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DUODENAL TUMOR RISK IN LYNCH SYNDROME

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Abstract

Background and Aims:

Lynch syndrome (LS) is associated with an increased risk of small bowel tumors but routine screening is not recommended in international guidelines. The aim of our study was to determinate the prevalence of duodenal tumors in a French cohort of LS patients.

Methods:

Patients carrying a germline pathogenic variant in a MMR gene, supported by our local network, in which at least one upper endoscopy had been performed, were included. We registered the occurrence of duodenal lesions in those patients.

Results:

154 LS patients were identified including respectively 85 *MSH2* and 41 *MLH1* mutated patients respectively. Seven out of 154 (4.5%) had at least one duodenal lesion. Median age at diagnosis was 58 years (range: 49-73). The twelve lesions locations were: descending duodenum (n=7), genu inferius (n=2), duodenal bulb (n=1), ampulla (n=1), fourth duodenum (n=1). Three lesions were invasive adenocarcinomas. The incidence rate of duodenal lesions in patients with *MSH2* or *MLH1* pathogenic variants was respectively 7.1% (6 out of 85) and 2.4% (1 out of 41) emphasizing a trend towards increased risk of developing duodenal lesion in *MSH2* mutated patients: OR: 5.17, IC95% (0.8–60.07), p=0.1307.

Conclusion:

Regarding this high prevalence rate, especially in *MSH2* patients, regular duodenal screening during upper endoscopy should be considered in routine in LS patients.

Introduction

Lynch syndrome (LS), is an autosomal dominant condition first described in 1966¹. It is caused by germline pathogenic variants in one of the four DNA mismatch-repair (MMR) genes: *MLH1*, *MSH2*, *PMS2* or *MSH6* or by deletions in the *EPCAM* gene (*MSH2* promoter)². Nearly 90% are located in *MLH1* and *MSH2* and approximately 10% in *MSH6* and *PMS2*³.

LS is associated with an increased risk of developing gastrointestinal, gynecological and other types of cancers^{4,5}. Among these, colorectal cancer is the one with the highest risk of occurrence. LS is accounting for about 3% of newly diagnosed cases of colorectal malignancy^{6, 7, 8}.

Small bowel adenocarcinomas (SBA) are rare tumors⁹. An increased risk of SBA has been reported in patients with MMR pathogenic variants. The lifetime risk for this cancer varies a lot depending on the studies ranging from 0.6% to 12.0%^{10,11,12} which corresponds to a more than 100 fold incidence increased compared to sporadic ones¹³.

In SBA, the duodenum is the most frequently involved segment with 50 to 80% of cases followed by the jejunum (10-25%) and finally ileum (5-15%)^{14,15}. In LS-associated SBA, these location data appear to be similar¹⁶. Therefore, based on these epidemiologic data, the majority of SBA can be diagnosed during conventional endoscopic examination such as esophagogastroduodenoscopy (EGD) and colonoscopy with ileal intubation.

However, based on several publications suggesting that routine surveillance of the small bowel in LS was not cost-efficient^{17,18}, both American and European recommendations, which agree on the realization of an initial EGD with *Helicobacter pylori* biopsies at age 30-35, do not include systematic screening surveillance of the small bowel in their guidelines. Some recent publications suggest that endoscopic investigations such as

small bowel capsule (VCE) might have an interest in this indication^{19,20} leading Giardello and al, to consider the realization of capsule endoscopic screening at 2-3 years intervals beginning at age 30-35.

Carriers of different MMR genes pathological variants exhibit distinct patterns of cancer risk²¹. In the ERISCAM study, Bonadona and al reported **differences** in tumor incidences depending on the DNA MMR genes involved in the LS pathogeny: **69 small bowel tumors** were reported with respectively 37 affecting patients with a MLH1 variant (n=814, 4,5%), 29 for MSH2 (n=697, 4.2%) and 3 for MSH6 (n=71, 4%). Interestingly, Moller et al (21) reported a 3-fold increased cumulative incidence risk at 75 years old for MLH1 patients.

According to these data and in regard with the low morbidity of upper endoscopy we aimed to determinate in this study the prevalence of duodenal lesions in a French cohort of patients with LS and to describe this condition, in order to precise surveillance recommendations in this population.

Patients and Methods

Patient selection and eligibility:

Since 2013, French national cancer institute (INCa) finances local network to coordinate the management of patients genetically predisposed to neoplastic lesions. The « Réseau PRED-IdF » is one of this **healthcare** networks, coordinating the management of patients predisposed to digestive cancers, including those with LS, in Paris area. Adult patients with an identified germline pathogenic **variant** in an MMR gene, supported by the local **Cochin University Hospital** PRED-IdF network, were eligible for data collection, if they had at least one diagnostic EGD performed.

EGDs were performed every 3 to 4 years, in the occasion of a colonoscopy, according to our PRED-IdF guidelines. We used either standard gastroscopes or pediatric colonoscopes according to the choice of the gastroenterologist performing the exam.

Chromoendoscopy with indigo carmine or virtual chromoendoscopy as Narrow Band Imaging or Blue Laser Imaging was not systematically performed.

The occurrence of a duodenal lesion might be diagnosed before or after the LS genetic confirmation but had to be recorded in the patient's medical file.

A written informed consent was obtained from all patients for participation into this trial.

Data collection:

Data on patient's characteristic (age, sex, smoking, body-mass-index), MMR gene involved, type of duodenal lesion (location, age at diagnosis, histological features

including immunohistochemistry, therapeutic intervention), familial history of small bowel tumor and follow-up were collected retrospectively.

All data sheets were reviewed by the same author (MD) in order to make a uniform interpretation of retrospective data.

Molecular data:

All LS patients had a class 4 or 5 **pathogenic variant** in one of the four MMR genes or EPCAM, identified by gene sequencing in index case or targeted analysis in the previously identified LS families

Pathological examination

All patients with duodenal tumor underwent immunohistochemistry of the MMR proteins in at least one of the lesion using respectively: MLH1 (G168-728, Pharmingen®), MSH2 (FE11, Zymed®), MSH6 (44, Clinisciences®), PMS2 (A16-4, Pharmingen®).

Statistics

Number of duodenal lesions in patients with either *MSH2* or other DNA mismatch repair gene **pathogenic variant** was assessed. Comparison between the two incidence rates was tested using a two-tailed Fisher's exact test. Statistical significance was reached if $p \leq 0,05$.

Results

Study population characteristics:

One hundred and fifty-four patients with LS were included in our study. 85 patients had a *MSH2* pathogenic variant (55.2%), 41 a *MLH1* pathogenic variant (26.6%), 26 a *MSH6* pathogenic variant (16.9%), 1 an *EPCAM* pathogenic variant (0.6%) and 1 a double pathogenic variant in both *MLH1* and *MSH2* genes (0.6%). No patients diagnosed with a *PMS2* pathogenic variant were included in Cochin's PRED-IdF network at the time of this study.

General Characteristics of patients with duodenal lesions:

Twelve duodenal lesions were diagnosed in 7 of our patients (Overall incidence: 4.5%). General characteristics of these 7 patients are reported in Table 1. The median age at diagnosis was 58 years (range: 49-73). Six out of 7 patients were male (85.7%). Three patients were overweighted (42.9%) and one presented with obesity (14.3%). The calculated mean BMI was 26.6 (range: 23.3-30.1). One patient of our cohort was a smoker (14.3%).

Three patients (42.9%) had a personal past history of colon cancer and 1 of gastric adenocarcinoma. This patient had also been treated for 3 successive urothelial carcinomas. Two patients had a Muir-Torre syndrome with a personal history of keratoacanthomas and sebaceous cutaneous lesions

Three patients developed cancers not originally considered of LS spectrum: two prostatic adenocarcinomas and one a sarcomatoid carcinoma of the adrenal gland.

Two patients from this cohort were first degree related, carrying the same *MSH2* pathogenic variant. None of the five other patients had a family history of duodenal lesion.

Six out of our 7 patients (85.7%) with duodenal lesions had a *MSH2* pathogenic variant. Only one patient had a *MLH1* (14.3%) pathogenic variant. No patient with *MSH6* or *EPCAM* pathogenic variant displayed any duodenal lesion.

Overall, the incidence rate of duodenal lesions in LS patients with *MSH2* or *MLH1* was respectively 7.1% (6 out of 85) and 2.4% (1 out of 41). These data emphasized a trend toward an increased risk of developing duodenal lesion when carrying a *MSH2* pathogenic variant compared to other LS genetic instabilities without reaching statistical significance: OR: 5.17, IC 95% [0.8 – 60.07], $p=0.1307$.

Duodenal lesions characteristics

Twelve duodenal tumors were diagnosed in our 7 patients. Characteristics of these lesions are reported in Table 2.

In these 12 tumors there were 3 invasive adenocarcinomas (25%), 1 intra-mucosal adenocarcinoma (8.3%), 6 adenomas in high-grade dysplasia (50%) and 2 adenomas in low-grade dysplasia (16.7%). No patient had metastatic disease.

The 4 adenocarcinomas were found in patients carrying an *MSH2* pathogenic variant. These findings underlined a trend toward an increased risk of developing duodenal adenocarcinomas in this subgroup of patients although without reaching statistical significance: OR 7.68, IC 95% [0.4-145.2], $p=0.1282$.

Lesions were located as follow: 7 (58.3%) in the second duodenum, 2 in the genu inferius (16.7%), 1 next to the Vater ampulla, 1 in the duodenal bulb and 1 in the fourth duodenum (8.3%).

All lesions were resected in a curative intention. The 3 invasive adenocarcinomas were treated surgically with lymph node dissection, 2 by cephalic duodenopancreatectomy and 1 by resection of the 3rd and 4th duodenum, with no major postoperative complications. Adjuvant chemotherapy (FOLFOX regimen) was prescribed to these

three patients due to lymph node invasion or a T4 tumoral stage according to the TNM classification in the pathological examination.

The 8 other lesions were treated endoscopically with endoscopic mucosal resection (EMR), 2 of which were piecemeal resection due to the size of the tumor. No post procedure complications were recorded including hemorrhage or perforation.

Immunohistochemistry of the MMR proteins was available for 8 among 12 lesions. At least one duodenal lesion in each patient underwent somatic screening. Immunohistochemistry showed loss of MSH2 and MSH6 proteins signal in the duodenal lesions of the 6 patients with a germline *MSH2* pathogenic variant. There was a loss of MLH1 and PMS2 proteins signal in the duodenal adenoma in high-grade dysplasia of the patient with a germline *MLH1* pathogenic variant.

Follow-up:

Mean follow-up time from diagnosis of the first duodenal lesion to the last multidisciplinary meeting for each patient was 4.2 years (range: 0.6 – 12.8).

Four patients underwent a complete small bowel examination during the follow-up period: 3 by videocapsule and 1 by Magnetic Resonance Enterography. Among them, 1 had a jejunal adenoma in high-grade dysplasia. This lesion was treated surgically because of its non-accessibility by endoscopic route. The 3 other patients presented no other small bowel lesion.

No patient was lost to follow-up during the study period and none of our 7 with duodenal lesion died of any cause.

Discussion

We there report, to the best of our knowledge, the first study evaluating the incidence of duodenal lesions by systematic EGD in patients with LS. Our data suggest a non-negligible risk of duodenal tumors, especially in patients with *MSH2* pathogenic variants, and highlights the need to redefine our management strategy in LS patients concerning small bowel lesions risk in order to diagnose and treat such lesions.

As reported in previous studies, 50 to 80% of small bowel lesions are found in the duodenum in sporadic neoplasias as in LS patients. The recent study published by Haanstra and al has even found lesions only in the duodenum. Their study evaluated prospectively the prevalence of small-bowel neoplasia in asymptomatic patients with LS by VCE and found a 1.5% rate in a cohort of 200 patients²². All neoplastic lesions were located in the duodenum. The relative low prevalence rate found in this study is to be compared to the higher (albeit highly variable) rate in other epidemiological studies described above (0.6 to 12%). VCE, although being a minimally invasive procedure, might miss duodenal lesions^{23,24} and a 100 fold increased incidence of small bowel neoplastic lesions has already been reported in LS patients.

The importance of early diagnosis of duodenal lesions, which can occur very early in these patients²⁵, in order to treat them and prevent its spread is a major challenge.

Conventional upper digestive tract endoscopy is a minimally invasive procedure that can be performed during the same general anesthesia that the screening colonoscopy regularly accomplished in these patients. The cost and the duration of the procedure performed are in these cases only slightly increased.

Despite not being part of the international recommendations, the regular realization of an upper digestive tract endoscopy concomitantly with a screening colonoscopy is

already part of the “Reseau PRED-IdF” guidelines regarding the minimally invasive nature of the procedure.

In our cohort, 4 out of the 12 (33%) duodenal lesions were located in the genu inferius or in the fourth duodenum out of access of a conventional upper endoscopy (Figure3). The use of a pediatric colonoscope frequently allows the visualization of the entire duodenal frame without increasing the morbidity of the procedure. Using a pediatric colonoscope to perform the upper digestive tract exploration might be useful in LS patients.

Furthermore, flat adenomas were found in patients of the cohort. Chromoendoscopy, using intravital staining of the duodenal mucosa with indigo carmine, could increase the detection rate of such lesions²⁶ and might also be helpful in this indication.

Differences in the tumor incidence rates considering the pattern of MMR gene pathogenic variant in patients with LS are reported. These differences are also described concerning small bowel lesions. In our cohort, the incidence of neoplastic duodenal lesions was higher in *MSH2* patients (7.1%) when compared with *MLH1* (2.4%) or other LS patients (0%). Moreover, these differences were also found in small bowel adenocarcinomas incidence rates in our cohort and those invasive lesions were exclusively found in patients with a *MSH2* pathogenic variant. Conflicting epidemiological data have been recently published in the literature^{11,12,21}. If *MSH6* seems to be the pathogenic variant associated with the less incident tumors overall in all the studies including ours, the difference in terms of small bowel lesions incidence (higher in *MSH2* patients) was also found in the Bonadona et al epidemiological work. In contrast to data recently published on the subject, we decided to consider all small bowel lesions and not only adenocarcinomas, which may have led to the distinct results with the Moller et al study.

Interestingly, we found that two of the patients diagnosed with a small bowel adenocarcinomas had been treated in their past medical history for prostatic cancer. Recent publications showed that patients with hypermutated prostate cancers often have mismatch repair gene mutations frequently affecting *MSH2*^{27,28}. Question may arise whether additional genetic factors could explain this occurrence in these two patients with *MSH2* pathogenic variants, and larger epidemiological studies are needed to answer this question.

Our study however presents limitations. First of all the small number of patients in our cohort, the monocentric and retrospective characters of the study does not permit us to generalize our data.

Moreover, the fact that the Cochin University Hospital is a tertiary endoscopic and digestive oncology center could have caused a selection bias with the recruitment of patients referred to our institution because of this specialization. However, because of the scarcity of the pathology discussed, this bias could difficultly be avoided.

Despite these potential bias, considering our data and experience on the topic, the relatively high incidence of duodenal lesions in LS patients (especially in *MSH2*), their frequently asymptomatic features, and the minimally invasive nature of an upper digestive tract endoscopy, performed during a general anesthesia for screening colonoscopy, we truly believe that adding this examination (potentially using a pediatric colonoscope to reach the fourth duodenum) to our practice could benefit to our patients, especially in the high risk patients such as those with *MSH2* and *MLH1* pathogenic variants.

These features and the time between two screening upper endoscopies cannot result in immediate large international recommendations. However, our findings underline the

crucial need for future larger collaborative nationwide studies involving healthcare networks specialized in Lynch Syndrome management to precise this issue.

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Tables and figures' legends

TABLE 1: General Characteristics of patients with duodenal lesions

TABLE 2: Characteristics of duodenal lesions

Abbreviations: LGD = Low-grade dysplasia; HGD = High-grade dysplasia; ADK = Adenocarcinoma

* Performed in at least one lesion per patient

FIGURE 1: Patient 1: Adenoma in high-grade dysplasia of the second duodenum (1a : white light ; 1b : with magnification by BLI FUJIFILM®)

FIGURE 2: Patient 4: Loss of expression of MSH2 protein in immunohistochemistry

FIGURE 3: Repartition of all duodenal lesions diagnosed in the 7 patients

1a

1b

HES coloration, X 20

MSH2 Antibody, X 200

Patient number	Gender	Gene with pathogenic	Smoker	BMI (kg/m ²)	Age at first duodenal lesion diagnosis (years)	Familial history of duodenal lesion	Personal history of digestive cancer related to LS (age of diagnosis)	Personal history of other LS or possible LS cancer (age of diagnosis)
1	Male	MSH2	No	26.9	71	Yes	No	No
2	Male	MSH2	Yes	30.1	49	Yes	No	No
3	Male	MSH2	No	24.9	51	No	2 synchronous colorectal adenocarcinomas (56-56)	Prostatic adenocarcinoma (58)
4	Female	MSH2	No	23.3	53	No	No	No
5	Male	MSH2	Former	27.6	71	No	Gastric adenocarcinoma (71)	Muir Torre syndrom; 3 Urothelial Carcinomas (60-61-72); Prostatic adenocarcinoma (63)
6	Male	MLH1	No	24.6	58	No	2 synchronous colorectal adenocarcinomas (53-53)	Sarcomatoid carcinoma of the adrenal gland (50)
7	Male	MSH2	No	28.7	54	No	Colorectal adenocarcinoma (43)	Muir Torre syndrom

Patient Number	Gene Mutated	Number of duodenal lesions diagnosed	Location	Histology of duodenal lesions (n°1/n°2/N°3)	Lesion Size (mm)	Paris Classification	Immuno Histochemistry*
1	MSH2	2	Second duodenum	LGD / HGD	10 / 8	Ila / Ila	Loss of MSH2/MSH6
2	MSH2	3	Second duodenum	HGD / HGD / invasive ADK	20 / 50 / 50	Ila / Ila / Ila+c	Loss of MSH2/MSH6
3	MSH2	1	Vater ampulla	Invasive ADK	70	III	Loss of MSH2/MSH6
4	MSH2	1	Duodenal bulb	HGD	70	Ila	Loss of MSH2/MSH6
5	MSH2	2	Genu inferius	Intramucosal ADK / HGD	25 / 20	Is / Ila	Loss of MSH2/MSH6
6	MLH1	2	Fourth duodenum	HGD / LGD	25 / 12	Ila / Ila	Loss of MLH1/PMS2
7	MSH2	1	Second duodenum	Invasive ADK	55	III	Loss of MSH2/MSH6