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SERRATED POLYPS OF THE COLON AND RECTUM

YARK HAZEWINKEL

SERRATED POLYPS OF THE COLON AND RECTUM

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Serrated polyps of the colon and rectum

Yark Hazewinkel

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Serrated polyps of the colon and rectum

ACADEMISCH PROEFSCHRIFT

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Faculteit der Geneeskunde

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1

General introduction and outline of this thesis

In part adapted from:
Serrated polyposis syndrome and the role of serrated polyps in colorectal cancer development

KS Boparai, Y Hazewinkel and E Dekker

Colorect Cancer. 2012;1(1):37-47

INTRODUCTION

Colorectal cancer and serrated polyps

Colorectal cancer (CRC) is one of most commonly diagnosed cancers in the Netherlands, with over 13.000 new cases and more than 5000 cancer-related deaths in 2011.[1] It is assumed that almost all CRCs arise from premalignant precursor lesions, called polyps. Until recently, colorectal polyps were divided into two separate groups, conventional adenomas and hyperplastic polyps. Traditionally, adenomas were considered to be the only lesions with an undisputable malignant potential. These adenomas progress into CRC through a sequence of genetic alterations involving key oncogenes and tumor-suppressor genes such as APC, KRAS and P53.[2] Hyperplastic polyps, on the other hand, were regarded as one homogenous group of benign lesions without any potential for malignant progression. However, morphological reappraisals of these previously-labeled hyperplastic polyps revealed that these lesions can be further subdivided into different histological entities with different malignant potential.[3,4] This redefined group of polyps is characterized by a saw-toothed (serrated) infolding the crypt epithelium and are now collectively known as serrated polyps.

The family of serrated polyps includes hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenomas. Hyperplastic polyps are typically diminutive polyps (<6 mm in diameter) that are predominantly located in rectosigmoid. Besides being generally small, these lesions are often flat or sessile in shape. Serration, which is caused by infolding of the crypt epithelium leading to a saw-toothed appearance in longitudinal section and a star-shaped appearance on cross-section, is limited to the upper half to one-third of the crypt. The deep portion of the crypts are generally narrow and straight, with a normal distribution of the proliferative zone in the base of the crypts.[3,4] Sessile serrated adenoma/polyps are typically larger than hyperplastic polyps and tend to have a predilection for the proximal colon. They are defined based on predominantly architectural distortion with irregular dilated crypts, including dilation of the base of the crypts that often have L or T shape.[3,4] Traditional serrated adenomas are most often located in the distal colon and are relatively rare. The architecture is characterized by a protuberant growth pattern with elongated villiform projections uniformly lined with columnar cells having elongated or pencillate nuclei and eosinophilic cytoplasm.[3,4] Also ectopic crypts, defined as premature crypt formation perpendicular to the longitudinal axis of the villi were pointed out as typical feature of these polyps.[5]

Serrated polyps may progress into cancer through a sequence of molecular events. Based on molecular as well as histological data, a "serrated neoplasia pathway" or "serrated CRC pathway" has been proposed involving the progression of serrated polyps to CRC.[6-16] Molecular evidence supporting the serrated pathway includes the finding of *BRAF* mutations, which down-regulates apoptosis, and extensive CPG-island methyla-

tion of multiple genes (CIMP) in a subset of CRCs.[17-20] These molecular alterations are also commonly observed in serrated polyps but are rarely found in sporadic adenomas.[18,20,21,23,24,25] This suggests that serrated polyps, instead of conventional adenomas, may represent precursor lesions of sporadic CIMP-high CRCs. In addition, histological evidence supporting the serrated pathway includes the finding of CRC in close vicinity of large serrated polyps, cases of serrated polyps with areas of dysplasia/cancer and adenocarcinomas with a so called serrated morphology.[26-30] More recent cross-sectional association studies also showed a strong and independent association between large (>1 cm) serrated polyps and synchronous advanced CRC.[31,32]

Growing evidence suggests that a significance proportion of CRCs arise via the serrated neoplasia pathway.[3,4] Since sessile serrated adenomas/polyps are considered to be the major precursor lesions of this pathway, adequate detection and removal of these lesions seems of utmost importance to further increase the effectiveness of colonoscopy. However, despite their increasingly recognized importance, little is known about their endoscopic appearance. Studies systematically describing the appearance of these lesions are scarce, and the role of advanced imaging techniques, like narrow-band imaging, in the real time recognition of these lesions is not well studied. In addition, little is known about the epidemiology. The first part of this thesis focusses on the epidemiology and endoscopic appearance of sessile serrated adenomas/polyps.

Serrated polyposis syndrome

Patients with serrated polyposis syndrome (SPS) harbour multiple serrated polyps affecting the entire large intestine. In contrast with most other polyposis syndromes, the underlying genetic defect of the disease is unknown. The diagnosis of SPS is therefore based on endoscopic findings in combination with histopathologic assessment. In 2010, the syndrome has been defined by the World Health Organization as the presence of 1) at least 5 histologically diagnosed serrated lesions proximal to the sigmoid colon, of which 2 larger than 10 mm in diameter, or 2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS or 3) more than 20 serrated polyps distributed throughout the colorectum.[33] Prior to this revised definition in 2010, only hyperplastic polyps were included in the criteria, and the condition was therefore called hyperplastic polyposis syndrome (HPS).

Besides serrated polyps, conventional adenomas are a common finding in this condition as well.[34,35] The mean age of presentation is in the fifth or sixth decade of life and men and women are equally affected.[34-36] The prevalence of SPS was recently estimated to be 0.3-0.7% among patients undergoing screening colonoscopy based on faecal immunochemical testing (FIT).[37,38] It should be noted that these reported prevalence figures are likely underestimates considering that the syndrome is often underdiagnosed by endoscopist due to the subtle endoscopic appearance of serrated polyps.[39] Even so,

the condition is more prevalent than other well-known polyposis syndromes such as familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome.[40]

Patients with SPS are believed to be at increased for CRC.[35,36] Previously published case series and cohort studies report CRC at first clinical presentation in up to 50% of SPS patients.[41-45] Moreover, several retrospective studies showed that these patients may develop advanced neoplasia under endoscopic surveillance (interval cancers).[35,36] Therefore, in lack of prospective studies, several expert groups advise close endoscopic surveillance for early detection of polyps and prevention of CRC. Amongst them, the US Multi-Society Task Force on Colorectal Cancer and the European Society of Gastrointestinal Endoscopy (ESGE) recently recommended a 1-year surveillance interval for these patients with removal of all polyps ≥ 5 mm.[46,47]

Although most SPS cases seem non-familial, presence of the disease in multiple family members has been described in previous reports.[48,49] In addition, first-degree relatives of patients diagnosed with the syndrome have an increased risk of developing CRC. Case series report that up to 50% of patients with SPS have a first-degree relative with CRC.[42,44,50] Moreover, cohort studies have demonstrated an approximately fivefold increased incidence of colorectal cancer in first-degree family members of patients with SPS compared with the general population.[51,52] For this reason, most authorities advise surveillance colonoscopies every 5 or 6 years for all first-degree relatives starting at age 35-50 years. The second part of this thesis focuses on the endoscopic treatment and surveillance of patients with SPS and screening of their first-degree relatives.

OUTLINE OF THIS THESIS

Part I serrated polyps

Chapter 2 describes the prevalence of the different serrated polyp subtypes in individuals who undergo a single screening colonoscopy. Although postpolypectomy serrated polyp surveillance recommendations were recently incorporated into formal guidelines, the epidemiology of these lesions is poorly understood. Insight into accurate prevalence rates, as provided in this chapter, is of utmost importance for the development of evidence based guidelines and detection standards. In chapter 3 we aimed to describe novel endoscopic features of sessile serrated adenomas/polyps. These lesions are easily missed because of their flat shape and unremarkable colour. A detailed description of the endoscopic appearance of these lesions, as provided in this chapter, may improve the recognition and detection of these lesions.

Part II serrated polyposis syndrome

Patients with SPS are advised to undergo regular endoscopic surveillance for early detection of polyps and prevention of CRC. However, the optimal treatment approach with regard to surveillance intervals and polypectomy protocol is still largely unknown. In chapter 4 we prospectively evaluated a standardized endoscopic surveillance and polypectomy protocol in a consecutive cohort of SPS patient undergoing annual endoscopic surveillance performed by dedicated and experienced endoscopists. The results of this study add substantially to our understanding of the longitudinal CRC risk of patients with SPS who undergo strict endoscopic surveillance. In chapter 5 we assessed the use of narrow-band imaging for the detection of polyps in patients with SPS. Data suggest that some patients with SPS, even if they undergo endoscopic surveillance, still develop advanced neoplasia. These so-called interval cancers may originate from lesions that are not detected with conventional colonoscopy techniques. Narrow-band imaging is an advanced imaging technique. By use of light of a shorter wavelength the mucosal pit pattern and microvasculature of lesions are highlighted which may improve visualization of polyps. Chapter 6 evaluates the yield of single screening colonoscopy in first degree relatives of patients with SPS. In chapter 7 we compared the prevalence of extracolonic cancers in patients with SPS and their first-degree with the background prevalence of these cancers in the general population.

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PART I

SERRATED POLYPS

2

Prevalence of serrated polyps and association with synchronous advanced neoplasia in screening colonoscopy

Y Hazewinkel, TR de Wijkerslooth, EM Stoop, PM Bossuyt, K Biermann, MJ van de Vijver, P Fockens, ME van Leerdam, EJ Kuipers and E Dekker

Endoscopy. 2014;46(3):219-24

ABSTRACT

Background and study aims

Serrated polyps of the large intestine comprise a heterogeneous group of lesions with distinct histological and malignant features. The aim of the study was to estimate the prevalence of serrated polyp subtypes in a cohort of individuals undergoing screening colonoscopy, and to identify associations between the detection of serrated polyp subtypes and advanced neoplasia.

Patients and methods

Data on serrated polyps, adenomas and cancers were collected from participants of a randomized screening trial comparing colonoscopy with CT-colonography. Only data from participants in the colonoscopy arm were used. Logistic regression analyses were performed to identify associations between patients' age, gender and prevalence of the different types of serrated polyps and to identify associations between the detection of these polyps and advanced neoplasia (defined as an adenoma ≥ 10 mm, villous component, high grade dysplasia or CRC).

Results

A total of 1,426 screen-naïve individuals (51% male) with a median age of 60 years (IQR 55-65) were included. The prevalence of hyperplastic polyps (HPs), sessile serrated adenomas/polyps (SSA/Ps) and traditional serrated adenomas (TSAs) was 24%, 4.8% and 0.1%, respectively. SSA/Ps comprised 7% of all polyps. No differences based on age or gender were observed in the prevalence of SSA/Ps. Proximal and large (≥ 10 mm) HPs as well as proximal and large (≥ 10 mm) SSA/Ps were associated with synchronous advanced neoplasia.

Conclusions

Serrated polyps, including SSA/Ps, are frequently encountered in routine screening colonoscopies. Large and proximal HPs, as well large and proximal SSA/Ps, are associated with advanced neoplasia.

INTRODUCTION

Recent studies have shown that screening colonoscopies are less effective in reducing the incidence of colorectal cancer (CRC) and related mortality in the proximal colon than in the distal colon.[1-3] One possible explanation for this observation is that a proportion of post-colonoscopy cancers originate from missed serrated polyps or those that were detected but not removed. These polyps are easily overlooked because of their flat morphology and unremarkable color and they can develop into CRC along an alternative pathway of colorectal carcinogenesis - the serrated neoplasia pathway.[4,5] This pathway might be responsible for up to 20% of all sporadic CRCs.[4-6]

Serrated polyps comprise a heterogeneous group of lesions with distinct histological and malignant features. They can be further classified as hyperplastic polyps, sessile serrated adenomas/polyps or traditional serrated adenomas.[7] The US Multi-Society Task Force on Colorectal Cancer recently emphasized the importance of these polyps and incorporated postpolypectomy surveillance recommendations for patients with sessile serrated adenomas/polyps and traditional serrated adenomas into their guidelines.[8] However, the prevalence and distribution of these lesions are not well known, mainly because most large population-based screening studies were conducted before the recognition of the different serrated polyp subtypes. Although some studies have reclassified the original pathological specimens to overcome this issue, accompanying polyp characteristics, such as size or colonic location, are often missing in these studies due to their retrospective design.[9,10] Moreover, most studies were performed in a period in which serrated polyps were thought to be completely benign, hence it is rather likely that a significant number of these lesions were not diagnosed or removed by endoscopists, or sent for histopathology. All of these factors may have led to an underestimation of the true prevalence.[11]

Knowledge of true prevalence rates and specific polyp characteristics of the different serrated polyp subtypes provide guidance for detection standards and may also help to optimize treatment and surveillance strategies. The aim of the current study was to estimate the prevalence of the different serrated polyp subtypes in a large cohort of individuals undergoing primary screening colonoscopy, and to identify associations between the detection of the different serrated polyp subtypes and synchronous advanced neoplasia.

PATIENTS AND METHODS

Study population

Data were collected from participants of a randomized, multicenter colonoscopy versus colonography (COCOS) screening trial. The design and main results (participation and diagnostic yield) of this population colorectal cancer screening program have been reported in detail previously.[12,13] Differences in proximal serrated polyp detection among endoscopists, as well as procedure-related and patient-related factors associated with proximal serrated polyp detection were described in detail elsewhere.[14]

In brief, between June 2009 and August 2010, 6,600 screen-naïve individuals, aged 50-75 years, living in the regions of Amsterdam and Rotterdam were randomly selected and invited to undergo primary screening by colonoscopy. Eligible persons were not invited or excluded if they had undergone a full colonic examination in the previous 5 years, were scheduled for surveillance colonoscopy because of a personal history of CRC, adenomas, inflammatory bowel disease, or had end stage disease, with a life expectancy less than 5 years. Ethical approval was obtained from the Dutch Health Council (2009/03WBO, The Hague, The Netherlands). The trial was registered in the Dutch Trial Register: NTR1888 (www.trialtregister.nl).

Colonoscopic procedure and equipment

Data from all screening participants allocated to the colonoscopy arm were included for this study. All colonoscopies were performed at two tertiary referral medical institutions by expert endoscopists (individual experience > 1000 colonoscopies) using forward viewing variable stiffness instruments (CF-Q160, CF-Q180 and PCF-Q180: Olympus Medical Systems, Tokyo, Japan). Procedures were performed under conscious sedation using intravenous midazolam and/or fentanyl. Individuals were prepared with 2 L of hypertonic polyethylene glycol solution (MOVIPREP; Norgine BV, Amsterdam, The Netherlands) with an additional 2 L of fluids and low fibre diet. A research nurse or fellow attended all procedures to enter variables on a standardized case record form. All colonoscopies were recorded on DVD.

Cecal intubation was confirmed by identification of appendiceal orifice, cecal valve and/or intubation of the ileum. During withdrawal all detected polyps were removed and retrieved for histological assessment. The size, as measured with an open biopsy forceps, colonic location and Paris-classification of all polyps was recorded.[15] The proximal colon was defined as proximal to the splenic flexure: transverse colon, ascending colon and caecum. Withdrawal time was recorded by a stopwatch and was demanded to be at least six minutes, after subtracting the time needed for polypectomies. The bowel preparation was scored using the validated Ottawa bowel preparation scale, ranging from excellent (score 0) to very poor (score 14).[16]

Histopathology

Tissue specimens were evaluated by one of the two study expert gastrointestinal pathologists, one in each center, according to the Vienna criteria.[17] The histopathological diagnosis was based on the morphological features on haematoxylin and eosin staining. All polyps were classified into serrated, tubular, tubulovillous, villous or carcinoma. Serrated polyps included hyperplastic polyps, sessile serrated adenomas/polyps or traditional serrated adenomas. A sessile serrated adenoma/polyp was defined based on predominantly architectural distortion with irregular dilated crypts, including dilation of the base of the crypts that often have L or T shape.[7] Traditional serrated adenomas were defined by a protuberant or pedunculated growth pattern with distorted villiform configurations with columnar cells having abundant eosinophilic cytoplasm or centrally located elongated nuclei.[7] Dysplasia was defined as either low or high grade. Advanced adenoma was defined as an adenoma ≥ 10 mm, a villous component, or with high grade dysplasia. Advanced neoplasia comprised advanced adenoma and CRC altogether.

Statistical analysis

Descriptive statistics were used to describe the study population and polyp characteristics. The prevalence rate was defined as the proportion of screen-naïve individuals in whom at least one serrated lesion was found. Multivariable logistic regression analyses were performed to identify associations between patients' age and gender and serrated subtype detection rates. Logistic regression was also used to identify associations between the detection of the different subtypes of serrated polyps and advanced neoplasia. Two-sided p-values of less than 0.05 were considered as statistically significant. SPSS for Windows software (Chicago, IL, USA) version 19.0.1 was used for analysis.

RESULTS

Patients and colonoscopy characteristics

A total of 1,426 screening-naïve subjects (51% male) with a median age of 60 years (IQR 55-65) underwent a primary screening colonoscopy. Ninety-seven percent (1377/1426) of all colonoscopies were performed by 5 endoscopists with experience of more than 1000 colonoscopies. Unadjusted cecal intubation rate was 98.7%, net median withdrawal time was 10 minutes (IQR 8-15). The median Ottawa bowel preparation score was 5 (IQR 3-8). One or more adenomas were detected in 419 participants (29%). One or more advanced adenomas were detected in 125 participants (9%). Advanced neoplasia, including 8 subjects with CRC, was detected in 130 (9%) subjects.

Serrated Polyps

Histology

A total of 1,782 specimens were collected and sent for pathology, of which 777 (44%) were adenomas and 744 (42%) serrated polyps. The remaining 261 lesions were classified as normal tissue, inflammatory polyp (pseudopolyps) or lipoma. Of the serrated polyps, 632 (85%) were classified as hyperplastic polyps, 111 (15%) as sessile serrated adenomas/polyps and one as a traditional serrated adenoma. The proportion sessile serrated adenomas/polyps relative to all histopathological diagnosed polyps (serrated or adenoma) was 7% (111/1521).

None of the patient fulfilled the WHO criteria for serrated polyposis syndrome (≥ 5 serrated polyps proximal to the sigmoid of which 2 ≥ 10mm in diameter or ≥ 20 serrated polyps).

Polyp characteristics

Serrated polyp subtype characteristics are shown in Table 1. In Figure 1 the ratio between hyperplastic polyp and sessile serrated adenoma/polyp histology is displayed, stratified per size group and colonic location. Sessile serrated adenomas/polyps comprised 8% of all distal serrated polyps 1-5 mm versus 21% of all proximal serrated polyps 1-5 mm in

Table 1. Summary of HPs, SSA/Ps and TSAs characteristics

	HP (632)	SSA/P (111)	TSA (1)
Location (%)			
Distal	474 (75)	45 (41)	1 (100)
Rectosigmoid	423 (67)	37 (33)	1 (100)
Descending	51 (8)	8 (7)	0
Proximal	158 (25)	66 (59)	0
Transverse	67 (11)	28 (25)	0
Ascending	64 (10)	25 (23)	0
Caecum	27 (4)	13 (12)	0
Paris classification (%)			
Sessile (Is)	511 (81)	92 (83)	1 (100)
Flat (IIa and IIb)	75 (12)	14 (13)	0 (0)
Pedunculated (Ip)	17 (3)	2 (2)	0 (0)
Median size (mm, IQR)			
Pan-colonic	3 (2-4)	5 (3-8)	5 (5-5)
Proximal	4 (2-5)	7 (4-8)	
Dysplasia (%)			
Any dysplasia	0 (0)	29 (26)	1 (100)

HP: hyperplastic polyp, SSA/P: sessile serrated adenoma/polyp, TSA: traditional serrated adenoma, IQR: interquartile range

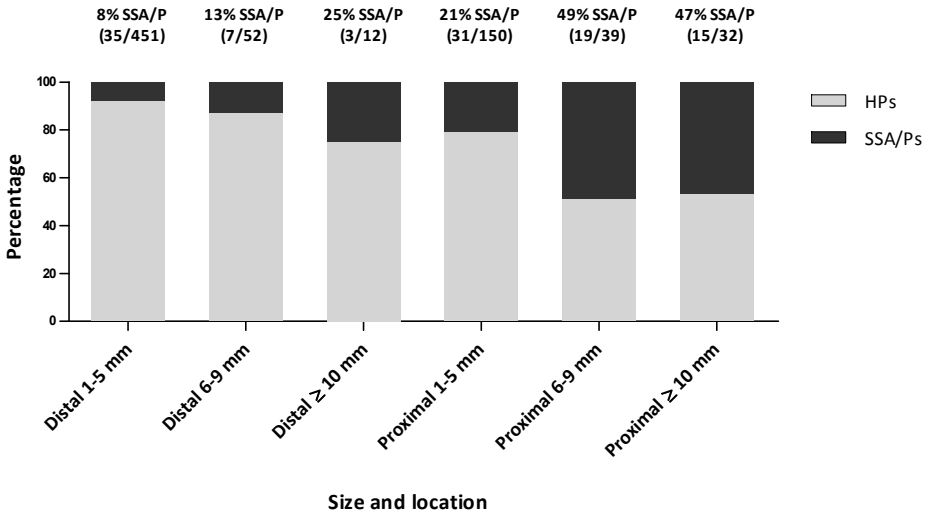

Figure 1. Ratio between HP and SSA/P histology stratified per size group and colonic location
HP: hyperplastic polyp, SSA/P: sessile serrated adenoma/polyp

size; 13% of all distal serrated polyps 6-9 mm versus 49% of all proximal serrated polyps 6-9 mm in size; and 25% of all distal serrated polyps ≥ 10 mm versus 47% of all proximal serrated polyps ≥ 10 mm in size.

Prevalence of serrated polyps

The prevalence of the different serrated polyp subtypes is summarized in Table 2. In 27% of individuals, one or more serrated polyps were detected. Al least one hyperplastic polyp, sessile serrated adenoma/polyp, or traditional serrated adenoma was detected in 24%, 4.8% and 0.1% of individuals, respectively. Associations between patient age and gender and the detection of (proximal) hyperplastic polyps and (proximal) sessile serrated adenomas/polyps are shown in Table 3. More hyperplastic polyps were detected in male, taking age into account. In contrast, neither age nor gender was significantly associated with the detection of sessile serrated adenomas/polyps or proximal sessile serrated adenomas/polyps.

Association of subtypes of serrated polyps and synchronous advanced neoplasia

Associations between the detection of the different subtypes of serrated polyps and synchronous advanced neoplasia are presented in Table 4. Proximal and large hyperplastic polyps, as well as proximal and large sessile serrated adenomas/polyps, were associated with synchronous advanced neoplasia.

Table 2. Prevalence of the different subtypes of serrated polyps

	Prevalence		
	Total (1426) *	Male (726)	Female (700)
At least 1 serrated polyp (%)	388 (27.2)	216 (29.8)	172 (24.6)
HP	339 (23.8)	189 (26.0)	150 (21.4)
SSA/P	68 (4.8)	35 (4.8)	33 (4.7)
TSA	1 (.1)		1 (.1)
At least 1 proximal serrated polyp (%)	174 (12.2)	84 (11.6)	90 (12.9)
Proximal HP	127 (8.9)	62 (8.5)	65 (9.3)
Proximal SSA/P	51 (3.6)	24 (3.3)	27 (3.9)
Proximal TSA	0 (.0)		
At least 1 serrated polyp ≥10 mm (%)	37 (2.7)	18 (2.5)	19 (2.7)
HP ≥ 10 mm	22 (1.5)	14 (1.9)	8 (1.1)
SSA/P ≥ 10 mm	16 (1.1)	4 (0.6)	12 (1.7)
TSA ≥ 10 mm	0. (.0)		
At least 1 serrated polyp with dysplasia (%)	22 (1.5)	13 (1.8)	9 (1.3)
SSA/P with dysplasia	21 (1.5)	13 (1.8)	8 (1.1)
TSA with dysplasia	1 (.1)		1 (.1)

* In a proportion of individuals more than one serrated subtype was found. Therefore the cumulative prevalence of all serrated subcategories together does not exactly add up to the total prevalence of serrated polyps.

HP: hyperplastic polyp, SSA/P: sessile serrated adenoma/polyp, TSA: traditional serrated adenoma

Table 3. Association between age and gender and the detection of the different subtypes of serrated polyps

		Age			Gender		
Subjects with at least one:	n	Median age (IQR)	Adjusted OR* (95% CI)	P	Male (%)	Adjusted OR** (95% CI)	P
Hyperplastic polyp							
No	1087	60 (55-65)	1.00		537 (49)	1.00	
Yes	339	61 (56-66)	1.01 (0.99-1.03)	0.23	189 (56)	1.31 (1.02-1.68)	0.03
Proximal hyperplastic polyp							
No	1299	60 (55-65)	1.00		664 (51)	1.00	
Yes	127	60 (55-66)	1.01 (0.98-1.04)	0.75	62 (49)	0.93 (0.64-1.35)	0.69
Sessile serrated adenoma/polyp							
No	1358	60 (55-65)	1.00		691 (51)	1.00	
Yes	68	60 (55-64)	0.99 (0.95-1.03)	0.45	35 (52)	1.07 (0.65-1.75)	0.79
Proximal sessile serrated adenoma/polyp							
No	1375	60 (55-65)	1.00		702 (51)	1.00	
Yes	51	60 (55-64)	1.00 (0.95-1.05)	0.84	24 (47)	0.85 (0.48-1.49)	0.56

* Odds ratios were calculated using multivariable logistic regression analysis including gender and quality of bowel preparation

** Odds ratios were calculated using multivariable logistic regression analysis including age and quality of bowel preparation

HP: hyperplastic polyp, SSA/P: sessile serrated adenoma/polyp, OR: odds ratio, CI: confidence interval

Table 4. Association of serrated subtypes and synchronous advanced neoplasia

Subjects with at least one:	N	Subjects with advanced neoplasia (%)	Adjusted OR* (95% CI)	p-value
Proximal serrated polyp				
No	1254	99 (9)	1.00	
Yes	174	31 (21)	2.44 (1.55-3.84)	< .001
Proximal hyperplastic polyp **				
No	1299	110 (8)	1.00	
Yes	123	20 (15)	1.95 (1.13-3.36)	.02
Proximal sessile serrated adenoma				
No	1375	119 (9)	1.00	
Yes	51	11 (22)	3.04 (1.50-6.15)	.002
Large serrated polyp (≥ 10 mm)				
No	1389	120	1.00	
Yes	37	10	4.02 (1.87-8.62)	< .001
Large hyperplastic polyp (≥ 10 mm) **				
No	1405	125 (9)	1.00	
Yes	21	5 (23)	3.18 (1.11-9.07)	.03
Large sessile serrated adenoma (≥ 10 mm)				
No	1410	125 (9)	1.00	
Yes	16	5 (32)	5.02 (1.69-14.86)	.004

* Odds ratios were calculated using multivariable logistic regression analysis including patients age, gender and quality of bowel preparation

** Subjects with both hyperplastic polyps and sessile serrated adenomas/polyps were classified as individuals with sessile serrated adenomas/polyps

DISCUSSION

In this study the prevalence and distribution of different serrated polyp subtypes were estimated in individuals undergoing primary screening colonoscopy. Hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenomas were detected in 24%, 4.8% and 0.1% of individuals, respectively. Sessile serrated adenomas/polyps comprised 7% of all histopathological classified polyps. No differences based on age or sex were observed in the prevalence of sessile serrated adenomas/polyps. Proximal and large hyperplastic polyps, as well as proximal and large sessile serrated adenomas/polyps, were associated with synchronous advanced neoplasia.

The prevalence and distribution of each subtype were evaluated within an invitational population based colonoscopy screening program. The study was conducted in a large homogenous screening-naïve population and the vast majority of procedures was performed by highly experienced endoscopists. Important quality indicators, such as cecal intubation rate, adenoma detection rate and net withdrawal time all met current

accepted standards, suggesting high performance colonoscopies.[18] All colonoscopies were attended by a research nurse or fellow to ensure accurate prospective data collection for quality parameters and polyp characteristics. The current study does have some limitations, the most important of which is that detection of serrated polyps was not a primary objective. Although all endoscopists were instructed to detect and remove all colonic polyps irrespective of their endoscopic appearance or size, these lesions still may have been missed or misdiagnosed as unimportant. This could have led to an underestimation of the true prevalence. Previous studies have shown interobserver variability between pathologists in the diagnosis of serrated polyps.[19,20] Although this risk was minimized in our study (all tissue specimens were evaluated by one of the two expert pathologists), observer variation could lead to distinct local differences in the diagnosis of the different serrated polyp subtypes.

Sessile serrated adenomas/polyps are the principal serrated precursor lesions of CRCs arising via the serrated neoplasia pathway and are thought to play a significant role in the occurrence of post-colonoscopy cancers. The prevalence of sessile serrated adenomas/polyps has been described in previous studies ranging from 1% to 14%.[9-11,21,22] Most of these studies, however, had a retrospective design, included symptomatic or high-risk patients or used chromoendoscopy, making the generalizability of these findings to a primary screening setting hazardous. In our study, 4.8% of screening participants harboured at least one sessile serrated adenoma/polyp. This finding is comparable with a recent study demonstrating a prevalence of 2.3% in asymptomatic average-risk patients.[23] Considering that the US Multi Society Task Force on Colorectal Cancer recently recommended to survey patients with these lesions, these data suggest that this advice will lead to a significant burden on surveillance programs, although the exact quantity is unknown.

Sessile serrated adenomas/polyps accounted in our series for 7% of all polyps, which illustrates that these lesions are rather frequently encountered in a routine screening colonoscopy. Various studies have shown a wide variability in serrated polyp detection rates between endoscopists, suggesting that a significant proportion of these lesions, including sessile serrated adenomas/polyps, are missed.[11,14,24] This may in part be explained by the flat morphology and unremarkable colour of these lesions, but the possibility that some endoscopists still disregard these lesions, assuming they harbour no premalignant potential, cannot be excluded. Another important issue is the recent finding that up to 31% of all sessile serrated adenomas/polyps are incompletely resected.[25] Each endoscopist should therefore be well aware of the clinical impact of these lesions and be sufficiently trained to detect and completely remove them.

Patient age was not associated with the detection of sessile serrated adenomas/polyps in the current study, suggesting that the prevalence of sessile serrated adenomas is comparable across age groups. There were no differences in prevalence based on

sex. Previous studies have reported conflicting results with respect to the occurrence of sessile serrated adenomas/polyps in men and women. Hetzel et al., Higuchi et al. and Singh et al. also found no significant sex difference, whereas Lash et al. and Spring et al. demonstrated that these lesions were more often found in women.[10,11,21,22,26]

The likelihood of a serrated polyp being histologically classified as a hyperplastic polyp or as a sessile serrated adenoma/polyp depends on the size and colonic location of the lesion. In the current study, almost 50% of all proximal serrated lesions larger than 5 mm were classified as sessile serrated adenomas/polyps. In contrast, only 8% of all distal serrated polyps 1-5 mm in size were classified as sessile serrated adenoma/polyp. These findings may provide guidance regarding the treatment of serrated polyps. An international expert panel consisting of endoscopists, pathologists and surgeons recently recommended complete removal of all detected serrated polyps with the exception of single diminutive (≤ 5 mm in size) serrated polyps located in the rectosigmoid.[27] They argued that these distal diminutive lesions are probably clinical irrelevant benign hyperplastic polyps that do not require treatment. Our findings support this proposal to a large extent; 92% of all diminutive distal serrated polyps in the current study were indeed hyperplastic polyps. One could also argue that our data suggest that all distal serrated polyps should be removed, given that 8% of lesions left in place would have been a sessile serrated adenoma/polyp. Yet this approach seems clinically unacceptable, since it would further increase the workload of endoscopists, inflate pathology costs, and probably also lead to avoidable complications. Moreover, these lesions probably have a very low risk of harbouring cancer or advanced histology.[10] Rather than to remove all distal serrated polyps, we believe further research should focus on the endoscopic appearance of sessile serrated adenomas/polyps and assess whether it is possible to endoscopically differentiate these from hyperplastic polyps located in the rectosigmoid.[28] The recommendation by the expert group to remove all proximal serrated polyps seems endorsed by our results, given that approximately one third are sessile serrated adenomas/polyps.

Previous studies have suggested that sessile serrated adenomas/polyps are predominantly located in the right-side of the colon.[21,29] This predilection for the proximal colon and the difficult detection were two reasons to believe that sessile serrated adenomas/polyps may have played an important role in the observed decreased protective value of colonoscopy for right-sided CRCs. Moreover, interval cancers are disproportionately BRAF-mutated and microsatellite instable, molecular features that are also commonly seen in sessile serrated adenomas/polyps.[21,30,31] In the current study, a significant proportion of sessile serrated adenomas/polyps (41%) were located distally to the splenic flexure. This finding is consistent with those of Buda et al. and suggests that these lesions do not exclusively develop in the right-side of the colon.[23] This is remarkable since distal (interval) cancers with serrated molecular hallmarks are less frequently

observed than proximal ones.[31] This favours the theory that proximal sessile serrated adenomas/polyps are more easily missed than distal ones, which is most likely caused by colonoscopy-related factors, such as an incomplete colonoscopy or a poor proximal bowel preparation. Another possible explanation is that the endoscopic appearance of proximal sessile serrated adenomas/polyps differs from distal ones. This rationale was recently supported by a study showing that large and dysplastic serrated polyps in the proximal colon were more often nonpolypoid than distal serrated polyps, making them more likely to be overlooked.[32] Finally, the possibility that distal sessile serrated adenomas/polyps harbour a different molecular profile with less malignant potential cannot be excluded.

Previous studies have shown that proximal and large serrated polyps are associated with synchronous advanced neoplasia.[33-35] As serrated polyps were not further distinguished in these studies, the precise association between each serrated polyp type and synchronous advanced neoplasia could not be determined. The current study demonstrated that proximal and large hyperplastic polyps, as well as proximal and large sessile serrated adenomas/polyps, are associated with synchronous advanced neoplasia. This may suggest that both serrated subtypes share similar environmental and genetic risk factors with conventional adenomatous lesions, although this remains speculative. Future molecular and clinical studies are needed on this issue.

In conclusion, the current study demonstrated that serrated polyps, including sessile serrated adenomas/polyps, are frequently encountered in routine screening colonoscopies. Endoscopists should be fully aware of the clinical impact of these lesions and be sufficiently trained in order to detect and completely remove them.

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3

Endoscopic features of sessile serrated adenomas: validation by international experts using high-resolution white light endoscopy and narrow-band imaging

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ABSTRACT

Background and study aims

Sessile serrated adenomas/polyps (SSA/Ps) are premalignant lesions susceptible to being easily overlooked by endoscopists. A detailed description of the endoscopic appearance of SSA/Ps might help endoscopists to recognize these lesions to improve the effectiveness of colonoscopy. The aim of the study was to identify various endoscopic features of SSA/Ps using high-resolution white light endoscopy (HR-WLE) and narrow-band imaging (NBI).

Patients and methods

HR-WLE and NBI images of 150 polyps (50 SSA/Ps, 50 hyperplastic polyps and 50 adenomas) were systematically assessed by 5 experts using various endoscopic descriptors. Images were derived from 45 patients with serrated polyposis syndrome, of whom the majority underwent annual surveillance colonoscopies in one tertiary referral center. Main outcome measurement was the prevalence of specific endoscopic features observed in SSA/Ps versus HPs.

Results

Multivariate analysis demonstrated that *indistinct borders* (OR 3.11, 95% 1.57-6.15) and a *cloud-like surface* (OR 2.65 95% CI 1.21-5.78) were associated with of SSA/P histology on HR-WLE. On NBI, a *cloud-like surface* (4.91 95% CI 2.42-9.97), *indistinct borders* (2.38 95% CI 1.14-4.96), *irregular shape* (3.17 95% CI 1.59-6.29) and *dark spots inside the crypts* (2.05 95% CI 1.02-4.11) were found to be endoscopic predictors of SSA/P histology. The sensitivity, specificity and accuracy of NBI for differentiating serrated polyps containing either none or all 4 endoscopic SSA/P features were respectively, 89%, 96% and 93%.

Conclusions

The current study demonstrates that SSA/Ps possess several specific endoscopic features compared to HPs. Recognition of these characteristics might assist endoscopists in the differentiation of these lesions and could possibly facilitate endoscopic detection of these rather subtle lesions.

INTRODUCTION

Over the last decades, much progress has been made in unravelling the development of colorectal cancer (CRC) along the adenoma-carcinoma sequence.[1,2] This has led to colonoscopic screening and surveillance programs aimed at the detection and removal of adenomas to prevent CRC.[3,4] However, population-based and case-controlled studies have shown that screening colonoscopies are less effective in decreasing the incidence and mortality of CRC in the proximal colon compared to the distal part.[5-7] A plausible explanation for this remarkable observation is the proposed alternative pathway of colorectal carcinogenesis, the *serrated neoplasia pathway*.[8] This pathway describes the progression of a subset of serrated polyps, called sessile serrated adenomas/polyps (SSA/Ps), to CRC and may be responsible for up to 20% of all sporadic CRCs.[9] This implies that all SSA/Ps should be accurately recognized and removed during colonoscopy. These lesions, however, are susceptible to being easily overlooked due to their flat morphology and unremarkable color, providing little contrast with surrounding colonic mucosa. Moreover, due to the morphological similarity with hyperplastic polyps (HPs), it seems likely that a proportion of detected SSA/Ps are left in situ when they are misinterpreted by colonoscopists as clinical irrelevant HPs.

Recognition of specific endoscopic characteristics of SSA/Ps by colonoscopists may improve SSA/P detection and eventually enhance the effectiveness of colonoscopy. Studies systematically describing the endoscopic appearance of SSA/Ps are scarce and the role of advanced imaging techniques, like narrow-band imaging (NBI), in real-time recognition of these lesions is not well studied. The aim of this image evaluation study was to identify specific endoscopic features of SSA/Ps using high-resolution white light endoscopy (HR-WLE) and NBI. Secondary aims were to assess the diagnostic accuracy of HR-WLE and NBI for the differentiation of SSA/Ps from HPs and to assess the interobserver agreement of these features.

PATIENTS AND METHODS

Endoscopic procedure

For this study we retrospectively collected data from colonoscopies that were performed with the Evis Lucera system (CLV-260; Olympus Inc, Tokyo, Japan) or the Evis Exera II system (CLV-180; Olympus Inc, Tokyo, Japan) in combination with high-resolution video colonoscopes (CF-H260Z, XCF-H240FZL or CF-H180AI, Olympus Inc, Tokyo, Japan). During all procedures, multiple HR-WLE and NBI images were taken of each polyp. All images were collected in a database and linked to the corresponding data of the polyps, including histopathology, size, location and the shape (Paris classification[10]). The Paris

classification divides lesions into 3 main categories: I) protruding lesions (Is=sessile or Ip=pedunculated) II) nonprotruding and nonexcavated lesions (IIa=flat elevated, IIb=completely flat and IIc=slightly depressed) and III) excavated lesions.

Data collection set

In total 243 polyps with corresponding images were registered in the database. For each histopathological entity 50 non-magnified images were selected based on quality (sharp and well-focused images). This resulted in a dataset of 150 polyps: 50 SSA/Ps, 50 HPs and 50 adenomas. Images were taken as part of previous studies as well as during one ongoing prospective study comparing polyp miss-rates of HR-WLE with those of NBI in patients with serrated polyposis syndrome.[11-13] All studies were approved by the medical ethical committee of our institution.

For all histopathological entities, the images were randomly assigned into 2 sets: (1) a learning set, consisting of 60 polyps (20 SSA/Ps, 20 HPs and 20 adenomas) and (2) a validation set, consisting of the remaining 90 polyps (30 SSA/Ps, 30 HPs and 30 adenomas). Images were incorporated into a slideshow (Microsoft PowerPoint 2003; Microsoft, Redmond, WA, USA) and stored as portable document format (PDF) file without any form of post processing.

Image evolution process

Exploratory meeting and learning set

An exploratory meeting with 2 expert endoscopists (ED and ML) and 1 expert pathologist (SvE) was arranged to discuss and to identify several potential endoscopic features of SSA/Ps. Subsequently, the learning set was used to determine which of the postulated features were associated with SSA/P histology. This assessment was performed by 2 observers (ED and JE) at the same time, both blinded to histopathology and polyp location. HR-WLE and corresponding NBI pictures were displayed simultaneously to both observers at the same time. The observers both stated their assessment of each polyp; in case of disagreement a consensus between the two was reached by a joint discussion. Only those features that demonstrated a significant association with SSA/P histology were subsequently scored in the validation set.

Validation set

The validation set was used to validate the endoscopic features derived from the learning set and to assess the diagnostic accuracy of each specific feature as well as to assess the interobserver variability among international experts. The data set was assessed individually by all 5 observers and consisted of the same observers of the learning set (ED and JE) and 3 additional observers (AR, TN, and MP). In contrast to the learning set, consecutive HR-WLE images and NBI images were scored separately, both in a random

order for each technique. Again the observers were blinded to histopathology and polyp location. In addition to these data, also the quality of the images was scored (poor, moderate, good or excellent)

Observers

The assessment of polyps was done by 5 experienced endoscopists from 5 different hospitals in Europe (ED, JE and MP), North-America (AR) and Asia (TN). They had all performed at least 50 colonoscopies with NBI prior to the start of this study.

Digital training module

Before assessment of the images, a short digital training module was provided to the assessors including descriptions and examples of all endoscopic features. Subsequently, a set of training polyps (3 SSA/Ps, 1 HP and 1 adenoma) was displayed to each endoscopist. After scoring these polyps, direct feedback was given to the observer by revealing the correct histopathology. All images used for this training were additional and not included in the final image evaluation process.

Reference standard

The histopathological diagnosis served as reference standard. All tissue specimens were evaluated by one expert gastrointestinal pathologist (SvE) according to the revised Vienna criteria.[14] The histopathological diagnosis was based on the morphological features on haematoxylin and eosin (H&E) staining. A SSA/P was defined as a serrated lesion with irregular dilated crypts, including dilatation of the base of the crypts that often have a boot, L or inverted T shape.[15] The pathologist was blinded to the endoscopic appearance of the lesions.

Statistical analysis

SPSS for Windows software (version 18.0.2; Chicago, IL, USA) was used for analysis. Descriptive statistics were used to describe the study population. Proportions of endoscopic features and comparison of image quality were tested with the χ^2 test. Features that were found to be significantly associated ($p < 0.05$) with SSA/P histology in the learning set were subsequently assessed in the validation set. For multivariate analysis, only features that demonstrated an association ($p < 0.05$) with SSA/P histology in univariate analysis were used in the model.

In the validation set, pooled data of 5 observers (5 x 90 images) were used. The diagnostic accuracy of the endoscopic features and the predictive models for differentiating SSA/Ps from HPs were assessed by comparison with histopathology and was reported according the STARD statements for diagnostic accuracy studies.[16] Diagnostic accuracy for all features was calculated for all 5 observers combined and derived from 2x2 tables.

Outcome parameters were sensitivity, specificity, and overall accuracy. The interobserver agreement was expressed by the percentage of full agreement among the observers as well as by an overall kappa statistic with 95%-confidence interval (95% CI). The interobserver agreement was calculated using the Fleiss kappa (more than two observers).[17] Interpretation of κ-values was done according to Landis and Koch.[18]

RESULTS

Polyp characteristics

All polyp data were derived from 45 patients (mean age 61± SD 9 y, 23 male) with serrated polyposis syndrome, of whom the majority underwent annual surveillance colonoscopies in one tertiary referral center. The median polyp size was 5 mm (IQR 3-8mm); 34 (23%) polyps were ≥ 10 mm and 97 (65%) polyps were located proximal to the sigmoid. In total, 76 (51%) polyps were flat (Paris IIa or IIb), 73 polyps were sessile (Paris Is) and one polyp had a pedunculated shape.

Exploratory meeting

During the exploratory meeting, a standard consensus list of 7 potential endoscopic features of SSA/Ps was developed. Detailed descriptions and endoscopic examples of each individual feature are provided in respectively table 1 and figure 1 A-I.

Learning set: determining relevant endoscopic features by 2 observers

The combined HR-WLE and NBI images of 48/60 (80%) polyps were scored as having excellent or good quality whereas the image quality of the remaining 12 (20%) polyps was scored as moderate or poor.

Univariate analyses showed that 6 features were significantly more often scored as present in SSA/Ps than in HPs: (1) *indistinctive borders* (100% vs. 60% p= 0.003), (2) *cloud-like surface* (90% versus 20% p= <0.001), (3) *pit pattern IISSA/P* (45% versus 10% p=0.031), (4) *dark spots inside the crypts* (75% versus 15% p= 0.001), (5) *normal vascular pattern intensity* (VPI) (85% versus 40%, p=0.008) and (6) *irregular shape* (95% versus 25%, p= <0.001).

Validation set: validation of endoscopic features by 5 observers

Ninety polyps with both HR-WLE and NBI images were scored by 5 observers, resulting in 450 assessments for each imaging modality. Sixty-six percent (299/450) of HR-WLE-images and 71% (319/450) of NBI-images were scored as having excellent or good quality (p=0.15). Apart from pit pattern analysis, all features could be assessed on all images by all endoscopists. A pit pattern could not be identified on 26% of HR-WLE-images and on 10% of NBI-images.

Table 1. Consensus meeting. Various potential endoscopic features of SSA/Ps. See figure 1 A-J for examples of each endoscopic feature

Feature	Description	Outcome	Figure 1
(1) Indistinctive borders	Vague demarcation of a border of a lesion	Present/not present	A, B, I
(2) Cloud-like surface	A bumpy, soft looking nodular surface resembling a cumulus cloud	Present/not present	C, D, E, F, I
(3) Dark spots inside the crypts	Small dark dots inside the open crypts. On HR-WLE they can also appear as red dots	Present/not present	D, F
(4) Irregular shape	An asymmetric shape, in contrast to the oval, circular shape of small HPs and conventional adenomas.	Present/not present	A, B, C, D, G, I
(5) Absence of tiny microvessels crossing the surface	Small superficial vessels or telangiectasias occasionally seen on the surface of particular distal HPs	Present/not present	A-I
(6) Pit pattern	Kudo pit pattern I-V or pit pattern IISSA/P (defined as a mixture of open crypts and small elongated star-shape pits)	Kudo type I-V or pit pattern IISSA/P	H
(7) Vascular pattern intensity (VPI)	Assessment of the darkness of the lines that outline each colonic crypt compared to the normal background mucosa. A darker (strong) VPI indicates neoplasia whereas a same (normal) or lighter (weak) VPI suggest a non-neoplastic lesion [19]	Weak, normal or strong	B, D, F, H

SSA/P: sessile serrated adenoma/polyp, HP: hyperplastic polyp, VPI: vascular pattern intensity, HR-WLE: high resolution white light endoscopy

Univariate analyses showed that all endoscopic SSA/P features were again significantly more often present in SSA/Ps compared to HPs (table 2) (all features $P \leq 0.002$). Subsequent multivariate analysis demonstrated that presence of an *indistinctive borders* (OR 3.11 95% CI 1.57-6.15) and a *cloud-like surface* (2.65 95% CI 1.21-5.78) were 2 independent predictive endoscopic characteristics of SSA/P histology on HR-WLE (table 3). Under NBI a *cloud-like surface* (OR 4.91 95% CI 2.42-9.97), an *irregular shape* (OR 3.17 95% CI 1.59-6.29), indistinctive *borders* (OR 2.38 95% CI 1.14-4.96) and *dark spots inside the crypts* (OR 2.05 95% CI 1.02-4.11) were found to be independent predictors of SSA/P histology. The sensitivities, specificities and diagnostic accuracies of the independent predicting feature are listed in table 4.

Validation set: differentiation of serrated polyps by combining endoscopic features

By combining the independent endoscopic features derived from the image evolution process, a prediction model per imaging technique was developed in order to differentiate SSA/Ps from HPs. A lesion was endoscopically considered as SSA/P if all independent SSA/P features were scored as present, which were 2 features on HR-WLE (*indistinctive borders* and *cloud-like surface*) and 4 features on NBI (*indistinctive borders*, *cloud-like*

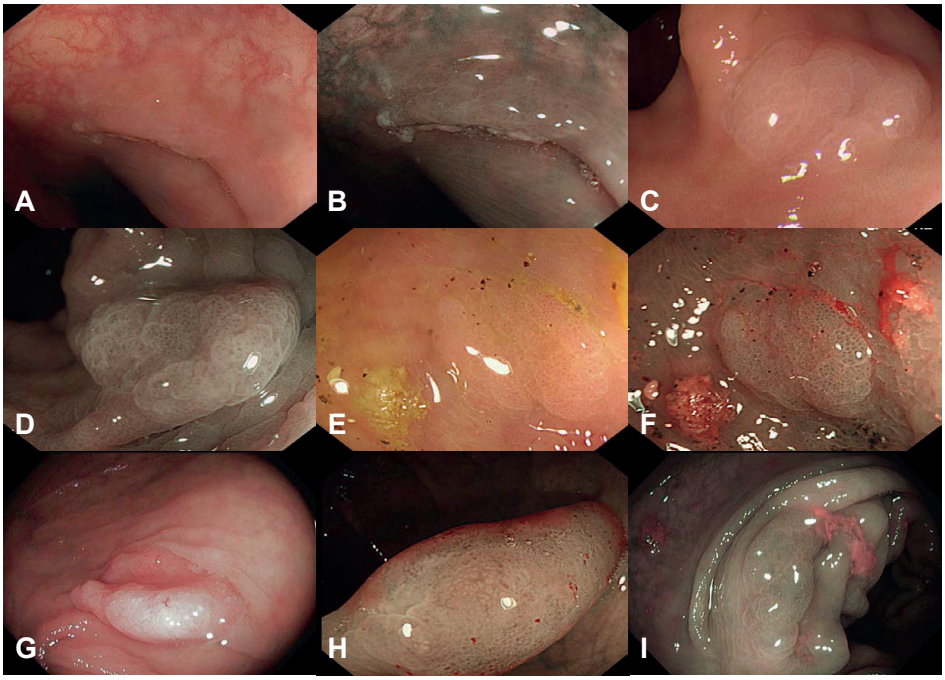

Figure 1. HR-WLE and NBI images of sessile serrated adenomas/polyps (SSA/Ps) illustrating the 7 potential features that were defined during the exploratory meeting. After assessment of the images, 4 features were independently associated with SSA/P histology, a *cloud-like surface* (C, D, E, F and I) and *indistinctive borders* (A and B) were predictive features on both HR-WLE and NBI whereas *dark spots* (D and F and an *irregular shape* (A, B, C, D, G and I) were predictive characteristics solely on NBI.
A) SSA/P demonstrating vague margins seen under HR-WLE. B) The same lesion as in A, seen under NBI. Again the borders of the lesion are not well defined. Note the nodular aspect of the surface (cloud-like surface) which was not seen under HR-WLE. C) SSA/P expressing a cloud-like surface under HR-WLE. D) The same lesion as in C, seen under NBI. Again the cloud-like surface is clearly visible. Note the dark spots inside the crypts. E) Flat SSA/P with a cloud-like surface and red dots inside the crypts. F) Same lesion as in E seen under NBI, again with a cloud-like surface and dark spots inside the crypts. G) Large proximal SSA/P with an irregular shape. H) SSA/P expressing a mixture of open crypts and small elongated star-shape pits (pit pattern IISSA/P). I) SSA/P on a fold seen under NBI. The lesion has the same vascular pattern intensity as the background mucosa and an irregular shape.

surface, *irregular shape* and *dark spots inside the crypts*). An endoscopic diagnosis of a HP was made if none of these features were present. These models were subsequently applied on all eligible lesions in the validation set and compared with histopathology. Of the 300 (5x60) serrated polyps, 207 (69%) lesions on HR-WLE and 116 (39%) lesions on NBI were included for differentiation as these lesions were scored as having either none or all SSA/P features. In these subsets of polyps a sensitivity, specificity and overall accuracy of respectively 75%, 79% and 77% on HR-WLE and 89%, 96% and 93% on NBI were obtained (table 5).

Table 2. Validation set. Prevalence of endoscopic feature in SSA/Ps, HPs and adenomas

	SSA/Ps N= 150 (5x30) % (95% CI)	HPs N=150 (5x30) % (95% CI)	Adenomas N=150 (5x30) % (95% CI)	P value**
(1) Indistinctive borders				
HR-WLE	73 (66-80)	35 (27-43)	27 (20-34)	<0.001
NBI	65 (57-73)	21 (15-28)	21 (15-28)	<0.001
(2) Cloud-like surface				
HR-WLE	58 (50-66)	21 (15-28)	4 (2-8)	<0.001
NBI	66 (58-73)	14 (9-20)	5 (3-10)	<0.001
(3) Pit pattern IISSA/P				
HR-WLE	36 (28-46)	12 (7-19)	6 (3-12)	<0.001
NBI	30 (23-38)	8 (4-14)	6 (3-12)	<0.001
(4) Dark spots inside the crypts				
HR-WLE	37 (30-45)	21 (16-29)	9 (6-15)	0.002
NBI	58 (50-66)	29 (22-36)	17 (12-24)	<0.001
(5) Normal VPI *				
NBI	80 (73-86)	49 (42-57)	30 (23-38)	<0.001
(6) Irregular shape				
HR-WLE	71 (63-77)	42 (34-50)	27 (20-34)	<0.001
NBI	78 (71-84)	31 (24-38)	25 (19-33)	<0.001

* Assessed on narrow-band imaging only

** P values results from χ^2 (comparison between SSA/Ps versus HPs)

SSA/P: sessile serrated adenoma/polyp, HP: hyperplastic polyp, VPI: vascular pattern intensity, HR-WLE: high resolution white light endoscopy, NBI: narrow-band imaging, CI: confidence interval

Validation set: interobserver variability

The interobserver agreement regarding the endoscopic features on HR-WLE and NBI among all 5 observers is listed in table 3. With both modalities, the best agreement was obtained for *cloud-like surface*, namely moderate with HR-WLE (K= 0.52 95% CI 0.46-0.59) and substantial with NBI (k= 0.67 95% CI 0.60-0.73).

DISCUSSION

The introduction of advanced imaging techniques, such as NBI, autofluorescence imaging (AFI) and confocal endomicroscopy has led to many clinical studies focusing on the endoscopic appearance of conventional adenomas.[19-22] In contrast, studies systematically describing and characterizing the endoscopic features of SSA/Ps are scarce and often lack a systematic approach.[23,24] The current study provides a systematic validation of novel endoscopic features of SSA/Ps using HR-WLE and NBI assessed by international experts. We demonstrate that SSA/Ps harbor specific endoscopic features compared

Table 3. Validation set. Independent endoscopic predictors for SSA/P histology and corresponding interobserver agreement among 5 observers

	HR-WLE				NBI			
	Multivariate analysis*		Interobserver agreement		Multivariate analysis*		Interobserver agreement	
	OR (95% CI)	P value	Full agreement (%)	κ-value** (95% CI)	OR (95% CI)	P value	Full agreement (%)	κ-value** (95% CI)
(1) Indistinctive borders	3.11 (1.57-6.15)	0.001	39	0.38 (0.32-0.45)	2.38 (1.14-4.96)	0.021	59	0.57 (0.50-0.63)
(2) Cloud-like surface	2.65 (1.21-5.78)	0.015	62	0.52 (0.46-0.59)	4.91 (2.42-9.97)	<0.001	71	0.67 (0.60-0.73)
(3) Pit pattern IISSA/P	1.89 (0.74-4.85)	0.186	18	0.04 (−0.06-0.15)	1.04 (0.37-2.94)	0.941	38	0.10 (0.02-0.17)
(4) Dark spots inside the crypts	0.79 (0.35-1.77)	0.562	48	0.29 (0.22-0.36)	2.05 (1.02-4.11)	0.044	46	0.40 (0.33-0.47)
(5) Normal VPI	-		-	-	1.58 (0.79-3.14)	0.194	34	0.34 (0.27-0.41)
(6) Irregular shape	1,57 (0.74-3.31)	0.237	37	0.40 (0.33-0.46)	3.17 (1.59-6.29)	0.001	34	0.38 (0.31-0.44)

*Adjusted for polyp size (size group ≥ 10 mm)

** Fleiss Kappa (more than 2 observers)

HR-WLE: high resolution white light endoscopy, NBI: narrow-band imaging SSA/P: sessile serrated adenoma/polyp, HP: hyperplastic polyp, VPI: vascular pattern intensity, OR: Odds ratio, CI: confidence interval

Table 4. Validation set. Sensitivity, specificity and diagnostic accuracy of the independent predictive SSA/Ps features assessed with HR-WLE and NBI

	HR-WLE % (95% CI)		NBI % (95% CI)			
	Indistinctive borders	Cloud-like surface	Indistinctive borders	Cloud-like surface	Dark spots inside the crypts	Irregular shape
Sensitivity	73 (66-80)	58 (50-66)	65 (57-73)	66 (58-73)	58 (50-66)	78 (71-84)
Specificity	65 (57-73)	79 (71-85)	79 (72-85)	86 (80-91)	71 (64-78)	69 (62-76)
Accuracy	73 (67-77)	68 (63-73)	71 (66-76)	76 (71-81)	65 (59-70)	74 (68-78)

HR-WLE: High resolution white light endoscopy, NBI: narrow-band imaging, CI: confidence interval

Table 5. Validation set. Sensitivity, specificity and accuracy of HR-WLE and NBI for serrated lesions exhibiting either none or all independent SSA/P features*

	HRE		NBI	
	Fraction	%, (95% CI)	Fraction	%, (95% CI)
Sensitivity	71/95	75 (65-82)	42/47	89 (77-95)
Specificity	89/112	79 (71-86)	66/69	96 (88-99)
Accuracy	160/207	77 (71-82)	108/116	93 (87-96)

Of the 300 serrated lesions, 207 lesions (95 SSA/Ps and 112HPs) on HR-WLE and 116 lesions (47 SSA/Ps and 69 HPs) on NBI were eligible for differentiation. * All features HR-WLE = 1) indistinctive borders and 2) cloud-like surface. All features on NBI = 1) Indistinctive borders 2) cloud-like surface 3) irregular shape 4) dark spots inside the crypts. HR-WLE: High resolution white light endoscopy, NBI: narrow-band imaging, CI: confidence interval

with HPs and we are able to predict the histology of a subset of serrated polyps with NBI with a high diagnostic accuracy.

Strengths of this study include the systematic study approach, the introduction of novel endoscopic features and the participation of international experts from various continents with different expertise. Moreover, the introduced features are easy to assess without the necessity of a magnifying endoscope, allowing a widespread implementation in a general practice setting. Our study has several limitations. First, the endoscopic images were assessed post-hoc rather than in real-time and there was a selection bias as only high quality images were selected. In a real-time situation, optimal visualization of polyps is not always possible and these lesions are consequently not evaluated in this study. However, also in the present study almost one third of all images were assessed as having moderate or poor quality by the different observers. A second potential shortcoming is that endoscopic features were postulated and formulated by the relatively small number of 2 endoscopists and one pathologist. Although this initial process can be considered as somewhat subjective, some of these features were compatible with features described by other research groups.[24,25] Moreover, we were able to validate these characteristics among various endoscopists from different international hospitals.

Finally, it can be discussed whether our results can be extrapolated to the general population as all polyps were derived from patients with serrated polyposis syndrome. We believe, however, that SSA/Ps in these patients are expressing a similar phenotype compared to SSA/Ps encountered in nonselected patients.

Four features were independently associated with SSA/P histology, a *cloud-like surface* and *indistinctive borders* were predictive features on both HR-WLE and NBI, whereas *dark spots* and an *irregular shape* were predictive characteristics solely on NBI. A *cloud-like surface*, defined as a bumpy, soft looking nodular surface and *indistinctive borders* were present in more than half of all SSA/Ps. Accordingly, Tadepalli et al. observed a focal, subtle irregularity or bumpiness to the mucosal surface in almost one third of all SSA/Ps.[25] Furthermore, a previous study from Japan reported that SSA/Ps possess a more granular surface and had vaguer borders compared to HPs.[24] *Dark spots or dots inside the crypts* were present in two third of all SSA/Ps under NBI. A recent Japanese study introduced a novel pit pattern as predictive feature for SSA/Ps; *Type II-0*.[26] The pits of this *Type II-O* pattern are wider and more rounded in shape and the authors hypothesized that an overproduction of mucin could be the cause of this phenomenon. Interestingly, the enclosed magnified images of the mentioned study suggest that these wider pits might be the same pits we observe as black dots on non-magnified NBI images.

The interobserver agreement regarding the assessed features was, except for *irregular shape*, better for NBI than for HR-WLE. On NBI, a substantial interobserver agreement was obtained for a *cloud-like surface* (κ=0.67). This is in agreement with the study of Tadepalli et al., that also demonstrated a substantial interobserver agreement for a nodular/cloud-like surface amongst just 2 observers (κ=0.8).[25] The interobserver agreement of the other endoscopic features ranged from moderate to slight. Although these last figures seem unsatisfactorily, one has to bear in mind that the endoscopists received only a minimal training. By gaining knowledge and experience with these specific features the interobserver agreement will likely increase.

Accurate differentiation of lesions during colonoscopy has the advantage that on-site decisions can be made. Although one could argue that complete resection is needed for all detected lesions, it seems likely that in general practice endoscopists compromise for time, costs and risks. Adequate recognition of SSA/Ps might aid endoscopists in selecting a polypectomy technique which more likely results in a complete resection (e.g. endoscopic mucosal resection), while HP-appearing lesions can be removed with relatively lower risk techniques. A second potential advantage is that differentiation of polyps could facilitate endoscopists in their decision to leave suspected distal diminutive (< 6mm) HPs in situ because these are generally considered as benign lesions harboring no malignant potential.[27] The advantage of this strategy is that it may reduce pathology costs, the workload for endoscopists and even the adverse event rate as less

unnecessary polypectomies are performed.[20] However this should not be accompanied by an increased risk of leaving potential neoplastic lesions in situ. Although SSA/Ps have a predilection for the proximal colon, a significant proportion of SSA/Ps also occur in the rectosigmoid and these lesions should not be left in place because they are endoscopically misinterpreted as HPs.[28] Therefore, if an endoscopist opts to leave a distal diminutive serrated appearing lesion in situ, an additional visual technique to differentiate between an HP and an SSA/P could be worthwhile in order to make a correct decision.

We estimated the diagnostic accuracy of all associated features of SSA/Ps. The highest diagnostic accuracy was obtained with the feature *indistinctive borders* on HR-WLE (73%, 95% CI 67-77), whereas the presence or absence of *a cloud-like surface* resulted in the highest accuracy on NBI (76%, 95% CI 71-81). As these accuracies of single features are clinical unacceptable for accurate on-site differentiation, the different associated endoscopic features were also used in combination. In this prediction model only serrated polyps that exhibited either none (considered as HP) or all independent significant SSA/P features (considered as SSA/P) were differentiated. Although we still observed a moderate sensitivity and accompanying accuracy for HR-WLE, a remarkable higher sensitivity and accuracy for NBI of, respectively, 89% and 93% was obtained. The drawback of this approach is that only a limited number of serrated polyps, namely 69% on HR-WLE and 39% on NBI, were eligible for differentiation. However in a real time setting this figure might be higher as the number of small distal HPs without any SSA/P feature is likely to be higher compared to that in our image evaluation set.[22]

To conclude, the current study demonstrates that SSA/Ps harbor specific endoscopic features compared to HPs. The presence of a *cloud-like surface*, *indistinctive borders*, *irregular shape* and *dark spots inside the crypts* are all features that might aid endoscopists in differentiating SSA/Ps from innocuous HPs during colonoscopy. Using a combination of these features, we were able to predict the histology of a subset of serrated polyps with NBI with a high diagnostic accuracy. Prospective studies of consecutive patients in a general setting are warranted to validate the endoscopic SSA/P features during real-time colonoscopy and to determine whether these features are a useful tool in a daily clinical setting.

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PART II

SERRATED POLYPOSIS SYNDROME

4

Incidence of colonic neoplasia in patients with serrated polyposis syndrome who undergo annual endoscopic surveillance

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ABSTRACT

Background and study aims

Patients with serrated polyposis syndrome (SPS) are advised to undergo endoscopic surveillance for early detection of polyps and prevention of colorectal cancer (CRC). The optimal surveillance and treatment regimen is unknown. We performed a prospective study to evaluate a standardized endoscopic treatment protocol in a large cohort of patients with SPS.

Methods

We followed a cohort of patients with SPS who received annual endoscopic surveillance at the Academic Medical Center in Amsterdam, the Netherlands from January 2007 through December 2012. All patients underwent clearing colonoscopy with removal of all polyps ≥3 mm. After clearance, subsequent follow-up colonoscopies were scheduled annually. The primary outcome measure was the incidence of CRC and polyps. Secondary outcomes were the incidence of complications and the rate of preventive surgery.

Results

Successful endoscopic clearance of all polyps ≥ 3 mm was achieved in 41/50 (82%) patients. During subsequent annual surveillance with a median follow-up time of 3.1 y (inter-quartile range, 1.5-4.3 y), CRC was not detected. The cumulative risks of detecting CRC, advanced adenomas, or large (≥ 10 mm) serrated polyps after 3 surveillance colonoscopies were 0%, 9%, 34%, respectively. Twelve patients (24%) were referred for preventive surgery; 9 at initial colonoscopy and 3 during surveillance. Perforations or severe bleedings did not occur.

Conclusions

Annual surveillance with complete removal of all polyps ≥3 mm with timely referral of selected high-risk patients for prophylactic surgery prevents the development of CRC in SPS patients without significant morbidity. Considering the substantial risk of polyp recurrence, close endoscopic surveillance in SPS seems warranted. www.trialregister.nl NTR2757

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers in the western world.[1] Until recently, the traditional adenoma-carcinoma sequence was considered to be the single pathway responsible for the development of CRC. During the last decade, however, an alternative pathway of colorectal carcinogenesis has been recognised, that is, the serrated neoplasia pathway.[2-8] This pathway involves the malignant transformation of serrated polyps into CRC, which, in turn, is associated with a poor prognosis.[8] Alongside the adenoma-carcinoma sequence, this serrated pathway also plays a significant role in patients with serrated polyposis syndrome (SPS).[9,10]

SPS is characterized by the presence of multiple serrated polyps spread throughout the colon and rectum and has been defined by the World Health Organization (WHO) as the presence of at least five serrated polyps proximal to the sigmoid colon, of which two measuring at least 10 mm in diameter (WHO criterion-1), any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with SPS (WHO criterion-2) and/or more than 20 serrated polyps spread throughout the colon (WHO-criterion-3).[11] The prevalence of SPS was recently estimated to be in between 1:151 and 1:294 among patients undergoing screening colonoscopy based on faecal immunochemical testing (FIT).[12,13] Another estimation of the prevalence of SPS (1:3000) was based on data in an average risk screening population undergoing flexible sigmoidoscopy.[14] This makes the condition rather common and more frequent in occurrence than other polyposis syndromes such as familial adenomatous polyposis (prevalence 1:13.000).[15]

SPS is associated with an increased personal and familial CRC risk. Previous published case series and cohort studies report CRC at first clinical presentation in up to 50% of SPS patients.[16-24] In addition, several retrospective studies showed that these patients can develop CRC under endoscopic surveillance (interval cancers).[16,19,20] Close endoscopic surveillance to prevent malignant progression of polyps has therefore been advised by several expert groups.[4,6,16,19,25] Also the US Multi-Society Task Force on Colorectal Cancer and the European Society of Gastrointestinal Endoscopy recently recommended a 1-year surveillance interval for these patients.[26,27]

However, due to a lack of prospective data, the optimal treatment approach with regard to surveillance intervals and polypectomy protocol is still largely unknown. As a consequence, patients with SPS might still be inadequately treated and consequently be at risk for developing CRC under surveillance. Conversely, over-treatment with unnecessary short surveillance intervals and removal of possible harmless lesions, which may result in complications, should also be avoided.

The aim of the present study was to prospectively evaluate a standardized endoscopic surveillance and polypectomy protocol in a consecutive cohort of SPS patients.

Primary outcome was the incidence of CRC and polyps and secondary outcomes the complication rate and the percentage of patients referred for preventive colorectal surgery.

METHODS

Patients and study design

Consecutive patients, aged ≥ 18 years, fulfilling SPS WHO criteria 1 or 3, who presented at the Academic Medical Centre (AMC), Amsterdam, the Netherlands, between January 2007 and December 2012 were enrolled. WHO criteria for SPS are: ≥ 5 histologically diagnosed serrated polyps proximal to the sigmoid colon, of which 2 measuring ≥ 10mm in diameter (WHO criterion 1), and/or ≥ 20 serrated polyps spread throughout the colon (WHO criterion 3).[28] The diagnosis of SPS was based upon all previously removed polyps at colonoscopies and/or surgery and those that were removed at clearing colonoscopy. As defined by the WHO, only histologically confirmed serrated polyps were counted for the diagnosis. Patients with a known germline mutation in the MutYH (biallelic) or APC gene, as well as patients with Lynch syndrome, inflammatory bowel disease (IBD) or a total proctocolectomy were excluded. Additionally, patients were excluded when they were not treated according to study protocol. Protocol violations were defined as surveillance interval longer than 2 years between 2 consecutive colonoscopies or the absence of an experienced colonoscopist (ED, KT and BB) during clearing colonoscopy.

The study had a prospective cohort design. This study was exempt from IRB review. Our IRB decided that the study did not apply to the requirements of the Medical Research Involving Human Subjects Act (WMO), as data were collected during routine care and no additional patient interventions were undertaken. Patients were verbally informed about the surveillance protocol. Considering that the study was exempt for IRB approval, written informed consent was not obtained. All authors had access to the study data and reviewed and approved the final manuscript. The study was registered on a publicly accessible website (Dutch Trial Register: NTR2757 www.trialregister.nl).

Endoscopic surveillance and treatment protocol

All SPS patients satisfying the WHO-criteria underwent initial clearing colonoscopy with complete removal of all polyps ≥ 3mm. When this was not possible during one procedure, an additional clearing colonoscopy was performed, preferably within 6 months. After clearance, subsequent follow-up colonoscopies were scheduled annually, again with complete removal of all polyps ≥ 3mm. Criteria for referring patients for preventive surgery were based on the multiplicity, size, type, and shape of lesions seen during colonoscopy.

Demographic data of patients concerning age, sex, personal history of CRC and family history of CRC were ascertained. Family history of patients was obtained by examining data from the department of Clinical Genetics or by examining general medical records. These records were based on self-reported information. During procedures, polyp variables were noted by an investigator or research nurse by using a case record form. When there was no nurse or research fellow present, variables were recorded in the digital colonoscopy report by one of study colonoscopists. Subsequently these data were linked with the pathology report and entered in a database. The following polyp parameters were documented; size, location, morphology and polypectomy technique. Complications were defined as perforations or post-procedure bleedings resulting in a hospital admission or repeat colonoscopy for haemostasis within 30 days after colonoscopy.

All clearing colonoscopies were performed by 3 endoscopists (ED, KT and BB) specialized in polyposis syndromes and with an experience of more than 1000 colonoscopies. Procedures were performed using standard or high-resolution white light endoscopy (HR-WLE) at a dedicated endoscopy program. A subset of consecutive patients underwent a tandem colonoscopy with HR-WLE and narrow-band imaging (NBI) as part of different studies comparing polyp miss rates of both imaging modalities.[29] Apart from these procedures, advanced imaging techniques for the detection of polyps (i.e. chromoendoscopy) were not used.

Patients were prepared with a standard bowel preparation, including a 4 L polyethylene glycol (PEG) solution or a 2 L hypertonic PEG solution with an additional 2-4 L of transparent fluids and a low fibre diet. Procedures were performed under conscious sedation with midazolam and/or fentanyl or under propofol when indicated. Cecal intubation was confirmed by documentation of the cecal landmarks (cecal valve, appendix orifice or intubation of the ileum). The proximal colon was defined as proximal to sigmoid (descending, transverse, ascending colon and cecum).

Outcomes

Primary outcome was the incidence of CRC and polyps during annual colonoscopic surveillance. Secondary outcomes were the complication rate and percentage of patients referred for preventive surgical resection.

Histopathological evaluation

Tissue specimens were routinely processed and reviewed by an expert gastrointestinal pathologist according to the Vienna criteria.[30] Serrated polyps were classified as hyperplastic polyp, sessile serrated adenoma/polyp with or without cytological dysplasia or traditional serrated adenoma based on histological criteria initially proposed by Torlakovic et al. which are now incorporated into the WHO classification for serrated

polyps.[11] A sessile serrated adenoma/polyp was defined by predominantly disorganized and distorted crypts, including dilation or branching of the basal portion of the crypt that often appears as a "boot" or "L" shape. Traditional serrated adenomas were defined by a protuberant or pedunculated growth pattern with distorted villiform configurations with columnar cells having abundant eosinophilic cytoplasm or centrally located elongated nuclei. When it was impossible to differentiate between the different serrated subtypes e.g. due to poor orientation or severe cauterisation artefacts, the lesion was classified as hyperplastic polyp. Advanced adenomas were adenomas ≥ 10 mm, with villous structure or with high-grade dysplasia.

Statistical analysis

Normal distributed variables are presented as means (±standard deviation), variables with skewed distribution are presented as median (interquartile range). Categorical variables are presented as frequencies (%). The cumulative probability of events (CRC, advanced adenomas and serrated polyps ≥ 10mm) during the study period was estimated with the Kaplan-Meier method, according to the surveillance colonoscopy number. Individuals where were censored at their last surveillance colonoscopy. Statistical analysis was performed using SPSS 20.0 (IBM Corporation, Somers, NY, United States).

RESULTS

Study flow

Figure 1 details the flow of patients throughout the study period (January 2007-December 2012). A total of 78 consecutive patients with SPS presented at our centre. Fourteen patients were excluded because of protocol violations (n=9), concomitant IBD (n=3) or Lynch syndrome (n=2). Protocol violations included the following: 1) absence of trained endoscopist at clearing colonoscopy (n=7) and 2) surveillance interval longer than 2 years between two consecutive colonoscopies (n=2). Another 14 (18%) patients were diagnosed with CRC at the time of initial presentation during the study period. The remaining 50 patients underwent clearing colonoscopy with the intention to remove all polyps ≥ 3mm. This was achieved in 41 patients (82%), whereas the other 9 (18%) patients were referred for prophylactic surgery because of an endoscopically untreatable number of polyps.

Endoscopic treatment and surveillance

The 41 patients who were successfully cleared from all polyps ≥ 3mm entered the annual endoscopic surveillance programme. These 41 patients belong to 39 families, including two sisters and a sister and a brother. Baseline demographics and colonoscopy details

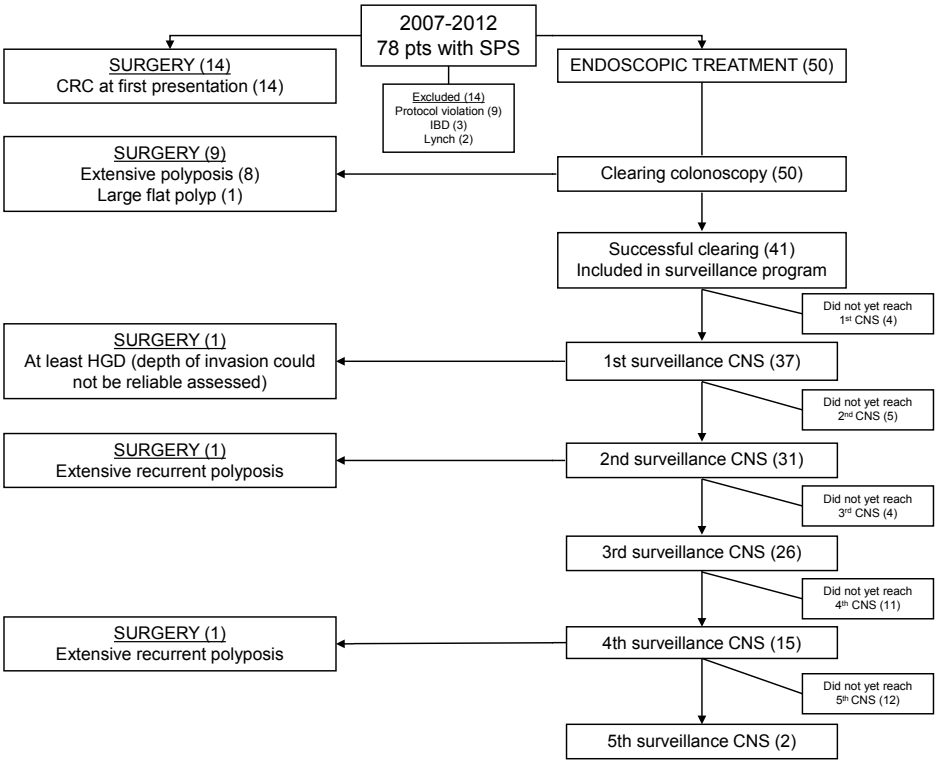


Figure 1. Flow of patients throughout the study period. 78 patients with SPS were identified. 14 patients were excluded because of protocol violations, IBD or Lynch syndrome. Another 14 (18%) patients were diagnosed with CRC at the time of initial presentation. The remaining 50 patient underwent clearing colonoscopy with intention to remove all polyps ≥ 3mm. This was achieved in 41 patients (82%) whereas 9 (18%) patients were referred for preventive surgery because of an endoscopically untreatable number of polyps. During subsequent surveillance, another 3 patients were referred for prophylactic surgery. CNS: colonoscopy

are displayed in table 1. The mean age at start of the surveillance program was 57 years (± SD 10) and 24 (59%) were male. Colonic resection prior to the first clearing colonoscopy was performed in 15 patients (37%) because of previous CRC (n=13) or extensive polyposis (n=2). Consequently, 26 patients underwent clearing of an intact colon, 6 patients of the remaining colon proximal to the rectosigmoid, 8 patients of the remaining distal colon and 1 patient of the remaining colon after a proximal segmental resection. A research nurse/investigator was present during 126/203 (62%) of all colonoscopies to record polyp variables. During the remaining procedures, variables were noted in the digital endoscopy report by one of study endoscopists.

Table 1. Baseline characteristics of SPS patients included in surveillance program (n=41)

Mean±SD age at diagnosis SPS in y (range)	56.5 ±10 (27-76)
Mean±SD age at inclusion surveillance program in y (range)	57.5 ±10 (27-76)
Male (%)	24 (59)
WHO SPS classification	
I	6 (15)
III	21 (51)
Combined (I +III)	14 (34)
Prior CRC (%)	13 (33)
Mean±SD age at diagnosis in y (range)	54 ± 6 (41-61)
Proximal	5
Distal	8
Prior colonic surgery (%)	15 (37)
Partial colonic resection	11
Subtotal colectomy with ileorectal anastomosis	4
First degree relative with CRC (%)	11 (27)
Total number of clearing colonoscopies	84
Median number of clearing colonoscopies per patient (range)	2 (1-4)
Total number of surveillance colonoscopies	119
Median number of surveillance colonoscopies per patient (range)	3 (0-7)
Median follow-up after first clearing colonoscopy in y (range)	3.6 (0-5.3)
Median follow-up after last clearing colonoscopy in y (range)	3.1 (0-5.3)
Median interval between surveillance colonoscopies in y (range)	1.0 (0.6-1.7)

y: years, SD: standard deviation, CRC: colorectal cancer

Clearing colonoscopy

The median number of colonoscopies needed to clear the colon from polyps ≥ 3 mm was 2 (IQR 1-3, range 1-4). A total of 773 polyps were detected; 441 (57%) hyperplastic polyps, 242 (31%) sessile serrated adenomas/polyps and 90 (12%) conventional adenomas. Detailed polyp characteristics are outlined in Table 2. The median number of polyps removed at clearing colonoscopy was 16 (range 0-72). At least one advanced adenoma or large (≥10mm) serrated polyp was detected in 11 (29%) and 21 (51%) patients respectively (Table 3).

Follow-up: surveillance colonoscopies

The median follow-up from last clearing colonoscopy until last surveillance colonoscopy of all 41 patients was 3.1 years (IQR 1.5-4.3, range 0-5.3 y), with a median of 3 (IQR 2-4, range 1-4) surveillance colonoscopies. The median interval between surveillance colonoscopies was 1.0 year (range 0.6-1.7).

Table 2. Prevalence and number of polyps removed at clearing and each surveillance colonoscopy

	Clearing n = 41	1st surv. N=37	2nd surv. n=31	3rd surv. n= 26	4th surv. n=15	5th surv. n=2
No. of pts with CRC (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No. of pts ≥ 1 polyp (%)	38 (93)	35 (95)	27 (87)	23 (88)	12 (80)	2 (100)
Median no. polyps (range)	16 (0-72)	5 (0-22)	4 (0-20)	4 (0-15)	1 (0-20)	2 (1-3)
Median size of polyps (range)	5 (3-25)	4 (3-15)	4 (3-12)	4 (3-10)	3 (3-10)	4 (3-5)
No. of pts ≥ 1 serrated polyp (%)	38 (93)	34 (92)	27 (87)	22 (81)	11 (73)	2 (100)
No of pts ≥ 1 serrated polyp ≥ 10 mm (%)	21 (51)	4 (11)	5 (16)	3 (12)	1 (7)	0 (0)
Median no. serrated polyps (range)	12 (0-72)	4 (0-19)	4 (0-20)	3 (0-14)	1 (0-19)	2 (1-3)
Median size of serrated polyps (range)	5 (3-25)	4 (3-15)	4 (3-12)	4 (3-10)	4 (3-10)	4 (3-5)
No. of pts ≥ 1 adenoma (%)	23 (56)	15 (41)	15 (48)	13 (50)	7 (47)	0 (0)
No. of pts ≥ 1 advanced adenoma (%)	11 (27)	2 (5)	1 (3)	0 (0)	0 (0)	0 (0)
Median no. adenomas (range)	1 (0-11)	0 (0-10)	0 (0-3)	0.5 (0-4)	0 (0-4)	0 (0-0)
Median size of adenomas (range)	4 (3-25)	4 (3-10)	3 (3-10)	3 (3-5)	3 (3-4)	0 (0-0)

Surv: surveillance, No.: number, Pts: patients

The incidence and number of polyps detected at each surveillance colonoscopy is displayed in Table 2. Polyp characteristics are outlined in Table 3. A total of 37 patients underwent at least one surveillance colonoscopy; none of them developed CRC during follow-up. During 119 surveillance colonoscopies, 575 polyps were detected; 346 (60%) hyperplastic polyps, 135 (23%) sessile serrated adenomas/polyps and 94 (16%) conventional adenomas. Traditional serrated adenomas were not diagnosed. Polyps were detected in at least 80% of patients at each follow-up time point. Most lesions were detected at first surveillance colonoscopy, with a median number of 5 polyps (range 0-22). The range of detected polyps varied greatly among patients; considering all surveillance colonoscopies (except number 5), a minimum difference of 15 polyps was observed between the patient with the lowest and the highest number of polyps.

During surveillance, advanced adenomas were detected in 3/37 (8%) patients. The median interval between last clearing colonoscopy and the detection of these advanced adenomas was 13 months (range 12-25 months). This included one tubular adenoma with high-grade dysplasia, one tubulovillous adenoma and one large (10 mm) tubular adenoma. The calculated cumulative risk of detecting at least one advanced adenoma after 3 surveillance colonoscopies was 9% (Table 4 and figure 2). When analysing this risk separately for patients with and without a history of CRC, the cumulative risk was 8% and 9%, respectively. Large serrated polyps (hyperplastic polyps or sessile serrated adenomas/polyps ≥ 10mm) were detected in 11/37 (30%) patients. The median interval between last clearing colonoscopy and detection of large serrated polyps was 21

Table 3. Histology, size, location and dysplasia of detected polyps at clearing and surveillance colonoscopies

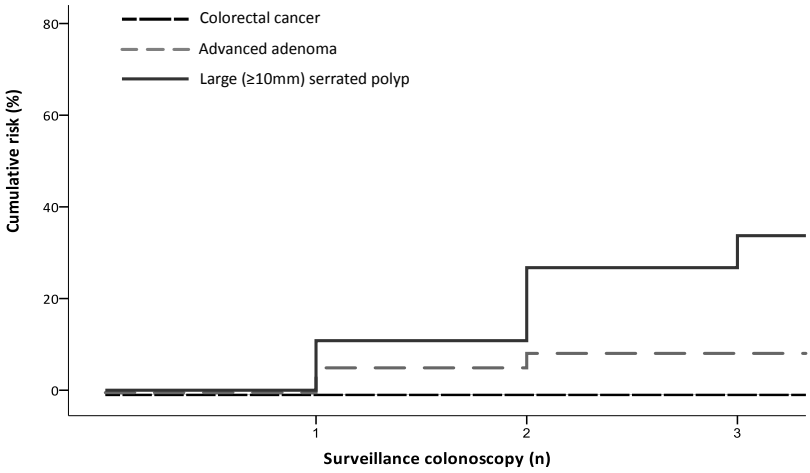
	HP	SSA/P	Adenoma	Total
Clearing colonoscopy: no. of polyps	441	242	90	773
Size				
3-5	356 (81)	96 (40)	63 (70)	515 (67)
6-9	61 (14)	59 (24)	15 (17)	135 (17)
≥ 10	24 (5)	87 (36)	12 (13)	123 (16)
Location *				
Proximal	208 (47)	188 (78)	63 (70)	459 (59)
Distal	159 (36)	42 (17)	18 (20)	219 (28)
Dysplasia				
LGD	0 (0)	7 (3)	86 (96)	93 (12)
HGD	0 (0)	0 (0)	4 (4)	4 (1)
Surveillance colonoscopies: no. of polyps	346	135	94	575
Size				
3-5	298 (86)	93 (69)	87 (93)	478 (83)
6-9	39 (12)	29 (21)	5 (5)	75 (13)
≥ 10	7 (2)	13 (10)	2 (2)	22 (4)
Location				
Proximal **	176 (51)	107 (79)	79 (84)	362 (63)
Distal	144 (42)	16 (12)	13 (14)	173 (30)
Dysplasia				
LGD	0 (0)	14 (10)	93 (99)	107 (19)
HGD	0 (0)	0 (0)	1 (1)	0 (0)

*Specified for 678/773 polyps, ** Specified for 535/575 polyps HP: hyperplastic polyp, SSA/P: sessile serrated adenoma/polyp, LGD: low grade dysplasia HGD: high grade dysplasia

Table 4. Calculated cumulative risk (%) of detecting CRC or advanced polyps after 3 surveillance colonoscopies*. Subgroup analysis was performed for patients with and without a history of CRC prior to the start of the study.

	All patients (n=37)	With prior CRC (n=12)	Without prior CRC** (n=25)
Mean ±SD age in years	57 ±10	60 ±8	56 ±12
Male sex (%)	21 (57)	6 (50)	15 (60)
Colorectal cancer (95% CI)	0 (0-0)	0 (0-0)	0 (0-0)
Advanced adenoma (95% CI)	9 (0-17)	8 (0-23)	9 (0-20)
Serrated polyp ≥ 10 mm (95% CI)	34 (15-48)	27(3-45)	38 (13-56)

*Cumulative risk was analysed by Kaplan-Meier survival analysis. Patients who did not reach 3rd surveillance colonoscopy were censored from their last surveillance colonoscopy.
** 23/25 patients had an intact colon



Colorectal cancer			
At risk (n)	37	31	26
Event (n)	0	0	0
Cumalative risk (%)	0	0	0
Advanced adenoma			
At risk (n)	37	30	24
Event (n)	2	1	0
Cumalative risk (%)	5	9	9
Large (≥10mm) serrated polyp			
At risk (n)	37	28	21
Event (n)	4	5	2
Cumalative risk (%)	11	27	34

Figure 2. Kaplan-Meier curves for detecting colorectal cancer (CRC), advanced adenomas and large (≥ 10 mm) serrated polyps during annual surveillance.

months (range 12-39 months). The calculated cumulative risk of detecting at least one large serrated polyp after 3 surveillance colonoscopies was 34% (Table 4 and figure 2). When analysing this risk separately for patients with and without a history of CRC, the cumulative risk was 27% and 38%, respectively. Detailed information regarding the number of patients at risk at each surveillance colonoscopy with corresponding cumulative risk estimates are summarized in figure 2.

Prophylactic surgery after successful colonic clearance of polyps was considered to be indicated in 3/37 (8%) patients. All three patients had an intact colon prior to start of the surveillance program. A 62-year old male patient underwent 4 previous clearing colonoscopies. During these procedures 25 polyps were removed, including 3 advanced adenomas. At first surveillance colonoscopy (14 months after last clearing colonoscopy), a proximal tubular adenoma of 10mm with at least high-grade dysplasia was detected, which was removed en-bloc by endoscopic mucosal resection (EMR). Unfortunately the

depth of invasion into the submucosal layer could not be reliable assessed by a panel of pathologists. For this reason and because of the large burden of recurrent polyps, a subtotal colectomy with an ileorectal anastomosis was performed. The resected specimen showed 27 serrated polyps. No malignant or dysplastic polyps were observed. In two male patients (64 and 54 years old) endoscopic treatment was no longer considered safe and feasible because of recurrent extensive polyposis. In both patients, numerous small and large lesions were seen throughout the entire colon. A subtotal colectomy with an ileorectal anastomosis was performed. The surgical resection specimen showed more than 100 serrated polyps (all smaller than 10 mm) without histological dysplasia in the first patient, and more than 200 serrated polyps (all smaller than 12 mm) without histological dysplasia in the second patient.

Complications

Perforations or post-procedural bleedings resulting in a hospital admission or repeat colonoscopy for haemostasis therapy did not occur during 84 clearing and 119 surveillance colonoscopies. One patient was admitted within 24 hours after colonoscopy with pneumococcal bacteraemia of unknown origin. The patient was treated with antibiotics and admitted for 3 days with uneventful recovery. Two other patients presented to the emergency room. The first patient had complaints of minor rectal blood loss and fever. Laboratory findings showed normal haemoglobin and leukocyte values. The second patient presented with abdominal pain without perforation, but with signs of inflammation. A post polypectomy syndrome was suspected. Both patients were managed conservatively without admission to the hospital.

Surgery

During the study period, 23 patients (median age 60 y, 43% male) were referred for surgery upon diagnosis and consequently not entered the endoscopic treatment protocol. Indications for surgery were; (i) CRC (n=14), (ii) extensive polyposis (n=8) and an endoscopically unresectable adenomatous polyp (n=1). Seven of the 8 patients with extensive polyposis underwent a subtotal colectomy with ileorectal anastomosis. The median number of polyps in the resection specimens of these patients was 35 (range 20-93); no carcinomas were detected.

DISCUSSION

In the present study, we prospectively evaluated the outcomes of a standardized endoscopic treatment protocol in a large cohort of SPS patients with regard to endoscopic findings, complications and prophylactic surgery rate. We demonstrate that annual

endoscopic surveillance with removal of all polyps ≥ 3 mm with timely referral of selected high-risk patients for prophylactic surgery prevents the development of CRC in SPS patients without significant morbidity. Considering the substantial risk of polyp recurrence in our cohort, close endoscopic surveillance seems warranted.

Our study has several strengths. All patients underwent a standardized predefined treatment protocol and were followed in a prospective manner. In addition, all clearing colonoscopies and most surveillance colonoscopies were performed by dedicated and experienced endoscopists specialized in polyposis syndromes. Several potential limitations should also be acknowledged. Due to the small sample size and relatively short follow-up period, results should be interpreted with caution as they may not be sufficiently representative for all patients with SPS. Also lack of certain clinical and sociodemographic data like obesity, smoking status and ethnicity can potentially limit the generalizability of our findings to other populations. Nonetheless, the present study is the largest prospective study available and the current findings add substantially to our understanding of the longitudinal CRC-risk of SPS patients under strict endoscopic surveillance. Another potential shortcoming of the study is that a subset of patients was diagnosed with SPS prior to the time-period of this study and consequently already received either endoscopic or surgical treatment. This might have affected the number of polyps detected at clearing colonoscopy. Another limitation is the fact that a proportion of patients underwent back-to-back colonoscopy because they were enrolled in studies comparing NBI with HRE. During these procedures, each colonic segment was inspected twice, which might have positively influenced our polyp detection rates. Lastly, as all patients were treated at a tertiary academic referral center with extensive expertise in the management of SPS, our findings cannot by default be extrapolated to general practice.

In a previous retrospective multicenter study from our group, we calculated a worrisome cumulative CRC-risk of 7% at 5 years in patients with SPS undergoing endoscopic surveillance.[16] Also Edelstein et al. recently reported a substantial incidence of interval CRCs (5%) in this patient group.[19] In contrast with the present study, screening intervals were not standardized in these studies which might have resulted in different recommended surveillance intervals and incomplete removal of all polyps. Moreover, since the clinical data of these studies dated back to 1982 and 2001, it is likely that the association between multiple serrated polyps and colonic neoplasia was not always made by endoscopists or underestimated. As a consequence, these patients might have been treated insufficiently with the development of CRC under surveillance in some of them. The present study reports the longest duration of prospective follow-up and shows that the actual CRC-risk is low in patients with SPS who undergo annual surveillance of the colon.

Considering the high polyp recurrence rate observed in our series, close endoscopic surveillance seems justified. Polyps were detected in at least 80% of patients at each sur-

veillance colonoscopy. Moreover, advanced adenomas, including one with high-grade dysplasia, and large serrated polyps were detected in 8% and 30% of patients during follow-up, respectively. The median interval between colonic clearing and the detection of these lesions was only 13 months for advanced adenomas and 21 months for large serrated lesions. Additionally, 2 (5%) patients developed such an extensive recurrent polyposis that endoscopic control of polyps was no longer considered safe and feasible (> 100 polyps were found in the surgical resection specimen). The detection of advanced lesions as well as the rapid recurrence of numerous polyps suggests that SPS is associated with an increased neoplastic growth and progression rate in at least a subset of patients. A future challenge will be to investigate whether it is possible to separate this subset of high risk patients from patients with a minimum risk of (recurrent) colonic neoplasia. This would allow for a more tailored endoscopic management with regard to surveillance intervals and preventive surgery. However, until distinctive molecular and genetic differences have been found and as long as we cannot predict CRC-risks in an assured manner, a strict surveillance regimen for all patients who fulfil the WHO criteria for SPS is recommended based on our findings.

With regard to the feasibility of our protocol, complete endoscopic clearing of all polyps ≥ 3 mm was achieved in 82%. Median number of polyps removed at clearing colonoscopy was 16 and more than 50% of patients had large serrated polyps. It seems therefore advisable that these clearing sessions are performed by endoscopists with experience in endoscopic mucosal resection (EMR) for complete and safe polyp removal. In addition, allowances should be made for sufficient procedure time, as the multiplicity of polyps and the use of advanced polypectomy techniques leads to longer procedure times.

Twelve patients (24%) (9 at initial colonoscopy and 3 during surveillance) underwent a preventive surgical resection. This decision for colectomy was made by an expert endoscopist based on the multiplicity, size, type, and shape of lesions seen during colonoscopy. We would like to emphasize that we did not use a standard cut-off point regarding the number of polyps because, in our opinion, the decision for a preventive colectomy needs to be individualized for each patient. In this respect, it is advisable to centralize endoscopic management of patients with SPS in institutions with experience in this field to ensure optimal treatment and follow-up.

The number of polyps found in the 2 of the 3 patients who underwent prophylactic surgery was much higher (> 100 polyps) than any of the polyp numbers found at any of the surveillance colonoscopies. This might suggest that endoscopy misses many polyps in patients with SPS. Although we cannot exclude that lesions were missed, it is important to realize that polyps seen during the last colonoscopy before surgery in these 2 patients were not removed, as the decision for surgery was made and these patients would undergo surgery anyway. At time of surgery these polyps were still in situ which

explains the relatively high number of polyps found in the resection specimen. In addition, polyps smaller than 3 mm were not removed or counted during endoscopy while these polyps were counted in the colonic resection specimens by the pathologist.

Concerning the removal of polyps, previous studies have shown that approximately 30% to 50% of all CRCs in patients with SPS arise via the serrated neoplasia pathway.[9,10] The other half presumably follows the traditionally adenoma-carcinoma sequence. In addition, it was shown that advanced neoplasia could be detected in polyps as small as 4 mm in SPS.[9] For this reason, removal of all type of polyps, including small lesions, seems advisable. On the other hand, over-treatment with unnecessary removal of possibly harmless lesions should be avoided. We chose to clear the colon from polyps ≥ 3 mm. Of note, 34% (339/993) of all removed lesions between 3-5 mm were adenomas or sessile serrated adenomas/polyps, suggesting that removal of these diminutive lesions might prevent malignant progression in SPS. Nonetheless, none of these lesions contained high-grade dysplasia or invasive cancer. Considering that patients with SPS have many diminutive lesions, leaving these lesions in situ until they reach a certain size (i.e. 6 mm) would substantially reduce the workload of the endoscopist and decrease the pathology costs, but the safety of this approach should first be prospectively assessed.

In conclusion, results from this study suggest that patients with SPS have a low risk of developing CRC when they undergo annual surveillance of the colon with removal of polyps ≥ 3 mm. Additional follow-up studies are required to evaluate whether endoscopic surveillance can be performed at longer time intervals and further studies are needed to identify high risk subgroups requiring prophylactic surgery. In addition, although removal of larger polyps seems necessary in any case, future studies should evaluate the safety of leaving diminutive lesions in situ as this would certainly save time and avoid over-treatment.

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5

Narrow-band imaging for the detection of polyps in patients with serrated polyposis syndrome: a multicenter, randomized, back-to-back trial

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ABSTRACT

Background and study aims

Serrated polyposis syndrome (SPS) is characterized by the presence of multiple serrated polyps spread throughout the colon. Patients with SPS are considered to be at risk for colorectal cancer (CRC) and are advised to undergo endoscopic surveillance. Narrow-band imaging (NBI) may improve the detection of polyps during these surveillance colonoscopies. The aim of study was to compare polyps miss-rates between NBI and high-resolution white light endoscopy (HR-WLE).

Methods

This study had a cross-over design. Patients underwent modified back-to-back colonoscopy with HR-WLE and NBI performed by the same endoscopist in 4 tertiary referral institutions. Patients were randomly allocated to one of the 2 arms: (1) HR-WLE group: first inspection with HR-WLE followed by a second inspection with NBI; 2) NBI group: first inspection with NBI followed by a second inspection with HR-WLE. The primary outcome was the polyp miss-rate of HR-WLE and NBI.

Results

In the HR-WLE group, 116 polyps were detected during the first inspection. Second inspection with NBI added 47 polyps, resulting in an overall polyp miss-rate of HR-WLE of 29% (95% confidence interval 22-36). In the NBI group, a total of 128 polyps were detected during the first inspection. Subsequent inspection with HR-WLE added 32 polyps, resulting in an overall polyp miss-rate of NBI of 20% (95% confidence interval 15-27). Comparison of the overall polyp-miss rate of HR-WLE and NBI shows no significant difference (p=0.065).

Conclusions

The results of our study suggest that NBI does not reduce polyp miss-rates in patients with SPS compared with HR-WLE. Further multinational studies with larger number of patients are warranted to verify these results.

INTRODUCTION

Serrated polyposis syndrome (SPS), formerly known as hyperplastic polyposis syndrome, is characterized by the appearance of multiple serrated polyps spread throughout the entire colon. Besides multiple serrated polyps, adenomas are also frequently observed. The syndrome has been defined by The World Health Organization (WHO) as at least five histologically confirmed serrated polyps proximal to the sigmoid with at least two being 10 mm in diameter or larger (WHO criterion 1), any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with SPS (WHO criterion 2) or more than 20 serrated polyps spread throughout the colon (WHO criterion 3).[1]

Patients with SPS are considered to be at increased risk for CRC.[2-5] Studies have shown that cancers detected in patient with SPS are generated by both the serrated neoplasia pathway as well as the traditional adenoma-carcinoma sequence.[6] This implies that in these patients all types of polyps should be considered clinically relevant as they may act as precursor lesions for CRC. In an effort to prevent CRC, patients are advised to undergo regular endoscopic surveillance with removal of these polyps.[7-9] However, data suggest that in some patients with SPS, even if they undergo endoscopic surveillance, CRC still develops.[2,4] These so-called interval cancers may originate from lesions that are not detected with conventional colonoscopy techniques.

Narrow-band imaging (NBI) is a technique that has been developed to enhance the detection of GI lesions.[10] By the use of light of a shorter wavelength the mucosal pit pattern and microvasculature of lesions are highlighted which may improve visualization. Previous studies have shown that NBI was helpful for the detection of hyperplastic polyps.[11,12] Furthermore, in a recent pilot study in patients with SPS, we demonstrated that NBI significantly reduced polyp-miss rates when compared with HR-WLE.[13] However, this pilot study was performed by a single endoscopist in a single academic center. To confirm our results, we conducted the present randomized multicenter study performed by multiple endoscopists. The primary aim was to compare polyp miss-rates of HR-WLE and NBI in patients with SPS.

METHODS

Patients

Between January 2011 and March 2013, consecutive patients with SPS scheduled for colonoscopy in 4 medical centers in the Netherlands were invited for participation. Patients meeting criteria 1 or 3 of the WHO criteria for SPS, defined as ≥ 5 serrated polyps proximal to the sigmoid colon of which 2 are greater than 10 mm in diameter (WHO

criterion-1) or ≥ 20 serrated polyps spread throughout the colon (criterion-3) were eligible for enrolment.[1] Patients were excluded in case of inflammatory bowel disease, a total colectomy, age < 18 years and an inadequate bowel preparation (Boston bowel preparation scale < 6).[14] At closure of the study, patients were excluded from data analysis in case an endoscopist performed less than 4 study procedures. The institutional review board (IRB) of all hospitals approved the study protocol, and written informed consent was obtained from all patients before inclusion. The study was registered at www.trialregister.nl: trial number: NTR2497

Study design

This study had a randomized cross-over design (figure 1). Patients underwent modified back-to-back colonoscopy with HR-WLE and NBI performed by the same endoscopist. Patients were randomly allocated to one of the 2 arms: (1) HR-WLE group: first inspection with HR-WLE followed by a second inspection with NBI; 2) NBI group: first inspection with NBI followed by a second inspection with HR-WLE. Polyps detected during the first examination were removed immediately. Consequently, polyps detected during the second examination were classified as missed polyps. All polyps ≥ 3 mm were removed. Polyps smaller than 3mm in size were not removed and not counted in the miss-rate. The order in which patients received both techniques was determined by block

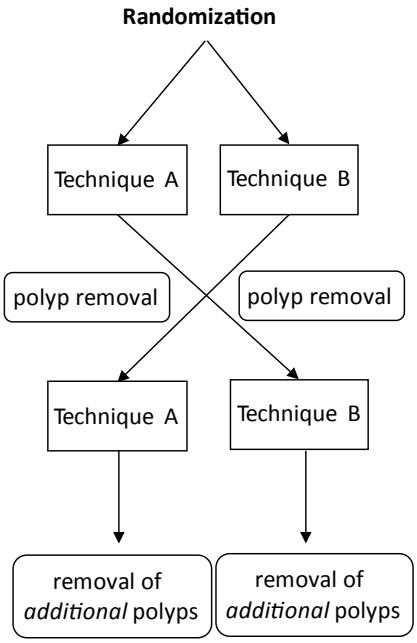

Figure 1. Randomized-cross over design with removal of polyps (adapted from Van den Broek et al.[18])

randomization (block sizes of 4) with stratification by endoscopist. Randomization was performed by opening a sealed opaque envelope once the cecum, or neo-terminal ileum in case of right hemicolectomy, was reached and bowel prep assessed as adequate.

The colon was divided into 5 segments (cecum, ascending, transverse, descending and rectosigmoid). During withdrawal, the 5 segments were sequentially inspected with the first imaging technique, followed by a re-examination with the second imaging technique. In case no other landmarks (e.g. liver shining through the colonic wall) were available, random biopsies were taken to mark the end of the first examination. For all polyps, size (measured with an open biopsy forceps), location, morphology (Paris classification[15]) and polypectomy technique was noted on a case record form by a research fellow or nurse. Withdrawal time during both examinations was recorded by a stopwatch. Time needed for polypectomies was subtracted. The proximal colon was defined as proximal to the sigmoid (cecum, ascending, transverse and descending colon). A maximum study time of 1.5 hours was set for withdrawal; otherwise the procedure could become too inconvenient for the patient. After passing this time limit, the study procedure was terminated. Polyps removed after stopping the study protocol were not used for data analysis.

Endoscopic equipment

All procedures were performed with CF-H180 AL endoscopes containing NBI (Olympus, Tokyo, Japan) in combination with an Evis Exera II processor (Olympus, Tokyo, Japan). During NBI, a narrow-band light filter is placed in front of the lamp located in the light source. During the endoscopic procedures, endoscopists could easily switch between HR-WLE and NBI, pressing a button on the endoscope.

Endoscopic procedure

Patients were prepared by 4 L polyethylene glycol solution (PEG) (Kleanprep; Norgine bv, Amsterdam, the Netherlands) or 2 L of PEG solution containing ascorbic acid (Moviprep; Norgine bv, Amsterdam, the Netherlands) with an additional 2 L of liquid fluids. Procedures were performed under conscious sedation with midazolam and/or fentanyl or under deeper sedation (propofol) when indicated. After advancing the endoscope (in HR-WLE mode) to the cecum or neo-terminal ileum, the endoscopist assessed the quality of the bowel preparation. No attention was paid to polyps during insertion and lesions were only removed during withdrawal. Quality of bowel preparation was assessed by the validated Boston Bowel Preparation Scale (BBPS), which includes a four-point scoring system (0 to 3) applied to each of three segments of the colon (right, transverse and left) and ranges from 9 (excellent) to 0 (very poor).[14] In individuals with a history of colonic surgery, a default score of 2 was applied for each missing colonic segment. Patients were not included in case of a poor bowel preparation (BBPS < 6). Cecal/neo-

terminal ileum intubation was confirmed by identification of the appendiceal orifice or/ and ileocecal valve or ileum and photographed.

Endoscopists

All colonoscopies were performed by experienced endoscopists, each having performed over 1000 colonoscopies. All endoscopists had performed a minimum of 30 NBI-colonoscopies prior to the start of the study.

Histopathology

All tissue specimens were reviewed by one single pathologist (SvE) with a special interest in gastrointestinal pathology. Specimens were classified according to the Vienna criteria of gastrointestinal epithelial neoplasia.[16] Serrated polyps (hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenomas) were classified according to WHO 2010 classification of tumors of the digestive system.[1] In case in it was not possible to differentiate between the different serrated subtypes due to poor orientation, severe artefacts or poor sampling, the serrated polyp was classified as hyperplastic polyp.

Outcomes

The primary outcome of the study was the polyp miss-rate of HR-WLE (second inspection with NBI) and NBI (second inspection with HR-WLE). Additional analyses were performed to identify factors associated with polyp miss-rates.

Statistics

Mean with standard deviation (SD) was used in case of a normal distribution and compared with independent t-rest. Median with interquartile range (IQR) was used for variables with a skewed distribution and compared with the Wilcoxon-rank sum test. Categorical variables are presented as frequencies (%) and compared with the chi-square test. Polyp miss-rates were defined as the number of polyps detected during the second-inspection divided by the total number of polyps detected during the first and second examination and compared with the chi-square test. Associations between polyp characteristics and miss-rates were evaluated with logistic regression analysis, expressed in odds ratios.

Sample size

Our previous pilot study showed a polyp miss-rate of 36% with HR-WLE and 10% with NBI in patients with SPS. To measure a conservative difference of 15% between NBI and HRE with a power of 80% and a significance level of 0.05, a minimum of 310 polyps was required. In a previous study of SPS patients undergoing annual surveillance we found median number of 6 polyps per SPS patient. The calculated sample size was therefore 52 patients.

RESULTS

Patient characteristics

A total of 52 eligible patients with SPS consented for participation in the study and underwent tandem colonoscopy. After closure of the study, one patient was excluded for data analysis as the endoscopist who performed the procedure performed less than 4 study procedures. Table 1 displays the clinical characteristics of the 51 included patients. Groups were comparable with respect to age, gender, prior colectomy, prior CRC, withdrawal time and number of previously removed polyps.

Colonoscopies were performed by 5 endoscopists in 4 different institutions. The number of procedures performed per individual endoscopist ranged from 6 to 18.

Table 1. Baseline demographics (n=51)

	First technique		P value
	HR-WLE (n=25)	NBI (n=26)	
Mean age, y (SD)	61 (9)	58 (10)	.346
Male (%)	15 (60)	10 (38)	.124
Personal history of CRC (%)	9 (36)	8 (31)	.692
Partial colectomy (%)	10 (40)	9 (35)	.691
WHO classification			.210
WHO 1 *	14 (56)	10 (38)	
WHO 3	11 (44)	16 (62)	
Mean number of previous polyps (cumulative) (SD)			
Hyperplastic polyps	18 (20)	19 (10)	.784
Sessile serrated adenomas/polyps	6 (7)	5 (5)	.360
Adenomas	3 (4)	4 (4)	.895
Mean net withdrawal time, minutes:sec (SD)			
First inspection	9:22 min (4:11)	9:11 min (3:57)	.871
Second inspection	8:58 min (3:57)	6:58 min (3:41)	.076
Median Boston Bowel Preparation Score (IQR)	7 (6-9)	7 (6-9)	.876
Colonoscopies per endoscopist (%)			.898
Endoscopist 1	9 (36)	9 (35)	
Endoscopist 2	8 (32)	6 (23)	
Endoscopist 3	3 (12)	4 (15)	
Endoscopist 4	2 (8)	4 (15)	
Endoscopist 5	3 (12)	3 (12)	

* Patients meeting WHO criteria 1 and 3 were classified as WHO 1

Polyp miss-rates

A total of 323 polyps were detected. In the HR-WLE group, 116 polyps were detected during the first inspection (table 2). During the second inspection with NBI, another 47 polyps were detected, including 40 hyperplastic polyps, 6 sessile serrated adenomas/polyps and 1 adenoma. Corresponding overall polyp miss-rate of HR-WLE was 29% (95% CI: 22-36). In the NBI group, 128 polyps were detected during the first inspection (table 2). Subsequent inspection with HR-WLE added 32 polyps, including 15 hyperplastic polyps, 9 sessile serrated adenomas/polyps and 8 adenomas. Corresponding overall polyp miss-rate of NBI was 20% (95%CI 15-27). When comparing the overall polyp-miss rate of HR-WLE and NBI, no significant difference was found (p=0.065).

Separate polyp miss-rates for hyperplastic polyps, sessile serrated adenomas/polyps and adenomas are shown in table 2. The hyperplastic polyp miss-rate of NBI was significantly lower compared with the hyperplastic polyp miss-rate of HR-WLE (p=<.001), while the adenoma miss-rate of NBI was significantly higher than the adenoma miss-rate of HR-WLE (p= .020). Miss-rates of sessile serrated adenomas/polyps did not differ between the two groups (p=.371).

Table 2. Polyp miss-rates of HR-WLE and NBI

	First technique		P value
	HR-WLE (n=25)	NBI (n=26)	
All polyps	163	160	
First inspection	116	128	
Second inspection	47	32	
Miss-rate, % (95% CI)	29 (22-36)	20 (15-27)	.065
Hyperplastic polyps	97	95	
First inspection	57	80	
Second inspection	40	15	
Miss-rate, % (95% CI)	41 (32-51)	16 (10-24)	<.001
Sessile serrated adenomas/polyps	46	45	
First inspection	40	36	
Second inspection	6	9	
Miss-rate, % (95% CI)	13 (6-26)	20 (11-34)	.371
Adenomas	20	20	
First inspection	19	12	
Second inspection	1	8	
Miss-rate, % (95% CI)	5 (1-24)	40 (22-61)	.020

Individual polyp miss-rates of each of the 5 endoscopists are shown in table 3. One endoscopist had a significantly lower polyp-miss rate with NBI as first inspection technique. The polyp miss-rates of the other endoscopists did not differ between HR-WLE and NBI.

Table 3. Polyp miss-rates of the different endoscopists

	No. colonoscopies	No. of lesions	Miss-rate HR-WLE	Miss-rate NBI	P value
Endoscopist 1	18	104	31%	19%	.210
Endoscopist 2	14	93	25%	26%	.926
Endoscopist 3	7	28	11%	11%	1.00
Endoscopist 4	6	59	25%	26%	.957
Endoscopist 5	6	39	71%	13%	.004

Polyp characteristics associated with miss-rates

Of the 323 polyps, 79 lesions were detected during the second inspection, resulting in an overall polyp-miss rate of 24% (95% CI 20-29). Table 4 demonstrates associations between polyp characteristics and polyp miss-rates. Polyps smaller than 10 mm were significantly more often missed compared with polyps ≥ 10 mm; OR 0.17 (95% CI 0.05-0.58). Flat lesions (Paris IIa/IIb/IIa+c) were significantly more often missed than protruding lesions (Paris Is/Ip); OR 1.78 (95% CI 1.05-3.03). In contrast, neither histology (adenomas vs. serrated polyps) nor colonic location (proximal vs. distal) was associated with polyp miss-rate; OR 1.19 (95% CI 0.52-2.73) and OR 1.21; (95% CI 0.69-2.11), respectively. Also total number of polyps detected during the procedure (< 5 polyps vs. ≥ 5 polyps) was not associated with polyp-miss rates; OR 1.22 (95% 0.58-2.58).

Table 4. Associations between polyp characteristics and miss-rates

	No.	Missed	Miss-rate (%)	Univariate		Multivariate	
				Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Histology							
Adenomatous	40	9	23	1.00		1.00	
Serrated	283	70	25	1.13 (0.51-2.49)	.758	1.19 (0.52-2.73)	.677
Size							
< 10 mm	279	76	27	1.00		1.00	
≥ 10 mm	44	3	7	0.20 (0.06-0.65)	.008	0.17 (0.05-0.58)	.005
Morphology *							
Protruded	188	39	21	1.00		1.00	
Flat	128	39	30	1.67 (1.00-2.80)	.050	1.78 (1.05-3.03)	.034
Location							
Distal	119	29	24	1.00			
Proximal	204	50	25	1.01 (0.60-1.71)	.977	1.21 (0.69-2.11)	.515
No. polyps removed during procedure							
< 5 polyps	53	12	23	1.00		1.00	
≥ 5 polyps	270	67	25	1.13 (0.56-2.27)	.737	1.22 (0.58-2.58)	.607

* Morphology was unknown for 7 polyps

DISCUSSION

The current study reports on the potential additional value of NBI in the detection of polyps in patients with SPS. The overall polyp miss-rate of NBI was lower compared with HR-WLE, but this difference did not reach statistical significance. Multivariate analysis showed that small and flat polyps were significantly more often missed than large and protruding lesions.

Our study has several strengths, including the multicenter design, the involvement of 5 different endoscopists and the equal withdrawal times in both arms. Moreover, all tissue specimens were reviewed by one single expert pathologist to minimize intraobserver variation in the diagnosis of the different serrated polyp subtypes. However, limitations should also be noted. First, the nature of the technique makes it impossible to blind endoscopists for the endoscopic imaging technique. Although this is inherent to all imaging studies, investigator bias in favor of one technique cannot be excluded. Second, both the first as well as the second inspection was performed by the same endoscopist. An ideal cross-over design would require that the second inspection is performed by another endoscopist blinded to the results of the first endoscopist. Unfortunately, in our study such a design was not possible due to practical limitations. A study with a randomized head-to-head comparison was not feasible due to the large number of patients needed to achieve adequate power. Last, due to the relatively small sample size, results should be interpreted with caution. Although no significant difference in the overall polyp miss-rate was found, a trend in favor of NBI was observed (p=0.065). Due to the relatively small sample size, one could argue that small differences in outcomes or inclusion of larger number of patients would have altered this trend into a significant difference. Nonetheless, we like to emphasize that this difference in overall polyp miss-rate is solely driven by a lower hyperplastic polyp miss-rate of NBI. We observed no trend in favor of NBI regarding the detection of sessile serrated adenomas/polyps and there was even a benefit of HR-WLE over NBI regarding adenoma detection. So, even if we would have found a significant lower overall polyp miss-rate with NBI, the lack of a clear benefit in reducing adenoma and/or sessile serrated adenoma/polyp miss-rates would have hampered its use in daily clinical practice.

Our previous randomized cross-over pilot study in patients with SPS, that was performed by a single endoscopist in a single academic center, demonstrated significantly lower polyp miss rates with NBI compared with HR-WLE (10% vs. 36% p= < 0.001).[13] The findings of the current study do not support this pilot-study. There are some possible explanations for this result. First, the pilot study was clearly limited by being conducted at a single institution by one single endoscopist. Even though this study was well executed, results might have been influenced due to investigator bias. The daily practice of surveillance of these patient is probably better reflected by a multicenter study. Another

explanation for the difference in outcome may be due to the difference in endoscopic equipment used in both studies. In the pilot study, procedures were performed with Lucera system and CF-H260Z video colonoscopes whereas procedures in the current study were performed with the Exera II system and CF-H180 AL colonoscopes.

NBI significantly reduced the polyp miss-rate of hyperplastic polyps. This is in concordance with the results of our pilot study as well as with several other large randomized studies in non-SPS patients.[11-13] In contrast, NBI did not prove of additional value for the detection of sessile serrated adenomas/polyps or adenomas. Regarding adenoma detection, NBI was even associated with an increased adenoma miss-rate. A possible explanation for this somewhat surprising finding is that hyperplastic polyps have a greater

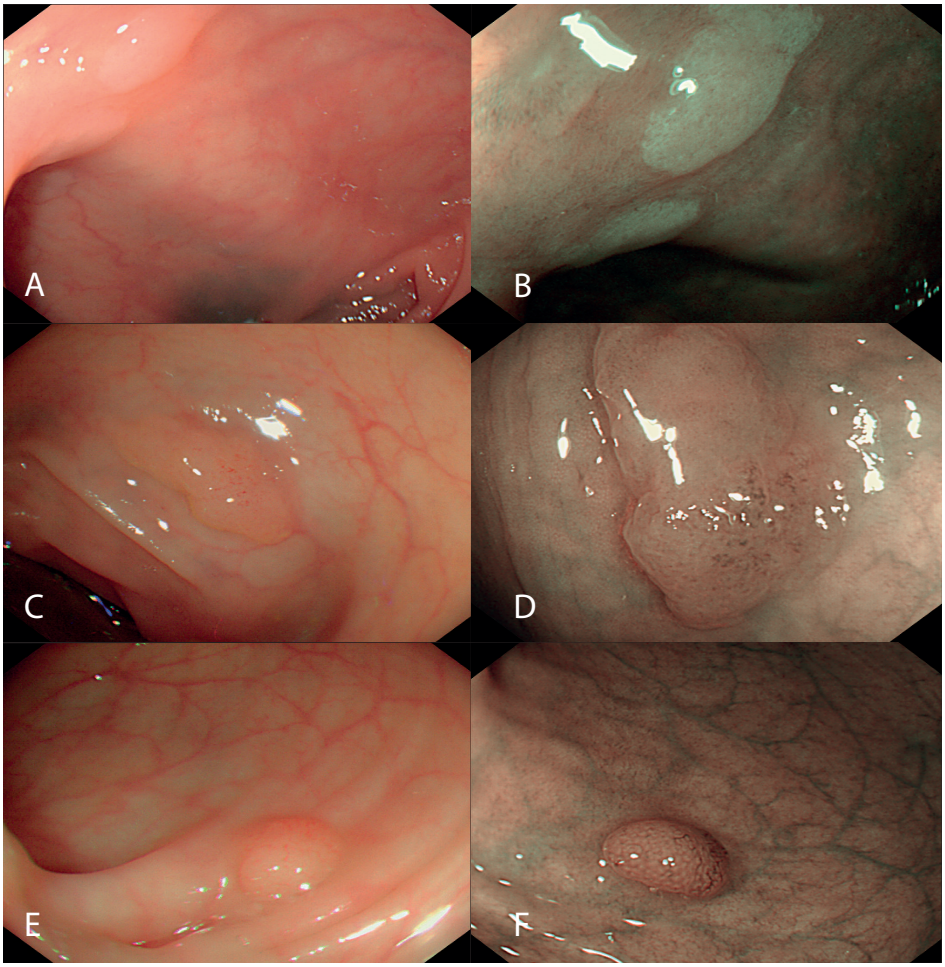

Figure 2. HR-WLE (left) and corresponding NBI (right) images of a hyperplastic polyp (A+B), sessile serrated adenoma/polyp (C+D) and adenoma (E+F).

color contrast to the adjacent mucosa than adenomas or sessile serrated adenomas/polyps under NBI. Most hyperplastic polyps appear white under NBI whereas adenomas and sessile serrated adenomas/polyps often appear darker than the surrounding mucosa (fig. 2). As NBI often generates a dark field of view, the contrast in color between adenomas and the surrounding tissue may be reduced. Hyperplastic polyps are still highlighted under these circumstances and might therefore be detected with greater ease.

Patients with SPS are at increased risk of the development of advanced neoplasia under surveillance.[2,4] One possible explanation is that these advanced polyps and CRCs may originate from polyps that are missed during surveillance. Among other reasons, these polyps might be missed due to the multiplicity of polyps seen in patients with SPS resulting in a suboptimal overview of all lesions. Interestingly, our study demonstrates that an increasing number of polyps was not associated with higher polyp-miss rates. Moreover, the overall polyp miss-rate in our cohort of SPS patients was 24% which is comparable with polyp miss-rates (22%) observed in average risk persons undergoing back-to-back colonoscopies.[17] Hence, these findings do challenge the hypothesis that increased polyp miss-rates are responsible for the relatively high incidence of interval CRCs in patients with SPS. In this respect, cancer biology, such as increased malignant progression rate leading to CRC, might play a greater role. However, this remains speculative and warrants further investigation.

The results of our study suggest that NBI does not reduce polyp miss-rates in patients with SPS compared with HR-WLE. Further multinational studies with larger number of patients are warranted to verify these results.

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6

Yield of screening colonoscopy in first-degree relatives of patients with serrated polyposis syndrome

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ABSTRACT

Background and study aims

Patients with SPS are at an increased risk for colorectal cancer. Although inheritance patterns are unknown, first-degree relatives of these patients have an increased risk for both colorectal cancer and SPS. Prospective studies evaluating the yield of screening colonoscopies in this group are however scarce. This information would be useful to evaluate a possible mode of inheritance and to investigate whether screening colonoscopies are justified in this group. We aimed to evaluate the diagnostic yield of screening colonoscopies in first-degree relatives of patients with serrated polyposis.

Methods

First-degree relatives of patients with SPS were invited to undergo colonoscopy. The diagnostic yield was expressed by the number of first-degree relatives with at least one significant polyp relative to the total number of included first-degree relatives. Significant polyps were defined adenomas, traditional serrated adenomas, sessile serrated adenoma/polyps and proximal hyperplastic polyps. Tissue specimens were reviewed by one expert pathologist.

Results

Seventy-seven first-degree relatives underwent colonoscopy (median age 52 y; interquartile range 41-60). Colorectal cancer was not diagnosed. One or more significant polyps were detected in 43% of first-degree relatives. No differences based on age, gender or familial relationship were observed in the detection of polyps. Seven first-degree (9%) relatives had multiple polyps (≥5). Eleven (14%) first-degree relatives fulfilled SPS WHO-criterion 2, of whom one sibling also met SPS WHO-criterion 3.

Conclusions

The yield of a single screening colonoscopy in first-degree relatives of patients with serrated polyposis is substantial, warranting a colonoscopy screening program for these individuals.

INTRODUCTION

Serrated polyposis syndrome (SPS), formerly hyperplastic polyposis syndrome, is characterized by numerous serrated polyps distributed throughout the colon and is associated with an increased colorectal cancer risk.[1-3] SPS is a relatively common finding in patients undergoing fecal immunochemical testing (FIT)-based colorectal cancer screening, with an estimated prevalence of 1:150 to 300.[4,5] In an average risk screening population the prevalence is estimated to be 1:1800, which is more frequent in occurrence than for instance familial adenomatous polyposis (1:13.000).[6,7] In contrast with most other polyposis syndromes, the underlying genetic defect of the disease is unknown. The diagnosis of SPS is therefore based on endoscopic findings in combination with histopathology. In 2010, the condition was defined by the World Health Organization (WHO) as follows: 1) at least 5 histologically diagnosed serrated lesions proximal to the sigmoid colon, of which 2 larger than 10 mm in diameter, or 2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS or 3) more than 20 serrated polyps distributed throughout the colorectum.[8] To prevent polyps from invasive growth, patients are advised to undergo frequent endoscopic surveillance. Surgery is indicated when endoscopic control of the polyp burden, e.g. because of the number or size of lesions, is not feasible.[9]

Although most SPS cases seem non-familial, presence of the disease in multiple family members has been described in previous reports.[10-12] In addition, first-degree relatives of patients with the syndrome have an increased risk of developing colorectal cancer. Case series report that up to 50% of patients with SPS have a first-degree relative with colorectal cancer. Moreover, two recent retrospective cohort studies demonstrated an approximately 5-fold increased incidence of colorectal cancer in first-degree family members of patients with SPS compared with the general population.[10-14] For this reason, most authorities advise colonoscopies every 5 or 6 years for all first-degree relatives starting at age 35-50 years or at an age 5-10 years younger than the age at time of diagnosis of SPS reported in the family member.[12,13,15,16]

The above-mentioned recommendations are based on data that were mainly retrospectively ascertained. Such study designs are prone to ascertainment bias, which may have inflated the risk estimates. Prospective screening studies in large series of first-degree relatives are necessary to adequately assess the prevalence, type and distribution of lesions in these individuals. The aim of this study was to evaluate the diagnostic yield of screening colonoscopies in first-degree relatives of patients with SPS.

METHODS

Invitation and population

Individuals (index patients) fulfilling the WHO-1 or WHO-3 criteria for SPS were identified in two tertiary referral hospitals in the Netherlands (the Academic Medical Center, Amsterdam and the University Medical Center, Groningen). First-degree relatives (parents, siblings and children) of these subjects were invited to undergo colonoscopy by means of a standard letter of invitation that was given to the relative by the index patient. Responders from the age of 35 years, or from an age 5 years younger than the age at which the index patient was diagnosed with SPS, were subsequently offered a colonoscopy at their local hospital or hospital of their choice. Relatives were excluded if they had personal history of colorectal cancer or serrated polyposis or if they had undergone a colonoscopy in the previous 3 years.

Endoscopy and histology reports were collected from all institutions to obtain data regarding clinical demographics, the quality of bowel preparation, cecal intubation and polyp characteristics. Subjects with an incomplete colonoscopy or poor bowel preparation (< 90% colonic mucosa visible) were excluded from further data analyses.

Ethical approval was obtained from our institutional review board and the study was registered in the Dutch Trial Register (www.trialregister.nl; trial number NTR3253).

Colonoscopic procedure

After providing informed consent, all eligible first-degree relatives underwent either a standard or high-resolution white light colonoscopy. Advanced imaging techniques, such as narrow-band imaging or chromoendoscopy, were not used. Procedures were performed under conscious sedation with midazolam and/or fentanyl at both community hospitals and tertiary referral institutions across the Netherlands. All colonoscopists were instructed to remove and retrieve all detected polyps for histological assessment and to document polyp size and colonic location. Subjects were prepared with a standard bowel preparation, including a 4 L polyethylene glycol (PEG) solution or a 2 L hypertonic PEG solution with an additional 2-4 L of transparent fluids and low fibre diet. Cecal intubation was confirmed by documentation of the cecal landmarks (cecal valve, appendix orifice or intubation of the ileum). The proximal colon was defined as proximal to sigmoid (descending, transverse, ascending colon and cecum).

Histopathology

All available tissue specimens were reviewed by one pathologist (SvE) with a special interest and expertise in gastrointestinal pathology. Serrated polyps were classified as hyperplastic polyp, sessile serrated adenoma/polyp or traditional serrated adenoma based on histological criteria recently incorporated in the WHO classification for serrated

polyps.[8] A sessile serrated adenoma/polyp was defined by predominantly disorganized and distorted crypts, including dilation or branching of the basal portion of the crypt that often appears as a "boot" or "L" shape. Traditional serrated adenomas were defined by a protuberant or pedunculated growth pattern with distorted villiform configurations with columnar cells having abundant eosinophilic cytoplasm or centrally located elongated nuclei. When it was not possible to differentiate between the different serrated subtypes, e.g. due to poor orientation, severe cautery artefacts or poor sampling the term "unclassified serrated polyp" was used.[15] Advanced adenomas were adenomas ≥ 10 mm, with villous structure or with high grade dysplasia.

Outcome measures and statistical analysis

Descriptive statistics were used to describe the study population and polyp characteristics. Prevalence rate was defined as the proportion of first-degree relatives in whom at least one polyp was found.

To express the diagnostic yield, patients were classified into 8 groups on the basis of the most advanced lesion found at colonoscopy: 1] no polyps 2] distal hyperplastic polyps 3] proximal hyperplastic polyps 4] sessile serrated adenoma/polyps 5] traditional serrated adenoma 6] tubular adenomas < 10 mm 7] advanced adenomas and 8] colorectal cancer. Adenomas, traditional serrated adenomas, sessile serrated adenomas/polyps and proximal hyperplastic polyps were defined as a clinical significant finding during colonoscopy. Consequently, the diagnostic yield was expressed by the number of first-degree relatives with at least one significant polyp relative to the total number of included first-degree relatives. A chi-square test was used to test significant differences between groups. Differences were expressed as relative risk with 95% confidence intervals. Two-sided p-values of less than 0.05 were considered as statistically significant. SPSS for Windows software (Chicago, IL, USA) version 19.0.1 was used for analysis.

RESULTS

Clinical and colonoscopy characteristics

The included relatives belong to 36 families and consisted of 43 (56%) siblings, 31 children (40%) and 3 parents (4%). The median number of participating first-degree relatives per index patient was 2 (range 1-5). Table 1 outlines the clinical characteristics of the 36 index patients.

A total of 82 eligible first-degree relatives underwent colonoscopy between October 2008 and October 2012. Five relatives were excluded after the procedure because of inadequate bowel preparation (n=2) or an incomplete colonoscopy (n=3). The remaining 77 first-degree relatives were all asymptomatic and underwent their procedure at

Table 1. Baseline characteristics of index patients with serrated polyposis (n=36)

Median age in years (IQR)	64 (59-71)
Male (%)	19 (53)
WHO criteria (%) *	
1	12 (33)
3	7 (20)
Combined (1 and 3)	17 (47)
Median number of serrated polyps (IQR)	25 (14-36)
Median number of proximal serrated polyps (IQR)	12 (5-22)
Median number of adenomas (IQR)	4 (1-9)
Number of patients with CRC (%)	16 (44)
Median number of FDRs per index patient (range)	2 (1-5)

* WHO 1: ≥ 5 histologically diagnosed serrated lesions proximal to the sigmoid colon, of which 2 larger than 10 mm in diameter. WHO 3: ≥ 20 serrated polyps distributed throughout the colorectum
IQR: interquartile range, CRC: colorectal cancer

20 different hospitals. Thirty-nine (51%) colonoscopies were performed at two tertiary referral institutions, 18 (23%) procedures at one single colonoscopy center and 20 (26%) procedures at 17 different community hospitals. Clinical characteristics of the included 77 first-degree relatives are shown in Table 2.

Table 2. Clinical characteristics of the included first-degree relatives (n=77)

Median age in years (IQR)	52 (41-60)
Male (%)	37 (48)
Siblings (%)	43 (56)
Children (%)	31 (40)
Parents (%)	3 (4)
Number of FDRs of index patients with CRC (%)	41 (53)

IQR: interquartile range, CRC: colorectal cancer, FDR: first-degree relative

Polyp characteristics

During screening colonoscopy in the first-degree relatives, a total of 139 polyps and no colorectal cancers were detected. Review of pathology specimens was performed in 133 polyps; for the 6 remaining specimens the original sign-out diagnosis by the local pathologist was used. Histopathology demonstrated: 72 (52%) hyperplastic polyps, 46 (33%) adenomas, 17 (12%) sessile serrated adenomas/polyps, 3 (2%) 'unclassified serrated lesions' and 1 (1%) juvenile polyp. The median polyp size was 3 mm (IQR 2-5mm); 8 (6%) polyps were ≥ 10 mm and 80 (58%) lesions were located proximal to the sigmoid.

Yield of colonoscopy

Prevalence and number of polyps

Prevalence and number of polyps stratified by gender, familial relationship and age is shown in Table 3. At least one hyperplastic polyp, sessile serrated adenoma/polyp or adenoma was detected in 28 (36%), 7 (9%) and 28 (36%) first-degree relatives, respectively. Proximal hyperplastic polyps and proximal sessile serrated adenomas/polyps were detected in 9 (12%) and 5 (6%) first-degree relatives, respectively.

Table 3. Number and prevalence of polyps, stratified by gender, familial relation and age

	Combined n=77	Male n=37	Female n=40	Siblings n=43	Non-siblings n=34	<50 y n=35	≥ 50 y n= 42
Prevalence (%)							
Adenoma	28 (36)	16 (43)	12 (30)	14 (33)	14 (41)	11 (31)	17 (40)
Traditional serrated adenoma	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sessile serrated adenoma/polyp	7 (9)	4 (11)	3 (8)	4 (9)	3 (9)	2 (6)	5 (12)
Hyperplastic polyp	28 (36)	16 (43)	12 (30)	21 (48)	7 (21)	7 (20)	21 (50)
Number of polyps (%)							
0	30 (39)	10 (27)	20 (50)	12 (28)	18 (53)	19 (54)	11 (26)
1	19 (25)	11 (30)	8 (20)	11 (26)	8 (24)	6 (17)	13 (31)
2-4	21 (27)	12 (32)	9 (23)	15 (35)	6 (18)	8 (23)	13 (31)
≥ 5	7 (9)	4 (11)	3 (8)	5 (12)	2 (6)	2 (6)	5 (12)

Diagnostic yield; findings according to the most advanced lesion detected at colonoscopy

Colonoscopy findings according to the most advanced lesion, stratified by gender, familial relation and age is listed Table 4. In 44 (57%) first-degree relatives either no lesions or only distal hyperplastic polyps were found. In the other 33 (43%) at least one 'significant polyp' (defined as an adenoma, traditional serrated adenoma, sessile serrated adenoma/polyp or a proximal hyperplastic polyp) was detected. In 6 first-degree relatives the most advanced finding was an advanced adenoma, in 22 a tubular adenoma < 10 mm, in 3 a sessile serrated adenoma/polyp and in 2 a proximal hyperplastic polyp. No significant difference was seen in the detection of significant polyps between siblings (brothers and sisters) and non-siblings (parents and children) (RR 1.07 95% 0.64-1.81), between male and female (RR 1.30 95% 0.77-2.18) or between first-degree relatives ≥ 50 years and < 50 years (RR 1.46 95% 0.84-2.52).

First-degree relatives with multiple polyps (≥ 5)

Multiple polyps (≥ 5) were detected in 7 (9%) first-degree relatives from 7 different probands; 5 siblings and 2 children. Clinical, polyp and pedigree characteristics of these 7 relatives are listed in Table 5. Four of the seven first-degree relatives with multiple polyps

Table 4. Diagnostic yield; colonoscopy findings according to the most advanced lesion detected, stratified by gender, familial relation and age

	Total n=77	Male n=37	Female n=40	Siblings n=43	Non-siblings n=34	<50 y n=35	≥ 50 y n= 42
Number of FDRs with at least one significant polyp (%)	33 (43)	18 (49)	15 (38)	19 (44)	14 (41)	12 (34)	21 (50)
Colorectal cancer (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Advanced adenoma (%)	6 (8)	5 (14)	1 (3)	6 (14)	0 (0)	1 (3)	5 (12)
Tub. Adenoma ≤ 10 mm (%)	22 (29)	11 (30)	11 (28)	8 (19)	14 (41)	10 (29)	12 (29)
Traditional serrated adenoma (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sessile serrated adenoma/polyp (%)	3 (4)	1 (3)	2 (5)	3 (7)	0 (0)	0 (0)	3 (7)
Proximal hyperplastic polyp (%)	2 (3)	1 (3)	1 (3)	2 (5)	0 (0)	1 (3)	1 (2)
Number of FDRs with distal hyperplastic polyps or no polyps (%)	44 (57)	19 (51)	25 (62)	24 (56)	20 (59)	23 (66)	21 (50)
Distal hyperplastic polyp (%)	14 (18)	9 (24)	5 (13)	12 (28)	2 (6)	4 (11)	10 (24)
No polyps (%)	30 (39)	10 (27)	20 (50)	12 (28)	18 (53)	19 (54)	11 (26)

To express the diagnostic yield, patients were classified into 8 groups on the basis of the most advanced lesion found at colonoscopy: 1] no polyps 2] distal hyperplastic polyps 3] proximal hyperplastic polyps 4] Traditional serrated adenoma 5] sessile serrated adenoma/polyps 6] tubular adenoma < 10 mm 7] advanced adenoma 8] colorectal cancer
Tub.: tubular FDRs: First-degree relatives

harboured at least one sessile serrated adenoma/polyp, of whom in 2 (FDR3 and FDR4) 4 sessile serrated adenomas/polyps were identified. Twelve other relatives from the same 7 families were screened in the present study; none of them had 5 or more polyps.

First-degree relatives fulfilling the WHO-criteria

A total of 11 (14%) first-degree relatives met at least one of the WHO criteria; all of them fulfilled WHO-criterion 2 (any number of serrated polyps proximal to the sigmoid in a first-degree relative of patient with SPS) and 1 (FDR 1, Table 5) also fulfilled WHO-criterion 3 (more than 20 serrated polyps spread throughout the colon). None of the first-degree relatives satisfied WHO-criterion 1. One child (FDR 2, Table 5) had 14 polyps; 9 proximal serrated polyps and 5 adenomas. Since none of the proximal serrated polyps were larger than 10 mm in diameter, this individual did not meet the WHO-criterion 1.

DISCUSSION

We prospectively evaluated the diagnostic yield of screening colonoscopies in first-degree relatives of patients with serrated polyposis. Colorectal cancer was not diagnosed. In 43% of first-degree relatives at least one significant polyp (defined as an adenoma,

Table 5. First-degree relatives with multiple (≥ 5) polyps detected by screening colonoscopy

	FDR 1	FDR 2	FDR 3	FDR 4	FDR 5	FDR 6	FDR 7
Age at endoscopy (y)	38	44	58	65	58	55	60
Sex	Female	Male	Male	Female	Male	Female	male
Relation	Sibling (sister)	Non-sibling (son)	Non-sibling (son)	Sibling (sister)	Sibling (brother)	Sibling (sister)	Sibling (brother)
Colonoscopy findings	21 polyps	14 polyps	7 polyps	7 polyps	7 polyps	5 polyps	5 polyps
	21 HP (9 prox) multiple distal HPs still in situ	8 HP (8 prox) 1 USP (1 prox) 5 AD (5 prox)	1 HP (0 prox) 4 SSA/P (4 prox) 2 AD (0 prox)	2 HP (1 prox) 4 SSA/P (3 prox) 1 AD (1 prox)	3 HP (2 prox) 1 SSA/P (0 prox) 3 AD (3 prox)	3 HP (1 prox) 2 SSA/P (2 prox)	1 HP (0 prox) 4 AD (3 prox)
Advanced adenoma	No	No	No	No	Yes Tub. AD ≥ 10 mm	No	Yes Tub. Vil. AD > 20 mm HGD
Fulfils WHO criteria	WHO-2 and 3	WHO-2	WHO-2	WHO-2	WHO-2	WHO-2	None
Index case characteristics	45 y, male WHO 1 and 3 CRC: no	74 y, female WHO-3 CRC: yes	85 y, female WHO-3 CRC: yes	69 y, male WHO-1 CRC: yes	63 y, male WHO-1 CRC: yes	59 y, male WHO-3 CRC: no	54 y, male WHO-1 and 3 CRC: yes
Other FDRs who underwent screening in the current study (relation to index)	None	None	1 sibling 1) 2 HPs, 1 AD	2 children 1) no lesions 2) no lesions	3 siblings 1) 1 HP; 1 AD 2) 1 HP 3) no lesions	3 siblings 1) 1 HP 2) no lesions 3) no lesions	3 siblings 1) 3 AD 2) 1 AD 3) no lesions

FDR: first-degree relative, Y: years, HP: hyperplastic polyp, USP: unclassified serrated polyp, SSA/P: sessile serrated adenoma/polyp, AD: adenoma, Tub: tubular, Vil: villous, HGD: high-grade dysplasia, WHO: World Health Organization, CRC: colorectal cancer

traditional serrated adenoma, sessile serrated adenoma/polyp or proximal hyperplastic polyp) was found. No differences based on age, gender or familial relationship were observed in the detection of significant polyps. Seven first-degree (9%) relatives had multiple polyps (≥5). A total of 11 (14%) first-degree relatives fulfilled SPS WHO-criterion 2, of whom one sibling also met SPS WHO-criterion 3.

Studies demonstrate that approximately half of all colorectal cancers in patients with serrated polyposis arises via the serrated neoplasia pathway.[17,18] The other half presumably follows the traditionally adenoma-carcinoma sequence, illustrating that both pathways are clinically relevant in patients with SPS. For this reason, both adenomas and serrated polyps (sessile serrated adenomas/polyps and proximal hyperplastic polyps) were defined as a clinical significant finding during screening colonoscopy. The diagnostic yield was then calculated as the number of first-degree relatives with at least one significant polyp relative to the total number of relatives undergoing colonoscopy. Thirty-three (43%) first-degree relatives had at least one significant lesion. Remarkably, we observed no difference in the detection of significant polyps in first-degree relatives over 50 years of age compared to those less than 50 years. In addition, no difference was observed in the detection of significant lesions in siblings versus non-siblings. These findings suggest that if screening is advised, this should be offered to siblings and non-siblings and should commence from a relatively young age.

Eleven first-degree relatives met SPS WHO-criterion-2 (any number of serrated polyps proximal to the sigmoid in a first-degree relative of a patient with serrated polyposis) of whom one sibling also fulfilled WHO-critierion-3. According to the WHO all these individuals should undergo annual surveillance as they fulfil one of the WHO criteria. We support this regimen for relatives meeting WHO-criteria 1 or 3 but believe that annual surveillance for relatives solely meeting WHO-criterion 2 is somewhat excessive. This criterion was initially incorporated in the WHO criteria to elevate the significance of smaller numbers of serrated polyps in a first-degree relative of a patient with SPS. This rational might be true, but the recently observed high prevalence of proximal serrated lesions in the general population (approximately 12%) clearly shows that these lesions are also frequently found in a non-familial context.[19,20] A more stringent WHO-criterion 2 seems therefore necessary to delineate relatives with a suspected increased familial risk from those with one or a few small sporadic serrated polyps with likely no greater cancer risk.

In a study from Portugal, 17 first-degree relatives of patients with SPS underwent a screening colonoscopy; 10 (59%) of them had at least one polyp (including distal hyperplastic polyps) and one fulfilled the WHO criteria for SPS.[11] Interestingly, 7 out of the 10 first-degree relatives with polyps were under the age of 50, which corresponds with the high detection of polyps in our group of relatives below 50 years of age. In a recent study from Spain, 78 first-degree relatives of patients with SPS were screened.[16] A total of 25 (32%) first-degree relatives fulfilled one of the WHO-criteria compared with 11 (14%) in

our study. Six relatives in the Spanish study fulfilled WHO-criterion-1 or 3 compared with only 1 (1%) relative in our cohort. The exclusion of first-degree relatives with a personal history of colorectal cancer or serrated polyposis in our series may, in part, explain these observed differences. We decided to exclude these relatives to minimize the risk of ascertainment bias. On the other hand it needs to be emphasized that this approach might underestimate the true familial risk of serrated polyposis, as relatives with known colonic abnormalities are excluded beforehand. Still, considering that the vast majority of first-degree relatives confronted with in clinical practice are screen-naïve individuals without a personal history of colorectal cancer or serrated polyposis, we believe our findings are clinical relevant.

Regarding the mode of inheritance, occasionally reported affected siblings in previous reports suggest an inheritance mode consistent with autosomal recessive or dominant mode with lower penetrance.[10-12] We found 2 first-degree relatives, one sibling and one non-sibling, with an extensive number (> 10) of polyps and 5 relatives, of whom 4 were siblings, with 5-10 polyps. The finding of multiple polyps was not associated with one WHO phenotype or/and colorectal cancer presence in the SPS proband and none of the other 12 relatives from the same 7 pedigrees had multiple polyps (Table 5). These findings are not consistent with one mode of inheritance. This is most likely due to the fact that SPS presents with a substantial phenotypic diversity and most experts believe that the syndrome, as currently defined by the WHO, represents a group of sub-conditions not yet further subcategorized. This makes it difficult to postulate a possible inheritance mode as inherited forms of SPS might be swamped by other cases in which no or a distinct inheritable component exists. Moreover, to gain more insight in this question it might be necessary to investigate second-degree relatives as well, who were not included in the present report. Still, the presence of 2 relatives with more than 10 polyps (Table 5: FDR 1 and 2) and an intermediate SPS phenotype of 5-10 polyps (including multiple sessile serrated adenomas/polyps and proximal hyperplastic polyps) in 4 other relatives (Table 5: FDR 3, 4, 5 and 6) could suggest a familial component in these cases. An autosomal recessive or a co-dominant mode of inheritance, involvement of one or more low penetrance genes, environmental factors or a combination of all might have played a role. It will be interesting to see whether these relatives will develop a more extensive polyp burden in the future. Further studies should focus on these individuals to quantify the longitudinal risk of developing additional lesions and to further explore the mode of inheritance.

Strengths of this study are the prospective design, the large number of included first-degree relatives, the revision of all polyp specimens by one expert pathologist and the fact that all identified index patients were asked to participate, irrespective of a personal or family history of colorectal cancer. Our study has also limitations that need to be acknowledged. An important question to answer is whether our detection rates are higher

compared with detections rates in asymptomatic persons without a first-degree relative with SPS. We believe a comparison with average risk persons was not appropriate as most of these study cohorts are not comparable with ours with respect to age, gender and family history of colorectal cancer. In addition, reliable prospective data on prevalence rates of sessile serrated adenomas/polyps and multiple polyps are scarce. Therefore, a matched control group of asymptomatic persons undergoing screening colonoscopy in the same hospitals would have been of additional value for the interpretation of our data. This, however, would certainly have raised ethical concerns as there is currently no primary screening program in the Netherlands. A second potential shortcoming is that our group of participating first-degree relatives may not fully represent the total group that was eligible for screening. As relatives were invited by a letter that was given to the relative by the index patients, we do not precisely know how many relatives did not participate in our study. Nonetheless, this does not seem likely to generate biased results. Finally, a possible weakness of the study is that colonoscopies were performed in 20 different hospitals spread throughout The Netherlands by colonoscopists with different level of experience.

We believe that the high yield of significant lesions, the finding of multiple polyps in 9% of relatives and the observed increased incidence of colorectal cancer reported in previous studies justify screening colonoscopies in this group.[12,13] Considering the observed early onset of polyps in our series, we advise to start surveillance in first-degree relatives, both siblings and non-siblings, at the age of 35 years or 5 years younger than the lowest age at time of diagnosis of SPS reported in the family. Subsequent surveillance intervals are based on the detection of polyps with a maximum interval of 5 or 6 years. However, future prospective studies are necessary to evaluate the optimal surveillance interval and to observe the longitudinal risk of colorectal cancer in this group.

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Extracolonic cancer risk in patients with serrated polyposis syndrome and their first-degree relatives

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ABSTRACT

Background and study aims

Serrated polyposis syndrome is associated with an increased colorectal cancer risk. Although the underlying genetic cause of the condition is unknown, first-degree relatives of patients with serrated polyposis have an increased risk for colorectal cancer compared with the general population. This suggests an inheritable component. Since other hereditary polyposis syndromes are often associated with an expanded extracolonic tumour spectrum, our aim was to determine the extracolonic cancer risks for patients with serrated polyposis and their first-degree relatives and compare these risks with the general population.

Methods

Serrated polyposis index patients from 5 medical centers were included. Demographic data concerning age, sex and reported malignancies were ascertained by reviewing medical charts and histopathology reports. Family history was obtained by examining pedigree records from the department of Clinical Genetics. Incidence rates of extracolonic malignancies were compared with the general population through a person-year analysis, adjusted for age and sex. Population-based incidence data were derived from the Eindhoven Cancer Registry.

Results

A total of 105 patients with serrated polyposis and 341 first-degree relatives were included. Among the patients with serrated polyposis, 9 extracolonic cancers were observed, compared to 13 expected malignancies in the general population (RR 0.69 95%-CI 0.36-1.33; p=0.27). Among the first-degree relatives, 44 extracolonic malignancies were observed, compared to 48 expected malignancies (RR 0.92 95%-CI 0.69-1.24; p=0.60).

Conclusion

In this study, the overall incidence of extracolonic malignancies in patients with serrated polyposis and their first-degree relatives was not increased. Large international studies are required to confirm these results.

INTRODUCTION

Serrated polyposis syndrome (SPS), formerly known as hyperplastic polyposis syndrome, is characterized by the appearance of multiple colorectal serrated polyps spread throughout the colon and is associated with an increased colorectal cancer (CRC) risk.[1-4] In 2010, SPS was defined by the World Health Organization (WHO) as follows: a patient with 1) at least 5 histologically diagnosed serrated lesions proximal to the sigmoid colon, of which 2 larger than 10 mm in diameter, or 2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS or 3) more than 20 serrated polyps distributed throughout the colorectum.[5] Because of the risk of malignant progression of polyps, patients with SPS are advised to undergo strict endoscopic surveillance with removal of all polyps larger than 3-5 mm in size.[4-7] When endoscopic resection is not possible because of size or multiplicity of lesions, a subtotal colectomy with an ileorectal anastomosis should be considered.

Studies have shown that first-degree relatives (FDRs) of SPS patients are also at increased risk of CRC.[8-9] Additionally, an increased risk for pancreatic cancer in FDRs of SPS patients was demonstrated.[9] These findings point to a hereditary condition with an underlying genetic defect and might suggest that SPS, like other polyposis syndromes, also encompass an increased risk for other cancers than CRC. Large cohort studies that have quantified the magnitude of this risk in SPS patients are however not available. The aim of this study was to estimate the extracolonic cancer risks for patients with SPS and their FDRs and to compare these risks with the general population.

METHODS

Study population and data collection

SPS (index) patients

Patients from 5 medical centers in the Netherlands fulfilling the diagnostic WHO-1 or/and WHO-3 criteria for SPS were included (Table 1).[5] Of these patients, demographic data concerning age, gender and reported malignancies were ascertained by reviewing medical charts and histopathology reports.

Table 1. Definition SPS according to the WHO in 2010[5]

1] At least 5 serrated polyps proximal to the sigmoid colon with two or more of these being > 10 mm.
2] Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS.
3] More than 20 serrated polyps of any size spread throughout the colon.

SPS: serrated polyposis syndrome, WHO: World Health Organization

First-degree relatives

Family history of the index patients was obtained by examining pedigree records from the department of Clinical Genetics. These records were available in one center (Academic Medical Center, Amsterdam) and were based on self-reported information. All index patients in this center were initially referred to the Clinical Genetics because of SPS, irrespective of their family history of CRC or extracolonic cancers. This study was conducted in accordance with the research code of our hospital on human research, as well as in agreement with the Helsinki Declaration in 1983.

Statistical analysis

SPS patients and FDRs were considered to be at risk for extracolonic malignancies from date of birth until death, last contact or the censory date (25th of March 2011). Pearson-years at risk continued after the first cancer diagnosis until above mentioned endpoints. If the exact date of birth or death of relatives was missing, these dates were set on 1st July. Person-years at risk were stratified according to 5-year age group and gender using SAS software, version 9.1. Age and gender specific cancer incidences during the period 1989-2008 from the Eindhoven Cancer Registry were used to compare the overall incidence of extracolonic malignancies in SPS patients and their FDRs with that of the general population.[10] Non-melanoma skin neoplasms were not included in risk analysis as these are highly environmental dependent. The expected number of cancers was calculated by multiplying the age and gender specific incidence rates of the general population with the corresponding follow up years of the study population. A relative risk for all cancers combined was calculated by dividing the observed cancers in the study cohort by the expected number in the general population. 95% confidence intervals were estimated by assuming that the occurrence of the cancer cases followed a Poisson distribution.

RESULTS

SPS patients

A total of 105 (60 male) patients with SPS were included, with a mean age at end of follow up of 63 years (IQR 57-68). All 105 patients met the WHO-1 or WHO-3 criteria for SPS. A total of 31 (30%) patients had CRC. In Table 2 patient demographics and polyp characteristics are shown. Table 3 summarises the variety of detected extracolonic cancers. We observed a total of 9 extracolonic malignancies at a median age of 56 years (IQR: 40-67), which did not significantly differ from the expected number of 13 in the general population (RR 0.69 95%-CI 0.36-1.33; p=0.27) (Table 4).

Table 2. Baseline characteristics of SPS patients (n=105)

Median age in y (IQR)	63 (57-68)
Male (%)	60 (57%)
Median number of HPs (IQR)	24 (13-38)
Median number of SSA/Ps (IQR)	2 (0-8)
Median number of adenomas (IQR)	3 (1-6)
CRC (%)	31 (30%)

SPS: serrated polyposis syndrome, y: years, HPs: hyperplastic polyps, SSA/Ps: sessile serrated adenomas/polyps, CRC: colorectal cancer, IQR: interquartile range

Table 3. Number and type of extracolonic malignancies observed in 105 SPS patients and 341 FDRs

Location	GI tract	Gyn tract	Urinary tract	Lymphoma	Other
SPS patients (n=105) 9 malignancies	1 Pancreas 2 Carcinoid	2 Cervix	1 Renal cell	1 Hodgkin	1 Fibrosarcoma 1 Melanoma
FDRs (n=341) 44 malignancies	2 Gastric 2 Pancreas 1 Esophagus	2 Ovary 1 Endometrium 1 Cervix	2 Prostate 1 Urothelial cell 1 Renal cell	3 NHL 1 Hodgkin	11 Breast 6 Lung 6 Unknown primary 3 Melanoma 1 Osteosarcoma

SPS: serrated polyposis syndrome, FDRs: first-degree relatives, GI: gastrointestinal, Gyn: gynaecologic, NHL: Non-Hodgkin Lymphoma

Table 4. Extracolonic cancer risk for SPS index patients compared with the general population

Group	Observed malignancies	Expected malignancies	RR (observed/expected)	95% CI	p
Males	4	7.4	0.54	0.21-1.50	0.25
Females	5	5.6	0.90	0.37-2.16	0.81
Combined	9	13.0	0.69	0.36-1.33	0.27

SPS: serrated polyposis syndrome, RR: relative risk, CI: confidence interval

First-degree relatives

Family history of 53 index patients from one institution could be evaluated. A total of 341 FDRs (171 male) were included with a median age at end follow up of 58 years (IQR 40-71). The FDRs consisted of 138 (41%) siblings, 104 (31%) parents and 99 (29%) children. Of this group 21 (6%) were diagnosed with CRC. Table 3 shows the different observed extracolonic cancers. A total of 44 (13%) extracolonic malignancies were detected at a median age of 59 years (IQR: 48-70), compared to 48 expected malignancies in the general population (RR 0.92 95%-CI 0.69-1.24; p=0.60) (Table 5).

Table 5. Extracolonic cancer risk for FDRs compared with the general population

Group	Observed malignancies	Expected malignancies	RR (observed/ expected)	95% CI	p
Males	20	23.9	0.84	0.54-1.30	0.42
Females	24	24.2	0.99	0.67-1.48	0.97
Combined	44	47.6	0.92	0.69-1.24	0.60

FDRs: first-degree relatives, RR: relative risk, CI: confidence interval

DISCUSSION

Our results show that the overall incidence of extracolonic malignancies in SPS patients and their FDRs is not increased compared to the general population. Although we did not estimate specific cancers risks, no dominant cancer type or a remarkable high number of rare malignancies were observed. Hence, preventive measures, like extracolonic cancer surveillance, do not seem indicated in SPS patients or in their FDRs.

To our knowledge this is the first study that has quantified the total extracolonic cancer risk in SPS patients. Strengths of the study include the uniquely large cohort of SPS patients, the participation of 5 different institutions and the use of well-documented pedigree records from the department of Clinical Genetics. Moreover, SPS index patient were ascertained because of SPS and not because of a previous history of extracolonic cancers. Therefore, no strong ascertainment bias is expected. Our study has also limitations, the most important of which is that we did not estimate cancer-specific risks because the number of cancer cases was too low to make reliable risk estimates for specific cancers. Although we did not observe one dominant cancer type or remarkable high number of rare cancers in either SPS patients or FDRs, future, large international studies are warranted to estimate the risks of specific extracolonic cancers. Another limitation was that our data were collected in retrospective manner based on medical charts and self-reported information about family history. Although this method of data collection could have led to an over or underestimation of cancer risk, previous studies that have determined the accuracy of probands reporting on cancer in FDRs showed acceptable accuracies of approximately 80 to 85%.[11-14] Moreover, over-reporting of cancer appears to be a rare finding in these studies. Lastly, included SPS patients were recruited from the outpatient clinic or the department of Clinical Genetics and thus represent a selected patient population. As there is currently no screening program in the Netherlands, these patients have mostly come to medical attention because they were symptomatic and may therefore have a more aggressive SPS phenotype accompanied with a higher extracolonic risk than asymptomatic individuals, which means that our findings may not be fully representative for asymptomatic screen-detected SPS cases. Lastly, as pedigree

records were only available in one center, family history of extracolonic cancers could only be evaluated in 53 out of 105 SPS index cases.

SPS is associated with increased risk of CRC. Approximately one third of SPS patients are diagnosed with co-existent CRC at first presentation and an additional proportion of patients develop colonic neoplasms under surveillance.[2,4] Regarding the risk of extracolonic cancers in SPS patients, limited literature is available. Some case-series have reported on the occurrence of extracolonic cancers in SPS patients, but these studies were mainly descriptive and lacked a systematic comparison with the general population.[1,8] We compared the observed cancers in our cohort with the expected cancer numbers in the general population and found no significant difference, suggesting that patients with SPS do not have increased extracolonic cancer risk.

Although no genetic substrate has yet been identified, there is evidence suggesting that SPS comprises a genetic component in at least some SPS cases. Up to 50% of all SPS patients have a family history of CRC and studies have also reported on multiple affected relatives with SPS in one family.[8,15,16] Moreover two independent large cohort studies have shown a 5-fold increased CRC incidence in FDRs of SPS patients.[8,9] For this reason, most authorities advise screening colonoscopies for FDRs from the age of 35-45 years, or from an age 5 years before the youngest effect relative.[6,8,9,17] Concerning the extracolonic cancer manifestations in FDRs, our study showed no difference in this group compared with the general population. This last observation appears to partly contradict the findings of a study by Win et al.[9] In this study a significant increased risk for pancreatic cancer among FDRs was observed, while brain, lung, prostate, breast and gastric cancer incidences were not increased. In the mentioned study, 6 pancreatic cancers among 609 FDRs were observed, compared to 1.65 expected pancreatic cancers in the general population, resulting in a standardized incidence ratio (SIR) of 3.64 (95% CI 1.70 to 9.21). In comparison, we found 2 pancreatic cancers in 349 first-degree relatives and 1 pancreatic cancer among the 105 SPS index patients. Due to our study design we cannot state whether these pancreatic cancers occurred more often than expected, however the ages at onset of the 3 cancers in our study were 71, 72 and 80 years, which is comparable with the mean age of onset in the general population. Likewise, also in the study of Win et al. the mean age of diagnosis was above 70 years and, remarkably, they did not observe any pancreatic cancer among the 100 SPS patients. Based on these findings we believe a surveillance program for pancreatic cancer in SPS patients or their relatives is not indicated.

The overall incidence of extracolonic malignancies in patients with SPS and their first-degree relatives was not increased in this study. Future large international studies are required to confirm these results.

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Thesis summary and future perspectives

SUMMARY

Colorectal cancer (CRC) is heterogeneous disease arising via multiple distinct pathways. One of these pathways is the serrated neoplasia pathway, which encompasses the malignant transformation of serrated polyps into CRC. It is now increasingly recognized that a substantial proportion of CRCs arises via this pathway and there are reasons to believe that the serrated neoplasia pathway may be responsible for a disproportional number of interval cancers. The research reported in this thesis focuses on the epidemiology and endoscopic appearance of serrated polyps, as well as, on the treatment and surveillance of patients with serrated polyposis syndrome and their relatives.

Part I serrated polyps

Despite the increasingly recognized importance of serrated polyps, little is known about their epidemiology. Chapter 2 describes the estimated prevalence rates and clinical characteristics of the different serrated polyp subtypes in a large cohort of individuals, aged 50-75 years, undergoing primary screening colonoscopy. The prevalence of hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenomas in this group was 24%, 4.8% and 0.1%, respectively. Sessile serrated adenomas/polyps comprised 7% of all polyps. These findings suggest that sessile serrated adenomas/polyps are frequently encountered in routine screening colonoscopies. Endoscopists should therefore be well aware of the clinical impact of these lesions and sufficiently trained to detect and completely remove them.

Sessile serrated adenomas/polyps are considered to be the most important type of precursor lesions of the serrated neoplasia pathway. These lesions are susceptible for being easily overlooked due to their flat morphology and unremarkable color. Moreover, given the morphological similarity with hyperplastic polyps, it seems likely that a proportion of sessile serrated adenomas/polyps are left in situ because they are misinterpreted by endoscopists as being clinical irrelevant hyperplastic polyps. The study described in chapter 3 aimed to identify novel endoscopic features of sessile serrated adenomas/polyps. Images of white light endoscopy and narrow-band imaging of a total of 150 polyps, including 50 sessile serrated adenomas/polyps, were systematically assessed by 5 international experts using various endoscopic descriptors. We concluded that sessile serrated adenomas/polyps possess specific endoscopic features compared to hyperplastic polyps. The presence of a *cloud-like surface*, *indistinctive borders*, *irregular shape* and *dark spots inside the crypts* all appeared independent endoscopic features associated with sessile serrated adenomas/polyps and these features might aid endoscopists in recognizing and differentiating these lesions from innocuous hyperplastic polyps.

Part II serrated polyposis syndrome

Serrated polyposis syndrome (SPS) is associated with an increased CRC risk. Studies have shown a that subset of patients with SPS develop CRC under endoscopic surveillance (interval cancers). Close endoscopic surveillance to prevent malignant progression of polyps has therefore been advised by several expert groups. However, due to a lack of prospective data, the optimal treatment approach with regard to surveillance intervals and removal of polyps is still largely unknown. As a consequence, patients with SPS may still be inadequately treated and consequently be at risk for developing CRC under surveillance. Conversely, over-treatment with unnecessary short surveillance intervals and removal of possible harmless lesions, which may result in complications, should also be avoided. In chapter 4 we prospectively evaluated a standardized endoscopic surveillance and polypectomy protocol. We followed a cohort of patients with SPS who received annual endoscopic surveillance from January 2007 through December 2012. All patients underwent clearing colonoscopy with removal of all polyps ≥3 mm. After clearance, subsequent follow-up colonoscopies were scheduled annually. During surveillance with a median follow-up time of 3.1 years, CRC was not detected. The cumulative risks of detecting CRC, advanced adenomas, or large (≥ 10 mm) serrated polyps after 3 surveillance colonoscopies were 0%, 9%, 34%, respectively. A total of 24% of patients were referred for preventive surgery because endoscopic treatment was not considered feasible. Based on these results we concluded that annual surveillance with complete removal of all polyps ≥3 mm with timely referral of selected high-risk patients for prophylactic surgery prevents the development of CRC in SPS patients without significantly increasing morbidity. Considering the substantial risk of polyp recurrence, close endoscopic surveillance seems warranted.

As mentioned before, previous studies have demonstrated that some patients with SPS do develop cancer under endoscopic surveillance. These so-called interval cancers may originate from lesions that are not detected with conventional colonoscopy techniques. Narrow-band imaging (NBI) is a technique that has been developed to enhance the detection of gastrointestinal lesions. By the use of light of a shorter wavelength the mucosal pit pattern and microvasculature of lesions are highlighted which may improve visualization. The study described in chapter 5 aimed to compare the polyp miss-rates of standard white light endoscopy with polyp-miss rates of narrow-band imaging in patients with SPS. Results of this study indicate that narrow-band imaging has no additional value in the detection of polyps compared with the standard technique of white light. We therefore do not support the routine use of NBI for polyp detection during endoscopic surveillance in patients with SPS. Whether other advanced imaging techniques may improve polyp detection is unknown and remains to be determined in future studies.

Although most SPS cases seem non-familial, presence of the disease in multiple family members has been described in previous reports. In addition, retrospective cohort

studies have demonstrated an approximately fivefold increased incidence of colorectal cancer in first-degree family members of patients with SPS compared with the general population. For this reason, most authorities advise surveillance colonoscopies for first-degree relatives of patients with SPS. Chapter 6 evaluates the diagnostic yield of single screening colonoscopy in first-degree relatives of patients with SPS. Significant polyps (defined as an adenoma, traditional serrated adenoma, sessile serrated adenoma/polyp or proximal hyperplastic polyp) were found in more than 40% of first-degree relatives. Multiple polyps were detected in almost 10% of first-degree relatives. Based on these results we believe that screening should be offered to all first-degree relatives of patients with SPS. Considering the observed early onset of polyps in our series, we advise to start surveillance at the age of 35 years or 5 years younger than the lowest age at time of diagnosis of SPS reported in the family.

Polyposis syndromes, such as familial adenomatous polyposis, are often associated with an expanded extracolonic tumor spectrum. Chapter 7 evaluates the extracolonic cancer risks for patients with SPS and their first-degree relatives. Our results show that the overall incidence of extracolonic malignancies in SPS patients and their FDRs is not increased compared with the general population. Hence, preventive measures, like surveillance for extracolonic cancer, are not indicated.

FUTURE PROSPECTIVES

Part I serrated polyps

Serrated polyps were once thought to have no clinical implications as they were regarded as innocuous lesions lacking any malignant potential. A growing body of evidence published over the past several years have challenged this traditional dogma and it is now widely recognized that serrated polyps may progress to CRC via the serrated neoplasia pathway.

Because of the potential neoplastic progression risk of serrated polyps, current guidelines recommend complete removal of all serrated polyps, except for diminutive serrated lesions in the rectosigmoid. Despite these recommendations studies have shown that serrated polyp detection rates vary greatly between endoscopists. This difference in serrated polyp detection rate might be caused by endoscopists who are not aware of the neoplastic progression risk of serrated polyps and therefore do not resect these lesions. Increasing the awareness of the malignant potential of serrated polyps among endoscopists is therefore a cornerstone for an improved detection of serrated polyps that might ultimately help to reduce the occurrence of interval cancers. In addition, improved endoscopic recognition of these lesions is also essential. Due to their flat morphology and unremarkable color, serrated polyps are easily overlooked. Knowledge

and recognition of specific endoscopic characteristics of serrated polyps could attract the attention of the endoscopist which may improve their detection rates. The research in this thesis demonstrated that sessile serrated adenomas/polyps harbor specific endoscopic features. Nonetheless, this concerned an image evaluation study performed by experts in the field. To assess whether these features can be used for recognition of sessile serrated polyps/adenomas and whether this will improve their detection remains to be determined in further validation studies. Also the value of advanced imaging techniques, such as chromoendoscopy and autofluorescence imaging, in specifically improving the detection of serrated polyps should be investigated in future studies.

Sessile serrated adenomas/polyps are considered to be the principal *high risk* serrated precursor lesion of CRCs arsing via the serrated neoplasia pathway. Adequate recognition of these high-risk serrated lesions may have several potential advantages. First, although one could argue that complete resection is needed for all detected serrated polyps, it seems likely that in general practice endoscopists compromise for time, costs and risks. Recognition of sessile serrated adenomas/polyps might aid endoscopists in selecting a polypectomy technique which more likely results in a complete resection (e.g. endoscopic mucosal resection), while a hyperplastic polyp appearing lesion can be removed with relatively lower risk techniques (e.g. cold snare polypectomy). Second, as mentioned above, current guidelines recommend to leave distal diminutive serrated polyps in situ as these polyps are considered as clinically irrelevant hyperplastic lesions that do not require treatment. However, the research in this thesis demonstrated that almost 10% of all distal diminutive lesions are actually sessile serrated adenomas/polyps which would be left in place with this treatment approach. Therefore, an endoscopist who opts to leave a distal diminutive serrated appearing lesion in situ should be able to adequately differentiate between a hyperplastic polyp and sessile serrated adenoma/polyp to make a correct decision. Future research should therefore evaluate whether it is possible to differentiate between hyperplastic polyps and sessile serrated adenomas/polyps during real time colonoscopy and should focus on the potential benefits in daily clinical practice.

Post-polypectomy surveillance guidelines for adenomas are based on observational studies that associate baseline colonoscopy findings to the risk of an advanced adenoma at follow up colonoscopy. Until recently, clinical guidelines did not recommend surveillance colonoscopies for individuals with serrated polyps. Several international societies have now incorporated postpolypectomy surveillance recommendation for serrated polyps into their guidelines. Also the recently updated Dutch post-polypectomy surveillance guideline has incorporated surveillance recommendations for individuals with large (≥10mm) serrated polyps. These recommendations are based on the hypothesis that patients with serrated polyps, likewise patients with adenomas, have an increased metachronous risk for developing colonic neoplasia at follow-up compared with individ-

uals without polyps. Although these guidelines are recognizing the clinical importance of these lesions, it should be noted that these surveillance recommendation are largely based on expert opinions without any clear evidence. Currently, a large multinational prospective trial (EPOS trial) is designed which will compare different surveillance intervals for patients with adenomas as well as patients with serrated polyps. The long-term results of this trial will be of imminent importance to our understanding of the natural history of serrated polyps and their potential metachronous cancer risk. Consequently this information should be used to establish an evidence based surveillance guideline for serrated polyps.

Serrated polyps provide not only challenges for gastroenterologists, also pathologists struggle to differentiate between the several different serrated polyp subtypes. In particular the hyperplastic polyp and sessile serrated adenomas/polyp are histologically hard to distinguish from each other and the interobserver agreement for the differentiation of serrated polyps among pathologists is only moderate. This may result in incorrect surveillance recommendations that could potentially lead to interval cancers. For this reason, any intervention that would improve the histological diagnosis of serrated polyp subtypes should be fully embraced. An interesting approach would be to use molecular markers for the differentiation of serrated polyps. Instead of relying on the interpretation of pathologists, this would provide a histological diagnosis without a human factor. To date, however, a reliable molecular marker has not been identified yet.

Part II serrated polyposis syndrome

SPS is a condition with an increased CRC risk for individuals, which is extended to their first-degree relatives. In contrast with most other polyposis syndromes, the underlying genetic defect of the disease is still unknown. What we do know is that SPS presents with a substantial phenotypic diversity and most experts believe that the syndrome, as currently defined by the WHO, represents a group of sub-conditions that are not yet further subcategorized. This makes it very difficult to assign a personal CRC risk to individual patients and their relatives. The research described in this thesis has shown that a subset of patients develop multiple recurrent serrated polyps and advanced adenomas while other patients may only develop a few small polyps during their subsequent surveillance colonoscopies. It is a future challenge to investigate whether it is possible to separate this high-risk subset of SPS patients from the ones with a minimal future risk of colonic neoplasia. For this reason, we believe it is important to centralize the management of patients with SPS in institutions with experience in this field to ensure optimal treatment, follow up and scientific research. Ultimately, it would be ideal to identify the genetic basis and penetrance of the disease. We would then hopefully be able to assign individual advanced neoplasia risks for patients with different phenotypes of SPS, allowing for a more tailored endoscopic management with regard to surveillance intervals,

polyp removal and consideration of preventive surgery. Until then, prospective screening studies should be performed to provide us with data to establish a safe and efficient surveillance protocol. The research in this thesis has shown that all patients with SPS undergoing annual surveillance with removal of polyps ≥3 mm have a very low risk of developing CRC. The next step will be to investigate whether we can safely extend the surveillance interval in certain subgroups to 2 years. In addition, future studies should evaluate the safety of leaving polyps smaller than 6mm in situ as this would certainly decrease the workload of the endoscopists and also avoid over-treatment.

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Jaarlijks worden ongeveer 13.000 mensen in Nederland gediagnosticeerd met darmkanker. Het is daarmee één van de meest voorkomende soorten van kanker in Nederland. Darmkanker ontstaat bijna altijd uit een poliep. Lange tijd is gedacht dat slechts één soort poliep, een adenoom, kan uitgroeien tot darmkanker. Echter, de laatste 10 jaar tonen studies aan dat ook ander soort poliepen, namelijk serrated poliepen, zich kunnen ontwikkelen tot darmkanker. Deze serrated poliepen werden tot voor kort altijd beschouwd als goedaardig en er bestond daarom geen reden om deze poliepen te verwijderen tijdens een colonoscopie. Dit is mogelijk één van de redenen waarom uit studies blijkt dat colonoscopie geen volledige bescherming biedt in het voorkomen van darmkanker. Dit proefschrift richt zich op de epidemiologie en de endoscopische kenmerken van serrated poliepen. Daarnaast bevat het proefschrift studies naar de optimale behandeling en surveillance termijn van patiënten met het serrated polyposis syndroom met behulp van conventionele en nieuwe endoscopie technieken.

Deel I serrated poliepen

Hoofdstuk 2 beschrijft de prevalentie van de verschillende soorten serrated poliepen in een groot cohort van patiënten (50-75 jaar) die een screening colonoscopie ondergaan. Doordat serrated poliepen lange tijd niet zijn opgespoord of niet zijn verwijderd tijdens een colonoscopie was er weinig bekend over de exacte prevalentie. In dit cohort betrof de prevalentie van hyperplastische poliepen, sessiel serrated adenomen/poliepen en traditionele serrated adenomen respectievelijk 24%, 4.8% and 0.1%. Van alle poliepen die werden verwijderd bleek 7% een sessiel serrated adenoom/poliep te zijn. Deze bevindingen suggereren dat serrated poliepen, inclusief sessiel serrated adenomen/poliepen, vaak worden gedetecteerd tijdens een screening colonoscopie. Dit betekent dat endoscopisten deze poliepen moeten kunnen herkennen en voldoende getraind moeten zijn om deze poliepen te verwijderen.

Sessiele serrated adenomen/poliepen zijn vaak vlak van vorm en hebben een onopvallende kleur. Hierdoor kunnen ze makkelijk worden gemist tijdens een colonoscopie. Daarnaast kunnen deze poliepen erg veel lijken op hyperplastische poliepen. Hyperplastische poliepen worden echter niet altijd verwijderd, omdat deze poliepen door sommige endoscopisten worden beschouwd als klinisch irrelevant. Het is daarom goed mogelijk dat een sessiel serrated adenomen/poliep wel wordt gedetecteerd, maar niet wordt verwijderd, omdat de endoscopist deze poliep beoordeelt als hyperplastische poliep. In hoofdstuk 3 hebben wij onderzocht of sessiele serrated adenomen/poliepen specifieke endoscopische kenmerken bezitten in vergelijking met hyperplastische poliepen. Endoscopische foto's van 150 verschillende soorten poliepen (adenomen, sessiele serrated adenomen/poliepen en hyperplastische poliepen) werden voorgelegd

aan verschillende endoscopisten uit verschillende landen en gescoord op bepaalde endoscopische kenmerken. Wij concludeerden dat een *wolkachtig oppervlakte*, een *onduidelijke begrenzing van de poliep*, een *onregelmatige vorm* en *zwarte stipjes in de crypten* specifieke endoscopische eigenschappen zijn van sessiele serrated adenomen/poliepen in vergelijking met hyperplastische poliepen. Deze specifieke eigenschappen zouden endoscopisten kunnen helpen om deze poliepen te herkennen en om ze beter te kunnen onderscheiden van hyperplastische poliepen.

Deel II serrated polyposis syndroom

Het serrated polyposis syndroom (SPS) is geassocieerd met een verhoogd risico op darmkanker. Uit onderzoek blijkt dat sommige patiënten met SPS darmkanker ontwikkelen ondanks dat zij endoscopische surveillance ondergaan (interval kankers). Frequente endoscopische surveillance wordt daarom geadviseerd door verschillende experts en internationale richtlijnen. Doordat prospectieve studies echter ontbreken is het optimale surveillance interval niet bekend. Bij een te lang surveillance interval lopen patiënt met SPS een risico op het ontwikkelen van darmkanker doordat zij inadequaat worden behandeld. Onnodig korte surveillance intervallen moet echter ook worden voorkomen omdat dit kan leiden tot onnodige complicaties. In hoofdstuk 4 beschrijven wij de resultaten van patiënten met SPS die jaarlijks een gestandaardiseerde colonoscopie ondergingen van 2007 tot 2012 in het Academisch Medisch Centrum. Alle patiënten ondergingen een *clearing* colonoscopie waarbij alle poliepen groter dan 2 mm werden verwijderd. Hierna ondergingen deze patiënten jaarlijks een surveillance colonoscopie waarbij opnieuw alle poliepen groter dan 2 mm werden verwijderd. Tijdens een mediane follow-up tijd van 3.1 jaar werd er geen darmkanker gediagnosticeerd. Het cumulatieve risico op het detecteren van darmkanker, hoog-risico adenomen en grote serrated poliepen na 3 surveillance colonoscopieën was respectievelijk 0%, 9% en 34%. Tijdens het onderzoek moest bijna een kwart van patiënten een preventieve (sub)totale colectomie ondergaan omdat het aantal gedetecteerde poliepen te veel was om endoscopisch te verwijderen. Op basis van deze resultaten concludeerden wij dat jaarlijkse surveillance in combinatie met het tijdig verwijzen van patiënten voor een preventieve colectomie de ontwikkeling van darmkanker helpt voorkomen in deze patiënten groep. Gezien het substantiële risico op het ontstaan van nieuwe poliepen lijkt frequente endoscopische controle gerechtvaardigd. Nieuwe studies zouden moeten uitwijzen of een verlenging van het surveillance interval naar 2 jaar bij bepaalde patiënten met SPS veilig kan worden geïntroduceerd.

Zoals eerder beschreven ontwikkelen sommige patiënten met SPS darmkanker ondanks dat zij endoscopische controles ondergaan. Deze zogenaamde interval kankers zouden mogelijk kunnen zijn ontstaan uit poliepen die niet worden gedetecteerd met conventionele colonoscopie technieken. Narrow-band imaging is een speciale licht-

techniek ontwikkeld om poliepen beter op te kunnen sporen. Door licht van een andere golflengte te gebruiken zou de microvasculatuur van poliepen beter zichtbaar worden en daardoor zou de poliep makkelijker gedetecteerd kunnen worden. In hoofdstuk 5 hebben wij twee endoscopische technieken met elkaar vergeleken, namelijk de standaard witlicht techniek en narrow-band imaging. De resultaten van dit onderzoek suggereren dat narrow-band imaging niet beter presteert in het detecteren van poliepen vergeleken met de standaard techniek. Wij zijn daarom van mening dat er geen plaats is voor narrow-band imaging in de behandeling van patiënten met SPS.

In de literatuur zijn verschillende families beschreven waarin meerdere familieleden worden beschreven met SPS. Daarnaast hebben retrospectieve cohort studies aangetoond dat eerstegraads familieleden van patiënten met SPS een verhoogd risico hebben op het ontwikkelen van darmkanker in vergelijking met een algemene populatie. Dit suggereert dat het syndroom mogelijk gepaard gaat met een erfelijk component. In de studie beschreven in hoofdstuk 6 hebben wij eerstegraads familieleden uitgenodigd om een screening colonoscopie te ondergaan. Significante poliepen, die wij definieerden als adenomen, traditionele serrated adenomen, sessiel serrated adenomen/poliepen of proximale hyperplastische poliepen werden in meer dan 40% van de eerstegraads familieleden gedetecteerd. Multipele poliepen (5 of meer) werden gevonden in bijna 10% van de eerstegraads familieleden. Gebaseerd op deze resultaten zijn wij van mening dat eerstegraads familieleden van patiënten met SPS een colonoscopisch onderzoek aangeboden dienen te krijgen. Gezien het hoge aantal gedetecteerde poliepen op een relatieve jonge leeftijd adviseren wij om deze colonoscopie aan te bieden vanaf de leeftijd van 35 jaar.

Polyposis syndromen gaan vaak gepaard met verhoogd risico op andere kankers dan alleen darmkanker. In hoofdstuk 7 beschrijven wij het risico op andere soorten kanker dan dikkedarmkanker in patiënten met SPS en hun eerstegraads familieleden in vergelijking met een algemene populatie. Wij tonen aan dat patiënten met het SPS en hun eerstegraads familieleden geen verhoogd risico hebben op het ontwikkelen van andere kankers dan darmkanker. Dit impliceert dat surveillance op andere kankers dan dikkedarmkanker niet noodzakelijk is.

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List of publications

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Yield of screening colonoscopy in first-degree relatives of patients with serrated polyposis syndrome
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C Hassan, E Quintero, JM Dumonceau, J Regula, C Brandão, S Chaussade, E Dekker, M Dinis-Ribeiro, M Ferlitsch, A Gimeno-García, Y Hazewinkel, R Jover, M Kalager, M Loberg, C Pox, B Rembacken, D Lieberman; European Society of Gastrointestinal Endoscopy
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Colonoscopy: basis principles and novel techniques
Y Hazewinkel and E Dekker
Nat Rev Gastroenterol Hepatol. 2011 Sep 6;8(10):554-64

PhD portfolio

PhD PORTFOLIO

Y. Hazewinkel
PhD period: 2010-2013
PhD supervisor: Prof. dr. E. Dekker and Prof. dr. P. Fockens

1. PhD training		
	Year	**Workload (ECTS)**
General courses		
- Practical Biostatistics	2011	1.1
- Clinical Epidemiology	2011	0.6
- Clinical Data Management	2011	0.3
- Basis Course in Legislation and Organization for Clinical Researchers	2010	0.9
Seminars, workshops and master classes		
- Weekly department seminars Gastroenterology	2010-2013	4
Oral presentations		
- Coloscopie surveillance na verwijdering van serrated poliepen (symposium)		
NVGE voorjaarsvergadering	2013	0.5
- Prevalence and distribution of serrated polyps in individuals undergoing primary screening colonoscopy		
NVGE voorjaarsvergadering	2013	0.5
- Feasibility and efficacy of a prospective annual surveillance protocol in serrated polyposis syndrome patients: 2 year follow up results.		
Digestive Disease Week, San Diego	2012	0.5
NVGE najaarsvergadering	2011	0.5
- High polyp detection rate in first-degree relatives of patients with serrated polyposis syndrome: A prospective study.		
Digestive Disease Week, San Diego	2012	0.5
NVGE voorjaarsvergadering	2012	0.5
- The risk of non-colorectal malignancies in serrated polyposis syndrome patients and their first-degree relatives.		
NVGE najaarsvergadering	2011	0.5
(Inter)national conferences		
- Digestive Disease Week	2012, 2013	2
- United European Gastroenterology Week	2011, 2012	1.5
- International Society for Gastrointestinal Hereditary Tumours	2010	1
- NVGE voorjaarsvergadering	2011, 2013	1
- NVGE najaarsvergadering	2010, 2011	1

Other			
-	Task group Dutch post-polypectomy colonoscopy surveillance guideline	2012-2013	3
-	Task group ESGE post-polypectomy colonoscopy surveillance guideline	2013	2
-	Editor of ESGE eLibrary colonoscopy video: the basics	2012-2013	4
-	Biweekly CRC research meeting	2010-2013	3

2. Teaching

		Year	Workload (Hours/ECTS)
Supervising			
-	D. van den Buijs Quality Indicators In Colonoscopy: Do independent performing fellows meet the accepted outcome measures?	2012	1
-	R.B. Klanderman Colonoscopy quality in fellows performing independently	2012-2013	2

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Lieve Iet, jij maakt mij significant gelukkig. Wij zijn nu met drieën, helemaal fantastisch!

Curriculum vitae

CURRICULUM VITAE

Yark Hazewinkel werd geboren op 11 november 1984 in Amsterdam. Vanaf zijn derde jaar groeide hij op in Hoofddorp. In 2003 behaalde hij zijn Atheneum diploma aan de Katholieke Scholengemeenschap Hoofddorp. Zijn artsexamen behaalde hij in 2010 aan de Universiteit van Amsterdam. Zijn keuze co-schap tropische geneeskunde doorliep hij in het St. Lukes Hospital in Malawi. Na deze enerverende en bijzondere ervaring begon hij als arts-onderzoeker aan een promotietraject onder begeleiding van prof. dr. E. Dekker en prof. dr. P. Fockens in het Academisch Medisch Centrum. Sinds september 2013 is hij begonnen aan zijn vooropleiding interne geneeskunde in het Onze Lieve Vrouwe Gasthuis in Amsterdam (opleider dr. Y.F.C. Smets). Na afronding van zijn vooropleiding zal hij starten met zijn opleiding tot maag-darm-leverarts in Academisch Medisch Centrum in Amsterdam (opleider prof. dr. U.H.W. Beuers).