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CANCER GENETICS AND EPIGENETICS

Value of upper gastrointestinal endoscopy for gastric cancer surveillance in patients with Lynch syndrome

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Abbreviations: AMST+, Amsterdam II criteria fulfilled; BETH+, revised Bethesda criteria fulfilled; CRC, colorectal cancer; EGD, esophagogastroduodenoscopy; FDR, first-degree relatives; FOBT, Fecal Occult Blood Test; GC, gastric cancer; H.p., *Helicobacter pylori*; LS, Lynch syndrome; MMR, mismatch repair; MSI, microsatellite instability; MSS, microsatellite stable; NCCN, National Comprehensive Cancer Network; path., pathogenic; SDR, second-degree relatives; UICC, Union for International Cancer Control.

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Abstract

In our study, we evaluated the effectiveness of upper gastrointestinal (GI) endoscopy as an instrument for early gastric cancer (GC) detection in Lynch syndrome (LS) patients by analyzing data from the registry of the *German Consortium for Familial Intestinal Cancer*. In a prospective, multicenter cohort study, 1128 out of 2009 registered individuals with confirmed LS underwent 5176 upper GI endoscopies. Compliance was good since 77.6% of upper GI endoscopies were completed within the recommended interval of 1 to 3 years. Forty-nine GC events were observed in 47 patients. *MLH1* (n = 21) and *MSH2* (n = 24) mutations were the most prevalent. GCs in patients undergoing regular surveillance were diagnosed significantly more often in an early-stage disease (UICC I) than GCs detected through symptoms (83% vs 25%; $P = .0231$). Thirty-two (68%) patients had a negative family history of GC. The median age at diagnosis was 51 years (range 28-66). Of all GC patients, 13 were diagnosed at an age younger than 45. Our study supports the recommendation of regular upper GI endoscopy surveillance for LS patients beginning no later than at the age of 30.

KEYWORDS
gastric cancer, HNPCC, Lynch syndrome, screening, surveillance

1 | INTRODUCTION

Accounting for about 3% of colorectal cancer (CRC) cases, Lynch syndrome (LS) is the most common dominantly inherited cause of CRC with an estimated population frequency of 1:279 to 1:2000 in Western populations.[1-7]

Apart from CRC, which represents the most frequent cancer type, LS is also associated with a higher risk for several other types of cancers. Gastric cancer (GC) is the second most common nongynecologic malignancy in patients with LS. Although the lifetime risk of being diagnosed with GC is estimated to be less than 1% for the general population of Western countries, the lifetime risk for LS patients is substantially higher at 6% to 13%.[8-15]

Due to the absence of evidence-based data, the value of esophagogastroduodenoscopy (EGD) for GC surveillance in LS patients remains a controversial issue leading to a variety of different national surveillance strategies. According to the German S3 guideline for CRC, regular EGDs beginning at the age of 35 are recommended for LS patients.[16] In the Netherlands, EGD is not included in the surveillance program for LS patients, but LS patients are advised to undergo regular screenings for *Helicobacter pylori* (H.p.) infection.[17] The National Comprehensive Cancer Network (NCCN) guidelines are rather noncommittal on which LS carriers should undergo EGD screening, stating that selected individuals with a higher risk, defined as patients with a family history of gastric, duodenal or small bowel cancer or those of Asian descent, may have an increased risk and may benefit from surveillance. For these patients an upper endoscopy at the time of colonoscopy every 3-5 years beginning at age 40 years "may be considered".[18]

What's new?

Risk of gastric cancer (GC) is significantly increased among patients with Lynch syndrome (LS). GC screening in LS patients, however, is fraught with uncertainty, particularly regarding the use of esophagogastroduodenoscopy (EGD). The authors of this study investigated the use of EGD for regular GC surveillance in a German cohort of LS patients. Regular surveillance by EGD resulted in more frequent diagnosis and significant down-staging of GC, relative to detection via symptoms alone. In most cases, family history of GC was negative. This study supports recommendations for regular gastroscopic surveillance in LS patients starting by age 30.

There were two objectives of our study. The first objective was to deliver an update on the German LS-associated GC cohort from the database of the *German Consortium for Familial Intestinal Cancer* with a focus on genetic characteristics, age of onset and family history of GC. The second and main objective was to evaluate the effectiveness of EGD as an instrument for early GC detection by using tumor stage as a surrogate endpoint. We hypothesized that the performance of regular EGDs in LS patients could increase the percentage of GC cases diagnosed in a resectable and curable stage.

2 | PATIENTS AND METHODS

2.1 | German Consortium for Familial Intestinal Cancer

For the present analysis, we retrieved patient data from the registry of the *German Consortium for Familial Intestinal Cancer*. The German registry has been collecting prospective data since 1999. Initially, the Consortium consisted of six clinical centers across Germany and the registry received approval by the local ethics committees of each center. A detailed description of the German registry's approach has been described elsewhere.[19-21] At study, registry patients were asked to share their surveillance activity including clinical and pathology reports to enable prospective outcome data, specifically focusing on the benefit of surveillance recommendations. Although at the time of counseling and study registry, all LS patients were recommended the programmatic LS surveillance schedule, defined by the German S3 guideline for CRC,[16] including regular EGDs (every 1-3 years) starting at the age of 35, the follow-up retrieval occurred on a voluntary basis on the patient's side. Hence, the sharing activity of, for example, surveillance reports differed between patients, explaining the incompleteness of some data.

2.2 | Patient selection and data collection

All included individuals are proven pathogenic germline mismatch repair (MMR) gene mutation carriers. Only clinically actionable class 4 or 5 mutations were considered as pathogenic, as defined by the InSiGHT Variant Interpretation Committee. Patients diagnosed with GC were identified by ICD10 code (C16.0-C16.9). For all subjects, data on the following variables were retrieved from the registry: date of birth, date of GC diagnosis, date of death, gender, type of MMR gene mutation, fulfillment of Amsterdam/ Bethesda criteria, tumor stage according to TNM classification, tumor localization, vital status and time of last follow-up, co-occurrence of other LS-related cancers, family history of GC with specification of affected numbers of first-degree relatives (FDR), second-degree relatives (SDR) and other relatives, complete EGD data with EGD at cancer detection as well as prior and following EGDs, H.p. status, information if the patient was symptomatic or asymptomatic at time of diagnosis with, if available, specification of symptoms.

2.3 | Data aalysis

We decided to use tumor stage at diagnosis as a surrogate endpoint for prognosis. Union for International Cancer Control (UICC) stages Ia and Ib were defined as early stage GC, with a significantly more favorable prognosis than advanced cancer and 5-year survival rates of over 80%.[9,22-24] Furthermore, UICC Ia and, in most cases, UICC Ib GC can be treated by primary surgical resection, for patients with higher stages standard therapy includes neoadjuvant/adjuvant chemotherapy. Consequently, UICC stages IIa and higher were considered as advanced stage disease.

TNM classifications of tumors were converted into UICC stages according to the 8th Edition of TNM Classification of Malignant Tumors.[25] Complete data on tumor staging were available for 69.4% of all included cases.

For evaluation of the effectiveness of EGD as an instrument for early GC detection in LS patients, we analyzed the available EGD data with respect to the purpose of the EGD (surveillance vs workup of symptoms) as well as the interval to the prior EGD. If the interval to the prior EGD was between 9 and 39 months in an asymptomatic patient, the endoscopy was considered to have been performed under the purpose of surveillance since this corresponds to the German S3 guideline for CRC, according to which regular (which means every 1-3 years) EGDs beginning at the age of 35 are recommended for LS patients.[16] We added ±3 months to the recommended interval of every 1 to 3 years as a tolerance limit. If the declared EGD purpose in our database was "investigation of symptoms," the cancer detecting EGD was considered to have been performed not in the purpose of surveillance. According to these definitions, our cohort was divided into two groups: (a) The group "Surveillance" included all GC patients who adhered to the recommended EGD surveillance program. (b) The group "Symptomatic" contained all patients whose GC diagnosis was made through presentation with symptomatic disease. Cases with missing information regarding symptoms or surveillance data as well as patients with incomplete tumor stages were excluded from further analysis. Differences between the two groups, "Surveillance" and "Symptomatic," regarding the stage distribution as a surrogate endpoint, were tested for statistical significance by Fisher's exact test (two-tailed). A P value below .05 was considered as statistically significant. The software GraphPad Prism Version 5.03 was used for creation of the EGD adherence curve (Figure 2).

3 | RESULTS

3.1 | Patient characteristics

At time of data cutoff, a total of 9565 patients at risk for hereditary CRC were registered in the *German Consortium for Familial Intestinal Cancer Registry* of which 2009 patients from 1224 families were proven pathogenic germline MMR gene mutation carriers (Figure 1). In total, 47 patients and accordingly 2.3% of all registered LS patients were diagnosed with GC before or after study inclusion in the registry. We detected a male predominance of 61.7%. The 47 GC patients were diagnosed with 49 cases of GC: One patient had a synchronous diagnosis of two GCs at different locations. Another patient had a metachronous GC in the time course of 15 years.

Overall, median age at GC diagnosis was 51 years (range, 28-66 years). Thirteen (27.7%) patients developed GC at an age of 45 years or younger (Table 1). Two patients (4.3%) developed GC before the age of 35 years. Both patients were pathogenic *MSH2* mutation carriers. Five patients (10.6%) with pathogenic *MLH1* (n = 1) or *MSH2* (n = 4) mutations were diagnosed with GC before the age of 40 years.

Regarding UICC stage distribution, 36.7% of all cancers were diagnosed at an early stage (UICC Ia-Ib), while 32.7% were detected

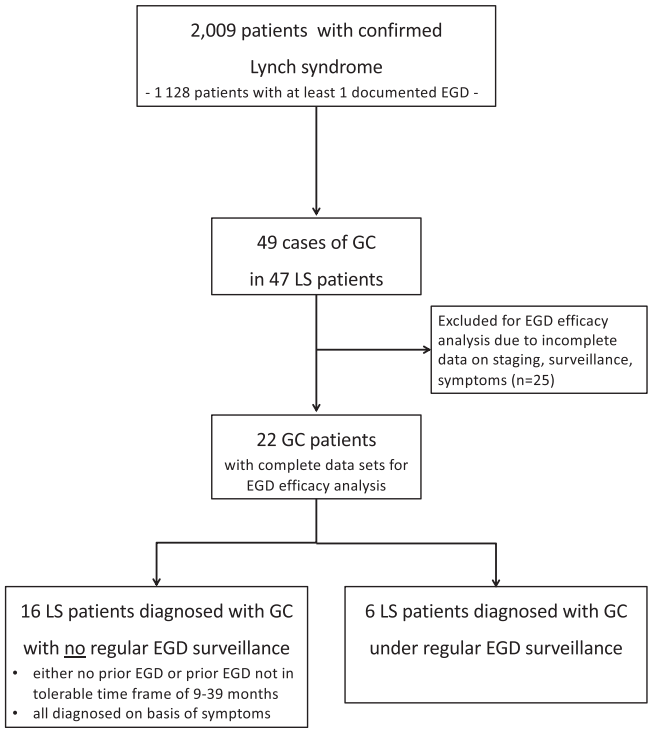


FIGURE 1 Flow diagram of eligible patients for data analysis

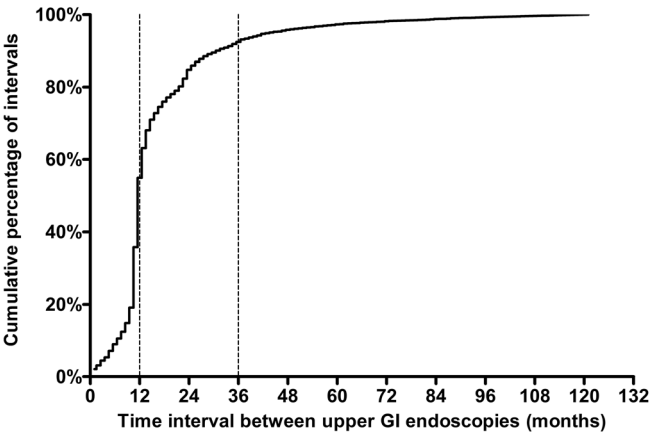


FIGURE 2 Adherence to the recommended upper GI endoscopy surveillance program. Cumulative frequency distribution of EGD intervals. Vertical dashed lines at 12 and 36 months indicate the recommended one to three annual interval. EGD, esophagogastroduodenoscopy; GI, gastrointestinal

in more advanced stages (UICC II-IV). In 30.6% of cases, TNM staging information was incomplete.

3.2 | Distribution of pathogenic germline MMR gene mutations

Pathogenic *MLH1* and *MSH2* mutations were most prevalent, adding up to 95.7% of the entire GC cohort (Table 1). Of the 47 subjects with GC, 21 GCs occurred among 725 *MLH1* mutation carriers (2.9%) and 24 among 949 *MSH2* mutation carriers (2.5%). *EpCAM* and *MSH6* mutations were rare with only one case each (among 29 *EpCAM* and 218 *MSH6* mutation carriers). No GC case was diagnosed among 88 *PMS2* mutation carriers in the German registry.

TABLE 1 Baseline characteristics of 47 GC patients with confirmed Lynch syndrome

Gender, n	
Male	29
Female	18
Mutations, n	
All path. MMR gene mutation carriers	47
MLH1	21
MSH2	24
MSH6	1
PMS2	0
EpCAM	1
Age at GC diagnosis in years, mean (range)	51 (28-66)
Gastric tumor localization, n	
Cardia	10
Fundus	1
Corpus	7
Antrum	7
Pylorus	0
Lesser curvature	2
Greater curvature	1
Multifocal	1
Not specified	20
UICC stage distribution, n	
I	18
II	8
III-IV[a]	2
IV	6
Unknown	15
Early cancer incidence, n (%)	
Cancer diagnosis <50 y	18 (38.3)
Cancer diagnosis <45 y	13 (27.7)
Cancer diagnosis <40 y	5 (10.6)
Cancer diagnosis <35 y	2 (4.3)

Abbreviation: GC, gastric cancer; UICC, Union for International Cancer Control.

[a]Two cases with Mx but at least stage III according to T- and N-staging.

3.3 | Co-occurring LS-related malignancies

Of all patients (n = 47), 45 (95.7%) were diagnosed metachronously with other malignancies (Suppl. Table 2). Mean age at first diagnosis of any cancer was 40 years (range 22-60 years), and the mean number of additional cancer diagnoses per patient was 3.6, ranging from a

minimum of 1 to a maximum of 8. The most frequent co-occurring malignancy was CRC, with 40 affected individuals (85.1%) of which 20 patients (42.6%) were diagnosed with more than one CRC (range of 2 to 6 times). Other common cancer diagnoses were endometrial cancer (n = 6; 12.8%), urinary tract cancer (n = 5; 10.6%), skin cancer (n = 8; 17%) and small bowel cancer (n = 3; 6.4%).

Overall, in 2 patients (4.3%), GC was the sole malignancy. Regarding the sequence of cancer diagnoses, the most frequently diagnosed first malignancy was CRC with 53.2% followed by GC with 29.8%. In the majority of cases (51.1%), GC was the second or third cancer diagnosis.

3.4 | Role of a positive GC family history

Of 47 patients who suffered from GC, 32 (68.1%) had a negative family history of GC (Table 2). Regarding the 15 patients with a positive family history, 12 patients (25.5%) had at least one FDR diagnosed with GC and another 3 patients (6.4%) had at least one SDR with GC.

3.5 | Adherence to EGD surveillance

A total of 1128 baseline and 4048 follow-up upper GI endoscopies were performed adding up to 5176 documented EGDs for 2009 LS patients. The median time interval between 2 EGDs was 12 months, and 77.6% of EGDs were performed in the recommended interval of 1-3 years (±3 months were added for tolerance limit), indicating a high patient compliance (Table 3). The distribution of intervals is shown in Figure 2, and the distribution of numbers of EGDs per patient in Suppl. Figure 1. Average number of EGDs per patient was 2.6 with a range between 0 and 19 and mean age at first EGD was 45 years.

3.6 | Efficacy of EGD surveillance

UICC staging at time of diagnosis was used as a surrogate parameter to determine EGD efficiency as described earlier. Complete data sets (UICC stage, purpose of EGD and presence of symptoms) for evaluation of surveillance effects could be obtained for 22 patients with GC. Of 6 patients in the "Surveillance" group, five were diagnosed with an early-stage disease (UICC Ia-b) and one patient with an advanced stage disease UICC IIb (Table 4). All patients in the "Surveillance" group were asymptomatic at the point of the cancer detecting EGD. None of the patients in the "Surveillance" group were diagnosed with a stage IV disease. The interval from the cancer diagnosis to the preceding upper-GI endoscopy was 9 to 30 months (median 14 months). The patients had undergone between 1 and 11 previous EGDs. Of the 16 patients in the "Symptomatic" group, 4 patients were diagnosed with an early-stage disease, 12 patients with an advanced stage GC (Suppl. Table S1). In this group 9, cases already had metastatic disease at the time of diagnosis. In the "Symptomatic" group, 10 patients were diagnosed with GC at the point of study initiation, five patients were diagnosed with GC prior and one patient was diagnosed after study registry. For 6 of the 16 patients of the "Symptomatic" group, GC was the index cancer diagnosis. All patients in the "Surveillance" group were diagnosed with GC after study registry.

Statistical comparison of the two groups with focus on staging at GC diagnosis as a surrogate endpoint using Fisher's exact test revealed that GCs in patients undergoing regular EGD-surveillance were diagnosed significantly more often with an early stage disease (UICC I) than GCs detected through symptoms (83% vs 25%; P = .0231; Figure 3).

Survival data were scarce (Table 4 and Suppl. Table S1). In the "Surveillance" group, 1 of 6 patients died 40 months after diagnosis of a Stage Ib GC, the reason of death was documented as unknown. In the "Symptomatic" group, 10 of 16 patients were deceased between <1 and 273 months from initial GC diagnosis. The cause of death for 8 of 10 patients was a malignant tumor.

Detection of adenomas was rare in the entire GC cohort: 1 patient of the "Symptomatic" group (UICC Ib) had two esophageal adenomas

TABLE 2 Family history of gastric cancer and other LS-associated cancers (n = 47)

Family history	n (%)
Negative	32 (68.1)
First- or second-degree relative with GC	15 (31.9)
Number of first-degree relatives with GC	Total: 12 (25.5)
1	11 (23.4)
2	1 (2.1)
At least one second-degree relative with GC	3 (6.4)
Any relative with any LS-associated cancer	41 (87.2)

Abbreviations: GC, gastric cancer; LS, Lynch syndrome.

TABLE 3 EGD surveillance characteristics of all Lynch syndrome patients in the German study cohort (n = 2009)

General EGD numbers	
All documented EGDs	5176
Baseline	1128
Follow-up	4048
Age at first EGD in years, mean (range)	45 (7-80)
No. of EGDs per individual, mean (range)	2.6 (0-19)
No. of EGDs per individual, no. (%) of patients	
At least 1 EGD	1128 (56.1)
At least 2 EGDs	868 (43.2)
At least 3 EGDs	726 (36.1)
At least 4 EGDs	604 (30)
5 and more EGDs	478 (23.8)
Interval between EGDs, mean (range)	12 (1-309)
No. of EGDs performed in the tolerable interval between 9 and 39 months, no. (%) of all follow-up EGDs (n = 4048)	3141 (77.6)

Abbreviation: EGD, esophagogastroduodenoscopy.

TABLE 4 Clinical and genetical characteristics of patients in the "Surveillance" group

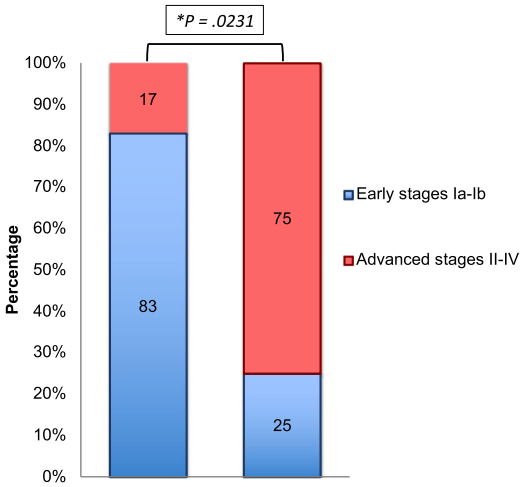
ID	Path. MMR mutation	Familial diagnostic criteria	Age at GC diagnosis/ gender	Family history of GC/no. of relatives with GC	UICC stage	H.p. status at time of GC diagnosis	Number of EGDs prior to GC diagnosis	Intervals between EGDs in months [a]	Last documented vital status[b]	Minimal survival after GC diagnosis in months[c]
EGD 1	*MLH1*	AMST+	71/m	Yes/1	Ia	Negative	11	17,29,7,27,13,12,12,13,14,5,**10**	Alive	>4
EGD 2	*MLH1*	BETH+	62/f	No	IIb	Negative	5	29,16,2,9,**13**	Alive	>1
EGD 3	*MSH2*	BETH+	61/m	Yes/1	Ib	Negative	5	64,15,3,6,**19**	Alive	>42
EGD 4	*EpCAM*	BETH+	54/w	Yes/1	Ib	Negative	1	**15**	Deceased (unknown cause of death)	40
EGD 5	*MLH1*	AMST+	50/w	No	Ia	N/A	2	145,**30**	Alive	>1
EGD 6	*MLH1*	AMST+	63/m	Yes/1	Ib	N/A	1	**9**	Alive	>100

Abbreviations: AMST+, Amsterdam II criteria fulfilled; BETH+, revised Bethesda criteria fulfilled; EGD, esophagogastroduodenoscopy; GC, gastric cancer; N/A, not available; path., pathogenic; UICC, Union for International Cancer Control.

[a]The last interval prior to GC diagnosis is emphasized.

[b]If applicable: cause of death.

[c]According to last follow-up.



n (%)	Under Surveillance	Symptomatic	Total
Early stages Ib-Ib	5 (83%)	4 (25%)	9
Advanced stages II-IV	1 (17%)	12 (75%)	13
Total	6	16	22

FIGURE 3 Comparison of distribution between UICC early- and advanced-staged gastric cancers depending on detection via regular EGD surveillance vs diagnosis after presentation with cancer symptoms. EGD, esophagogastroduodenoscopy; UICC, Union for International Cancer Control [Color figure can be viewed at wileyonlinelibrary.com]

removed, 5 and 6 years after GC diagnosis; a second patient of the "Surveillance" group (UICC IIb) had a hyperplastic gastric polyp removed, 3 years prior to GC diagnosis. Regarding the rest of the German LS cohort (n = 1962), two gastric polyps were documented for two patients. The first patient had a gastric tubular adenoma (MSS) with high-grade intraepithelial neoplasia removed in the age of 45 years. The second patient had a tubular gastric adenoma with a low-grade intraepithelial neoplasia in the age of 63 years, MSI testing was not performed.

4 | DISCUSSION

LS patients carry about 10 times higher lifetime risk for GC than the general population in Western countries (6-13% vs <1%).[8-15] In contrast to worldwide comparable guidelines for colonoscopic surveillance in LS patients, there is currently no consensus on EGD surveillance. Here, we provide the first evidence for the efficacy of regular EGD surveillance for early GC detection in LS patients in the setting of a study conducted in one of the worldwide largest national LS patient cohorts, the *German Consortium for Familial Intestinal Cancer Registry*.

Our study is, to our knowledge, to date the largest to prospectively investigate the efficacy of upper-GI endoscopy for GC surveillance in LS patients. In a total cohort of 2009 patients fulfilling the criteria for LS (pathogenic MMR gene mutation carriers), 1128 individuals underwent 5176 upper GI endoscopies. Our data show that

adherence to the annual surveillance recommendation in our multicenter setting was good, since 77.6% of EGDs were performed in recommended interval of 1-3 years (±3 months were added for tolerance limit). Forty-nine GC events were observed in 47 patients. Out of these, 6 patients undergoing regular EGD-surveillance were diagnosed significantly more often with an early-stage disease (UICC I) than 16 GCs detected through symptoms (83% vs 25%; $P = .0231$). None of the patients in the "Surveillance" group had stage IV disease.

It has been demonstrated and discussed previously that the German LS study cohort shows a higher GC risk compared to the Dutch.[11,26] We identified 47 individuals out of 2009 confirmed LS patients (2.3%) in our LS registry who were diagnosed with GC compared to 1.6% (32 subjects out of 2014 LS patients) in the Dutch study cohort. Median age at GC diagnosis and male predominance were in concordance to previously published reports.[11,12,15,27,28] Consistent to previous studies, we confirm the predominance of GC diagnoses in *MLH1* and *MSH2* mutation carriers, whereas it seems to be a rather rare cancer type in *MSH6*, *PMS2* and *EpCAM* carriers.[10-12,29] In contrast to other authors, but in alignment with Geary et al as well as Karimi et al, we did not see an *MSH2* predominance compared to *MLH1* mutation carriers since comparable rates of 2.9% of all *MLH1* and 2.5% of all *MSH2* mutation carriers were observed in the German cohort developing GC.[10,15,29-33] GC in *MSH6* carriers was rare in our cohort with only one case in 218 *MSH6* mutation carriers (0.4%) and somewhat higher in the Swedish cohort with 4% (8/191), while in the Dutch LS registry none of the 378 Dutch *MSH6* mutation carriers suffered from GC.[10,15] We are the first to report an *EpCAM* mutation carrier with GC out of a total of 29 *EpCAM* mutation carriers in our registry (3.4%). In alignment to some previous reports, none of the 88 *PMS2* mutation carriers in the German registry were diagnosed with GC. The Swedish registry was the only one to report three GC cases in 41 patients with a pathogenic *PMS2* mutation (7%). The so far largest international study with 513 confirmed *PMS2* mutation carriers did also not see a clear increase in GC risk in *PMS2* carriers.[34]

Interestingly, in 29.8% of our cohort GC was the first cancer diagnosis, while CRC accounted for 53.2% of index cancer diagnoses (Suppl. Table 2).

Unlike the strong consensus about recommendation of regular colonoscopies for CRC screening in LS patients throughout different societies, there is discordancy regarding EGD screening for gastric and duodenal cancer. While in Germany, regular EGDs beginning at the age of 35 have been recommended to all LS patients at the time of study conduct,[16] the American guidelines are rather noncommittal on which LS carriers should undergo EGD surveillance.[18] Individuals with a higher risk, defined as patients with a family history of gastric, duodenal or small bowel cancer or those of Asian descent, may have a benefit and are recommended to start with regular screenings beginning at the age of 40 years, every 3-5 years. Repeatedly, the recommendation to perform EGD surveillance in patients with a positive family history of gastric or duodenal cancer can be found in previous reports, although clear evidence supporting familial clustering of these cancer types in LS families is lacking.[35-41] In agreement with Capelle et al, reporting from the Dutch registry, our study strongly suggests that the majority of LS patients with GC do not have a positive family history for GC. Interestingly, the percentage of GC patients with a negative family history in the Dutch and German registry is identical with 68%.[10] In a Swedish study, the amount of GCs that occurred as single cases within LS families was even higher with 87%.[15] In another report, a collaborative work of four Western registries with 6041 family members with known *MLH1* or *MSH2* mutations likewise found no cases of familial accumulation of GC.[29] In a recent multivariate analysis in a large US American study, the factor of having a FDR with GC was, among other risk factors, found to be independently associated with GC among LS patients.[42] However, the proportion of LS carriers with a family history of GC of 9.1% was lower than in the aforementioned studies. Conclusively, although a positive family history for GC appears to be a risk factor, the absence of GC family history should not be used as a discriminator to exclude patients from GC surveillance.

Since all interventional procedures carry a certain complication risk as well as financial implications for healthcare systems, a general recommendation of regular surveillance EGDs for LS carriers can only be justified if this results in an earlier diagnosis and better prognosis for the patients. Up to date, unfortunately there are no prospective studies on large cohorts of LS patients providing clear evidence for the efficacy of EGD as a suitable surveillance method for early detection of GC leading to possible survival benefits. So far, there are only three studies addressing GC surveillance by EGD in LS patients. Firstly, a Finish study reported about the performance of a single EGD per patient in 73 *MLH1* mutation-positive (mainly *MLH1* founder mutations) as well as 32 mutation-negative family members in order to compare gastric histopathology. One advanced duodenal cancer was detected in the mutation-positive group, but no gastric neoplastic lesions were found in any group.[43] Limitations are the small cohort size with a median age of 49 years (being on the lower end of the expected age of onset of GC in LS patients) and a female predominance of 64% as well as the one-EGD-per-patient concept, taken together making it hardly possible to sufficiently evaluate the efficacy of a procedure. Secondly, a study by the Dutch registry investigated the prevalence of H.p. infections in a cohort of 443 mutation carriers. Here, upper GI endoscopy was performed in 132 patients, revealing 4 cases of intestinal metaplasia (3%) and 8 cases of GC (4.5%).[44] The third study is a small Canadian study analyzing retrospective data of the performance of 32 gastroscopies in 21 LS patients without finding any GC.[45] Once again, the small cohort size does not allow reliable efficacy evaluation.

However, there are a few limitations to our study warranting consideration. One issue of a registry is that most patients get their surveillance in an outpatient setting by practicing gastroenterologists. Therefore, the quality and amount of incoming data into our registry are highly dependent on the patients' and practicing physicians' willingness to regularly submit surveillance reports. Consequently, less than half of all patients in our cohort could be included in statistical analysis regarding endoscopic surveillance. Certainly, survival data, which was hardly available, would be a better endpoint than tumor stage at time of diagnosis. A pivotal issue with survival data in a retrospective registry focusing on hereditary tumor syndromes such as LS

is the often problematic identification of the malignancy, which finally causes death. In our cohort, patients had an average of 3 (in the range of up to 8) different cancer diagnoses over the course of time. Due to limited survival data we used the tumors' UICC stage at diagnosis as an arbitrary endpoint to define patient prognosis, since it is reasonable that an early diagnosis and treatment will result in an improved prognosis. By consideration of the last documented follow-up at any of our centers as the minimum survival of a patient (Table 4 and Suppl. Table S1), we calculated a minimum median OS of 103.5 months for the early-stage group and 18 months for the advanced stage group, adding at the least some evidence to a discrimination by our staging system. Also, we only retrieved complete UICC-staging data on 69.4% of our cohort, which limited the outcome analysis, so that actual numbers in the two subgroups ("Surveillance" vs "Symptomatic") are still small. Since missing staging information was equally distributed throughout all included risk groups, we considered the missingness as completely random and therefore most likely not leading to a bias. Furthermore, some of the cases have already been used in previous reports, though under different study objectives,[11,19,34,46] none of the data on upper GI endoscopies regarding GC surveillance has been previously published on the German cohort.

Another important aspect regarding possible further benefits of EGDs apart from early cancer detection is the possibility of primary cancer prevention by detection and removal of adenomas. Due to the small number of only five detected adenomas, the question of primary prevention cannot be answered by our data.

In summary, many LS patients developing GC are diagnosed before the age of 50 years (in our cohort 38.3%), whereas 90% of sporadic GCs are found after the age of 55 years.[9,13] Western healthcare systems justify CRC screening for the general population with CRC lifetime risks of 5% to 7%, being lower than the GC risk for LS patients of 6% to 13%.[8-15] Our data show that EGD surveillance is a feasible strategy for early GC detection in LS patients, since tumor stages were significantly lower among GCs detected by follow-up EGDs compared with GCs detected by symptoms. Since the majority of GCs (68%) in our cohort occurred as single cases within LS families, a positive family history appears to be a rather weak indicator for individual GC risk in LS patients. Also, gene-specific surveillance programs, like already being discussed for CRC surveillance, should be considered.

Due to the finding that 10.6% of the patients in our cohort were diagnosed with GC at an age younger than 40 years and 4.3% younger than 35 years, we recommend a starting age for EGD surveillance of no later than 30 years. Although our study cannot directly verify the optimal interval for EGD surveillance, we suggest a 2- to 3-year interval. Practically, a "one-stop shop" surveillance approach for CRC, GC and duodenal cancer by performing an upper GI endoscopy at the time of every or every other colonoscopy (based on colonoscopy intervals of every 1-2 years) during one session appears to be most convenient. For economic reasons, a "stand alone" upper GI endoscopy in the absence of symptoms should be avoided, if possible. Our study has to be validated by large scale, preferably controlled clinical trials, especially to define an optimal interval for EGD surveillance.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article. Additional data will be made available upon reasonable request.

ETHICS STATEMENT

The ethics committees of each participating institution approved the study (Bochum ethics committee approval no. 1151, last update in 12/2019 to no. 19-6766). Written informed consent for anonymized data analysis was obtained from all patients at the time of registry inclusion.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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