Serrated polyps
IJspeert, J.E.G.

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CHAPTER 13
Thesis summary and future prospects
**CHAPTER 13**

**THESIS SUMMARY**

Colorectal cancer (CRC) arises from polyps during the course of several years. Besides adenomatous polyps, serrated polyps have been identified as precursors of colorectal cancer (CRC) and 15-30% of all CRCs may arise via the “serrated neoplasia pathway”. This finding has resulted in a paradigm shift in cancer prevention, since nowadays also all clinically relevant serrated polyps should be detected and resected during colonoscopy. Post-colonoscopy interval carcinomas are defined as CRCs, diagnosed within the time interval to the next surveillance colonoscopy. A relatively large proportion of these post-colonoscopy interval CRCs arise from serrated polyps. This problem seems to be caused by an assemblage of several clinical as well as translational issues. Firstly, serrated polyps are difficult to detect during colonoscopy, due to their discrete appearance. As a result, the detection rate of serrated polyps is widely variable among endoscopists. Secondly, not every serrated polyp is routinely removed during colonoscopy in daily practice, and especially small and diminutive hyperplastic polyps in the distal colon are often not resected by endoscopists. As the endoscopic differentiation of premalignant sessile serrated polyps (SSP) and hyperplastic polyps tends to be difficult for endoscopists as well as for pathologists, also premalignant lesions might not be removed. Furthermore, as the genomic changes responsible for the serrated polyp to CRC progression have only been partially unravelled, identification of those serrated polyps truly at risk to develop into CRC remains a serious challenge. Thirdly, the endoscopically indistinct borders of SSPs are a risk for incomplete resection, resulting in residual tissue. Lastly, current faecal immunochemical test (FIT) based population screening programs are not targeted at detecting advanced serrated polyps, besides advanced adenomas and CRCs.

The studies described in this thesis were performed to further clarify the serrated neoplasia pathway and to try and improve the clinical management of serrated polyps in order to decrease the number of CRCs arising from serrated polyps.

**Chapter 1** is a review highlighting the existing literature documenting the serrated neoplasia pathway and describing the clinical implications of the association between serrated polyp subtypes and CRC occurrence. Based on current evidence, we concluded that, although progression has been made compared with a decade ago, substantial gaps remain in the understanding of the malignant progression of benign serrated polyps. Much of the included studies represent retrospective observational analyses, lacking high-quality endoscopic, histopathological and molecular data.

In **Chapter 2** we have studied a comprehensive panel of SSPs with a focus of dysplasia or cancer and explored molecular alterations related with the serrated neoplasia pathway. Cancer cell signalling pathways associated with progression in SSPs were evaluated and clinical as well as molecular features of MLH1 deficient and MLH1 proficient SSPs with a component of dysplasia or cancer were characterized. Two independent pathways were found. The first pathway, characterized by
an early BRAF mutation, broad promoter CpG island methylation and loss of MLH1 was present in 60% of cases and almost exclusively detected in SSPs in the proximal colon of women at a relatively older age. Microsatellite instability could be found even in the smallest lesions with loss of MLH1 expression. The second pathway, characterized by an early BRAF mutation, a more mild promoter CpG island methylation phenotype and frequent dysfunctional signalling in the WNT, TP53 and/or the TGF-β pathway was present in 40% of lesions, both in male and female patients of a relatively younger age. Identification of these pathways in SSPs "caught in the act" to develop into cancer contributes to better understanding early carcinogenesis of full-blown BRAF mutated/microsatellite instable (pathway one) as well as BRAF mutated/microsatellite stable (pathway two) CRCs and might eventually facilitate tailored methods for screening and treatment of SSPs and SSP-derived CRCs.

In Chapter 3 these options for screening are highlighted from a more clinical point of view, by evaluating the prevalence of serrated polyt subtypes among two primary colonoscopy CRC screening cohorts and three screening cohorts in which a faecal occult blood test (FOBT) was used as triage test before colonoscopy. Data were collected from five European countries. This study was performed in an attempt to better understand reported serrated polyp prevalence among Western countries and to enable guidance for detection standards. The prevalence of patients with any serrated polyp ranged between 15.1-27.2% (median 19.5%), with any SSP between 2.2-4.8% (median 3.3%) and with any clinically relevant serrated polyp between 2.1-7.8% (median 4.6%). Regarding the prevalence of SSPs or clinically relevant serrated polyps, no structural differences were found between the FOBT-based screening cohorts and the primary colonoscopy cohorts. Furthermore, in the current study no uniform gender and/or age differences in number needed to screen to detect at least one SSP or at least one clinically relevant serrated polyp were present. Therefore, the median prevalence of serrated polyp subtypes, as found in this study, could contribute to define minimum standards for detection in both males and females between 50-75 years in CRC screening programs.

Results from this study can be compared with the results from Chapter 4, in which we evaluated the prevalence, distribution and risk of SSPs in a colonoscopy centre with a high adenoma detection rate and experienced gastrointestinal pathologists. We showed that in general colonoscopy practice the prevalence of SSPs is higher than earlier reported (8.2% overall, increasing to 9.0% for individuals above 50 years of age) and dependent on the indication for colonoscopy (association with the indications surveillance and familial CRC risk as compared to the indication symptoms). Furthermore, we showed that SSPs have an evident association with the presence of synchronous advanced neoplasia, although lower than earlier reported in literature. Results from this study can guide standards for the detection rate of serrated polyps in colonoscopy practice. These standards should be adjusted to the predominant type of patients in an individual colonoscopy centre.

Besides FOBT-based screening, other triage tests to be used in CRC screening have been discussed in recent literature. Among others, computed tomography colonography (CTC) was evaluated for
detection of high-risk adenomas and CRCs, but not for the performance in the detection of high-risk SSPs. In Chapter 5 we compared the performance of CTC to colonoscopy for the detection of large and/or dysplastic SSPs. We demonstrated that, in average-risk individuals aged 50 years and above, the detection rate of high-risk SSPs is significantly higher for colonoscopy than CTC as primary CRC screening modality, with an odds ratio to detect at least one high-risk SSP of 5.5 (95% CI 2.6-11.6; p<0.001) overall and an odds ratio to detect at least one high-risk SSP as most advanced lesion of 7.7 (95% CI 2.7-21.6; p<0.001). As compared to the findings in the colonoscopy arm, especially flat SSPs with dysplasia located in the proximal colon were often not detected with the current CTC screening strategy. Therefore, CTC might be of less value as a primary screening tool for CRC.

Alternatively, risk stratification systems using clinical risk factors can also be used to triage patients for colonoscopy in a CRC screening setting. In Chapter 6 we evaluated whether the well-known clinical risk factors for the detection of advanced adenomas and CRCs, such as smoking, could also act as risk factors for advanced serrated polyps. Our analysis showed that current smoking was strongly associated with advanced serrated polyps as most advanced detected lesion in an asymptomatic screening population, with an odds ratio of about four. In addition, higher fibre intake was moderately associated with the presence of advanced serrated polyps. Other CRC risk factors, including faecal haemoglobin level, did not show a significant association with the presence of at least one advanced serrated polyp. We believe that the low performance of FIT in detecting advanced adenoma and advanced serrated polyps, and the promising information of CRC risk factors, could and should lead to the development of more accurate screening programs for CRC. These would be programs that not only detect CRCs and advanced adenomas, but also advanced serrated polyps. Such programs may include faecal haemoglobin, DNA-testing or other molecular markers, but should also explore the incremental value of easy-to-collect information on CRC risk factors, such as smoking behaviour.

The subsequent four chapters of this thesis discuss efforts to improve the clinical management of serrated polyps by endoscopists as well as pathologists in daily practice. As stated above, the detection rate of serrated polyps is widely variable among endoscopists, increasing the risk of interval cancers among low detectors. Establishment of a colonoscopy quality parameter for the detection of serrated polyps might help to increase colonoscopy quality. In Chapter 7 we compared the proximal serrated polyp detection rate among endoscopists and analysed the association between this parameter and the adenoma detection rate as well as the detection rate of all clinically relevant serrated polyps. We demonstrated that the detection rate of proximal serrated polyps is widely variable among endoscopists and strongly correlated with the detection rate of all clinically relevant serrated polyps, while the detection rate of proximal serrated polyps and adenomas was moderately correlated. Variability in detection of serrated polyps could largely be explained by a difference in the detection rate of serrated polyps above 5mm and even above 9mm, which suggests that a significant number of relevant and premalignant serrated polyps are missed during colonoscopy. Therefore, the measurement of the proximal serrated polyp detection rate, alongside the adenoma detection rate,
seems a valuable parameter to ensure a high quality colonoscopy. To endorse this recommendation, future research should determine the relationship between the detection rate of proximal serrated polyps and the risk of interval carcinomas.

In Chapter 8 we focused on another aspect of colonoscopy quality: endoscopic polyp differentiation. A high accuracy of optical polyp diagnosis is important to enable targeted polyp treatment for polyps during colonoscopy. We demonstrated that endoscopic characterization of diminutive SSPs in daily practice is challenging as only 24.4% of diminutive SSPs were accurately identified during real time colonoscopy in an ambulatory endoscopy unit. As a result, incorporating SSPs in an optical diagnosis strategy for diminutive polyps has considerable impact. Diminutive SSPs determined 6.9% of post-polypectomy surveillance assignments using the 2012 USMTF surveillance guideline. The accuracy of post-polypectomy surveillance assignments based on an optical diagnosis strategy was significantly lower for patients with diminutive SSPs compared to those without diminutive SSPs (53.3% vs. 78.1%, p<0.01). Furthermore, the pooled negative predictive value per polyp for diminutive neoplastic histology in the recto-sigmoid was significantly lower in patients with diminutive SSPs than in patients without diminutive SSPs (50.0% vs 84.3%; p<0.01). These data demonstrate the need for a validated and structured classification system for the optical diagnosis of all diminutive polyps, including SSPs.

In Chapter 9 we discussed the development and validation of such a classification system. We developed the first integrative classification system for optical diagnosis of small and diminutive adenomas, hyperplastic polyps and SSPs (the WASP-classification), combining the existing NICE-classification and criteria by Hazewinkel et al. in a stepwise approach. A structured training about the use of the WASP-classification resulted in an overall significant increase in diagnostic accuracy of optical diagnosis for ten consultant gastroenterologists predicting polyp histology. The improved diagnostic accuracy of optical diagnosis showed to be sustainable during long-term follow-up in an image evaluation setting. Furthermore, the pooled negative predictive value with high confidence of diminutive neoplastic lesions was 91%, while 7 out of 10 individuals scored a negative predictive value ≥90%. This is the first classification system that facilitates the optical characterization of all prevalent polyp subtypes, including premalignant SSPs and could eventually contribute to realize a safe implementation of targeted polyp treatment based on the optical diagnosis of polyps. Before this could be realized, the diagnostic performance of the WASP-criteria should be assessed during real-time colonoscopy.

In Chapter 10 we focused on the diagnosis of serrated polyps by pathologists. Within histopathology laboratories, we evaluated the nationwide variability in the frequency of diagnosing SSPs as compared to hyperplastic polyps within the Dutch national faecal immunochemical test based screening program for CRC. Besides, we assessed the effect of the implementation of an e-learning module on the interlaboratory consistency. The overall median frequency of diagnosing a SSP as compared to all serrated polyps was 23% and ranged between 5 and 47% for the different laboratories. In total, 22/44
(50%) laboratories showed a significantly higher or lower OR for the diagnosis of a SSP, as compared to the laboratory with the median odds. After implementation of an obligatory e-learning module the variability between laboratories significantly decreased (p=0.02). These results first of all demonstrate that interlaboratory variability in the frequency of diagnosing SSPs is still an important issue in daily practice. This is of clinical relevance since ideally, post-polypectomy surveillance intervals should rely on the histopathological classification of serrated polyp subtypes as the different lesions carry different risks for malignant transformation and probably also for metachronous lesions. Secondly, the results from this study show that the implementation of an obligatory e-learning module might help to diminish interlaboratory variability, which indicates that education and awareness about this topic is necessary and should be globally advocated.

In the last two chapters the clinical management of serrated polyposis syndrome is discussed. This syndrome is characterized by multiple serrated polyps throughout the colon and is associated with an increased risk for CRC. As germline mutations for serrated polyposis syndrome have not yet been found, this disease has been defined by a clinical diagnosis by the World Health Organisation (WHO). In Chapter 11 a case report is described regarding the clinical course of a 59 year-old woman, in whom serrated polyposis syndrome was not recognized during initial colonoscopy, resulting in occurrence of metachronous colorectal cancer during surveillance. This case-report illustrates the risks of serrated polyposis syndrome, and demonstrates the importance of proper diagnosis and treatment strategies for these patients. Finally, in Chapter 12 we assessed CRC risk factors in a large international cohort of 434 patients with serrated polyposis syndrome and evaluated the overall risk of CRC during surveillance. The presence of at least one serrated polyp containing dysplasia, at least one advanced adenoma and/or a combined WHO 1&3 phenotype was associated with CRC. Conversely, patients with a history of smoking showed an inverse association with CRC, possibly due to a different pathogenesis of disease. After clearing of all relevant lesions, the incidence rate of CRC during surveillance was 1.9 events/1000 person years of surveillance, corresponding to a 5-year cumulative risk of 1.5%. These results suggest a lower risk for CRC during surveillance than reported in literature. Personalised treatment and surveillance based on individual risk factors might decrease patient burden as well as the number of colonoscopy interval CRCs in patients with serrated polyposis syndrome.

FUTURE PROSPECTS

When evaluating the current knowledge regarding serrated polyps of the colorectum, one can appreciate the fact that many dogmas have been breached in the past decade. While polyps from the serrated class were regarded as homogeneous and innocuous lesions in the recent past, nowadays some of these lesions are proven as being premalignant. Furthermore, several serrated polyp subtypes have been acknowledged, accompanied by a variable risk of malignant progression. This
growing body of evidence about the risk of serrated polyps has gradually led to a paradigm shift in both cancer prevention as well as treatment strategies. The results of the studies described in this thesis have contributed to reach these goals.

Although substantial progress in our knowledge has been made compared with a decade ago, substantial gaps remain. For instance, the pathophysiology of malignant progression of benign serrated polyps is only marginally understood. Also, optimal strategies for screening, treatment and surveillance for those polyps have not yet been developed. Ongoing research should mainly focus on unravelling the biological mechanisms underlying this disease, which might enable us to translate this knowledge into better diagnostic as well as therapeutic strategies. Simultaneously, national and international organisations should stimulate awareness about the proper clinical management of serrated polyps in order to improve quality of care and should implement adapted screening and surveillance strategies to decrease the number of cancers derived from serrated polyps.

**Molecular biology of the serrated neoplasia pathway**

As mentioned above, one of the main goals of ongoing research should be to further unravel the serrated neoplasia pathway. Studies that linked the molecular characteristics of SSPs with CRC have provided useful insight in the pathogenesis of the serrated neoplasia pathway. However, less well understood are the (epi)genetic alterations directly responsible for the progression from a benign polyp to malignant disease, as well as the behaviour of these cancers in its earliest form. Results from chapter 2 of this thesis demonstrated two separate pathways of carcinogenesis in SSPs, both characterized by unique molecular as well as clinical characteristics. The main difference between both pathways was the presence or absence of functional impairment of the mismatch repair system due to MLH1 promoter hypermethylation. Identification of these pathways in SSPs “caught in the act” in becoming cancer appears of great importance, since these lesions are the designated precursors of either BRAF mutated/microsatellite instable (pathway one) as well as BRAF mutated/microsatellite stable (pathway two) CRCs. To facilitate uniform practice, a large international consortium has recently developed an overarching classification system, identifying four CRC molecular subtypes based on gene expression profiles (Guinney et al. Nature Medicine 2015). Each of these subtypes had an unique course and prognosis. In this classification system, CRC from consensus molecular subtype 1, associated with a relatively good prognosis, show remarkable comparisons with our group of MLH1 deficient SSPs with dysplasia or cancer. On the other hand, SSPs with dysplasia or cancer and a MLH1 proficient phenotype show similarities with BRAF mutated CMS4 CRC, which is associated with a worse prognosis. Linkage of the CMS subtypes and its precursor lesions could help to optimize screening and personalize options for treatment. Identification of these pathways, however, should only be seen as a stimulus of future research. Hopefully, comparison of the whole exome as well as the whole methylome of both the non-progressed and the progressed component of SSPs with dysplasia or cancer can help to identify essential tumour suppressor genes involved in the malignant transformation of benign serrated polyps. These results should be translated to the
Clinical management of serrated polyps

Screening

In order to enable meaningful progress in the prevention and treatment of CRCs derived from serrated polyps, efforts should also focus on improvement of the clinical management of serrated polyps. As mentioned above, optimal clinical management of serrated polyps and disentangling the biology of the serrated neoplasia pathway are both intertwined. In January 2014 population based screening was introduced in the Netherlands, using a FIT as triage modality. Similar population screening programs were introduced in multiple other Western countries. These screening programs were set up to detect individuals with advanced adenomas and CRCs. However, results from chapters 3 and 6 demonstrate that FIT does not select individuals with an increased risk of advanced serrated polyps. Public health organisations and research groups should collaborate and lay the groundwork for other screening modalities, designed to detect patients with CRCs and advanced adenomas, but also advanced serrated polyps. Studies using molecular stool testing as a triage modality have shown promising results, but the diagnostic accuracy of the current tests should be increased in order to improve efficacy of screening programs. Moreover, currently whole stool samples are needed to enable molecular stool testing, resulting in an unattractive and laborious situation for population based screening. Another screening modality that might include information on the serrated pathway is measurement of circulating tumour DNA in the blood. At the moment, this is mainly investigated as a method to detect individuals with recurrence of CRC. However, this technique might also have a role in CRC screening in the near future.

Polyp detection

Irrespective of the type of triage modality used for screening, colonoscopy will remain the reference standard to detect and resect colonic polyps and cancer, including serrated polyps. However, also colonoscopy has its shortcomings, as at least 10% of lesions are missed during inspection. Results from chapter 7 demonstrated that the detection rate of proximal serrated polyps is widely variable among endoscopists, suggesting a high miss-rate of serrated polyps by low detectors. Increasing awareness, targeted training, monitoring and benchmarking might help to increase overall detection of serrated polyps and should be globally advocated. Of importance, this policy should already be implemented during gastroenterology residency in order to reach optimal results. Use of advanced
imaging techniques should also be further investigated to increase serrated polyp detection, but will only be supportive to proper training and colonoscopy experience. Another matter of debate is the question whether the proximal serrated polyp detection rate should be established as autonomous colonoscopy quality parameter, besides the adenoma detection rate. As mentioned, endoscopists show a widely variable detection rate of proximal serrated polyps and results from chapter 7 demonstrated that this parameter is only moderately correlated with the adenoma detection rate. Therefore, acknowledging their importance in interval carcinomas, one can argue that endoscopists should demonstrate appropriate scores regarding both parameters. However, a clear correlation was demonstrated between lower adenoma detection rate and the occurrence of colonoscopy interval cancers, which was not yet demonstrated for the proximal serrated polyp detection rate. Such studies should be performed in order to establish the proximal serrated polyp detection rate as independent quality parameter. Ideally, studies should evaluate the difference between three groups of endoscopists, being 1) high adenoma and high serrated polyp detectors, 2) high adenoma and low serrated polyp detectors and 3) low adenoma and low serrated polyp detectors. Only if endoscopists from groups 1 show better results than endoscopists from group 2 with regard to the occurrence of colonoscopy interval cancer, the proximal serrated polyp detection rate seems of value to increase colonoscopy quality.

Polyp resection
Besides detection, colonoscopy is also the reference standard for polyp resection. Incomplete resection of premalignant polyps is one of the major reasons of colonoscopy interval cancer, and should therefore be prevented. Research suggested that SSPs demonstrate a higher risk of incomplete resection, as compared to adenomas. However, more recent studies show that with the use of proper polypectomy techniques, such as endoscopic mucosal resection, this risk seems negligible. The crux of the matter might be to appropriately delineate the borders of SSPs, before performing polypectomy. Lifting of the lesion with a solution including a dye (methylene blue or indigo carmine) enables sharp delineation and should be advocated when resecting a SSP. Digital chromoendoscopy might also enable delineation, but validation data on either technique are not available. Validated classification systems for the endoscopic differentiation of adenomas, hyperplastic polyps and SSPs might aid to choose targeted polyp resection techniques. The WASP classification, as discussed in chapter 9, might be such as classification system using digital chromoendoscopy, but should be validated during real time colonoscopy before implemented in daily practice. The WASP classification might also be of use to facilitate the implementation of a resect-and-discard policy, but this topic is beyond the scope of the current discussion.

Post-polypectomy surveillance
Another aspect of clinical management that will help to decrease the occurrence of serrated polyp derived CRCs is pursuing proper post-polypectomy surveillance. To improve the safety and cost-effectiveness of current post-polypectomy surveillance intervals, several challenges have to be
overcome. Currently, the long-term risk of advanced neoplasia after the resection of serrated polyp subtypes is not yet well known. This is mostly due to the lack of well-designed prospective cohort studies. Results from retrospective studies do exist. These studies only evaluated and compared the post-polypectomy surveillance of those patients that were diagnosed with serrated polyps during a time-period that the risk of serrated polyps was not well established. This would most probably have resulted in major selection bias and unreliable results. Recently, research groups from several European countries have joined hands to set up such a study. In this so-called European Polyp Surveillance (EPoS) study individuals diagnosed with a clinically relevant serrated polyp will receive a surveillance colonoscopy after 5 and 10 years, in order to assess the risk of CRC. Hopefully, results from this study will enable tailored surveillance in the near future.

A second challenge is the fact that distinguishing SSPs from hyperplastic polyps tends to be difficult for pathologists in daily practice. As a result, both the current European as well as the Dutch surveillance guidelines do not distinguish histopathological subtypes of serrated polyps with regard to post-polypectomy surveillance advice. Therefore, a considerable number of patients with serrated polyps will receive an inadequate post-polypectomy surveillance advice, resulting in an increased risk of both over as well as under treatment. Results from chapter 10 of this thesis demonstrated that implementation of a structured e-learning module may help to decrease interobserver variability between pathologists. However, education alone will not be enough to overcome this issue, as another problem is the lack of a clear and uniform definition for SSPs. This is probably caused by the fact that hyperplastic polyps and SSPs seem part of a continuous spectrum. However, defining sharp margins in this morphological continuum will help to increase the understanding their clinical relevance. Only if SSPs and hyperplastic polyps are distinguished based on the same characteristics throughout the world, the risk of both entities can be properly assessed and comparisons can be made between countries. Ideally, a well-substantiated definition should be established, directed by the World Health Organisation.

Serrated polyposis syndrome

Finally, a better management of patients with serrated polyposis syndrome is of importance to reach the goals of this thesis. As germline mutations for serrated polyposis syndrome are unknown, this disease has been clinically defined by the World Health Organisation (WHO) by the presence of at least five serrated polyps proximal to the sigmoid colon, of which two ≥ 10 mm in diameter (WHO criterion-1), the presence of one serrated polyp proximal to the sigmoid and a first degree relative with SPS (WHO criterion-2) and/or 20 serrated polyps or more, irrespective of size, but located throughout the colorectum (WHO criterion-3). Based on current knowledge, some aspects of the current WHO guidelines for the diagnosis of serrated polyposis syndrome can be questioned. For instance, it would seem appropriate to remove WHO criterion-2 from the definition of serrated polyposis syndrome and to offer 5-yearly surveillance to all first degree relatives of a patient with serrated polyposis syndrome. In addition, in the current WHO guideline, rectal lesions are excluded from the clinical
diagnostic criteria and for criteria 1 and 2 lesions in the sigmoid colon are also excluded. This seems mainly driven by the fact that diminutive hyperplastic polyps in the rectosigmoid should probably not be taken into account for the diagnosis of serrated polyposis syndrome. However, results from chapter 12 showed that almost 50% of all CRCs in serrated polyposis syndrome patients were located in the rectosigmoid. These cancers were detected in patients that were significantly younger than patients with CRCs located proximal to the rectosigmoid. It has not been excluded that a proportion of these CRCs may have arisen from an adenoma rather than a serrated polyp, but the substantial proportion of the CRC arising in the rectosigmoid at a young age suggests that those serrated polyps located in the rectosigmoid, are of clinical importance. It would seem reasonable then to re-assess the WHO criteria and not exclude lesions purely on their location without taking in to account their size and histopathology. Hopefully these adjustments to the current WHO guidelines could help to assign those patients that are truly at increased risk of developing CRC.

Besides redefining the current WHO criteria for serrated polyposis syndrome, future studies should focus on the safety and feasibility of personalised treatment and surveillance for patients with serrated polyposis syndrome in order to decrease patient burden as well as the incidence of colonoscopy interval CRCs. Several risk factors, as described in chapter 12, e.g., history of at least one serrated polyp containing dysplasia, at least one advanced adenoma, a combined WHO 1&3 phenotype and/or no history of smoking, could help to risk stratify the individual patients with serrated polyposis syndrome for different surveillance intervals.

In conclusion, both translational as well as clinical studies from recent years have rapidly enhanced the knowledge about the clinical management of serrated polyps. These studies have triggered an ongoing global improvement in colonoscopy quality. However, several essential gaps remain in our understanding, which could be dissolved in the years to come. Hopefully, this would result in a rapid decrease of post-colonoscopy interval carcinomas that arose from serrated polyps.