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Optimizing quality and efficacy of colorectal cancer diagnosis and endoscopic therapy

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Valorization

Colorectal cancer (CRC) is the third leading type of cancer worldwide, among both men and women. Since it is known that CRC derives from precursor lesions, detection and resection of these precursor lesions leads to a decrease in incidence, morbidity and mortality of CRC. With this goal, CRC screening programs have successfully been introduced and implemented.[1] Patients with an increased risk to develop CRC (i.e. post-CRC status, post-polypectomy or familial/genetic risk) enter surveillance programs.[2]

Valorization is described as "*the process of creating value from knowledge by making knowledge suitable and available for societal and/or economic application by transforming it into products, services, processes and new business*."[3]

In the framework of this thesis, we identified several steps in the process of CRC diagnosis and endoscopic therapy, following the patient journey in order to point out specific characteristics, strengths and weaknesses of each step (*Table 1*), so that recommendations can be made for future research and clinical practice.

By optimizing these steps, value is created through implementation of obtained knowledge into clinical practice, hence societal and economic application.

Pre-selection	Which patients should be invited for a colonoscopy and what are the best methods to identify patients (with precursor lesions) at risk for CRC?
Colonoscopy	Invasive tool to detect precursor lesions with the option to resect these lesions; How can we make sure that all (relevant) lesions are detected and determined? How well is the endoscopist trained and equipped to differentiate between the different types of lesions?
Treatment	Where surgery used to be the "gold standard" for treatment of CRC, a shift occurs towards more advanced endoscopic treatments, that potentially are less invasive and have lower complication rates compared to surgery. How well can invasive lesions be differentiated from non-invasive lesions? And what is the best, less-invasive (endoscopic) technique to resect these (non) invasive lesions?
Surveillance	In current practice the surveillance population enters the colonoscopy-based surveillance program. What are (less invasive) alternative surveillance strategies or can intervals for colonoscopy be prolonged?

Table 1. Steps and questions in the process of optimizing quality and efficacy of CRC diagnosis and endoscopic therapy.

Value for patients

For patients it is crucial that each of the four steps, described above, is effective and of high quality while the burden of each step should be as low as possible.

In current CRC screening programs, fecal immunochemical testing (FIT) is used for pre-selection. Since FIT based preselection is not optimal in detecting precursor lesions, it is essential to develop and test other diagnostic tools, where new biomarkers could possibly increase sensitivity and specificity and result in a more optimal pre-selection, so that a better selected group of patients is receiving a colonoscopy. Our systematic review (**chapter 2**) revealed that of the studies addressing diagnostic CRC DNA methylation markers, the majority of markers have been studied in tissue, which can only be obtained via colonoscopy. Bodily fluids (i.e. blood and stool) can be collected with a much lower burden to the patients, since these are less invasive to obtain. In case a minimal invasive test (with high sensitivity and specificity) is available, unnecessary (invasive) colonoscopies can be avoided.

To reach this goal, additional research is needed. For future DNA methylation biomarker studies it is important to define the clinical need and intended biomarker use before starting the study and to evaluate the current available research and the level of evidence. It is important that the specimen and cohort complement available evidence and that it is compared to current gold standard methods. This way the study adds substantially to the already performed research and can make a difference in bringing biomarkers to clinical practice.

Patients with a history of CRC or polypectomy, or familial/genetic risk enter into a surveillance program. Current surveillance is fully colonoscopy-based: patients receive colonoscopies on regular basis, thereby increasing the patient's burden. With implementation of nationwide CRC screening programs, and the increased quality of colonoscopy, the added value of intensive, high frequency colonoscopy-based surveillance programs is under debate. In this thesis we investigated an alternative surveillance method, using a multitarget stool DNA (mt-sDNA) test (Cologuard), including biomarkers and hemoglobin (MOCCAS study). The interim analysis (**chapter 6**) of that study shows that the mt-sDNA test has a higher sensitivity than

FIT for precursor lesions in the surveillance population. When a low-test cut-off is used in order to reach 50% positivity rate, the mt-sDNA test sensitivity increases and the number of unnecessary colonoscopies will be reduced by 50%. This interim analysis already shows promising results. After completion of the study, full analyses will be performed, and mathematical modelling will be applied to determine the optimal stool-based surveillance strategy.

Colonoscopy is an invasive procedure, which can be used for both diagnosis and treatment. Data from patient reported outcome measures (PROM's) and patient questionnaires show that bowel preparation and post-colonoscopy abdominal complaints are perceived as most burdensome by patients undergoing colonoscopy.[4] Colonoscopy remains the most important tool for diagnosis of precursor lesions and for diagnosis of CRC. Colonoscopy allows us to take biopsies or resect (precursor) lesions. Optimization of colonoscopy procedures may help to significantly reduce patient burden while not affecting quality and efficacy.

To optimize the diagnostic process, adequate detection and determination of polyps is crucial. We investigated the additional value of image enhancement strategies in patients with Lynch Syndrome. These patients have a significantly increased risk of developing CRC. In these patients it is crucial to optimize the detection of the precursor lesions, so that development and progression to CRC can be prevented. In **chapter 3** an overview of current literature was given, where a large heterogeneity among study designs was shown. For future research, standardization of study designs is needed, with a randomized, cross-over, back-to-back study design as best option. Important factors to increase the quality and efficacy of colonoscopy include 1) use of image-enhancement, 2) training of endoscopists in detection and removal of non-polypoid colorectal neoplasms and 3) stricter adherence to surveillance intervals.

The determination and in-vivo estimation of histology (i.e. optical diagnosis), was studied in the screening population. Two potential strategies in low-risk, diminutive (≤5mm) polyps were investigated, aiming for less resections and saving costs by not

sending these polyps for histological evaluation. According to our study (**chapter 4**), the accuracy for optical diagnosis of adenomatous histology is currently too low and does not consistently meet the set thresholds (PIVI criteria). Therefore, we are not ready to implement these strategies in current daily practice. For implementation of optical diagnosis in the CRC screening program, several adjustments need to be done: in the reporting of lesions by standard use of optical classification systems and by inclusion of the 'level of confidence' of the endoscopist performing the colonoscopy. Additional endoscopist training in optical diagnosis should be undertaken. Only when detection and determination have been optimized, colonoscopy as a diagnostic tool will reach optimum diagnostic accuracy and efficacy.

Nowadays, new endoscopic resection techniques are available. With implementation of the CRC screening program, more lesions are detected, and more early (T1) CRCs are diagnosed. For a subset of T1 CRCs, these less-invasive endoscopic treatments are alternative strategies for colorectal surgery. It is of great importance to correctly estimate the CRC risk in patients when choosing for the less-invasive treatment strategy. In current clinical practice however, only 20.9% of the T1 CRCs were recognized as such. Incorrect optical diagnosis results in non-curative endoscopic resections, this often leads to salvage surgery, which in a substantial number of cases appears to be unnecessary (**chapter 5**).
Implementation of the validated OPTICAL risk chart provides guidance by estimating CRC risk and should therefore be considered for implementation in daily practice.[5]

Value for society
In 2003, the European Committee advised all countries to implement CRC screening programs. After years of study, in 2014 the biannual FIT-based program was implemented in the Netherlands.[1] In the first years of the program, colonoscopy capacity was limited due to a shortage of certified endoscopists and higher participation rates than expected.

Because of the initially limited colonoscopy capacity and high participation rates among the population, waiting lists increased for CRC screening and also for symptomatic patients. Based on capacity issues, it was decided to increase the FIT cut-off value six months after implementation of the screening program. In 2018, four years after implementation, nationwide colonoscopy capacity is sufficient to accommodate all FIT positive referrals.

With implementation of the CRC screening program, more low-risk (small and diminutive) polyps are diagnosed and resected. In this thesis, the implementation of cost-effective strategies, i.e. 'resect and discard' and 'diagnose and leave' for diminutive polyps was studied. In case optical diagnosis can be optimized, diminutive polyps might be left in place or are resected but not sent in for histology. This strategy will result in substantial financial benefit.

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As a consequence of implementation of the CRC screening program, more patients will enter colonoscopy-based surveillance programs. This results in a rapidly expanding surveillance population, adding substantially to colonoscopy capacity. Nowadays more than 25% of colonoscopies is performed for surveillance, while the cost-benefit of colonoscopy surveillance is not yet clear. Therefore, it is worthwhile to investigate alternative surveillance strategies. Better pre-selection of patients will lead to less (unnecessary) colonoscopies, with financial impact. Furthermore, the pressure on colonoscopy capacity will decrease and attention can be given to other important health issues in endoscopy practice such as innovation in therapeutic endoscopic interventions.

In the MOCCAS study (MOlecular stool testing for Colorectal CAncer Surveillance), an observational cross-sectional study, patients are approached to collect stool samples for molecular testing and FIT prior to their scheduled surveillance colonoscopy (**chapter 6**). The currently ongoing study will after completion, be used as input for mathematical modelling to find the optimal (stool-based) surveillance strategy. This should add to reduction of patient burden and increasing (cost-) effectiveness.

Overall and future value

Diagnosing CRC in an early or precursor stage, may lead eventually to prevention of CRC. It is worthwhile to take steps to optimize this process, because by early diagnosis and treatment significant costs are saved from chemotherapy and surgery.

Steps taken to optimize the process of CRC diagnosis and treatment are of value, both for patients as well as society. The future value for each step is shown in *Table 2*.

Pre-selection	Role of diagnostic biomarkers/biomarker panels in the pre-selection, complementary to the currently used FIT-test.
Colonoscopy	Optimal detection and determination of (pre) malignant lesions is key. To improve this, endoscopist training is important, as well as the potential role of artificial intelligence (AI) for correct optical diagnosis. Further research and evidence is needed before AI can be used in daily endoscopy practice.[6]
Treatment	Shift from surgical to endoscopic/minimal invasive treatment with a personalized plan for every patient/lesion, starting with improvement of correct estimation and recognition of early CRCs.
Surveillance	Biomarkers may play a role in future surveillance strategies. When determining the optimal personalized surveillance strategy, several factors, e.g. risk differences in a heterogeneous population, should be taken into account.

Table 2. Steps and potential ways for optimizing quality and efficacy of CRC diagnosis and endoscopic therapy.

In this thesis several aspects have been explored that may help to optimize quality and efficacy of CRC diagnosis and endoscopic therapy. Additional research is needed to adequately implement these adjustments in CRC diagnosis and treatment in daily practice. In this respect, costs and quality remain key factors.

References

1. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Bevolkingsonderzoek Darmkanker. Available via: http://www.rivm.nl/.

2. NVMDL. Dutch Guideline Colonoscopy Surveillance 2013.

3. Maastricht.University. Valorisation - Knowledge Transfer Office, via: https://www.maastrichtuniversity.nl/about-um/other-offices/knowledge-transfer-office. 2019.

4. Denters MJ, et al. Patient burden of colonoscopy after positive fecal immunochemical testing for colorectal cancer screening. Endoscopy 2013;45(5):342-9..

5. Backes Y, et al. Multicentre prospective evaluation of real-time optical diagnosis of T1 colorectal cancer in large non-pedunculated colorectal polyps using narrow band imaging (the OPTICAL study). Gut 2019;68(2):271-9.

6. Kudo SE, et al. Artificial intelligence and colonoscopy: Current status and future perspectives. Dig Endosc 2019.

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