Standardizing TrAining for endoscopic Resection of Large Non-Pedunculated Colorectal Polyps: *STAR-LNPCP

(version 2; September 2018)

PROTOCOL TITLE 'Standardizing TrAining for endoscopic Resection of Large Non-Pedunculated Colorectal Polyps: it is prime-time to change practice' (*STAR-LNPCP)

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Laboratory sites <*if applicable*>	***Not applicable***
Pharmacy <*if applicable*>	***Not applicable***

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1. SUMMARY

Rationale: A fecal immunochemical test (FIT)-based colorectal cancer (CRC) screening program was implemented in the Netherlands in 2014. Nearly 15,000 patients are yearly diagnosed with a *large complex* (*non-pedunculated) colorectal polyp* (LNPCP) for which endoscopic resection is the first-line therapy. LNPCPs carry a high malignant potential. Endoscopic resection of LNPCPs is technically challenging, with a risk of local recurrence, repeat colonoscopy and additional surgery, resulting in a negative impact on clinical outcome, patient's quality of life, and increased colonoscopy burden for repeat procedures.

Objective: Development of a standard training program for advanced endoscopic resection techniques is urgently needed to improve outcomes at both a patient and program level. Improvement of *education* and *colonoscopy training* is the first key-step.

- **(I)** **A**. To develop a systematic training program for treatment of LNPCPs
  B. To investigate if additional training improves clinical outcomes
- **(II)** To assess the impact of performing endoscopic resection for LNPCPs on the patients quality of life (QoL).
- **(III)** To perform an economic analysis comparing post-training endoscopic resection vs. common endoscopy practice vs laparoscopic surgery.

We hypothesize that a series of measures, i.e. *a priori* endoscopic and histological diagnosis followed by a therapeutic plan and high-quality endoscopic resection performance will improve outcome.

Study design: A multicenter randomized controlled trial (RCT) will be conducted to compare the performance of additionally trained endoscopists (n=15 centers, n=30 endoscopists) vs. regularly trained endoscopists (control group; n=15 centers, n=30 endoscopists).
The period of inclusion and follow-up will be from 2019-2021, where the duration of the follow-up of an individual patient will be 6 months, confirm the current guidelines.

Study population: Patients (18 years and older) who have an indication for colonoscopy, in particular patients from the nationwide screening program.
Inclusion criteria for participating endoscopists will be:

1. Experienced endoscopists (i.e. total number of colonoscopies performed will be at least 250 procedures under supervision plus 500 colonoscopies independently) including documentation of the key-performance indicators (cecal intubation rate, adenoma detection rate and polypectomy rate)

Intervention (if applicable): The intervention group will comprise 30 endoscopists (from 15 centers) who receive the additional training package. The control group will comprise 30 endoscopists (from 15 centers) who receive regular training.

Participating centers will be randomized to the *intervention group* vs. *control group*. To mitigate the effect of contamination, i.e. exchange of knowledge, practical skills between participants, we prefer to randomize centers instead of endoscopists. In each center two endoscopists will participate in the study.

Main study parameters/endpoints:

- Primary endpoints: local recurrence rate (6 months after resection).
- Secondary endpoints: radical (R0) resection rate, complication rate, number of repeat colonoscopies, referral rate to surgery and patient satisfaction regarding clinical outcomes of endoscopic resection (at two or three time points (before endoscopic resection (is not applicable in all cases)/1 week after endoscopic resection/6 months after endoscopic resection) and cost-effectiveness (post-training situation vs current situation vs laparoscopic surgery).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

This project aims to provide the fundamentals for best practice in the treatment of large complex (non-pedunculated) colorectal polyps (LNPCPs). Increased quality and effectiveness of endoscopic resection of LNPCPs will reduce CRC incidence. The project proposes strategies to reduce the patient burden (additional colonoscopy and surgical procedures) and risk of complications, which in turn will improve patient's quality of life and the effectiveness and efficiency of the national population screening program.

2. INTRODUCTION AND RATIONALE

Professionalism in the colonoscopy practice clearly changed the clinical course of colorectal cancer (CRC). Both CRC incidence and mortality continue to decline {Nishihara, 2013;Zauber, 2012}. With the introduction of the nationwide FIT-based CRC screening program, nearly 15,000 patients are yearly diagnosed with **l**arge (≥2cm) complex (**n**on-**p**edunculated) **c**olorectal **p**olyps (abbreviated as LNPCPs), for which endoscopic resection is the first-line therapy. The post-colonoscopy CRC rate did not drop over the past decade {Pullens, 2015;le Clercq, 2014}. Besides missed cancer/ precursors, incomplete polyp resection explains at least 20% of all PCCRCs {Robertson, 2014}, a situation which must be clearly improved.

Recent guidelines of gastrointestinal professional societies provide a conceptual basis to perform endoscopic treatment for LNPCPs {Pimentel-Nunes, 2015;Rutter, 2015}. In clinical practice, endoscopic resection outcomes vary and are far from perfect. As the nationwide screening program progresses, it is important to optimize performance and outcomes of endotherapy.
Two recent meta-analysis examined the local recurrence rate after endoscopic resection of large colorectal polyps {Belderbos, 2014;Ortiz, 2014}. Belderbos et al. showed local recurrence rates in 15% (95% CI: 12-19%) of cases after endoscopic resection of nonpolypoid neoplasms. Ortiz et al. reported a local recurrence rate of 13.1% after resection of both polypoid and nonpolypoid neoplasms. Several factors are associated with risk of local recurrence with the most common ones being proximal location, lesion size and shape {Moss, 2011}. Importantly, piecemeal (instead of en-bloc) resection is often associated with local recurrence (OR 4.39, 95% CI: 2.05-9.41; 20%, CI: 16-25%) {Ortiz, 2014;Belderbos, 2014}. Studies from Japan showed a 4-times more frequent recurrence rate for piecemeal resection of LSTs (granular type) than en-bloc resection {Oka, 2015}. Another meta-analysis on the efficiency and safety of endotherapy for large (≥20 mm) colorectal polyps showed that 8% (95% CI: 7-10%) of such patients required additional surgery because of a non-curative endoscopic resection. An important finding was that >90% of the recurrences could be successfully treated by additional endoscopic therapy {Hassan, 2015}.

To ensure en-bloc resection of lesions with high suspicion of malignancy, the endoscopic submucosal dissection (ESD) technique should be adopted. Practical performance of ESD is however difficult and requires a long and steep learning curve, additional equipment and longer procedural time {Saito, 2001}. Risk of perforation is also higher for ESD vs EMR: 5.4% (1.3%-20.4%) vs. 0.7% (0%-6%) {Tanaka, 2013}. A strategic multistep plan is therefore

required to implement ESD in the Western endoscopy practice {Sanduleanu, 2016}. Pre-treatment diagnosis of the depth of submucosal (SM) invasion which takes into consideration lesion appearance, epithelial surface pit-pattern and vascular pit-pattern is a key-step towards successful endotherapy {Yamada, 2016}. Additional technical and non-technical (logistic, strategic) skills are required. As this takes considerable time, referral to specialized centers where complex endotherapy can be performed in a timely manner is recommended in the meantime {Rutter, 2015}. For example, in the case of a LNPCP ≥20 mm in size, with a non-invasive pit-pattern, the lesion is likely an adenoma, or intramucosal cancer (Tis) or superficial submucosal invasive carcinoma (T1a cancer, i.e. SM invasion depth <1000µm, sm1) with a very low risk of lymph node metastasis and ESD is the preferred therapy {Kitajima, 2004;Nakajima, 2013}. When deep submucosal invasive cancer (T1B cancer, i.e. SM invasion depth >1000µm, sm 2-3) is suspected, given the high risk of lymph node metastasis, surgery is recommended {Yamada, 2016}.

Differentiation of an invasive from a non-invasive epithelial surface pit-patterns is challenging and ideally requires magnifying chromoendoscopy {Hayashi, 2013}. A large prospective study at the National Cancer Center in Tokyo (Japan) showed a sensitivity, specificity and diagnostic accuracy of differentiating mucosal cancer or superficial (sm1) invasion from deeper (sm2-3) invasion using magnifying chromoendoscopy of 85.6%, 99.4% and 98.8%, respectively {Matsuda, 2008}. A recent study of the same group showed the importance of a thorough macroscopic examination. Because both *granular typ*e LSTs with a large nodule or depression and *non-granular type* LSTs are associated with a substantial risk of submucosal (SM) and multifocal invasion, *en-bloc* endoscopic resection is the preferred therapy in such cases {Yamada, 2016}.

2.1 OBJECTIVES

This project aims to integrate current knowledge and technical expertise on treatment of LNPCPs from leading centers worldwide in the Dutch colonoscopy practice. Development of a standard training program to be supported by education and structured training is a prerequisite for best practice in the management of LNPCPs.

2.1.1 Primary Objective:

To investigate if systematic stepwise training improves the outcome of endoscopic treatment for LNPCPs, i.e. local recurrence (6 months after resection), radical (R0) resection rate, complication rate and referral rate to surgery.

2.1.2 Secondary Objective(s):

The patient's quality of life (QoL) will be assessed. Because a validated questionnaire is not yet available, we will adapt the Medical Outcomes Study Short Form 36 {McHorney, 1993;Ware, 1992} and a colorectal-specific European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire {Theodoropoulos, 2013}. Questionnaires will be applied at two or three time points, depending on logistics in the particular hospital (see 5.3; study procedures).

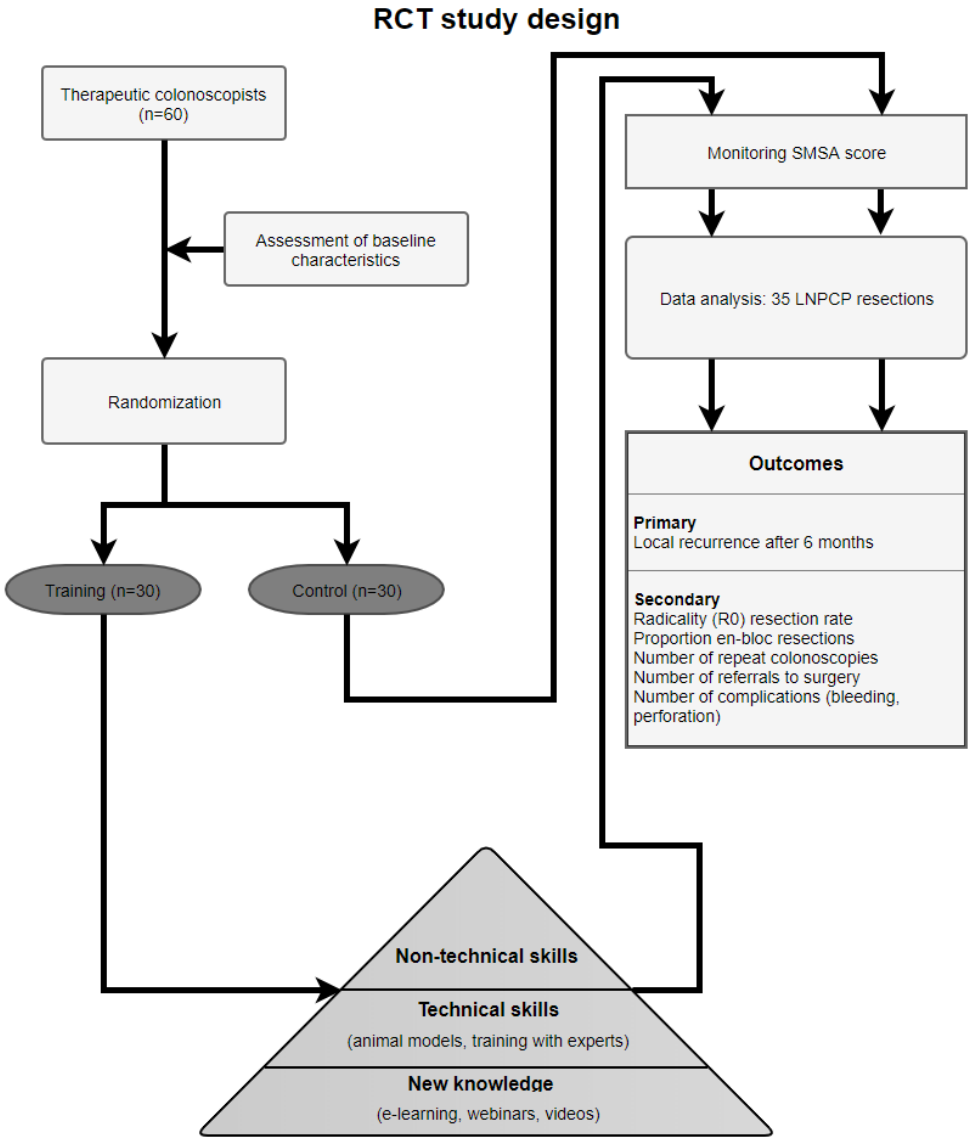
To perform a cost-effectiveness analysis to compare post-training endotherapy vs common practice vs laparoscopic surgery for management of LNPCPs.

3. STUDY DESIGN

A standard training program will be developed to improve endoscopic detection of LNPCPs, real-time diagnosis of the depth of SM invasion and endotherapy. We will examine the effect of additional training in a multicenter randomized controlled trial. Specifically, we will compare the safety (complication rate) and effectiveness (local recurrence at 6 months follow-up examination) of endoscopic resection in a group of at least 30 endoscopists who are exposed to a systematic training program on advanced endoscopic imaging, pit-pattern recognition and resection techniques vs 30 endoscopists doing regular training. The training package will comprise modern educational tools (e-learning modules, webinars, video-training). Hands-on training will be provided in animal models (ex-vivo).

The period of inclusion and follow-up will be from 2019-2021, where the duration of the individual patient will be 6 months.

A flow diagram of the study design is presented in the figure below.



3.1 STUDY POPULATION

3.1.1 Population (base)

Patients (18 years and older) who have an indication for colonoscopy, in particular patients from the nationwide screening program.

3.1.2 Inclusion criteria

Inclusion criteria for participating endoscopists will be:

1. Experienced endoscopists (i.e. total number of colonoscopies performed will be at least 250 procedures under supervision plus 500 colonoscopies independently) including documentation of the key-performance indicators (cecal intubation rate, adenoma detection rate and polypectomy rate)

3.1.3 Exclusion criteria

No exclusion criteria.

3.1.4 Sample size calculation

Based on meta-analysis data (1), we expect that the a priori risk for recurrence after endoscopic resection of LNPCPs is approximately 20% after 6 months (conservative estimates). We hypothesize that additional training will reduce this risk by 50%. In the initial version of this project proposal, we assumed that each therapeutic colonoscopist will perform endoscopic resection in at least 50 LNPCPs per year. In the revised version, we propose that 2 colonoscopists will participate per center. Taking into account a drop-out risk of 20%, inclusion of at least 35 LNPCPs per colonoscopist (70 LNPCPs per center) during 1.5 year will be achieved.

Because randomization is performed on a **cluster level** (center level instead of patient level) and patients are **nested** (randomly assigned) between colonoscopists, we determined the **Intraclass correlation coefficient** (ICC), i.e. correlation of observations in different clusters (design effect). As reference for power calculation, we used the methodology proposed in a large cluster randomized trial in the UK (2). The ICCs in this study ranged from less than 0.01 to 0.05, with a mean of ±0.015. Several factors could influence the cluster design in the above-mentioned study (e.g. socioeconomic differences, differences in local available care, differences in housing between clusters). It is unlikely, however, that such factors influence the results in our study, which could lead to a higher ICC. Because of differences in observation between colonoscopists In our project, we expect to find interobserver variation in measurements. We therefore estimate an ICC of 0.025 which is within the range of previously reported data (2). Intuitively, the variation between colonoscopists is expected to be greater than between centers. For this reason, we will calculate the ICC at colonoscopist level. Of note, in the context of the nationwide CRC screening program, quality measures are standardized at both center and individual colonoscopist level.

After correction for the design effect (= 1+(m-1)*ICC, where ICC = 0.025 and the mean number of patients per colonoscopist is 35, i.e. m = 35), 10% loss in efficiency due to the variation in the number of colonoscopies performed during the study period per colonoscopist (3), and a 20% drop-out risk for patients with LNPCP, the number of LNPCP cases required to detect a difference of 10% (20% local recurrence in the control group vs 10% in the intervention group) with a power of 90% and using a significance level alpha of 5% is 683 per group. This means that 20 colonoscopists per group are required. In the revised protocol, we have increased the power of analyses from 80% to 90%. In conclusion, in the 20 participating centers (10 per arm), a total of 20 colonoscopists will perform approximately 35 endoscopic resections each over 1.5 year.

4. METHODS

4.1 Study parameters/endpoints

4.1.1 Main study parameter/endpoint

- Local recurrence rate (6 months after resection).

4.1.2 Secondary study parameters/endpoints (if applicable)

- Radical (R0) resection rate
- Complication rate
- Number of repeat colonoscopies
- Referral rate to surgery
- Quality of life
- Cost-effectiveness

4.1.3 Other study parameters (if applicable)

Not applicable

4.2 Randomisation, blinding and treatment allocation

Participating centers will be randomized to the *intervention group* vs. *control group*, as detailed in **Figure 1**. To mitigate the effect of contamination, i.e. exchange of knowledge, practical skills between participants, we prefer to randomize centers instead of endoscopists. In each center, two endoscopists will participate in the study. Both the control (n=30 endoscopists) and the intervention group (n=30 endoscopists) will receive an e-learning module regarding the OPTICAL I model focused on optical diagnosis of T1 carcinomas, and assessment of an EMR scar to recognize recurrence.
In addition to this, the intervention group will receive an additional EMR training package, consisting of an e-module and a two-day symposium.

We will target our intervention (training) to this specific group because endoscopists at the beginning of their career may be more compliant to implement a change in their practice. An additional questionnaire will be used to provide baseline information regarding total number of endoscopic resections over the past year, resection techniques used (EMR vs ESD), the complication rate (bleeding, perforations) and the referral rate to surgery in order to select 20 endoscopists with comparable experience and endoscopic proficiency. We realize that such selection is associated with difficulty – baseline characteristics among the 2 groups will never be the same. Evaluation of such baseline information is, however, of importance for a meaningful interpretation of the study outcomes.

4.3 Study procedures

4.3.1 Standard optical training and registration (control group)

A training package will be developed to train endoscopists in optical diagnosis based on the features in the OPTICAL I model (Paris classification, location, depression, easy friability and advanced imaging (NBI or chromoendoscopy)). The training will also concern the recognition of recurrence in a post-EMR scar. All participants will register a standardized and pre-defined set of parameters within their endoscopy report for every colonoscopy were a LNPCP >20mm is encountered or removed (Appendix A).
Because size, morphology, site and access to a lesion predict the completeness of resection (SMSA score) {Rutter, 2015}, the difficulty of endoscopic resection will be stratified according to the SMSA score (Figure 1). The features of the SMSA score will also be included in the standardized set of parameters.

Photo documentation will be performed by the endoscopists at the following moments:

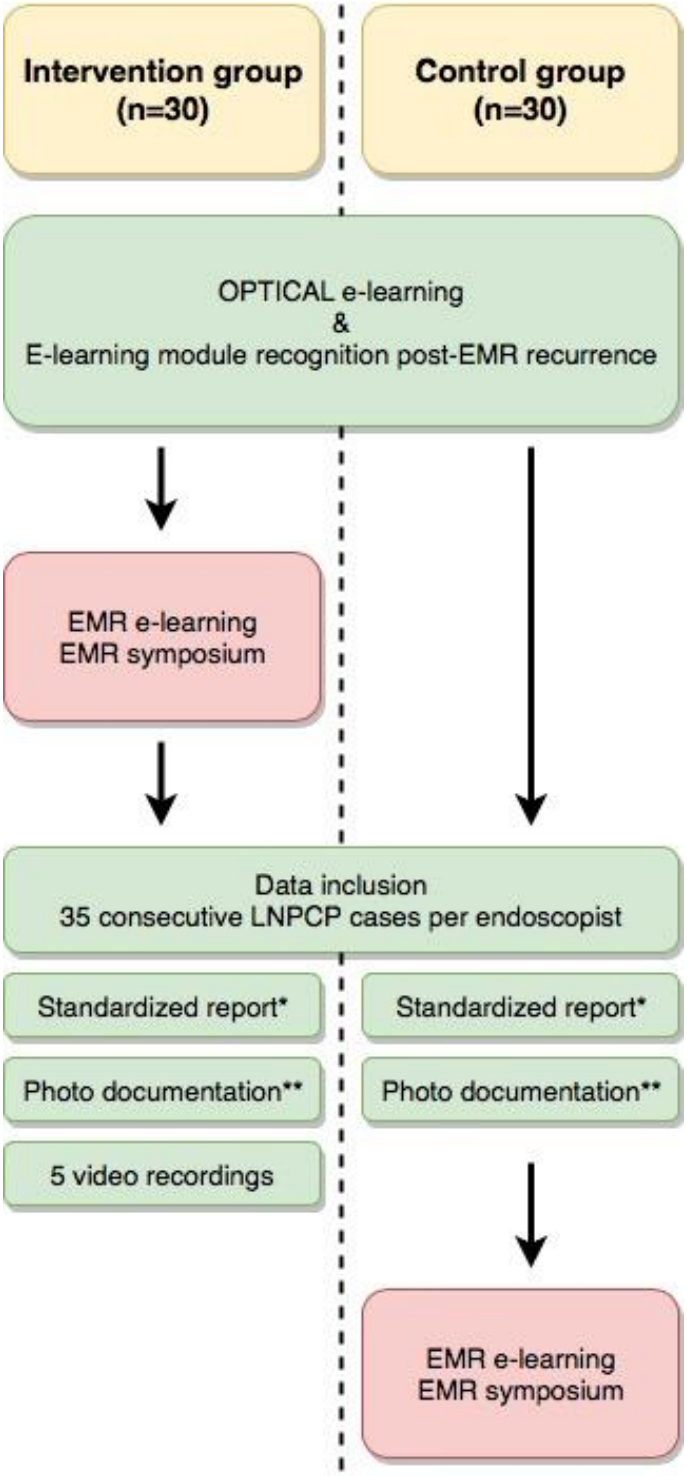
1. During lesion assessment
    a. In white light
    b. Zoom with advanced imaging (e.g. NBI, I-scan)
2. After performing the EMR
    a. Scar before adjunctive treatment
    b. Scar after adjunctive treatment/before adjuvant treatment
    c. Scar after adjuvant treatment

4.3.2 Training of EMR (intervention group)

For the intervention group, an additional training package will be developed to familiarize the therapeutic colonoscopists on the most recent state-of-the-art *knowledge*, and on *technical* and *non-technical* skills {Matharoo, 2014}. We will create modern training tools (e-learning modules, webinars, video training) in addition to hands-on training to systematically train the colonoscopists on endoscopic mucosal resection of LNPCPs.
To develop additional technical skills we will organize hands-on trainings using animal models. At Maastricht UMC+ there is already a tradition on hands-on training (Master-class September 2012, Master-class September 2014). Furthermore, non-technical skills will be trained and assessed using the Endoscopic Non-Technical Skills (ENTS) system (i.e. situation awareness, judgement and decision making, teamwork and leadership skills) {Matharoo, 2014}.
In addition to the registration of the standardized endoscopy report (Appendix A), the 30 endoscopists in the intervention group perform video recording of the first five EMRs they

perform. These video recordings will be evaluated by an expert panel and the endoscopists will receive individualized feedback regarding their EMR procedure.

Figure 1. Flowchart intervention vs. control group STAR-LNPCP study

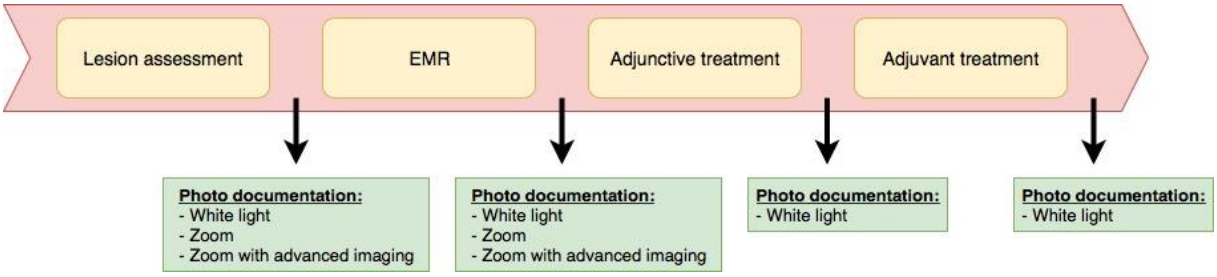


Legend:

* standard documentation of parameters according to the checklist/template.

** Photodocumentation consists of an image of the polyp in white light, followed by zoom together with advanced imaging modality, post-EMR pre adjunctive therapy, after adjunctive therapy, after adjuvant therapy

Figure 2: *flowchart of photodocumentation during the different phases of the EMR*



4.3.3 Quality of life questionnaires

In both groups, we will assess the impact of performing endoscopic resection for LNPCPs on the patient's quality of life (QoL). Because a validated questionnaire is not yet available, we will adapt the Medical Outcomes Study Short Form 36 {McHorney, 1993;Ware, 1992} and a colorectal-specific European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire {Theodoropoulos, 2013}. Questionnaires will be applied at two or three time points, depending on logistics in the particular hospital. When the LNPCP is resected during the index colonoscopy, the patient receives the first questionnaire after this procedure and the second questionnaire after 6 months. When the LNPCP is not resected during the index colonoscopy, but during a new scheduled intervention colonoscopy, the patient receives the first questionnaire after the index colonoscopy, the second questionnaire after the intervention colonoscopy and the third questionnaire after 6 months (when surveillance colonoscopy takes place).

4.3.4 Data inclusion

All endoscopists will perform at least 35 consecutive endoscopic resections of LNPCPs. During the procedure, a tattoo will be placed 2 cm distal of the lesion at the same side, to make sure the scar can be find during the surveillance colonoscopy. Six months follow-up data will be collected for all cases. During this surveillance colonoscopy, endoscopists are asked to report whether there is recurrence and how this is treated. In addition, the scar will be photo documented in white light and zoom with advanced imaging (e.g. NBI, I-scan, blue light). Furthermore, the scar will be biopsied, with one biopsy every 5 mm (with the biopsies being presented to the pathology in separate jars).

Beyond this project proposal, we will monitor long-term (36 months) outcomes after endoscopic resection (I.e. local recurrence, referral to surgery). LNPCP patients will receive surveillance colonoscopy according to the Dutch post-polypectomy surveillance guideline {Dekker, 2013}.

4.3.5 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

5. STATISTICAL ANALYSIS

Baseline characteristics will be reported as proportions (%) for categorical variables and numerical (mean with SD or median with IQR) where appropriate. The primary outcome is the recurrence rate at 6 months after resection (binary variable). Because of the nested study design (multiple patients within a cluster of colonoscopists), a logistic mixed-effects models with a random intercept at cluster level (colonoscopists) will be used. The study group (intervention groups vs. control group), previous experience on endoscopic resection of LNPCPs (questionnaires) and lesion complexity (SMSA score) will be used as main variables in the model. For the secondary outcomes, the same mixed model will be used as for the primary outcome, in which a linear mixed model analysis will be used for numerical outcome variables (number of repeat colonoscopies and number of complications) and logistic mixed model analysis for categorical outcome variables (referral to surgery). In case of missing variables multiple imputation as well as complete case analysis will be performed. IBM SPSS statistics version 25 will be used for the analyses.

5.1 Primary study parameter(s)

The primary outcome is the recurrence rate at 6 months after resection (binary variable). Because of the nested study design (multiple patients within a cluster of colonoscopists), a logistic mixed-effects models with a random intercept at cluster level (colonoscopists) will be used. The study group (intervention groups vs. control group), previous experience on endoscopic resection of LNPCPs (questionnaires) and lesion complexity (SMSA score) will be used as main variables in the model.

5.2 Secondary study parameter(s)

For the secondary outcomes, the same mixed model will be used as for the primary outcome, in which a linear mixed model analysis will be used for numerical outcome variables (number of repeat colonoscopies and number of complications) and logistic mixed model analysis for categorical outcome variables (referral to surgery). In case of missing variables multiple imputation as well as complete case analysis will be performed. IBM SPSS statistics version 23 will be used for the analyses.
Furthermore, we will look at quality of life and cost-effectiveness of endoscopic resection vs. surgical resection of LNPCPs.

6. ETHICAL CONSIDERATIONS

6.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki.

6.2 Recruitment and consent

Because there is no patient randomization, the project does not change the regular patient care. Patients will be informed about the evaluation of routine endoscopic treatments and the need to collect objective data in a standardized fashion. Informed consent will be obtained in an anonymous register and include the routine clinical parameters. Based on our previous experience with clinical trials, we assume that most patients will agree on data collection, but in case of drop-outs, the inclusion period may need to be extended.

Participating endoscopists inform the patients about the trial and will give them an information package including the patient information folder (PIF), an informed consent form, a Quality-of-Life questionnaire and a return envelope. The endoscopists place a comment in their endoscopy report regarding having informed the patient about the study. Furthermore, the endoscopists note the patient's information in the patient identification log.

Patients can send their informed consent form and QoL-questionnaire to the executive researcher (PhD student) when they want to participate in the questionnaire study.

6.3 Benefits and risks assessment, group relatedness

The project does not change the regular patient care, so there are no additional risks from this study, compared to the standard care.

The outcome of this project will clearly benefit our patients (fewer colonoscopy follow-up examinations and fewer surgical resections). We also expect that implementation of the new endoscopic resection techniques in practice will improve patient's quality of life. Importantly, the reduced number of unnecessary procedures will enable a better utilization of colonoscopy resources in the context of the national population screening program.

6.4 Compensation for injury

The project does not change the regular patient care, so there is no obligation to provide insurance.

7. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

7.1 Handling and storage of data and documents

Participating endoscopists will keep a patient identification log at the site.

An electronic case report form (eCRF) will be used to collect the data (i.e. indication for colonoscopy, colonoscopy findings, endoscopic resection technique used, local recurrence rate, number of repeat colonoscopies, complication rate, and number of referrals to surgery). Informed consents and QoL-questionnaires will be send to the executive researcher by the patients and will be stored in Maastricht.

An external PhD-student (executive researcher) will collect the data in the eCRF. Data collection and storage will be done in Castor Data Management System.

7.2 Monitoring and Quality Assurance

There will be no monitoring.

7.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

7.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

7.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

7.6 Public disclosure and publication policy

The intellectual property rights pertaining to training materials created within the framework of this project will be owned by the project leader. Part of the training materials (photo documentation, powerpoint slides) will be provided by international experts in this field and thereby remain their intellectual property, in accordance with national and international law on authorship {World Intellectual Property Organization, 1979}. The rights to use these materials in the Dutch training program will be granted. There will be no conflicting contracts preventing from publication and implementation of the training program that will be developed during this study.

8. REFERENCES

1. Bogie R, et al. UEG Week 2015 Oral Presentations: OP046 LATERALLY SPREADING TUMORS ARE A RISK FACTOR FOR SYNCHRONOUS NEOPLASMS. United European Gastroenterology Journal. 2015 October 1, 2015;3(5 suppl):15-6.
2. Nishihara R, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013 Sep 19;369(12):1095-105. PubMed PMID: 24047059. Pubmed Central PMCID: 3840160.
3. Zauber AG, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med. 2012 Feb 23;366(8):687-96. PubMed PMID: 22356322. Pubmed Central PMCID: 3322371.
4. Pullens HJ, Leenders M, Schipper ME, van Oijen MG, Siersema PD. No decrease in the rate of early or missed colorectal cancers after colonoscopy with polypectomy over a 10-year period: a population-based analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2015 Jan;13(1):140-7. PubMed PMID: 24815328.
5. le Clercq CM, et al. Postcolonoscopy colorectal cancers are preventable: a population-based study. Gut. 2014 Jun;63(6):957-63. PubMed PMID: 23744612. Epub 2013/06/08.
6. Robertson DJ, et al. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. Gut. 2014 Jun;63(6):949-56. PubMed PMID: 23793224.
7. Rutter MD, et al. British Society of Gastroenterology/Association of Coloproctologists of Great Britain and Ireland guidelines for the management of large non-pedunculated colorectal polyps. Gut. 2015 Dec;64(12):1847-73. PubMed PMID: 26104751. Pubmed Central PMCID: 4680188.
8. Soetikno RM, et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. Jama. 2008 Mar 5;299(9):1027-35. PubMed PMID: 18319413. Epub 2008/03/06.
9. Rotondano G, et al. The Cooperative Italian FLIN Study Group: prevalence and clinico-pathological features of colorectal laterally spreading tumors. Endoscopy. 2011 Oct;43(10):856-61. PubMed PMID: 21826628. Epub 2011/08/10.
10. Yamada M, Saito Y, Sakamoto T. Endoscopic predictors of deep submucosal invasion in colorectal laterally spreading tumors. Endoscopy. 2016.
11. Kudo S, et al. Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc. 2008 Oct;68(4 Suppl):S3-47. PubMed PMID: 18805238. Epub 2008/10/01.
12. Matsuda T, et al. Macroscopic estimation of submucosal invasion in the colon. Techniques in Gastrointestinal Endoscopy. 2011 1//;13(1):24-32.
13. Uraoka T, et al. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. Gut. 2006 Nov;55(11):1592-7. PubMed PMID: 16682427. Pubmed Central PMCID: PMC1860093. Epub 2006/05/10.

14. Saito Y, et al. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). Gastrointest Endosc. 2007 Nov;66(5):966-73. PubMed PMID: 17524403.
15. Tamegai Y, et al. Endoscopic submucosal dissection: a safe technique for colorectal tumors. Endoscopy. 2007 May;39(5):418-22. PubMed PMID: 17516348.
16. Tanaka S, Terasaki M, Hayashi N, Oka S, Chayama K. Warning for unprincipled colorectal endoscopic submucosal dissection: Accurate diagnosis and reasonable treatment strategy. Digestive Endoscopy. 2013;25(2):107-16.
17. Rondagh EJ, et al. Endoscopic appearance of proximal colorectal neoplasms and potential implications for colonoscopy in cancer prevention. Gastrointestinal endoscopy. 2012 Jun;75(6):1218-25. PubMed PMID: 22482917. Epub 2012/04/10.
18. Pimentel-Nunes P, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2015 Sep;47(9):829-54. PubMed PMID: 26317585.
19. Belderbos TD, Leenders M, Moons LM, Siersema PD. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. Endoscopy. 2014 May;46(5):388-402. PubMed PMID: 24671869.
20. Ortiz AM, Bhargavi P, Zuckerman MJ, Othman MO. Endoscopic mucosal resection recurrence rate for colorectal lesions. Southern medical journal. 2014 Oct;107(10):615-21. PubMed PMID: 25279863. Epub 2014/10/04.
21. Moss A, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology. 2011 Jun;140(7):1909-18. PubMed PMID: 21392504.
22. Oka S, et al. Local Recurrence After Endoscopic Resection for Large Colorectal Neoplasia: A Multicenter Prospective Study in Japan. Am J Gastroenterol. 2015 Apr 7. PubMed PMID: 25848926.
23. Hassan C, et al. Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. Gut. 2015 Feb 13. PubMed PMID: 25681402.
24. Saito Y, et al. Endoscopic treatment for laterally spreading tumors in the colon. Endoscopy. 2001 Aug;33(8):682-6. PubMed PMID: 11490384. Epub 2001/08/08.
25. Sanduleanu S, Siersema PD. Laterally spreading tumor through the magnifying glass: we only see what we know Endoscopy. 2016;Not yet published(?):?
26. Kitajima K, et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol. 2004 Jun;39(6):534-43. PubMed PMID: 15235870.
27. Nakajima T, et al. Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. Surgical endoscopy. 2013 Sep;27(9):3262-70. PubMed PMID: 23508817.

28. Hayashi N, et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. Gastrointestinal endoscopy. 2013;78(4):625-32.
29. Matsuda T, et al. Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. Am J Gastroenterol. 2008 Nov;103(11):2700-6. PubMed PMID: 18853968.
30. Sanduleanu S, le Clercq CM, Dekker E, Meijer GA, Rabeneck L, Rutter MD, Valori R, Young GP, Schoen RE, Expert Working Group on 'Right-sided l, interval cancers CCSCWEO. Definition and taxonomy of interval colorectal cancers: a proposal for standardising nomenclature. Gut. 2015 Aug;64(8):1257-67. PubMed PMID: 25193802.
31. Dik VK, et al. Multicenter, randomized, tandem evaluation of EndoRings colonoscopy - results of the CLEVER study. Endoscopy. 2015 Dec;47(12):1151-8. PubMed PMID: 26220283.
32. Leufkens AM, et al., Third Eye Retroscope Randomized Clinical Evaluation Study G. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. Gastrointest Endosc. 2011 Mar;73(3):480-9. PubMed PMID: 21067735.
33. Gralnek IM, et al. A prospective cohort study evaluating a novel colonoscopy platform featuring full-spectrum endoscopy. Endoscopy. 2013 Sep;45(9):697-702. PubMed PMID: 23939509.
34. van Doorn SC, et al. Adenoma detection with Endocuff colonoscopy versus conventional colonoscopy: a multicentre randomised controlled trial. Gut. 2015 Dec 16. PubMed PMID: 26674360.
35. Sanduleanu S, Rondagh EJ, Masclee AA. Development of expertise in the detection and classification of non-polypoid colorectal neoplasia: Experience-based data at an academic GI unit. Gastrointestinal endoscopy clinics of North America. 2010 Jul;20(3):449-60. PubMed PMID: 20656243. Epub 2010/07/27.
36. le Clercq CM, et al. Temporal trends and variability of colonoscopy performance in a gastroenterology practice. Endoscopy. 2016 Mar;48(3):248-55. PubMed PMID: 26808394.
37. Bouwens MW, et al. Endoscopic characterization of sessile serrated adenomas/polyps with and without dysplasia. Endoscopy. 2014 Mar;46(3):225-35. PubMed PMID: 24573732.
38. Bouwens MW, et al. Simple clinical risk score identifies patients with serrated polyps in routine practice. Cancer prevention research. 2013 Aug;6(8):855-63. PubMed PMID: 23824513.
39. Sanduleanu S. A Roadmap to the Implementation of Chromoendoscopy in IBD Colonoscopy Surveillance Practice. GIE: Gastrointestinal Endoscopy Author Interviews: Youtube; 2016. Available from: https://www.youtube.com/watch?v=Io2qUAxjGUo.
40. Sanduleanu S, le Clercq CM, Dekker E, Meijer GA, Rabeneck L, Rutter MD, Valori R, Young GP, Schoen RE, Expert Working Group on 'Right-sided l, interval cancers CCSCWEO.

Definition and taxonomy of interval colorectal cancers: a proposal for standardising nomenclature. Gut2015. Available from: https://www.youtube.com/watch?v=I6IgEyQjVLU.

41. Marx R, et al. 498 Training on Detection and Resection of Nonpolypoid Colorectal Neoplasms Reduces the Postcolonoscopy Colorectal Cancer Rate. Gastroenterology. 2015;148(4):S-96.
42. Voorham QJ, et al. Tracking the molecular features of nonpolypoid colorectal neoplasms: a systematic review and meta-analysis. The American journal of gastroenterology. 2013 Jul;108(7):1042-56. PubMed PMID: 23649184. Epub 2013/05/08.
43. Belderbos TD, et al. Comparison of cecal intubation and adenoma detection between hospitals can provide incentives to improve quality of colonoscopy. Endoscopy. 2015 Aug;47(8):703-9. PubMed PMID: 26090725.
44. Belderbos TD, van Oijen MG, Moons LM, Siersema PD. The "golden retriever" study: improving polyp retrieval rates by providing education and competitive feedback. Gastrointest Endosc. 2016 Mar;83(3):596-601. PubMed PMID: 26324388.
45. Bogie R, et al. UEG Week 2015 Poster Presentations: P1644 UNDERSTANDING THE EPIDEMIOLOGY AND CLINICAL SIGNIFICANCE OF LATERALLY SPREADING TUMORS: A META-ANALYSIS. United European Gastroenterology Journal. 2015 October 1, 2015;3(5 suppl):146-687.
46. Mulder C, Terhaar sive Droste J, Ben Larbi I. Rapportage enquête ‘’endoscopiecapaciteit in 2011’’. Rijksinstituut voor Volksgezondheid en Milieu, 2013.
47. Rijksinstituut voor Volksgezondheid en Milieu. Capaciteit 2016 [cited 2016 03-03-2016]. Available from: http://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek_darmkanker_voor_professionals/Kwaliteit_capaciteit_gegevens_en_ICT/Capaciteit.
48. Kaltenbach T, Soetikno R. Endoscopic resection of large colon polyps. Gastrointestinal endoscopy clinics of North America. 2013 Jan;23(1):137-52. PubMed PMID: 23168124.
49. Tanaka S, et al. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society. 2015 May;27(4):417-34. PubMed PMID: 25652022.
50. Higaki S, et al. Long-term follow-up of large flat colorectal tumors resected endoscopically. Endoscopy. 2003 Oct;35(10):845-9. PubMed PMID: 14551863.
51. Matharoo M, Haycock A, Sevdalis N, Thomas-Gibson S. Endoscopic non-technical skills team training: the next step in quality assurance of endoscopy training. World journal of gastroenterology. 2014 Dec 14;20(46):17507-15. PubMed PMID: 25516665. Pubmed Central PMCID: PMC4265612.
52. Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy. 2001 Apr;33(4):367-73. PubMed PMID: 11315901.
53. Kudo S, et al. Colorectal tumours and pit pattern. Journal of clinical pathology. 1994 Oct;47(10):880-5. PubMed PMID: 7962600. Pubmed Central PMCID: 502170.

54. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Medical care. 1993 Mar;31(3):247-63. PubMed PMID: 8450681. Epub 1993/03/01. eng.
55. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care. 1992 Jun;30(6):473-83. PubMed PMID: 1593914. Epub 1992/06/11. eng.
56. Theodoropoulos GE, Karantanos T, Stamopoulos P, Zografos G. Prospective evaluation of health-related quality of life after laparoscopic colectomy for cancer. Tech Coloproctol. 2013 Feb;17(1):27-38. PubMed PMID: 23065134. Epub 2012/10/16. eng.
57. Dekker E, et al. Nederlandse Richtlijn Coloscopie Surveillance. NVMDL, 2013.
58. Kaminski MF, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2014 May;46(5):435-49. PubMed PMID: 24639382.
59. Sanduleanu S, et al. A roadmap to the implementation of chromoendoscopy in inflammatory bowel disease colonoscopy surveillance practice. Gastrointest Endosc. 2016 Jan;83(1):213-22. PubMed PMID: 26364967.
60. Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R, Panel SGD. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology. 2015 Mar;148(3):639-51 e28. PubMed PMID: 25702852.
61. van Breukelen GJ, Candel MJ, Berger MP. Relative efficiency of unequal versus equal cluster sizes in cluster randomized and multicentre trials. Stat Med. 2007 Jun 15;26(13):2589-603. PubMed PMID: 17094074.
62. Law R, et al. Endoscopic resection is cost-effective compared with laparoscopic resection in the management of complex colon polyps: an economic analysis. Gastrointest Endosc. 2015 Dec 1. PubMed PMID: 26608129.
63. Berne Convention for the Protection of Literary and Artistic Works, 10 (1979).

9. Appendix A

Checklist EMR endoscopists STAR study

Colonoscopy – Patient with LNPCP (≥20mm)

STEP 1: ASSESSMENT OF THE LESION

1. **Optical description in endoscopy report**
    a. Location (segment)
    b. Access → easy/difficult?
    c. Size (in millimeters)
    d. Morphological description according to Paris classification
    e. Granular or non-granular?
        i. Granular
            1. Homogeneous granular
            2. Granular with dominant nodule
            3. Granular with non-granular, erythematous area
        ii. Non-granular
    f. Well demarcated depression
    g. Spontaneously bleeding → yes/no?
    h. Advanced imaging
        i. Vascular pattern according to JNET (type 1/2A/2B/3)
        ii. Kudo pit pattern (I,II,III,IV,Vi,Vn)
    i. Optical diagnosis
        i. Low-grade dysplasia
        ii. High-grade dysplasia
        iii. Superficial submucosal invasive carcinoma (T1)
        iv. Deep invasive carcinoma (≥1TSm3)
    j. Certainty of optical diagnosis > 90%
2. **Photodocumentation**
    a. White light
    b. Zoom
    c. Zoom with advanced imaging modality (e.g. NBI, I-scan)

STEP 2: ENDOSCOPIC MUCOSAL RESECTION

1. **EMR documentation in endoscopy report**
    a. Lifting fluid → NaCl / Gelofusin/ Venofundin

b. Dye included in the injection fluid →yes/no
c. Adjuvant adrenalin in lifting fluid → yes/no?
d. En-bloc or piecemeal?
e. Number of pieces [n = … / >10 fragments]
f. Intraprocedural bleeding yes/no?
    i. Number of intraprocedural bleedings
    ii. Treatment intraprocedural bleeding
        1. Clipping
        2. Snare tip coagulation
        3. Coagulation grasper
        4. Adrenalin injection
g. Residual tissue after EMR yes/no?
    i. In case of residual tissue, adjunctive treatment?
        1. Cold avulsion with biopsy forceps
        2. Cold avulsion with thermal ablation (CAST)
        3. Hot avulsion
        4. Snare tip coagulation
        5. Suck and snare
        6. APC
h. Adjuvant treatment performed to prevent recurrence yes/no?
    i. Argon plasma coagulation
        1. Borders (y/n)
        2. Scar surface (y/n)
    ii. Snare tip soft coagulation
        1. Borders (y/n)
        2. Scar surface (y/n)

2. Tattoo 2 cm distal at the same side (to make sure the scar can be retrieved during surveillance colonoscopy)

3. Photo/videodocumentation

a. Recording first 5 EMRs (intervention group)
b. Photodocumentation of the scar
    i. Before adjunctive treatment
    ii. Before adjuvant treatment
    iii. After adjuvant treatment

STEP 3: AFTER COLONOSCOPY

1. Informing the patient about the study

2. Providing the information package
3. Note patient data on study list (patient number, sex, birthdate)
4. Schedule 6 month FU colonoscopy

STEP 4: SURVEILLANCE COLONOSCOPY AFTER 6 MONTHS

1. **Endoscopy report**
    a. Recurrence yes/no?
    b. Unifocal or multifocal [n]
    c. Size of largest recurrence (in mm)
    d. In case of recurrence, treatment yes/no?
        i. Re-EMR
        ii. Cold avulsion
        iii. Cold avulsion with snare tip coagulation (CAST)
        iv. Hot avulsion
        v. Suck and snare
        vi. eFTR
        vii. ESD
        viii. APC
        ix. Snare tip soft coagulation (STSC)
2. **Biopsy the scar**
    a. Take a biopsy every 5 mm [e.g. in a scar of 18mm, 3 biopsies are taken]
    b. Present every biopsy in a separate PA jar
3. **Photodocumentation**
    a. Scar [white light, zoom and advanced imaging modality]