Serrated polyps
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General introduction and Outline of this thesis
**GENERAL INTRODUCTION**

Colorectal cancer (CRC) is among the most common types of cancer worldwide and is a major challenge for clinicians in daily practice. Endoscopic detection and resection of colorectal precursor lesions for cancer, i.e. polyps, significantly decreases both CRC incidence as well as mortality. For this reason, population based CRC screening programs have been enrolled worldwide, often with the use of a non-invasive triage modality to select high risk individuals for colonoscopy. Implementation of CRC screening programs showed to be feasible as well as cost-effective. However, the diagnostic accuracy of commonly used triage tests, such as the faecal immunochemical test (FIT), are far from perfect. Furthermore, also colonoscopy itself is not fully protective. A substantial number of CRCs arise in patients that underwent colonoscopy in the previous years, especially in the right-sided colon. In a recent study these so-called colonoscopy interval cancers showed to be responsible for up to 9% of all diagnosed CRCs. For this reason, the overarching performance of CRC screening strategies as well as the individual performance of endoscopists should be continuously monitored and, if necessary, improved in order to decrease CRC incidence. Management of serrated polyps seems to play a key role in this process.

**Serrated polyps**

Until recently, adenomas were considered to be the only type of colonic polyps with malignant potential. However, research from recent years suggests that 15-30% of CRCs might originate from serrated polyps 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. Though, not all serrated polyps appear to be premalignant. The recent classification of the World Health Organization categorized serrated polyps into hyperplastic polyps, sessile serrated polyps without dysplasia, sessile serrated polyps with dysplasia and traditional serrated adenomas. Diminutive hyperplastic polyps located in the rectosigmoid are generally considered benign, whereas larger and/or proximally located hyperplastic polyps, as well as all sessile serrated polyps and traditional serrated adenomas are considered to possess a higher neoplastic potential. Identification of the serrated polyps truly at risk to develop into CRC, however, remains a serious as well as clinically relevant challenge.

Recent studies demonstrated that of all colonoscopy interval carcinomas, the largest proportion seems to arise from serrated polyps rather than from adenomas. Among other reasons, this might be due to an inadequate clinical management of serrated polyps. First, serrated polyps in general and sessile serrated polyps in specific are easily missed during colonoscopy due to their inconspicuous appearance. Second, the clinical relevance of serrated polyps is not yet widely accepted among gastroenterologists. As a result, serrated polyps that are detected during colonoscopy are often not resected nor reported. Third, also complete endoscopic resection of serrated polyps seems to be challenging. Last, the surveillance intervals after polypectomy of serrated polyps are not yet well defined, resulting in both over- as well as under-treatment. This is partly due to the inconsistency
in histopathological differentiation of serrated polyp subtypes.\textsuperscript{26,27} To decrease the number of CRCs arising from serrated polyps, studies that clarify the serrated neoplasia pathway and improve the clinical performance in the management of serrated polyps are needed. The studies in this thesis aimed to contribute to these goals.

\textbf{OUTLINE OF THIS THESIS}

As an introduction to this thesis, we describe the basic concepts of the serrated neoplasia pathway and its clinical implications in cancer prevention in \textit{chapter 1}. These known concepts form the basis for \textit{chapter 2}, in which we report on epigenetic as well as genetic alterations responsible for the transition from sessile serrated polyp to CRC and evaluate the differences between MLH1 proficient and MLH1 deficient lesions with dysplasia or cancer.

In \textit{chapter 3} we present the prevalence of serrated polyp subtypes, as reported in five large European CRC screening cohorts. The influence of age and gender on serrated polyp detection rate are discussed in this chapter as well as the potential incremental value of FIT as triage modality to detect serrated polyps. Results from this study can be compared with the results from \textit{chapter 4}, in which we discuss the prevalence of sessile serrated polyps in a centre with a high adenoma detection rate and experienced gastrointestinal pathologists. In the subsequent chapters we report on the value of several screening strategies with regard to the detection of serrated polyps. In \textit{chapter 5} the performance of computed tomography colonography is compared with colonoscopy for the detection of high-risk serrated polyps, while in \textit{chapter 6} the association between putative clinical risk factors, including smoking status, and serrated polyps is assessed.

Subsequent chapters discuss the efforts to improve clinical management of serrated polyps by endoscopists as well as pathologists in daily practice. In \textit{chapter 7} we compare the proximal serrated polyp detection rate among endoscopists and validate this colonoscopy quality parameter as a more easy to measure proxy for the detection rate of all clinically relevant serrated polyps. In \textit{chapter 8} we describe endoscopist performance in the optical diagnosis of diminutive sessile serrated polyps, showing the need for a validated and structured classification system, which we discuss in \textit{chapter 9}. In \textit{chapter 10} we evaluate the performance of pathology laboratories in the diagnosis of sessile serrated polyps and describe the effect of a structured training on inter-laboratory variability.

The final part of this thesis covers two chapters about serrated polyposis syndrome, characterized by multiple serrated polyps throughout the colorectum and associated with an increased lifetime risk of CRC. In \textit{chapter 11} we discuss the risk of serrated polyposis syndrome when undetected, by means of a case report. Finally, in \textit{chapter 12} we report on risk factors of CRC in a large population of patients with serrated polyposis syndrome as well as the absolute risk of CRC under surveillance.
REFERENCES