Real-time use of artificial intelligence (CAD EYE) in the colorectal cancer surveillance of Lynch syndrome patients - an international multicenter trial

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Primary Objective:- To compare adenoma detection rate (ADR) with versus without real-time automated detection (CAD EYE, Fujifilm)Secondary Objectives:- To compare the size, morphology and histology of adenomas detected and resected in both arms of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Observational invasive

Summary

ID

NL-OMON53384

Source
ToetsingOnline

Brief title
CADLY II

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
colon polyps, colorectal polyps

Research involving
Human

Sponsors and support

Primary sponsor: Universitätsklinikum Bonn

Source(s) of monetary or material Support: Department of Internal Medicine I;Universitätsklinikum Bonn (afdeling Inwendige Geneeskunde Universiteitziekenhuis Bonn)

Intervention

Keyword: Artificial intelligence, Colorectal cancer, Colorectal polyp, Lynch syndrome

Outcome measures

Primary outcome

Primary Endpoint:

- Adenoma detection rate (ADR)

Secondary outcome

Secondary endpoints:

- Total/mean number and size of detected adenomas

- Detection rate, mean and total number of polyps

- Detection rate, mean and total number of advanced adenomas

- Detection rate, number of adenomas in relation to morphology (accord-ing to

Paris classification)

- Detection rate and number of colorectal carcinomas

- Detection rate, mean and total number of sessile serrated lesions

- Detection rate, total and mean number of proximal serrated polyps

- Detection rate, total and mean number of proximal adenomas

- Detection rate, total and mean number of sessile serrated lesions, ade-nomas

and carcinomas in dependence to the previous colonoscopy re-sult and interval

and underlying pathogenic variant

- Detection rate, total and mean number of sessile serrated lesions, ade-nomas

and carcinomas in dependence to previous CAD EYE experience and/or center

- Mean examination/procedure time with and without CAD EYE system (examination time and time of endoscopic therapy)

- Specificity and sensitivity of the polyp differentiation mode of the CAD EYE system

- Occurrence of (serious) adverse events

- Rate of false positives of the CAD EYE system

Study description

Background summary

Colorectal cancer (CRC) is one of the most common cancers, with ~61.000 new diagnoses and over 25.000 deaths per year in Germany. Lynch syndrome (LS) is the most common hereditary colorectal cancer syndrome and accounts for ~3% of all CRCs. This autosomal dominant disorder is caused by germline mutations in DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2 and EPCAM). One in 279 individuals of the general population is a mutation carrier. Thus, almost 300.000 individuals are expected to have LS in Germany. Carriers of pathogenic variants are at high risk of CRC with a cumulative incidence of up to 70% by the age of 70 despite regular endoscopic surveillance, and also at elevated risk to develop metachronous CRC. LS also includes a variety of extracolonic malignancies. The number of patients identified with LS is expected to rise in the next years due to the increasing use of universal screening for mismatch repair deficiency in solid tumors.

For patients with LS it has been suggested to undergo surveillance colonoscopy every 1 to 2 years. The ade-noma-carcinoma sequence is considered a major pathway in the carcinogenesis of CRC also in Lynch syndrome. This opens a window of opportunity for endoscopic surveillance with removal of adenomatous polyps. It has been shown that advanced histology (high-grade dysplasia; villous component) was already apparent in adenomas with a size of 2 - 5 mm. Thus, it is of paramount importance to endoscopically detect and remove adenomas as early and sensitive as possible before they can develop into invasive CRC.

Adenomas are considered to represent the main precursors of colorectal cancer in Lynch syndrome. Due to the accelerated progression from adenoma to CRC in LS, high ADR is particularly important in these patients to minimize the risk of carcinoma development. Accordingly, intensified surveillance strategies with

colonos-copies every one to two years have been shown to reduce both CRC incidence and CRC-associated mortality. However, several studies have shown that a relevant proportion of adenomas are missed even when examinations are performed by experienced endoscopists. This is especially true for flat lesions, which are typical for LS. These missed adenomas are considered a possible reason why patients with Lynch syn-drome are at very high risk for post-colonoscopy CRC with a cumulative 10-year incidence of up to 8% despite endoscopic surveillance. Furthermore, small colorectal polyps in Lynch syndrome patients have a higher risk of harboring cancer or high-grade dysplasia compared to an average-risk population.

Epidemiological studies have reported that the cumulative CRC rate at 70 years among individuals with LS undergoing colonoscopy surveillance can be as high as 46% among MLH1, 35% among MSH2, 20% among MSH6, and 10% among PMS2 pathogenic mutation carriers. Some authors postulate that some post-colonoscopy CRCs in LS may emerge from MMR-deficient crypt foci without a polypoid growth pattern and therefore can be difficult to detect by colonoscopy. However, retrospective descriptive studies evaluating post-colonoscopy CRC showed associations with incomplete examination, inadequate bowel preparation, and possible incomplete resection of lesions.Furthermore, high miss rates for colorectal neoplasia (12%-74 %) have been reported in several back-to-back colonoscopy studies. Therefore, it can be concluded that high quality standards for colonoscopy are not always met in individuals with LS. However, the evidence regarding key performance indicators for colonos-copy in individuals with LS is limited. Almost one third (28%) of these small adenomas are missed according to a recently published meta-analysis. Often the non-polypoid shape hampers endoscopic detection.

Several approaches have been made to enhance endoscopic detection of adenomas by using new endoscopic techniques. Conventional chromoendoscopy is conducted by the use of indigo carmine as pan-colonic dye applied via spray catheter. This was studied in several back-to-back endoscopic studies as well as two ran-domized controlled trial comparing chromoendoscopy to standard white-light endoscopy. The by far largest and well-designed trial by Rivero-Sánchez et al showed that high-definition white-light endoscopy is not inferior to chromoendoscopy. The European Society for Gastrointestinal Endoscopy (ESGE) states that *the use of chromoendoscopy may be of benefit in individuals with Lynch syndrome undergoing colonoscopy; routine use must be balanced against costs, training, and practical considerations*. In individual patient data meta-analysis of studies comparing chromoendoscopy with WLE endoscopy in Lynch syndrome for ade-noma detection, chromoendoscopy showed no apparent increase in adenoma detection.

Several trials have studied the effect of virtual chromoendoscopy (Narrow-Band-Imaging, Fuji Intelligent Color Enhancement, Linked-Colour-Imaging) on adenoma or polyp detection. The most recent trial by Houwen et al. showed no effect on polyp detection as the primary endpoint but

on adenoma detection rate as a secondary endpoint.

Limitations in human visual perception and other human biases such as fatigue, distraction, level of attention during examination increase such detection errors. A possible way to mitigate these could be another key to improve polyp detection and further reduce CRC incidence. The use of artificial intelligence might be a prom-ising approach in this high-risk patient cohort. In recent years, several clinical trials in the general population have demonstrated that AI-assisted colonoscopy is a promising approach, showing significant improvement in the detection of polyps and adenomas compared with standard white light endoscopy. These auto-mated intelligence systems can be easily activated via button on the endoscope. It analyzes the colonic mu-cosa real-time during the examination and signals the detection of a polyp by an optical and also acoustic signal.

Fujifilm has developed a technology known as *CAD EYE* to support colonic polyp detection and characteri-zation during colonoscopy, utilizing Fujifilm's medical AI technology named REiLI (CADE-EYE, Fujifilm, Japan). CAD EYE is a customized detection and characterization support compatible with the ELUXEO and ELUXEO Lite system. CAD EYE Detection is activated when the clinicians are observing in White Light Mode or LCI Mode. When a suspicious polyp is detected within the endoscopic image, a Detection Box indicates the area where the suspicious polyp has been detected accompanied by a sound signal. Furthermore, it is also able to distinguish polyps between *neoplastic* or *hyperplastic* by their macroscopic appearance.

We have recently conducted a randomized controlled pilot trial, where Lynch syndrome patients were random-ized to their regular surveillance colonoscopy either with or without the use of CADe. In the HD-WLE arm, adenomas were detected in 12/46 patients compared to 18/50 in the AI arm (26.1% [95% CI 14.3-41.1] vs. 36.0% [22.9-50.8]; p=0.379). In this study, we now want to confirm these results that the adenoma detection rate (ADR) using CADe is higher than using HD-WLE.

Study objective

Primary Objective:
- To compare adenoma detection rate (ADR) with versus without real-time automated detection (CAD EYE, Fujifilm)

Secondary Objectives:
- To compare the size, morphology and histology of adenomas detected and resected in both arms of the study in terms of mean/absolute num-ber and anatomical localisation (proximal/distal)
- To compare the size, morphology and histology of advanced adeno-mas detected and resected in both arms of the study in terms of mean/absolute number, detection rate and anatomical localisation (proximal/distal)

- To compare the size, morphology and histology of serrated polyps (sessile serrated lesions, hyperplastic polyps, traditional serrated ade-nomas) detected and resected in both arms of the study in terms of mean/absolute number, detection rate and anatomical localisation (proximal/distal)
- To compare the size, morphology and histology of polyps detected and resected in both arms of the study in terms of mean/absolute number, detection rate and anatomical localisation (proximal/distal)
- To compare detection rate and mean/absolute number of adenomas and serrated polyps (sessile serrated lesions, hyperplastic polyps, tra-ditional serrated adenomas) with and without CAD EYE depending on center/previous experience using artificial intelligence systems
- To compare detection of colorectal cancer with and without CAD EYE
- To compare examination/procedure times with and without CAD EYE
- To assess risks of formation of sessile serrated lesions/adenoma/carci-noma formation depending on the interval to the last colonoscopy as well as on the findings of the previous examination and underlying pathogenic variant
- To assess specificity/sensitivity of the polyp differentiation mode of the CAD EYE system
- To explore false positives lesions by the CAD EYE system

Study design

The study is a prospective, international, multicenter, randomized, controlled, open-label, two-arm study carried out by experienced endoscopists in expert centers. Once a subject is determined to be eligible for the study, the subject will be randomized to one of the two trial arms. Asymptomatic patients with a diagnosis of Lynch syndrome will be enrolled in this trial. All subjects will be randomized to 1 of the 2 treatment groups in a 1:1 ratio as described below. Randomization will be stratified by previous colorectal cancer (yes or no), underlying (likely-) pathogenic variant (MLH1, MSH2 (EPCAM), MSH6, PMS2), center, gender (male/female) and interval to last colonoscopy (12-23 months, 24-36 months, index colonoscopies or >36 months). Randomization arms: - Arm 1: standard high-definition white light endoscopy (HD-WLE) without real-time use of artificial intelligence software (CAD EYE) for polyp detection, but with use of artificial intelligence software for polyp characterization - Arm 2: standard high-definition white light endoscopy (HD-WLE) with real-time use of artificial intelligence software (CAD EYE) for both detection and characterization of colorectal polyps

Study burden and risks

No additional risk or burden associated with study participation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

General inclusion criteria:
- Age >=18 years
- Written informed consent of the subject for voluntary participation in the study
- Subjects with the ability to follow study instructions and likely to attend and complete all required visits

Indication-specific inclusion criteria:
- Diagnosis of Lynch-syndrome (presence of a (likely-) pathogenic germline variant in MLH1, MSH2, MSH6, PMS2; deletion in the 3` region of the EPCAM gene)
- Surveillance colonoscopy

Exclusion criteria

General exclusion criteria:
- Subject without legal capacity who is unable to understand the nature, scope, significance and consequences of this study
- Patients with a physical or psychiatric condition / a systemic disease which at the investigator*s discretion may compromise safety of the sub-ject, may confound the trial results, may interfere with the subject*s par-ticipation in this clinical study or may prevent sufficient compliance
- Simultaneously participation in any clinical trial involving administration of an investigational medicinal product within 30 days prior to clinical trial beginning

Exclusion criteria regarding special restrictions for females:
- Current pregnancy

Indication specific exclusion criteria:
- Previous extensive colorectal surgery (proctocolectomy or colectomy with ileorectal anastomosis)
- Recent surveillance colonoscopy within 12 months from current exami-nation
- Symptoms such as rectal bleeding, change in bowel habits, unexplained weight loss, anemia
- Concomitant inflammatory bowel disease

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-10-2023

Enrollment:	200
Type:	Actual

Medical products/devices used

Generic name:	CAD EYE
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	09-08-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	DRKS00030695
CCMO	NL83630.018.23