No more hide and seek

Summary

Colorectal cancer is a prevalent cancer which develops from precursor lesions, so called colorectal neoplasms. Because transformation from early neoplasm to colorectal cancer takes years, colorectal cancer is in theory and in practice, a largely preventable disease. Colonoscopy is used for the prevention of colorectal carcinoma by diagnosis and treatment (removal) of colorectal neoplasms. However, not all polyps have the same malignant potential, and some are more difficult to detect or resect. Furthermore, colonoscopy is not able to prevent all colorectal cancers because some neoplasms are missed during colonoscopy or because of incorrect (incomplete) treatment. Large non-pedunculated (flat and sessile) colorectal neoplasms (LNPCPs) are neoplasms which are especially difficult to detect and to treat endoscopically. This thesis consists of two parts. Firstly, LNPCPs were studied in detail focusing on morphology and treatment. Secondly, colorectal cancers occurring after colonoscopy, the so-called post-colonoscopy colorectal cancers (PCCRCs) were studied with the focus on etiology.

An introduction on both topics was provided in **Chapter 1**. The prerequisites for high quality colonoscopy were outlined, including the remaining difficulties and challenges of modern colonoscopy. High quality colonoscopy is essential for preventing PCCRCs. One of the prerequisites is effective, adequate treatment of precursor lesions. This is becoming more difficult with increasing size of a neoplasm. This is especially true for the LNPCPs, large colorectal neoplasms (of minimal 20 mm in size) without a stalk. Large flat (non-polypoid) colorectal neoplasms are a large subset of the LNPCPs. These lesions are also called laterally spreading tumors (LSTs). LSTs are of special interest because their substantial variation in morphology. Four morphological LST subtypes have been defined in the Kudo LST classification. These subtypes are used to assess submucosal invasion risk in the LSTs based on general morphology.

In **Chapter 2**, the agreement of applying the Kudo LST classification was tested among experts and trainees. An educational web-based system was developed and used for this goal. First, well-documented LST cases from the Maastricht University Medical Center (Maastricht UMC+) and from the National Taiwan University Hospital (NTUH) were collected. The 72 cases with the highest quality images were then presented to 14 international experts on the topic of large flat colorectal neoplasms. They were asked to provide the most applicable Kudo LST classification, the applicable Paris morphology classification and the most appropriate treatment modality of each case. The experts showed substantial interobserver agreement in applying the Kudo LST classification (Gwet's AC1 0.62, 95% CI: 0.55 – 0.69), especially in recognition of the nodular-mixed granular LSTs (Fleiss kappa 0.76, 95% CI: 0.73 – 0.78). Based on the input of the experts, an online training module consisting of background information and cases for practicing was developed. The next step was to invite 21 endoscopy fellows from the Maastricht UMC+ and NTUH to answer the same questions as the experts for all 72 cases. After this, each fellow followed the new online training module. Several weeks after this individual e-learning, each fellow answered the same questions for the 72 cases, now hustled in a different order. Initially, the fellows scored a lower interobserver agreement as the experts (Gwet's AC1 0.43, 95% CI: 0.37 – 0.50), but after this single training it improved to a comparable level as the experts (Gwet's AC1 0.59, 95% CI: 0.53 – 0.65). This study showed that the Kudo LST classification is a useful classification since there was substantial agreement among experts, and that it was teachable to novices using an online training module.

To summarize the features of each LST subtype, a meta-analysis was performed in **Chapter 3**. After an extensive search, data of 48 papers were used to study the prevalence of LSTs, the prevalence of each subtype, the submucosal invasion rate of each subtype and the preferred colonic location of LSTs. The results showed an overall prevalence of 0.83% (95% CI: 0.62 – 1.07) among all

colonoscopies, consisting of 3.6% of all colorectal neoplasms detected (95% CI: 2.5 – 4.9). Generally, LSTs are equally prevalent in the proximal and distal colon, but granular LSTs may be more prevalent distally than proximally. The prevalence and the rate of submucosal invasion at diagnosis varies between the LST Kudo subtypes. Homogeneous granular LSTs are most common (35.4%, 95% CI: 27.2 – 43.6) with the lowest rate of submucosal invasion (0.5%, 95% CI: 0.1 – 1.0). Pseudo-depressed non-granular LSTs have the lowest prevalence (5.5%, 95% CI: 3.2 – 7.8) while having the highest risk of submucosal invasion (31.6%, 95% CI: 19.8 – 43.4). The study showed that the classification of LSTs based on macroscopic appearance is helpful in assessing risk on submucosal invasion and should be used to determine the most appropriate treatment strategy.

The high risk of submucosal invasion in some LST subtypes, suggests that inadequate resection could contribute to the risk of developing colorectal cancer. Whether patients with LSTs have a specific risk profile for developing metachronous colorectal neoplasms has not yet been studied. In **Chapter 4**, data from a prospective polyp database was used to study LSTs and to compare them with large polypoid neoplasms. Follow-up data from all patients with larger colorectal neoplasms (of minimal 10 mm in diameter) were additionally collected. The results showed that LST patients had significantly more synchronous colorectal neoplasms than patients with large polypoid colorectal neoplasms (mean 3.34 vs 2.34, $P<0.001$). Patients with LSTs also developed significantly more often metachronous neoplasms within the six year follow-up (71.6% vs 54.2%, $P=0.0498$) and more often colorectal neoplasms with high grade dysplasia or submucosal invasion (36.4% vs 15.8%, $P<0.001$). After correction for age and gender, compared to large polypoid neoplasm patients, LST patients had a higher risk (hazard ratio 2.9) of developing a new colorectal neoplasm with high grade dysplasia or submucosal invasion. These results warrant the need for strict surveillance in LST patients, as they appear to be a population at higher risk.

The importance of this finding for current clinical practice is highlighted in **Chapter 5**. Data on LNPCP prevalence in the first years of the Dutch colorectal cancer screening program showed that LNPCPs occurred in 8% of all participants undergoing colonoscopy. Detailed data of the findings during the first years of screening, including follow-up, were collected in three hospitals in the South-Limburg region of the Netherlands. The local prevalence of LNPCPs was comparable to the national prevalence. Overall, 30% of the LNPCPs that were encountered, were not resected directly. This rate increased with LNPCP size. The overall technical success rate of endoscopic resection was 87% (95% CI: 82 – 91). The clinical success rate was shown also to be 87% (95% CI: 80 – 92) and was defined as no residue after one year. Both rates decreased with increasing LNPCP size. Overall recurrence after a technical successful resection was 22% (95% CI: 15 – 32) for piecemeal and 8% (95% CI: 2 – 22) for en-bloc resection. Most of the recurrences could successfully be treated by repeated endoscopic resection, but two recurrences were carcinomatous and required additional surgery. These data show that in current endoscopy practice, endoscopic treatment of LNPCPs is still difficult with room for further improvement.

To investigate whether simple interventions could reduce LNPCP recurrence risk, a systematic meta-analysis was performed in **Chapter 6**. The goal of this meta-analysis was to study the effectiveness of thermal ablations of the resection borders after endoscopic mucosal resection. A total of 10 studies investigated snare tip soft coagulation (STSC) or argon plasma coagulation (APC) in relation to recurrence after large neoplasm resection. Pooling the risk difference of one of both interventions in comparison with no additional treatment, showed a risk reduction of 18% (95% CI: -26 – -11) after 6 to 12 months. Since STSC does not require use of additional materials during colonoscopy, this technique is probably most cost-effective.

In the next part of the thesis, post-colonoscopy colorectal cancer was the main topic of interest. In **Chapter 7**, a review of colonoscopy surveillance prerequisites was performed. An overview of the

current surveillance guidelines in 2015 was presented with an update of the new guidelines published up to the end of 2021. The intervals of surveillance differ among international guidelines. However, all guidelines stress the importance of high-quality bowel preparation, complete colonoscopy, clear communication about intervals and high adenoma detection rates of endoscopists. Additionally, the intervals are all based on risk stratification using clinicopathological characteristics of the removed neoplasms. Over the last 10 years, new evidence about colorectal cancer risk after polypectomy showed a lower risk than expected after a high-quality index colonoscopy. The risk of developing colorectal cancer after removal of sessile serrated lesions is now estimated to be higher and has led to intensification of colonoscopic surveillance in these patients.

For the determination of post-polypectomy surveillance intervals, histopathology is used. However, using optical diagnosis could reduce histopathology costs. In **Chapter 8**, the accuracy of optical diagnosis during national CRC screening colonoscopies was studied. Data of the first 3028 small polyps detected in the national CRC screening program in the South-Limburg region was used to compare the endoscopist's diagnosis with the pathologist's diagnose. Taking into account the complete colon, a diagnostic accuracy of only 76% (95% CI: 74 – 77) was found, with a negative predictive value for adenomatous histology of 69% (95% CI: 66 – 73). Taking into account only the rectosigmoid region, the diagnostic accuracy was even lower with 71% (95% CI: 69 – 74), but the negative predictive value for adenoma was higher with 84% (95% CI: 80 – 87). Applying the resect and discard strategy (i.e. removing the neoplasms without sending them for histopathology) for lesions up to 5 mm in size, would have led to more than 90% identical surveillance intervals than after pathological assessment of all resected neoplasms. In about 6% the interval was even shorter than based on histopathological outcomes. Based on these results, the accuracy of optical diagnosis is currently too low to omit the histopathological diagnostic process.

Whether training on colonoscopy quality and detection of flat colonic neoplasms can indeed reduce the PCCRC incidence, was studied in **Chapter 9**. This comparison was performed based on estimated PCCRC incidence rates derived from multiple sources. The PCCRCs were obtained and identified from a database containing all CRC diagnoses between 2004 en 2014 in the Maastricht UMC+. Using a prospective colonoscopy database from 2008 to 2012 with follow-up data, the person years of follow-up within this period could be calculated (sum of years between index and end of follow-up or PCCRC occurrence). The training occurred late 2007. The number of colonoscopies between 2004 and 2008 was registered in the hospital. The mean follow-up time per patient for this period was estimated based on the data from 2008. Year of last colonoscopy before PCCRC diagnosis was used for comparison. Because of the lack of full prospective data on PCCRC before training, the results are partly based on extrapolation of person years of follow-up, using this data from the year 2007 for estimates of 2004 till 2006. Before training, in 2.0 per 1000 colonoscopies, a PCCRC occurred afterwards, while after training this was 0.8 per 1000 colonoscopies. Incidence rates expressed per patient years of follow-up (PYFU) showed a rate of 0.79/1000 PYFU before and 0.34/1000 PYFU after training. Despite the bias that may have occurred based on the estimation on surveillance occurrence prior to training we made, a positive effect of training on the detection and resection of flat colonic neoplasms on PCCRC incidence was observed.

Additional evidence for PCCRC occurrence from flat neoplasms was provided in **Chapter 10**. A prospective database containing all detected CRCs and all PCCRCs was used, where all PCCRCs and an equally sized random selection of detected CRCs were sent for molecular analysis. This analysis comprised of whole genome sequencing for comparing copy number changes, detection of mutations in 48 commonly affected genes in CRC, CpG island methylator phenotype determination and presence of microsatellite instability. Loss of chromosome 18q was significantly less common in PCCRCs compared to detected CRCs (46.7 vs 72.7%, false discovery rate 0.11). Microsatellite

instability (21.7 vs 9.6%, *P*=0.029) and a high CpG island methylator phenotype (50.0 vs 32.7%, *P*=0.014) were significantly more common in PCCRCs. An unsupervised clustering model was applied showing three main branches of PCCRCs, corresponding to the hypermethylation pathway, the microsatellite instability pathway and the chromosomal instability pathway. Previous studies showed that sessile serrated lesions were associated with the hypermethylation pathway and in lesser degree with the microsatellite instability pathway. For non-polypoid neoplasms, BRAF gene mutations were more common. PCCRCs were overrepresented in the hypermethylation and microsatellite pathway (62% and 68% PCCRCs resp.), while underrepresented in the chromosomal instability pathway (47% PCCRCs). This study showed no specific separate pathway for PCCRCs. The pathways associated with sessile serrated lesions and flat lesions were more common in PCCRCs however. The hypothesis that both sessile serrated lesions and non-polypoid neoplasms may be precursor lesions of PCCRCs still applies and is supported by our data.

Chronic inflammation of the colon mucosa is a risk factor for developing neoplasms. Therefore, patients with inflammatory bowel disease (IBD) need colonoscopic surveillance. In **Chapter 11**, the occurrence of PCCRCs in patients with IBD was studied. For this study, the population based IBD South-Limburg cohort was used. This cohort contains all adult IBD patients diagnosed between 1991 and 2011. All diagnoses of CRC that we encountered were cross-checked with the national cancer registry. Colonoscopies performed in the 5 years preceding the diagnosis of CRC led to the identification of a PCCRC. In the included group of 2801 IBD patients, 20 CRCs occurred, with a incidence rate of 0.77/1000 patient-years. Nine CRCs were identified as PCCRC (45%, 0.39/1000 patient-years at risk). Of them, five PCCRCs were classified as most likely occurring from missed neoplasms. Another important finding was that six of all CRCs were detected before the start of colonoscopic surveillance (within 8 years after diagnosis recommended). The conclusion of the study is that IBD patients have a higher risk on PCCRC development, but also on developing CRC before start of the surveillance. New endoscopy techniques improving dysplasia detection in IBD patients should be developed. Applying an index colonoscopy earlier after first remission is obtained, could possibly help to prevent CRC development prior to the first surveillance colonoscopy, which is planned based on recommendations in current guidelines.

In the final chapter, **Chapter 12**, the relevance of the endoscopic subclassification of LSTs in clinical practice was discussed. The incorporation of morphological assessment with knowledge on features of submucosal invasion, prior to endoscopic resection was advocated. LST treatment and surveillance recommendations were discussed. The links between LSTs and development of PCCRCs was also discussed. The hypothesis from chapter 1 was tested with the findings from chapter 2 to 11, concluding that LST patients may be at higher risk for PCCRC development due to more metachronous neoplasms and higher chance of incomplete resection. We conclude that attention for high quality detection, determination and resection of colorectal neoplasms is probably still the most effective PCCRC prevention measure.