Serrated polyps of the colon and rectum

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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% CI 1.57-6.15) and a cloud-like surface (OR 2.65 95% CI 1.21-5.78) were associated with 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
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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. 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. 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 \( \chi^2 \) 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. 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). Interpretation of \( \kappa \)-values was done according to Landis and Koch.

**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 \( \geq \) 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 II SSA/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.
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...
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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).

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.
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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. In contrast, studies systematically describing and characterizing the endoscopic features of SSA/Ps are scarce and often lack a systematic approach. 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 to HPs and adenomas.
Table 3. Validation set. Independent endoscopic predictors for SSA/P histology and corresponding interobserver agreement among 5 observers

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR-WLE</th>
<th>NBI</th>
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<tr>
<td></td>
<td>Multivariate analysis</td>
<td>Interobserver agreement</td>
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<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
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<tr>
<td>(1) Indistinctive borders</td>
<td>3.11 (1.57-6.15)</td>
<td>0.001</td>
</tr>
<tr>
<td>(2) Cloud-like surface</td>
<td>2.65 (1.21-5.78)</td>
<td>0.015</td>
</tr>
<tr>
<td>(3) Pit pattern IISSA/P</td>
<td>1.89 (0.74-4.85)</td>
<td>0.186</td>
</tr>
<tr>
<td>(4) Dark spots inside the crypts</td>
<td>0.79 (0.35-1.77)</td>
<td>0.562</td>
</tr>
<tr>
<td>(5) Normal VPI</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(6) Irregular shape</td>
<td>1.57 (0.74-3.31)</td>
<td>0.237</td>
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</table>

*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
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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.

<table>
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<th>Table 4. Validation set. Sensitivity, specificity and diagnostic accuracy of the independent predictive SSA/P features assessed with HR-WLE and NBI</th>
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<tr>
<td><strong>HR-WLE % (95% CI)</strong></td>
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<tr>
<td>Indistinctive borders</td>
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<td>Sensitivity</td>
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<td>Specificity</td>
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<td>Accuracy</td>
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HR-WLE: High resolution white light endoscopy, NBI: narrow-band imaging, CI: confidence interval

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<tr>
<th>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*</th>
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<tr>
<td><strong>HRE</strong></td>
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<tr>
<td>Fraction %, (95% CI)</td>
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<tr>
<td>Sensitivity</td>
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<tr>
<td>Specificity</td>
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<td>Accuracy</td>
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</table>

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 HRE = 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
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 nonelected 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. Furthermore, a previous study from Japan reported that SSA/Ps possess a more granular surface and had vaguer borders compared to HPs. 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. The pits of this Type II-0 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). 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. 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. 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. 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.

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.
REFERENCE LIST


