendicitis patients in whom the in-hospital delay leads to perforation of the appendix and in these patients, appendectomy should be performed as soon as possible (Sammalkorpi et al. 2015).

An appendicolith has been regarded as one of the most common reasons to cause a mechanical obstruction of the appendiceal lumen. Even though the presence of an appendicolith is not histopathologically considered as complicated acute appendicitis, Vons et al (2011) noted that an appendicolith was associated with a significantly increased risk of complicated acute appendicitis (Vons et al. 2011). There are several other studies supporting the finding that the presence of an appendicolith in acute appendicitis is associated with earlier and higher rates of perforation (Alaedeen et al. 2008, Kondo et al. 2009). In the study of Singh et al (2013), the appendicolith prevalence was 27.5% in perforated appendicitis and 12.0% in non-perforated appendicitis in adults while in pediatric patients, it was 56.1% and 22.7%, respectively (Singh et al. 2013).

Periappendicular abscess is the result of a walled-off perforation of the appendix that is localized, resulting from an inflammatory mass turning into a pus-containing collection. Appendiceal abscess is encountered in 2-10% of adult patients with acute appendicitis (Oliak et al. 2001, Meshikhes 2008). The incidence of appendicolith was 24.4 % in periappendicular abscess patients in the study of Otake et al (Otake et al. 2014).

In a large retrospective study, the overall incidence of appendiceal tumors was low (0.7%), however 80% of tumors presented with a periappendicular abscess

(Lee et al. 2011). In addition, in several other studies, appendiceal tumors seem to be overrepresented among periappendicular abscess patients (Mentula et al. 2015, Carpenter et al. 2012, Deelder et al. 2014, Andersson et al. 2007).

Table 2 Histopathological classification of acute appendicitis (Bhangu et al. 2015, Carr 2000)

Normal appendix	Uncomplicated acute appendicitis	Complicated acute appendicitis
Absence of any abnormality	Transmural inflammation, ulceration, or thrombosis, with or without extramural pus	Transmural inflammation with necrosis (gangrenous)
Luminal neutrophils only with no mucosal abnormality		Transmural inflammation with perforation (perforated)
Mucosal or submucosal neutrophils and/or ulceration		Transmural inflammation with pus with or without perforation (periappendicularabscess)

2.6 Diagnosis of acute appendicitis

2.6.1 Clinical symptoms and physical examination

Clinical symptoms and physical signs of acute appendicitis have been the cornerstone of the diagnostic process for over a century, and these still remain an essential part of the evaluation of patients with acute abdominal pain (Fitz 1886, McBurney 1891, Yeo C.J. 2012). Although the symptoms or signs are weak discriminators individually, they achieve a much higher discriminatory power when combined. The diagnostic accuracy of clinical evaluation and laboratory tests together is about 80% in acute appendicitis (Andersson 2004, Rao et al. 1999, Raja et al. 2010, Gilmore et al. 1975, Berry et al. 1984).

The symptomatic history in acute appendicitis may vary, but cardinal symptoms are usually present (Lewis et al. 1975, Eskelinen et al. 1994). The symptoms usually begin with abdominal pain often localized to the epigastrium or the periumbilical area, followed by anorexia and nausea. Vomiting appears next, although it is not invariably present. After a variable period, usually about 8 hours, the pain shifts to the right lower quadrant. At the time of presentation, the duration of pain has been less than 24 hours in 75% of patients (Yeo C.J. 2012).

In the early stage of acute appendicitis, autonomic visceral pain afferent fibers mediate the symptoms and they begin as a midabdominal or periumbilical discomfort or ache. As the inflammation extends to the parietal peritoneum, the activation of somatic pain fibers localizes the pain to the right lower quadrant (re-

gion of the appendix) (Nase et al. 1980, Yeo C.J. 2012, Andersson et al. 2008, Alvarado 1986, Korner et al. 2000). This typical presentation occurs only in 50-60% of patients. In older and pregnant patients, and patients in whom the appendix is in an atypical location, unusual presentations and pain patterns are not uncommon.

The most usual clinical finding is tenderness in the right lower quadrant. An area of maximal tenderness, located two thirds of the distance along a line from the umbilicus to the right anterior superior iliac spine, is called McBurney's point (McBurney 1894, Grover et al. 2012). Signs of peritoneal inflammation or irritation can be demonstrated by many methods. Asking the patient to cough or bounce elicits pain in the right lower quadrant. Rebound tenderness is tested by the sudden release of abdominal palpation pressure (Blumberg's test). Rovsing's sign is pain in the right lower quadrant with palpation pressure in left lower quadrant. A positive psoas sign (hip extension or hip flexion against resistance) reflects irritation to the iliopsoas muscle by inflamed appendix. This is seldom seen in early acute appendicitis but is clearer in retrocecal acute appendicitis. As the inflammation of the parietal peritoneum proceeds, muscle guarding as resistance to palpation comes clearer (reflex involuntary rigidity). When appendicitis is sufficiently advanced, it may be possible to palpate a tender mass in the right lower quadrant (Alvarado 1986, Andersson 2004, Yeo C.J. 2012). Temperature is often mildly elevated in acute appendicitis patients, but provides very little diagnostic significance in acute appendicitis (Andersson et al. 1999, Andersson 2004). Although the initial temperature does not have any significant diagnostic value, it still remains a parameter worth measuring when observing a person with suspected acute appendicitis (Andersson et al. 2000).

Nausea or vomiting, peritoneal irritation and migration of pain are the most significant predictors of acute appendicitis (Korner et al. 2000, Andersson 2004). However, many of these variables have exhibited heterogeneous results between the studies, probably for several reasons (Andersson 2004). The clinical evaluation is a subjective appraisal of the patient's reaction to the surgeon's examination. This process cannot be standardized, which explains the relatively low interobserver reliability of clinical findings (Bjerregaard et al. 1983). Another reason is related to the heterogeneous nature of study populations with respect to the proportions of patients with different stages of acute appendicitis (Andersson 2004). Even clinical findings and laboratory test results combined have been shown to have a poor ability to discriminate between uncomplicated and complicated appendicitis (Atema et al. 2015c).

2.6.2 Laboratory tests

Patients with suspected acute appendicitis have been mainly managed on the basis of their disease history and physical examination. The value of laboratory examinations is controversial, but several diagnostic laboratory values that measure the inflammatory response have been proposed as beneficial in diagnosing acute appendicitis. All clinical and laboratory variables are weak discriminators on their own, but they achieve a much higher discriminatory power when combined (Andersson et al. 1999, Andersson 2004, Farooqui et al. 2015). None of these factors, neither independently nor combined, can provide 100% certainty in ruling out acute appendicitis (Andersson et al. 1999, Andersson 2004, Farooqui et al. 2015).

2.6.2.1 White blood cell

Although most studies claim that the white blood cell (WBC) count is elevated in acute appendicitis diagnosis, its significance varies greatly (Grönroos et al. 1999, Andersson 2004). The WBC has been shown to have sensitivity for acute appendicitis, especially in the early phase of disease, and it has been claimed to be the preferred diagnostic laboratory test (Schellekens et al. 2013, Grönroos et al. 1999, Paajanen et al. 2002a, Andersson et al. 1999). However, the determined cutoff points using ROC curves have poorly discriminated between patients with or without acute appendicitis, which reduces the clinical usefulness of the test (Grönroos et al. 1999, Schellekens et al. 2013). The WBC is increased in 70% of patients with other causes of pain in the right lower quadrant abdominal pain (Andersson 2004).

2.6.2.2 C-reactive protein

C-reactive protein (CRP), although more specific in acute appendicitis than WBC, is less sensitive in the early stage of disease (Andersson 2004, Grönroos et al. 1999). The relatively slow activation of CRP limits its diagnostic value, and even normal levels cannot rule out a diagnosis of acute appendicitis (Wu et al. 2005, Grönroos et al. 1999). CRP may be more sensitive in detecting complicated acute appendicitis (Grönroos et al. 1999, Andersson 2004, Yu et al. 2013, Farooqui et al. 2015, Moon et al. 2011, Sammalkorpi et al. 2015). This might be related to the results showing that the duration of symptoms is known to correlate with the diagnostic accuracy of CRP in acute appendicitis. CRP reacts to inflammation more slowly than the WBC (Colley et al. 1983). Wu et al (2005) de-

termined different cutoff points of CRP (with corresponding sensitivity and specificity) based on the duration of symptoms (Wu et al. 2005). They showed an increase in diagnostic accuracy with a longer duration of symptoms (Wu et al. 2005). However, not all studies support this conclusion (Atema et al. 2015a). Despite the low positive predictive value of WBC and CRP alone, their combined use may increase the negative predictive value as high as over 90% (Grönroos et al. 1999, Atema et al. 2015a). In female patients especially, normal levels of WBC and CRP have been reported to more accurately exclude the diagnosis of acute appendicitis (Atema et al. 2015a, Gronroos et al. 1999).

2.6.2.3 Other laboratory values

Neutrophils are known to be associated with acute appendicitis (Alvarado 1986). Al-Gaithy et al (2012) demonstrated that neutrophil counts were higher in uncomplicated and complicated acute appendicitis than in negative appendectomy patients, with similar results being reported by Beecher et al (Al-Gaithy 2012, Beecher et al. 2016). One recently suggested laboratory evaluation is the determination of the neutrophil-to-lymphocyte ratio. This has not only been shown to be useful in the diagnosis of acute appendicitis, but also in predicting of its severity (Kelly et al. 2015, Shimizu et al. 2016, Beecher et al. 2016). However, the sensitivity and specificity of the neutrophil count or the neutrophil-to-lymphocyte ratio is no better than that of the WBC or CRP nor is it clinically useful (Shin et al. 2017, Al-Gaithy 2012). The delta neutrophil index (DNI) measures the fraction of immature granulocytes (known to increase in infectious or inflammation conditions) in the circulation and it has recently been introduced as a new inflammatory marker. Shin et al (2017) showed that DNI was an independent predictor of acute appendicitis and complicated acute appendicitis (Shin et al. 2017).

Hyperbilirubinemia is sometimes observed in patients suffering from a septic condition (Miller et al. 1976). Bacteremia is known to cause endotoxemia leading to impaired excretion of bilirubin from the bile canaliculi (Miller et al. 1976). Perhaps for this reason, most of the studies have detected hyperbilirubinemia in the diagnosis of perforated appendicitis (Giordano et al. 2013, Sand et al. 2009). If symptoms and signs suggest the presence of a perforated appendicitis, serum bilirubin measurement is one additional tool in making a diagnosis (Sand et al. 2009, Chaudhary et al. 2013, Eren et al. 2016). Hyperbilirubinemia alone is not a sensitive enough predictor, but might be more useful when integrated with other laboratory tests (Giordano et al. 2013, Eren et al. 2016). Recent studies found that hyperbilirubinemia had also high specificity (but low sensitivity) for distinguishing between patients with acute appendicitis and patients without appendici-

tis (Adams et al. 2016, Sandstrom et al. 2017, Al-Abed et al. 2015, Emmanuel et al. 2011).

Urinalysis is helpful in the differential diagnosis of patients with right lower quadrant abdominal pain. Minimal numbers of red blood cells and WBCs are seen in normal patients as well as in acute appendicitis patients. Abnormal urinalysis was found in 48% of patients with acute appendicitis (Puskar et al. 1995). In a previous study, the correlation between urinalysis and acute appendicitis was equivocal (Kretchmar et al. 1963). However, in a recent study examining a pediatric population, urinalysis was even shown to be able to discriminate between uncomplicated and complicated acute appendicitis (Chen et al. 2013).

There is ongoing research attempting to discover more accurate and specific laboratory markers for acute appendicitis. The diagnostic potential of the pro- and anti-inflammatory cytokines has been evaluated, but the improvement in the diagnosis of acute appendicitis has been minimal (Rivera-Chavez et al. 2003, Andersson et al. 2014, Paajanen et al. 2002a). Plasma markers calprotectin and serum amyloid A were significantly elevated in acute appendicitis patients, but that study was not able to accurately demonstrate cut-off points for diagnostic use (Schellekens et al. 2013). In another report, serum levels of amyloid A and procalcitonin were associated with acute appendicitis (Abbas et al. 2014). Procalcitonin has been claimed to have some diagnostic value in identifying complicated acute appendicitis (Yu et al. 2013). In addition, changes in the coagulation profile have been observed in acute appendicitis patients (Li et al. 2011).

2.6.3 Diagnostic imaging

2.6.3.1 Ultrasound

In 1986, Puylaert introduced the ultrasound (US) graded compression technique in the diagnosis of acute appendicitis; this approach has a sensitivity of 89% and specificity of 100% (Puylaert 1986). It implies that when a steady pressure is applied in the right iliac fossa by the US transducer, the normal or gas-filled intestinal loops will be moved away from the field of vision or become compressed between the anterior and posterior abdominal walls. On the other hand, an inflamed appendix which is noncompressible will be clearly visualized. This noncompressibility of the appendix is one of the characteristic features of acute appendicitis on US. Other features include local pain over the appendix with compression of the transducer, a thickened appendix (>6mm), increased echogenicity of inflamed periappendiceal fat, fluid in the right lower quadrant and a

possible appendicolith (Birnbaum et al. 2000, Kessler et al. 2004, Jeffrey et al. 1988, van Randen et al. 2011). Lymphoid hyperplasia may result in a noncompressible appendix 6–8 mm in diameter and may be misdiagnosed as acute appendicitis, especially in pediatric patients (Xu et al. 2016). True-positive diagnoses of acute appendicitis can be more accurately identified by the presence of at least two characteristic US features (Xu et al. 2016).

The advantages of US include the lack of ionizing radiation and intravenous contrast agent, and the cost of US is lower as compared to CT or MRI (Parker et al. 2014). Unlike CT and MRI, US is easily accessible and can be performed bedside. However, an important disadvantage is that US has a lower diagnostic accuracy than CT or MRI (van Randen et al. 2011, Birnbaum et al. 1998). The test performance is highly variable and depends on patient specific (obesity, appendix location) and interpreter specific (experience) variables (Keyzer et al. 2005, Kaewlai et al. 2015). The sensitivity and specificity of US in diagnosing acute appendicitis have been 67-88% and 78-100%, respectively (van Randen et al. 2011, Parker et al. 2014, Poortman et al. 2003, Kaiser et al. 2002, Johansson et al. 2007, Shirah et al. 2017). Rates of indeterminate exams are high, with 50-85% of normal appendices not visualized (Yabunaka et al. 2007, Williams et al. 2007). Therefore, a negative or inconclusive US finding does not reliably rule out acute appendicitis and imaging by CT is required (Atema et al. 2015b, Lameris et al. 2009, Parker et al. 2014, Pacharn et al. 2010). Nonetheless, in a pediatric population, a negative US in cases of suspected acute appendicitis had a negative predictive value of 86.4% and when combined with laboratory tests, it increased to 98.9% (Cohen et al. 2015). While US is a safe and generally effective imaging modality, its utility is limited because it is highly operator dependent and has limited sensitivity and specificity in the diagnosis of acute appendicitis, particularly outside of the pediatric population. However, US is the preferred imaging exam in children and pregnant women, in whom the radiation dose should be minimized (Doria et al. 2006, Kaiser et al. 2002, Williams et al. 2007).

2.6.3.2 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an alternative cross-sectional imaging method that uses no ionizing radiation and for that reason, is preferred imaging in children and during pregnancy (Jung et al. 2018, Rosines et al. 2014, Konrad et al. 2015, Rapp et al. 2013). However, MRI is not suited for patients with certain contraindications (e.g. metallic implants, claustrophobia, etc.). MRI features associated with acute appendicitis include appendix diameter >7 mm, possible appendicolith, periappendiceal fat infiltration, periappendiceal fluid, absence of gas

in the appendix, appendiceal wall destruction, restricted diffusion of the appendiceal wall or lumen, or local fluid collections (Leeuwenburgh et al. 2014a). Combinations of two of these features were associated with a probability of appendicitis of 88 % and if three were present, then the value rose to 92 % (Leeuwenburgh et al. 2014a).

Historically, MRI has been limited by its cost and availability, particularly in emergency situations. However, the cost of MRI has become more aligned with CT over time and recently MRI scanners have become increasingly available. In a survey of randomly sampled emergency departments in the United States, 86% were found to have access to MRI scanners and as many as 39% had MRI availability round-the-clock (Ginde et al. 2008). MRI should be used preferentially to US because of the former technique's superior test characteristics and fewer inconclusive findings (Leeuwenburgh et al. 2014c). Repplinger et al (2016, 2018) recently demonstrated that MRI is also an effective alternative to CT in the diagnosis of acute appendicitis (Repplinger et al. 2016, Repplinger et al. 2018), which is in line with several other studies highlighting its high accuracy in the diagnosis of acute appendicitis (Barger et al. 2010, Petkovska et al. 2016, Inci et al. 2011, Martin et al. 2018). The sensitivity and specificity for MRI were 96.9% and 81.3%, compared to those of CT i.e. 98.4% and 89.6%, respectively (Repplinger et al. 2016, Repplinger et al. 2018). However, there have been studies with lower sensitivity and specificity around 80% and 70%, respectively being reported (Konrad et al. 2015, Leeuwenburgh et al. 2014c, Rapp et al. 2013). The results are dependent, at least to some extent, on the expertise of the radiologist analyzing the MRI findings (Leeuwenburgh et al. 2014b, Leeuwenburgh et al. 2012). Even though MRI's diagnostic accuracy is comparable to CT, there is a difference in these techniques' accuracies in grading disease severity. MRI was unable to discriminate accurately between uncomplicated and complicated acute appendicitis, and missed 43% of patients with perforated appendicitis (Leeuwenburgh et al. 2014c).

2.6.3.3 Computed tomography

Computed tomography (CT) was introduced in the 1990s in diagnosing acute appendicitis. The use of preoperative imaging has increased over the past decade in order to reduce the negative appendectomy rate (NAR) (Rao et al. 1998, Lahaye et al. 2015, Raja et al. 2010). Reported CT signs of acute appendicitis can be grouped into an abnormal appendix (enlarged appendix, appendicolith, wall enhancement, wall thickening), right lower abdominal quadrant inflammatory changes (fat stranding, fluid, phlegmon, abscess, extraluminal air, adenopathy,

adjacent bowel wall thickening), and cecal apical changes (focal cecal apical thickening, arrowhead sign, cecal bar) (Table 3) (Rao et al. 1997a, Rao et al. 1997b, Kim et al. 2018a). Multiple CT features are present in most suspected acute appendicitis cases (Rao et al. 1997a, Rao et al. 1997b, Kim et al. 2018a). Many of these same signs, however, are also present with alternative conditions that can clinically mimic appendicitis so closely as to disturb the appendiceal CT evaluation. Out of the CT features for acute appendicitis, the appendicular enlargement (>6mm) has been shown to be the most specific CT finding with the highest sensitivity and negative predictive value (Limon et al. 2015, Rao et al. 1997a). The presence of an enlarged appendix with periappendiceal fat stranding occurs in 93% of acute appendicitis CT cases and other signs were considered as additional findings (Rao et al. 1997a). There are studies that have claimed that the experience of the interpreter exerts a remarkable influence on the result of CT diagnosis for acute appendicitis (Ceydeli et al. 2006, Wise et al. 2001, Poortman et al. 2010). However, contradictory results where the experience of radiologist exerted no significant impact on the accuracy of CT diagnosis have been also reported (Albano et al. 2001, Limon et al. 2015).

CT has been criticized of causing a delay in diagnosis and a possible risk for appendiceal perforation. Nonetheless, it has been shown that waiting for CT results does not increase the time spent in the emergency department and is not associated with an increased perforation rate (Jones et al. 2004). Studies that have compared the NAR, before and after the implementation of CT, have detected an association between the increased use of CT and a reduced NAR (Rao et al. 1999, Wagner et al. 2008, Raman et al. 2008, Raja et al. 2010, Coursey et al. 2010, van Rossem et al. 2016a). In the Netherlands, the NAR decreased from 19% to 5% after the implementation of a guideline for mandatory preoperative imaging of all suspected acute appendicitis patients (Boonstra et al. 2015, Lahaye et al. 2015); and other studies support this result (Raja et al. 2010, Soyer et al. 2013). CT has been shown to have high sensitivity and specificity and for that reason, it has become the gold standard imaging modality for suspected acute appendicitis (Rao et al. 1998, Pickhardt et al. 2011). Since the treatment paradigm of uncomplicated and complicated acute appendicitis may be changing, an accurate diagnosis for severity of acute appendicitis in essential. Recently, Kim et al (2018) analyzed CT features for differentiating complicated and uncomplicated acute appendicitis (Kim et al. 2018a). Several features were informative for complicated appendicitis i.e. an extraluminal appendicolith, abscess, appendiceal wall enhancement defect, extraluminal air, ileus, periappendiceal fluid collection, ascites, intraluminal air, and intraluminal appendicolith showed a pooled specificity greater than 70% (range, 74%-100%), but sensitivity was limited (range, 14%-59%). Periappendiceal fat stranding was the only feature that showed high sensitivity (94%) but low specificity (40%) (Kim et al. 2018a, Foley 2018). CT imag-

es of normal, uncomplicated and complicated acute appendicitis are shown in Figure 1-3.

The concern regarding CT imaging is the ionizing radiation exposure (Pearce et al. 2012, Brenner et al. 2007, Smith-Bindman et al. 2009, Rogers et al. 2015). New data confirm that the cancer risk associated with the radiation from a CT imaging is very small, but not zero (Pearce et al. 2012, Hall et al. 2008, Rogers et al. 2015). The incidence of acute appendicitis is high in adolescents and young adults, emphasizing the need for reducing the radiation dose. The individual risk is very small and is outweighed by the benefit of the diagnosis, provided that the imaging is clinically justified. Nevertheless, preoperative imaging has reduced the NAR by almost 15% (Sartelli et al. 2018). Although clinical benefits should outweigh the small absolute risks of radiation, it should not be ignored (Rogers et al. 2015) and radiation doses from CT scans ought to be kept as low as possible.

Kim et al (2011) showed that contrast enhanced low-dose CT did not differ, in terms of radiologist diagnostic confidence, appendiceal visualization or sensitivity for suggesting some other diagnosis as compared to standard-dose CT (Kim et al. 2011). Similar results were reported by Sippola et al (2018), in which the same patient with suspected acute appendicitis underwent both standard and low-dose CT (radiation dose 4.44 vs 3.33mSv) (Sippola et al. 2018). The diagnostic accuracy was 79% (95% CI 66%-89%) in low-dose and 80% (95% CI 67%-90%) in standard CT as assessed by the primary radiologist. The accuracy in classifying the severity of the acute appendicitis was 79% with both protocols. Overall, low-dose CT in suspected acute appendicitis has not been found to be inferior to standard-dose CT (Kim et al. 2012, Kim et al. 2011, Sippola et al. 2018). Storz et al (2018) analyzed the impact of the reduction of the radiation dose in CT on the diagnostic performance in patients with suspected appendicitis (Storz et al. 2018). Appendicitis was correctly identified in all reference and low-dose datasets (75%, 50%, 25% of standard dose), with sensitivity of 100% and negative predictive value of 100% (Storz et al. 2018). The presence of complications was correctly detected in all reference, 75%, and 50% datasets, but was decreased in 25% datasets (sensitivity 77.8% and negative predictive value 97.4%) (Storz et al. 2018). These results indicate that 75% - 50% of the standard radiation dose is sufficient to achieve a CT-based diagnosis of acute appendicitis, but a further reduction in the radiation dose is associated with a decreased diagnostic performance (Storz et al. 2018). The LOCAT group (2017) showed that the radiation dose of appendiceal CT for adolescents and young adults could be reduced to 2 mSv, from the standard <8mSv, without impairing clinical outcomes (Group 2017). Low-dose CT is highly effective for the diagnosis of suspected appendicitis since it possesses a similar sensitivity and specificity than standard-dose CT

(96.2% and 93.2% vs 96.4% and 92.1%, respectively) and thus can be considered as a valid first-line imaging test (Yun et al. 2017).

Table 3 CT criteria for uncomplicated and complicated acute appendicitis (Kim et al. 2014, Kim et al. 2018a)

Uncomplicated acute appendicitis	Complicated acute appendicitis
appendiceal diameter >6mm	appendicolith (intra- or extraluminal)
appendiceal wall thickening	periappendiceal abscess formation
abnormal contrast enhancement of the appendiceal wall	appendiceal wall enhancement defect
inflammatory edema	extraluminal gas
	periappendiceal fluid collection
	free peritoneal fluid
	acute appendicitis with tumor

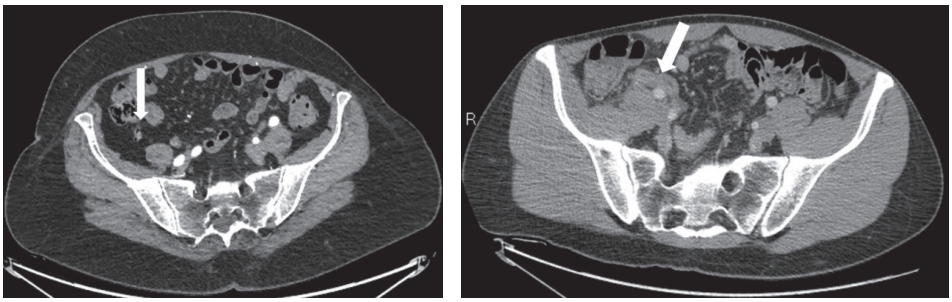

Figure 1 On the left, CT image of normal appendix and on the right, an uncomplicated acute appendicitis with appendiceal wall thickening and edema.

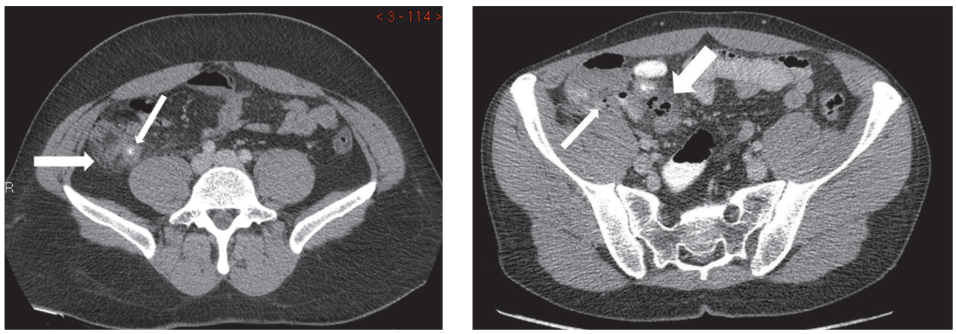

Figure 2 On the left, acute appendicitis with appendiceal wall thickening and edema and an intraluminal appendicolith (narrow arrow). On the right, complicated acute appendicitis with perforation with free extra-luminal air (narrow arrow) and abscess formation (thick arrow).

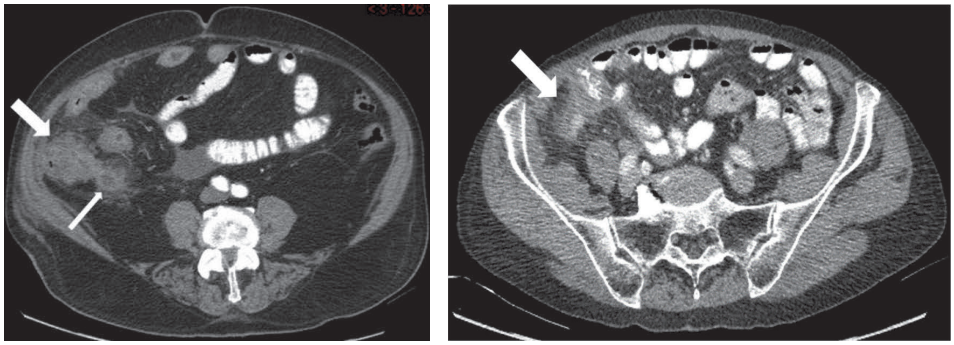

Figure 3 CT images of two appendiceal tumor patients with acute appendicitis. No obvious signs of any tumor, but wall thickening of cecum (thick arrow) and appendiceal lumen dilatation (narrow arrow).

2.6.4 Differential diagnosis of acute appendicitis

The evaluation of patients with suspected acute appendicitis is driven by the goal of identifying all patients presenting with acute appendicitis as early in their clinical course as possible while minimizing the nontherapeutic surgery rate. Missed diagnosis of acute appendicitis, especially when perforated, can result in severe adverse patient outcomes, while nontherapeutic surgery incurs surgical morbidity without treating the underlying condition. As the treatment paradigm of uncomplicated and complicated acute appendicitis may be changing, it is evident that a more precise differential diagnosis is needed (Gronroos 2011).

The differential diagnosis of acute appendicitis includes a wide spectrum of diseases ranging from conditions that require prompt surgical intervention to benign self-limiting disorders (Purysko et al. 2011, Heller et al. 2012, Kraemer et al. 2000). Non-specific acute abdominal pain (NSAP) is one of the most frequent causes of admission to an emergency room along with acute appendicitis (Sheridan et al. 1992). The differential diagnosis between these two conditions can be challenging. NSAP is a condition to describe cases with an atypical expression, and for which no specific reason for abdominal pain can be found. The incidence of NSAP patients has varied from 10% up to 67%, and it seems to be higher in younger age groups (Sheridan et al. 1992, Morino et al. 2006, Pennel et al. 2014, Dominguez et al. 2011). After NSAP, the two main differential diagnoses of patients with suspected acute appendicitis are gynecological disorders and acute diverticulitis (Ma et al. 2010, Kim et al. 2008, Schellekens et al. 2013). A comparison of alternative diagnoses between men and women did not reveal any major differences other than in gynecological disorders between the two genders (Pooler et al. 2012).

Although the differential diagnosis of acute appendicitis is difficult, the correct preoperative evaluation of the severity of appendiceal inflammation is even more challenging. To be able to optimize the treatment strategy for both uncomplicated and complicated acute appendicitis, preoperative differential diagnosis is essential. Frequently described predictors of perforated acute appendicitis include higher age (Augustin et al. 2011, Guller et al. 2011), longer duration of symptoms (Körner et al. 1997, Augustin et al. 2011, Broker et al. 2012, Lin et al. 2005), and clearly increased levels of inflammatory markers (Lin et al. 2005, Broker et al. 2012, Andersson 2004). Although these elements in the routine diagnostic assessment are weak discriminators individually, their combination can achieve a higher discriminatory power for the diagnosis of acute appendicitis (Andersson 2004, Atema et al. 2015c). None of the previous predictors was able of ruling out appendicolithic acute appendicitis (Shindoh et al. 2011). The need for a differential diagnosis within appendicitis for treatment optimization seems to account for and support the increased use of imaging modalities. US and MRI are unable to accurately grade appendiceal inflammation severity (Leeuwenburgh et al. 2014c, Birnbaum et al. 1998), whereas CT has demonstrated the highest ability in the differential diagnosis between uncomplicated and complicated acute appendicitis (Kim et al. 2014, Verma et al. 2015, Kim et al. 2018a).

2.6.4.1 Appendiceal neoplasms

As the nonoperative management of appendicitis gains popularity, the identification of patients who are at increased risk for appendiceal tumors becomes increasingly important. Appendiceal tumors are commonly incidental findings in appendectomy specimens from patients who presented with acute appendicitis. The incidence of an appendiceal tumor in appendectomy specimens has ranged from 0.9%–2.5% (Andersson et al. 2007, Murphy et al. 2006, Teixeira et al. 2017, Loftus et al. 2017). The differential diagnosis of acute appendicitis with or without a tumor has been shown to be challenging. For patients presenting with acute appendicitis, some features displayed at admission may predict the presence of an underlying appendiceal tumor: advanced age, multiple comorbidities, atypical clinical presentation, and complicated appendicitis in imaging (Loftus et al. 2017, Carpenter et al. 2012, Furman et al. 2013, Wright et al. 2015). Unfortunately, all of these features lack good enough specificity for clinical use. With the development of diagnostic capabilities like CT, appendiceal tumors may increasingly be suspected preoperatively (Whitley et al. 2009, Pickhardt et al. 2002). However, most of the CT signs related to appendiceal tumors are unspecific and can be obscured by signs of acute inflammation (Whitley et al. 2009). In addition, many tumors are small and even neuroendocrine tumors (NET) may be hypovascular in up to 20%

of all cases (Emre et al. 2013, Ganeshan et al. 2013). These facts can explain why most tumors are not identified on preoperative CT (Loftus et al. 2017).

2.6.4.2 Negative appendectomy rate

The NAR for presumed acute appendicitis is defined as the proportion of all appendix specimens removed in which there is no pathological evidence of acute inflammation. NAR is usually considered a quality metric in the treatment of acute appendicitis along with the perforation rate. Historically, the acceptable NAR has varied depending upon the patient's age and gender. In young healthy men with right lower quadrant abdominal pain, a NAR less than 10% has been considered acceptable. In women of reproductive age in whom other pelvic processes can confound the evaluation, the NAR has approached levels as high as 20% (Wagner et al. 2008, Mariadason et al. 2012, Ma et al. 2010, Colson et al. 1997). This is partially explained by the fact that diagnostic laparoscopy has been suggested especially for women of reproductive age with an atypical presentation of acute appendicitis (van den Broek et al. 2000, Bachar et al. 2013). Diagnostic laparoscopy achieves early and accurate diagnosis of acute appendicitis combined with the possibility to treat any intra-abdominal pathology (van den Broek et al. 2000, Bachar et al. 2013, Moberg et al. 1998). On the other hand, regular use of laparoscopy in suspected acute appendicitis patients can increase the costs and it is an invasive procedure (Moberg et al. 1998, Lu et al. 2016, Mock et al. 2016). The NAR has decreased over the past decade in parallel with the improved diagnostic accuracy attributable to the more frequent exploitation of imaging (Lu et al. 2016, Raja et al. 2010, Rao et al. 1999, Wagner et al. 2008, Boonstra et al. 2015, Lahaye et al. 2015).

2.6.5 Diagnostic scoring

Several scoring systems have been created to aid in the clinical diagnosis of acute appendicitis (Alvarado 1986, Andersson et al. 2008, Sammalkorpi et al. 2014, Lintula et al. 2010). The Alvarado score is the most well-known and first created clinical scoring system for improved diagnostics of acute appendicitis (Alvarado 1986). This score was constructed when there were no reliable imaging methods for diagnosing acute appendicitis. At that time, the diagnosis of acute appendicitis relied on clinical symptoms and signs, and laboratory test findings. Since its creation, the Alvarado score has been validated in several studies and has been the gold standard of acute appendicitis diagnostic scoring (Ohle et al. 2011, Mariadason et al. 2012). Studies on the feasibility of the Alvarado score being

applied as a screening method for imaging have also been published (Mariadason et al. 2012, Tan et al. 2013, McKay et al. 2007, Golden et al. 2016, Douglas et al. 2000). In 2008, Andersson et al published The Appendicitis Inflammatory Response (AIR) Score (Andersson et al. 2008). Similar to the Alvarado score, AIR is based on clinical symptoms and signs, and laboratory test findings. When compared to the Alvarado score, the AIR score has displayed a better diagnostic performance in all published studies (Kollar et al. 2015, de Castro et al. 2012, Andersson et al. 2008). An AIR score-based risk classification has also been shown to safely reduce the use of diagnostic imaging (Andersson et al. 2017). The Adult Appendicitis Score published in 2014 by Sammalkorpi et al (Sammalkorpi et al. 2014) was the first scoring system taking into account all well-known features of acute appendicitis: the differences in diagnostics between sexes, duration of symptoms and all inflammatory laboratory tests (WBC, CRP, neutrophils). In addition, the strength is that this score is based on prospectively collected data of all patients with right lower quadrant pain, not only on those operated for suspected acute appendicitis. The Adult Appendicitis Score was superior to the previously published Alvarado Score and the AIR score in its diagnostic performance (Sammalkorpi et al. 2014). After implementation of the Adult Appendicitis Score algorithm, the NAR declined from 18.2% to 8.7% (Sammalkorpi et al. 2017). However, these scoring systems were developed to accurately diagnose acute appendicitis and none of the scoring systems can produce a differential diagnosis of uncomplicated and complicated acute appendicitis. Atema et al (2015) described a scoring system that combined clinical and imaging features with a promising discriminative performance in identifying severity of acute appendicitis (Atema et al. 2015c).

2.7 Management of acute appendicitis

2.7.1 Nonoperative management

In 1886, Fitz published his observations assembled from a large amount of autopsy data that acute appendicitis progressed from mild mucosal inflammation to perforation (Fitz 1886). In 1889, McBurney published the landmark study showing that appendectomy could prevent pelvic abscess resulting from perforated acute appendicitis (McBurney 1891). In the absence of antibiotics at that time, early appendectomy in the case of acute appendicitis saved lives. So powerful was the evidence of the benefits of appendectomy for acute appendicitis that surgical treatment remained the unquestioned gold standard of treatment for over a century. Fitz's (1886) observation was long neglected i.e. that one-third of autop-

sy examinations showed evidence of spontaneous resolution of previous episodes of acute appendicitis, as was the report by Coldrey et al (1956) of a large series of acute appendicitis patients treated nonoperatively with antibiotics (Fitz 1886, Coldrey 1956). In the 1960s and 1970s, the Navy realized that treatment of sailors with acute appendicitis while at sea on submarines was best accomplished by nonoperative antibiotic therapy and postponing surgical therapy until the ship surfaced, often weeks after the initial episode of acute appendicitis occurred. Perforations were only rarely observed with this treatment strategy (Rice 1964). Nevertheless, mortality from perforated acute appendicitis was high, and appendectomy could be performed with relatively little morbidity. Because of the potential for reducing the complications associated with perforated acute appendicitis, emergency appendectomy remained the accepted treatment for patients with presumed appendicitis for over a century.

During the last decades, initial nonoperative management of acute appendicitis has been investigated in the adult population and several randomized controlled trials (RCTs) have reported an effectiveness of >60 %, with the recurrence rate ranging from 13.9% to 35% at 1-year follow- up (Eriksson et al. 1995, Styrud et al. 2006, Hansson et al. 2012, Vons et al. 2011, Salminen et al. 2015, Park et al. 2017). Earlier studies by Styrud et al (2006) and Hansson et al (2009) were limited by study design limitations such as reliance on clinical diagnosis alone, suboptimal antibiotic selection and restricted patient selection (Styrud et al. 2006, Hansson et al. 2009). Even though these studies had several limitations, they were able to demonstrate that acute appendicitis could be successfully treated with antibiotics. Vons et al (2011) were the first to use CT imaging confirmation for acute appendicitis diagnosis which permitted a more accurate distinguishing between uncomplicated acute appendicitis from its complicated counterpart (Vons et al. 2011). However, they did not exclude uncomplicated acute appendicitis patients with an intraluminal appendicolith. As a result, they noted that appendicoliths were significantly associated with a greater risk for nonoperative treatment failure and complicated acute appendicitis. Another limitation of this study was the antibiotic selection, as the chosen compounds, amoxicillin-clavulanic acid, provide only limited coverage for Escherichia coli, the most common pathogen present in acute appendicitis (Vons et al. 2011). In 2015, Salminen et al used CT diagnosis to minimize the diagnostic uncertainty and enrolled into a nonoperative treatment group uncomplicated acute appendicitis patients without an appendicolith (Salminen et al. 2015). In that study, the more broad-spectrum antibiotic, ertapenem, was used to cover all major gastrointestinal tract pathogens. The differences found in these studies are shown in Table 4. Meta-analyses of these studies revealed that nonoperative treatment of acute appendicitis is less effective but could avoid surgery in 60–85 % of patients (Sallinen et al. 2016, Harnoss et al. 2017, Poon et al. 2017, Podda et al. 2017). Antibiotic therapy is only intended for patients with uncomplicated appen-

dicitis with surgical treatment being needed in complicated acute appendicitis with appendicolith or perforation. Although antibiotic treatment alone can be successful, patients should be made aware of a failure rate at 1 year of around 25-30% with the need for readmission and surgery (Varadhan et al. 2012). It is also unclear whether the success in avoiding immediate surgery justifies the potential risk of recurrence or missed appendiceal neoplasms, especially in older patients (Teixeira et al. 2017). Even though, none of the RCTs could demonstrate the non-inferiority of nonoperative antibiotic treatment over appendectomy, it is definitely a feasible and effective alternative for surgical treatment. The nonoperative treatment has been shown to diminish the length of hospital stay during the first admission (Di Saverio et al. 2014) and to reduce the numbers of lost work days, both leading to lower costs compared to surgical treatment (Sippola et al. 2017, Allievi et al. 2017). Patients with uncomplicated acute appendicitis averse to surgery are likely to choose an initial trial of antibiotics; those not favoring the possibility of recurrence may prefer appendectomy. The choice between nonoperative and operative management is dependent on the patient's values and preferences, and requires shared decision-making (Flynn et al. 2012, Sallinen et al. 2016, O'Connell et al. 2018).

Table 4 Major randomized clinical trials comparing nonoperative antibiotic therapy with appendectomy in patients with acute appendicitis

Reference	Inclusion Criteria	Age	Number of Patients	Antibiotics Used for Nonoperative Treatment	Appendectomy in Patients Treated Nonoperatively	Limitations
Eriksson et al 1995	US imaging	18-75	Surgery: 20 Antibiotic: 202	IV: cefotaxime, tinidazole Oral: ofloxacin, tinidazole	7/20 (35%)	Small number of patients
Styrud et al 2006	Clinical diagnosis	18 - 50	Surgery: 124 Antibiotic: 128	IV: cefotaxime, tinidazole Oral: ofloxacin, tinidazole	31/128 (24%)	Female patients excluded
Hansson et al 2009	Clinical diagnosis	>18	Surgery: 167 Antibiotic: 202	IV: cefotaxime, metronidazole Oral: ciprofoxacin, metronidazole	96/202 (48%)	96/202 patients in the nonoperative group crossed over to the surgery group
Vons et al 2011	CT imaging	>18	Surgery: 119 Antibiotic: 120	IV: amoxicillin plus clavulanic ac Oral: amoxicillin pluc clavulanic acid	44/120 (37%)	Complicated (appendicolith) acute appendicitis included in nonoperative treatment group; Suboptimal antibiotic for acute appendicitis
Salminen et al 2015	CT imaging	18 - 60	Surgery: 273 Antibiotic: 257	IV: ertapenem Oral: levofloxacin, metronidazole	70/257 (27%)	Slow enrolment; <20% of the patients treated for uncomplicated acute appendicitis in the study hospitals recruited to study

The spontaneous resolution of uncomplicated acute appendicitis may be an important issue in the future treatment of appendicitis. Park et al (2017) published the results of their trial where nonoperative treatment failure rates in patients with CT confirmed uncomplicated acute appendicitis appeared to be similar in no-antibiotics and antibiotic-treated patients (Park et al. 2017). The one month follow-up treatment failure was 7.3% in the no-antibiotics group and 7.4% in the antibiotic-treated group, with the corresponding values at the 1-year follow-up being total treatment failures of 23.4% and 20.7% (Park et al. 2017). Similar spontaneous resolution results have been described in acute uncomplicated diverticulitis patients (Brochmann et al. 2016, Livingston et al. 2011, Mali et al. 2016, Isacson et al. 2014, Isacson et al. 2015, de Korte et al. 2012, Chabok et al. 2012).

It has been suggested that nonperforating appendicitis and nonperforating diverticulitis are different manifestations of the same underlying colonic process (Livingston et al. 2011). Although the uncomplicated acute appendicitis group includes patients who will probably experience a spontaneous resolution, unfortunately they cannot be reliably identified a priori based on the currently available clinical, laboratory, and radiologic data. More importantly, those patients who are destined to fail nonoperative antibiotic treatment still cannot be pinpointed for early appendectomy.

2.7.2 Surgical management

2.7.2.1 Open and laparoscopic

McBurney first described appendectomy in 1894 (McBurney 1894). After being introduced, it rapidly became one of the most common abdominal surgical operations due to the high incidence of appendicitis and furthermore the large number of patients with suspected acute appendicitis. Open appendectomy was used without technical changes for almost one century. In open appendectomy, a right lower muscle-splitting incision is performed at the point of maximum of tenderness (i.e. McBurney's point). Fascia transversalis and peritoneum are opened and usually the cecum presents almost immediately. The appendix can be found near the ileocecal fold and delivered out from the wound. The mesentery of the appendix is ligated, the stump of the appendix crushed and ligated. The appendix is divided from the base above the ligature and removed. The appendiceal stump can be invaginated into the cecal wall with a purse-string suture. The wound is closed in layers (Zollinger Robert M. 2011).

In 1983, a German gynecologist Semm performed the first laparoscopic appendectomy (Semm 1983). Although not accepted at first, laparoscopy has become the operative approach in the majority of abdominal procedures and laparoscopic appendectomy is currently the gold standard. In laparoscopic appendectomy, the pneumoperitoneum is created, the first port for the laparoscope is inserted above umbilicus in the midline. Under direct vision, two additional ports are inserted into the abdomen, one is usually in the left lower quadrant with the other in the suprapubic position in the midline. Once the appendix is visualized, the mesentery is divided at its base with a diathermy instrument or an ultrasound scalpel. The base of the appendix is closed with loop-sutures, clips or an endoscopic linear stapler depending on the surgeon's preference and the type of appendicitis in question. The resected appendix is removed in a plastic bag through the ab-

dominal wall. Ports are removed under the direct vision with an endoscope and wounds are sutured closed (Zollinger Robert M. 2011, Sallinen et al. 2017). Laparoscopic images of normal uninflamed appendicitis, uncomplicated and complicated acute appendicitis are shown in Figure 4 and 5.

Traditionally peritoneal irrigation and postoperative drainage have been used in the case of peritonitis to avoid the risk of a postoperative intra-abdominal abscess. It is advised that the bacterial load should be reduced by suction; especially the fluid from the right paracolic and pelvic area should be cleaned (St Peter et al. 2012). However, irrigation of intra-abdominal space in case of perforated appendicitis seems to make no difference or even to lead to higher number of abscesses compared to suction alone (St Peter et al. 2012, Moore et al. 2011). In addition, postoperative drainage has not been shown to reduce the incidence of postoperative abscess (Rather et al. 2013, Allemann et al. 2011, Cheng et al. 2015).

In 2010, a Cochrane review indicated that laparoscopic appendectomy was superior to the open approach (Sauerland et al. 2010). In numerous studies, the laparoscopic approach has been shown to be the preferable surgical technique in both uncomplicated and complicated acute appendicitis for several reasons (Masoomi et al. 2011, Tiwari et al. 2011, Horvath et al. 2017, Sohn et al. 2017). Wound infection, incidence of incisional hernias, postoperative pain, time to regular bowel function, hospital stay and time to daily activities can be significantly reduced by adopting an laparoscopic approach (Sauerland et al. 2010). The duration of laparoscopic surgery was 10 min longer and it leads to higher in-hospital but lower post-hospital costs (Biondi et al. 2016, Sauerland et al. 2010). At the beginning of the laparoscopic era, one of the disadvantages of laparoscopic approach was the higher rate of intra-abdominal abscesses (Jaschinski et al. 2015, Sauerland et al. 2010). However, this has not been reported in any of the more recent studies and may be related to the early years of laparoscopic approach (Taguchi et al. 2016, Dai et al. 2017). In 2014, Andersson et al published a population based study where the laparoscopic approach was associated with fewer wound complications but a higher rate of abdominal abscesses and intestinal injuries (Andersson 2014). In the same study, the rate of conversion from laparoscopy to open appendectomy decreased from 75.3% in 1992 to 19.7% in 2008, demonstrating the significance of experience on the conversion rate. A population based analysis from Finland by Kotaluoto et al in 2017 reported that open appendectomy was associated with six-fold mortality as compared to laparoscopic technique (Kotaluoto et al. 2017). However, there are several limitations in this study as negative explorations performed via laparoscopy were not included in the study, with the patient selection favoring the laparoscopic approach being provided to healthier patients and the study design included converted laparoscopic operations in the open surgery group (Kotaluoto et al. 2017). Nevertheless, these re-

sults explain the prompt increase in the use of laparoscopic technique reported by Sahm et al (Sahm et al. 2013) showing that in 2005 47% of all appendectomies in Germany were performed laparoscopically but that this rate had increased up to 86% in 2009 (Sahm et al. 2013). Both open and laparoscopic appendectomy techniques are still in clinical use round-the-clock. However, the laparoscopic approach is the current state-of-the-art in the treatment of acute appendicitis. The recognized disadvantages of the laparoscopic approach as compared to the open technique are its procedural length, the rate of intra-abdominal abscesses and costs. However, these decrease with increasing experience and operation frequency. An additional benefit of laparoscopy is the possibility to evaluate the intra-abdominal condition and to detect other reasons for abdominal pain.

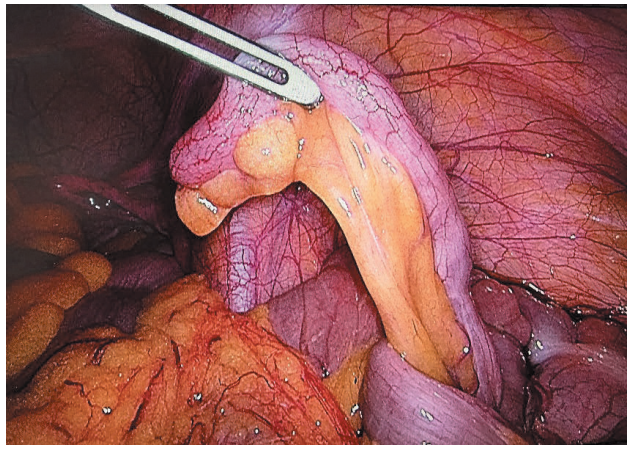

Figure 4 Laparoscopic image of normal appendix without inflammation.

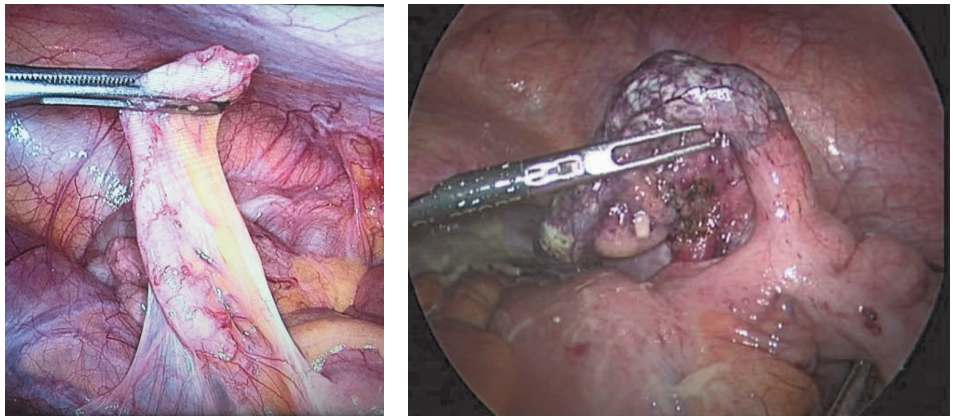

Figure 5 Laparoscopic image of uncomplicated acute appendicitis (left) and complicated acute appendicitis (right).

2.7.2.2 Other mini-invasive techniques

To further reduce the surgical trauma, a single-incision laparoscopic surgery (SILS) for appendectomy was first reported by Pelosi et al in 1992 (Pelosi et al. 1992). SILS has been shown to be associated with comparable post-operative morbidity rates as the laparoscopic approach (Gill et al. 2012, Antoniou et al. 2014). The disadvantages of SILS are that it is a more difficult technique with a higher failure rate in inexperienced hands, its longer operating time and higher costs (St Peter et al. 2011, Kim et al. 2015, Aly et al. 2016). A higher conversion rate has been observed, especially in complicated acute appendicitis operations (Kim et al. 2015, Deng et al. 2017). The main advantages of SILS are less post-operative pain and better cosmetic outcomes (Aly et al. 2016); however no significant difference to laparoscopic approach has been shown in every study (Qiu et al. 2014). The larger opening through the umbilicus also seems to result in an increased rate of hernias (Antoniou et al. 2018). The role of SILS technology seems to provide marginal gains in selected patients, but it seems unlikely that it will find widespread use in light of its higher costs and increased procedural complexity (Sohn et al. 2017).

Natural orifice transluminal endoscopic surgery (NOTES) is a technological adaptation of laparoscopy and its use has recently been studied also in abdominal emergencies such as in acute appendicitis (Bingener et al. 2014, Bulian et al. 2017). Its role and application are controversial and this technique still remains experimental and should be performed only in registered clinical trials.

2.7.3 Treatment of periappendicular abscess

The optimal management of complicated acute appendicitis presenting with a periappendicular abscess after initial conservative treatment remains controversial (Cheng et al. 2017). The most common primary therapy is nonoperative treatment with antibiotics, with or without percutaneous radiological drainage possibly followed by interval appendectomy. In 2010 the meta-analysis conducted by Simillis et al showed that, as compared with immediate surgery, initial nonoperative management of periappendicular abscess was associated with fewer complications, a similar length of hospital stay and duration of antibiotic therapy (Simillis et al. 2010). The randomized study of Mentula et al (2015) showed that an immediate laparoscopic appendectomy was feasible for treating a periappendicular abscess, resulting in fewer readmissions and reinterventions than nonoperative management (Mentula et al. 2015). At the same time, a substantial amount of patients who underwent immediate surgery required conver-

sion to open surgery (10%), a more extensive bowel resection (10%) or had incomplete appendectomy (13%) (Mentula et al. 2015). Immediate appendectomy is needed in cases where the nonoperative treatment has failed with signs of bowel obstruction, sepsis, persistent pain, fever or elevated inflammatory markers without a response to antibiotic treatment. The failure rate of the nonoperative treatment of periappendicular abscess has been shown to be 7.2% (Andersson et al. 2007). In the study of Young et al (2018), nonoperative management failed to treat 25.7% of patients (Young et al. 2018). Similar results were demonstrated by Mentula et al (2015) i.e. 30% of nonoperatively treated patients had to be operated at a median of 9 days after primary admission (Mentula et al. 2015). However, there was also a 13% treatment failure and 10% residual abscess in patients treated with immediate surgery (Mentula et al. 2015). Percutaneous, transgluteal or transrectal drainage results in fewer complications and a shorter overall length of stay than surgical drainage (Oliak et al. 2001, Brown et al. 2003). An abscess smaller than or equal to 3 cm will usually resolve with administration of antibiotics alone. Percutaneous drainage with antibiotics is more efficient, achieving a lower recurrence rate than treatment with antibiotics alone in patients with periappendicular abscess greater than 3 cm (Zerem et al. 2007).

The need for interval appendectomy after initial successful nonoperative treatment has been questioned as the risk of appendicitis recurrence has been shown to be rather low, 5-20% (Andersson et al. 2007). However, there are some recent studies reporting alarming rates of appendiceal neoplasms detected at interval appendectomy (Wright et al. 2015, Furman et al. 2013), especially in patients over 40 years of age (Wright et al. 2015, Carpenter et al. 2012, Furman et al. 2013). The study of Carpenter et al (2012) revealed a 28% rate of appendiceal malignancies among interval appendectomy patients with a mean age of 62 years (Carpenter et al. 2012). Similar results were found by Wright et al (2015) i.e. an appendiceal neoplasm incidence of 12% (11/89) following interval appendectomy. The rate of neoplasm in patients over 40 years was 16% (10/62) compared with 4% (1/27) for those under 40 years (Wright et al. 2015). Similar results were also shown in study of Furman et al (Furman et al. 2013).

Taking into account both the risk of missing an underlying malignancy and the recurrence of appendicitis, interval appendectomy is usually recommended (Corfield 2007). For example, in a retrospective study conducted by Lee et al (2011), it was demonstrated that 80% of appendiceal tumors presented with a periappendicular abscess (Lee et al. 2011). Due to the high incidence of appendiceal neoplasms among periappendicular abscess patients, Teixeira et all (2017) concluded in their study that all patients subjected initially to nonoperative treatment (percutaneous drainage and antibiotics) should be submitted to interval ap-

pendectomy and this is in line with another guideline provided by Gorter et al (Gorter et al. 2016, Teixeira et al. 2017).

2.8 Outcomes of acute appendicitis treatment

2.8.1 Treatment success

The treatment effectiveness of appendectomy is almost 100% in terms of removal of the inflamed organ. However, the complication free treatment success varies depending on severity of the appendiceal inflammation, surgical modality, patient characteristics, surgeon's experience, the time of the study and the number of patients treated by that procedure. The reported overall complication rates of appendectomy vary between 8% and 31% (Bhangu et al. 2015, Sauerland et al. 2010, van Rossem et al. 2016b). In the past decade, improved diagnostics due to the increased use of imaging preoperatively have allowed a more accurate preoperative differentiation of uncomplicated and complicated acute appendicitis. Because of this and the increasing knowledge of the different pathophysiology of uncomplicated and complicated acute appendicitis, the nonoperative treatment of acute appendicitis has become a major focus of appendicitis research. The nonoperative management of uncomplicated acute appendicitis has been investigated in the adult population and several RCTs reported an effectiveness of >60 %, with the recurrence rate ranging from 13.9% to 35% at the 1-year follow- up (Eriksson et al. 1995, Styrud et al. 2006, Hansson et al. 2012, Vons et al. 2011, Salminen et al. 2015, Park et al. 2017). Treatment success or effectiveness of these RCTs has somewhat varied depending on study design limitations, statistical issues and different primary outcomes. When comparing between two fundamentally different treatment methods (nonoperative vs surgical approach), selecting one relevant primary outcome is challenging; in some respects the operative management, i.e. removal of the inflamed organ, will be self-evidently more effective. However, meta-analysis of these studies has revealed that the majority, 60–85 %, of patients with acute appendicitis with nonoperative treatment have been able to avoid surgery (Sallinen et al. 2016, Harnoss et al. 2017, Mason et al. 2012, Varadhan et al. 2010, Varadhan et al. 2012, Poon et al. 2017, Podda et al. 2017). In the RCT conducted by Vons et al (2011), in the Cochrane study from 2011 and in the meta-analysis performed by Varadhan el al (2010), the treatment success of appendectomy was superior to nonoperative treatment (Vons et al. 2011, Wilms et al. 2011, Varadhan et al. 2010). However, in their study, Vons et al (2011) used a suboptimal antibiotic for acute appendicitis in the nonoperative treatment and their primary outcome was post-treatment peritonitis which is chal-

lenging to define. Even though Vons et al (2011) was the first study to use a CT diagnosis of uncomplicated acute appendicitis, appendicolith patients were not excluded from the trial. If Vons et al (2011) had excluded these appendicolith appendicitis patients (i.e. complicated acute appendicitis), no significant difference in outcomes would have been found between the nonoperative and operative group (Vons et al. 2011). In the study of Hansson et al (2009), the results of the nonoperative treatment of acute appendicitis were good; however, these results are limited by study design weaknesses such as reliance on clinical diagnosis alone and patients allocated to antibiotic treatment were able to change to the intervention group. Hansson et al (2009) also compared their nonoperative treatment results to the complications associated with operative treatment (Hansson et al. 2009). Regardless of these limitations, Hansson et al (2009) raised an important point that the characteristics of these patients, switching from the intended antibiotic treatment to surgery, at the time of inclusion did not differ significantly from those patients who completed nonoperative treatment successfully (Hansson et al. 2009). The same observation was made by Salminen et al (2015) in the APPAC study, as 8 patients from 15 patients in the nonoperative group that underwent appendectomy during the primary hospitalization (i.e. evaluated by the on-call surgeons as non-responders) had uncomplicated acute appendicitis (Salminen et al. 2015). This suggests that indications for changing patients from the intended nonoperative treatment to surgery (i.e. treatment failure) were at least in part dependent on a surgeon's individual judgement or preferences more than on the patient's clinical status. In recent meta-analyses, nonoperative treatment of uncomplicated acute appendicitis has been demonstrated to be both safe and efficient (Varadhan et al. 2012, Mason et al. 2012, Harnoss et al. 2017). In the meta-analysis conducted by Harnoss et al (2017), the rate of surgery within 30-days after antibiotic therapy was as low as 13.4% (Harnoss et al. 2017).

In the study of Hansson et al (2009), the recurrence of symptoms within one year was 13.9% for nonoperative treatment. The majority (96.7%) of these nonoperative treatment failure patients eventually underwent surgery. In the study of Vons et al (2011), 36.7% of patients initially treated nonoperatively underwent appendectomy within one year and in the study by Salminen et al (2015), the corresponding value was 27.3%. Salminen et al (2015) excluded patients with appendicolith acute appendicitis from the nonoperative group, explaining the difference also in the one-year treatment success. Overall, 68% (Vons et al. 2011) and 72.7% (Salminen et al. 2015) of nonoperative treatment group patients did not need appendectomy for acute appendicitis during one year of follow-up. At present, the study of Salminen et al (2018) is the only RCT with a 5-year follow-up; the overall recurrence rate was 39.1% as evaluated by the percentage of antibiotic group patients undergoing appendectomy (Salminen et al. 2018). There were a total of 100 patients in the antibiotic group, who underwent appendectomy dur-

ing the 5-year follow-up with 15 were already being operated during the primary hospitalization. Out of the 85 patients who underwent surgery for suspected appendicitis recurrence, seven patients did not have acute appendicitis according to the histopathological examination (Salminen et al. 2018), i.e. the true appendicitis recurrence rate was 30.4 % (78/256).

2.8.2 Mortality

Mortality following appendectomy is rare, but seems to vary by geographic locations. In the industrialized countries, the reported mortality rate varies in a range 0.09-0.24% (Kotaluoto et al. 2017, Tsioplis et al. 2013, Margenthaler et al. 2003, Blomqvist et al. 2001, Andersson et al. 2011, Bregendahl et al. 2013, van Rossem et al. 2016b) whereas in the developing countries, the mortality rate is higher, between 1-4% (Ali et al. 2012, Ohene-Yeboah et al. 2006, Bhangu et al. 2015). In a worldwide observational study of patients from 44 different countries treated for acute appendicitis (95% surgical treatment), the overall mortality rate was 0.28% (Sartelli et al. 2018). Appendectomy mortality is mainly associated with the severity of the disease and patient related factors. As shown by Kotaluoto et al (2017), only 2.6% of immediate causes of death in patients dying within 30-day post-appendectomy were surgery or anesthesia related (Kotaluoto et al. 2017). The mortality rate of emergency appendectomy varies from 0.07-0.7% in uncomplicated acute appendicitis to 0.5-2.4% in perforated acute appendicitis (Margenthaler et al. 2003, Blomqvist et al. 2001, Kraemer et al. 2000). In addition to disease severity, patient related predictors of mortality include the patient's age (>80 years), comorbidities, especially immunosuppression, and cardiovascular diseases (Kotaluoto et al. 2017, Blomqvist et al. 2001, Andersson et al. 2011). In the study of Blomqvist et al (2001), cardiovascular disease was the most common cause of death (25.8%) after appendectomy, followed by perforated appendicitis (19.9%), nonperforated appendicitis (14.3%), and tumors (12.9%) (Blomqvist et al. 2001). Similarly Andersson et al (2011) showed that cardiovascular disease was the most common cause of death (45.8%) (Andersson et al. 2011). A population-based analysis by Kotaluoto et al (2017) showed six times higher mortality after open appendectomy as compared to the laparoscopic technique (Kotaluoto et al. 2017). On the contrary, laparoscopic and open appendectomy had similar values of short-term mortality in the study of Andersson et al (Andersson et al. 2011). Negative appendectomy is strongly associated with mortality and thus the decrease in overall mortality is probably attributable to the improved, more accurate diagnostics and the increased use of laparoscopy, which both have decreased the NAR (Andersson et al. 2011, Kotaluoto et al. 2017, Andersson 2013). The reason for the increased mortality after negative appendec-

tomy is not fully clear. In some of these patients, the underlying condition that caused the death was probably missed at the primary admission and was only diagnosed during follow-up or after death. One reason for this may be that the true diagnosis can be masked by the appendectomy related postoperative pain. Only a few fatal complications related to nonoperative treatment have been described so far, however patients with many of the above mentioned risk factors predicting higher mortality have been excluded from these studies (Allievi et al. 2017, Salminen et al. 2015, Sallinen et al. 2016). Thus, it is possible that only the least sick patients were enrolled in these trials and the true mortality of the nonoperative treatment will be revealed later if nonoperative treatment becomes more popular.

2.8.3 Morbidity

There are reports that the overall complication rates following appendectomy vary from 8.2 to 31.4%, with wound infection rates of 3.3-10.3% and pelvic abscess rates up to 9.4% (Bhangu et al. 2015, Sauerland et al. 2010). The most common complication following appendectomy is surgical site infection, either a superficial wound infection or an intra-abdominal abscess. Both are rare in patients with uncomplicated acute appendicitis and typically occur in those with complicated acute appendicitis. Masoomi et al (2011) reported that the overall complication rates of uncomplicated acute appendicitis were 4.2% for laparoscopic appendectomy and 6.4% in open appendectomy with the corresponding values in perforated acute appendicitis being 18.8% and 26.8% (Masoomi et al. 2011). The most common complications were intra-abdominal abscess (0.3-3.6%), wound infection (0.2-2.8%) and postoperative ileus (1.9-16.6%). The highest rates of complications were reported in complicated acute appendicitis patients treated with open appendectomy (Masoomi et al. 2011). Similarly to mortality, negative appendectomy is also associated with higher rates of complications than appendectomy for uncomplicated acute appendicitis (Jeon 2017, Mock et al. 2016). Urinary tract infection, pulmonary embolism and myocardial infarction were not related to either the surgical approach or disease severity (Masoomi et al. 2011). In the study of Andersson et al (2014), laparoscopy was associated with lower rates of surgical complications overall, but the pattern of complications was different with a lower rate of wound rupture, but a higher rate of intestinal damage associated with the laparoscopic approach (Andersson 2014). Overall wound ruptures are rare, but occur sometimes with open surgery, especially in complicated acute appendicitis (Sauerland et al. 2010). The study of Kim et al (2018) showed that the duration of symptoms before hospital admission was related to the appendiceal perforation rate and complications, but the

time from admission to appendectomy (i.e. hospital delay) was not associated with either of these parameters (Kim et al. 2018b).

The incidence of antibiotic-associated diarrhea appears to be dependent upon which antibiotic is administered and varies from 5% to 25%. The major form of intestinal disorder is the pseudomembranous colitis associated with Clostridium difficile which occurs in 10–20% of all antibiotic-associated diarrheas (Bergogne-Berezin 2000). In their meta-analysis, Harnoss et al (2017) stated that only four recently published prospective studies had investigated these antibiotic related adverse effects (Hansson et al. 2012, Hansson et al. 2009, Salminen et al. 2015, Vons et al. 2011, Harnoss et al. 2017). Two of these studies reported no cases of diarrhea, fungal infection or exanthema, possibly suggesting that there had been under-investigation or under-reporting (Salminen et al. 2015, Vons et al. 2011, Harnoss et al. 2017).

Meta-analyses of mainly retrospective studies recommend initial nonoperative treatment of periappendicular abscess with antibiotics and percutaneous drainage of the abscess if needed (Andersson et al. 2007). Immediate surgery is associated with increased morbidity as compared with nonsurgical treatment (OR, 3.3) and may increase the risk of larger bowel resection for technical reasons (Andersson et al. 2007, Simillis et al. 2010). Immediate surgery has been associated with significantly higher overall complications (OR, 0.24), wound infections (OR, 0.28), abdominal/pelvic abscesses (OR, 0.19), ileus/bowel obstructions (OR, 0.35), and reoperations (OR, 0.17) (Simillis et al. 2010). Wound complications occur in up to 17% of patients with periappendicular abscess after open appendectomy (Simillis et al. 2010, Oliak et al. 2001). However in their randomized study, Mentula et al (2015) demonstrated that immediate laparoscopic surgery in experienced hands was a safe and feasible treatment for appendiceal abscess. It was associated with fewer readmissions and fewer additional interventions than conservative treatment with comparable durations of hospital stay. The rate of uneventful recovery was 90% in the immediate laparoscopic surgery group versus 50% in the conservative group, (p= 0.002) (Mentula et al. 2015).

2.8.4 Long-term outcomes

2.8.4.1 Nonoperative management

There are possible drawbacks of treating uncomplicated acute appendicitis nonoperatively with antibiotics such as the well-recognized risk of increased antibiotic resistance, possible changes in gut bacteria flora and the recurrence of ap-

pendicitis. Conversely, major complications following surgery are also a risk to patients (Hansson et al. 2012). The long-term impact of antibiotic treatment on the patient's quality of life and health care costs is unknown (Harnoss et al. 2017). In at least 1% of appendectomies, there is a histologic demonstration of an appendiceal neoplasm (Teixeira et al. 2017). If these patients were given nonoperative antibiotic treatment, the neoplasm would remain untreated with potentially fatal consequences (Harnoss et al. 2017). Even though the tumor risk has been shown to be higher in complicated acute appendicitis, the risk of missed appendiceal tumors related to antibiotic therapy of uncomplicated acute appendicitis needs to be acknowledged. Enblad et al (2017) reported patients undergoing nonoperative treatment of acute appendicitis as having an increased short- and long-term incidence of bowel cancer as compared to the general population (Enblad et al. 2017). Time to cancer diagnosis was less than three months in 44% of the patients and the majority of patients with cancer had a complicated appendicitis with appendiceal abscess (63%). However, the incidence of bowel cancer (especially right sided colon cancer and appendiceal cancer) was increased both for uncomplicated acute appendicitis and complicated acute appendicitis with a periappendicular abscess. The chain of causation between nonoperative treatment of appendicitis and bowel cancer is unknown (Enblad et al. 2017).

The most widely investigated short- and long-term outcome has been the recurrence of appendicitis after the initial nonoperative management of acute appendicitis in the adult population. Several RCTs have reported a recurrence rate ranging from 13.9% to 35% at 1-year follow- up (Eriksson et al. 1995, Styrud et al. 2006, Hansson et al. 2012, Vons et al. 2011, Salminen et al. 2015, Park et al. 2017). In the study of Salminen et al (2015), the recurrence rate within the first year was 27.3% (70/256). At the 5-year follow-up of that study, the recurrence rate was 39.1% as 30 additional antibiotic-treated patients had undergone an appendectomy between 1 and 5 years (Salminen et al. 2018).

2.8.4.2 Surgical management

Incisional hernia after appendectomy with a McBurney incision is a rare condition despite the fact that the wound is commonly in contact with contaminated tissues (inflamed appendix) and fluids. Complicated acute appendicitis, wound infection, postoperative seroma, diabetes and female gender are risk factors for incisional hernia. Regardless of the high risk of infection, only 34 patients of 4523 patients undergoing open McBurney incision appendectomy developed incisional hernia. Oblique incisions are regarded as low-risk incisions for incisional hernia, which may be one explanation for this low incidence (0.7%) (Beltran et al. 2008).

Andersson et al (2014) demonstrated that the risk for ileus after appendectomy was 1.4%, and there was no clear difference in the risk between laparoscopic and open surgery (1.4% and 1.5%, respectively) (Andersson 2014). Similarly, it was reported by Leung et al that there was no difference between the ileus risks with the laparoscopic versus an open approach (Leung et al. 2009). However, these investigators detected an overall higher incidence of 2.8% and perforated appendicitis and a midline incision were significant risk factors for this condition (Leung et al. 2009). In the study of Rasmussen et al (2018), the overall prevalence of ileus after appendectomy was 1.1%; for the laparoscopic approach it was 0.8% against a value of 1.2% for the open approach. This is evidence of the relatively lower risk of ileus after laparoscopic appendectomy compared with open appendectomy (Rasmussen et al. 2018).

The appendix may have an immunological role, at least in intestinal diseases (Kooij et al. 2016, Sahami et al. 2016, Cheluvappa et al. 2014). It has been investigated whether removal of the appendix could have a role in the development of inflammatory bowel disease or cancer (Lee et al. 2015, Russel et al. 1997, Becker et al. 2005). Already in 2001, Andersson et al reported that the incidence of ulcerative colitis was low after appendectomy for inflammatory conditions such as appendicitis (Andersson et al. 2001). However, in their study, no relationship was found after appendectomy for NSAP. This finding suggested that the inflammatory condition preceding appendectomy rather than appendectomy itself was inversely related to the development of ulcerative colitis (Andersson et al. 2001). Whereas Rasmussen et al (2018) showed that the overall prevalence of ulcerative colitis was 0.15% after appendectomy and 0.19% in the studied controls; for Crohn's disease, the corresponding values were 0.20% and 0.12% (Rasmussen et al. 2018). Though none of these results were statistically significant, appendectomy seems to increase the prevalence of Crohn's disease, but to reduce the rate of ulcerative colitis (Rasmussen et al. 2018). This proposal is in line with previous studies (Gardenbroek et al. 2012). There was no difference in the prevalence of the majority of the examined cancers in the appendectomy groups compared with the background populations (Rasmussen et al. 2018).

The association between acute appendicitis and appendectomy and infertility in women has been studied. The inflammation and possible scarring caused by a perforated appendicitis has been suspected as a reason for infertility (Elraiyah et al. 2014). However, neither appendectomy nor perforated appendicitis was found to be associated with impaired fertility in a recent meta-analysis (Rasmussen et al. 2018).

Stump appendicitis was reported for the first time in 1949 by Baumgardner (Baumgardner 1949). Stump appendicitis is a form of recurrent appendicitis re-

lated to incomplete appendectomy that leaves an excessively long stump after surgery, more commonly for perforated appendicitis (Kanona et al. 2012). The increasing prevalence might have been due to the rapid development of laparoscopic appendectomy that prompted the recognition of stump appendicitis as an entity (Devereaux et al. 1994, Greenberg et al. 1996). However, two meta-analyses investigating stump appendicitis showed that 34.5-37% of the primary appendectomies had been open and 63-65.5% laparoscopic (Kanona et al. 2012, Subramanian et al. 2012). Its true incidence and exact causes remain unclear due to the difficulty in making a reliable diagnosis (Feigin et al. 1993). A history of a previous appendectomy may delay the diagnosis and surgical therapy even more. The delay is associated with increased morbidity because of the high incidence of perforation and the need for more extensive surgery. Subramanian et al (2012) demonstrated a 59% incidence of perforated stump appendicitis or cecal perforation, which is higher than that described in acute appendicitis (Subramanian et al. 2012). This high incidence of perforation may be associated with the delay in diagnosis. The time from appendectomy to the development of stump appendicitis has ranged from 2 months to 50 years (Subramanian et al. 2012, Kanona et al. 2012). The length of the stump has ranged from 0.5 cm to 6.5 cm (Kanona et al. 2012).

2.9 Appendiceal neoplasms

Appendiceal tumors are rare, usually incidental findings, most often detected during the histological evaluation of the appendix specimen. The reported incidence has varied from 0.7% to 2.5% of appendectomy specimens in several large studies (Andersson et al. 2007, Murphy et al. 2006, Teixeira et al. 2017, Loftus et al. 2017). The pathological types and behavior of appendiceal tumors are diverse, and both the classification and terminology have undergone major changes over the last decades (Shaib et al. 2016, Hsu et al. 2013, Brathwaite et al. 2016). The World Health Organization (WHO) has classified appendiceal tumors into two main groups: neuroendocrine tumors (NET) and appendiceal carcinomas (Teixeira et al. 2017). The overall survival rate related to the tumor depends on the histologic subtype (Turaga et al. 2012). The appendiceal NETs belongs to a sub-group of neoplasia where about 80% of diagnoses are incidental among patients treated for acute appendicitis or appendectomy performed for other reasons (Pape et al. 2016). NETs are the most common primary tumors in the appendix (Hsu et al. 2013, Pape et al. 2016). Appendiceal NETs are detected in younger patients than other primary malignant appendiceal tumors, with their incidence being highest at 40 years of age (McCusker et al. 2002, Modlin et al. 2003). In most cases, prognosis is excellent, with a 100% five years' survival rate for a

localized disease and 85-100% for a regional disease (Teixeira et al. 2017). Clinical behavior and prognosis are best predicted by tumor size. At presentation, 90% of tumors are less than 2cm in size and are unlikely to have metastasized, while up to one-third of >2cm lesions have regional lymph node metastasis (Rault-Petit et al. 2018). Treatment of NETs over 2cm and smaller tumors with mesoappendiceal invasion, positive margins, higher proliferative rate and angioinvasion, is right sided hemicolectomy (Pape et al. 2016). Otherwise appendectomy alone is adequate. The more malignant NETs are mixed phenotype tumors: goblet cell tumors and mixed adeno-neuroendocrine carcinoma (MANEC). The incidence of these tumors is rare, accounting for less than 5% of all primary appendiceal tumors (McGory et al. 2005). The five year survival is lower, varying between 40-75% depending on the neuroendocrine and adenocarcinoma component distribution (Landry et al. 2008, Brathwaite et al. 2016). Treatment for these mixed histology NETs is right-sided hemicolectomy regardless of tumor size (Pape et al. 2016).

Appendiceal carcinomas are epithelial tumors and can be further divided into mucinous-type and colonic-type adenocarcinomas (Cortina et al. 1995, Deans et al. 1995, Tang 2010). The 2010 WHO classification recognizes three main categories of mucinous neoplasms: mucinous adenoma, low-grade appendiceal mucinous neoplasm (LAMN) and appendiceal mucinous adenocarcinoma. Although appendiceal mucinous tumors are considered to be benign, these neoplasms can progress to peritoneal dissemination resulting into pseudomyxoma peritonei (Tang 2010). This contains a spectrum of diseases, quite often difficult to classify histopathologically and only the clinical behavior over time ultimately defines the true nature of the tumor (Ronnett et al. 2001). Since mucinous tumors remain a biologically heterogeneous disease entity, varying incidences have been described (Chua et al. 2012). The prognosis of these neoplasms is dependent on whether they have perforated and mucin and epithelial cells are presented outside the appendix (Chua et al. 2012). Centers using complete macroscopic cytoreduction and hyperthermic intra-peritoneal chemotherapy (HIPEC) have reported five year survivals of over 75% in pseudomyxoma peritonei; if there is a more local situation, survival is closer to 100% (Chua et al. 2012). Treatment varies from simple appendectomy to right sided hemicolectomy and cytoreductive surgery with HIPEC depending on histopathology and peritoneal involvement (Chua et al. 2012).

The appendiceal colonic-type adenocarcinomas are rare, with an incidence less than 0.1% of all appendectomies (McCusker et al. 2002). When compared to other primary appendiceal tumors, the colonic-type has the highest incidence of lymph node metastasis (Nitecki et al. 1994, Benedix et al. 2010). When compared to colon cancer, appendiceal colonic-type adenocarcinomas have worse

outcomes, this being attributed to the higher perforation rate occurring in appendiceal tumors (Son et al. 2016). The reported five-year survival has varied between 48-58% depending on the tumor histopathology and perforation (Son et al. 2016, Benedix et al. 2010). The optimal treatment is right sided hemicolectomy (Ito et al. 2004).

3 AIMS OF THE STUDY

This study was carried out to investigate the diagnostics and severity assessment of acute appendicitis, and also the association of an appendiceal tumor with different forms of acute appendicitis. The specific aims of the present study were:

1. To evaluate the feasibility of clinical history and findings and common laboratory tests in diagnosing acute appendicitis.

2. To assess the feasibility of clinical history and findings and common laboratory tests in the differential diagnosis of complicated and uncomplicated acute appendicitis with a special focus on predicting the presence of an appendicolith.

3. To analyze the accuracy of CT in emergency setting in diagnosing acute appendicitis and to assess the effect of the radiologist's experience on the diagnostic accuracy.

4. To determine both the incidence of appendiceal tumors among acute appendicitis patients and the possible tumor association to acute appendicitis severity.

4 MATERIALS AND METHODS

4.1 The APPAC trial

In all of the studies I-III, the analyses were based on the data of the randomized multicenter study protocol comparing appendectomy and antibiotic therapy in the treatment of uncomplicated acute appendicitis (the APPAC trial). A total of 1379 patients were evaluated for enrollment in the APPAC trial. Data used in these studies I-III was collected from all of the patients who were evaluated for enrollment in the APPAC study and underwent a CT scan according to the APPAC trial protocol. The details of the APPAC study protocol and the 1-year follow-up results have been previously published (Paajanen et al. 2013, Salminen et al. 2015). There were six Finnish hospitals participating in this study: three university hospitals (Turku, Tampere and Oulu) and three central hospitals (Mikkeli, Jyväskylä and Seinäjoki). All patients aged 18–60 years admitted to the emergency departments with a clinical suspicion of uncomplicated acute appendicitis were examined by the surgeon on call. Age, gender, body temperature, pain scores (VAS) and the duration of symptoms (< 12 h, 12–24 h or > 24 h) before admission to the hospital were recorded. If acute appendicitis was suspected on the basis of the clinical history and physical investigation, blood tests [blood hemoglobin (Hgb, g/L) and WBC (upper limit of the reference interval 8.2 × 109/L), plasma CRP (reference < 10 mg/L) and creatinine (mmol/L), serum human chorionic gonadotropin (HCG, U/L)] and urine analysis were undertaken. The patients were informed of the study protocol and invited to participate in the APPAC trial and thereafter a CT scan was performed to confirm the diagnosis. The CT scan criteria for uncomplicated acute appendicitis included an appendiceal diameter exceeding 6 mm and there was at least one of the following findings: abnormal contrast enhancement of the appendiceal wall, inflammatory edema, or fluid collections around the appendix. Complicated acute appendicitis at CT was defined as the presence of an appendicolith, free air around the appendix (perforation), or a periappendiceal abscess or the suspicion of a tumor (Table 5).

Table 5 Classification of acute appendicitis in APPAC study

Uncomplicated acute appendicitis
Complicated acute appendicitis
appendicolith
perforation
periappendicular abscess
tumor

4.2 Patients

Information of patient data analyzed in each study is shown in Table 6. The patient data examined in studies I-III were collected prospectively in the APPAC trial. In study IV, a nationwide population-based registry study was accessed in order to assess all diagnosed appendiceal tumors in Finland from 2007 to 2013. Diagnoses were classified according to the WHO International Classification of Disease, version 10 (ICD-10). The study population of appendiceal primary tumors was collected from the Finnish Cancer Registry (FCR) that is responsible for maintaining a nationwide database of all cancer cases in Finland. From the patient population diagnosed with a histologically proven appendiceal primary tumor, we collected medical record data on patients treated in all five university hospitals (Helsinki, Tampere, Turku, Kuopio and Oulu) and three larger central hospitals (Jyväskylä, Mikkeli and Lahti). The medical record data collection included patient demographics, how the tumor was diagnosed and related imaging and operative findings, tumor histology reports and associated treatments. Some of the medical records were not available due to the lack of common hospital district databases at the time of the study. In order to assess the true incidence of appendiceal tumors among all acute appendicitis patients, we collected information from the National Institute for Health and Welfare (NIHW) registry which has data on both acute appendicitis diagnosis and appendectomies during the study period. Dates of admission and discharge, discharge diagnosis, surgical procedure, and demographic data of the patient were recorded.

Table 6 Patient data used in each original study.

	Number of patients	Study details
Study I*	1321 patients	CT performed, age >18
	CT: 970 acute appendicitis	Both uncomplicated and complicated acute appendicitis
	CT: 351 normal/other diagnosis	Patients without acute appendicitis
Study II*	705 patients	CT performed, age >18
	CT: 337 complicated acute appendicitis	
	CT: 368 uncomplicated acute appendicitis	APPAC trial operative treatment group patients, patients who declined to participate in the APPAC trial, or excluded based on age >60
Study III*	1065 patients	CT performed, no age limitations
	CT: 337 complicated acute appendicitis	
	CT: 377 uncomplicated acute appendicitis	APPAC trial operative treatment group patients (n=273), patients who declined to participate in the APPAC trial (n=91), or excluded based on age <18 or >60 (n=13)
	CT: 351 normal/other diagnosis	Patients without acute appendicitis
Study IV	Finnish Cancer Registry: 840 patients with appendiceal tumor	
	504 patients in study hospitals (32 patients excluded based on missing data)	
	472 patients included in study	
	250 patients with appendical tumor and acute appendicitis	
	102 complicated acute appendicitis	
	148 uncomplicated acute appendicitis	
	National Institute for Health and Welfare registry: 19976 patients with both acute appendicitis diagnosis and appendectomy procedure in eight study hospitals	

*APPAC trial: 1379 patients assessed for eligibility, basis for the patient data for studies I-III

4.3 Data collection and methods

4.3.1 Studies I-II

In study I, out of the 1379 APPAC trial patients, we evaluated all of the patients (n = 1321), who had undergone a CT scan including both patients older than 60 years and patients declining to participate in the APPAC trial. These patients were divided into two groups according to the CT findings. In the first group (n = 970), patients either had uncomplicated or complicated acute appendicitis. In the second group (n = 351), patients did not have acute appendicitis i.e. either they exhibited no abnormal findings or they received some other diagnosis after the CT. This group was further divided into four subgroups for subsequent analyses: non-specific abdominal pain (NSAP), acute diverticulitis, gynecological disorders and other diagnoses. Out of 970 patients with an acute appendicitis diagnosis on CT, 705 patients were analyzed in study II. To ensure the diagnosis of uncomplicated acute appendicitis, we included in study II only uncomplicated acute appendicitis patients randomized to the operative treatment in the APPAC trial. All patients with acute complicated appendicitis underwent appendectomy, excluding patients presenting with a periappendicular abscess on CT scan. These

patients were treated with antibiotic therapy and possible drainage of the abscess, unless their clinical condition demanded an urgent operation. In these conservatively treated patients, the CT finding was considered accurate. Patients with false positive CT findings (no acute appendicitis noted after the operation) were excluded from the study II. In the further analyses, we divided the complicated acute appendicitis group into two subgroups: complicated appendicitis with an appendicolith and complicated appendicitis with perforation and/or periappendicular abscess. A total of 368 patients had uncomplicated acute appendicitis (group UA), and 337 patients had complicated acute appendicitis according to the findings of the abdominal CT (group CA). Of the 337 complicated acute appendicitis patients, 256 had appendicolith appendicitis (excluding patients already presenting with a perforation/abscess in addition to the appendicolith) (group CA1); 78 had a perforation and/or periappendicular abscess (group CA2); and 3 patients had an appendiceal tumor evident in the CT images.

4.3.2 Study III

The APPAC trial evaluated altogether 1379 patients for enrollment. Out of these, 1065 patients were evaluated in study III. First, we included uncomplicated acute appendicitis patients randomized to appendectomy (n = 273). Second, we included patients excluded from the original APPAC trial based on either their age (under 18 years and over 60 years, n = 13) or a CT finding of a complicated acute appendicitis patients (n = 337). Third, we included also patients who declined to participate in the APPAC trial randomization after the CT scan (n = 91) and those with a normal or some other diagnosis which was made after the CT scan (n = 351). The APPAC patients randomized to conservative treatment (n = 257) were excluded from this study.

All abdominal CT scans were performed from the diaphragm to the symphysis pubis using multi-detector row helical CT scanners with intravenous administration of contrast medium. The CT images were preoperatively analyzed by the radiologist on call and they were divided into experienced radiologists (consultants, at least 6 years of training) and their inexperienced counterparts (residents, less than 6 years of training). The primary CT findings assessed as false-negative and false-positive were blindly reassessed by one body imaging radiologist and one resident in radiology. The preoperative and reassessed CT findings were compared with surgical and histopathological findings. With respect to the patients who had a normal or some other diagnosis on the CT scan, the final diagnosis was determined from medical records.

4.3.3 Study IV

A total of 840 appendiceal primary tumor patients were identified from the FCR database. Out of these, 504 (60%) patients were treated in the hospital districts of the eight study hospitals and their medical reports were reviewed. The diagnosis was inaccurate in one patient (0.2%) or there was no patient record available in 30 patients (6%), leaving 473 patients with an appendiceal tumor. These 473 patients were further divided into three groups according to how the tumors had been identified. In 276 (58%) patients, the appendiceal tumor was diagnosed at surgery for suspected acute appendicitis or interval appendectomy (group 1), in 142 (30%) patients, it had been diagnosed during abdominal surgery for other indications (group 2), in 54 (11%) patients diagnosed during any preoperative imaging (group 3), and at autopsy in one (0.2%) patient (excluded from the analysis). There were altogether 19,976 patients with both an acute appendicitis diagnosis and an appendectomy procedure identified in both the records of the eight study hospitals and the NIHW register during the study period.

4.4 Statistics

4.4.1 Study I

The statisticians chose and provided specific tests for calculating the association between the variables and differences between the groups. Shapiro-Wilk's test was used to test for the normality assumption of the distribution. The differences in laboratory values between two groups were tested using Mann-Whitney test. The similarity of the gender and duration of symptoms were tested using Pearson's Chi-Squared test and the age distribution with Kruskal-Wallis- and Mann-Whitney U-tests. Pearson's chi-squared test was used for categorical data. Post-hoc tests were adjusted with the Bonferroni correction.

Univariate logistic regression analysis was used for each principal covariate. Statistically significant covariates were chosen for further analysis. Differences between the groups were determined using multivariable logistic regression analysis controlling for age, gender, duration of symptoms before admission and laboratory values. Receiver operating characteristic (ROC) analyses were conducted to assess the clinical value of the laboratory tests and to obtain ideal cutoff points. Cut-off points were assessed according to the Youden index (sensitivity + specificity -1) and with maximum sensitivity. Ninety-five percent confidence intervals (CI) were bootstrapped with 500 samples using the percentile method.

All of the statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

4.4.2 Study II

Summary measurements are presented as mean and standard deviation (SD) unless otherwise stated. Comparisons were performed using Student's t-test or X^2-test. The area under the receiver operating characteristic curve (AUC) was calculated. An AUC value ≥0.70 was considered as a clinically meaningful diagnostic test. Cutoff points were assessed according to the Youden index and sensitivities of 80% and 90% were estimated. Positive and negative likelihood ratios (LR±) were used to calculate post-test probabilities for the combinations of clinically meaningful tests. A pre-test probability of 0.2 was used to calculate post-test probabilities. The analyses were performed using SPSS for Windows (IBM SPSS Statistics for Windows, Version 21.0, IBM Corp., Armonk, NY, USA; released 2012).

4.4.3 Study III

As in Study II, summary measurements are presented as mean with SD unless stated otherwise. Sensitivity, specificity and positive and negative predictive values with 95% CIs were calculated to assess the diagnostic accuracy. Student's t-test was used in the between group comparisons for continuous variables and Pearson X^2-test when comparing categorical data. Two-sided p-values are presented, except that we assumed experienced radiologists to have superior accuracy in establishing the correct diagnosis, and, therefore, a one-sided p-value is presented when comparing the impact of experience. Analyses were performed using SPSS for Windows (IBM SPSS Statistics for Windows, Version 21.0, IBM Corp., Armonk, NY, USA; released 2012).

4.4.4 Study IV

The differences in background variables between the three study groups were tested for a numeric variable (age) with one-way analysis of variance and for categorical variables using Chi-Square test. The risk of having an appendiceal tumor was calculated using the Chi-Square test and Odds Ratio with 95% CI. All of the statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

4.5 Study approval

The APPAC trial (clinicaltrials.gov, NCT01022567) was approved by the Ethics Committee and Institutional review board of Turku University Hospital and all participating hospitals, and the Finnish Medicines Agency (FIMEA). All patients gave written informed consent to participate in the APPAC trial (studies I-III). Study IV was approved by Ethics Committee and Institutional review board of Turku University Hospital and all participating hospitals. Study IV was also was granted approval by FCR and given the right to access the NIHW register.

5 RESULTS

5.1 Clinical and laboratory findings in the diagnosis of right lower quadrant abdominal pain (study I)

In the examined 1321 patients, clinical and laboratory findings suggested acute appendicitis. Of these, 970 (73%) of these patients had acute appendicitis after imaging with CT, with the diagnosis changing after CT in 351 (27%) patients. Thus, 191 (54%) patients had a normal finding on CT whereas the remaining 160 (46%) patients received another specific diagnosis for acute abdomen. Among other diagnosis there were 45 acute diverticulitis patients, 39 patients had gynecological disorders and 76 patients had other miscellaneous diagnosis.

The patient data and clinical and laboratory characteristics of the patients with right lower quadrant abdominal pain are presented in Table 7. Patients with acute appendicitis were older than patients with some other diagnosis ($p < 0.0001$). The mean age of the patients with acute appendicitis was 37 years; with gynecological disorders it was 32 years and with NSAP it was 30 years. Patients with acute diverticulitis were significantly older with a mean age of 47 years. The risk increase (Odds ratio, OR) of having acute appendicitis according to demographic, clinical and laboratory characteristics is presented in detail in Table 8. Men had a 2.17 times increased risk of having acute appendicitis. Diagnosing acute appendicitis was more accurate in men than in women [80% (95% CI, 77.1%–82.9%) vs. 65% (95% CI, 60.9%–68.7%), respectively; $p < 0.0001$]. Furthermore, when all the background factors (duration of symptoms and both WBC and CRP elevated vs. normal) were standardized, the differences between the genders in terms of disease incidence remained statistically significant.

The duration of abdominal symptoms was shorter in the acute appendicitis group ($p < 0.0001$) and the patients who had symptoms 12–24 h before admission had the highest risk of having acute appendicitis. The patients with an elevated WBC had a 2.52 higher risk ($p < 0.0001$) and those with elevated CRP had a 1.48 ($p = 0.005$) times higher risk of having acute appendicitis than the patients who had normal WBC and CRP. However, the risk of having acute appendicitis was 11.66 times higher in those patients who had both WBC and CRP elevated compared with those in whom both values were normal ($p < 0.0001$). The proportion of patients with both WBC count and CRP normal was significantly ($p = 0.0007$) lower in acute appendicitis patients (0.9%; 95% CI, 0.43%–1.77%) than in patients with some other diagnosis (8.3%; 95% CI, 5.62%–11.68%). The optimal cut-off points of the laboratory tests for clinical use were evaluated in an attempt to discriminate patients with acute appendicitis from those without acute appen-

dicitis. The clinical value of the laboratory tests in separating patients with acute appendicitis from those without according to receiver operating characteristic (ROC) analyses are shown in Table 9. The results indicated that even the ideal cut-off points lead to a poor discrimination between patients with and those without acute appendicitis in clinical decision making. None of the markers nor their combination accurately differentiated between these patients.

Table 7 Demographic, clinical and laboratory characteristics of the 1321 patients with right lower quadrant abdominal pain.

		Acute appendicitis			Other diagnosis		Overall
	n (%)	Median (IQR)	Min-Max	n (%)	Median (IQR))	Min - Max	n (%)
Age	970	35.0 (26.0-47.0)	17.0-64.0	351	31.0 (24.0-42.0)	18.0-65.0	1321 (100%)
Sex							
Men	600 (80%)			150 (20.0%)			750 (56.8%)
Women	370 (64.8%)			201 (35.2%)			571 (43.2%)
Symptoms							
<12h	195 (74.4%)			67 (25.6%)			262 (20.1%)
12-24h	348 (88.3%)			46 (11.7%)			394 (30.2%)
>24h	415 (63.8%)			236 (36.3%)			651 (49.8%)
Hgb[1] (g/l)		144.0 (134.0-152.0)	84.0-193.0		140.0 (129.0-148.0)	93.0-172.0	1311 (99.2%)
WBC[2] (E9/l)		12.2 (9.5-15.2)	2.0-33.8		10.0 (7.7-12.3)	2.8-26.2	1313 (99.4%)
CRP[3] (mg/l)		35.8 (11.2-74.0)	0.0-412.0		32.0 (6.0-77.0)	0.0-348.0	1313 (99.4%)
VAS[4]		6.0 (4.0-7.0)	1.0-10.0		6.0 (5.0-7.5)	2.0-10.0	622 (47.1%)
Temp		37.5 (37.1-38.0)	35.4-40.6		37.5 (37.0-38.0)	35.9-39.8	521 (39.4%)

[1] Hgb = blood hemoglobin, [2] WBC = white blood cell count, [3] CRP = C-reactive protein, [4] VAS = visual analogue scale for pain

Table 8 The risk increase (OR) of having acute appendicitis according to demographic, clinical and laboratory characteristics.

	p	OR	95% CI
Age	0.0003	1.02	1.01-1.03
WBC[1] high vs normal	<0.0001	2.52	1.88-3.38
CRP[2] high vs normal	0.005	1.48	1.13-1.94
WBC[1] and CRP[2] high vs normal	<0.0001	11.66	5.41-25.12
Temperature	0.72	1.05	0.81-1.35
VAS[3]	0.11	0.90	0.79-1.02
Hgb[4]	<0.0001	1.02	1.01-1.03
Men vs Women	<0.0001	2.17	1.70-2.79
Symptoms			
12-24h vs <12h	<0.0001	2.60	1.72-3.93
<12h vs >24h	0.006	1.66	1.20-2.28
12-24h vs >24h	<0.0001	4.30	3.04-6.09

[1] WBC = white blood cell count, [2] CRP = C-reactive protein, [3] VAS = visual analogue scale for pain,
[4] Hgb = blood hemoglobin

Table 9 The clinical value of the laboratory tests in separating patients with acute appendicitis from those without acute appendicitis according to ROC.

Diagnostic Accuracy of WBC[1] and CRP[2] in patients with suspected AA[3] using ROC[4] curves							
Variable	**Cutoff Point**	**Sensitivity**	**Specificity**	**PPV[5]**	**NPV[6]**	**AUC[7]**	**p-value**
WBC	9.2 (E9/l)	70.7% (56.9-82.0%)	63.7% (51.7-78.3%)	84.3% (81.4-88.3%)	44.2% (83.1-51.2%)	0.710 (0.679-0.742)	<0.0001
CRP	5 (mg/l)	65.0% (52.1-82.9%)	57.6% (39.0-71.5%)	80.7% (77.7-84.4%)	37.5% (33.3-47.3%)	0.635 (0.599-0.670)	<0.0001
WBC+ CRP	9.0/6	70.2% (54.8-81.5%)	64.0% (53.7-79.1%)	84.3% (81.4-88.2%)	43.9% (37.3-51.9%)	0.711 (0.679-0.742)	<0.0001
The overall accuracy is represented by AUC of WBC, CRP and WBC+CRP. Ideal cutoff points were assessed as maximum sun of sensitivity and spesificity (Youden index).							
Ideal cutoff Point determined by the maximum sensitivity							
Variable	**Cutoff Point**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**AUC**	**p-value**
WBC	3.4 (E9/l)	100%	0.00%	73.30%	0.00%	0.710 (0.679-0.742)	<0.0001
CRP	3 (mg/l)	100%	0.00%	73.20%	0.00%	0.635 (0.599-0.670)	<0.0001
WBC+ CRP	3.4/12	100%	0.00%	73.30%	0.00%	0.711 (0.679-0.742)	<0.0001
[1]WBC= white blood cell count; [2]CRP= C-reactive protein; [3]AA= acute appendicitis; ROC= receiver operating characteristic							
[5]PPV=positive predictive value; [6]NPV= negative predictive value; [7]AUC= area under the ROC curve							

5.2 Differential diagnosis of uncomplicated and complicated acute appendicitis (study II)

A total of 705 patients received a diagnosis of acute appendicitis after the CT and were treated operatively. Uncomplicated acute appendicitis (UA, n=368) was compared with complicated acute appendicitis: appendicolith, perforation, periappendicular abscess, or suspicion of a tumor (CA, n=337). This complicated acute appendicitis group was further divided into two groups: appendicolith appendicitis (CA1, n=256), and complicated acute appendicitis with perforation and/or periappendicular abscess (CA2, n=78). Patient demographics with clinical and laboratory findings are presented in Table 10. The UA patients were similar to CA and CA1 patients with respect to sex, age, WBC, and body temperature. In clinical terms, the mean CRP was significantly higher only in group CA2 when compared with group UA ($p<0.001$). With regard to the duration of symptoms, there was no clinically significant difference between the groups UA, CA, and CA1, in contrast to the clinically and statistically significant difference between UA and CA2 groups, as 81% of group CA2 patients had symptoms >24 hours before admission ($P <0.001$).

The clinical value of the laboratory tests and temperature in differentiating group UA patients from those with CA, CA1, and CA2 according to ROC is presented in Table 11. The CRP values and body temperature were higher in CA2 patients compared with UA patients (AUC >0.7 in ROC analysis). The optimal cut-off points of the CRP value and the temperature for clinical use were evaluated, to be able to discriminate the UA patients from the CA2 patients. The results shown in Table 10 prove that the cut-off points assessed with the Youden index led to a fairly good discrimination between groups UA and CA2, by applying CRP >84

mg/L or temperature >37.8°C. In the clinical situation most useful is considered cut-off points with the maximum sensitivity. When using a sensitivity of 90%, the cut-off points lead to poor discrimination (CRP >13mg/L and temperature >37.1°C) as shown in Table 12. The post-test probabilities were analyzed. None of the combinations was a useful positive diagnostic test, with a value of 0.61 being the maximum post-test probability. Nonetheless, after a negative test result in both CRP and temperature, the post-test probability was 0.03-0.05 thus ruling out rather confidently the presence of perforated appendicitis and/or periappendicular abscess.

Table 10 Patient demographics with clinical and laboratory findings of all of the patients with acute appendicitis.

	Uncomplicated AA	Complicated AA		Appendicolith AA	Perforated AA/abscess	
	Group UA	Group CA	p1	Group CA1	Group CA2	p2
	n=368	n=337		n=256	n=78	
male, n(%)	229 (62.2)	215 (63.8)	0.67	171 (66.8)	43 (55.1)	0.15
age, mean (SD)	36.8 (12.4)	37.6 (13.0)	0.36	36.4 (13.0)	41.7 (12.5)	0.004
CRP, mean (SD)	47.4 (47.0)	66.3 (74.6)	<0.001	48.3 (57.5)	122.2 (92.9)	<0.001
WBC, mean (SD)	12.0 (4.0)	13.7 (3.9)	<0.001	13.8 (3.5)	13.5 (4.8)	<0.001
temperature, mean (SD)	37.5 (0.7)	37.7 (0.9)	0.004	37.6 (0.9)	38.0 (0.8)	0.001
Duration of symptoms (%)			<0.001			<0.001
<12 hours, n (%)	69 (19.0)	69 (20.5)		63 (24.6)	6 (7.7)	
12-24 hours, n (%)	157 (43.1)	87 (25.8)		78 (30.5)	9 (11.5)	
>24 hours, n (%)	138 (37.9)	181 (53.7)		115 (44.9)	63 (80.8)	
AA = acute appendicitis, CRP = C-reactive protein (mg/l), WBC = white blood cell count (E9/l), temperature (°C)						
p1 = p-value between UA and CA, p2 = p-value between UA, CA1 and CA2						

Table 11 Clinical value of the laboratory tests and temperature in separating UA patients from CA patients according to the ROC curves.

	Complicated AA	Appendicolith AA	Perforated AA/abscess
	Group CA	Group CA1	Group CA2
	AUC (CI95%)	AUC (CI95%)	AUC (CI95%)
CRP	0.53 (0.49-0.58)	0.45 (0.41-0.50)	0.77 (0.70-0.84)
WBC	0.63 (0.59-0.67)	0.64 (0.60-0.68)	0.60 (0.53-0.67)
Temperature	0.61 (0.54-0.67)	0.57 (0.50-0.64)	0.70 (0.61-0.79)
AA = acute appendicitis, AUC = area under the ROC curve, CRP = C-reactive protein (mg/l), ROC = receiver operating characteristic, WBC = white blood cell count (E9/l), temperature (°C)			

Table 12 Evaluation of the optimal cut-off points of the CRP and temperature in separating patients with UA from patients with CA2.

					Post-test probability			
					Temp ≥ 37.4		Temp < 37.4	
	Sensitivity	Specificity	LR+	LR-	CRP+	CRP-	CRP+	CRP-
CRP ≥ 84[1]	0.65	0.84	4.1	0.41	0.61	0.13	0.31	0.04
CRP ≥ 40	0.81	0.53	1.7	0.36	0.39	0.12	0.15	0.04
CRP ≥ 13	0.91	0.24	1.2	0.37	0.31	0.12	0.11	0.04
					CRP ≥ 40		CRP < 40	
					Temp+	Temp-	Temp+	Temp-
Temp ≥ 37.8[1]	0.60	0.75	2.4	0.53	0.50	0.18	0.18	0.05
Temp ≥ 37.4	0.80	0.47	1.5	0.43	0.39	0.12	0.15	0.04
Temp ≥ 37.1	0.90	0.27	1.2	0.38	0.34	0.10	0.14	0.03

Cut off points were assessed for these parameters as maximum of sensitivity + specificity-1 (Youden's index[1]) and with (approx.) 80% and 90% sensitivity. Pre-test probability of 0.2 was used for post-test calculations

CRP = C-reactive protein (mg/l), Temp = temperature (°C)

5.3 The accuracy of computed tomography in the diagnosis of acute appendicitis (study III)

The study population comprised 1065 patients with a clinical suspicion of acute appendicitis that had undergone a CT according to the APPAC trial protocol. The patients were 17-65 years old (mean 36.2 years); 44.1% (n=470) of them were women. Out of these patients, 714 had acute appendicitis and 351 had a normal finding or were given some other diagnosis after the CT. Overall, there were 65.7% (n=700) true-positive, 30.7% (n=327) true-negative, 1.3% (n=14) false-positive and 2.3% (n=24) false-negative cases. Thus, the sensitivity of CT was 96.7% (95% CI 95.1-97.8) with the corresponding value for its specificity being 95.9% (95% CI 93.2-97.5). As shown in Table 13, the rate of false CT diagnosis was 4.2% for experienced consultant radiologists and 2.2% for inexperienced resident radiologist (p=0.071). Slightly more (5.5%) of the female patients received a false CT diagnosis than was the case in male patients (2.0%) (p=0.002). The mean ages of the patients with false and correct CT diagnosis were 35.0 and 36.9 years respectively (p=0.014).

The results of the reassessments of the primarily false-negative and false-positive CT findings (n=38) by one body imaging radiologist and one radiology resident are shown in Table 14. Out of these re-evaluated CT scans, 21 were correctly interpreted by both radiologists. In eight of the cases, the CT diagnosis was incorrect after all three interpretations; of these six were false-positive with the

other two being false-negative cases. In nine cases, one or the other of the radiologists had made an inaccurate interpretation.

Table 13 The accuracy of the CT in suspected acute appendicitis in emergency setting.

	Overall CT diagnosis	CT interpretation by experienced radiologist	CT interpretation by inexperienced radiologist
	n=1065	n=742	n=322
False-negative results	24 (2.3%)	21 (2.8%)	3 (0.9%)
False-positive results	14 (1.3%)	10 (1.3%)	4 (1.2%)
Sensitivity	96.7% (95% CI 95.1-97.8)	95.9% (95% CI 93.8-97.3)	98.6% (95% CI 96.0-99.5)
Specificity	95.9% (95% CI 93.2-97.5)	95.7% (95% CI 92.3-97.7)	96.3% (95% CI 90.8-98.5)
PPV	98.0% (95% CI 96.7-98.8)	98.0% (95% CI 96.3-98.9)	98.1% (95% CI 95.3-99.3)
NPV	93.2% (95% CI 90.0-95.4)	91.4% (95% CI 87.3-94.3)	97.2% (95% CI 92.0-99.0)
PPV= positive predictive value, NPV= negative predictive value			
experienced radiologist= consultant, inexperienced radiologist= resident			

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Table 14 The primary CT analysis in suspected acute appendicitis (n=1065) and the reassessed CT analyses of false-positive (n=14) and false-negative (n=24) cases.

Final diagnosis	Positive	Negative	Total
Primary CT analysis			
Positive	700	14	714
Negative	24	327	351
Total	724	341	1065
Reassessed CT analysis			
body imaging radiologist			
Positive	21	7	28
Negative	3	7	10
Total	24	14	38
Reassessed CT analysis			
resident			
Positive	17	8	25
Negative	7	6	13
Total	24	14	38

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5.4 Appendiceal neoplasms and acute appendicitis (study IV)

A total of 840 appendiceal primary tumor patients were identified from the FCR database and 504 (60%) patients were treated in the hospital districts of the study

hospitals. From these, 472 patients with available diagnostic and clinical data were included in this study (Figure 6). In the whole study group, preoperative imaging was performed for 58% (n=293/472) of the patients and the main imaging modality (n=231/293, 79%) was contrast enhanced CT scan. Out of these 472 patients, the appendiceal tumor was diagnosed at surgery either for suspected acute appendicitis or interval appendectomy after the primary conservative treatment of periappendicular abscess in 276 (58%) patients (group 1), at abdominal surgery for other indications in 142 (30%) patients (group 2), or at any preoperative imaging in 54 (11%) patients (group 3). Detailed patient demographics, clinical and diagnostic findings, histology and additional treatments according to study groups 1-3 are presented in Table 15.

In group 1, the vast majority, 92%, of patients underwent appendectomy and 7% had a more extensive bowel resection. The majority of the operations (87%) were emergency cases. In 13% of the cases, the operation was performed as elective interval surgery after initial conservative treatment of a periappendicular abscess. The negative appendectomy rate was 14%, as 235 patients (86%) had acute appendicitis at histology. Diagnostic imaging had been performed in 53% of patients and in none of them had a tumor been suspected preoperatively. The tumor was macroscopically suspected at surgery in 11% of operations and 41% (n=12/29) of these were interval operations after conservatively treated periappendicular abscess.

In group 2, surgery was performed for some indication other than suspected acute appendicitis. The majority i.e. 77% (n=110/142), of the patients had undergone elective surgery, most often for gynecological indications (52%). Four patients undergoing elective surgery were diagnosed with a periappendicular abscess at surgery and histology. Three out of these four patients were operated on due to the suspicion of gynecological tumor and one for suspected cecal tumor. Out of the 23% (n=32/142) emergency procedures in this group, seven of the patients had acute appendicitis at surgery and histology. Preoperative imaging was done for 66% (n=94/142) of the patients. Out of these, 83% were contrast enhanced CT and, as in Group 1, none of the tumors had been suspected preoperatively.

In group 3, all patients had undergone preoperative imaging (with tumor suspicion); in the majority of cases (89%), this had been contrast enhanced CT. Most, i.e. 91% (n=49/54), of the patients had undergone elective surgery. Only four (7%) of these patients had acute appendicitis. In the preoperative imaging, tumor staging had been accurate in 74% (n=40) of the cases. In two patients, the imaging over-estimated and in 9 patients it under-estimated the tumor staging, when compared to operative and histological findings. In three patients, the disease had disseminated and no operation was performed. In two of these patients, the ap-

pendiceal tumor histology was obtained during the radiological tumor biopsy and in one patient at autopsy.

During the study period, there were altogether 19,976 patients with an acute appendicitis diagnosis but without an appendiceal tumor identified both in the eight study hospitals and the NIHW registry (Figure 6), resulting in an appendiceal tumor prevalence of 1.24% ($p<0.001$) in the acute appendicitis patient population. Altogether there were 250 patients with both acute appendicitis and an appendiceal tumor based on both histology and surgical findings (Figure 6). Out of these, 102 (41%) patients had complicated and 148 (59%) had uncomplicated acute appendicitis. The complicated acute appendicitis cases included 66 patients with a periappendiceal abscess and 36 with perforated acute appendicitis. The appendiceal tumor risk was statistically significantly higher in complicated acute appendicitis as compared with uncomplicated acute appendicitis (3.24% vs. 0.87%, $p<0.001$). The OR was 3.83 (CI 95% 2.96-4.93) for having an appendiceal tumor if one had a complicated acute appendicitis as compared to uncomplicated acute appendicitis. A separate subgroup analysis of the tumor risk encountered in periappendiceal abscess patients (n=66) also showed a significantly higher tumor risk compared with uncomplicated acute appendicitis (n=148) (4.99% vs. 0.87%, $p<0.001$). The OR was 6.01 (CI 95% 4.47-8.08) for having an appendiceal tumor in complicated acute appendicitis presenting with periappendicular abscess as compared to uncomplicated acute appendicitis. These comparisons are presented in detail in Table 16.

In the whole patient cohort of 472 appendiceal tumor histology, 49% (n=232) were NETs, 11% (n=52) were MANEC or goblet cell tumors, 14% (n=65) were mucinous tumors or pseudomyxomas, and 26% (n=123) were adenocarcinomas. The NET proportion was higher (61%, $p<0.001$) in group 1 patients as compared to the whole patient population (49%). In group 1, 39% (109/276) of patients had a non-NET tumor histology. Of these, 109 patients, 57% (n=62) of the patients had complicated and 32% (n=35) patients had uncomplicated acute appendicitis; 12 patients had no acute appendicitis or it could not be histologically determined. In group 1, 19% (n=51/276) of patients had a local lymph node metastasis or disseminated disease according to surgical findings or histology. In contrast, more metastatic disease was present in group 2 i.e. 53% (n=75/142) and in 78% (n=42/54) of group 3 patients.

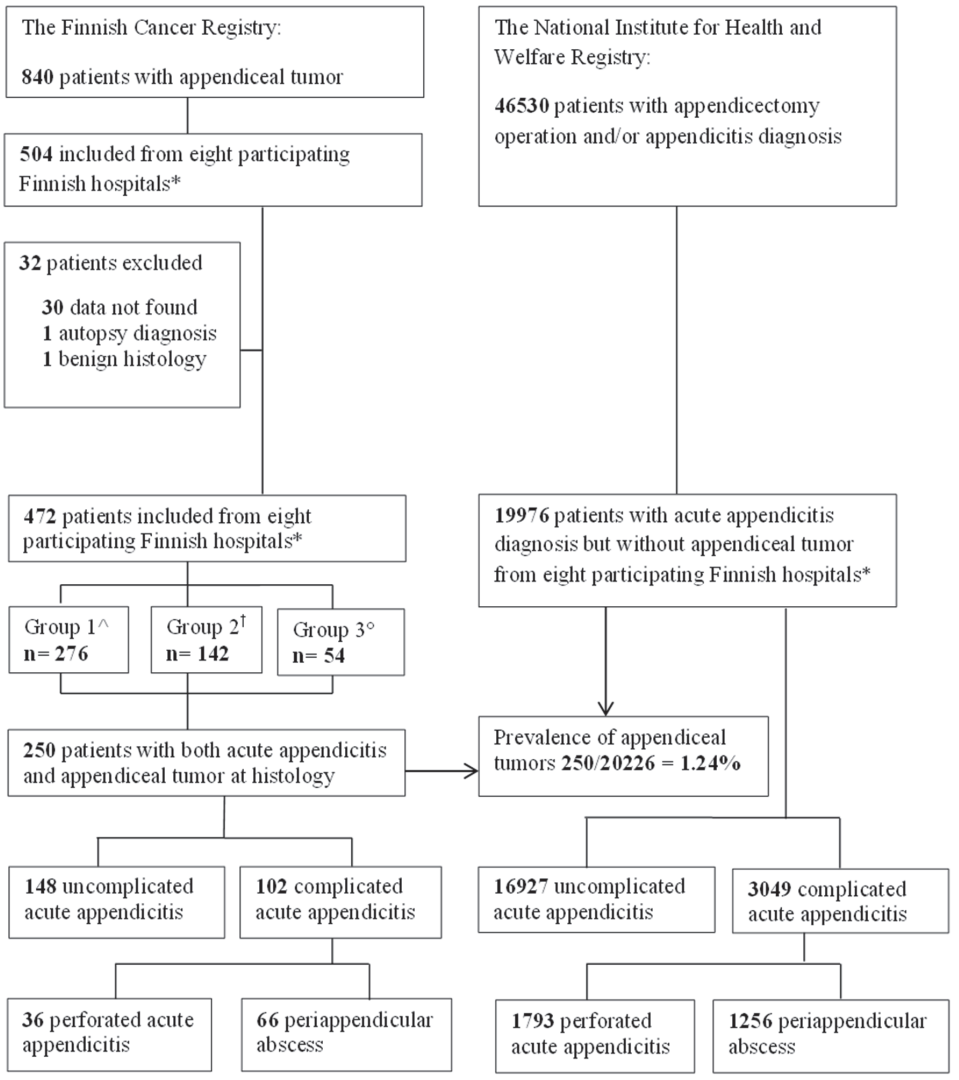

Figure 6 Patient inclusion from The Finnish Cancer Registry (FCR) and The National Institute for Health and Welfare Registry (NIHW) between the years 2007-2013.

Table 15 The Finnish Cancer Registry (FCR) database from 8 participating hospitals (n=472), patient demographics, clinicopathological characteristics and treatment regimens.

	Group 1	**Group 2**	**Group 3**	**p**
	n=276	n=142	n=54	
Age, years				<0.001
mean	45.7 ± 18.7	59.6 ± 15.2	59.2 ± 12.7	
range	9-94	11-97	27-85	
Gender				<0.001
Men	120 (43%)	40 (28%)	33 (61%)	
Women	156 (57%)	102 (72%)	21 (39%)	
Preoperative imaging	n=145 (53%)	n=94 (66%)	n=54 (100%)	<0.001
CT with iv contrast	105	78	48 (89%)	
CT without contrast	1	4	1 (2%)	
ultrasound	38	3	1 (2%)	
MRI	1	1	4 (7%)	
X-ray	-	7	-	
Surgery	n=276	n=142	n=51	<0.001
elective	35 (13%)	110 (77%)	49 (91%)	
emergency	241 (87%)	32 (23%)	2 (4%)	
no surgery	-	-	3 (5%)	
Macroscopic tumor suspicion	n=276	n=142	n=54	<0.001
no	244 (89%)	71 (50%)	6 (11%)	
yes	29 (11%)	65 (46%)	45 (83%)	
unclear*	3 (1%)	6 (4%)	3 (6%)	
Operation	n=276	n=142	n=51	<0.001
appendectomy	176 (64%)	61 (43%)	5 (9%)	
laparoscopic appendicectomy	78 (28%)	17 (12%)	7 (13%)	
ileocecal resection	12 (4%)	19 (13%)	2 (4%)	
right hemicolectomy	8 (3%)	24 (17%)	17 (31%)	
HIPEC	-	-	6 (11%)	
other	2 (0.7%)	21 (15%)	14 (26%)	
Acute appendicitis†	n=276	n=142	n=54	<0.001
no	39 (14%)	127 (90%)	44 (81%)	
uncomplicated	142 (51%)	5 (3%)	1 (2%)	
complicated	93 (34%)	6 (4%)	3 (6%)	
unclear*	2 (0.7%)	4 (3%)	6 (11%)	
Tumor histology	n=276	n=142	n=54	<0.001
NET	167 (61%)	58 (41%)	7 (13%)	
MANEC, Goblet cell	36 (13%)	15 (11%)	1 (2%)	
adenocarcinoma	64 (23%)	42 (30%)	17 (31%)	
pseudomyxoma peritonei	9 (3%)	27 (19%)	29 (54%)	
Metastasis†	n=276	n=142	n=51	<0.001
no	225 (82%)	67 (47%)	9 (17%)	
local	10 (4%)	3 (2%)	5 (9%)	
disseminated	41 (15%)	72 (51%)	37 (69%)	
Additional operation	n=111 (40%)	n=41 (29%)	n=19 (35%)	<0.001
ileocecal resection	15	-	2	
right hemicolectomy	85	12	3	
HIPEC	6	20	6	
other	5	9	8	
Group 1: appendiceal tumor was found at surgery for suspected acute appendicitis,				
Group 2: at surgery done for other indications, Group 3: at preoperative imaging				
*no histology or surgical report available, †based on histological and surgical classification				
CT=computed tomography, MRI=magnetic resonance imaging, HIPEC= Hyperthermic Intra				
Peritoneal Chemotherapy, NET=neuroendocrine tumor, MANEC= mixed adeno-neuroendocrine carcinoma				

Table 16 The risk of having appendiceal tumor among acute appendicitis patients was estimated by comparing patients with an appendiceal tumor and acute appendicitis from FCR register data to patients with an acute appendicitis diagnosis in NIHW register. Comparison was done between uncomplicated and complicated acute appendicitis, and uncomplicated acute appendicitis and complicated acute appendicitis presenting as periappendiceal abscess.

	Appendiceal tumor		
	No°	**Yes†**	**Total^**
Uncomplicated appendicitis	16927 (99.13%)	148 (0.87%)*	17075
Complicated appendicitis	3049 (96.76%)	102 (3.24%)*	3151
Total	19976 (98.76%)	250 (1.24%)*	20226
Uncomplicated appendicitis	16927 (99.13%)	148 (0.87%)*	17075
Periappendiceal abscess	1256 (95.01%)	66 (4.99%)*	1322
Total	18183 (98.84%)	214 (11.63%)*	18397
°NIHW register; †FCR register; ^NIHW and FCR register patients; *p<0.001			

6 DISCUSSION

6.1 Diagnosis of acute appendicitis

Our study reveals that in clinical decision making, there is no single clinical finding or laboratory marker sufficiently reliable to predict acute appendicitis among patients in whom it is suspected. However, acute appendicitis is very unlikely if the values of both WBC and CRP are normal. Our results highlight the role of CT imaging, as it had a sensitivity of 96.7% and a specificity of 95.9% in diagnosing acute appendicitis.

Acute appendicitis is one of the most common causes of abdominal pain encountered in the emergency department. The clinical diagnosis, even with the help of laboratory tests, is challenging as patients do not invariably have a typical clinical presentation and conversely, not every typical presentation is acute appendicitis. The differential diagnosis of acute appendicitis includes a wide spectrum of diseases (Purysko et al. 2011, Heller et al. 2012, Kraemer et al. 2000). In our study, there were overall 24 different CT diagnoses in patients with suspected acute appendicitis. The most common other diagnosis was NSAP 54%, followed by acute diverticulitis 13% and gynecological disorders 11% in accordance with several other studies (Ma et al. 2010, Schellekens et al. 2013, Kim et al. 2008).

To date, no reliable specific marker for acute appendicitis has been identified. There are several earlier studies on the role of laboratory tests in the diagnosis of acute appendicitis (Andersson 2004, Schellekens et al. 2013, Andersson et al. 2008, Grönroos et al. 1999, de Castro et al. 2012). In practice, the diagnosis of acute appendicitis is supported by the presence of elevated inflammatory markers, e.g. WBC and CRP (Grönroos et al. 1999). However, our study shows that neither of these markers is diagnostic nor specific for acute appendicitis. In our study, the levels of WBC, but not CRP, were significantly higher in patients with acute appendicitis when compared to the values in patients not suffering from appendicitis. If both values were normal, acute appendicitis was very unlikely. According to our results, WBC and CRP do not possess sufficient sensitivity and specificity to allow them to diagnose acute appendicitis since an elevation of these markers may be associated with various other intra-abdominal infections. Similarly in their study, Al-Gaithy et al (2012) reported that neither WBC nor neutrophil counts were reliable enough in suspected acute appendicitis (Al-Gaithy 2012). Here, the diagnosis of acute appendicitis was more likely in patients with a duration of symptoms less than 24 hours at admission. This finding has been reported earlier and Wagner et al (2008) stated that the use of CT may

be more beneficial in patients with a longer duration of symptoms (Wagner et al. 2008).

For years, the diagnosis of acute appendicitis was based on clinical symptoms and signs, supplemented by laboratory tests. The Alvarado score was the first clinical scoring system attempting to improve the diagnostics of acute appendicitis (Alvarado 1986). This score was constructed when there were no reliable imaging methods for diagnosing acute appendicitis. In 2008, Andersson et al published the AIR Score (Andersson et al. 2008); similar to the Alvarado score, the AIR is based on clinical symptoms and signs, and laboratory test findings. The Adult Appendicitis Score published in 2014 by Sammalkorpi et al was the first scoring system taking into account all of the well-known features of acute appendicitis and it was found to be superior to both the Alvarado Score and AIR score in its diagnostic performance (Sammalkorpi et al. 2014). After implementation of the Adult Appendicitis Score algorithm, the NAR decreased from 18.2% to 8.7% (Sammalkorpi et al. 2017).

Over the past decade, the use of preoperative imaging in acute appendicitis diagnostics has steadily increased. As CT has high accuracy, it has become the gold standard in the differential diagnosis of the right lower quadrant pain (van Randen et al. 2008) and high sensitivity (96.7%) and specificity (95.9%) of CT was also reported in our study. As a diagnostic tool for acute appendicitis, an accurate and precise interpretation of images is needed around-the-clock. In the emergency situation, there can be differences in the expertise of the on-call radiologist. There are studies that have shown that this expertise exerts a significant influence on the interpretation of CT images (Ceydeli et al. 2006, Wise et al. 2001, Poortman et al. 2010, in't Hof et al. 2009). In our study, the experience of radiologist did not significantly improve the diagnostic accuracy, which is in line with the study of Albano et al (Albano et al. 2001). This may be explained by the good training of the residents (Song et al. 2017) and the relatively small number of re-evaluated cases in our study although also there were only 33 patients in the study of Albano et al (2001) having acute appendicitis (Albano et al. 2001). In most cases, the identification of enlarged appendix (>6mm in diameter) with contrast enhancement of the wall and periappendicular fat stranding confirmed the diagnosis of acute appendicitis (Rao et al. 1997a). With respect to these CT criteria, appendicular enlargement has been shown to be the most specific finding for acute appendicitis with the highest sensitivity (Limon et al. 2015, Rao et al. 1997a). In our study, no diagnoses of acute appendicitis were missed in cases when the appendiceal diameter exceeded 15mm and in 65.9% of the cases with a false CT diagnosis, the diameter of the appendix was not registered or identified. The optimization of CT interpretation and a reassessment of possible unclear cases may further improve diagnostic accuracy of CT in acute appendicitis.

The more accurate diagnosis of acute appendicitis attributable to CT can result in improved patient care and cost savings (Rao et al. 1998, Lahaye et al. 2015, Wagner et al. 2008, Mariadason et al. 2012). The increased use of CT in patients with acute appendicitis suspicion has resulted in a clear decrease in NAR (Boonstra et al. 2015, Coursey et al. 2010, Raja et al. 2010, Rao et al. 1998). Decreased NAR, i.e. avoiding unnecessary surgery, results in further cost savings and reduced morbidity. At the same time, one concern regarding CT imaging is exposing the patient to ionizing radiation (Pearce et al. 2012, Brenner et al. 2007, Smith-Bindman et al. 2009, Rogers et al. 2015). Although clinical benefits should outweigh the small absolute risks of radiation, the CT radiation dosage should be kept as low as possible. Recent studies have shown that contrast enhanced low-dose CT was not inferior to standard-dose CT and was highly effective in cases of suspected acute appendicitis as well as in the severity assessment of appendiceal inflammation (Kim et al. 2011, Kim et al. 2012, Yun et al. 2017, Sippola et al. 2018). Future studies will determine whether the low-dose CT will replace standard CT as the first-line imaging test for acute appendicitis and how far the radiation dose can be reduced in CT while still maintaining a diagnostic performance.

6.2 Differential diagnosis of uncomplicated and complicated acute appendicitis

Traditionally, the diagnosis of acute appendicitis has been based on physical examination, clinical features and laboratory findings (Yu et al. 2013, Grönroos et al. 1999). However, the diagnostic accuracy has been shown to be as low as 75-80% (Berry et al. 1984, Körner et al. 1997). Estimating the severity of acute appendicitis has been shown to be even more complicated as it has proved difficult to define ideal cutoff points for clinical use (Shindoh et al. 2011, Moon et al. 2011). This finding was shown also in the APPAC study by Salminen et al (2015) as no predictive factors for nonoperative treatment failure in uncomplicated acute appendicitis could be identified (Salminen et al. 2015). In our study, we used the same APPAC trial material to evaluate whether it would be feasible to differentiate between complicated and uncomplicated acute appendicitis without CT imaging. We analyzed the clinical history, physical investigation and inflammatory laboratory markers, but it proved impossible to make a differential diagnosis between uncomplicated and complicated acute appendicitis by either using any one of these parameters or by combining two of them. In our study, the study design was retrospective and therefore the prospective collection of all of these parameters was not adequate enough to create our own scoring system. Although a higher CRP value and temperature, and a longer duration of symp-

toms (>24 hours) were evident in patients with perforated acute appendicitis with or without abscess, we were not able to find ideal cutoff points with reasonable values of sensitivity and specificity. This result is in line with previous studies (Paajanen et al. 2002a, Grönroos et al. 1999, Moon et al. 2011).

Several scoring systems combining clinical and laboratory findings have been created (Alvarado 1986, Andersson et al. 2008, Sammalkorpi et al. 2014, Lintula et al. 2010). However, these scoring systems were developed to accurately diagnose acute appendicitis and none of the scoring systems can achieve a differential diagnosis of uncomplicated and complicated acute appendicitis. Atema et al (2015) published a scoring system that combined clinical and imaging results (CT) and 95% of patients were correctly identified as having uncomplicated acute appendicitis (Atema et al. 2015c). The need not only for more accurate acute appendicitis diagnosis, but also for a differential diagnosis of complicated and uncomplicated acute appendicitis has led to the increased reliance on diagnostic imaging. It is of pivotal importance to be able to identify patients with a more complicated course of acute appendicitis needing surgery and at the same time, to be able to differentiate patients with uncomplicated appendicitis who would be candidates for nonoperative treatment. Today, CT is the gold standard for diagnosing acute appendicitis. The specificity of CT imaging is very high, but its sensitivity has not been optimal, especially in accurately assessing the severity of the appendicitis (Kim et al. 2018a).

In the APPAC study, acute appendicitis presenting with an appendicolith was considered as complicated acute appendicitis i.e. not eligible for antibiotic therapy alone. The presence of an appendicolith has been shown to be associated with a more complicated course of the disease (Alaedeen et al. 2008, Shindoh et al. 2010). Both Shindoh et al (2010) and Vons et al (2011) reported that the presence of an appendicolith was associated with a failure of nonoperative treatment in acute appendicitis patients (Shindoh et al. 2010, Vons et al. 2011). Alaedeen et al (2008) showed that pediatric patients with appendicolith acute appendicitis had significantly higher CRP levels than those without an appendicolith (Alaedeen et al. 2008). In contrast, we observed no difference in the CRP values of patients with an appendicolith and patients with uncomplicated acute appendicitis. In our study, neither clinical findings nor inflammatory markers were able to identify acute appendicitis patients with an appendicolith underlining the importance of CT imaging when evaluating the best possible treatment paradigm for uncomplicated acute appendicitis.

The preoperative clinical identification of an appendiceal tumor is difficult, even though several risk factors have been identified: advanced age, multiple comorbidities, atypical presentation and complicated acute appendicitis (Loftus et al.

2017, Carpenter et al. 2012). The lack of preoperative diagnostic tools for detecting appendiceal tumors highlights the role of preoperative imaging, with CT being the gold standard. Even though imaging techniques have advanced over the years and have significantly improved the diagnostics of acute appendicitis, only a few of appendiceal tumors are identified preoperatively (Roggo et al. 1993, Whitley et al. 2009). Several CT features suggestive of coexisting appendiceal tumor have been described (Bennett et al. 2009, Hines et al. 2016, Whitley et al. 2009). However, there is an overlap with acute appendicitis CT findings and tumors are infrequently detected in the preoperative CT (Hines et al. 2016). The sensitivity of tumor diagnosis with CT increases with a greater appendiceal diameter and with secondary tumor findings, i.e. metastasis (Whitley et al. 2009, Pickhardt et al. 2002). These findings are in line with our results i.e. only 11% of patients with an appendiceal tumor were diagnosed preoperatively and out of these, 78% presented with metastatic disease at the time of diagnosis.

Currently, appendicitis is defined as complicated or uncomplicated acute appendicitis based on radiological, intraoperative or histological findings. However, the difficulty lies in identifying complicated and uncomplicated acute appendicitis preoperatively. At present, without conducting a radiological investigation, stratifying disease severity would appear to be unreliable if based only on clinical findings. According to our results, neither clinical findings nor laboratory markers were reliable enough to differentiate between complicated and uncomplicated acute appendicitis. Our results highlight the essential role of CT in this differential diagnosis and also in diagnosing the presence of an appendicolith, which is known to be associated with a more complicated course of appendicitis. The differential diagnosis of complicated and uncomplicated acute appendicitis with preoperative imaging is crucial in both evaluating treatment options and also with regard to the tumor risk, shown to be associated with complicated acute appendicitis.

6.3 Appendiceal neoplasms and acute appendicitis

In this study, the overall prevalence of an appendiceal tumor among acute appendicitis patients was very low (1.24%). Of these patients, 59% had uncomplicated and 41% had complicated acute appendicitis. The risk of carrying an appendiceal tumor was statistically significantly higher in patients with complicated acute appendicitis as compared with uncomplicated acute appendicitis, 3.24% vs. 0.87%, respectively. In a subgroup analysis comparing periappendicular abscess appendicitis to uncomplicated acute appendicitis, the risk was even higher, 4.99% vs. 0.87%, respectively.

The tumor rate in the APPAC trial (2015) in patients with uncomplicated acute appendicitis was 1.5% (Salminen et al. 2015). This result is in accordance with the 0.7-1.7% tumor rate reported in many retrospective studies evaluating histopathology of the appendectomy specimens (Tchana-Sato et al. 2006, Lee et al. 2011, Charfi et al. 2014). However, these studies have not differentiated between uncomplicated and complicated acute appendicitis. According to Andersson et al (2007), the rate of malignant tumors diagnosed with periappendicular abscess appendicitis was similar to the tumor rates detected among uncomplicated acute appendicitis in APPAC trial (Andersson et al. 2007). However, more alarming rates of appendiceal tumors, i.e. from 10% to 29%, have recently been reported in patients presenting with complicated acute appendicitis and periappendicular abscess (Wright et al. 2015, Furman et al. 2013, Carpenter et al. 2012, Teixeira et al. 2017). In a large retrospective study, 80% of appendiceal tumors presented with a periappendicular abscess (Lee et al. 2011). This is in line with our study which observed a significantly higher tumor risk with complicated acute appendicitis, with this being most evident among patients with periappendicular abscess. In our study, there were 250 patients with both acute appendicitis and an appendiceal tumor. Out of these, 41% (n=102/250) had complicated acute appendicitis and 65% (n= 66/102) had a periappendicular abscess. Our study and previous results highlight the need for accurate differential diagnosis between the different forms of acute appendicitis as well as evaluating the need for interval appendectomy after the initial nonoperative treatment of a periappendicular abscess. At the same time, the tumor risk is significantly lower in patients with uncomplicated acute appendicitis who have been treated with antibiotics alone (Hansson et al. 2012, Salminen et al. 2015, Vons et al. 2011). The risk of missing an appendiceal tumor related to these patients appears to be minimal. Appendiceal tumors are not generally suspected preoperatively (Lee et al. 2011). This is in line with our APPAC trial result (study III) and with the data from the FCR registry study (study IV) where none of the tumors were suspected preoperatively in patients operated for suspected or CT confirmed acute appendicitis. Tumors are also macroscopically hard to identify, in our study, in only 11% of cases was there a suspicion of the presence of a tumor visible during the operation.

The pathological types and behavior of appendiceal tumors are diverse and the overall survival rate is associated with the histologic type (Turaga et al. 2012). Recognizing the differences of primary appendiceal tumors is essential when evaluating the risk of misdiagnosis among acute appendicitis patients. NETs are the most common tumors of the appendix; in most cases the prognosis is excellent (Teixeira et al. 2017, Pape et al. 2016, Hsu et al. 2013). About 80% of NET diagnoses are incidental among acute appendicitis patients or appendectomy performed for other reasons (Pape et al. 2016). In our study population of 472 patients with an appendiceal tumor, 49% were NETs and this proportion was even

higher, 61%, in patients treated for suspected acute appendicitis. The more malignant NETs are mixed phenotype tumors: Goblet cell tumors and MANEC. The incidence of these tumors is rare, representing less than 5% of primary appendiceal tumors (McGory et al. 2005). In our study population, 11% of the tumors were these mixed phenotype neoplasms. Appendiceal carcinomas are epithelial tumors which can be further divided into mucinous-type and colonic-type adenocarcinomas (Cortina et al. 1995, Deans et al. 1995, Tang 2010). Although appendiceal mucinous tumors are recognized as benign, these tumors can progress to peritoneal dissemination resulting into pseudomyxoma peritonei (Tang 2010, Ronnett et al. 2001). In our study, 14% were mucinous tumors or pseudomyxomas. The appendiceal colonic-type adenocarcinomas are rare with an incidence of less than 0.1% of all appendectomies (McCusker et al. 2002). When compared to other primary appendiceal tumors, the colonic-type has the highest incidence of lymph node metastasis (Nitecki et al. 1994, Benedix et al. 2010) and worse outcomes compared to colon cancer (Son et al. 2016). Altogether 26% of tumors in our study were adenocarcinomas.

In conclusion, in our study, the incidence of appendiceal tumor among acute appendicitis was low. Tumors were detected rarely in preoperative imaging and even more rarely in early stage of disease. The tumor risk was significantly higher in complicated acute appendicitis, especially in periappendicular abscess patients. While there is a theoretical risk of misdiagnosing a tumor in uncomplicated acute appendicitis patients treated nonoperatively, it does seem that the risk appears to be very low.

6.4 The limitations of the study

The limitations of studies I-III include the retrospective study design in a prospectively collected patient material. We analyzed the clinical history, physical investigation and inflammatory laboratory markers collected in the APPAC randomized controlled trial (Salminen et al. 2015). Due the retrospective study design, unfortunately, the prospective collection of all of these parameters was not sufficiently comprehensive to create our own scoring system. The APPAC trial was able to recruit only 31.5% of all acute appendicitis patients and 20% of the patients treated for uncomplicated acute appendicitis during study period. Even though the study encountered difficulties in recruiting patients, the study population closely resembled the nonparticipants who were treated with appendectomy during the same period in the study hospitals (Salminen et al. 2015).

In study III, a number of different CT scanners were used causing variations in section thickness. A structured reporting template was used to identify uncompli-

cated and complicated acute appendicitis, but otherwise no structured imaging reporting criteria were used. For this reason, the prospective collection of all CT parameters for acute appendicitis was not sufficiently adequate to allow further analysis. With respect to the 1065 patients evaluated in study III, only those primary CTs assessed as either false-negative or false–positive were reassessed. Even though the reassessment was blinded, the two radiologists were aware of the primarily false CT diagnosis, but were unaware of the CT referral text and surgical and histological diagnoses.

In study IV, we included only patients from eight study hospitals (Turku, Helsinki, Tampere, Oulu, Kuopio, Jyväskylä, Lahti, Mikkeli) instead of the whole FCR registry data. Even though these study hospitals cover 70.1% of Finnish population and registry data accounted for 60% of patient population, there is no reason to assume that the patients included in the study would differ significantly from the patients in the excluded smaller hospitals.

6.5 Future prospects

The modern line of thinking in diagnostics of acute appendicitis first aims to confirm or eliminate appendicitis diagnosis, and secondly to define the disease severity, i.e. uncomplicated or complicated acute appendicitis. The optimal strategy that limits harm while maintaining a high degree of accuracy has still not achieved a general consensus.

As the treatment paradigm of acute appendicitis may be changing due to the promising results of antibiotic or even symptomatic treatment of uncomplicated acute appendicitis, future studies should focus on the early identification of patients who might respond well to nonoperative management as well as pinpointing those patients needing emergency surgery. The role of the preoperative diagnostic work-up is crucial in achieving an evaluation and execution of the optimal treatment strategy for both uncomplicated and complicated acute appendicitis. Future trials combining CT and scoring systems are needed, as neither clinical findings nor laboratory markers are reliable enough to determine disease severity. Even though CT is considered as the gold standard in diagnostics for acute appendicitis, it is not perfect in differentiating uncomplicated from complicated acute appendicitis and this differential diagnosis in CT needs to be further refined. Moreover, there is a concern regarding the fact that the patient is exposed to ionizing radiation during CT imaging. The impact of radiation dose reduction in CT on the diagnostic performance should be evaluated to achieve the lowest possible radiation dose without impairing the diagnostic accuracy, as low-dose CT has already been shown not to be inferior to standard CT (Sippola et al.

2018). Studies are needed to determine the feasibility of devising a scoring system which can screen those patients who will clearly benefit from imaging, aiming to reduce the numbers of patients undergoing imaging in the diagnosis of acute appendicitis.

Appendiceal neoplasms in acute appendicitis patients are rare. However, the differential diagnosis of acute appendicitis with or without a tumor has been shown to be challenging. The tumor risk is known to be higher in complicated acute appendicitis, but research clarifying the risk factors for appendiceal neoplasms, is needed.

As the unnecessary use of antibiotics should be avoided, future research should be focused on the correct antibiotic treatment regimen and duration. To further minimize any possible antibiotic related risks, studies focusing on early identification of those patients in whom antibiotics are not needed and spontaneous resolution will occur are necessary. When considering the treatment costs of acute appendicitis, further research is required to be devise an optimal strategy that limits harm while maintaining a high degree of efficacy with as low as possible costs.

7 CONCLUSIONS

The following conclusions can be made from the present data:

1. Single clinical or laboratory findings are unable to reliably distinguish between patients with and those without acute appendicitis.

2. In clinical decision making, neither clinical nor laboratory findings are reliable enough to estimate accurately the severity of the acute appendicitis or to determine the presence of an appendicolith.

3. The accuracy of CT in the emergency setting for the diagnosis of acute appendicitis is high and furthermore the experience of the radiologist does not improve the diagnostic accuracy.

4. Appendiceal tumor incidence in acute appendicitis is low. The tumor risk is significantly higher in complicated acute appendicitis compared with uncomplicated acute appendicitis.

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