Risk of neoplastic change in large gastric hyperplastic polyps and recurrence after endoscopic resection

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ABSTRACT

Background Gastric hyperplastic polyps (GHPs) have a risk of neoplastic transformation reaching 5 %. Current endoscopic resection techniques appear suboptimal with a high risk of local recurrence. This study assessed the outcomes of endoscopic resection for GHPs and identified risk factors for recurrence and neoplastic transformation.

Methods This retrospective, multicenter, European study included adult patients with at least one GHP ≥ 10 mm who underwent endoscopic resection and at least one follow-up endoscopy. Patients with recurrent GHPs or hereditary gastric polyposis were excluded. All data were retrieved from the endoscopy, pathology, and hospitalization reports.

Results From June 2007 to August 2018, 145 GHPs in 108 patients were included. Recurrence after endoscopic resection was 51.0 % (74/145) in 55 patients. R0 resection or en bloc resection did not impact the risk of polyp recurrence. In multivariate analysis, cirrhosis was the only risk factor for recurrence (odds ratio [OR] 4.82, 95 % confidence interval [CI] 1.33 – 17.46; $P = 0.02$). Overall, 15 GHPs (10.4 %) showed neoplastic transformation, with size > 25 mm (OR 10.24, 95 %CI 2.71 – 38.69; $P < 0.001$) and presence of intestinal metaplasia (OR 5.93, 95 %CI 1.56 – 22.47; $P = 0.01$) being associated with an increased risk of neoplastic transformation in multivariate analysis.

Conclusions Results confirmed the risk of recurrence and neoplastic transformation of large GHPs. The risk of neoplastic change was significantly increased for lesions > 25 mm, with a risk of high grade dysplasia appearing in polyps ≥ 50 mm. The risk of recurrence was high, particularly in cirrhosis patients, and long-term follow-up is recommended in such patients.

Introduction

The incidental finding of gastric polyps occurs in about 1.2 % – 8.0 % of patients undergoing upper gastrointestinal endoscopy [1 – 4]. The exact prevalence of gastric hyperplastic polyps (GHPs) is unknown, being reported in 7 % – 88 % of lesions resected in the stomach [4 – 6]. Several risk factors for GHPs have been identified, such as chronic *Helicobacter pylori* infection, chronic atrophic gastritis [7], liver cirrhosis and portal hypertension [8], autoimmune gastritis [9], partial gastric surgery [10], and Ménétrier's disease [11].

Although mostly asymptomatic, GHPs can present as anemia due to occult bleeding or, in rare cases, as severe gastrointestinal bleeding. Their potential for neoplastic transformation has been demonstrated, with a prevalence of dysplasia (low and high grade) ranging from 1.5 % to 4.4 %, and a prevalence of adenocarcinoma of between 1.1 % and 2.1 % [12 – 14]. A GHP size > 10 mm has been identified as a risk factor for neoplastic transformation [12]. Current French guidelines recommend the resection of gastric polyps when symptomatic or when their size is > 10 mm [15]. For the latter, the goal of endoscopic resection is to diagnose and treat the GHP with neoplastic transformation. However, many cases of local recurrence are reported in the literature, sometimes with severe profuse gastric spreading, even following R0 resection with free lateral and deep margins [16]. Thus, the benefit – risk balance of the resection remains unclear.

The present study aimed to evaluate the risk of GHP recurrence after endoscopic resection of large GHPs (≥ 10 mm), and to identify risk factors for recurrence and neoplastic transformation.

Methods

Study design

This work was a retrospective European multicenter study focusing on GHPs, and included patients from seven academic and three nonacademic hospitals in France, Spain, and Croatia, between June 2007 and August 2018. All participating operators had extensive experience in endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).

Inclusion and exclusion criteria

Patients were included if they fulfilled the following criteria: age ≥ 18 years, endoscopic resection of at least one GHP with a size ≥ 10 mm, and an endoscopic follow-up at least 3 months after resection. Patients were excluded if the GHP was already a recurrence at the time of the first endoscopy, or if they underwent surgical resection of GHPs or had hereditary gastric polyposis (familial adenomatous polyposis or hamartomatous polyposis).

Definitions

The histological diagnosis of GHP was made using the following criteria: the presence of foveolar hyperplasia, with long, deep, and hypersecreting crypts, an inflammatory and abundant chorion, and sometimes an ascension of smooth muscle cells. A large GHP was defined as a size ≥ 10 mm. A GHP was considered recurrent if it had grown at the site of the previous resection, on the scar when visible. En bloc resection was defined as a complete resection without fragmentation during removal of the piece. R0 resections were defined histologically by free lateral and deep margins. Neoplastic transformations were defined histologically by the presence of dysplasia or adenocarcinoma within GHPs.

Patients and data collection

All patients were retrospectively included using either the disease coding software or the prospectively collected databases of each center. All data were retrieved from the endoscopy, pathology, and hospitalization reports, collected anonymously, and collated in an Excel spreadsheet (Excel; Microsoft, Redmond, Washington, USA).

Objectives

The primary end point was the proportion of recurrence, defined by the presence of a histologically confirmed GHP at the site of a previous complete endoscopic resection at least 3 months after the initial complete resection.

Secondary end points were: risk factors for recurrence of GHPs, proportion and risk factors for neoplastic transformation in GHPs, proportion of en bloc and R0 resections according to the technique used (EMR, ESD, hybrid), and safety of the procedure (within the first month) including perforations (complete or partial, i. e. with target sign) and bleedings.

Statistical analyses

Quantitative variables were described by the mean and standard deviation (SD), the range, or the median and interquartile range (IQR); qualitative variables were described by the frequency and percentage of each modality (excluding missing data from percentages). The effect of factors on the risk of recurrence or neoplastic transformation was quantified using odds ratios (ORs) with their 95 % confidence intervals (CIs). Comparison between groups was performed by Student's *t*, chi-squared or Kruskall – Wallis tests. Univariate analyses were performed using mixed logistic regressions (multiple polyp by patient). Multivariate analysis was then performed by including all factors with *P* values < 0.2 in univariate analyses, followed by backward selection. The survival without recurrence curve was produced by the Kaplan – Meier method. A *P* value < 0.05 was considered significant. Analyses were performed using R software version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria. https://cran.r-project.org/mirrors.html). Statistical analyses were performed on all available data.

Ethical considerations

The study was conducted according to the Declaration of Helsinki and received approval from the ethics committee of the Hospices Civils de Lyon (28 August 2018).

Results

Patient and lesion characteristics

From June 2007 to August 2018, 145 GHPs of ≥ 10 mm were included in the study. Macroscopic aspects of GHPs are presented in ▶ **Fig. 1**. Endoscopic resection of GHPs was performed in 108 patients (mean age 65.9 years [SD 11.9]; 56.1 % male (n = 60). The mean number of GHPs was 1.34 per patient (range 1 – 6). A single polyp was recorded in 79.6 % of patients, two polyps in 13.0 % of patients, and three or more polyps in 7.4 % of patients.

Of the 108 patients, 17.8 % had cirrhotic and 13.6 % had a noncirrhotic chronic liver disease. A history or ongoing infection with *H. pylori* was detected in 14.7 % of patients. Histological findings showed gastritis in 77.5 % of patients, intestinal metaplasia in 30.2 %, and gastric atrophy in 28.1 % of patients.

Finally, 45.4 % of patients had a clinical manifestation of their GHPs. Of these, 80.0 % had anemia, 11.4 % had upper gastrointestinal bleeding, and 8.6 % had an isolated iron deficiency. Other nonspecific upper gastrointestinal symptoms were reported, such as epigastric pain and gastroesophageal reflux disease.

The median size of GHPs was 15.0 mm (IQR 10.0 – 25.3) and 66.2 % of were located in the antrum (including the angulus). ESD was used in 17.9 % of GHP resections, EMR in 77.2 %, and a hybrid technique in 4.8 %. R0 resection was achieved in 108 resections (75.5 %) (▶ **Table 1**). The median time to the first endoscopic follow-up was 8.8 months (IQR 3.7 – 16.6). The number of endoscopic follow-ups following the first resection ranged from 1 (57.2 % of GHP resections) to 5 (2.0 % of GHP resections).

Primary objective

After initial resection, 74 recurrent GHPs (51.0 %, 95 %CI 42.6 – 59.4) were identified in 55 patients (▶ **Table 1**). At 48 months, survival without recurrence was estimated at 22.2 % (95 %CI 13.8 – 35.7). The median survival without recurrence was 20.0 months (95 %CI 15.8 – 31.9) (▶ **Fig. 2**).

Risk factors for GHP recurrence

Univariate analysis found that patients aged ≤ 65 years, or with cirrhosis, or GHPs located in the antrum had a higher risk of recurrence. Among patients with cirrhosis, 79.3 % of resected GHPs recurred vs. 43.5 % in the noncirrhotic population. Following a resection of antral GHP, the recurrence proportion was 59.4 % vs. 34.7 % for corpus GHPs (▶ **Table 1**).

Multivariate analysis followed by backward selection found that, although antral location tended to be a risk factor (P = 0.08), only cirrhosis remained significant for GHP recurrence after endoscopic resection (adjusted OR 4.82, 95 %CI 1.33 – 17.46; P = 0.02) (▶ **Table 2**).

Patients with cirrhosis

In patients with cirrhosis, the proportion of males was higher (78.9 %) than in the noncirrhotic population (51.1 %), but the proportions of en bloc and R0 resections were similar in both populations (85.8 % and 77.0 % vs. 89.7 % and 69.0 %, respectively). Neoplastic transformation was found in 6.9 % of GHPs in patients with cirrhosis vs. 11.4 % of GHPs in the noncirrhotic population.

Recurrence after several endoscopic resection

Of the 74 recurrent GHPs, 43 were re-treated endoscopically. Of these, six were lost to follow-up. A recurrence frequency of 78.4 % (29/37) was reported after endoscopic resection of the first recurrence. After a third resection, without taking into account the large number of patients lost to follow-up, this proportion reached 88.9 % (8/9).

Risk factors for neoplastic transformation

Data were missing for one GHP. Of the 144 GHPs, 15 showed neoplastic transformation, with dysplastic or carcinomatous tissue found during their work-up, representing a percentage of 10.4 % (95 %CI 6.2 – 16.9). Low grade dysplasia was observed in 12 GHPs, high grade dysplasia in 2, and adenocarcinoma in 1 GHP; these latter 3 GHPs measured ≥ 50 mm. It should be noted that before therapeutic endoscopy, 10 of these polyps had been biopsied and 50.0 % of them did not reveal any neoplastic tissue. Finally, 7 of the 15 GHPs (46.7 %) with neoplasia recurred after resection. Of these, two retained low grade dysplasia and one had progressed to adenocarcinoma (initially low grade dysplasia before resection). Furthermore, neoplastic transformation appeared in six recurrent GHPs that were non-neoplastic at the histological examination of the initial resection.

Univariate analyses found that age > 65 years, gastric intestinal metaplasia, no PPI intake, and GHP size > 25 mm were associated with neoplastic transformation. The median size of GHP containing neoplasia was 40.0 mm (IQR 17.0 – 55.0) compared with 15.0 mm (IQR 10.0 – 25.0) for those without any neoplastic component. The occurrence of neoplastic transformation was significantly higher in GHPs > 25.0 mm than in those ≤ 25.0 mm (28.6 % vs. 4.6 %; OR 8.24, 95 %CI 2.59 – 26.26; P < 0.001) (▶ **Table 3**). The proportion of GHPs with neoplastic transformation reached 58.3 % in GHPs > 40 mm. Multivariate analysis after backward selection found that gastric intestinal metaplasia (OR 5.93, 95 %CI 1.56 – 22.47; P = 0.01) and GHP size > 25.0 mm (OR 10.24, 95 %CI 2.71 – 38.69; P < 0.001) remained significantly associated with neoplastic transformation (▶ **Table 4**).

En bloc and R0 resection

At the first endoscopy, the proportion of en bloc resections was 86.7 %. After considering specimen fragmentation (12.9 %) and final histological analysis, an endoscopic R0 resection was obtained in 75.5 % of cases. The mean size of the resected GHPs was 40.2 mm (SD 39.4) when treated with ESD, 17.9 mm (SD 10.6) with EMR, and 38.9 mm (SD 23.7) with the hybrid procedure (P < 0.001). There was no significant difference in the rate of en bloc resection when using ESD (96.1 %), EMR (85.4 %) or a hybrid technique (71.4 %) (P = 0.12). Similarly, the R0 resection rate did not differ significantly according to the endoscopy technique used (ESD 76.9 %, EMR 76.4 %, and hybrid 57.1 %; P = 0.53).

▶ **Table 1** Baseline characteristics of patients and risks factors of recurrence in univariate analysis.

Characteristic	Total numbers[1]		Recurrence[2]		Univariate analysis	
	Patients n = 108	GHPs n = 145	No n = 71	Yes n = 74	OR (95 %CI)	*P*
Age	65.9 (11.9)	65.6 (11.2)	66.7 (12.3)	64.5 (10.2)		0.24
mean (SD), years						
▪ ≤ 65 years, n (%)	43 (39.8)	63 (43.4)	24 (38.1)	39 (61.9)		
▪ > 65 years, n (%)	65 (60.2)	82 (56.6)	47 (57.3)	35 (42.7)	0.34 (0.12 – 0.96)	0.03
Sex, n (%)						
▪ Male	60 (56.1)	88 (61.1)	37 (42.0)	51 (58.0)	2.48 (0.91 – 6.73)	0.06
▪ Female	47 (43.9)	56 (38.9)	34 (60.7)	22 (39.3)		
▪ Missing data	1	1	0	1		
Cirrhosis, n (%)						
▪ Yes	19 (17.8)	29 (20.1)	6 (20.7)	23 (79.3)	6.57 (1.74 – 24.84)	0.002
▪ No	88 (82.2)	115 (79.9)	65 (56.5)	50 (43.5)		
▪ Missing data	1	1	0	1		
H. pylori infection, n (%)						
▪ Yes	15 (14.7)	19 (13.7)	9 (47.4)	10 (52.6)	1.22 (0.30 – 4.91)	0.78
▪ No	87 (85.3)	120 (86.3)	58 (48.3)	62 (51.7)		
▪ Missing data	6	6	4	2		
Gastritis, n (%)						
▪ Yes	79 (77.5)	106 (76.3)	50 (47.2)	56 (52.8)	2.20 (0.62 – 7.80)	0.20
▪ No	23 (22.5)	33 (23.7)	19 (57.6)	14 (42.4)		
▪ Missing data	6	6	2	4		
Gastric intestinal metaplasia, n (%)						
▪ Yes	29 (30.2)	41 (30.8)	18 (43.9)	23 (56.1)	1.83 (0.58 – 5.76)	0.30
▪ No	67 (69.8)	92 (69.2)	50 (54.3)	42 (45.7)		
▪ Missing data	12	12	3	9		
Gastric atrophy, n (%)						
▪ Yes	27 (28.1)	33 (24.8)	20 (60.6)	13 (39.4)	0.61 (0.60 – 0.62)	0.41
▪ No	69 (71.9)	100 (75.2)	48 (48.0)	52 (52.0)		
▪ Missing data	12	12	3	9		
PPI intake, n (%)						
▪ Yes	66 (62.3)	97 (67.8)	44 (45.4)	53 (54.6)	1.87 (0.68 – 5.20)	0.22
▪ No	40 (37.7)	46 (32.2)	27 (58.7)	19 (41.3)		
▪ Missing data	2	2	0	2		
NSAID or aspirin intake, n (%)						
▪ Yes	22 (22.4)	31 (23.0)	10 (32.3)	21 (67.7)	3.04 (0.89 – 10.33)	0.07
▪ No	76 (77.6)	104 (77.0)	58 (55.8)	46 (44.2)		
▪ Missing data	10	10	3	7		

▶ **Table 1** (Continuation)

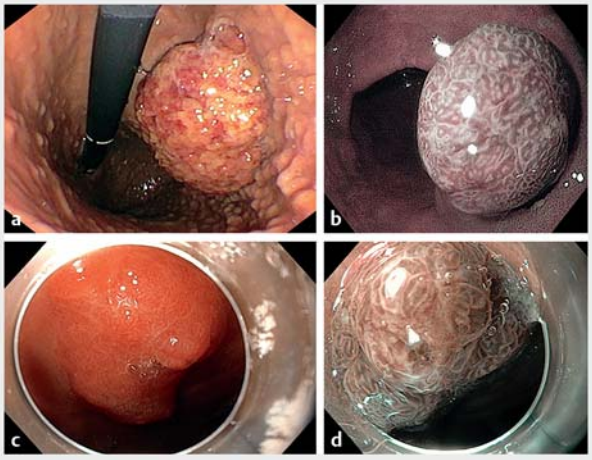
Characteristic	Total numbers[1]		Recurrence[2]		Univariate analysis	
	Patients n = 108	GHPs n = 145	No n = 71	Yes n = 74	OR (95 %CI)	*P*
History of gastric surgery, n (%)						
▪ Yes	6 (6.1)	8 (5.8)	5 (62.5)	3 (37.5)	0.61 (0.08 – 4.87)	0.64
▪ No	94 (95.9)	129 (94.2)	64 (49.6)	65 (50.4)		
▪ Missing data	10	8	2	6		
GHP size						
▪ Median (IQR), mm			15.0 (12.0 – 25.0)	20.0 (10.0 – 29.0)		
▪ 10 – 25 mm, n (%)		108 (75.0)	54 (50.0)	54 (50.0)		
▪ > 25 – 200 mm, n (%)		36 (25.0)	17 (47.2)	19 (52.8)	1.42 (0.50 – 4.04)	0.51
▪ Missing data, n (%)		1	0	1		
Location, n (%)						
▪ Antrum-angulus		96 (66.2)	39 (40.6)	57 (59.4)		
▪ Corpus		49 (33.8)	32 (65.3)	17 (34.7)	0.35 (0.14 – 0.87)	0.02
Neoplastic transformation at the resection time, n (%)						
▪ Yes		15 (10.4)	8 (53.3)	7 (46.7)	1.06 (0.25 – 4.59)	0.94
▪ No		129 (89.6)	63 (48.8)	66 (51.2)		
▪ Missing data		1	0	1		
En bloc resection, n (%)						
▪ Yes		124 (86.7)	62 (50.0)	62 (50.0)	0.71 (0.19 – 2.68)	0.61
▪ No		19 (13.3)	9 (47.4)	10 (52.6)		
▪ Missing data		2	0	2		
R0 resection, n (%)						
▪ Yes		108 (75.5)	55 (50.9)	53 (49.1)	0.91 (0.31 – 2.67)	0.86
▪ No		35 (24.5)	16 (45.7)	19 (54.3)		
▪ Missing data		2	0	2		
Endoscopic resection procedure, n (%)						
▪ EMR		112 (77.2)	52 (46.4)	60 (53.6)		
▪ ESD		26 (17.9)	14 (53.8)	12 (46.2)	0.87 (0.27 – 2.78)	0.61
▪ Hybrid		7 (4.8)	5 (71.4)	2 (28.6)	0.34 (0.04 – 3.06)	

GHP, gastric hyperplastic polyp; OR, odds ratio; CI, confidence interval; SD, standard deviation; PPI, proton-pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; IQR, interquartile range; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.
[1] Missing data not included in percentage calculations.
[2] Percentages calculated as proportion of GHPs for the respective characteristics.

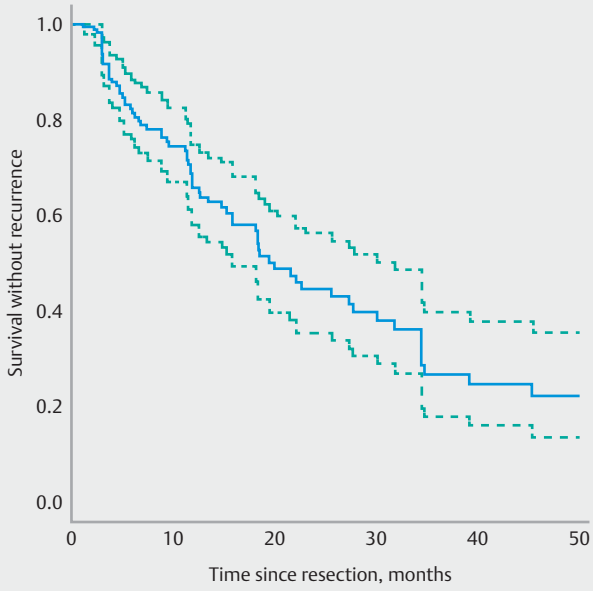
▶ **Table 2** Risk factors for recurrence in multivariate analysis after backward selection.

	OR (95 %CI)	*P*
Cirrhosis (yes)	4.82 (1.33 – 17.46)	0.02
Location (corpus vs. antrum-angulus)	0.44 (0.17 – 1.10)	0.08

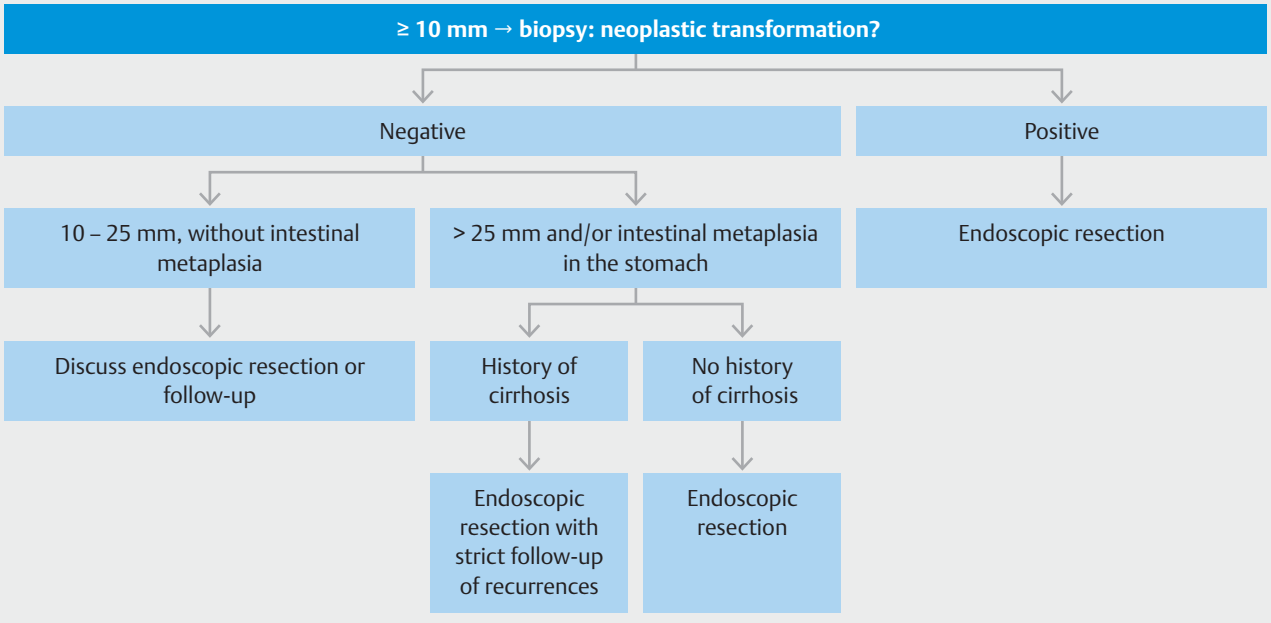
OR, odds ratio; CI, confidence interval.



▶ **Fig. 1** Endoscopic pictures of different cases of gastric hyperplastic polyps. **a** Large reddish hyperplastic polyp of the fundus on white light imaging. **b** Hyperplastic polyp of the antrum on narrow band imaging, with large regular mucosal pattern. **c** Flat hyperplastic polyp of the corpus, with reddish aspect. **d** Irregular mucosal pattern of large hyperplastic polyp without dysplasia on narrow band imaging.



▶ **Fig. 2** Survival without recurrence. solid line, survival curve; dashed lines, 95 % confidence interval.



▶ **Fig. 3** Suggested algorithm for the management of gastric hyperplastic polyps ≥ 10 mm.

Adverse events

The only adverse event recorded was digestive bleeding: 3 (11.5 %) in the ESD group, 5 (4.5 %) in the EMR group, and none in the hybrid technique group. No gastric perforations or deaths occurred. As the occurrence of adverse events was very low, no comparative analysis was carried out.

Discussion

The present study showed local recurrence in more than half of GHPs ≥ 10 mm after endoscopic resection. To our knowledge, this study represents the largest European cohort of stomach supra-centimetric hyperplastic polyps in which the proportion of GHP recurrence following endoscopic resection has been investigated. Surprisingly, GHP recurrence occurred even when

▶ **Table 3** Risk factors of neoplastic changes in univariate analysis.

	Neoplastic transformation[1]		Univariate analysis	
	No n = 129	**Yes n = 15**	**OR (95 %CI)**	***P***
Age				
▪ Mean (SD), years	65.01 (11.61)	69.08 (6.44)		
▪ ≤ 65 years, n (%)	60 (95.2)	3 (4.8)		
▪ > 65 years, n (%)	69 (85.2)	12 (14.8)	3.48 (0.94 – 12.91)	0.04
Sex, n (%)				
▪ Male	80 (90.9)	8 (9.1)	0.69 (0.23 – 2.01)	0.49
▪ Female	48 (87.3)	7 (12.7)		
▪ Missing data	1	0		
Cirrhosis, n (%)				
▪ Yes	27 (93.1)	2 (6.9)	0.58 (0.12 – 2.71)	0.46
▪ No	101 (88.6)	13 (11.4)		
▪ Missing data	1	0		
H. pylori Infection, n (%)				
▪ Yes	14 (77.8)	4 (22.2)	3.14 (0.87 – 11.37)	0.10
▪ No	110 (91.7)	10 (8.3)		
▪ Missing data	5	1		
Gastritis, n (%)				
▪ Yes	93 (88.6)	12 (11.4)	2.00 (0.42 – 9.43)	0.35
▪ No	31 (93.9)	2 (6.1)		
▪ Missing data	5	1		
Gastric IM, n (%)				
▪ Yes	33 (80.5)	8 (19.5)	4.22 (1.29 – 13.82)	0.02
▪ No	87 (94.6)	5 (5.4)		
▪ Missing data	7	2		
Gastric atrophy, n (%)				
▪ Yes	28 (84.8)	5 (15.2)	2.05 (0.62 – 6.78)	0.25
▪ No	92 (92.0)	8 (8.0)		
▪ Missing data	9	2		
PPI intake, n (%)				
▪ Yes	90 (93.8)	6 (6.2)	0.32 (0.10 – 0.98)	0.04
▪ No	38 (82.6)	8 (17.4)		
▪ Missing data	1	1		
NSAID or aspirin intake, n (%)				
▪ Yes	28 (90.3)	3 (9.7)	1.01 (0.26 – 3.91)	0.99
▪ No	94 (90.4)	10 (9.6)		
▪ Missing data	7	2		

▶ **Table 3** (Continuation)

	Neoplastic transformation[1]		Univariate analysis	
	No n = 129	**Yes n = 15**	**OR (95 %CI)**	***P***
GHP size				
▪ Median (IQR), mm	15.0 (10.0 – 25.0)	40.0 (17.0 – 55.0)		
▪ 10 – 25 mm, n (%)	103 (95.4)	5 (4.6)		
▪ > 25 – 200 mm, n (%)	25 (71.4)	10 (28.6)	8.24 (2.59 – 26.26)	< 0.001
▪ Missing data	1	0		
Location, n (%)				

▶ **Table 4** Risk factors of neoplastic changes in multivariate analysis after backward selection.

	OR (95 %CI)	***P***
Gastric intestinal metaplasia (yes)	5.93 (1.56 – 22.47)	0.01
Size of GHP (> 25 mm)	10.24 (2.71 – 38.69)	< 0.001

OR, odds ratio; CI, confidence interval; GHP, gastric hyperplastic polyp.

the initial lesion underwent en bloc and R0 resection. In contrast with other digestive neoplasia, R0 resection does not seem to protect against the risk of local recurrence. Moreover, unlike the observations reported for gastric adenomas and early gastric cancer, the present study showed that ESD does not seem to offer a benefit over piecemeal EMR [17, 18]. Furthermore, the occurrence of profuse recurrence (i. e. more extensive than the initial lesion) suggests that these lesions are partly related to an exuberant wound healing process [16]. Medical history of liver cirrhosis was the only risk factor for recurrence. It has been shown previously that cirrhosis is a risk factor for the development of GHPs [8], possibly related to portal hypertension [19]. However, the notion of increased risk of recurrence after resection in patients with cirrhosis is novel and should probably be considered in order to limit endoscopic treatment in this population. Conversely, when resection has been performed, systematic follow-up should be proposed to patients with cirrhosis in order to detect recurrence or metachronous GHPs; this follow-up could be performed, for example, during variceal evaluation surveillance.

The study showed that GHP recurrence was much more frequent in the antrum than in the corpus, although antral location did not remain significantly associated with the risk of recurrence in multivariate analysis. This could be explained by a lack of power of the study; therefore, the impact of location of GHP recurrence should be considered in future studies. One of the possible hypotheses for taking into account GHP location is that the mucosal trauma induced by contractions of the antrum or duodenogastric reflux could promote the hyperplastic wound healing process [20]. Recurrent lesions can be treated by endoscopic resection despite the presence of submucosal fibrosis; however, the proportion of recurrence gradually increases with the number of repeat resections, supporting the notion that recurrence is induced, at least in part, by the iteration of the wound healing process. In any case, the mechanism of recurrence remains unclear; for example, are there any precursor abnormalities in the submucosa or the surrounding mucosa that could explain GHP recurrence? As the etiology of recurrence remains unclear, long term follow-up seems necessary in order to detect and treat recurrences to prevent a poor outcome (i. e. a larger recurrent lesion and/or neoplastic changes). However, the presence of a neoplastic component in 10 % of GHPs does not favor a watchful waiting strategy for all cases. It is important to note that the majority of neoplastic polyps contained low grade dysplasia and that high grade dysplasia or early adenocarcinomas were found in only 2.1 % of cases (in GHPs measuring ≥ 50 mm) compared with 6.2 % of GHPs > 10 mm in the cohort of Han et al. [12]. The neoplastic progression sequence in GHPs is poorly known and extrapolating the Correa cascade [21, 22] to these lesions would be premature. Nevertheless, in the current study, the presence of intestinal metaplasia emerged as a risk factor for neoplastic transformation of GHPs, as previously demonstrated [21, 22]. The relationship between polyp size and risk of neoplastic transformation had already been demonstrated by others [12, 13], with 5.2 % of neoplastic transformations in all GHPs vs. 8.3 % in those > 10 mm [12]. We were able to identify a threshold of 25 mm, above which the risk of neoplastic transformation became unacceptable. According to our pathologist's experience, the diagnosis of low grade dysplasia is not easy, particularly for polyps with an ulcerative component. Distinguishing low grade dysplasia from common dystrophy or inflammation can be very difficult. Therefore, it is possible that some GHPs with low grade dysplasia were false positives, which could explain the larger proportion of dysplastic component observed in this study compared with other studies. Furthermore, in the present study, the sizes of high risk GHPs (with high grade dysplasia or adenocarinoma) ranged from 50 mm to 200 mm. These last two points suggest

that resection of GHPs could be performed on a size-dependent basis, but further prospective studies are needed to validate this hypothesis. At the first follow-up endoscopy, almost half of GHPs with neoplasia had recurred, two of them still had dysplasia, and one had progressed to invasive adenocarcinoma, demonstrating an unusual risk of neoplasia in recurrent lesions despite complete initial resection. The risk of neoplastic transformation of GHPs is low but difficult to predict based on their endoscopic aspect. Indeed, the biopsies performed on polyps detected neoplastic foci in only half of GHP cases with dysplasia. In the absence of endoscopic criteria to predict malignant transformation, an alternative option could be to perform biopsies of the GHPs before considering resection.

While resection is indicated for all patients with clinical manifestations, resection of asymptomatic hyperplastic polyps is more questionable. Indeed, the risk – benefit balance does not seem to favor resection in the case of polyps containing no dysplasia. It is even more surprising to note that neoplasia appeared in six local recurrences despite no dysplasia found in the initial lesion, indicating that neoplastic transformation might be induced by the healing process. These findings do not support the systematic resection of polyps ≥ 10 mm but instead favor a tailored approach in which the risk of neoplasia and the risk of local recurrence is assessed for each patient. Lesions containing dysplasia on biopsies, or those >25 mm, or developing on diffuse intestinal metaplasia should be resected, while lesions without these elements, particularly in patients with cirrhosis, should be monitored by repeated endoscopies with biopsies to detect neoplastic progression as early as possible (▶ **Fig. 3**).

All these results need to be put into perspective. The present study shows some biases associated with the retrospective design, mainly due to missing data. Moreover, one of the main biases concerns the endoscopic follow-up of patients. Indeed, the time to first follow-up endoscopy was highly variable, ranging from 3 months to more than 81 months. Furthermore, the majority of patients underwent only one follow-up endoscopy, whereas others had up to five. In addition, the diagnosis of polyp recurrence in itself can be considered a bias. Although a recurrence was defined as a GHP developing at the resection site, including on the resection scar if present, it is possible that a number of de novo GHPs were mistakenly considered as recurrent lesions, owing to close proximity, a faded scar, or evaluation by another endoscopist. Finally, the study does not define a follow-up protocol after endoscopic resection. A prospective cohort study seems warranted to confirm these results and better define the recurrence timing and patterns. Further studies concerning the management of recurrence are needed to compare a systematic resection of recurrences with a long-term follow-up strategy using biopsy samples to resect only neoplastic recurrent lesions.

In conclusion, GHPs are a very different entity from gastric adenomas and should be managed differently. The risk of neoplastic change is significantly increased for lesions >25 mm, with a risk of high grade dysplasia and cancer appearing in lesions ≥ 50 mm. The risk of recurrence is high, particularly in patients with cirrhosis, and long term follow-up is recommended in these patients.

Competing interests

Dr. Pioche has provided training funded by Olympus, Norgine, and Cook. Dr. Vanbiervliet is a consultant for Boston Scientific Corp. and Cook Medical. Dr. Albéniz has participated in practical courses or talks with Olympus, Boston, Norgine, and Casen-Recordati, and has received a grant from "La Caixa/Caja Navarra" Foundation. Dr. Marín-Gabriel has provided training funded by Olympus Iberia, SimMedica, Norgine Iberia, Casen Recordati, and Cook, and has received research funding from Cook. Dr. Giovannini is a consultant for Cook Medical and Pentax Medical. All other authors declare no conflicts of interest.

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