Capsule endoscopy in Lynch Syndrome for small intestinal tumour screening: the CELSIUS study

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Primary objectiveThe primary aim of the study is to determine the prevalence and incidence of small bowel neoplasia in Lynch syndrome patients using small bowel CE and DBE.Secondary objectivesThe secondary aim is to identify risk factors for small...

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

Summary

ID

NL-OMON32285

Source
ToetsingOnline

Brief title
CELSIUS

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
HNPCC, Lynch syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Acertys BV,Given Imaging,KWF Kankerbestrijding

Intervention

Keyword: Capsule endoscopy, Double balloon enteroscopy, Lynch syndrome, Small bowel cancer

Outcome measures

Primary outcome

Endpoints

The primary endpoint will be the number of neoplastic small bowel lesions, with determination of size, location and histological characteristics at baseline and at follow-up after 2 years.

Several characteristics of the lesions will be recorded.

Size

The size of all lesions encountered will be determined by the pathologist.

Location

The location of all lesions encountered will be recorded subdivided in duodenum, jejunum and ileum.

Histology

Biopsy samples and excised lesions will be examined by local pathologists with special interest in gastroenteropathology. Lesions will be classified according to the WHO criteria. Findings will be reported as normal mucosa, hyperplastic polyp, adenomatous polyp or carcinoma. Adenomatous polyps will be classified as serrated, tubular, tubulovillous or villous. Degree of dysplasia will be classified as low-grade or high-grade. Adenomatous polyps or cancer will be considered as neoplastic lesions. In addition, all lesions will be reviewed centrally by a pathologist (Prof Morreau, Leiden University Medical Centre).

Secondary outcome

The secondary endpoint will be the number of complications following endoscopic procedures: rates of capsule retention and postpolypectomy bleeding and perforation. Immediate bleeding following polypectomy can usually be managed by epinephrin injection, application of electrocautery or hemoclips. Rates of immediate bleeding will be recorded. Postpolypectomy bleeding will be defined as delayed hemorrhage following the endoscopic procedure. Patients will be instructed about possible postpolypectomy bleeding and instructed to return to the emergency department. Postpolypectomy perforations usually present in a delayed manner, with abdominal pain and localised peritoneal signs. Most of these patients will recover with conservative therapy. Patients will be instructed about possible postpolypectomy perforation and instructed to return to the emergency department.

Study description

Background summary

Lynch syndrome (LS), or hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominantly inherited disorder characterized by a very high risk of early-onset colorectal and endometrial cancer and an increased risk of other cancers, including cancers of the stomach, ovary, urinary tract, hepatobiliary tract, pancreas and small bowel [1]. LS is caused by germline mutations in one of the mismatch repair (MMR) genes, mostly hMLH1, hMSH2 and hMSH6. Recently, several studies, including one from the Netherlands, have evaluated the life-time risk of small bowel cancer (SBC) in LS patients [2-6]. From these studies the life-time risk of SBC is estimated around 4 %. This is similar to the life-time risk of colorectal cancer in the general population, for which screening is generally advised [7]. The risk of SBC increases with age, with an estimated prevalence of 1:500 at the age of 40, rising to an estimated prevalence of around 1:70 at the age of 60. Compared with the general population, LS patients with SBC generally present 10-20 years earlier as most

patients with sporadic SBC are in their sixth or seventh decade of life [8]. The localisation of SBC in LS is almost equal in the duodenum and jejunum, with localisation in the ileum generally occurring at a lower frequency [8].Until now, screening for small bowel neoplasia in Lynch syndrome patients is generally not recommended [9,10]. However, the development of two new techniques to visualize the small intestine has raised the question whether screening might be useful and advisable. Small bowel capsule endoscopy (CE) has been developed as a safe, patient-friendly, minimally invasive modality for visualization of the small bowel [11]. In addition, double-balloon enteroscopy (DBE) has been developed, a technique which allows endotherapeutic interventions [12]. The diagnostic yields of both techniques are markedly higher than the conventional methods, such as push-enteroscopy and enteroclysis. To date, no study has been performed on screening for small bowel neoplasia in Lynch syndrome patients by means of these techniques.
This study will provide data on the prevalence and incidence of small bowel lesions in Lynch syndrome. Together, the results will indicate whether screening for small bowel neoplasia in patients with Lynch syndrome is useful.

References

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Study objective

Primary objective
The primary aim of the study is to determine the prevalence and incidence of small bowel neoplasia in Lynch syndrome patients using small bowel CE and DBE.
Secondary objectives
The secondary aim is to identify risk factors for small bowel pathology useful in clinical practice to identify patients that might benefit from screening and to determine the additional interventional risk associated with the endoscopic procedures.

Study design

This is a national multi-centre study evaluating the yield of small bowel screening using capsule endoscopy and double balloon enteroscopy in Lynch syndrome subjects. The intervention consists of performing a capsule endoscopy procedure at baseline and at 2-year follow-up. In patients with polyps or malignant appearing abnormalities on capsule endoscopy, double balloon enteroscopy will be performed with subsequent endoscopic or surgical removal of neoplastic lesions. In patients with unexpected findings at capsule endoscopy, the findings will be weighed in relation to the clinical context by the attending physician.

Study burden and risks

Capsule endoscopy.
All participating centres have local experience with or easy access to capsule endoscopy facilities. Bowel preparation for capsule endoscopy will consist of 2 L of polyethylene glycol electrolyte solution (Moviprep®), allowing adequate inspection of the small bowel. Patients will be allowed to drink fluids after 3 h and to consume a light meal after 5 h after ingestion of the capsule. Capsules will be used from Given Imaging (Yoqneam, Israel), with a recording time of 8 hours, using Rapid 5.0 ® software.
All capsule endoscopy procedures will be evaluated by an experienced local endoscopist. In addition, capsule endoscopy procedures will be processed on a

DVD disk and subsequently assesses centrally by the principal investigator. Findings of capsule endoscopy will be recorded. Only if capsule endoscopy reveals polyps or malignant appearing lesions, a double balloon enteroscopy will be performed.
Double balloon enteroscopy.
All participating centres have local experience with or easy access to double balloon enteroscopy facilities. Bowel preparation for DBE will consist of 2 L of polyethylene glycol electrolyte solution (Moviprep®), allowing adequate inspection of the small bowel. Patients will start fasting from midnight before the procedure. DBE can be carried out through the oral (antegrade) or the anal (retrograde) route. The choice of route will be determined by the capsule endoscopy findings: if abnormalities at CE are seen within the first two-thirds of the CE procedure, the antegrade approach will be chosen [13]. In all other cases, the retrograde approach will be chosen. At the farthest point of introduction, a tattoo mark will be left behind. If no abnormalities are encountered with one approach, the alternative approach will be chosen in a second procedure. If the target lesion(s) are reached, biopsy samples will be taken for routine histology and, if possible also for snap frozen storage. If considered amenable, lesions will be removed. If lesions are considered too large to allow endoscopic resection, a tattoo mark will be placed to facilitate surgical identification and resection. All mucosal lesions will be recorded with regard to location (duodenum, jejunum, ileum).
Expected complications.
Previous studies indicate that the risk of complications with capsule endoscopy is extremely low. The clinically most relevant risk of capsule endoscopy is that of capsule retention, which is reported to occur in up to 2.5 % of procedures [14]. The most important risk factor for capsule retention is Crohn's disease. Patients with suspected capsule retention will be evaluated with an abdominal X-ray. The risk of complications associated with DBE is low, especially for diagnostic DBE procedures. In a recent multicenter survey, reporting on 2362 DBE procedures, the complication rate of diagnostic DBE was 0.8 % and that of therapeutic DBE procedures 4.3 % [15].

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

- Asymptomatic proven mutation carriers, with a known mutation in the hMLH1, hMSH2 or hMSH6 gene
- Age between 35 and 70 years
- Written informed consent provided

Exclusion criteria

- Subjects with a strong suspicion on a small bowel stricture.
- Subjects with previous small bowel surgery
- Pregnancy
- Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

Study design

Design

Study type: Observational invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2008
Enrollment:	200
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
CCMO	NL23088.042.08