Klinik und Poliklinik für Innere Medizin II, Klinikum rechts der Isar

Optical Diagnosis of Colorectal Polyps using Narrow Band Imaging and Acetic Acid

Hayley Rebecca Brown

Vollständiger Abdruck der von der Fakultät für Medizin der Technischen Universität München zur Erlangung des akademischen Grades eines Doktors der Medizin (Dr. med.) genehmigten Dissertation.

Vorsitzender: Prof. Dr. Jürgen Schlegel

Prüfende/-r der Dissertation:
1. apl. Prof. Dr. Stefan von Delius
2. Priv.-Doz. Dr Jeannine Bachmann

Die Dissertation wurde am 09.05.2019 bei der Technischen Universität München eingereicht und durch die Fakultät für Medizin am 08.10.2019 angenommen

Table of Contents

List of Tables

List of Figures

Abbreviations

ADR	Adenoma Detection Rate
ASA	American Society of Anaesthesiologists
BBPS	Boston Bowel Preparation Scale
EMR	Endoscopic Mucosal Resection
ESD	Endoscopic Sub-mucosal Dissection
FAP	Familial Adenomatous Polyposis
FOBT	Fecal Occult Blood Test
HDWL	High Definition White Light
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
NBI	Narrow Band Imaging
NICE	NBI International Colorectal Endoscopic
PDR	Polyp Detection Rate
SSA	Sessile Serrated Adenoma
TSA	Traditional Serrated Adenomas

1. Introduction

1.1 Colorectal Cancer

1.1.1 Epidemiology

Each year there are approximately 11 million new cases of cancer worldwide with around one million of these being colorectal cancer. The highest incidence of colorectal cancer is found in Central Europe, Australasia and North America with the lowest incidence being seen in Africa and in South Central Asia (Ajani, Curley et al. 2005, Messmann 2006, Zavoral, Suchanek et al. 2009, NICE 2014). With the ever increasing dietary and environmental changes in Asia and Africa, rates are increasing (Ajani, Curley et al. 2005). Cancer is a major cause of morbidity worldwide, with a third of people developing cancer at some stage in life. It is mainly prevalent in the elderly population but it can develop at any age (NICE 2014).

Together with lung, breast and prostate cancer, colorectal cancer has the highest incidence and mortality worldwide (Ajani, Curley et al. 2005). Colorectal cancer is the third most common cancer in men after prostate and lung cancer. For women breast cancer is the leading type of cancer followed by colorectal cancer (NICE 2014, Koch-Institut 2015). Morbidity rates began to decline in 2003 and have since declined further. The five-year survival rate is 62% for both men and women (Koch-Institut 2015). Manifestation is strongly linked to age, as the frequency rises steadily with increasing age (Messmann 2006, Bokemeyer 2007). Incidence rates increase greatly over the age of 60 with around three-quarters of cases presenting in patients aged 65 or over (Ajani, Curley et al. 2005, NICE 2014). Rates of colorectal cancer in men and women are very similar up until the age of 50, however later in life, rates in

men increasingly exceed those of women (NICE 2014). In Germany, figures estimate the current incidence of colorectal cancer to be between 55,000 and 60,000 per annum, from which there are a predicted 25,000 to 30,000 cancer related deaths. The lifetime risk is currently estimated at 6% (Ajani, Curley et al. 2005, Messmann 2006, Bokemeyer 2007, Leitlinienprogramm-Onkologie 2017).

Colorectal cancer currently causes around half a million deaths worldwide each year, with approximately two thirds of these deaths occurring in the more developed areas (NICE 2014). Mortality rates for colorectal cancer have fallen since the 1990s in the majority of European countries, however it is still the second most common cause of cancer-related deaths in Germany (Schmiegel, Adler et al. 2000, NICE 2014).

The five-year survival rate for patients with stage I colorectal cancer is 90% and for stage IV less than 10%. Ten-year survival rates do not differ much from five-year survival rates, indicating many patients who survive after five years have a very good prognosis. Around 25% of patients present with metastases at diagnosis, with 50% of patients developing metastases over time. Tumor stage is classified using the TNM system with the tumor stage correlating to the five-year survival rate. Survival rates have improved over the last 30 to 40 years due to earlier diagnosis, improved diagnostic techniques and better treatment programs (Ajani, Curley et al. 2005, NICE 2014).

Around 85% of carcinomas in the colon and 90% of carcinomas in the rectum develop from adenomas via the adenoma-carcinoma sequence. The majority of colorectal carcinomas are located in the colon (60%) and around 40% in the rectum.

Of those located in the colon, 60% are found in the sigmoid colon (Ajani, Curley et al. 2005, Messmann 2006, NICE 2014).

1.1.2 Risk Factors

There are many different factors that have an influence on an individuals risk. Patients who are at high risk of developing colorectal cancer are those with chronic inflammatory bowel disease, carriers for hereditary colorectal cancer and those with a positive family history where genetic factors are not yet known (NICE 2014, Leitlinienprogramm-Onkologie 2017).

Inflammatory bowel disease increases the risk of developing colorectal cancer 20 to 30 times. Patients who are diagnosed at an early age, and those with active disease have the highest risk. However in recent years the incidence of colorectal cancer in these patients has decreased, thought to be due to better therapy and surveillance (Ajani, Curley et al. 2005, Messmann 2006).

Hereditary conditions of importance include familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC)/ Lynch syndrome and Peutz-Jeghers syndrome. Subjects with hereditary conditions have not only an increased risk for colorectal cancer but also for extra-colonic neoplasias (Leitlinienprogramm-Onkologie 2017). HNPCC is the most common of all hereditary conditions and is thought to be responsible for around 5% of all colorectal cancers. It is relatively difficult to diagnose HNPCC clinically and for this reason the Amsterdam criteria and the less specific Bethesda criteria have been developed. HNPCC carriers have a general tumor risk of 80 to 90%. Besides colorectal cancer, female subjects have an

increased risk of endometrial cancer (Leitlinienprogramm-Onkologie 2017). Patients with FAP make up around 1% of patients with colorectal cancer. Classical FAP is defined by the presence of over 100 colorectal adenomas (Leitlinienprogramm-Onkologie 2017). It is a hereditary autosomal dominant disease (Messmann 2006). Patients have a 100% chance of developing colorectal cancer when left untreated (Ajani, Curley et al. 2005, Bokemeyer 2007). An attenuated form of FAP (AFAP) is a condition where fewer than 100 polyps are present. Patients with AFAP tend to develop polyps and colorectal cancer later in life. However unlike FAP colorectal cancer does not present in all patients who are left untreated (Tao, Shinmura et al. 2010, Ibrahim, Barnes et al. 2014).

For subjects with a positive family history, the risk doubles if a first-degree relative has had colorectal cancer, and doubles again if two first-degree relatives have been diagnosed. The risk increases further if the relative developed colorectal cancer before the age of 60. The level of risk varies depending on the age of diagnosis of the affected relative. If diagnosed before the age of 60 the subject has a slightly increased risk, however if diagnosed younger than 50 the risk increases more than fourfold (Ajani, Curley et al. 2005, Messmann 2006, Bokemeyer 2007, Leitlinienprogramm-Onkologie 2017).

Other risk factors, aside from age include a western lifestyle and colon adenomas (Ajani, Curley et al. 2005). Western lifestyle refers to obesity and inactivity as well as dietary components. Inactivity has a strong association with colorectal cancer especially in men, with moderate daily exercise reducing the risk. The highest risk is seen in individuals with a body mass index >30kg/m^2 (Schmiegel, Adler et al. 2000, Ajani, Curley et al. 2005, Leitlinienprogramm-Onkologie 2017). Regular sport is

defined as around 30 to 60 minutes of moderate activity per day and reduces the incidence of colorectal cancer significantly (Bokemeyer 2007, Leitlinienprogramm-Onkologie 2017). Subjects with a high level of physical activity have been shown in studies to have a reduced risk of colorectal cancer of up to 30% (Leitlinienprogramm-Onkologie 2017). Various clinical trials have shown a “western diet” to play an important role, suggesting that diets low in saturated fat and high in fibre and antioxidants protect from development of colorectal cancer (Schmiegel, Adler et al. 2000, Ajani, Curley et al. 2005, Bokemeyer 2007, NICE 2014). Current German guidelines recommend a daily fibre intake of at least 30g per day to reduce the risk of colorectal cancer (Leitlinienprogramm-Onkologie 2017). Consumption of red meat including beef and lamb has an increased colorectal cancer risk however poultry products do not (Leitlinienprogramm-Onkologie 2017). Alcohol consumption has been found to be a weak risk factor for the development of colorectal cancer hence a restriction in alcohol consumption is recommended (Ajani, Curley et al. 2005, Leitlinienprogramm-Onkologie 2017). Cigarette smoke is associated with development of colorectal adenomas and less directly with colorectal cancer (Ajani, Curley et al. 2005, Leitlinienprogramm-Onkologie 2017).

1.1.3 Symptoms

Clinical findings are often inconsistent and unspecific (Bokemeyer 2007). Typical presenting complaints that may indicate colorectal cancers are rectal bleeding, changes in bowel habits, weight loss and fatigue. Symptoms are often specific to localisation in the colon. Fatigue is associated with right-sided colon carcinomas as they often present initially with iron-deficiency anaemia. In contrast left-sided neoplasia tends to present with changes in bowel habits and bleeding. However it is

not uncommon that patients present with no clinical symptoms. Approximately 10% of colorectal carcinomas are diagnosed in emergency situations following gastrointestinal bleeding, an ileus or perforation (Ajani, Curley et al. 2005, Messmann 2006, Bokemeyer 2007).

1.1.4 Diagnostic

Diagnosis is based on family history and clinical findings. Complete colonoscopy is essential and is the primary diagnostic procedure. It allows for complete visualisation of the colon, it identifies the exact location of the primary tumor and at the same time allows for biopsies to be taken and sent for histological confirmation in the pathology. Digital rectal exams are also important and should always be carried out at the beginning of a colonoscopy considering that 40% of colorectal carcinomas are located in the rectum (Ajani, Curley et al. 2005, Messmann 2006).

Other diagnostic procedures for screening include sigmoidoscopy and fecal occult blood tests (FOBT). Sigmoidoscopy should be offered to patients who do not wish to undergo a colonoscopy. It should be used in combination with a FOBT to help detect potential lesions in the proximal colon (Messmann 2006, Leitlinienprogramm-Onkologie 2017). Once colorectal cancer has been diagnosed, computer tomography scans are then used in staging to asses the local extent of the tumor and to detect metastases (Ajani, Curley et al. 2005).

1.1.5 Screening Program in Germany

Screening aims to reduce the incidence of colorectal cancer through close medical observation. The aim of any screening program is early detection (Ajani, Curley et al.

2005). Around 90% of colorectal carcinomas arise from benign adenomas, which could have been prevented by complete resection (Schmiegel, Adler et al. 2000). There are a number of good reasons why the colon is a favorable organ to screen. Firstly the colon is a relatively easily accessible organ and through early detection and complete resection of neoplastic lesions the development of invasive cancer through the adenoma-carcinoma sequence can be prevented (Ajani, Curley et al. 2005). Secondly it is one of the worlds leading causes of morbidity and mortality and through screening, incidence and death rates can be dramatically reduced and prognoses improved. As with most types of cancer the prognosis depends heavily on the clinical stage at diagnosis. On average an adenoma takes a minimum of 10 years to develop into colonic cancer through the adenoma-carcinoma sequence (Bokemeyer 2007, Zavoral, Suchanek et al. 2009). Hence this gives physicians a relatively large timeframe in which to detect premalignant lesions early on. Screening programs across Europe have improved over the last 20 years. This is largely due to successful awareness campaigns and improved education to the target population (Schmiegel, Adler et al. 2000, Zavoral, Suchanek et al. 2009).

It is important to differentiate between those at risk for colorectal cancer and those who are not. For asymptomatic patients a general screening program is needed whereas high risk groups need to be routinely monitored (Bokemeyer 2007). In October 2002 a new screening program for colorectal cancer was introduced in Germany, offering asymptomatic patients a complete colonoscopy. Following the introduction of the program, colorectal incidence has decreased for both men and women in Germany. For the asymptomatic population who do not wish to undergo colonoscopy an FOBT is offered annually. If the FOBT test is positive, colonoscopy is then indicated. Following a negative colonoscopy another re-examination is

recommended in 10 years. An exam is deemed to be negative when no adenomas are found. Adenomas that develop into invasive cancer through the adenoma-carcinoma sequence tend to do so over a minimum of 10 years hence a 10-year time span is recommended for follow-up (Bokemeyer 2007, Zavoral, Suchanek et al. 2009, Stock, Ihle et al. 2011, Koch-Institut 2015, Leitlinienprogramm-Onkologie 2017). The incidence of colorectal cancer increases exponentially after the age of 50 thus screening is recommended for patients aged from 50 years. Studies have also shown a very low rate of adenomas in subjects between 40 and 49 years of age, supporting the idea that there is no need for a screening program earlier in life for asymptomatic subjects (Bokemeyer 2007, Leitlinienprogramm-Onkologie 2017).

Current screening measures used worldwide include testing for fecal occult blood, flexible sigmoidoscopy and colonoscopy (Ajani, Curley et al. 2005). FOBT detects bleeding whereas colonoscopy and sigmoidoscopy have the additional advantage of not only being able to detect the source of the bleed but also allow for diagnostic intervention (Leitlinienprogramm-Onkologie 2017).

Using colonoscopy in screening has its advantages in terms of identifying and removing neoplasia, although it has been criticised for being expensive and rather high risk for routine screening. A reported 4-6% of cancers are not detected during the initial exam (Ajani, Curley et al. 2005). A high quality exam is important in colonoscopy with a number of quality features of particular importance. The most important quality indicator is the adenoma detection rate (ADR). A high ADR lowers the lifetime risk of colorectal carcinoma in subjects. The recommended ADRs to demonstrate satisfactory colonoscopy quality for examiners are ≥25% for male patients and ≥15% for female patients (Corley, Jensen et al. 2014, Inra, Nayor et al.

2017). A withdrawal rate of ≥6 minutes is widely recognised as being acceptable to allow for detection of adenomas. Cecal intubation together with a withdrawal time of ≥6 minutes gives the colonoscopist sufficient time to examine the mucosa carefully. Bowel preparation is also an important quality feature of colonoscopy. If the bowel is poorly prepared, this can lead to an increased adenoma miss rate due to poor visibility of the colon mucosa (Inra, Nayor et al. 2017, Leitlinienprogramm-Onkologie 2017). Different prospective studies have shown that through removal of adenomatous polyps during colonoscopy, the incidence of colorectal cancer can be significantly reduced. Removal of early neoplastic lesions prevents cancer as the progression of the adenoma-carcinoma sequence is inhibited. As well as polyps, mucosal tumors can also be successfully removed in early operable stages (Bokemeyer 2007). Colonoscopy should be offered to all patients who do not have major comorbidity. A digital rectal examination should be performed at the beginning of each colonoscopy (Leitlinienprogramm-Onkologie 2017). Colonoscopy is a very effective screening method. Of all the methods mentioned it has the highest sensitivity and specificity in terms of early detection of lesions including adenomas and cancer (Bokemeyer 2007, Leitlinienprogramm-Onkologie 2017).

Fecal occult blood tests (FOBT) are widely used for screening and decrease mortality. An annual FOBT should be carried out for patients who do not wish to have a colonoscopy. No special preparation is needed for the test and it is relatively straightforward, hence it is suitable for screening. Bleeding is often intermittent and therefore repeated testing is required. Sensitivity is however limited as cancers and their precursors do not always bleed enough to be detected. FOBT is considerably cheaper than colonoscopy although numerous false-negative and false-positive results have been reported (Ajani, Curley et al. 2005, Bokemeyer 2007,

Leitlinienprogramm-Onkologie 2017). A positive FOBT result requires a follow up colonoscopy of the entire colon following a digital rectal examination (Leitlinienprogramm-Onkologie 2017).

Flexible sigmoidoscopy is relatively cost effective, safe and good at detecting lesions. It has taken over from rigid proctoscopy due to patient preference and acceptance. Flexible sigmoidoscopy is limited as not all sections of the colon can be viewed. Approximately one third of neoplasias are located proximally and these lesions cannot be detected using sigmoidoscopy (Ajani, Curley et al. 2005, Leitlinienprogramm-Onkologie 2017). The combination of FOBT and flexible sigmoidoscopy has proven to detect significantly more neoplasia as either of the techniques on their own (Bokemeyer 2007). Sigmoidoscopy should only be used as an alternative to colonoscopy when preparation of the bowel is not possible (Leitlinienprogramm-Onkologie 2017).

Screening guidelines in Germany for risk groups vary to those of the asymptomatic population. The screening methods remain the same however screening is carried out considerably earlier in life. For subjects who have a positive family history screening is recommended either 10 years before the age at which their relative was diagnosed with cancer or at the latest at 40-45 years of age. As with the asymptomatic population, if no polyps are found during the exam then it should be repeated in 10 years time (Leitlinienprogramm-Onkologie 2017). Screening for patients with inflammatory bowel disease is currently recommended for patients with ulcerative colitis no longer than eight years after symptoms begin. The benefit of screening for patients with Crohn's disease is currently unknown (Leitlinienprogramm-Onkologie 2017). HNPCC-patients should undergo a

colonoscopy annually as of 25 years of age (Leitlinienprogramm-Onkologie 2017). Subjects at risk for FAP should undergo a rectosigmoidoscopy form the age of 10 years. If adenomas are found then a complete colonoscopy should be performed (Leitlinienprogramm-Onkologie 2017).

1.2 Polyps

1.2.1 Epidemiology

Colonic polyps are the most frequently found abnormality seen during colonoscopy. They are defined as an abnormal protrusion into the lumen of the colon (Williams, Pullan et al. 2013). Colonic polyps are estimated to be present in 20 to 50% of all examinations (Blackstone 1987, Messmann 2006). Just like colorectal cancer, the prevalence of colonic polyps differs worldwide and they are more prevalent in developed countries (Messmann 2006). Age is the most important determining factor. In 50-59 year old subjects the prevalence is estimated at between 21-28%, rising to 40-45% in 50-59 year olds and increasing further to 53-58% in 60-69 year olds (Williams, Pullan et al. 2013). Through careful inspection during colonoscopy and histological examination, pre-cancerous lesions can be differentiated from non pre-cancerous lesions. The majority of adenomas are found in the proximal colon (Klare, Phlipsen et al. 2017). Polyps should be inspected carefully during colonoscopy and after complete resection examined histologically (Blackstone 1987, Group 2005, Messmann 2006, Bujanda, Cosme et al. 2010, Williams, Pullan et al. 2013). Diminutive polyps (≤5mm) and small polyps (6-9mm) make up for approximately 90% of polyps that are detected during colonoscopy. Diminutive polyps seldom develop into invasive cancer (Leitlinienprogramm-Onkologie 2017, Rees, Rajasekhar et al. 2017).

The risk of transformation into malignant cancer is dependent upon the number of adenomas found, their size and their histology (Messmann 2006, Williams, Pullan et al. 2013, Rees, Rajasekhar et al. 2017). Adenomas ≥1cm have a fourfold increased risk of developing into colorectal cancer (Blackstone 1987, Leitlinienprogramm-Onkologie 2017). Approximately 10% of adenomas with a 1.5cm diameter become malignant, whereas about 50% of polyps with a 3cm diameter develop malignancy (Pott 1995).

Lesions that do not penetrate the muscularis mucosa are termed carcinoma in situ and are not regarded as malignant. Only lesions that penetrate the muscularis mucosa are deemed to be malignant and are classified as T1 in the TNM classification system (Netzer, Forster et al. 1998, Bujanda, Cosme et al. 2010). Approximately 10% of adenomas develop into carcinoma in situ and around 3% develop into invasive carcinoma. Carcinoma in situ has the potential to further develop into invasive cancer (Blackstone 1987). Typical surface changes imply malignancy. Typical changes include bleeding, depressed ulceration and the non-lifting sign. The non-lifting sign is a sign of invasive colonic cancer and suggests invasion beyond the submucosa (Messmann 2006, Bujanda, Cosme et al. 2010, Friedland, Shelton et al. 2013, Rutter, Chattree et al. 2015). Polyps are described morphologically as being pedunculated, sessile or flat. Sessile lesions are more prone to be invasive than pedunculated polyps (van Doorn, Hazewinkel et al. 2015).

1.2.2 Symptoms

Polyps are unlikely to cause symptoms. Smaller polyps may present as anal bleeding whilst larger polyps could cause abdominal pain and signs of obstruction (Messmann 2006).

1.2.3 Histopathological Polyp Classification

Polyps can be classified in different ways. The classical pathological classification of colonic lesions is to differentiate them into neoplastic and non-neoplastic polyps (Blackstone 1987, Pott 1995, Messmann 2006, Leitlinienprogramm-Onkologie 2017).

Neoplastic polyps include tubular adenomas, villous adenomas and tubulovillous adenomas. They are all premalignant lesions and make up approximately 70% of colonic polyps. Non-neoplastic polyps include hyperplastic and inflammatory polyps as well as Peutz-Jeghers and juvenile polyps. (Blackstone 1987, Pott 1995, Messmann 2006, Leitlinienprogramm-Onkologie 2017).

Tubular adenomas are the most common adenomas. They are responsible for approximately two thirds of adenomas. They tend to be either sessile or stalked and can be either smooth or lobular on the surface. Approximately 50% are located in the rectosigmoid (Blackstone 1987, Messmann 2006, Bujanda, Cosme et al. 2010). Villous adenomas tend to be sessile and measure >1cm in diameter, with one third of them measuring >3cm. In 50% of villous adenomas >3cm in size malignancy is seen, particularly when there are depressions or signs of ulceration (Blackstone 1987). Villous adenomas are mainly located in the rectum and sigmoid, they make up around 5% of adenomas. They are often described as looking like a cauliflower-like

mass as they are nodular with finger-like processes. On the surface they are pale yellow and irregular. They have the greatest tendency for malignant change and around 40% are already malignant at diagnosis (Blackstone 1987, Messmann 2006, Bujanda, Cosme et al. 2010). Between 5-10% of adenomas are tubovillous. Tubovillous adenomas are a mixture of villous and tubular adenoma components and tend to be between 1cm - 2cm in size. They are predominantly pedunculated are have a thicker, shorter stalk compared to tubular adenomas (Blackstone 1987). They are often erythematous and nodular or lobular (Pott 1995). The risk of developing cancer tends to correlate with the villous part of the lesion (Messmann 2006).

Non-neoplastic lesions consist largely of hyperplastic and inflammatory polyps. Hyperplastic polyps have practically no malignant potential. They are routinely sessile and measure 5 - 10mm in diameter. They are usually pale or similar in colour to the mucosa. They tend to be solitary however in a small percentage of patients they present in a single colon segment. They are most commonly located in the rectum and sigmoid (Messmann 2006). Like hyperplastic polyps, inflammatory polyps tend not to be at risk of developing into cancer. They are usually unspecific and are found in patients with inflammatory bowel disease tissue (Pott 1995, Messmann 2006).

1.2.4 Serrated Polyps

Serrated polyps have considerably grown in significance over the last 30 to 40 years. Originally thought of as insignificant and hyperplastic today they are known to be fast growing with malignant potential (O'Connell and Crockett 2017). The World Health Organisation has divided serrated polyps into three groups: Hyperplastic polyps,

sessile serrated adenomas (SSA) and traditional serrated adenomas (TSA) (Singh, Zorron Cheng Tao Pu et al. 2016). Only TSAs and SSAs are precursors for colorectal cancer and develop via the serrated pathway (Andrew, Baron et al. 2017). The serrated polyp pathway is an alternative to the familiar adenoma-carcinoma sequence. The serrated polyp pathway is due to methylation in promoter regions of specific genes, whereas the adenoma-carcinoma sequence is due to mutations in both tumor-suppressor genes and oncogenes (Bordacahar, Barret et al. 2015). It is predicted that up to 35% of sporadic colorectal cancer develops through the serrated pathway (O'Connell and Crockett 2017). Between 4%-25% of serrated polyps are SSAs. They are typically characterised by their jagged appearance under the microscope (Bordacahar, Barret et al. 2015). SSAs are located predominantly in the proximal colon, are flat and can grow very rapidly compared to conventional adenomas cancer (Crockett 2017, O'Connell and Crockett 2017). The miss rate for SSAs during colonoscopy is very high, up to 50%, even by experienced examiners. This is due to their very subtle and flat appearance, the fact that they bleed less than conventional adenomas and due to their proximal location which is more likely to be sub-optimally cleansed compared to the distal colon (O'Connell and Crockett 2017). Stool and bile have a tendency to cover SSA's, increasing the difficulty in their identification during examination (Bordacahar, Barret et al. 2015).

1.2.5 Polypectomy

Polyp removal during colonoscopy using polypectomy is a routine procedure (Messmann 2006). Polypectomy interrupts the adenoma-carcinoma sequence and as a result reduces colorectal mortality by 40 - 60% (Leitlinienprogramm-Onkologie 2017, Rees, Rajasekhar et al. 2017). The examiner should always have clear

visualisation whilst carrying out the procedure to reduce the risk of complications (Messmann 2006). Bleeding and perforation are the most common complications following polypectomy however they are both minimal. Large polyp size and location in the proximal colon are both risk factors for bleeding (Seo, Sohn et al. 2010, Leitlinienprogramm-Onkologie 2017). The examiner should carefully inspect each polyp and determine its size. Polyps should be removed from proximal to distal and all fragments must be assessed histologically (Messmann 2006). The resection margin in polypectomy plays an important role in significantly reducing the chance of recurrent carcinoma or residual disease. It is widely accepted that a margin of ≥2mm is satisfactory (Bujanda, Cosme et al. 2010). Removal of each polyp is currently mandatory to allow for an exact classification (Leitlinienprogramm-Onkologie 2017). Polyps that measure ≤5mm can be completely removed with biopsy forceps, anything measuring >5mm should be completely removed with a snare (Messmann 2006, Bokemeyer 2007). Flat and or depressed polyps are associated with deep infiltration in the colon wall and are primarily treated surgically (Bokemeyer 2007). Contraindications for polypectomy include a blood clotting disorder, blood thinner medication or a lack of informed patient consent (Messmann 2006). A diagnostic colonoscopy should only be carried out if polypectomy is possible (Leitlinienprogramm-Onkologie 2017).

Endoscopic mucosal resection (EMR) and endoscopic sub-mucosal dissection (ESD) are both types of endoscopic resection used as an alternative to surgery to resect sessile polyps that are too big for cold snare polypectomy. For both techniques a substance is injected under the targeted lesion (Seo, Sohn et al. 2010). EMR often uses the piecemeal technique to help with the removal of large sessile polyps (>2cm) however there is a high recurrence rate linked to incomplete resection, which leads to

an increased risk for developing cancer (Brooker, Saunders et al. 2002, Arebi, Swain et al. 2007, Seo, Sohn et al. 2010). A follow-up exam is therefore recommended after two to six months (Seo, Sohn et al. 2010). EMR is both a safe and effective method for removing large sessile polyps. It is minimally invasive, patient quality of life is good following the procedure and it is cost effective (Wang, Zhang et al. 2014). Complications include bleeding and perforation however the main problem with this technique is that lesions ≥2cm often prove difficult to resect. With an experienced examiner, ESD has better resection outcomes than EMR as the technique allows for the removal of potentially deeper and larger lesions (Seo, Sohn et al. 2010). ESD has a higher complication rate than EMR and it can take up to five hours to complete the procedure (Vormbrock and Monkemuller 2012). There is a high degree of technical difficulty with this procedure, however *en bloc* resection can be achieved (Vormbrock and Monkemuller 2012, Wang, Zhang et al. 2014). The clear advantage of ESD over EMR is that the entire lesion can be successfully removed, although this must be weighed up against the fact that it is a very lengthy, high risk and complicated procedure (Wang, Zhang et al. 2014).

1.3 Endoscopic Polyp Characterisation

1.3.1 Optical Polyp Characterisation

There has been increasing interest from gastroenterologists in optical diagnosis, especially of small and diminutive polyps, over the last few years (Puig and Kaltenbach 2018). Currently polyps are extracted and sent to pathologists for examination to determine their exact histology. Histopathological results are the gold standard in terms of polyp diagnosis. The potential for optical diagnosis has been explored to determine if it could replace the routine polypectomy and

histopathological examination. Optical diagnosis is performed in real time during colonoscopy where endoscopists differentiate polyps, for example adenomatous polyps from non-adenomatous polyps. It is an attractive approach, which would enable immediate determination of surveillance intervals and reduce complications of polypectomy and the cost of histopathology (Rees, Rajasekhar et al. 2017, Puig and Kaltenbach 2018). Image enhancing technology is needed to help examiners in their optical diagnosis if they want to be able to provide a comparable service to pathologists. Narrow band imaging (NBI) has been widely used and it helps examiners to assess surface patterns and vascular structures. Morphological surface changes are key in differentiating non-neoplastic from neoplastic lesions (Rees, Rajasekhar et al. 2017, Patrun, Okresa et al. 2018).

Serrated sessile adenomas present one of the biggest challenges for optical diagnosis during endoscopy. As mentioned earlier SSAs have a miss rate of up to 50%. A further problem with SSAs is distinguishing them from hyperplastic polyps (O'Connell and Crockett 2017, Puig and Kaltenbach 2018). The accuracy of optical diagnosis when compared to histopathological results presents another problem. Accuracy rates have previously varied widely however recent studies have reported high accuracy rates and suggested optical diagnosis to be a promising tool in the near future (McGill, Evangelou et al. 2013, Chandran, Parker et al. 2015).

In 2011 the American Society for Gastrointestinal Endoscopy (ASGE) Preservation and Incorporation of Valuable endoscopic Innovation (PIVI) initiative put forward two strategies regarding optical diagnosis. The two strategies are displayed in Table 1 below.

Resect and discard	≤5 mm polyps	≥90% agreement in assignment of postpolypectomy surveillance intervals, using pathology standard
Do not resect	Rectosigmoid hyperplastic ≤5 mm	≥90% negative predictive value for adenoma

Table 1; Strategies regarding optical diagnosis from the American Society for Gastrointestinal Endoscopy, adapted from ASGE PIVI Statement Guidelines (Abu Dayyeh, Thosani et al. 2015).

The first strategy is a “resect-and-discard” method for high confident colorectal adenomas ≤5mm when optical diagnosis is used in combination with NBI. The second is a “diagnose-and-leave” strategy for high confident diminutive rectosigmoid hyperplastic polyps. In 2015 a meta-analysis stated that a “resect-and-discard” strategy along with a “diagnose-and-leave” strategy for diminutive polyps would be substantially more cost effective than the current system of sending every polyp to be examined histopathologically. As well as keeping costs down “diagnose-and-leave” would mean lower polypectomy complication rates (Abu Dayyeh, Thosani et al. 2015, Sakata, Kheir et al. 2016, Puig and Kaltenbach 2018).

Acetic acid helps to distinguish neoplastic from non-neoplastic lesions on the mucosal colonic wall and has been investigated in various studies looking into polyp optical diagnosis. Like NBI, acetic acid helps to better examine and determine structural differences that appear. It is a technique that is not currently used in daily practice but results so far have been very promising. Acetic acid is widely available and has an immediate effect making it a very promising diagnostic tool for the future in endoscopy (Goto, Kusaka et al. 2014, Chedgy, Subramaniam et al. 2016, Bhandari 2017).

1.3.2 Chromoendoscopy

Chromoendoscopy and magnification techniques allow for better differentiation between normal mucosa, non-neoplastic lesions and neoplastic lesions (Messmann 2006, Bujanda, Cosme et al. 2010). Magnifying colonoscopy is used with chromoendoscopy or NBI (Parra-Blanco, Fu et al. 2007). Chromoendoscopy was introduced in 1980 and uses either an absorptive or a contrast dye to differentiate between healthy and diseased tissue (Li, Ali et al. 2014). Contrast dyes collect in small grooves on the surface of the colonic mucosa and accentuate surface detail. Indigo carmine is the most frequently used dye and is more commonly used than absorptive dyes (Messmann 2006). Absorptive dyes are resorbed differently in healthy tissue compared to in malignant tissue, resulting in distinctive staining patterns on the mucosa surface. Methylene blue and crystal violet are commonly used absorptive dyes (Messmann 2006). Chromoendoscopy improves detection and resection of flat or sunken lesions that are commonly missed during a routine examination (Messmann 2006, Leitlinienprogramm-Onkologie 2017).

In 1996 Kudo et al developed and introduced pit pattern classification to identify neoplastic from non-neoplastic polyps, using magnification endoscopy to help describe a polyps appearance (Messmann 2006, Bujanda, Cosme et al. 2010, Li, Ali et al. 2014, Leitlinienprogramm-Onkologie 2017). Kudo et al divided polyps into five groups (pit patterns I-V) related to their structure, appearance and staining patterns. Type I and II are classified as benign (hyperplastic, inflammatory polyps), whereas types III-IV are classified as malignant (Messmann 2006, Li, Ali et al. 2014, Leitlinienprogramm-Onkologie 2017). The five classes are shown in Figure 1. Pit pattern classification has proven to be a frequently used system in detecting colorectal neoplasm however it is currently not a standard procedure due to being

rather time consuming and magnification endoscopes not being widely available (Messmann 2006, Li, Ali et al. 2014, Leitlinienprogramm-Onkologie 2017).

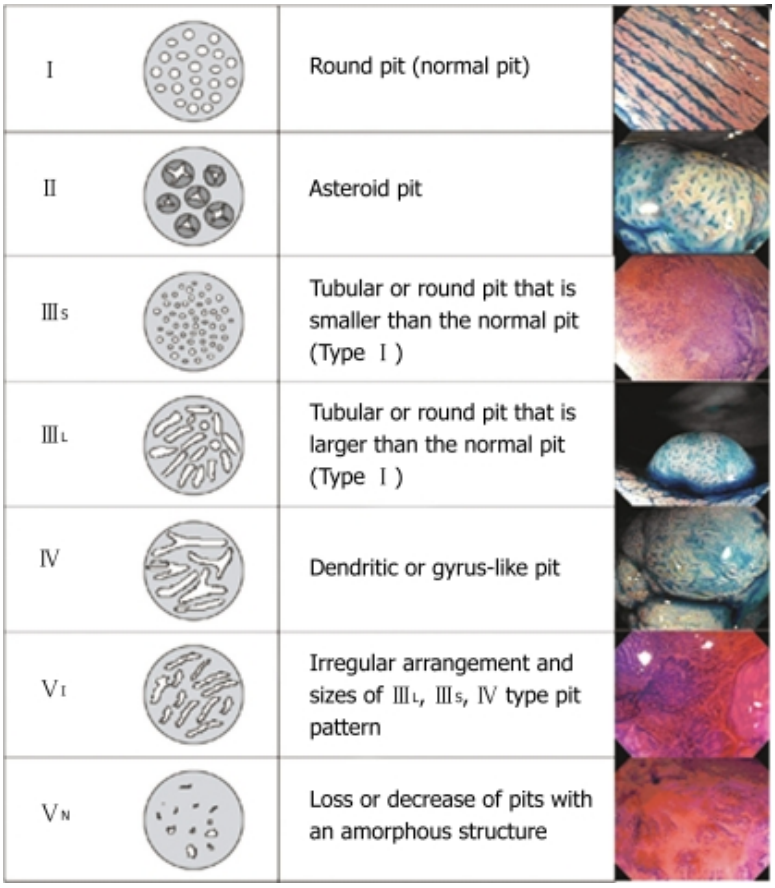

Figure 1; Pit pattern classification. Reprinted from Kanao, H., et al. *(Kanao, Tanaka et al. 2008).*

Colonic polyps are further classified by their morphology using the Paris classification system. The Paris classification was refined and adapted from earlier work from Kudo et al. The Paris classification is shown in Figure 2 and classifies superficial neoplastic colorectal lesions. Superficial refers to the fact that only the mucosa and submucosa are invaded (Group 2005). The Paris classification system further differentiates between polypoid (pedunculated or sessile) and non-polypoid lesions (flat or ulcerated) (Bujanda, Cosme et al. 2010). Polypoid type lesions are defined as protruding >2.5mm above the mucosal layer, whilst non-polypoid lesions tend to be

slightly elevated, flat or slightly depressed. Differentiation between polypoid and non-polypoid is not always easy (Facciorusso, Antonino et al. 2015).

Paris classification of superficial colorectal lesions

Polypoid type[1]	Pedunculated (0-1p)
	Sessile (0-1s)
	Mixed (0-1sp)
Non-polypoid type	Slightly elevated (0-IIa)
	Flat (0-IIb)
	Slightly depressed (0-IIc)
Mixed types	Elevated and depressed (0-IIa + IIc)
	Depressed and elevated (0-IIc + IIa)
	Sessile and depressed (0-1s + IIc)

[1]Elevated more than 2.5 mm above the mucosal layer.

Figure 2; Paris classification. Reprinted from Facciorusso, A., et al. *(Facciorusso, Antonino et al. 2015).*

Slightly elevated or flat lesions tend to grow laterally however depressed lesions grow into the colonic wall and increase the risk of submucosal invasion. This explains why non-polypoid lesions have a higher risk for invasiveness than polypoid lesions do. Non-polypoid lesions are located throughout the colon unlike polypoid lesions, which tend to be restricted to the left hand side of the colon (Facciorusso, Antonino et al. 2015).

A further classification system known as NBI International Colorectal Endoscopic (NICE) will be discussed later. It is a simple system that classifies colorectal cancer

based on three characteristics; colour, microvascular architecture and surface pattern (Utsumi, Iwatate et al. 2015).

1.3.3 Narrow band imaging

Narrow band imaging (NBI) is an optical imaging technology widely used in gastroenterology and urological endoscopy and is common practice in Japan, Europe, USA and other western countries (Gono 2015, Nishiyama, Oka et al. 2016, Nienstedt, Muller et al. 2017). There are no special requirements for patients and unlike chromoendoscopy there is no need for a dye (Gheorghe 2006, Akarsu, Sahbaz et al. 2016). It is quick to use as normal inspection can be easily switched to NBI mechanically (Gheorghe 2006, Nishiyama, Oka et al. 2016). It was introduced in 2005 and enhances the visibility of vessels and mucosal surface (Gono 2015, Akarsu, Sahbaz et al. 2016). It allows for a better analysis of both vascular structures and pit patterns than with normal white light and has been used to help differentiate between hyperplastic and adenomatous polyps during colonoscopy (Gheorghe 2006). Blood vessels in the submucosa are displayed in cyan whist capillary networks on the mucosal surface have a brownish appearance (Gono 2015). Compared to traditional methods NBI allows for better visualisation of the lesion boundaries, which increases the likelihood of complete resection (Gono 2015, Akarsu, Sahbaz et al. 2016). NBI takes advantage of the fact that different wavelengths behave differently in different biological tissues (Gono 2015). NBI uses narrow-bandwidth filters, using green and blue wavelengths but blocking red wavelengths (Gheorghe 2006, Akarsu, Sahbaz et al. 2016). Both the green and blue wavelengths are absorbed by haemoglobin in the blood. As cancerous tissue tends to be more highly vascularised than healthy tissue polyps and tumors appear darker

than their neighboring tissue (Facciorusso, Antonino et al. 2015, Gono 2015, Rees, Rajasekhar et al. 2017).

Figure 3 shows the difference between an adenoma using high definition white light (HDWL) and NBI during real time colonoscopy.

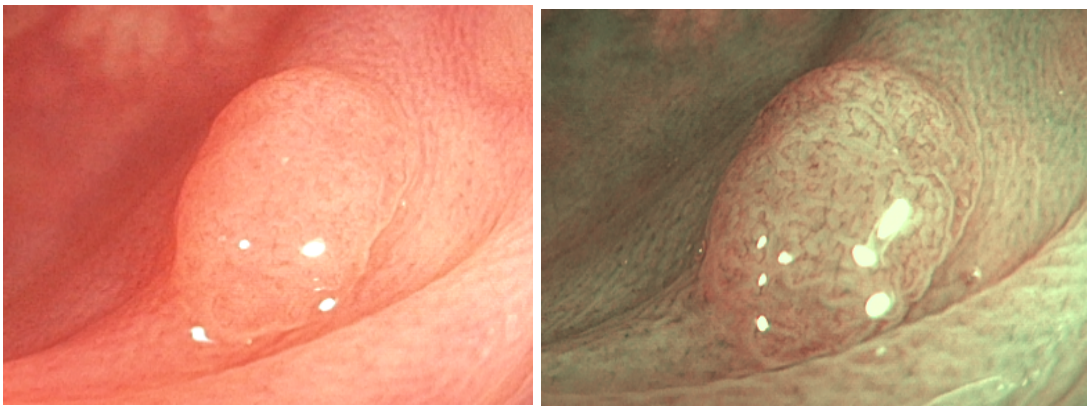

Figure 3; Differences between an adenoma using HDWL and NBI. Figure 3a (left) in HDWL, and Figure 3b (right) in NBI; the image on the right shows tubular and branched white structures surrounded by brown vessels. This surface pattern is typical for adenomas. In comparison it is more difficult to determine the surface pattern for the image on the left in HDWL. When examined closely, tubular structures can be identified however dark and white spots can also be seen which are typical for hyperplastic lesions.

Several studies have tried to use NBI to predict histology of neoplastic lesions. The Paris classification system was mentioned earlier, where NBI can be used to help assess mucosal pit pattern. A second classification system, also mentioned earlier, called the NBI International Colorectal Endoscopic (NICE) classification evaluates neoplastic lesions based on colour, microvascular architecture and surface pattern. Observation of the lesion may be done with or without the use of a magnifying endoscope. NICE differentiates between hyperplastic polyps, adenomas and deep

submucosal invasive cancer (Utsumi, Iwatate et al. 2015, Patrun, Okresa et al. 2018). The NICE classification system is shown in Table 2 below.

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels may be present coursing across the lesion	Brown vessels surrounding white structures[a)]	Has area(s) of disrupted or missing vessels
Surface pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structures[b)] surrounded by brown vessels	Amorphous or absent surface pattern
Most likely pathology	Hyperplastic & sessile serrated polyp[c)]	Adenoma[d)]	Deep submucosal invasive cancer

Table 2; NICE, narrow band imaging (NBI) International Colorectal Endoscopic. Reprinted from Takahiro, 2015 (Utsumi, Iwatate et al. 2015).

1.3.4 Acetic acid

Using acetic acid in medicine originally derived from gynecology. Gynecologists used acetic acid whilst examining the cervix to better identify cervical intraepithelial tissue during screening [22]. In gastroenterology, acetic acid has primarily been used to study gastric cancer and Barrett's oesophagus (Parra-Blanco, Fu et al. 2007, Goto, Kusaka et al. 2014). Current diagnostic and follow up guidelines in Germany for dysplasia and early stage carcinoma detection in the oesophagus, stomach and duodenum recommend modern endoscopic techniques such as chromoendoscopy and NBI (Denzer 2015).

Barrett's oesophagus is defined by the presence of intestinal metaplasia. Four-quadrant biopsies have been the standard for endoscopic surveillance to date. Four-quadrant biopsies are taken in 2cm intervals for non-dysplastic tissue, and in 1cm intervals for dysplastic tissue (Bhandari 2017). In contrast to the multiple untargeted

biopsies collected by taking four-quadrant biopsies, acetic acid allows for targeted biopsies. Acetic acid highlights neoplastic segments from the healthy surrounding tissue more effectively than using white light endoscopy alone (Longcroft-Wheaton, Duku et al. 2010). Acetic acid can be used in conjunction with other techniques such as magnification endoscopy and four-quadrant biopsy. Acetic acid has been demonstrated to accurately identify intestinal metaplasia with high specificity and sensibility (Chedgy, Subramaniam et al. 2016, Kandiah, Chedgy et al. 2018). Combining acetic acid with NBI has been shown to help in differentiating neoplastic from non-neoplastic lesions (Goto, Kusaka et al. 2014).

Currently the use of acetic acid is not a standard technique in colonoscopy. Studies have looked into how effective the technique is in differentiating between neoplastic and non-neoplastic tissue, estimating the depth of invasion in the mucosal wall and comparing it to other chromoendoscopy techniques such as indigo carmine (Fu, Kato et al. 2007, Goto, Kusaka et al. 2014, Zhang, Gu et al. 2015).

Acetic acid removes surface mucous material and in doing so accentuates the surface pit pattern (Kawamura, Togashi et al. 2005, Goto, Kusaka et al. 2014, Yamamoto and Shafazand 2017). The exact mechanism of acetic acid is unclear. Most theories are based upon the fact that neoplastic tissue contains less cytoplasmic proteins than non-neoplastic areas. By adding acetic acid a reversible degenerative reaction of the cellular proteins takes place which results in aceto-whitening. Initially both neoplastic and non-neoplastic appear white (Bhandari 2017, Kandiah, Chedgy et al. 2018). The reduced cytoplasmic protein in neoplastic areas causes an early loss of aceto-whitening. Neoplastic tissue then appears as red spots known as a focal erythema. This change in colour provides the examiner with an

enhanced contrast of the different tissue types (Chedgy, Subramaniam et al. 2016, Chedgy, Fogg et al. 2018, Sun, Ma et al. 2018).

Acetic acid is cost effective and works immediately unlike the time consuming methods mentioned above such as indigo carmine (Kawamura, Togashi et al. 2005, Parra-Blanco, Fu et al. 2007). Acetic acid is widely available and its effects are reversible. The method can be repeated at the same location as tissue is not damaged (Chedgy, Fogg et al. 2018, Kandiah, Chedgy et al. 2018). It can be used with any endoscopic system and does not rely on the most up to date camera or endoscopic equipment. Both expert endoscopists and those with less experience can use the technique (Chedgy, Kandiah et al. 2017). Not only is it highly sensitive, it is also a very simple method to use and to learn. Only a very small amount of acetic acid is needed per patient, on average around 5ml per lesion examined. Compared to other modern endoscopic techniques this method requires no financial investment. It has been reported that using acetic acid leads to prolonged oozing from the site post biopsy. However prolonged bleeding has not been reported (Chedgy, Subramaniam et al. 2016, Bhandari 2017).

Figure 4 below shows two different polyps after combining NBI with acetic acid. They show the difference in surface appearance of an adenoma and a hyperplastic polyp.

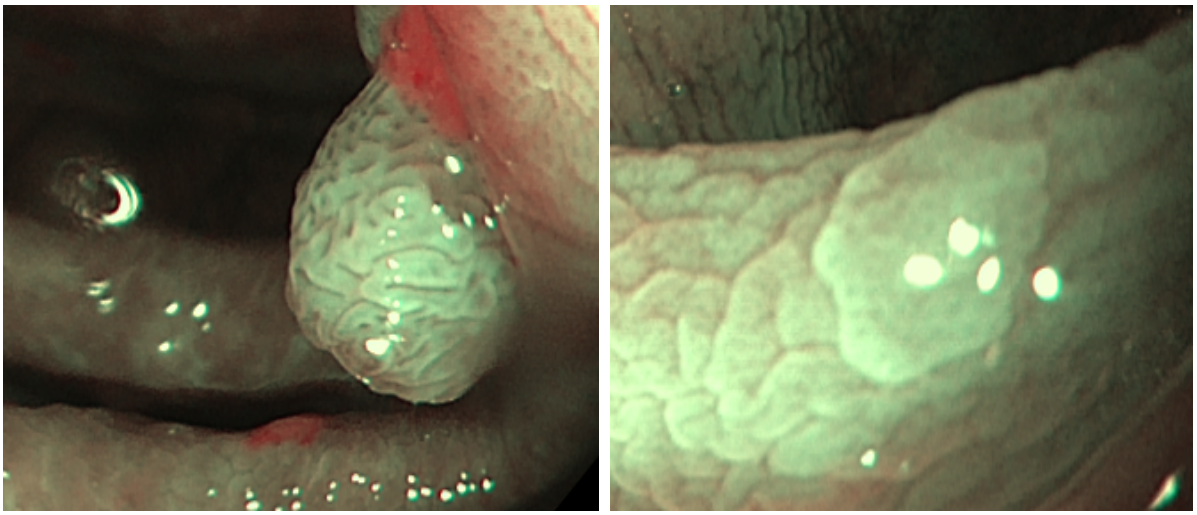

Figure 4; Two different polyps after combining NBI with acetic acid. Figure 4a (left); Polyp, example of an adenoma using NBI with acetic acid. Figure 4b (right); Polyp, example of a hyperplastic polyp using NBI with acetic acid.

The following two images in Figure 5 show the same adenoma firstly in high definition white light (HDWL) and then following the application of acetic acid and NBI.

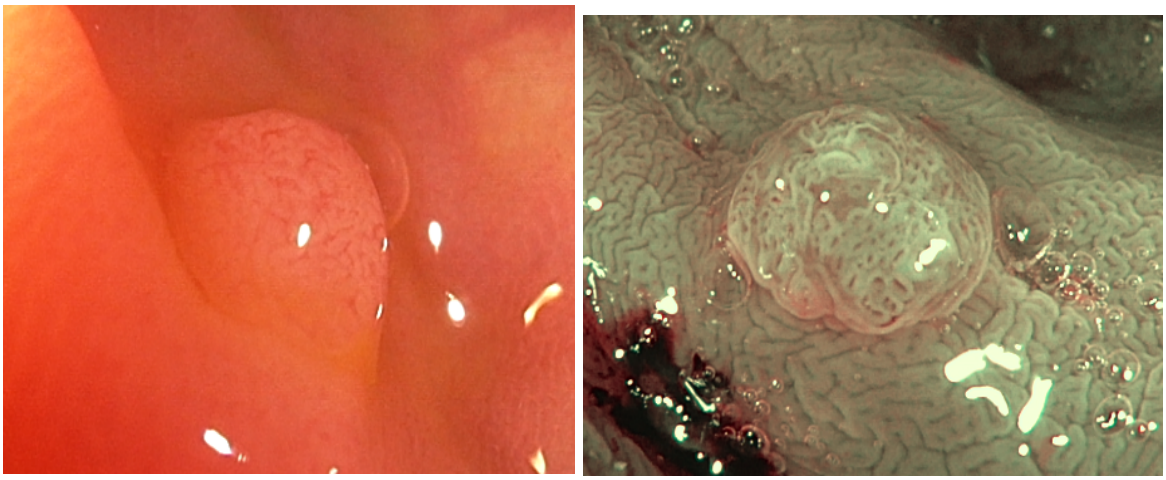

Figure 5; Adenoma in HDWL and then following the application of acetic acid and NBI. Figure 5a (left); Polyp in HDWL. Figure 5b (right); Polyp in NBI after applying acetic acid. When examined closely tubular structures can be seen in the image on the left hand side, however parts of the adenoma are homogenous in pattern. After the addition of acetic acid and with the use of NBI the image on the right hand side shows a much clearer surface patter, tubular and branched white structures can be clearly identified and there is no hint of a homogenous pattern. Brown vessels clearly surround white structures and using the NICE classification the image can be clearly identified as an adenoma.

Figure 6 below shows the same hyperplastic polyp before and after addition of acetic acid in HDWL.

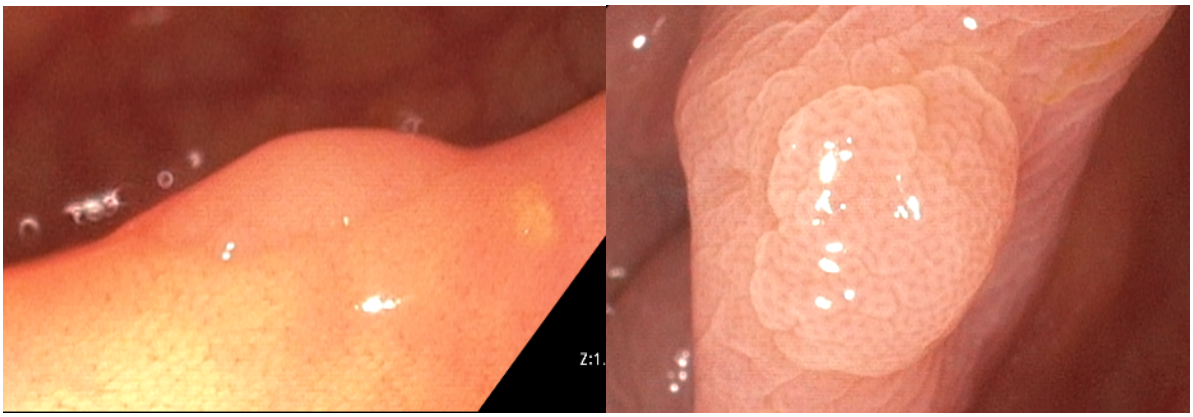

Figure 6; Hyperplastic polyp before and after the application of acetic acid and NBI. Figure 6a (left); Polyp in HDWL. Figure 6b (right); Polyp in HDWL after applying acetic acid. When comparing the two images, it is clear to see that after acetic acid application spots can be more easily seen of uniform size, which is classic surface pattern for identifying hyperplastic polyps using the NICE classification system.

2. Method

2.1 Study Design and Aim

We carried out a prospective observational study with 55 patients. Our aim was to see if acetic acid in combination with NBI could be used to optically predict and correctly diagnose the histology of colorectal adenomas. It was an open trial, as neither patients nor researches were blinded. Optical diagnoses were compared with the histological diagnoses to determine how accurate we were. We predicted an accuracy of at least 75%. Before the study began we applied for permission from the ethics committee at Klinikum rechts der Isar, which was granted in due course. The study was also registered at clinicaltrials.gov (identification number: NCT02760381).

2.2 Sample Size Calculation

We hypothesised that optical prediction when using NBI and acetic acid would be accurate in 90% of all optical diagnoses. We calculated the sample size for an exact binominal test assuming one polyp per patient. Under the given assumptions a sample size of 55 cases was required in a single arm study in order to detect 75% accuracy with a power of 90%. The significance level was 0.05 for these calculations.

We predicted that by using acetic acid with NBI on the colon mucosa we would accurately be able to optically diagnose colorectal adenomas in >75% of the adenomas found.

2.3 Patient Recruitment

Data collection took place from April 2016 until September 2016 at the Klinik and Poliklinik für Innere Medizin des Klinikum Rechts der Isar der Technischen Universität München. Patients who had a colonoscopy appointment within this timeframe and fitted the inclusion criteria were considered as potential candidates for the study. All patients were informed about the clinical trial including aims, procedure, data protection and complications. Patients were approached in the endoscopy department on the morning of their scheduled examination. They received written information about the trial and each patient that participated had to give written consent.

2.4 Study Procedure

Patients scheduled for colonoscopy that met our inclusion criteria (see below), and had given written consent were included in our trial. The examinations were carried out using an Olympus Evis Exera® III CF – HQ 190 colonoscope (Olympus, Tokio, Japan).

During the endoscopic examination an examiner, an endoscopic nurse and a student were present. When patients with an ASA III score were examined, a second physician was present for the sedation. The nurse was responsible for positioning the patient in the examining bed and documenting patients' vital parameters. Pulse rate, oxygen saturation and blood pressure were measured throughout the examination. Patients also received supplementary oxygen (4 L/min) through a nasal cannula. In the study we used propofol IV and midazolam IV. The majority of patients (94.4%)

were sedated with propofol and a small percentage with midazolam as well. The student's role was to collect data for the study. The case form is provided (see Appendix).

Before every colonoscopy a digital rectal examination was carried out. The colonoscopy officially began with the insertion of the endoscope. The time at the beginning of the colonoscopy was noted. The endoscope was then carefully maneuvered through the large intestines until the caecum was reached. The time was noted when the appendiceal orifice in the caecum had been identified by the examiner. Under certain circumstances the endoscope was pushed through the ileocaecal valve to examine the distal small intestine. This was carried out for example in patients who presented with diarrhoea and patients being examined to exclude or diagnose inflammatory bowel disease. Following examination of the caecum the endoscope was then slowly withdrawn. The surface mucosa was closely examined macroscopically for any irregularities. On finding a polyp in the colon its localisation and size were documented. Size was estimated by comparing the polyp to the biopsy forceps. The morphology of the polyp was initially examined using standard HDWL and the examiner stated their optical diagnosis. On making their diagnosis the examiner stated how confident they were, high confidence was described as ≥90% whilst low confidence was <90%. Examiners also had to examine the margin of each polyp found and determine whether or not there was a clear distinction between the polyp margin and normal healthy colonic mucosa. The area of mucosa containing the polyp was then sprayed with approximately 5ml of a 1.5% acetic acid solution and the NBI function was turned on. The examiner then reassessed their optical diagnosis. To assess each polyp the NICE classification was used (hyperplastic polyp, adenoma or deep sub-mucosal invasive cancer).

Photographs were taken in both HDWL and NBI of each polyp. After the examiner had stated their diagnosis the polyp was extracted using either forceps or a snare and the sample was sent to the pathology department for histological evaluation. The pathology department was not told of the optical diagnosis made by the examiner during colonoscopy. For internal quality assurance, two different pathologists examined the extracted polyps independently.

The extraction of the endoscope from the patient was defined as the end of the colonoscopy. Following completion of the exam, patients were further monitored in the recovery room until fully alert.

2.5 Criteria

2.5.1 Inclusion Criteria

Inclusion criteria were as follows:

- Indication for colonoscopy
- Patient ≥ 18 years old

2.5.2 Exclusion Criteria

Exclusion criteria were as follows:

- Patient refused written consent
- ASA (American Society of Anesthesiologists) class IV, V and VI
- Colonoscopy indication: Polypectomy of known adenoma/polyp
- Known colon carcinoma
- Polypectomy contraindication e.g. uncorrected bleeding disorders

- Emergency colonoscopy

The ASA classification system, shown in detail below in Table 3, was introduced in the 1940's. Patients are given a score from ASA I to ASA VI. It allows clinicians to assess a patient's physiological status prior to anesthesia. An ASA score is used to help predict perioperative mortality. The higher the ASA score, the higher the incidence of perioperative mortality (Doyle and Garmon 2018, Kisa, Yucel et al. 2018, Knuf, Maani et al. 2018).

ASA PS Classification	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

Table 3; ASA Physical Status Classification System (Doyle and Garmon 2018).

2.6 Endpoint

2.6.1 Primary Endpoint

Our primary endpoint was the accuracy in which a colorectal adenoma is optically diagnosed using acetic acid with NBI. The optical diagnosis was then compared to the histological diagnosis for confirmation of accuracy.

2.6.2 Secondary Endpoints

Secondary endpoints of the trial included sensitivity, specificity, positive and negative predictive values of the optical diagnosis, duration of colonoscopy and the adenoma detection rate (ADR). ADR is an important quality assessment indicator of colonoscopy as talked about earlier in the introduction (Greenspan 2013 , Brenner 2015). The amount of propofol (mg) needed for each examination, complications of colonoscopy as well as colon cleanliness were further secondary endpoints of the study. Colon cleanliness was assessed using the Boston Bowel Preparation Scale (BBPS). BBPS is a rating scale from 0-9 and describes bowel cleanliness (Calderwood 2010, Heron 2017). The colon is assessed in three segments; right colon, transverse colon and ascending colon. Each segment is given a score from 0-3 with 3 being the cleanest. The scores from each segment are then added together to give the BBPS. High BBPS scores indicate better visualisation during colonoscopy than low scores (Calderwood 2010, Heron 2017).

2.7 Data Collection

We used pseudonymisation to preserve patient privacy and data confidentiality. Shortly before the examination data from each patient was collected. This data

included colonoscopy indication, age, height, weight, gender, short medical history including current medication, diabetes, smoking status and alcohol consumption. Each patient's ASA score was recorded and whether they were an inpatient or an outpatient. The date and examiner's name were noted. During the trial two different examiners participated. The time was noted at the beginning and at the end of the colonoscopy, as well as the time it took to reach the caecum (caecal intubation time). The amount of propofol (mg) and of midazolam (mg) required during the examination was noted, as well as the colon cleanliness score (BBPS) and any complications that occurred. During the colonoscopy vital parameters were recorded (oxygen saturation, pulse and blood pressure). On detection of a polyp its location, size and morphology (Paris classification) was noted. Also noted was the examiners optical polyp diagnosis, how confident they were in their diagnosis (<90% or >90%), how many photos of the polyp were taken (in HDWL and in NBI with acetic acid), how long the examiner took to examine the polyp (in HDWL and in NBI with acetic acid), if the border of the polyp was clearly defined or not (in HDWL and in NBI with acetic acid), if forceps or a snare were used for the polypectomy and any other extra comments. The total number of polyps found during examination and total number of photos taken was also recorded. All data was put into a Microsoft-Excel table.

2.8 Statistical Analysis

Accuracy was the primary endpoint and refers to the amount of agreement between the results from optical diagnostic and those from the histopathological examination (van Stralen, Stel et al. 2009). Accuracy was calculated using Table 4 below.

	Adenoma	**Non-adenoma**
Optical diagnosis: Adenoma	True positive (A)	False positive (B)
Optical diagnosis: Non-adenoma	False negative (C)	True negative (D)

Table 4; Table used to calculate accuracy, sensitivity, specificity, positive predictive value and negative predictive value: Accuracy = (A+D)/(A+B+C+D); sensitivity = A/(A+C) x 100; specificity = D/(D+B) x 100; PPV = A/(A+B) x 100; NPV = D/(D+C) x 100.

Sensitivity and specificity are statistical measures used in our study. Sensitivity is a tests ability to correctly identify those patients with the disease. Specificity on the other hand is a tests ability to correctly identify those patients without the disease.

Positive and negative predictive values were used to analyse data collected in our study. The positive predictive value represents as a percentage all patients with a positive test who have the disease. In our study this represented adenomas that were optically diagnosed as adenomas and confirmed as adenomas in the histopathological examination. The negative predictive value is the percentage of patients who have a negative test and do not have the disease. In our study this referred to optically diagnosed non-adenomas that were confirmed as non-adenomas by the pathologist.

For analysis of our primary endpoint, a one-sided exact binomial test was performed on a significance level of 5% to test whether the accuracy of NBI and acetic acid was greater than 75%. Accuracies, sensitivities, specificities, positive predictive values and negative predictive values were presented for NBI with acetic acid and for

HDWL. For relevant quantities, exact 95% confidence intervals (Clopper-Pearson intervals) were calculated. McNemar tests were performed to compare accuracies, sensitivities and specificities between the two devices. For comparison of sensitivity and specificity, data were stratified by histological outcome. All tests for comparisons of devices were performed two-sided using a significance level of 5%. Statistical analysis was performed using R, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Absolute and relative frequencies were presented for categorical variables. For continuous measures means and standard deviations or medians and interquartile ranges were given.

3. Results

3.1 Patient Characteristics and Clinical Data

Patient characteristics and clinical data are shown below in Tables 5 and 6. The average (mean) age of patients who took part in the study was 62.3 years old. Of the 55 patients who consented to take part 31 were male and 24 were female. One third of patients were classified as ASA I, almost two thirds were classified as ASA II, whilst only 10.9% were ASA III. Of all participants 14.5% were regular smokers, 14.5% suffered from diabetes mellitus and 16.4% consumed alcohol on a daily basis.

Figure 7 below shows the process of patient inclusion in our study.

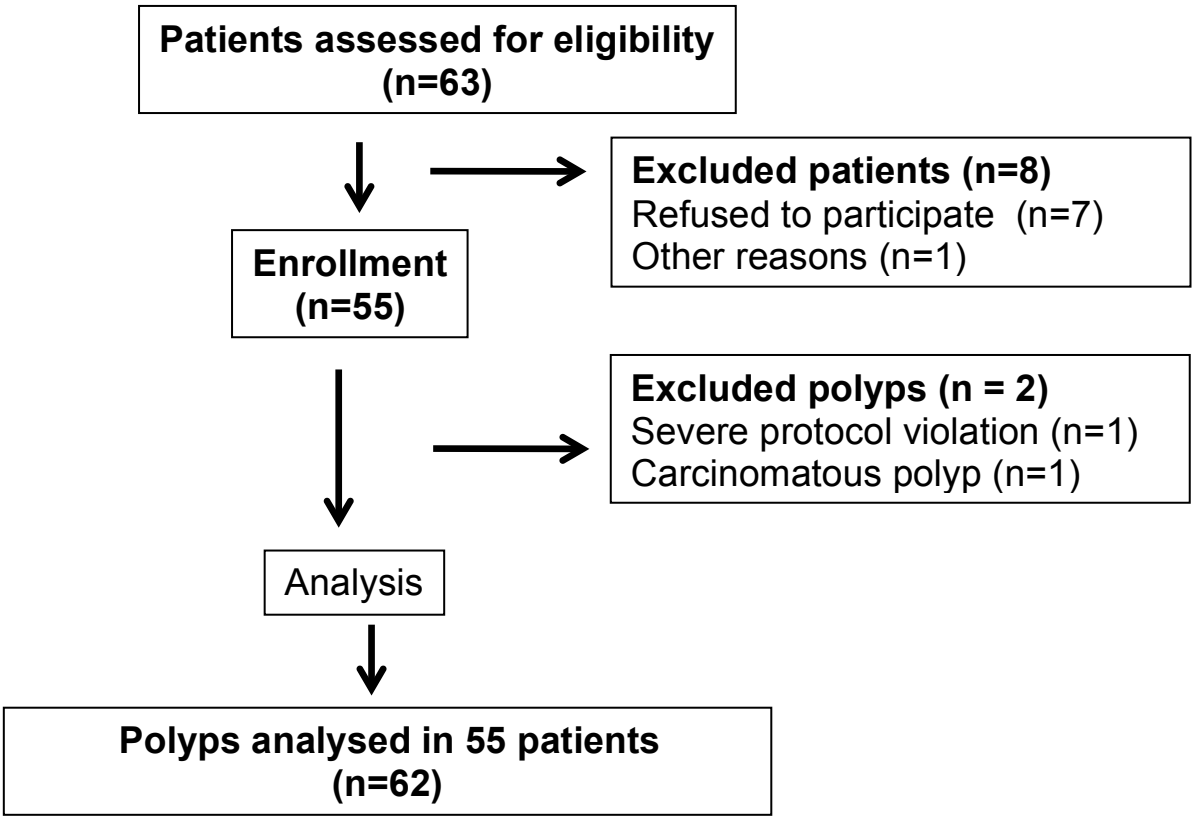

Figure 7; Flow chart showing the process of inclusion.

Patient characteristics (n =55)	
Average age in years, mean (SD)	62.3 (13.7)
Gender	
- Male	31 (56.4%)
- Female	24 (43.6%)
Body mass index (kg/m²), mean (SD)	26.5 (5.30)
ASA Classification	
- I	16 (29.1%)
- II	33 (60.0%)
- III	6 (10.9%)
Smokers	8 (14.5%)
Regular alcohol consume	9 (16.4%)
Diabetes mellitus	8 (14.5%)

Table 5; Patient characteristics. Absolute values are displayed. Values are presented as (%) or median (1st quartile to 3rd quartile) unless stated otherwise. ASA American Society of Anethesiologists, SD standard deviation, m² square metre.

Of all the patients that participated over two thirds were outpatients. The median duration of colonoscopy was 27 minutes, with a median cecal intubation time of nine minutes. The median retraction time was 18 minutes. The majority of patients were undergoing screening colonoscopy procedures. Further reasons for colonoscopy were gastrointestinal bleeding (10.9%), stool irregularities (12.7%), abdominal pain (14.5%) and suspicion of a neoplasia (12.7%). Fifteen percent of the participants did not fit into any of the above-mentioned categories and were classified in a group called ‘Other indications’. The average Boston Bowel Preparation Scale was seven.

Clinical data	
Monitoring	
- Inpatient	17 (30.9%)
- Outpatient	38 (69.1%)
Colonoscopy indication:	
- Screening	19 (34.5%)
- Gastrointestinal bleeding	6 (10.9%)
- Stool irregularities and diarrhea	7 (12.7%)
- Abdominal pain	8 (14.5%)
- Tumor	7 (12.7%)
- Other	8 (14.5%)
Duration of colonoscopy (median, IQR)	27 (20 – 39)
Caecal intubation time	9 (7 – 11)
Withdrawal time	18 (11 – 29)
Boston bowel preparation scale	7 (6 – 9)

Table 6; Clinical data. Absolute values are displayed. Values are presented as (%) or median (1st quartile to 3rd quartile) unless stated otherwise.

3.2 Detection of Polyps and Tumors

In total 65 lesions were detected in 55 patients. Of these 65 lesions 64 were polyps and one was a large exulcerated tumor. The exulcerated tumor was confirmed as an adenocarcinoma histopathologically. One polyp was excluded from optical characterisation as when examined in HDWL acetic acid was present. A further polyp showed intramucosal carcinoma and was therefore excluded from the analysis. A total of 62 polyps were examined optically and histopathologically. Of the 62 polyps examined, 40 (64.5%) were neoplastic lesions and 22 (35.5%) were non-neoplastic lesions. Polyp characteristics are presented below in Table 7.

Characteristics of polyps (n=62)	
Number of polyps (total)	62
- Adenomatous polyps	35 (56.5%)
- Non-adenomatous polyps	22 (35.5%)
- Serrated adenomas	5 (8.1%)
Large polyps (≥10 mm)	4 (6.5%)
Small polyps (6-9 mm)	11 (17.7%)
Diminutive polyps (≤5 mm)	47 (75.8%)
Median polyp size (mm), mean (IQR)	4 (2 – 5)
Pedunculated polyps (Paris class 0-Ip)	3 (4.8%)
Sessile polyps (Paris class 0-Is)	45 (72.6%)
Flat elevated polyps (Paris class 0-IIa)	12 (19.4%)
Flat polyps (Paris class 0-IIb)	2 (3.2%)

Table 7; Polyp Characteristics. Characteristics of 62 polyps detected in 55 patients. Absolute values are displayed. Values are presented as (%) or median (1st quartile to 3rd quartile) unless stated otherwise.

3.3 Primary Endpoint

Our primary outcome was the accuracy in which colorectal polyps were optically diagnosed using acetic acid with NBI. The optical diagnosis was then compared to the histological diagnosis for confirmation of accuracy. Accuracy of optical diagnoses was 85.5% (95% CI 74.2% - 93.1%) in this study. In comparison, when using HDWL alone to optically diagnose polyps we achieved an accuracy of 80.6% (95% CI 68.6% - 89.6%). Accuracy of optical predictions did not differ significantly between HDWL and NBI with acetic acid (p= 0.453).

Accuracy values are presented in Table 8 below, together with values for sensitivity, specificity and positive and negative prediction values.

Parameter	HDWL	NBI + Acetic acid	p-value
Accuracy for neoplastic Polyps	*80.6% (50/62)* *68.6% - 89.6%*	*85.5% (53/62)* *74.2% - 93.1%*	*0.453*
Sensitivity for neoplastic Polyps	*82.5% (33/40)* *67.2% - 92.7%*	*90.0% (36/40)* *76.3% - 97.2%*	*0.375*
NPV for neoplastic Polyps	*70.8% (17/24)* *48.9% - 87.4%*	*81.0% (17/21)* *58.1% - 94.6%*	*N/A*
Specifity for neoplastic Polyps	*77.3% (17/22)* *54.6% - 92.2%*	*77.3% (17/22)* *54.6% - 92.2%*	*1.000*
PPV for neoplastic Polyps	*86.8% (33/38)* *71.9% - 95.6%*	*87.8% (36/41)* *73.8% - 95.9%*	*N/A*

Table 8; Comparison of NBI + AA with HDWL after optical diagnosis of neoplastic colorectal polyps. Values are presented as % (n) unless stated otherwise P-values correspond to χ2 test or Fisher`s exact test as appropriate. Second row in each column indicates 95% confidence interval. N/A P-values were not calculated in these rows as different polyps were rated as positive/negative based on the two devices and different polyp assessments were rated as being of high confidence. NPV negative predictive value, PPV positive predictive value.

3.4 Secondary Endpoints

Sensitivity, specificity, positive and negative predictive values were calculated as secondary endpoints in this study and are shown above in Table 8. As mentioned earlier a total of 62 polyps were examined both optically and histopathologically in this study, 40 of which were confirmed as adenomas and 22 of which were confirmed as non-neoplastic. Sensitivity of optical diagnoses using NBI and acetic acid was 90.0% (95% CI 76.3% - 97.2%) compared to 82.5% (95% CI 67.2% - 97.2%) using HDWL (p = 0.375). NBI and acetic acid specificity was 77.3% (95% CI 54.6% - 92.2%) compared to 77.3% (95% CI 54.6% - 92.2%) in the HDWL mode (p = 1.000).

The positive and negative predictive values using NBI and acetic acid were 87.8% (95% CI 73.8% - 95.9%) and 81.0% (95% CI 58.1% - 94.6%) respectively. When using the HDWL mode the positive predictive value was 86.8% (95% CI 71.9% - 95.6%) and the negative predictive value was 70.8% (95% CI 48.9% - 87.4%).

A further secondary endpoint was the ADR. The ADR was 43.6% and the polyp detection rate (PDR) was 58.2%.

3.5 High Confident Predictions

Polyps defined as high confident using NBI and acetic acid had an accuracy of 90.2% (95% CI 78.6% - 96.7%) and in HDWL an accuracy of 90.2% (95% CI 76.9% - 97.3%). Sensitivity and specificity when using NBI and acetic acid was 94.1% (95% CI 80.3% - 99.3%) and 82.4% (95% CI 56.6% - 96.2%) respectively. HDWL based diagnoses in high confidence revealed a sensitivity of 92.0% (95% CI 74.0% - 99.0%) and a specificity of 87.5% (95% CI 61.7% - 98.4%). The results for high confident predictions are presented in Table 9 below.

Parameter	HDWL	NBI + AA
Accuracy for neoplastic Polyps	*90.2% (37/41)* *76.9% - 97.3%*	*90.2% (46/51)* *78.6% - 96.7%*
Sensitivity for neoplastic Polyps	*92.0% (32/25)* *74.0% - 99.0%*	*94.1% (32/34)* *80.3% - 99.3%*
NPV for neoplastic Polyps	*87.5% (14/16)* *61.7% - 98.4%*	*87.5% (14/16)* *61.7% - 98.4%*
Specifity for neoplastic Polyps	*87.5% (14/16)* *61.7% - 98.4%*	*82.4% (14/17)* *56.6% - 96.2%*
PPV for neoplastic Polyps	*92.0% (23/25)* *74.0% - 99.0%*	*91.4% (32/35)* *76.9% - 98.2%*

Table 9; Comparison of high confidence NBI + AA with HDWL after optical diagnosis of neoplastic colorectal polyps. Values are presented as % (n) unless stated otherwise Second row in each column indicates 95% confidence interval. NPV negative predictive value, PPV positive predictive value.

3.6 Polyp Margins

More polyp margins were identified clearly when using the NBI function with acetic acid compared to using the HDWL mode (98.4% vs. 75.8%, $p < 0.001$).

3.7 Sessile Serrated Adenomas

Serrated polyps were classified as neoplastic lesions in this study. In total five serrated adenomas were identified. Using NBI and acetic acid three of the five lesions (60%) were correctly optically diagnosed as serrated adenomas compared to just one out of five polyps (20%) using HDWL.

3.8 Colonic Polyp Photos

For every polyp that was examined during our study, photos were taken in both HDWL and then again once the acetic acid had been applied and the NBI function had been turned on. On some occasions photos were also taken in the NBI function without acetic acid, or with acetic acid in HDWL. Although not part of our study, photographs allowed the examiners to reevaluate their diagnosis once we had confirmation from the pathology. The optical diagnosis within the study was however not altered. Examples of photographs taken are shown below in Figures 8 to 13. The first section shows photographs where the endoscopists correctly optically diagnosed colonic polyps in both HDWL and NBI with acetic acid. The second part shows where there were differences between optical diagnoses and the histopathological results, or between HDWL and NBI with acetic acid optical diagnoses.

3.8.1 Examples of polyps that were correctly optically diagnosed

The polyps in Figure 8 shown below were diagnosed during colonoscopy as hyperplastic. The pathology results confirmed this diagnosis.

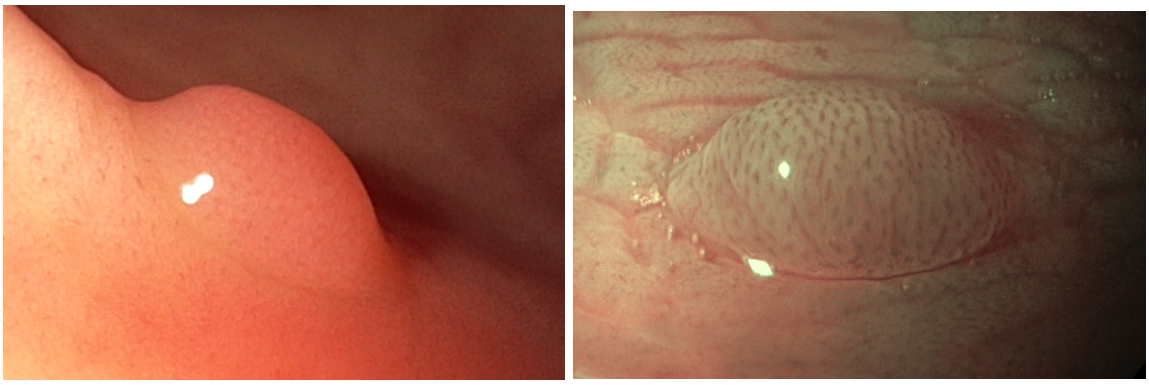

Figure 8; Hyperplastic polyp. Figure 8a (left); HDWL, Figure 8b (right); NBI and acetic acid. Histopathological diagnosis: Hyperplastic polyp.

The following polyp in Figure 9 was optically diagnosed as an adenoma in both HDWL and NBI with acetic acid. The pathological results agreed with the optical diagnosis.

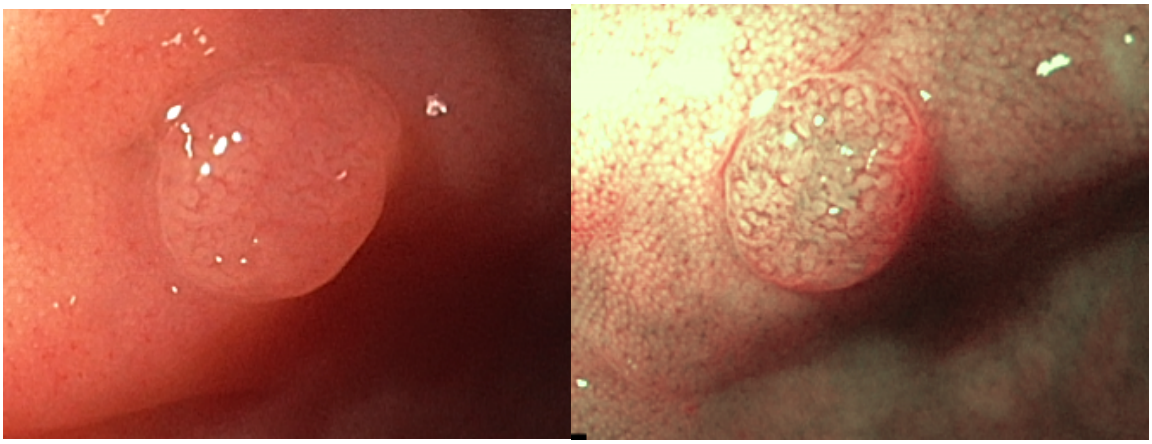

Figure 9; Adenoma. Figure 9a (left); HDWL, Figure 9b (right); NBI and acetic acid. Histopathological diagnosis: Adenoma.

3.8.2 Examples of polyps that were incorrectly optically diagnosed

The following two images in Figure 10 taken in HDWL and NBI with acetic acid were both optically diagnosed as adenomas. However the pathological results determined this polyp to be hyperplastic.

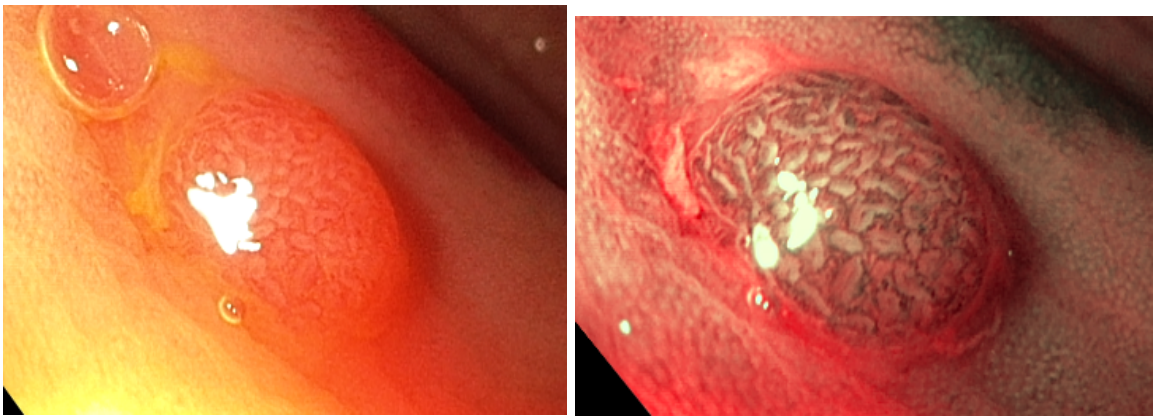

Figure 10; Hyperplastic polyp. Figure 10a (left); HDWL, Figure 10b (right); NBI and acetic acid. Histopathological diagnosis: Hyperplastic.

The examiner diagnosed the polyp in Figure 11 as hyperplastic, however once acetic acid was added and the light was switched to NBI mode the examiner diagnosed the colonic lesion as an adenoma. Histopathologically it was diagnosed as an adenoma.

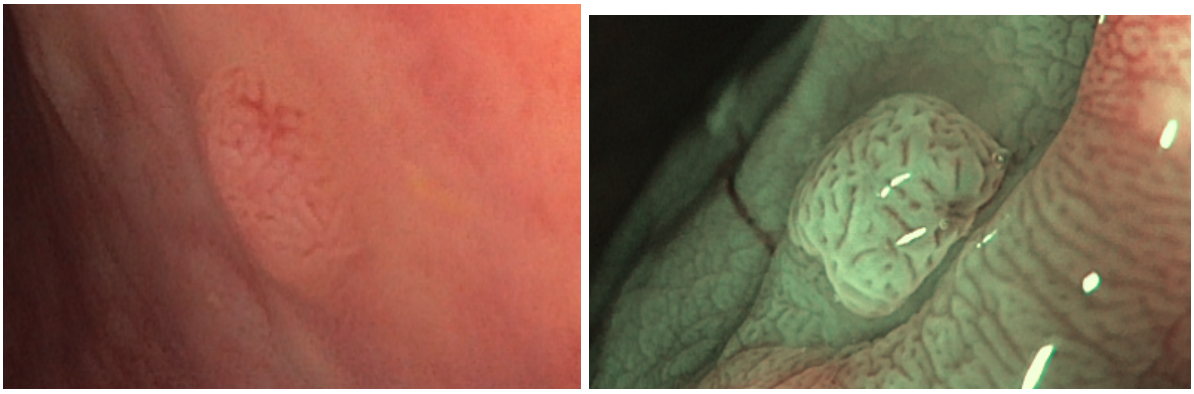

Figure 11; Adenoma. Figure 11a (left); HDWL, Figure 11b (right); NBI and acetic acid. Histopathological diagnosis: Adenoma.

Figure 12a below was diagnosed as an adenoma, whereas Figure 12b was thought to be hyperplastic. Histopathologically the polyp was diagnosed as an adenoma, agreeing with the HDWL prediction.

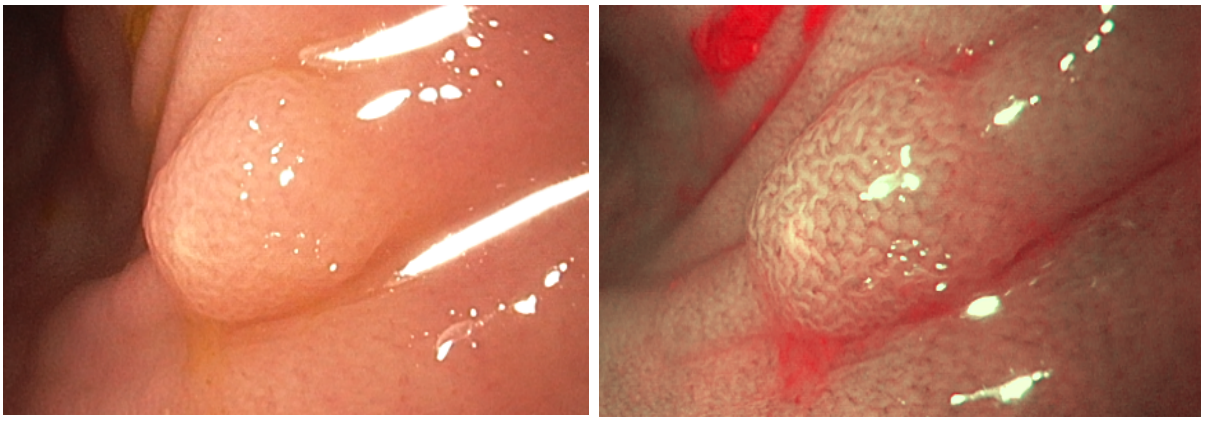

Figure 12; Adenoma. Figure 12a (left); HDWL, Figure 12b (right); NBI and acetic acid. Histopathological diagnosis: Adenoma.

Both photographs in Figure 13 below were optically diagnosed as hyperplastic polyps. The pathology results determined the polyp to be an adenoma.

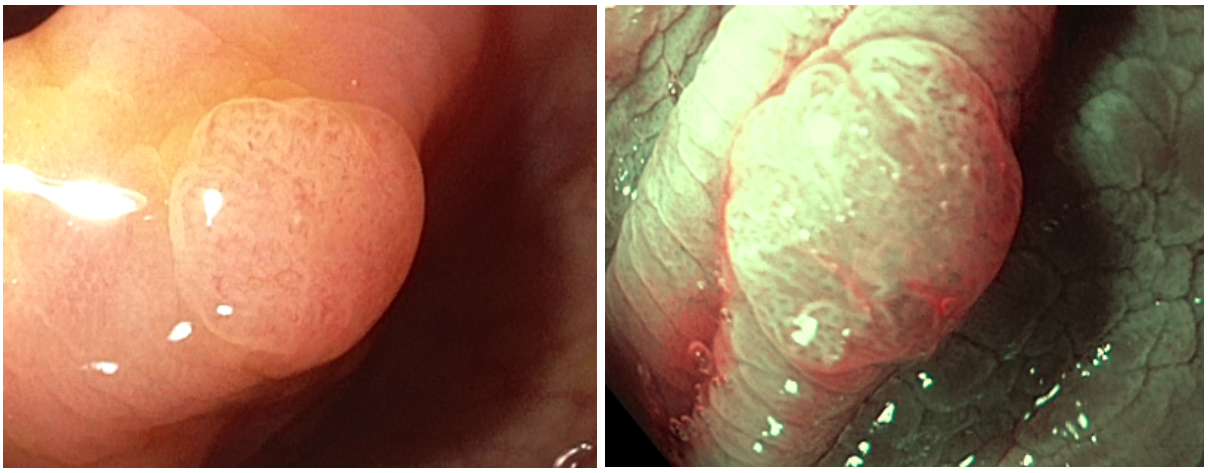

Figure 13; Adenoma. Figure 13a (left); HDWL, Figure 13b (right); NBI and acetic acid. Histopathological diagnosis: Adenoma.

3.9 Complication Rate

There were no complications to report.

3.10 Deviations and Comments

During one of the examinations the acetic acid was injected before the examiner had a chance to examine the third polyp in HDWL that was found in the colon transversum. This polyp was excluded from our results and any further analysis.

4. Interpretation and Conclusion

4.1 Interpretation of Results

4.1.1 Optical Diagnosis Accuracy

In total 64 polyps were detected, two were excluded from any further investigation and the remaining 62 were examined both optically and histopathologically. Of the 62 polyps examined 40 were adenomas and 22 were hyperplastic. In this study we aimed to investigate whether combining NBI with acetic acid would be an effective method to acquire highly accurate predictions. We demonstrated an accuracy of 85.5% for real-time optical diagnoses using NBI with acetic acid. Accuracy increased to 90.2% when predictions were made with high confidence, which meets the criteria stated in the ASGE PIVI statement.

Studies that have looked at optical diagnosis have focused on using NBI with accuracy reported of up to 98% (Sakata, Kheir et al. 2016). A meta-analysis that was carried out by the ASGE concluded that NBI experts were able to optically diagnose high confident polyps with 90% accuracy (Sakata, Kheir et al. 2016). In another meta-analysis from McGill et al. accuracy was reported as being 92.6%, and supported the introduction of optical diagnosis in clinical use (McGill, Evangelou et al. 2013). In a further study, again using NBI, accuracy was reported to have exceeded 90% (Raghavendra, Hewett et al. 2010).

All of the above results are positive findings, however not all studies have found such convincing results concerning accuracy. Sola-vera et al. looked into accuracy of optical diagnosis using white light and NBI and concluded that it was not suitable to

be used in clinical practice (Sola-Vera, Cuesta et al. 2015). Patrun, J et al. also concluded that optical diagnosis during real time colonoscopy was not appropriate for routine clinical practice. The average accuracy was 76.7% however accuracy varied between 60% - 85% depending on the examiner's expertise (Patrun, Okresa et al. 2018).

Despite promising results, real time diagnosis has not become daily clinical practice. Most studies have concentrated on diminutive polyps and current standards from the ASGE PIVI statement only refer to diminutive polyps. Diminutive colorectal polyps make up more than 80% of colonic polyps, and their risk of cancer is said to be negligible when they are benign-appearing (McGill, Evangelou et al. 2013, Sakata, Kheir et al. 2016). Pathologists themselves are 85-95% accurate in determining polyp characterisation (McGill, Evangelou et al. 2013). Hence with studies showing accuracy rates regularly above 90% it is no surprise that the method of optical diagnosis has been further investigated. We opted not to discriminate which polyps we optically diagnosed, with the aim of searching for a technique that could be used on every polyp identified during colonoscopy and not restrict optical diagnosis to one anatomical area or particular classification or size.

Although still promising, results for non-experts have shown slightly lower accuracy findings compared to results with experts. The examiners ability to correctly identify polyps and reach PIVI standards is crucial in real time assessment of polyps. One study showed that non-experts in NBI recorded an accuracy of only 82% (Sakata, Kheir et al. 2016). Another study from Kuiper et al. focused especially on non-academic examiners and reported a decrease in accuracy. They suggested examiners needed more teaching and continued learning in order to meet the current

required standards set out by the ASGE (Kuiper, Marsman et al. 2012). The effect of teaching in different scenarios has been described in a some literature. One study showed that after a 20-minute teaching session on the NICE classification system for non-experts, examiners managed to achieve an accuracy of >90% when presented with NBI photographs. Yet another study reported that having trained non-experts in optical diagnosis for NBI, 11 of 12 participants achieved >90% when presented with pictures, but only 3 of the participants managed to achieve the same accuracy once in clinical practice (Raghavendra, Hewett et al. 2010). Non-expert examiners far outweigh expert examiners. This could mean that initially the future of optical diagnosis may only be performed by a limited number of physicians until an adequate training program is set in place. What is promising however is that a significant improvement in accuracy appears to be achievable within a relatively short timeframe (McGill, Evangelou et al. 2013).

As mentioned earlier, NBI has dominated the literature in terms of optical diagnosis. Much less has been written about acetic acid and its potential beneficial use in optical diagnosis of colonic tissue. We chose to investigate NBI with acetic acid to try to further broaden optical diagnosis. We wanted to go further than just diminutive polyps and wanted to see if accuracy rates could consistently be of even higher standard than other studies have shown when using acetic acid in combination with NBI. Goto N. et al. aimed to evaluate accuracy of acetic acid and NBI in differentiating early colorectal adenocarcinomas from adenomas. They reported 73% accuracy (Goto, Kusaka et al. 2014). A further study from Togashi K et al. using magnification colonoscopy showed 95% accuracy of polyps assessed in real time after having been sprayed with acetic acid. They suggested the method could be applied routinely in the scenario of magnification colonoscopy (Togashi, Hewett et al.

2006). Magnification scopes are not widely used in Europe and means that these studies have little impact. Our study used standard resolution endoscopy. Shibagaki K. et al. reported a diagnostic accuracy of 90.5% (95% CI 86.7 – 94.1%) when using magnification endoscopy with NBI and acetic acid to optically diagnose gastric mucosal neoplasms (Shibagaki, Amano et al. 2016).

Acetic acid is readily available at little financial expense. Once applied it has an immediate effect. Minimal bleeding at the application site has been reported but it has not been associated with any long-term risks (Goto, Kusaka et al. 2014, Chedgy, Subramaniam et al. 2016, Bhandari 2017). On the downside acetic acid application could be time consuming, storage space would be needed and examiners would need to familiarise themselves with the effect of acetic acid on the colonic mucosa. Currently optical diagnosis is carried out with the help of the NICE classification system, which was not designed with acetic acid or its effects in mind.

Our study showed no significant difference between accuracy when NBI and acetic acid was compared with HDWL [85.5% (95% CI 74.2% - 93.1%) vs. 80.6% (95% CI 68.6% - 89.6%)]. Other studies that have looked into accuracy of optical diagnosis with HDWL have mainly focused on small colorectal polyps. According to a review by Sakata et al these studies have reported 70% accuracy (Sakata, Kheir et al. 2016).

Although there was not a significant difference we still achieved our target of over 75% and with high confident polyps >90% accuracy in HDWL and NBI with acetic acid. It can therefore also be argued that optical diagnosis was successful. A different number of arguments can be put forward in an attempt to explain why there was no significant difference between the two groups. Firstly this study was not designed to

compare NBI and acetic acid with HDWL. Potential differences may be detectable in a larger setting containing more patients. Compared to other studies the sample size of 55 patients is small and the number of polyps identified and examined held to a very limited number. Secondly all examiners in this study were deemed to be experts in the field of optical polyp characterisation, which could have influenced the results in terms of increased accuracy when using HDWL. Thirdly the study design needs to be considered. Each polyp that was identified was first examined in HDWL before being looked at with NBI and acetic acid and therefore examiners could have been influenced by their initial diagnosis. Lastly it could also be argued that we did not find there to be a significant difference when comparing these two techniques for optical diagnosis because no difference exists.

4.1.2 Level of Confidence

Accuracy was even higher (90.2%) when only high confident polyps optically diagnosed using NBI with acetic acid were looked at. However just as we saw earlier, there was no great difference in accuracy between high confident optical diagnoses when polyps were examined using HDWL.

Our results became more interesting when we looked into differences between polyps described as high or low confident when examined. A significant number of polyps were identified as high confident when using NBI and acetic acid, but as low confident when using HDWL. Of these high confident polyps 91% were correctly diagnosed when compared to the histopathological results. High confident predictions were highly accurate and we can use these results to conclude that by

increasing the number of high confident polyps we examined, the more accurate our results were in terms of optical diagnosis.

A further interesting observation is that when high confident polyps were compared, there was total agreement in the optical diagnosis between HDWL and NBI with acetic acid. This finding again supports the importance of high confidence. Fewer polyps were identified as being high confident using HDWL compared with the study results when using NBI and acetic acid. However when polyps were identified as high confident, the outcome from this study suggested that the quality of optical diagnosis with HDWL is comparable with NBI and acetic acid.

A meta-analysis of 28 studies also stated the importance of confidence levels. The study reported better performance outcomes in terms of optical diagnosis when high confident polyps were examined and reported 95% accuracy.

As mentioned earlier the ASGE review supported optical diagnosis of diminutive polyps when assessed with NBI. The PIVI initiative was carried out to assess whether acceptable performance thresholds for optical diagnosis could be clinically adopted. However the PIVI stated that only high confident polyps are eligible for the “resect-and-discard” and the “diagnose-and-leave” strategies (Abu Dayyeh, Thosani et al. 2015). This is therefore an interesting point in view of our results. When more high confident polyps are identified, the “resect-and-discard” and the “diagnose-and-leave” strategies become more realistic. In our study more polyps were identified as high confident when using NBI and acetic acid compared to using HDWL ($p=0.006$). Hence our results suggest that by using NBI and acetic acid, optical diagnosis of polyps could soon be implemented in clinical practice.

Our results show that confidence levels are very important in improving optical diagnostic accuracy during endoscopy, however they also show that by using NBI in combination with acetic acid we can upgrade polyps from being low confident to high confident. Hence it could be argued that if endoscopists feel uncertain whilst examining a polyp, they could turn on the NBI function and add acetic acid to help increase the confidence level.

Other studies have specifically used confidence levels for polyp examination and diagnosis. In a meta-analysis from McGill et al. mentioned earlier, accuracy was seen to improve when only high confident neoplasms were examined (91% vs. 94%) (McGill, Evangelou et al. 2013). Utsumi et al. looked at colorectal polyps using magnifying chromoendoscopy that were diagnosed with low confidence. Similarly to our study, polyps were then independently examined microscopically. They concluded that all polyps diagnosed with low confidence should be resected and examined histopathologically (Utsumi, Iwatate et al. 2018). Pohl et al. used NBI to differentiate neoplastic from non-neoplastic lesions in real-time interpretation. They too integrated confidence levels into their evaluation. They concluded that if small polyps ≤5mm can be diagnosed in real-time with high confidence then there is no need for polypectomy (Pohl and Robertson 2009).

In summary, high confidence is an important aspect when it comes to optically diagnosing polyps. Our results significantly suggest that in using NBI and acetic acid more polyps are identified as being high confident compared to using HDWL. With high confident polyps, accuracy was >90% irrespective of the technique used. Looking at other studies and in particularly the PIVI report we can see just how

important high confident polyps are when it comes to optical diagnosis. Our results are very promising and suggest that optical diagnosis may be around the corner in terms of clinical practice.

4.1.3 Colonic Polyp Margins

When using NBI and acetic acid 98.4% of polyp margins were clearly identified by endoscopists. These results were significantly better than when HDWL was used. Our results show that using NBI and acetic acid clearly has a positive impact on helping identify the border of polyps from colonic mucosal tissue compared to using HDWL. A limitation to our study design was that border identification was purely subjective on the part of the examiner.

Once colonic lesions are found, it is important that the margins are evaluated carefully. Serra-Aracil, X. et al. reported that difficulties in determining margins could potentially lead to an increase risk of residual disease or recurrence for neoplastic lesions due to incomplete endoscopic resection (Serra-Aracil, Pallisera-Lloveras et al. 2018). Jang, E. J et al. reported that malignant polyps have an increased recurrence rate when endoscopic resection of the free margin is <1mm (Jang, Kim et al. 2011).

Our results are an important finding. By improving determination of margins in colorectal neoplastic lesions, patients would be less likely to need further endoscopic resections or surgical interventions.

4.1.4 Sessile Serrated Adenomas

As mentioned earlier the significance of SSAs has increased over the last few decades. Once thought of as hyperplastic polyps we now acknowledge their importance as an alternative pathway to the adenoma-carcinoma-sequence in cancer development (O'Connell and Crockett 2017). In our study SSAs were classified as neoplastic polyps and a total of five SSAs were diagnosed histopathologically. Using HDWL only one was correctly diagnosed optically whilst using acetic acid and NBI just three from five were optically diagnosed correctly. No conclusion can be drawn from a sample size of only five SSAs, however we can see from just these five SSAs that there is a tendency to misdiagnose SSAs. Other studies have looked into evaluating SSAs in real time during colonoscopy. Yamamoto et al. evaluated how effectively SSA margins could be determined using acetic acid-indigocarmine mixture compared to using NBI and indigo carmine. They concluded acetic acid/indigo carmine to be a promising method to determine SSA margins (Yamamoto and Shafazand 2017). Other studies into SSAs have reported poor resection rates. These have been largely attributed to their inconspicuous margins (Singh, Zorron Cheng Tao Pu et al. 2016). During our study we took into account if the margin from the identified polyp was easily distinguishable from healthy colonic mucosa tissue.

The Workgroup Serrated Polyps and Polyposis (WASP) classification is a combination of the NICE classification and further criteria that differentiates hyperplastic polyps from SSAs. On top of the NICE criteria, four features of SSAs were incorporated (irregular shape, indistinctive borders, clouded surface and dark spots within crypts). It showed promising results for high confident polyps (NVP of 91%) however they were only evaluated as still images (Sakata, Kheir et al. 2016). The NICE classification system was used exclusively in this study, however a

comparison of the NICE and WASP classification systems could be an interesting approach to compare SSA accuracy levels in optical diagnosis.

As mentioned above a sample size of five SSAs is far too small to be able to make any significant conclusions. However a further investigation of SSAs in terms of optical diagnosis is warranted due to their colorectal cancer risk and difficulties in identification and resection.

4.2 Limitations

The primary limitation was the study size as only 55 patients were included. Another limiting factor was that our examinations were all carried out at a tertiary referral centre such as a university hospital. As a general assumption patients being examined out in a university hospital tend to have more comorbidities and are at risk of more severe complications, hence the examination takes place at a tertiary referral centre. Therefore to be able to use our results on a broader scale and to be able to compare within the general population data would need to be collected from different hospitals and outpatient facilities.

Only two examiners were used throughout the study, both of which are experienced (minimum experience of 500 independently conducted investigations) and have worked in an academic setting for many years. What needs to be considered is would similar results, especially in terms of accuracy, have been achieved if non-academic endoscopists with less experience had carried out the examinations?

A further limitation to this study is that only a single classification system was used, NICE. A single classification system has its benefits, allowing all polyps to be compared in the same way. It means that literature worldwide uses the same terminology making communication on the topic easier. However using a second or third system could allow for better clarification and could potentially produce better results in terms of accuracy. The NICE classification that we used is not designed for use with acetic acid. Currently there is no specific classification system with respect to acetic acid, and it is unclear if using the NICE system was to our advantage or not. As discussed earlier, acetic acid removes surface mucous material and in doing so accentuates the surface pit pattern (Kawamura, Togashi et al. 2005, Goto, Kusaka et al. 2014, Yamamoto and Shafazand 2017). The addition of acetic acid initially results in whitening of the colonic tissue. Neoplastic tissue then appears as red spots and the change in colour allows the examiner to differentiate between neoplastic and non-neoplastic tissues (Chedgy, Subramaniam et al. 2016, Chedgy, Fogg et al. 2018, Sun, Ma et al. 2018). NICE differentiates between colour, vessels and surface pattern. However colour refers to brown relative to background and not to red. It also does not refer to any colour changes. This could be of disadvantage when examining polyps with acetic acid.

4.3 Could acetic acid and Narrow Band Imaging be used in Clinical practice?

The aim of our study was to assess accuracy in optical diagnosis. Our results showed that although there was no significant difference between accuracy when using HDWL or NBI with acetic acid, (80.6% and 85.5% respectively) we did achieve an accuracy of >75%. Accuracy was >90% when high confident polyps were optically

diagnosed using NBI and acetic acid. In addition our results showed that using NBI and acetic acid, a significant amount of polyps were defined as high confident. Our results also significantly showed that polyp margins are easier to identify when using NBI and acetic acid compared to HDWL ($p<0.001$). Although our results are promising there are certain points that need first be considered before changes in clinical practice can be considered.

Endoscopists need to be prepared to learn and improve their in vivo diagnostic skills. A training programme of some sort would need to be introduced to keep endoscopists up to date and to test their skills on a regular basis so that accuracy is kept at a high standard. It is important that endoscopists regularly have their results verified by pathology, to ensure that standards are maintained and training is effective. Hence a continuous analysis of performance needs to be implemented. A considerable challenge here comes in the identification of SSAs. As mentioned earlier, the risks of SSAs developing into colorectal cancer has been well documented. Although examiners are now more aware of SSAs, they are still often misdiagnosed as hyperplastic polyps (Pohl and Robertson 2009). As well as appropriate training, photographic documentation should also play an important role in maintaining high standards. Photographs should be stored and made accessible in the event the examiners assessment or clinical decision becomes subject to review.

Acceptance would be needed for a slightly longer examination time from patients and examiners although the study did not quantify exactly how much extra time would be needed to optically diagnose every polyp found upon examination. The process was initially time consuming, once the polyp was identified acetic acid had to be drawn up into a syringe, then the examiner gave the nurse instructions to apply it. It often took

several attempts until the whole of the polyp was covered in acetic acid. Going forward, once examiners and their assistants become more accustomed to the method, the time required to prepare and apply acetic acid would decrease and polyp observation time should also decrease.

It was mentioned earlier that a limitation of this study was that only a single classification system was used to identify and diagnose polyps. If optical diagnosis is going to be used on a day-to-day basis it could be that more than one classification system is needed. A classification system for the use of acetic acid could prove to be useful, as this could help examiners when they are unsure or finding it difficult to identify certain features that belong to the NICE classification system. A further option could be to combine NICE with a new classification system for acetic acid. It could however also be argued that using more than one system could lead to confusion.

Using optical diagnosis during colonoscopy has its benefits too. Healthcare costs are a challenge to the sustainability of every healthcare system. One of the main benefits resulting from optical diagnosis would be cost efficiencies. Pathological assessments would not be necessary, biopsies would not have to be stored and transported, and follow up appointments could potentially be avoided. Patients would eventually see an improvement in quality in many areas, which may well increase compliance and patient satisfaction. Firstly they would be given immediate notice of potential follow-up appointments and surveillance intervals, meaning they would not have to wait several days for results. Secondly logistically it would prevent potential errors in the transport and processing of biopsy samples. Using optical diagnosis would reduce the need to remove all lesions. Small hyperplastic lesions could be left in the colon,

using the “diagnose-and-leave” strategy, avoiding the need for polypectomy. At the same time small adenomas may undergo the “resect-and-discard” strategy, as there would be no need for histopathological evaluation. Although polypectomy is considered a minor procedure is it not without complications. The risk of bleeding during colonoscopy increases ten fold when polypectomy is performed (Pohl and Robertson 2009). Polypectomy is a time consuming process during colonoscopy, and it often takes more than one attempt to completely remove a given polyp. Pathological evaluation is not only expensive it is also time consuming for the pathologist. Hence although optical diagnosis appears more time consuming at first, it could well be that it saves both time and costs for the health economy.

Surveillance intervals were mentioned as one of the benefits of optical diagnosis in the paragraph above. This point needs to be considered carefully however. If sufficient optical diagnosis accuracy is not achieved, inappropriate surveillance intervals may be determined. Non-neoplastic colonic tissue incorrectly diagnosed as being neoplastic would result in an earlier follow-up colonoscopy, unnecessarily increasing the need for a procedure with attendant risks and costs. Whereas neoplastic tissue incorrectly diagnosed as non-neoplastic tissue could potentially develop into colorectal cancer before the next examination with poor outcomes for the patient and significant costs. The meta-analysis from McGill et al. reports that of all follow-up appointments that differed from the pathological recommendation, around half of the appointments were too early and around half too late (Nienstedt, Muller et al. 2017). Optical diagnosis could be cost saving; accuracy however needs to be of good standard.

However to even begin to consider using this technique during routine examinations further evaluation and exploration needs to take place. As noted there is substantial body of literature regarding optical diagnosis however the majority concentrates on using NBI alone and diminutive polyps. Limited research exists for benefits of acetic acid in the colon and for real time examination of larger polyps. An appropriate level of accuracy needs to be considered that is comparable if not equal to the quality of histological diagnosis. As before quality and accuracy of diagnosis remains a priority to be able to provide patients with optimum surveillance and treatment plans. Results in similar studies have shown appropriate standards can be achieved for optical diagnosis that are acceptable for clinical use. High confidence has played an important role and if standards are to be continually met, examiners must make sure they are confident in their judgment and take biopsies where there is any ambiguity. Any polyps lacking clear endoscopic features always have the option of a histopathological examination. Until there is the same level of confidence in results from optical diagnosis of polyps of all sizes as those that currently come from the pathology department, histology will remain the gold standard.

4.4 Recommendations for further Research Projects

Following on from this study there are several areas of interest that could be further investigated. Although we were able to prove a good level of accuracy in terms of optical diagnosis we were unable to prove that there was a significant difference between using HDWL and NBI and acetic acid. An interesting project would be to look at the effects of HDWL compared to acetic acid alone without NBI. Another project of interest would be to concentrate on SSA optical diagnosis. It would be interesting to see if the use of more than one classification system with the use of

magnification and chromoendoscopy would have a positive or negative impact on optical diagnosis accuracy during colonoscopy. Lastly it would be interesting to create a new classification system using acetic acid in the colon.

Appendix

Case report form

Prüfbogen: ATOMIC I Study (AceTic acid for Optical diagnosis of Colonrectal polyps)			
Studiennummer:			
Untersuchungstag: __.__.__		Ambulant? ☐	Stationär? ☐
Endoskopiker:		ASA (Kreuz): 1 2 3	
Indikation:			
Diabetes? (ja/nein)			
Alter: ____ Jahre		Geschlecht (M/W):	
Größe ____ cm		Nikotin? (J/N):	
Gewicht ____ kg		C2-Abusus? (J/N):	
Kommentare:			

Überwachungswerte, Sauberkeit und Nachsorgeintervall

Endo Start:	____ : ____ Uhr	Zökum Intubation:	____ : ____ Uhr
Endo Ende:	____ : ____ Uhr	Darmsauberkeit (BBPS 0-9):	____ Punkte
Dosis Propofol:	____ mg	Dosis Midazolam:	____ mg
Anzahl Polypen:	____	Anzahl Polypen-Photograpien (gesamt):	
Komplikationen:			

Polypen: Bei Beurteilung mit NBI bitte NICE Klassifikation verwenden

NICE Classification: *(please mark **one** box in each row with a cross)*			
Color:	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark, brown relative to background; sometimes patchy whiter areas
Vessels:	None, or isolated lacy vessels coursing across the lesion	Brown vessels surrounding white structures	Has area(s) of disrupted or missing vessels
Surface pattern:	Dark or white spots of uniform size, or homogenous absence of pattern	Oval, tubular or branched white structures surrounded by brown vessels	Amorphous or absent surface pattern
Diagnosis:	Hyperplastic Polyp (NICE I)	Adenoma (NICE II)	Depp submucosal invasive cancer (NICE III)

Polyp Nr. 1	**Lokalisation:**	**Größe: ____ mm**
Paris Klassifikation: (I.Vorgewölbt II. Flach III. Ulzeriert/exkaviert)		
I p) gestielt I s) sessil	IIa) IIb) IIc)	III.

Polyp Nr: 1 (HDWL)		Gesamtdauer HDWL Beurteilung P1 ____ sec.	
Diagnosis:	Hyperplastic Polyp	Adenoma	Depp submucosal invasive cancer
Confidence < 90%		Confidence >90%	
Anzahl Fotos Weißlicht:		***Polypenrand komplett abgrenzbar?***	***(j/n)***
Polyp Nr: 1 (NBI+ES)		Gesamtdauer NBI Beurteilung P1 ____ sec.	
Diagnosis:	Hyperplastic Polyp	Adenoma	Depp submucosal invasive cancer
Confidence < 90%		Confidence >90%	
Anzahl Fotos NBI:		***Polypenrand komplett abgrenzbar?***	***(j/n)***
Zangenresektion ( )		Schlingenresektion ( )	
Abweichenungen/Kommentare:			

Polyp Nr. 2	**Lokalisation:**	**Größe: ____ mm**
Paris Klassifikation: (I.Vorgewölbt II. Flach III. Ulzeriert/exkaviert)		
I p) gestielt I s) sessil	IIa) IIb) IIc)	III.

Polyp Nr: 2 (HDWL)		Gesamtdauer HDWL Beurteilung P2 ____ sec.	
Diagnosis:	Hyperplastic Polyp	Adenoma	Depp submucosal invasive cancer
Confidence < 90%		Confidence >90%	
Anzahl Fotos Weißlicht:		***Polypenrand komplett abgrenzbar?***	***(j/n)***
Polyp Nr: 2 (NBI+ES)		Gesamtdauer NBI Beurteilung P2 ____ sec.	
Diagnosis:	Hyperplastic Polyp	Adenoma	Depp submucosal invasive cancer
Confidence < 90%		Confidence >90%	
Anzahl Fotos NBI:		***Polypenrand komplett abgrenzbar?***	***(j/n)***
Zangenresektion ( )		Schlingenresektion ( )	
Abweichenungen/Kommentare:			

References

Abu Dayyeh, B. K., N. Thosani, V. Konda, M. B. Wallace, D. K. Rex, S. S. Chauhan, J. H. Hwang, S. Komanduri, M. Manfredi, J. T. Maple, F. M. Murad, U. D. Siddiqui and S. Banerjee (2015). "ASGE Technology Committee systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps." Gastrointestinal Endoscopy **81**(3): 502.e501-502.e516.

Ajani, J. A., S. A. Curley, N. A. Janjan and P. M. Lynch (2005). Gastrointestinal Cancer. United States of America, Springer Science+Business Media, Inc.

Akarsu, C., N. A. Sahbaz, A. C. Dural, M. G. Unsal, O. Kones, A. Kocatas, I. Halicioglu and H. Alis (2016). "FICE vs Narrow Band Imaging for In Vivo Histologic Diagnosis of Polyps." Journal of The Society of Laparoscopic & Robotic Surgeons **20**(4): e2016.00084.

Andrew, A. S., J. A. Baron, L. F. Butterly, A. A. Suriawinata, G. J. Tsongalis, C. M. Robinson and C. I. Amos (2017). "Hyper-Methylated Loci Persisting from Sessile Serrated Polyps to Serrated Cancers." International Journal of Molecular Sciences **18**(3).

Arebi, N., D. Swain, N. Suzuki, C. Fraser, A. Price and B. P. Saunders (2007). "Endoscopic mucosal resection of 161 cases of large sessile or flat colorectal polyps." Scandanavian Journal of Gastroenterology **42**(7): 859-866.

Bhandari, P. (2017). "Acetic Acid Chromoendoscopy in the Setting of Neoplastic Barrett Esophagus." Gastroenterology and Hepatology **13**(8): 508-510.

Blackstone, M., O. (1987). Endoscopic Interpretation - Normal and Pathologic Appearances of the Gastrointestinal Tract. Stuttgart, Germany, Georg Thieme Verlag.

Bokemeyer, C. (2007). Das Kolorektale Karzinom - Grundlagen, Parävention und moderne Therapiekonzepte. Augsburg, Himmer AG.

Bordacahar, B., M. Barret, B. Terris, M. Dhooge, J. Dreanic, F. Prat, R. Coriat and S. Chaussade (2015). "Sessile serrated adenoma: from identification to resection." Digestive and Liver Disease **47**(2): 95-102.

Brenner, H., Altenhofen, L., Kretschmann, J., Rösch, T., Pox, C., Stock, C., Hoffmeister, M. (2015). "Trends in Adenoma Detection Rates During the First 10 Years of the German Screening Colonoscopy Program." Gastroenterology **149**(2): 356-366.e351.

Brooker, J. C., B. P. Saunders, S. G. Shah, C. J. Thapar, N. Suzuki and C. B. Williams (2002). "Treatment with argon plasma coagulation reduces recurrence after piecemeal resection of large sessile colonic polyps: a randomized trial and recommendations." Gastrointestinal Endoscopy **55**(3): 371-375.

Bujanda, L., A. Cosme, I. Gil and J. I. Arenas-Mirave (2010). "Malignant colorectal polyps." World Journal of Gastroenterology **16**(25): 3103-3111.

Calderwood, A. H., Jacobson, B., C. (2010). "Comprehensive Validation of the Boston Bowel Preparation Scale." Gastrointestal Endoscopy **72**(4): 686–692.

Chandran, S., F. Parker, S. Lontos, R. Vaughan and M. Efthymiou (2015). "Can we ease the financial burden of colonoscopy? Using real-time endoscopic assessment of polyp histology to predict surveillance intervals." Internal Medicine Journal **45**(12): 1293-1299.

Chedgy, F., C. Fogg, K. Kandiah, H. Barr, B. Higgins, M. McCord, A. Dewey, J. De Caestecker, L. Gadeke, C. Stokes, D. Poller, G. Longcroft-Wheaton and P. Bhandari (2018). "Acetic acid-guided biopsies in Barrett's surveillance for neoplasia detection versus non-targeted biopsies (Seattle protocol): A feasibility study for a randomized tandem endoscopy trial. The ABBA study." Endoscopy International Open **6**(1): E43-E50.

Chedgy, F. J., S. Subramaniam, K. Kandiah, S. Thayalasekaran and P. Bhandari (2016). "Acetic acid chromoendoscopy: Improving neoplasia detection in Barrett's esophagus." World Journal of Gastroenterology **22**(25): 5753-5760.

Chedgy, F. J. Q., K. Kandiah, H. Barr, J. De Caestecker, S. Dwerryhouse, B. Eross, C. Gordon, S. Green, A. Li, J. Brown, G. Longcroft-Wheaton and P. Bhandari (2017). "Development and validation of a training module on the use of acetic acid for the detection of Barrett's neoplasia." Endoscopy **49**(2): 121-129.

Corley, D. A., C. D. Jensen, A. R. Marks, W. K. Zhao, J. K. Lee, C. A. Doubeni, A. G. Zauber, J. de Boer, B. H. Fireman, J. E. Schottinger, V. P. Quinn, N. R. Ghai, T. R. Levin and C. P. Quesenberry (2014). "Adenoma detection rate and risk of colorectal cancer and death." New England Journal of Medicine **370**(14): 1298-1306.

Crockett, S. D. (2017). "Sessile Serrated Polyps and Colorectal Cancer." The Journal of the American Medical Association **317**(9): 975-976.

Denzer, U., Beilenhoff, U., Eickhoff, A., Faiss, S., Hüttl, P., In der Smitten, S., Jakobs, R., Jenssen, C., Keuchel, M., Langer, F., M., Lerch, M., Lynen Jansen, P., May A., Menningen, R., Moog, G., Rösch, T., Rosien, U., Vowinkel, T., Wehrmann, T., Weickert, U. (2015). "S2k-Leitlinie Qualitätsanforderungen in der gastrointestinalen Endoskopie, AWMF Register Nr. 021–022."

Doyle, D. J. and E. H. Garmon (2018). American Society of Anesthesiologists Classification (ASA Class). Treasure Island (FL), StatPearls Publishing LLC.

Facciorusso, A., M. Antonino, M. Di Maso, M. Barone and N. Muscatiello (2015). "Non-polypoid colorectal neoplasms: Classification, therapy and follow-up." World Journal of Gastroenterology **21**(17): 5149-5157.

Friedland, S., A. Shelton, S. Kothari, R. Kochar, A. Chen and S. Banerjee (2013). "Endoscopic management of nonlifting colon polyps." Diagnostic and Therapeutic Endoscopy **2013**: 412936.

Fu, K. I., S. Kato, T. Fujii and A. Parra-Blanco (2007). "Acetic acid as an effective mucolytic in magnification with chromoendoscopy for pit patterns analysis." Endoscopy **39**(10): 922-923.

Gheorghe, C. (2006). "Narrow-band imaging endoscopy for diagnosis of malignant and premalignant gastrointestinal lesions." journal of Gastrointestinal and Liver Diseases **15**(1): 77-82.

Gono, K. (2015). "Narrow Band Imaging: Technology Basis and Research and Development History." Clinical Endoscopy **48**(6): 476-480.

Goto, N., T. Kusaka, Y. Tomita, H. Tanaka, Y. Itokawa, Y. Koshikawa, D. Yamaguchi, Y. Nakai, S. Fujii and H. Kokuryu (2014). "Magnifying narrow-band imaging with acetic acid to diagnose early colorectal cancer." World Journal of Gastroenterology **20**(43): 16306-16310.

Greenspan, M., Rajan, K. B., Baig, A., Beck, T., Mobarhan, S., Melson, J. (2013). "Advanced adenoma detection rate is independent of nonadvanced adenoma detection rate." American Journal of Gastroenterology **108**(8).

Group, E. C. R. (2005). "Update on the paris classification of superficial neoplastic lesions in the digestive tract." Endoscopy **37**(6): 570-578.

Heron, V., Parmar, R., Ménard, C., Martel, M., Barkun A. N. (2017). "Validating bowel preparation scales." Endoscopy International Open **5**(12): E1179–E1188.

Ibrahim, A., D. R. Barnes, J. Dunlop, D. Barrowdale, A. C. Antoniou and J. N. Berg (2014). "Attenuated familial adenomatous polyposis manifests as autosomal dominant late-onset colorectal cancer." European Journal of Human Genetics **22**(11): 1330-1333.

Inra, J. A., J. Nayor, M. Rosenblatt, M. Mutinga, S. I. Reddy, S. Syngal and F. Kastrinos (2017). "Comparison of Colonoscopy Quality Measures Across Various Practice Settings and the Impact of Performance Scorecards." Digestive Diseases and Sciences **62**(4): 894-902.

Jang, E. J., D. D. Kim and C. H. Cho (2011). "Value and interpretation of resection margin after a colonoscopic polypectomy for malignant polyps." Journal of the Korean Society of Coloproctology **27**(4): 194-201.

Kanao, H., S. Tanaka, S. Oka, I. Kaneko, S. Yoshida, K. Arihiro, M. Yoshihara and K. Chayama (2008). "Clinical significance of type V(I) pit pattern subclassification in determining the depth of invasion of colorectal neoplasms." World Journal of Gastroenterology **14**(2): 211-217.

Kandiah, K., F. J. Q. Chedgy, S. Subramaniam, G. Longcroft-Wheaton, P. Bassett, A. Repici, P. Sharma, O. Pech and P. Bhandari (2018). "International development and validation of a classification system for the identification of Barrett's neoplasia using acetic acid chromoendoscopy: the Portsmouth acetic acid classification (PREDICT)." Gut **67**(12): 2085-2091.

Kawamura, Y. J., K. Togashi, J. Sasaki and F. Konishi (2005). "Acetic acid spray in colonoscopy: an alternative to chromoendoscopy." Gut **54**(2): 313.

Kisa, E., C. Yucel, S. Budak, M. Ucar, M. Z. Keskin, O. Cakmak, G. Koc and Z. Kozacioglu (2018). "The effect of the American Society of Anesthesiology classification scores on complications associated with percutaneous nephrolithotomy." Archivo Italiano di Urologia e Andrologia **90**(2): 112-116.

Klare, P., H. Phlipsen, B. Haller, H. Einwachter, A. Weber, M. Abdelhafez, M. Bajbouj, H. Brown, R. M. Schmid and S. von Delius (2017). "Longer observation time increases

adenoma detection in the proximal colon - a prospective study." Endoscopy International Open **5**(12): E1289-E1298.

Knuf, K. M., C. V. Maani and A. K. Cummings (2018). "Clinical agreement in the American Society of Anesthesiologists physical status classification." Perioperative Medicine **7**: 14.

Koch-Institut, R. (2015). Krebs in Deutschland für 2015/2016. Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. 12. Ausgabe. Berlin.

Kuiper, T., W. A. Marsman, J. M. Jansen, E. J. van Soest, Y. C. Haan, G. J. Bakker, P. Fockens and E. Dekker (2012). "Accuracy for optical diagnosis of small colorectal polyps in nonacademic settings." Clinical Gastroenterology and Hepatology **10**(9): 1016-1020.

Leitlinienprogramm-Onkologie (2017). S3-Leitlinie Kolorektales Karzinom, (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), Langversion 2.0, 2017, AWMF-Registrierungsnummer: 021/007OL. Retrieved ovember 01, 2017, from http://www.leitlinienprogramm-onkologie.de/leitlinien/kolorektales-karzinom/

Li, M., S. M. Ali, S. Umm-a-OmarahGilani, J. Liu, Y. Q. Li and X. L. Zuo (2014). "Kudo's pit pattern classification for colorectal neoplasms: a meta-analysis." World Journal of Gastroenterology **20**(35): 12649-12656.

Longcroft-Wheaton, G., M. Duku, R. Mead, D. Poller and P. Bhandari (2010). "Acetic acid spray is an effective tool for the endoscopic detection of neoplasia in patients with Barrett's esophagus." Clinical Gastroenterology and Hepatology **8**(10): 843-847.

McGill, S. K., E. Evangelou, J. P. Ioannidis, R. M. Soetikno and T. Kaltenbach (2013). "Narrow band imaging to differentiate neoplastic and non-neoplastic colorectal polyps in real time: a meta-analysis of diagnostic operating characteristics." Gut **62**(12): 1704-1713.

Messmann, H. (2006). Atlas of Colonoscopy: examination techniques and diagnosis . Stuttgart, Germany, Georg Thieme

Netzer, P., C. Forster, R. Biral, C. Ruchti, J. Neuweiler, E. Stauffer, R. Schonegg, C. Maurer, J. Husler, F. Halter and A. Schmassmann (1998). "Risk factor assessment of endoscopically removed malignant colorectal polyps." Gut **43**(5): 669-674.

NICE (2014). Colorectal Cancer: Diagnosis and Management (The National Institue of Clincal Excellence full guideline November 2011, updated 2014).

Nienstedt, J. C., F. Muller, A. Niessen, S. Fleischer, J. C. Koseki, T. Flugel and C. Pflug (2017). "Narrow Band Imaging Enhances the Detection Rate of Penetration and Aspiration in FEES." Dysphagia **32**(3): 443-448.

Nishiyama, S., S. Oka, S. Tanaka, S. Sagami, R. Hayashi, Y. Ueno, K. Arihiro and K. Chayama (2016). "Clinical usefulness of narrow band imaging magnifying colonoscopy for assessing ulcerative colitis-associated cancer/dysplasia." Endoscopy International Open **4**(11): E1183-e1187.

O'Connell, B. M. and S. D. Crockett (2017). "The clinical impact of serrated colorectal polyps." Clinical Epidemiology **9**: 113-125.

Parra-Blanco, A., K. I. Fu, D. Nicolas-Perez, A. Z. Gimeno-Garcia, M. Carrillo and E. Quintero (2007). "Is acetic acid really effective as a mucolytic agent for magnifying colonoscopy diagnosis?" Endoscopy **39**(10): 920-923.

Patrun, J., L. Okresa, H. Ivekovic and N. Rustemovic (2018). "Diagnostic Accuracy of NICE Classification System for Optical Recognition of Predictive Morphology of Colorectal Polyps." Gastroenterology Research and Practice **2018**: https://doi.org/10.1155/2018/7531368.

Pohl, H. and D. J. Robertson (2009). "Confidence with narrow band imaging: will it change our practice of polyp resection?" Gastroenterology **136**(4): 1149-1151.

Pott, G. (1995). Koloskopie-Atlas. Stuttgart, Germany, F.K. Schattauer Verlagsgesellschaft mbH.

Puig, I. and T. Kaltenbach (2018). "Optical Diagnosis for Colorectal Polyps: A Useful Technique Now or in the Future?" Gut Liver **12**(4): 385-392.

Raghavendra, M., D. G. Hewett and D. K. Rex (2010). "Differentiating adenomas from hyperplastic colorectal polyps: narrow-band imaging can be learned in 20 minutes." Gastrointestinal Endoscopy **72**(3): 572-576.

Rees, C. J., P. T. Rajasekhar, A. Wilson, H. Close, M. D. Rutter, B. P. Saunders, J. E. East, R. Maier, M. Moorghen, U. Muhammad, H. Hancock, A. Jayaprakash, C. MacDonald, A. Ramadas, A. Dhar and J. M. Mason (2017). "Narrow band imaging optical diagnosis of small colorectal polyps in routine clinical practice: the Detect Inspect Characterise Resect and Discard 2 (DISCARD 2) study." Gut **66**(5): 887-895.

Rutter, M. D., A. Chattree, J. A. Barbour, S. Thomas-Gibson, P. Bhandari, B. P. Saunders, A. M. Veitch, J. Anderson, B. J. Rembacken, M. B. Loughrey, R. Pullan, W. V. Garrett, G. Lewis and S. Dolwani (2015). "British Society of Gastroenterology/Association of Coloproctologists of Great Britain and Ireland guidelines for the management of large non-pedunculated colorectal polyps." Gut **64**(12): 1847-1873.

Sakata, S., A. O. Kheir and D. G. Hewett (2016). "Optical diagnosis of colorectal neoplasia: A Western perspective." Digestive Endoscopy **28**(3): 281-288.

Schmiegel, W., G. Adler, U. Fölsch, P. Layer, C. Pox and T. Sauerbruch (2000). "Kolorektales Karzinom: Prävention und Früherkennung in der asymptomatischen Bevölkerung – Vorsorge bei Risikogruppen." Deutsches Ärzteblatt **97**: 34-35.

Seo, G. J., D. K. Sohn, K. S. Han, C. W. Hong, B. C. Kim, J. W. Park, H. S. Choi, H. J. Chang and J. H. Oh (2010). "Recurrence after endoscopic piecemeal mucosal resection for large sessile colorectal polyps." World Journal of Gastroenterology **16**(22): 2806-2811.

Serra-Aracil, X., A. Pallisera-Lloveras, L. Mora-Lopez, S. Serra-Pla, V. Puig-Divi, A. Casalots, E. Martinez-Bauer and S. Navarro-Soto (2018). "Transanal endoscopic surgery is effective and safe after endoscopic polypectomy of potentially malignant rectal polyps with questionable margins." Colorectal Disease **20**(9): 789-796.

Shibagaki, K., Y. Amano, N. Ishimura, H. Taniguchi, H. Fujita, S. Adachi, E. Kakehi, R. Fujita, K. Kobayashi and Y. Kinoshita (2016). "Diagnostic accuracy of magnification

endoscopy with acetic acid enhancement and narrow-band imaging in gastric mucosal neoplasms." Endoscopy **48**(1): 16-25.

Singh, R., L. Zorron Cheng Tao Pu, D. Koay and A. Burt (2016). "Sessile serrated adenoma/polyps: Where are we at in 2016?" World Journal of Gastroenterology **22**(34): 7754-7759.

Sola-Vera, J., R. Cuesta, F. Uceda, E. Morillo, E. Perez, M. D. Pico, J. Saez, E. Girona, L. Buendia and M. Garcia-Sepulcre (2015). "Accuracy for optical diagnosis of colorectal polyps in clinical practice." Revista Española de Enfermedades Digestivas **107**(5): 255-261.

Stock, C., P. Ihle, I. Schubert and H. Brenner (2011). "Colonoscopy and fecal occult blood test use in Germany: results from a large insurance-based cohort." Endoscopy **43**(9): 771-781.

Sun, Y., S. Ma, L. Fang, J. Wang and L. Dong (2018). "Circular stripes were more common in Barrett's esophagus after acetic acid staining." BMC Gastroenterology **18**(1): 17.

Tao, H., K. Shinmura, H. Yamada, M. Maekawa, S. Osawa, Y. Takayanagi, K. Okamoto, T. Terai, H. Mori, T. Nakamura and H. Sugimura (2010). "Identification of 5 novel germline APC mutations and characterization of clinical phenotypes in Japanese patients with classical and attenuated familial adenomatous polyposis." BMC Research Notes **3**: 305.

Togashi, K., D. G. Hewett, D. A. Whitaker, G. E. Hume, L. Francis and M. N. Appleyard (2006). "The use of acetic acid in magnification chromocolonoscopy for pit pattern analysis of small polyps." Endoscopy **38**(6): 613-616.

Utsumi, T., M. Iwatate, W. Sano, H. Sunakawa, S. Hattori, N. Hasuike and Y. Sano (2015). "Polyp Detection, Characterization, and Management Using Narrow-Band Imaging with/without Magnification." Clinical Endoscopy **48**(6): 491-497.

Utsumi, T., M. Iwatate, H. Sunakawa, A. Teramoto, D. Hirata, S. Hattori, W. Sano, N. Hasuike, K. Ichikawa, T. Fujimori and Y. Sano (2018). "Additional chromoendoscopy for colorectal lesions initially diagnosed with low confidence by magnifying narrow-band imaging: Can it improve diagnostic accuracy?" Digestive Endoscopy **30** (Suppl 1): 45-50.

van Doorn, S. C., Y. Hazewinkel, J. E. East, M. E. van Leerdam, A. Rastogi, M. Pellise, S. Sanduleanu-Dascalescu, B. A. Bastiaansen, P. Fockens and E. Dekker (2015). "Polyp morphology: an interobserver evaluation for the Paris classification among international experts." American Journal of Gastroenterology **110**(1): 180-187.

van Stralen, K. J., V. S. Stel, J. B. Reitsma, F. W. Dekker, C. Zoccali and K. J. Jager (2009). "Diagnostic methods I: sensitivity, specificity, and other measures of accuracy." Kidney International **75**(12): 1257-1263.

Vormbrock, K. and K. Monkemuller (2012). "Difficult colon polypectomy." World Journal of Gastrointestinal Endoscopy **4**(7): 269-280.

Wang, J., X. H. Zhang, J. Ge, C. M. Yang, J. Y. Liu and S. L. Zhao (2014). "Endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal tumors: a meta-analysis." World Journal of Gastroenterology **20**(25): 8282-8287.

Williams, J. G., R. D. Pullan, J. Hill, P. G. Horgan, E. Salmo, G. N. Buchanan, S. Rasheed, S. G. McGee and N. Haboubi (2013). "Management of the malignant colorectal polyp: ACPGBI position statement." Colorectal Disease **15** (Suppl 2): 1-38.

Yamamoto, S. and M. Shafazand (2017). "Acetic acid-indigocarmine mixture for evaluating the margins of sessile serrated adenomas/polyps." Digestive Endoscopy **29**(7): 817-818.

Zavoral, M., S. Suchanek, F. Zavada, L. Dusek, J. Muzik, B. Seifert and P. Fric (2009). "Colorectal cancer screening in Europe." World Journal of Gastroenterology **15**(47): 5907-5915.

Zhang, J. J., L. Y. Gu, X. Y. Chen, Y. J. Gao, Z. Z. Ge and X. B. Li (2015). "Endoscopic diagnosis of invasion depth for early colorectal carcinomas: a prospective comparative study of narrow-band imaging, acetic acid, and crystal violet." Medicine (Baltimore) **94**(7): e528.