Prevalence of small-bowel neoplasia in Lynch syndrome assessed by video capsule endoscopy

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ABSTRACT
Objective The aim was to determine the prevalence of small-bowel neoplasia in asymptomatic patients with Lynch syndrome (LS) by video capsule endoscopy (VCE).

Design After obtaining informed consent, asymptomatic proven gene mutation carriers aged 35–70 years were included in this prospective multicentre study in the Netherlands. Patients with previous small-bowel surgery were excluded. After bowel preparation, VCE was performed. The videos were read by two independent investigators. If significant lesions were detected, an endoscopic procedure was subsequently performed to obtain histology and, if possible, remove the lesion.

Results In total, 200 patients (mean age 50 years (range 35–69), M/F 88/112), with proven mutations were included. These concerned MLH1 (n=50), MSH2 (n=68), MSH6 (n=76), PMS2 (n=3) and EpCAM (n=3) mutation carriers. In 95% of the procedures, caecal visualisation was achieved. Small-bowel neoplasia was detected in two patients: one adenocarcinoma (T3N0Mx) and one adenoma, both located in the duodenum. In another patient, a duodenal cancer (T2N0Mx) was diagnosed 7 months after a negative VCE. This was considered a lesion missed by VCE. All three neoplastic lesions were located in the duodenum and within reach of a conventional gastroduodenoscope. All patients with neoplasia were men, over 50 years of age and without a family history of small-bowel cancer.

Conclusions The prevalence of small-bowel neoplasia in asymptomatic patients with LS was 1.5%. All neoplastic lesions were located in the duodenum and within reach of conventional gastroduodenoscopy. Although VCE has the potential to detect these neoplastic lesions, small-bowel neoplasia may be missed.

Trial registration number NCT00898768.

INTRODUCTION

Cancer of the small intestine is uncommon. One of the conditions associated with an increased risk of small-bowel cancer (SBC) is Lynch syndrome (LS), formerly known as hereditary non-polyposis colorectal cancer.3 LS is caused by a germline mutation in one of the mismatch repair (MMR) genes MLH1, MSH2/Epcam, MSH6 or PMS2. It is clinically characterised by a high lifetime risk of colorectal cancer, but also of various extracolonic malignancies. These include cancer of the endometrium, ovary, stomach, urinary tract, small bowel, biliary tract, pancreas, brain and skin.2

For some malignancies of the tumour spectrum in LS, international guidelines recommend surveillance colonoscopy is recommended every 1–2 years starting from the age of 20–25 years.3,4 Regular colonoscopy reduces the risk of developing colorectal cancer and reduces the mortality from colorectal cancer.5–7 Also recommended are annual transvaginal ultrasound and endometrial sampling of the uterus for endometrial cancer, urine analysis with cytology for urinary tract cancer and screening mutation carriers for the presence of an Helicobacter pylori infection with subsequent eradication, but evidence supporting surveillance of extracolonic malignancies is scarce.2,4

Up till now, surveillance of the small bowel is not recommended in mutation carriers. This may be
partly due to limited options for visualisation of the small bowel in the past.\cite{Haanstra2014} Introduction of small-bowel video capsule endoscopy (VCE) enables visualisation and thereby also surveillance of the small bowel. This raises the question whether surveillance of patients with LS for small-bowel neoplasia may now be feasible.

Before implementing a surveillance programme, in general, the target group needs to have an increased lifetime risk for a certain condition. In LS, the estimated lifetime risk of developing SBC is 4.2%, corresponding to a relative risk of more than 100 compared with the general population.\cite{Haanstra2014a,Haanstra2014b} SBC also occurs at an earlier age in mutation carriers compared with the general population.\cite{Haanstra2014c} However, exact data on prevalence and incidence of SBC in LS are still unknown. Before statements can be made concerning surveillance of SBC in patients with LS, it is important to obtain more robust data about SBC prevalence and incidence.

The aim of this study was to determine the prevalence of small-bowel neoplasia by VCE in asymptomatic patients with LS.

### MATERIALS AND METHODS

#### Study design

This study was a nationwide prospective multicentre trial in the Netherlands to determine the prevalence of small-bowel neoplasia by VCE in asymptomatic patients with LS. The study was registered in the ClinicalTrials.gov registry with identifier NCT00898768. The study protocol was approved by the local medical ethical committee of the University Medical Center Groningen and all participating centres. Patients were included between March 2009 and January 2013.

#### Study population

The study population consisted of asymptomatic proven carriers of a MMR-gene mutation (MLH1, MSH2/Epcam, MSH6 or PMS2) between the age of 35 and 70 years. Exclusion criteria were (1) previous small-bowel surgery or large-bowel surgery involving the ileocaecal valve, (2) a strong clinical suspicion of small-bowel stricture, (3) pregnancy and (4) presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

#### Study procedures

Patients fulfilling the inclusion criteria were identified by the gastroenterologists of each participating hospital. A written informed consent was obtained from these patients. VCE procedures in all participating centres were performed according to a standardised protocol. Bowel preparation based on polyethylene glycol electrolyte solution was given, starting the day before the procedure. The video capsules used were supplied by Given Imaging (SBI, Yoqneam, Israel), with a recording time of 8 h.

All VCE recordings were reviewed by two experienced gastroenterologists; the local VCE-responsible gastroenterologist and the study coordinator (JJK). This double revision method was chosen as a control to limit the possibility of missing an important lesion and purpose was not to study the concordance between the observers. The most relevant findings obtained from VCE were documented and categorised according to standard terminology as angiectasia(s); ulcer(s); bleeding of unknown origin; erosion(s) and polyp(s)/tumour(s).\cite{Haanstra2014d,Haanstra2014e,Haanstra2014f,Haanstra2014g} Other VCE findings including quality of bowel preparation, gastric transit time (GTT), small-bowel transit time (SBTT) and completeness of the VCE procedure were also recorded. GTT was defined as the interval in minutes between the entrance of the capsule into the stomach and the first image of the duodenum. SBTT was defined as the interval in minutes between the entrance into the duodenum and the entrance into the caecum. VCE was considered complete if caecal visualisation was achieved. To evaluate the quality of bowel preparation, a semi-quantitative evaluation by means of a grading scale was used. The small-bowel preparation was scored as poor, fair or good. Small-bowel preparation was defined as good if the mucosa was generally clean with no or minimal residual fluid or debris; fair, if the visualisation of the mucosa was impaired because of moderate fluid and debris; and poor if the mucosa visualisation was highly limited because of excessive residual fluid and debris.

If polyps with an estimated size of at least 1 cm or malignant-appearing lesions were seen on the VCE recordings, additional endoscopic procedures were performed. When lesions were identified in the duodenum, a gastroduodenoscopy was performed. Otherwise, balloon-assisted enteroscopy was planned. The aim of these endoscopic procedures was to obtain histology and, if possible, remove the lesion. If endoscopic resection was not possible, a tattoo mark was placed to facilitate surgical identification and resection. For balloon-assisted enteroscopy, patients were fasting from midnight if an oral/antegrade approach was used, and received bowel preparation in case of an anal/retrograde approach. The choice of route (antegrade or retrograde) was determined by the VCE findings. If abnormalities were seen within the first two-thirds of the capsule recording time, the antegrade approach was chosen. In other cases, the retrograde approach was chosen. When no lesions were found with one approach, the maximum point of introduction was marked with ink. Subsequently, the alternative approach was chosen in a second procedure if considered necessary.

Since this study is the first part of a longitudinal study, every patient remains in follow-up for 2 years. After 2 years, each patient participates in a second VCE examination.

#### Endpoints

The primary endpoint of this study was the number of patients with neoplastic small-bowel lesions. Lesion characteristics recorded were morphology according to the Paris Classification\cite{Haanstra2014h} size, location and histology. Secondary endpoint was the number of complications following capsule endoscopy and subsequent endoscopic procedures.

#### Statistical analysis

Statistical analysis was done with SPSS V20.0. Descriptive statistics were used to determine demographic characteristics and to analyse VCE results.

#### RESULTS

Two hundred and one patients were included. After informed consent, one patient withdrew because of depression. Two hundred patients with a mean age of 50 years (range 35–69 years) were analysed. Table 1 shows the demographic characteristics of the included patients.

#### Performance VCE

The small bowel was completely examined in 190 patients (95%). Mean gastric and SBTTs were 40 (1–435) and 232 (14–479) minutes, respectively. In the majority of cases, bowel preparation was good (81%), while bowel preparation was fair in 16% and poor in 3%. Besides polypoid lesions other lesions were demonstrated as well: lymphangiecasisia (n=7), angiodysplasia (n=7), ulceration (n=6) and hypertrophic Brunner’s gland (n=5).
Prevalence of neoplasia
Possible polypoid or malignant-appearing lesions were suspected by VCE in 23 patients. All abnormalities were protruding-type lesions. Six of these lesions were considered insignificant because of small size (estimated smaller than 1 cm) and an endoscopic aspect resembling lymphangiectasia(s). No further investigations were performed in these six patients.

The remaining 17 patients with possible polypoid lesions on VCE all subsequently underwent an endoscopic procedure within 3 months of the VCE procedure, except for one patient. In this patient, balloon-assisted enteroscopy was not available at the time; instead MR enteroclysis was performed, which showed no abnormalities. Ten patients underwent a gastrodupodenoscopy and six underwent balloon-assisted enteroscopy (table 2 and figure 1).

In eight of the 16 patients (50%), lesions were found that matched the findings of VCE. Histological examination of these eight lesions revealed two nonneoplastic lesions: one carcinoma and one adenoma. All other histological diagnoses were nonneoplastic (three cases of hypertrichic Brunner’s glands, two cases of lymphoid hyperplasia and one case of heterotopic gastric mucosa). In eight patients, no lesions were encountered.

In one, retrograde balloon-assisted enteroscopy was performed after the oral approach, also showing no lesions. In the other seven patients, no further investigations were carried out. The VCE findings were considered as falsely positive, because definitely the whole area, including the lesion location seen on VCE, was thoroughly examined during the endoscopy.

Characteristics of patients with small-bowel neoplasia
Neoplasia was diagnosed in two patients by VCE (figure 2). Both patients were men over 50 years of age, without a family history of SBC. Different MMR gene mutations were involved: MSH6 and MSH2. Both neoplastic lesions were located in the duodenum and were within reach of a conventional gastroduodenoscope.

The carcinoma (TisN0Mx) was removed by performing a pylorus preserving pancreaticoduodenectomy; the low-grade dysplastic tubulovillous adenoma was removed endoscopically.

Follow-up
During follow-up, it became clear that one SBC was missed with VCE. In one MLH1 mutation carrier, a 65-year-old man, SBC was diagnosed during follow-up. Seven months after a negative VCE procedure, a gastroduodenoscopy was performed because of unexplained weight loss. On this occasion, a semicircular ulcerative lesion was found in the duodenum. Histology revealed adenocarcinoma (T2N0Mx). Reassessment of the earlier VCE recording by two gastroenterologists again revealed no abnormalities. The patient underwent surgery and unfortunately died of postoperative complications.

Positive and negative predictive value
In two of the 23 patients with polyps or malignant appearance on VCE, small-bowel neoplasia was present, corresponding to a positive predictive value of 9%. Assuming that all capsule endoscopy procedures with normal findings were truly negative except for the one reported, the negative predictive value was 99%.

Table 1 Patient characteristics (n=200)

<table>
<thead>
<tr>
<th>Age (mean, range, in years)</th>
<th>50.4 (35–69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>88 (44)</td>
</tr>
<tr>
<td>Mutation type, n (%)</td>
<td></td>
</tr>
<tr>
<td>MLH1</td>
<td>50 (25)</td>
</tr>
<tr>
<td>MSH2</td>
<td>68 (34)</td>
</tr>
<tr>
<td>Epcam</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>MSH6</td>
<td>76 (38)</td>
</tr>
<tr>
<td>PMS2</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Positive family history for SBC, n (%)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Personal history of neoplasia, n (%)</td>
<td>50 (25)</td>
</tr>
</tbody>
</table>

SBC, small-bowel cancer.

Table 2 Results of further procedures investigating possible suspicious lesions found on VCE

<table>
<thead>
<tr>
<th>Age, sex</th>
<th>Mutation</th>
<th>VCE finding*</th>
<th>Location</th>
<th>Procedure</th>
<th>Final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>52, M</td>
<td>MSH2</td>
<td>Thickened fold</td>
<td>Duodenum</td>
<td>Gastroduodenoscopy</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>61, M</td>
<td>MSH6</td>
<td>Polyp &lt;5 mm</td>
<td>Duodenum</td>
<td>Gastroduodenoscopy</td>
<td>Tubulovillous adenoma</td>
</tr>
<tr>
<td>52, F</td>
<td>MSH6</td>
<td>Polyp &lt;5 mm</td>
<td>Jejunum</td>
<td>DBE antegrade</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>46, F</td>
<td>MSH2</td>
<td>Polyp 6–9 mm</td>
<td>Jejunum</td>
<td>DBE retrograde and antegrade</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>57, M</td>
<td>MLH1</td>
<td>Polyp &lt;5 mm</td>
<td>Duodenum</td>
<td>DBE antegrade</td>
<td>Lymphoid hyperplasia</td>
</tr>
<tr>
<td>44, F</td>
<td>MLH1</td>
<td>Polyp 6–9 mm</td>
<td>Duodenum</td>
<td>Gastroduodenoscopy</td>
<td>Brunner’s gland</td>
</tr>
<tr>
<td>48, M</td>
<td>MLH1</td>
<td>Polyp &lt;5 mm</td>
<td>Duodenum</td>
<td>Gastroduodenoscopy</td>
<td>Brunner’s gland</td>
</tr>
<tr>
<td>39, M</td>
<td>MSH6</td>
<td>Lymphoid hyperplasia</td>
<td>Jejunum</td>
<td>DBE antegrade</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>40, M</td>
<td>MLH1</td>
<td>Polyp &lt;5 mm</td>
<td>Jejunum</td>
<td>DBE antegrade</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>61, M</td>
<td>MSH6</td>
<td>Polyp &lt;5 mm</td>
<td>Jejunum</td>
<td>DBE antegrade</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>37, F</td>
<td>MLH1</td>
<td>Polyp 6–9 mm</td>
<td>Jejunum</td>
<td>Gastroduodenoscopy</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>60, M</td>
<td>MSH6</td>
<td>Polyp 6–9 mm</td>
<td>Jejunum</td>
<td>Gastroduodenoscopy</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>40, M</td>
<td>MLH1</td>
<td>Polyp 10 mm</td>
<td>Duodenum</td>
<td>Gastroduodenoscopy</td>
<td>tubulovillous adenoma</td>
</tr>
<tr>
<td>54, F</td>
<td>MLH1</td>
<td>Haematin pigmentation</td>
<td>Duodenum</td>
<td>Gastroduodenoscopy</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>40, M</td>
<td>MSH2</td>
<td>Polyp &lt;5 mm</td>
<td>Duodenum</td>
<td>Gastroduodenoscopy</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>54, F</td>
<td>MSH6</td>
<td>Polyp &lt;5 mm</td>
<td>Stomach</td>
<td>Gastroduodenoscopy</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>38, F</td>
<td>MSH6</td>
<td>Polyp 10 mm</td>
<td>Duodenum</td>
<td>MRI enteroclysis</td>
<td>No abnormalities</td>
</tr>
</tbody>
</table>

*According to the Paris Classification.
DBE, double balloon enteroscopy; VCE, video capsule endoscopy.
Complications

One complication was observed. One patient had capsule retention 2 weeks after the VCE examination as was demonstrated on abdominal X-ray. A few days later a retrograde balloon-assisted enteroscopy was performed. The capsule was not encountered. When the X-ray was repeated, the capsule was not visible anymore. Apparently, the capsule had been discharged in the period between the first X-ray and the enteroscopy. No complications were observed from the 16 endoscopic procedures performed in this study.

DISCUSSION

The aim of the present study was to determine, by VCE, the prevalence of small-bowel neoplasia in asymptomatic LS mutation carriers. We found that VCE revealed small-bowel neoplasia in two of 200 persons, and it became apparent during the study period that a third patient had SBC which had not been seen with the VCE 7 months before. Overall, the prevalence of small-bowel neoplasia was 1.5%. All neoplastic lesions were found in men over 50 years of age and were located in the duodenum, within reach of a conventional gastroduodenoscope.

Two previous studies evaluated the performance of VCE in LS. Saurin et al. investigated the prevalence of small-bowel neoplasia in asymptomatic patients with LS by both VCE and CT enteroclysis. In 35 proven gene carriers, histologically confirmed small-bowel neoplasms were detected by VCE in three patients (8.6%): one carcinoma and two adenomas. CT enteroclysis detected the carcinoma, but missed the two adenomas. Based on these results, the authors concluded that surveillance for small-bowel neoplasia in LS by VCE might be efficient. The difference between their and our results may well be due to the much smaller sample size of their study. Another possible explanation might be that a relatively high number of MSH6 mutation carriers was included in the present study, as previous
data suggest a lower incidence of SBC in MSH6 mutations carriers than in those with a MLH1 or MSH2 mutation.8

Another recent study evaluated the use of VCE combined with non-endoscopic techniques (mainly MR, and in some patients CT enteroclysis) to detect small-bowel neoplasia. In the 46 asymptomatic proven mutation carriers that were included in this study, one SBC was detected (2%).14

Taking the three studies together, the prevalence of small-bowel neoplasia in asymptomatic patients with LS was 2.5%.

Despite the large number of patients included in this prospective trial, this study has limitations that could potentially influence the results. First, for the assessment of neoplastic lesions in the small bowel, no standard reference was available. Intraoperative panenteroscopy would provide such information, but the invasive nature of this procedure in relation to the probably not even present lesion was considered disproportional and, therefore, was considered not feasible. We did not include a radiological method since no radiological modality demonstrated a significantly higher sensitivity or specificity than VCE in detecting neoplastic lesions in the small bowel. Of various radiological imaging techniques, CT enterography appears to have a good sensitivity to detect small-bowel tumours.15 In patients with familial adenomatous polyposis, VCE has demonstrated higher sensitivity for polyps than radiological investigations such as small-bowel follow-through and MR enteroclysis.16 A recent report indicated that CT enterography may be more sensitive than VCE in the detection of small-bowel tumours.17 However, this was not demonstrated in patients with LS.13 In a retrospective study, MR enteroclysis was shown to have a high overall diagnostic accuracy and to be more specific than VCE.18 19

Second, it is known that VCE may miss small-bowel tumours, especially when located in the duodenum.20-23 This also appeared to be the case in the present study. Therefore, one might speculate that because of the possibility of false negative results, the true prevalence of small-bowel neoplasia may be higher than we demonstrated here.

Third, the distribution of small-bowel neoplasia in our study, exclusively found in the duodenum, is not representative of the real distribution of small-bowel neoplasia. In a review considering all described small-bowel tumours in LS, 43% of the SBCs were located in the duodenum, 37% in the jejunum and 20% in the ileum.8 Based on this, one could have expected to detect neoplasia in the jejunum and ileum as well. The quality of bowel visualisation in VCE is generally higher in the proximal small bowel than in the distal small bowel.24 25 So this may have influenced the zero detection rate in the distal part of the small bowel in our study. On the other hand, we chose to use bowel preparation with polyethylene glycol to optimise the diagnostic yield and to minimise this possible bias.23 26 Bowel preparation was considered good in the great majority of the VCE procedures. Therefore, we think the quality of visualisation of the distal small bowel was not an influential factor on the distribution of neoplastic lesions as found.

Finally, capsule endoscopy in our study was associated with some false positive findings. It is known that abnormalities seen on capsule endoscopy are not always reproduced in subsequent endoscopic investigations.27 It must be emphasised that all cases where endoscopy revealed no abnormalities, were cases in which the initial capsule endoscopy findings were relatively non-suspicious and in those cases, further investigations were considered not to be warranted.

Before statements can be made concerning the value of small-bowel surveillance in asymptomatic patients with LS, it is important to obtain more data about incidence of SBC in LS. All patients included in this study will undergo a second capsule endoscopy procedure 2 years after the first procedure as part of a follow-up study which will provide additional data.

If surveillance subsequently is considered, the question is which surveillance instrument should be used. One strong point of VCE is its safety. In our study, only one patient experienced capsule retention which finally did resolve without an endoscopic intervention. In previous large studies, capsule retention occurred in 0.75%–2.5% of cases.28 No other complications, like bleeding or perforation were observed. VCE, therefore, has the potential to be a safe surveillance instrument in LS. However, in the present study, all detected neoplastic lesions were within reach of a conventional gastroduodenoscope. One strong point of a conventional gastroduodenoscope is the possibility to thoroughly examine the gastric mucosa as well. Some authors already recommend to consider surveillance gastroduodenoscopy in LS because of substantial risks of developing gastric cancer.29 Because of these advantages of gastroduodenoscopy, and given the fact that the retrospectively demonstrated overall miss rate of small-bowel neoplasia of VCE is about 10%,30 it may be worthwhile to determine the role of gastroduodenoscopy as a surveillance tool in LS for small-bowel neoplasia, also in view of cost effectiveness. For clinical practice at this moment, our data suggest no role for surveillance of the small bowel in LS by VCE.

In conclusion, the prevalence of small-bowel neoplasia in asymptomatic LS mutation carriers was 1.5%, and two out of three lesions were detected by VCE. These neoplastic lesions were detected in men over 50 years of age. All lesions were located in the duodenum and within reach of a conventional gastroduodenoscope. VCE has the potential to safely detect neoplastic lesions at an early stage, although small-bowel neoplasia may be missed.

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Contributors All authors were involved in data acquisition, statistical analysis, interpretation of data and critical review of the manuscript for important intellectual content. HFAV, JHK and JJK were responsible for study concept and design. JFH drafted the manuscript.

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