No more hide and seek

Impact paragraph

Colorectal cancer (CRC) is one of the most prevalent cancers in the Western world with high impact on quality of life.[1] Because of the natural course of CRC development, through precursor lesions, population-based CRCs screening programs can be (cost)effective.[2] CRC screening comprises early detection of CRC precursor lesions. Colonoscopy has a major role in the detection of these precursors lesions (mostly adenomas) and enables immediate treatment by endoscopic resection, with proven reduction of CRC occurrence and mortality.[3] However, colorectal lesions vary in their characteristics and difficulties in being detected and resected. Furthermore, some patients still develop CRC after colonoscopy, meaning that prevention failed.[4] These CRCs are called post-colonoscopy colorectal cancers. This thesis has focused on a) specific large colorectal neoplasms because of their high malignant potential and difficulties in being detected and adequately resected and, b) the etiology of post-colonoscopy cancers in combination with possible associations with specific precursor lesions.

Large non-pedunculated colorectal polyps

Large non-pedunculated colorectal polyps (LNPCPs) comprise of colorectal neoplasms without a stalk, 20 mm or larger in size.[5] Flat neoplasms within this group are called laterally spreading tumors and can be subclassified into four types with each a different surface morphology using the Kudo LST classification.[6] The aims of this thesis were to validate the Kudo LST classification, to study the risk of submucosal invasion (malignancy rate) in each LST subtype and to study whether patients with LSTs have a higher risk of synchronous and metachronous neoplasms. Additionally, we studied the quality of LNPCP resections in current practice and explored ways to optimize these procedures.

Our results show that although agreement among experts in the application of the Kudo LST is not perfect, substantial agreement was achieved. Additionally, the same classification can be taught to endoscopy trainees by using e-learnings. After a relatively short intensified online training program, the trainees reached substantial agreement in scoring when applying the Kudo LST classification. These data indicate that online training is a valuable tool for learning to apply endoscopic classifications and that the Kudo LST classification can be used by all endoscopists after a short training. Studies like these may stimulate e-learnings to become default in endoscopy training of residents in Gastroenterology and Hepatology.

The next step was to study whether the Kudo LST subtypes indeed have a different risk of containing cancer, information that is essential for safe endoscopic treatment. Multiple studies, both case-series and population-based cohorts, already have reported on LST prevalence and histopathological outcomes. A large meta-analysis was performed merging all these data of various studies. This meta-analysis showed that the risk of containing cancer was indeed very different among the Kudo LST subtypes. This knowledge has contributed to new recommendations for treatment of large non-pedunculated polyps, as described in current European, American and Japanese guidelines.[7-9]

Whether patients with large flat colorectal polyps are at higher risk of developing new lesions during follow-up, was studied using a prospective database of alle consecutive colonoscopies performed between 2004 and 2008. All patients with at least a large (10 mm or larger) polyp were included and follow-up data were obtained for at least 5 years after the first colonoscopy. Comparison of patients with non-polypoid (flat) lesions to patients with polypoid lesions showed more synchronous lesions at index colonoscopy and more metachronous lesions during surveillance

colonoscopies in patients with non-polypoid (flat) lesions. These data indicate that in patients with flat colorectal neoplasms, new neoplasms develop at higher speed. Furthermore, these new neoplasms are more often flat, with more risk of being missed by colonoscopy. Current guidelines on surveillance after polyp removal do not stratify for interval of follow-up colonoscopy based on polyp morphology.[10-12] With these results in mind, future guidelines may take into account the number of flat neoplasms found at index colonoscopy. Large prospective studies on the safety of expanding surveillance intervals should take "flat morphology" into account in their analysis.

Post-colonoscopy colorectal cancers

Post-colonoscopy colorectal cancers were studied in detail to find clues for clinical improvements in order to reduce the incidence of PCCRCs. One goal was to study critical factors to further optimize colonoscopy surveillance and whether training may help to reduce PCCRC incidence. A small scale study we performed, focusing on PCCRC incidence before and after implementation of center-wide training on the detection and resection of flat colorectal polyps, pointed to a reduction in PCCRC incidence after training. Although there are several biases and also technical advancements during the years when this study was performed, these results stress the importance of training in endoscopy. It could guide other centers in providing more systematical endoscopy education to endoscopists (in training).

The biology of PCCRCs was also studied. Therefore, molecular profiling was performed, to test whether specific mutations are more prevalent among PCCRCs compared to commonly occurring colorectal cancers. Our comprehensive molecular analysis included not only 48 genes often mutated in CRC but also whole genome sequencing of PCCRCs and commonly occurring CRCs. These samples were all retrieved from a population-based cohort with specific attention for tumor characterization. No PCCRC specific molecular pattern was found, indicating that PCCRCs develop from the same precursor lesions as commonly occurring CRCs. Some molecular features, however, were more common in PCCRCs than in other CRCs. These features are often found in specific colorectal polyps, namely sessile serrated lesions and flat lesions. Both were already hypothesized to be frequent precursors of PCCRCs. Based on our in-depth analysis, it is now clear that PCCRCs are not biologically different from commonly occurring CRCs. It is also clear that more subtle, and therefore more difficult to detect lesions may contribute to PCCRC development. Our data strengthen that further research should focus on improvements in detection and resection of colorectal lesions to prevent them from developing into PCCRC.

Starting from 2014, population-based screening for colorectal cancer was implemented in the Netherlands. This screening is organized by bi-annual fecal occult blood testing as first step. In case of a positive (unfavorable) test outcome, patients are referred for colonoscopy.[13] Despite this stepwise approach, negative (unnecessary) colonoscopies are common (in 30-35%) after an initial positive fecal occult test. In the future, the fecal occult blood tests may be supplemented by molecular stool tests in which mutations will be tested pointing to colorectal neoplasia. In these cases, it is important that there is a high sensitivity for mutations frequently found in PCCRCs. This is also important because the fecal occult blood test is thought to be less sensitive for neoplasms located in the right sided colon.[14] Such strategies may yield a higher detection rate during colonoscopy for subtle lesions with malignant potential. The data on PCCRC etiology indicate that research should focus on techniques to help endoscopists in detecting the more subtle lesions. Reducing or even eliminating miss rates will probably also reduce PCCRC rates. Introducing new endoscopic resection techniques thereby limiting recurrence risks will also contribute to reduce PCCRC rates.

Our data show for the first time that patients with large flat colorectal neoplasms have a higher

risk of developing new neoplasms during follow-up. All data on PCCRCs presented in this thesis show that PCCRCs occur through known CRC pathways and that the key for PCCRC reduction will lie in education of endoscopist and optimizing detection and resection of precursor lesions. This knowledge is useful for programs to reduce the occurrence of PCCRCs and in developing practical endoscopy guidelines. In conclusion, data obtained by the research presented in this thesis will help to develop diagnostic and therapeutic strategies to end the “hide and seek" game of complex colorectal neoplasms.

References

1. Dutch Cancer Figures. Incidence and mortality of cancer of the large intestines: Integraal Kankercentrum Nederland; 2016 [Available from: http://www.cijfersoverkanker.nl.
2. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. Epidemiologic reviews. 2011;33:88-100.
3. Pilonis ND, Bugajski M, Wieszczy P, . . . Kaminski MF. Long-Term Colorectal Cancer Incidence and Mortality After a Single Negative Screening Colonoscopy. Ann Intern Med. 2020;173(2):81-91.
4. Singh S, Singh PP, Murad MH, Singh H, Samadder NJ. Prevalence, risk factors, and outcomes of interval colorectal cancers: a systematic review and meta-analysis. Am J Gastroenterol. 2014;109(9):1375-89.
5. Rutter MD, Chattree A, Barbour JA, . . . Dolwani S. British Society of Gastroenterology/Association of Coloproctologists of Great Britain and Ireland guidelines for the management of large non-pedunculated colorectal polyps. Gut. 2015;64(12):1847-73.
6. Kudo S, Lambert R, Allen JI, . . . Hurlstone PD. Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc. 2008;68(4 Suppl):S3-47.
7. Kaltenbach T, Anderson JC, Burke CA, . . . Rex DK. Endoscopic Removal of Colorectal Lesions-Recommendations by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2020;158(4):1095-129.
8. Bisschops R, East JE, Hassan C, . . . Dekker E. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2019. Endoscopy. 2019;51(12):1155-79.
9. Tanaka S, Kashida H, Saito Y, . . . Tajiri H. Japan Gastroenterological Endoscopy Society guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. Digestive Endoscopy. 2020;32(2):219-39.
10. Hassan C, Antonelli G, Dumonceau JM, . . . Quintero E. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2020. Endoscopy. 2020;52(8):687-700.
11. Gupta S, Lieberman D, Anderson JC, . . . Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2020;158(4):1131-53.e5.
12. Dekker E, Leerdam van ME, Hazewinkel Y, . . . Nagtegaal ID. Nederlandse Richtlijn Coloscopie Surveillance. NVMDL; 2013.
13. Breekveldt ECH, Lansdorp-Vogelaar I, Toes-Zoutendijk E, . . . Dutch National Colorectal Cancer Screening Working G. Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands: a population-based study. Lancet Gastroenterol Hepatol. 2022;7(1):60-8.
14. Chiu HM, Lee YC, Tu CH, . . . Wu MS. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2013;11(7):832-8 e1-2.