Turk J Gastroenterol *2017; 28: 434-8*

Gastrointestinal Tract

Low yield of gastroscopy in patients with Lynch syndrome

Polymnia Galiatsatos[1], Christopher Labos[2], Marie Jeanjean[3], Kyle Miller[4], William D. Foulkes[3, 5]

[1]Division of Gastroenterology, Department of Medicine, Jewish General Hospital, Québec, Canada
[2]Institute of Clinical and Evaluative Sciences, Ontario, Canada
[3]Lady Davis Institute, Segal Cancer Center, Jewish General Hospital, Québec, Canada
[4]McGill University, Québec, Canada
[5]Department of Oncology and Human Genetics, McGill University, Québec, Canada

Cite this article as: Galiatsatos P, Labos C, JeanJean M, Miller K, Foulkes WD. Low yield of gastroscopy in patients with Lynch syndrome. Turk J Gastroenterol 2017; 28: 434-8.

Original Article

ABSTRACT

Background/Aims: Lynch syndrome (LS) is the most common hereditary colorectal cancer syndrome, caused by germline mutations in mismatch-repair genes. Besides a lifetime risk of colorectal cancer averaging 70%-80%, there is an increased risk of extracolonic tumors including gastric cancer. The utility of screening gastroscopy in Lynch syndrome has long been debated. This study aimed to determine the proportion of abnormal gastroscopies among patients screened, including the incidence of gastric cancer and prevalence of precursor lesions.

Materials and Methods: Charts of patients with mutation-proven Lynch syndrome between January 1, 2004, and December 31, 2014, from the Genetics clinic and Hereditary Gastrointestinal Cancer Clinic of our institution were retrospectively reviewed.

Results: A total of 66 Lynch syndrome patients were identified. Thirty-two gastroscopies were performed in 21 (32%) of them. No gastric cancers were found. The prevalence of precursor lesions (*Helicobacter pylori* gastritis, atrophic gastritis, and gastric intestinal metaplasia) was 19.05%. A family history of gastric cancer was associated with a non-significant increased risk of abnormal gastroscopy, while sex and specific gene involved did not affect the abnormality rate.

Conclusion: Gastric screening in asymptomatic individuals with Lynch syndrome is probably best reserved for high-risk individuals, based on the family history and perhaps ethnicity as suggested by several governing bodies. Larger studies are required to achieve the statistical power necessary to address this controversial issue.

Keywords: Lynch syndrome, gastric cancer, screening gastroscopy, precursor lesions

INTRODUCTION

Lynch syndrome (LS) is the most common hereditary colorectal cancer (CRC) syndrome, accounting for 1%-4% of all CRCs and 10% of CRCs under the age of 50 years (1). It is an autosomal dominant condition caused by germline mutations in one of four DNA mismatch-repair (MMR) genes, namely *MLH1, MSH2, MSH6,* and *PMS2*, as well as mutations in the *EPCAM* gene, which inactivates *MSH2* via promoter hypermethylation. Besides a lifetime risk of CRC averaging 70%-80%, there is also an increased risk of extracolonic tumors, including carcinoma of the endometrium (40%-60% lifetime risk), ovary, stomach, small bowel, pancreas, hepatobiliary tree, brain, and urinary tract (2). The Amsterdam II criteria are a clinical tool used to help identify LS mutation carriers (Figure 1).

The utility of routine surveillance gastroscopy in LS has been a topic of debate for several years. While gastric cancer (GC) was a predominant feature of LS a century ago, it is much less common now, indicating the significant decline in GC incidence in the Western world over the last few decades (3). Until recently, screening gastroscopies were periodically performed for LS patients followed in the Genetics clinic or Hereditary Gastrointestinal Cancer Clinic (GENGI) of our institution.

Address for Correspondence: Polymnia Galiatsatos E-mail: pgaliatsatos@jgh.mcgill.ca
Received: March 24, 2017 **Accepted:** July 25, 2017 **Available Online Date:** October 25, 2017

At least 3 relatives with a Lynch-associated cancer and:

- One should be a first-degree relative of the other 2
- 2 consecutive generations must be affected
- At least one affected individual should be diagnosed before age 50
- Familial adenomatous polyposis must be ruled-out
- Tumors should be verified by pathologic examination

Figure 1. Amsterdam II Criteria (1998)

We conducted a retrospective cohort study to determine the diagnostic yield of screening gastroscopy in this select group of patients to evaluate if this practice should be continued in the future.

MATERIALS AND METHODS

This retrospective study was conducted in a university-affiliated hospital following approval of the study protocol by the hospital's ethics committee. We reviewed charts of patients with LS seen in the outpatient Genetics clinic and specialized GENGI clinic from January 1, 2004, to December 31, 2014. Patients were included in the analysis if they had a proven mutation in one of the culprit genes, namely *MLH1, MSH2, MSH6, PMS2,* and *EPCAM*, following work-up for Amsterdam II criteria or screening of asymptomatic individuals belonging to the Lynch families. Patients were excluded if they were <18 years old or if they had been diagnosed with a gastric malignancy prior to 2004. The following data were extracted from selected charts: patient's age, sex, mutation, smoking status, family history of GC, number of performed gastroscopies, and ensuing diagnoses.

The primary endpoint was the proportion of abnormal gastroscopies among the screened patients. Secondary endpoints included the proportion of LS patients who underwent at least one gastroscopy, mean number of gastroscopies per patient, incidence of GC, prevalence of precursor lesions (including *Heliocobacter pylori* gastritis, atrophic gastritis, and gastric intestinal metaplasia), impact of family history of GC on the likelihood of having an abnormal gastroscopy, and impact of sex on the risk of having an abnormal gastroscopy.

Statistical Methods

Continuous variables were reported as means with standard deviations. Categorical variables were reported as counts with proportions. The proportion of patients with abnormal gastroscopies was calculated directly, with 95% confidence intervals (CI) calculated using the exact method instead of the normal approximation of the binomial distribution due to the small sample size. The process was repeated for each of the binary secondary outcomes. For the impact of family history on having an abnormal gastroscopy, the risk ratio was calculated from the constructed 2×2 table using the standard formula.

All statistical testing was performed using STATA version 12 (StataCorp, College Station, Texas, USA).

RESULTS

A total of 66 patients with LS were identified from the Genetics and GENGI clinics, who met the inclusion and exclusion criteria. In fact, there were no patients with a prior history of GC or age <18 years to exclude. Of the 66 patients, 28 were probands, while 38 were individuals tested because of a known family history of LS. Among the probands, 22 had cancer themselves, while 6 had a family history but no personal history of cancer.

Of the 66 patients, 34 were females and 32 males. The average age was 50.8 years, with ages ranging from 19 to 79 years. The categorization of mutations was as follows: 22 (33%) *MLH1*, 26 (40%) *MSH2*, 14 (21%) MSH6, and 4 (6%) *PMS2*. In terms of malignancies affecting the group, there were 17 cases of colon cancer, 7 of uterine cancer, 2 of ovarian cancers, 2 of breast cancers (one with confirmed *MLH1* absence on immunohistochemistry), one small bowel cancer (jejunal), one glioblastoma, one sebaceous carcinoma of the thigh (absent *MSH2* and *MSH6*), and one leiomyosarcoma of the shoulder (absent *MSH2* and MSH6).

Thirty-two gastroscopies were performed in only 21 (32%) of the patients. The average number of gastroscopies per screened individuals was 1.5. The interval between repeat gastroscopies varied between 12 and 31 months, with an average of 17.2 months. Ten (31.2%) of the gastroscopies were abnormal (Table 1). Among patients with abnormal gastroscopies, the breakdown was 3:7 for males:females, and the average age was 58.2 years. No GCs were found. The prevalence of precursor lesions, including *H. pylori* gastritis (2 patients), atrophic gastritis (none), and gastric intestinal metaplasia (2 patients) was 19.05% (95% CI: 5.4-41.9) among the screened patients. A positive family history of GC (unspecified subtype) was associated with a non-significant >2-fold increase in having an abnormal gastroscopy, with a relative risk (RR) of 2.67 (95% CI: 0.82-8.69, p=0.09). There was no statistically significant association between the male sex and the risk of an abnormal gastroscopy, with a RR of 0.46 (95% CI: 0.13-1.61, p=0.20). The specific gene involved also demonstrated no effect on the rate of an abnormal gastroscopy, Fisher's exact test p=0.199.

For the 45 patients not having undergone screening gastroscopies during the stated study period, none of them developed GC upon chart review up to March 2017.

DISCUSSION

Lynch syndrome is the most common hereditary CRC syndromes. While there have been many strides in CRC prevention with the advent of screening colonoscopy protocols, patients remain at risk for a number of other malignancies for which effective or practically feasible screening methods do not always exist. While gastroscopy seems relatively accessible and innocuous, it is considered an invasive procedure with asso-

Table 1. Characteristics of patients with abnormal gastroscopies

Patient	Age	Sex	Mutation	Family history GC	GC	HP	PUD	Atrophy	GIM	RG	Esophagitis
1	71	F	MSH2	+		+	+			+	
2	76	F	MSH2	+					+		
3	41	M	MSH2								+
4	69	F	MLH1	+					+		
5	79	F	MLH1	+						+	
6	33	F	MLH1							+	
7	52	F	MSH2								+
8	73	M	PMS2							+	
9	27	F	MLH1								+
10	61	M	MLH1			+					

GC: gastric cancer; HP: *Helicobacter pylori* infection; PUD: peptic ulcer disease; GIM: gastric intestinal metaplasia; RG: reactive gastropathy

ciated risks, not to mention a non-negligible price tag, which should be considered whether covered by a public health plan (as in Canada), private insurance, or the patient.

With regards to GC risk, a study from the Dutch Hereditary Cancer registry estimated an overall standardized incidence ratio (SIR) of 3.4 (95% CI: 2.1-5.2) for LS mutation carriers as opposed to the general population, with an absolute risk of 8% for males and 5.3% for females (4). In this study, there also seemed to be a predilection for *MSH2* mutation carriers (SIR, 6.1 as opposed to 2.9 for *MLH1*). An Australian Colon Cancer Family Registry study estimated the 10-year gastric and hepatobiliary cancer risk to be 1% (95% CI: 0.2%-2%), with an SIR of 5.65 (95% CI: 2.32-9.69) (5). A more recent retrospective cohort study combining data from the German and Dutch national registries quoted cumulative risks of GC approaching 6.7% and 2.6%, with SIRs as high as 9.8 and 7.2 for males and females, respectively (6). There appears to be no clustering of GC cases among LS families (4,7).

The National Comprehensive Cancer Network guidelines do not recommend routine surveillance gastroscopy for patients with LS, but recommend it be considered for select groups, such as families of Asian descent (8). The Mallorca group (consortium of European experts) also advises against routine gastroscopic surveillance, but recommends screening mutation carriers for *H. pylori* infection and treating those affected (9). The American College of Gastroenterology in its latest guidelines suggests considering a baseline gastroscopy at the age 30-35 years for *H. pylori* screening and possibly continued surveillance every 3-5 years for individuals with a family history of GC or duodenal cancer (10).

Arguments in favor of screening would be the detection of precursor lesions or early curable GC. In a Finnish study of 73 MMR mutation carriers, 26% had *H. pylori* infection, 14% had atrophic gastritis, and 14% had gastric intestinal metaplasia, which are all cancer-predisposing diagnoses (11). Unfortunately, screening of these precancerous conditions even in the general population is a topic that is also wrought with controversy (12).

In our patient sample, we found no cases of GC among those LS patients who underwent gastroscopy. We did however find a non-negligible rate of precursor lesions among the 21 (19%) individuals tested. The risk for an abnormal gastroscopy appeared to be more elevated in those with a positive family history of GC, although there remains considerable uncertainty regarding the magnitude of this effect.

The major limitation of this study was its small sample size, which resulted in uncertainty regarding the magnitude of the effect size. Almost 20% of cases had precursor lesions; however, it remains to be seen if any will prospectively evolve to dysplasia or carcinoma over a long follow-up period. This value resembles the results of a Dutch retrospective observational cohort study, considering the prevalence of *H. pylori* in LS patients. In their study, Soer et al. (13) reported that 46% of LS patients from 5 Dutch hospitals had undergone screening for *H. pylori* (mainly by serology), and of those screened, 20% were found to be infected. However, this proportion was not higher in individuals with a family history of GC (13). In their study, Renkonen-Sinisalo et al. (11) also found similar occurrence rates of *H. pylori* infection among mutation-positive and mutation-negative family members. Thus, it remains unclear whether screening patients, even non-invasively, for *H. pylori* infection is a worthwhile endeavor in LS, despite being recommended by the Mallorca group (9). While we do not advocate universal non-invasive screening of *H. pylori* in LS patients, if one does chose to test individuals non-invasively, we recommend a ^{13}C or ^{14}C urea breath test (UBT) over serology due to sensitivity of 96% and specificity of 93% for UBT versus 58%-100% and 59%-97%, respectively, for serology (14).

A family history of GC may increase the likelihood of an abnormal gastroscopy. If this association is true, it may reflect the higher *H. pylori* exposure/clustering for members raised in the same household, as opposed to true heritability. Regardless, a family history of GC may be a valid criterion to prompt screening, if one is looking to restrict gastroscopies to a select group of patients.

It is reasonable to expect that the yield of screening gastroscopies would be low in LS, where the lifetime GC incidence is estimated at 1%-8% (4-6), based on the fact that gastroscopy is a poor screening tool in other hereditary syndromes, such as Hereditary Diffuse Gastric Cancer (HDGC), which confer a much higher GC risk. In HDGC, a syndrome caused by truncating mutations in the E-cadherin (*CDH1*) gene, the cumulative risk of GC by the age of 80 years is 67% for men and 83% for women (15). In HDGC patients, gastroscopy has been proven inadequate as a screening tool, and total gastrectomy is generally recommended as prophylactic.

In the last few years, chromoendoscopy has been emerging as a new endoscopic adjunct for the detection of preneoplastic colonic lesions in LS. In one study, the use of chromoendoscopy detected an additional 45 lesions in 20 patients compared to conventional colonoscopy alone (16). In a retrospective study of 33 *CDH-1* mutation carriers having undergone screening gastroscopies, 41% of chromoendoscopy-guided biopsies revealed signet-ring cell carcinoma (in 10 patients) in lesions that would have otherwise been missed by white-light endoscopy (17). Perhaps there could be some significance for applying this technique to help increase the yield of screening gastroscopies in LS patients, although prospective studies are still lacking.

In conclusion, the role of screening gastroscopy in LS has been debated for years, and there remains much uncertainty about its effectiveness and the groups wherein it may be more effective. Most expert bodies currently advise against routine screening however suggest considering it in certain higher-risk individuals. While no cases of GC were detected in this retrospective study, a 19% rate of precursor lesions was detected on gastroscopy in this patient group. There is a potentially higher likelihood of abnormal gastroscopies in individuals with a family history of GC but this result remains uncertain. We suggest restricting gastric screening in asymptomatic individuals to high-risk groups, based on family history and perhaps ethnicity. Ultimately, we suggest researchers pool their data to address this pending question. Only in this way can we as a community achieve the statistical power to reduce uncertainty in our estimates. Thus, we can better define the diagnostic yield of gastroscopy and determine in which groups it may be most effective.

Ethics Committee Approval: Ethics committee approval was received for this study from Jewish General Hospital Research Ethics Committee (Decision Date: 08.07.2017).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - P.G.; Design - P.G.; Supervision - P.G., W.F.; Resource - P.G.; Materials - P.G., M.J.; Data Collection and/or Processing - M.J., K.M.; Analysis and/or Interpretation - C.L.; Literature Search - P.G.; Writing - P.G., C.L.; Critical Reviews - P.G., W.F.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

ORCID ID: William Foulkes: 0000-0001-7427-4651

REFERENCES

1. Kwak EL, Chung DC. Hereditary colorectal cancer syndromes: an overview. Clin Colorectal Cancer 2007; 6: 340-4. [CrossRef]
2. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003; 348 : 919-32. [CrossRef]
3. Warthin AS. Heredity with reference to carcinoma. Arch Intern Med 1913; 9: 546-55. [CrossRef]
4. Capelle LG, Van Grieken NC, Lingsma HF, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterol 2010; 138: 487-92. [CrossRef]
5. Win AK, Lindor NM, Young JP, et al. Risks of primary extracolonic cancers following colorectal cancer in Lynch syndrome. J Natl Cancer Inst 2012; 104: 1363-72. [CrossRef]
6. Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with Lynch syndrome. J Clin Oncol 2012; 30: 4409-15. [CrossRef]
7. Watson P, Lynch HT. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. Cancer 1993; 71: 677-85. [CrossRef]
8. National Comprehensive Cancer Network. NCCN guidelines version 1.2015 (Lynch syndrome). Available at: http://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.
9. Vasen HFA, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut 2013; 62: 812-23. [CrossRef]
10. Syngal S, Brand RE, Church JM, et al. AGA guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015; 110: 223-62. [CrossRef]
11. Renkonen-Sinisalo L, Sipponen P, Aarnio M, et al. No support for endoscopic surveillance for gastric cancer in hereditary non-polyposis colorectal cancer. Scand J Gastroenterol 2002; 37: 574-7. [CrossRef]
12. Galiatsatos P. Surveillance of Gastric Intestinal Metaplasia: Is It Warranted? J Gastroenterol Hepatol Res 2014; 3: 1364-6. [CrossRef]

13. Soer EC, Leicher LW, Langers AM, et al. Equivalent Helicobacter pylori infection rates in Lynch syndrome mutation carriers with and without a first-degree relative with gastric cancer. Int J Colorectal Dis 2016; 31: 693-7. [CrossRef]
14. Wang Y, Kuo FC, Liu CJ, et al. Diagnosis of Helicobacter pylori infection : current options and developments. World J Gastroenterol 2015; 21: 11221-35. [CrossRef]
15. Pharoah PD, Guilford P, Caldas C. International Gastric Cancer Linkage Consortium. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology 2001; 121: 1348-53. [CrossRef]
16. Lecompte T, Cellier C, Barbier JP, et al. Chromoendoscopic colonoscopy for detecting preneoplastic lesions in hereditary nonpolyposis colorectal cancer syndrome. Clin Gastroenterol Hepatol 2005; 3: 897-902. [CrossRef]
17. Shaw D, Blair V, Framp A, et al. Chromoendoscopic surveillance in hereditary diffuse gastric cancer: an alternative to prophylactic gastrectomy? Gut 2005; 54: 461-8.[CrossRef]