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► **To cite this version:**

Capucine Bres, Thibault Voron, Leonor Benhaim, Damien Bergeat, Yann Parc, et al.. Management of Pathogenic CDH1 Variant Carriers Within the FREGAT Network. *Annals of Surgery*, 2022, 276 (5), pp.830-837. 10.1097/SLA.0000000000005626 . hal-04012352

HAL Id: hal-04012352

<https://hal.science/hal-04012352>

Submitted on 16 May 2023

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Management of Pathogenic CDH1 Variant Carriers Within the FREGAT Network

A Multicentric Retrospective Study

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Objective: To describe the management of pathogenic *CDH1* variant carriers (pCDH1vc) within the FREGAT (FRench Eso-GAsTric tumor) network. Primary objective focused on clinical outcomes and pathological findings, Secondary objective was to identify risk factor predicting postoperative morbidity (POM).

Background: Prophylactic total gastrectomy (PTG) remains the recommended option for gastric cancer risk management in pCDH1vc with, however, endoscopic surveillance as an alternative.

Methods: A retrospective observational multicenter study was carried out between 2003 and 2021. Data were reported as median (interquartile range) or as counts (proportion). Usual tests were used for univariate analysis. Risk factors of overall and severe POM (ie, Clavien-Dindo grade 3 or more) were identified with a binary logistic regression.

Results: A total of 99 patients including 14 index cases were reported from 11 centers. Median survival among index cases was 12.0 (7.6–16.4)

months with most of them having peritoneal carcinomatosis at diagnosis (71.4%). Among the remaining 85 patients, 77 underwent a PTG [median age = 34.6 (23.7–46.2), American Society of Anesthesiologists score 1: 75%] mostly via a minimally invasive approach (51.9%). POM rate was 37.7% including 20.8% of severe POM, with age 40 years and above and low-volume centers as predictors ($P=0.030$ and 0.038). After PTG, the cancer rate on specimen was 54.5% ($n=42$, all pT1a) of which 59.5% had no cancer detected on preoperative endoscopy ($n=25$).

Conclusions: Among pCDH1vc, index cases carry a dismal prognosis. The risk of cancer among patients undergoing PTG remained high and unpredictable and has to be balanced with the morbidity and functional consequence of PTG.

Keywords: *CDH1* mutation, gastrectomy, morbidity, prophylactic surgery (*Ann Surg* 2022;00:000–000)

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Author contributions: C. Bres: analysis and interpretation of data, drafting the manuscript, and final approval. T.V.: analysis and interpretation of data, vouchement of the data, revision of the manuscript, final approval. L.B., D.B., Y.P., M.K., L.G., G. Péré, J.A.D., O.B.-O., G.L., J.T., C.G., P.D., M.S., G. Bouzillé, A.B., A.C.B., B.R., C.D., C. Bazille, L.D., G. Belleannee, S.L., M.P.B., F.R., F.N., P.R.B., and J.V. C.E.: analysis and interpretation of data, revision of the manuscript, final approval. G. Piessen: design of the study, decision of publishing the paper, analysis and interpretation of data, revision of the manuscript, final approval.

The authors report no conflicts of interest.

1 Gastric cancer (GC) is the fifth most frequently diagnosed 65
2 cancer worldwide and the third leading cause of cancer 66
3 death.¹ The vast majority of GCs are sporadic, but it has now 67
4 been established that 1% to 3% of GCs arise as a result of 68
5 inherited cancer predisposition syndromes.² Hereditary Diffuse 69
6 Gastric Cancer (HDGC) was first described in a New Zealand 70
7 Maori family in 1998. Most confirmed HDGC cases are caused 71
8 by inactivating germline mutations in the *CDH1* tumor sup- 72
9 pressor gene, encoding the tumor suppressor protein e-cadherin 73
10 that has functions in cell-to-cell adhesion and signal 74
11 transduction.³ The cumulative risk of HDGC for pathogenic 75
12 *CDH1* variant carriers (pCDH1vc) by the age of 80 was reported 76
13 to be as high as 67% to 70% for men and 56% to 83% for women 77
14 in families with ≥ 3 cases of HDGC or fulfilling the 2010 78
15 International Gastric Cancer Linkage Consortium (IGCLC) 79
16 genetic testing criteria.^{4,5} However, recent studies with less 80
17 stringent selection criteria estimated the GC penetrance to be 81
18 37.2% to 42% for males and 24.7% to 33% for females.^{6,7} Of 82
19 note, once HDGC is present, this signet ring cell (SRC) histo- 83
20 logical type is associated with a devastating prognosis.^{8,9} *CDH1* 84
21 mutations also increase the lifetime risk of developing lobular 85
22 breast cancer in women ranging from 39% to 55%.⁴⁻⁷

23 According to the updated clinical practice published in 86
24 2020, pCDH1vc from families with confirmed HDGC should be 87
25 advised to consider a prophylactic total gastrectomy (PTG), 88
26 irrespective of endoscopic findings.¹⁰ When possible, surgery is 89
27 recommended in early adulthood, generally between the age of 90
28 20 and 30 years old, preferably when growth is completed to 91
29 avoid malnutrition consequences.^{2,11} Because of the risk of 92
30 postoperative morbidity (POM) and mortality associated with 93
31 PTG and the risk of malnutrition along with a decrease in 94
32 quality of life, some patients, and even physicians, may be 95
33 reluctant to consider this major procedure. If PTG is declined or 96
34 delayed, annual endoscopic surveillance can be proposed but, 97
35 even when meticulously performed, the effectiveness is 98
36 uncertain.^{10,12} Although surveillance in expert centers suggests 99
37 that superficial SRC carcinoma lesions can be indolent for 100
38 several years, the rate of progression is unpredictable.¹³ Con- 101
39 sequently, patients must be informed that endoscopic surveil- 102
40 lance could delay the identification and treatment of GC. Thus, 103
41 the timing of PTG before the onset of cancer remains difficult 104
42 to evaluate and data in recent literature regarding the best strategy 105
43 for pCDH1vc are scarce. So far, few large surgical series (>20 106
44 patients) of PTG have been published.^{11,14-18} Most of them were 107
45 monocentric and did not analyze index patients nor patients 108
46 declining surgery. 109

47 The aim of our study was to describe the management of 110
48 pCDH1vc within the FREGAT (French Eso-GasTric tumor) 111
49 network. The primary objective focused on clinical outcomes 112
50 and pathological findings. A secondary objective was to identify 113
51 risk factors predicting POM. 114

53 METHODS 115

55 Population of the Study 116

56 The survey was conducted within the FREGAT (FRench 117
57 Eso-GAsTric tumor) network. The 38 centers were solicited by 118
58 e-mail to clinicians with 2 reminders. Inclusion criteria was 119
59 pCDH1vc followed-up between September 2003 and December 120
60 2021. We defined index cases as patients with HDGC in which 121
61 pathogenic *CDH1* variant was previously unknown in the family 122
62 and newly identified. Known pCDH1vc were separated into 123
63 PTG, and endoscopic surveillance groups. Screening of patients 124

65 was performed following the recommendations of the IGCLC 66
67 that have been regularly updated since 1999 and mostly con- 68
69 cerned patients with familial history of diffuse GC or lobular 70
71 breast cancer and more recently cleft lip/palate.^{2,10,19,20} 72

73 Management of Patients and Data Collection 74

75 Data collection included baseline characteristics: sex, age 76
77 and body mass index at the time of surgery, American Society of 78
79 Anesthesiologists (ASA) grade score,²¹ smoking habits, personal 80
81 and family history of cancer, including breast cancer and/or GC 82
83 with histological type. Weight loss and potential accompanying 84
85 symptoms were also recorded. Data regarding preoperative 86
87 endoscopy (macroscopic abnormalities, number and character- 88
89 istics of biopsies (positivity, location, targeted vs random), use of 90
91 image enhancing technics (IET) (chromoendoscopy and more 92
93 recently virtual chromoendoscopy) were also collected. Intra- 94
95 operative data collection included surgical approach (open, 96
97 laparoscopic or robotic and/or converted), extent of lymphade- 98
99 nectomy, type of anastomosis, creation of a jejunal pouch, 100
101 associated procedure, occurrence of intraoperative complication, 102
103 and length of procedure. 104

105 In-hospital mortality and POM were defined as death or 106
107 complications during the same hospital admission or before 108
109 postoperative day 30. Ninety-day mortality was reported. 110
111 Complications were graded according to Clavien-Dindo 112
113 classification²² and classified according to the Gastrectomy 114
115 Complications Consensus Group.²³ Length of hospital stay and 116
117 the need for readmission were also recorded as well as 118
119 oncological data. 120

121 In this retrospective multicentric study, there was no 122
123 standardized histological protocol for the management of the 124
125 specimen. We retrospectively classified the level of pathological 126
127 examination into 3 levels in accordance with the recently 128
129 updated clinical practice (1: minimal examination for patient 130
131 care, 2: intermediate, 3: total gastric embedding and mapping).¹⁰ 132
133 The number of histological blocks was recorded. Histopatho- 134
135 logical analysis included the presence of SRC foci in PTG 136
137 specimens and the number and positivity rate of lymph nodes 138
139 retrieved. All cases of adenocarcinoma were classified according 140
141 to the eighth International Union Against Cancer (UICC)/ 142
143 American Joint Committee on Cancer (AJCC) classification.²⁴ 144

145 To assess the impact of PTG, the patient's weight was 146
147 measured preoperatively and during 1- and 6-month follow-up 148
149 visits, and every 6 months until the second postoperative year, 150
151 then annually for 3 more years. 152

153 Statistical Analysis 154

155 Results are reported as median (interquartile range) or as 156
157 counts (proportion). In univariate analysis, categorical data were 158
159 compared by the χ^2 test or Fisher exact test. For continuous 160
161 data, the independent-samples *t* test or nonparametric Mann- 161
162 Whitney test were used. Risk factors of overall and severe 162
163 postoperative complications (ie, Clavien-Dindo grade 3 or more) 163
164 among patients operated in a prophylactic setting were identified 164
165 with a binary logistic regression. The association between the 165
166 occurrence of cancer and age were evaluated using the Mann- 166
167 Whitney test when age was considered as a continuous variable 167
168 and using a χ^2 test when age was dichotomized using the 168
169 R-package Evaluate cutpoints.²⁵ Number of gastrectomies for 169
170 cancer in the participating centers were evaluated using the 170
171 PMSI (Programme de Médicalisation des Systèmes d'Informa- 171
172 tion database as previously described.²⁶ Determination of high- 172
173 volume versus low-volume centers was based on the mean 173
174 number of total gastrectomies for cancer performed annually 174

1 using the R-package Evaluate cutpoints.²⁵ Survival and follow-up were calculated according to Kaplan-Meier and Shempers methods, respectively. All tests were 2 sided at a 0.05 significance level. All statistical analyses were otherwise performed using SPSS, version 22.0 (IBM Corp., Armonk, NY).

7 RESULTS

9 Overall Population

11 Among the 15 centers that responded to the survey, 4 declared that they had no patients that met the inclusion criteria. Ninety-nine pCDH1vc from were identified in 11 centers that included between 1 and 31 patients each. Among these, 14 were index cases. Eighty-five patients were pCDH1vc from either a confirmed HDGC family (94.8%) or hereditary lobular breast cancer family (5.2%). Type of mutation in 15 families are detailed in the additional Table 1. Among these, 77 underwent PTG (90.5%) and 8 patients declined surgery and were therefore monitored by annual endoscopic surveillance. In the same period 4548 gastrectomies for cancer were performed in those centers.

23 Index Patients

25 Considering the 14 index cases, 9 of them were men. Median age was 41 (31.6–48.4) years. All of them were ASA 1 or 2. The median weight lost observed at the time of diagnosis was 8.5%. Overall, 71.4% had peritoneal carcinomatosis. Seven patients had diffuse peritoneal carcinomatosis at the time of diagnosis and exclusively received palliative chemotherapy and/or best supportive care. Among the 7 patients that underwent resection, 4 had preoperative chemotherapy. Three of them had localized peritoneal carcinomatosis that was resected during gastrectomy [cytoreduction alone (n=1): recurrence at 5 months, died at 8.9 months; cytoreduction+hyperthermic intraperitoneal chemotherapy (n=1): no recurrence after 27.7 months; cytoreduction+immunotherapy with catumaxomab within a phase 2 protocol²⁷ (n=1): relapsed at 1.8 months and died at 4.9 months]. During the postoperative course, 4 patients experienced complications, including 1 anastomotic leak requiring revisional surgery. There was no postoperative mortality. Median length of stay was 14.5 (11.5–30) days.

43 **TABLE 1.** CDH1 Variants Identified in 15 Families

45 Family ID	CDH1 Variant*	Predicted Consequence*
1	c.1565+2dup	r.spl, p.?
47 2	c.(?-124)_(163+1_164-1)del (del exons 1 and 2)	p.0?
49 3	c.2386del	p.(Arg796Glyfs*20)
4	c.1901C>T	p.(Ala634Val)
51 5	c.1595G>A	p.(Trp532*)
6	c.1147C>T	p.(Gln383*)
7	c.1565+1G>A	r.spl, p.?
53 8	c.1565+1G>C	r.spl, p.?
9	c.603del	p.(Val202Leufs*13)
55 10	c.(163+1_164-1)_(687+1_688-1)del (del exons 3 to 5)	p.(Val55Alafs*14)
57 11	c.187C>T	p.(Arg63*)
12	c.531+2T>A	r.spl, p.?
59 13	c.(1565+1_1566-1)_(1711+1_1712-1)del (del exon 11)	p.(Tyr523Phefs*16)
61 14	c.2195G>A	p.(Arg732Gln)
15	c.1565+1G>A	r.spl, p.?

63 *Variant nomenclature follows the Human Genome Variation Society guidelines (<https://varnomen.hgvs.org/>) and is referred to the NM-004360.5.

65 Pathological analysis revealed only 2 limited tumors (pT1aN0M0, n=1 and pT2N0M0, n=1), the rest was categorized as pT3 or more and/or pN+ tumors. Median survival among all index cases was 12 (7.6–16.4) months. Only 4 patients are still alive, respectively, 16, 7, 5 years, and 6 months after surgery. When excluding the 2 limited tumors median survival was 9 (7.5–10.5) months.

73 Patients Undergoing PTG

75 Characteristics of the 77 patients who underwent PTG are summarized in Table 2. Most patients were female (sex ratio: 1.14/1) with a median age at surgery of 34.6 (23.7–46.2) years. Almost half of the 77 patients had a family history of lobular breast cancer (41.6%) and 94.8% had a family history of GC, but only 9 patients (11.7%) had a personal history of cancer. The vast majority of patients were ASA grade 1 (75%).

81 Preoperative endoscopic surveillance was conducted in all patients. Nine patients who had no macroscopic abnormalities had no random biopsies. The remaining 68 patients had either random biopsies or targeted biopsies or both. Correlation between biopsies type (random vs targeted vs both) and results (positive vs negative) according to the use of IET are detailed in Table 3. Overall, 20 patients (26%) had macroscopic abnormalities on endoscopy. Among the 68 patients who underwent biopsies, 13 patients (19.1%) had preoperative endoscopic biopsies with mucosal SRC foci. Biopsies had a higher risk to be positive in the case of targeted and random biopsies or in the case of targeted biopsies only (respectively, 28.6% vs 66.7% vs 10.4%; $P=0.003$). Adding IET did not improve the detection of precancerous lesions because of a lower specificity (61.9% with IET vs 8.2% without IET). When evaluating the results of endoscopic biopsies compared with those in the surgical specimen, sensitivity was 34%, specificity was 100%, positive predictive value was 100%, negative predictive value was 54.5%, and accuracy was 63.2%.

99 Surgical data are detailed in Table 2. The majority of patients underwent a minimally invasive approach (51.9%), mostly laparoscopically with a risk of conversion in 15.0%. Rate of minimally invasive surgery increased during the study period (2003–2016: 47.1% and 2017–2021: 61.5%, $P=0.229$). D1-modified and D2-modified lymphadenectomies were almost equally performed at the time of resection (respectively, 50.6% and 45.5% overall). A mechanical anastomosis was performed preferentially (52.6%) with the addition of a jejunal pouch in 10 patients (13%). Intraoperative confirmation of esophageal squamous mucosa in the proximal margin and duodenal mucosa in the distal margin was rarely performed (n=16, 21.1% and n=10, 13.2%, respectively).

113 Pathological analysis is detailed in Table 2. The median number of blocks examined was 71 (26–124). Forty-two specimens (54.5%) exhibited features of SRC foci, all early stage (pT1a). The median number of SRC foci was 6 (2–13). We did not observe any significant correlation between age and the occurrence of SRC foci ($P=0.751$). The median number of lymph nodes retrieved was 14 (9–21) with none of them being positive. Presence of esophageal mucosa was noted in 86.8% of cases.

121 Intraoperative and postoperative complications are detailed in Table 4. The 3-month postoperative mortality rate was 1.29%: one patient died after 1.5 month due to an unrelated cause. POM occurred in 29 patients (37.7%), including 16 patients (20.8%) in whom severe POM were observed. Eleven patients underwent revisional surgery. Median length of stay was 11 (9–15) days and decreased during the study period

TABLE 2. Description of Characteristics, Surgical Data, Pathological Analysis, and Weight Loss in Patients Who Underwent PTG

Variables	Patients Undergoing PTG (N = 77) [n (%)]
Patients characteristics	
Age at surgery [median (IQR)] (y)	34.6 (23.7–46.2)
Sex	
Male	36 (46.8)
Female	41 (53.2)
Family history of diffuse GC	73 (94.8)
Family history of lobular breast cancer	32 (41.6)
Personal history of cancer	9 (11.7)
BMI at time of surgery (kg/m ²)	24.7 (21.4–27.1)
ASA grade	
I	58 (75)
II	19 (25)
Smoking history	
Current	11 (14.3)
Past	5 (6.5)
Never	61 (79.2)
Surgical data	
Surgical approach	
Open	37 (48.1)
Laparoscopic	27 (35.1)
Laparoscopic with conversion	5 (6.5)
Robotic	7 (9.0)
Robotic with conversion	1 (1.3)
Lymphadenectomy	
D0	3 (3.9)
D1	39 (50.6)
D2	35 (45.5)
Jejunum pouch	10 (13.0)
Esophagojejunal anastomosis	
Manual	37 (48)
Mechanical	40 (52)
Additional procedure	
Cholecystectomy	21 (27.3)
Feeding Jejunostomy	7 (9.1)
Duration of surgery [median (IQR)] (min)	240 (185–308)
Pathological analysis	
Cancer in specimen	42 (54.5)
No. harvested lymph nodes [median (IQR)]	14 (9–21)
No. positive lymph nodes [median (IQR)]	0
Presence of esophageal mucosa	66 (86.8)
Level of pathological examination ¹⁰	1: 45 (58.4) 2: 19 (24.7) 3: 10 (13.0) Unknown: 3
Weight loss [median (IQR)]	
1 mo	-9.76 (-13.13 to -4.69), n = 54
6 mo	-15.18 (-23.78 to -8.92), n = 44
12 mo	-14.07 (-23.67 to -7.97), n = 36
18 mo	-12.39 (-21.18 to -3.11), n = 24
24 mo	-14.94 (-20.51 to -2.5), n = 25
36 mo	-13.64 (-17.65 to -6.66), n = 17
48 mo	-14.04 (-20.45 to -7.64), n = 13
60 mo	-14.03 (-17.53 to -8.20), n = 15

BMI indicates body mass index; IQR, interquartile range.

[2003–2016: 11 (10–14.5) days and 2017–2021: 10 (7.5–15) days, $P = 0.091$]. Thirteen patients (16.9%) were readmitted within 2 months following surgery. Ten patients presented with an esophagojejunal anastomotic fistula (13%) without significant differences between minimally invasive and open approach (15.2% vs 11.4%, $P = 0.737$). Two patients were reoperated for postoperative bowel obstruction.

Potential risk factors of overall or severe POM are showed in Table 5. Age 40 years and older (33.3% vs 12.8% $P = 0.030$) and low-volume center (30% vs 10.8%, $P = 0.038$) were associated with a risk of severe POM. Rates of reoperation (22.5% vs 5.4%, $P = 0.032$) and esophageal leakage (15% vs 10.8%, $P = 0.739$) were also worsen in low-volume centers.

The evolution of average weight loss following PTG is represented on Figure 1. The decrease was essentially observed in the first 6 postoperative months. Patient weight then stabilized at around 85% of the preoperative value. Insertion of an enteral feeding tube (n = 7) or adjunction of a jejunal pouch (n = 10) did not seem to have a significant impact on average weight loss. The median follow-up for patients undergoing PTG was 30 (22.6–37.7) months. Except 1 patient who died of other cause, all of them are alive without evidence of disease. Overall 3- and 5-year survival rate were both $98.6 \pm 1.4\%$. Median overall survival and recurrence-free survival were 30.2 (11.7–54.7) months.

Patients Declining Surgery

Eight patients eligible for PTG declined surgery. Their median age was 49.3 (19.1–64.0) years with a median follow-up of 48 (12–54) months. One patient missed her annual endoscopy in 2020 because of the COVID-19 pandemic and was diagnosed a Siewert III cT2N+SRC adenocarcinoma at the endoscopy in 2021 without any symptoms after 8 years of surveillance. She is currently receiving a perioperative FLOT regimen.

DISCUSSION

In this cohort of 99 pCDH1vc, most candidates for PTG underwent surgery (91.1%). We found a relatively lower rate of cancer (54.5%) on pathological specimen than in previous series. This risk remained high and unpredictable, despite the use of endoscopy even with targeted and random biopsies.

The rate of minimally invasive gastrectomy increased during the study period (47.1% vs 61.5%) without reaching the

TABLE 3. Correlation Between Type of Biopsies, Use of IET During Endoscopy, and Result of Biopsies

	n (%)		
	Negative Biopsies	Positive Biopsies	Total
Random biopsies			
Without IET	30 (90.9)	3 (9.1)	33
With IET	13 (86.7)	2 (13.3)	15
Both	43 (89.6)	5 (10.4)	48
Random and targeted biopsies			
Without IET	4 (66.7)	2 (33.3)	6
With IET	6 (75)	2 (25)	8
Both	10 (71.4)	4 (28.6)	14
Targeted biopsies only			
Without IET	0	3 (100)	3
With IET	2 (66.7)	1 (33.3)	3
Both	2 (33.3)	4 (66.7)	6
Total	55 (80.9)	13 (19.1)	68

TABLE 4. Relative Incidence of Complications by Category With Grading According to International Consensus Among Patients Who Had Complications (N = 33) and Among Patients Who Underwent PTG (N = 77)

	No. Adverse Events	% of Adverse Events* (N = 77)	No. Adverse Event With Clavien-Dindo Score ≤ 2	No. Adverse Event With Clavien-Dindo Score > 2
Intraoperative				
Unintended intraoperative damage to major vessels and/or organs requiring reconstruction or resection	1	1.3	NA	NA
Intraoperative bleeding requiring urgent treatment				
Unexpected medical conditions interrupting or changing the planned procedure				
Postoperative general complications				
Stroke causing patient's permanent deficit				
Need for CPR				
Myocardial infarction				
Cardiac dysrhythmia requiring invasive treatment				
Acute myocardial failure with acute pulmonary edema				
Pulmonary embolism	2	2.6	2	
Respiratory failure requiring reintubation				
Need for tracheostomy				
Pleural effusion requiring drainage				
Pneumothorax requiring treatment				
Need for prolonged intubation (> 24 h after the surgical procedure)	1	1.3		1
Acute liver dysfunction (the Child-Pugh score > 8 for longer than 48 h)				
Acute renal insufficiency/renal failure requiring CVVH/dialysis				
Infections (gastrointestinal, respiratory, urinary, or other) with both symptoms and germ isolation	9	11.7	9	
Postoperative surgical complications				
Postoperative bleeding requiring invasive treatment	3	3.9		3
Postoperative bowel obstruction	3	3.9		3
Postoperative bowel perforation or necrosis				
Duodenal leak	1	1.3		1
Anastomotic leak	10	13.0	3	7
Postoperative pancreatic fistula				
Postoperative pancreatitis diagnosed both clinically and radiologically	1	1.3	1	
Other postoperative abnormal fluid from drainage and/or abdominal collections without gastrointestinal leak(s) preventing drainage removal or requiring treatment	4	5.2	1	3
Delayed gastric emptying (by 10th postoperative day)				
Other major complications requiring reintervention or other invasive procedures				

*The number in the column indicates the incidence of the 27 major complications in patients who underwent PTG. CPR indicates cardiopulmonary resuscitation; CVVH, continuous venovenous hemofiltration; NA, not available.

statistical significance. However, rates of minimally invasive surgery (51.9%) and median length of stay [11 (9–15)] compared favorably to French National Data recently published [12.88% and 15 (11–22), respectively].²⁶ The overall and severe POM rate in our series were 37.7% and 20.8%, respectively, and the distribution of complications were similar to those in previous series.^{11,14,17} We classified complications according to the recently published Gastrectomy Complications Consensus Group²³ and found a slightly higher risk of overall complication (37.7% vs 29.8%).²⁸ However, total gastrectomy is a recurring well-known risk factor for surgical complications. A 13% leakage rate of the esophagojejunal anastomosis was similar to what we observed in the FREGAT database concerning patients undergoing total gastrectomy for cancer. In our cohort, the 2 risk factors for severe POM were age 40 years and above and low-volume center ($P = 0.030$ and 0.039). Technical aspects such

as the minimally invasive approach or the type of anastomosis did not have an impact on the POM risk.

The long-term nutritional outcome is another major issue in this context. Overall median weight loss following total gastrectomy was 15%, which is similar to previous series of PTG.^{11,18,29} After total gastrectomy for cancer, Davis et al²⁹ reported a 15% weight loss at an early stage and a 17% weight loss at an advanced stage, with a maximum weight change expected within 12 months after surgery.²⁴ Adjunction of a jejunal pouch and/or insertion of a feeding jejunostomy tube concerned few patients (13% and 9.1%, respectively) and cannot lead to robust conclusions on their potential value to attenuate weight loss after PTG. Results regarding the interest of a feeding tube on nutritional outcomes after total gastrectomy remain conflicting with a potential risk of increased POM^{30,31} and cannot, therefore, be advocated. In a recent meta-analysis, Syn

TABLE 5. Univariate Analyses Testing Potential Risk Factors of Overall and Severe Postoperative Complications Among Patients Who Underwent PTG

	n (%)			n (%)		
	Overall Complication	No Overall Complication	P	Severe Complication	No Severe Complication	P
Age ≥ 40	15 (51.7)	15 (31.3)	0.074	10 (62.5)	20 (32.8)	0.030
Sex: male vs female	15 (51.7)	16 (33.3)	0.111	7 (43.8)	24 (39.3)	0.749
Obesity (BMI > 30): yes vs no	3 (13)	9 (20.9)	0.519	1 (7.7)	11 (19)	0.444
Personal history of cancer: yes vs no	3 (10.3)	6 (12.5)	0.725	3 (18.8)	6 (9.8)	0.383
Smoker: yes vs no	4 (13.8)	12 (25)	0.240	2 (12.5)	14 (23)	0.499
ASA score 2 vs 1	7 (24.1)	12 (25)	0.932	3 (18.8)	16 (26.2)	0.747
Minimally invasive approach in ITT : yes vs no	16 (55.2)	24 (50)	0.660	8 (50)	32 (52.5)	0.861
Lymphadenectomy: D2-modified vs other	12 (41.4)	23 (47.9)	0.577	8 (50)	27 (44.3)	0.682
Pouch: yes vs no	3 (10.3)	7 (14.6)	0.734	1 (6.3)	9 (14.8)	0.678
Type of anastomosis: mechanical vs manual	16 (55.2)	24 (50)	0.450	10 (62.5)	30 (50)	0.374
Cholecystectomy: yes vs no	7 (24.1)	14 (29.2)	0.631	2 (12.5)	19 (31.1)	0.209
Jejunostomy: yes vs no	4 (13.8)	3 (6.3)	0.265	2 (12.5)	5 (8.2)	0.631
Cancer on specimen: yes vs no	16 (55.2)	26 (55.3)	0.990	8 (50)	34 (55.7)	0.682
Volume (> 25 total gastrectomies annually for cancer: yes vs no)	11 (37.9)	26 (54.2)	0.167	4 (10.8)	33 (54.1)	0.038

BMI indicates body mass index; ITT, intent to treat.

et al³² showed that long-term functional and nutritional outcomes after total gastrectomy were improved by adding a jejunal pouch, without compromising perioperative morbidity. Its adjunction after PTG remains at the discretion of the surgeon.¹⁰ It has already been emphasized that in patients who

had PTG, strict multidisciplinary follow-up including nutritional evaluation should be applied, similarly to follow-up after bariatric surgery.^{10,33} Long-term survival data in the PTG population was favorable with no surgery or disease-related death. Despite a relative long follow-up in patients declining surgery,

Evolution of weight-loss following prophylactic total gastrectomy (N=65)

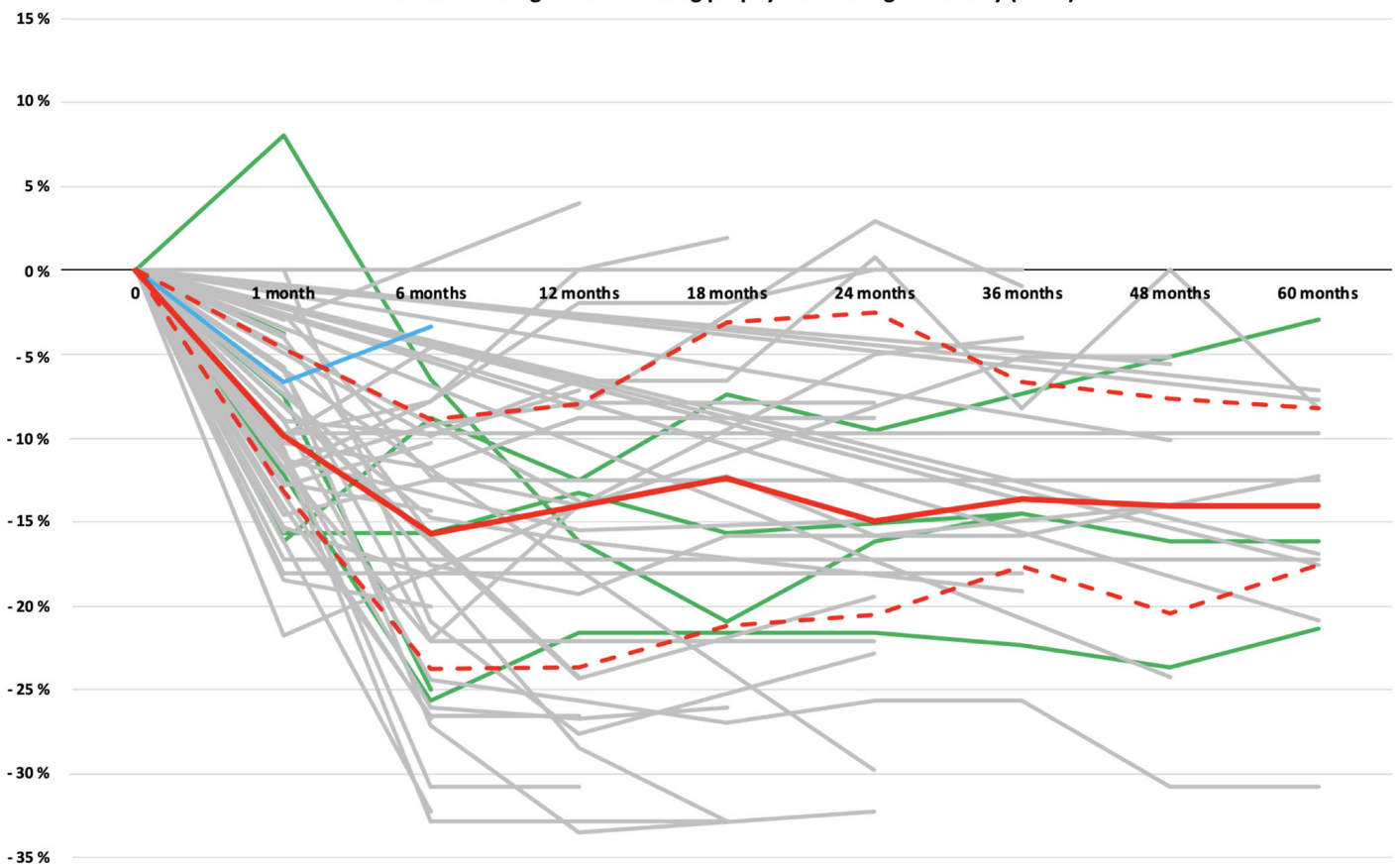


FIGURE 1. Weight loss after prophylactic gastrectomy (N=65). Green lines represent patients with jejunostomy. Blue line represents patient with jejunal pouch.

1 no definitive conclusion can be done concerning the oncological
safety of this approach due to the low number of patients.

3 Despite these short-term and long-term concerns,
pCDH1vc from families with confirmed HDGC remain advised
5 to consider PTG, irrespective of endoscopic findings¹⁰ In the
present cohort, only 19.1% of patients who had random or tar-
7 geted biopsies had positive biopsies, whereas 54.5% exhibited
SRC foci on PTG specimen. This discrepancy between endo-
9 scopic findings and pathological results on the PTG specimen is
well known.^{14,18,34} These findings emphasize how much endo-
11 scopic surveillance is likely to miss preclinical lesions and tend to
favor PTG. In a previous study focusing on endoscopic sur-
13 veillance among pCDH1vc, Fujita et al¹² estimated that 1768
biopsies per patient would be necessary to obtain a 90% detec-
15 tion rate. Current recommendations state that, in patients
declining or wishing to postpone surgery, a specific endoscopic
17 surveillance protocol should be proposed in an expert center.¹⁰
Rates of SRC foci on specimens are usually as high as 75% to
19 96%.^{11,14,18,34,35} In the largest series of PTG that focused on
pathological features in 174 patients, Rocha et al²⁹ found no
21 significant correlation between age and sex and findings of SRC
foci. We hypothesize that our lower rate of SRC foci may be due
23 to the multicentric nature of our series within a context of real-
life practice conditions including variable pathological expertise
25 as well as a problem of resources which is well discussed in the
recent recommendations describing 3 different levels of patho-
27 logical examinations.¹⁰ Systematic use of a specific protocol for
the assessment of the totality of gastric mucosa showed to sig-
29 nificantly increase the rate of SRC foci on PTG specimen (62.3%
vs 95.4%, $P < 0.001$).³⁴ The hypothesis of variants of uncertain
31 significance to explain this low rate of SRC foci is unlikely since
patients in the present study fulfilled all of the criteria of the
33 IGCLC.^{2,10,19,20}

Recently published studies suggest that HDGC risk varies
35 between families, and therefore, family history should be con-
sidered when estimating an individual carrier's risk.^{6,7} SRC
37 carcinomas have, however, been reported in PTG specimens
from carriers with no family history of HDGC.³⁶ SRC carci-
39 noma is likely to have a submucosal spreading pattern, which
can translate into a diffuse gastric thickening aspect without any
41 visible mass. Patients delaying or refusing pTG may therefore be
diagnosed at an advanced stage with a high risk of peritoneal
43 carcinomatosis, as showed in index patients. Five-year overall
survival in such conditions is reported to be under 20%.⁸ Chen
45 et al³⁷ clearly demonstrated that overall survival was poor and
significantly altered in patients with symptomatic tumors when
47 compared with asymptomatic patients undergoing PTG.

Our study has several limitations. Due to its retrospective
49 nature, we could not evaluate impact of PTG on Quality of life.
In a large prospective cohort study, physical and mental func-
51 tioning was reduced in the first month after surgery but recov-
ered to baseline by 12 months and 3 to 9 months, respectively.¹⁵
53 Residual symptoms including diarrhea, fatigue, discomfort when
eating, and reflux remained present in more than half of patients.
55 Another prospective study showed that at 2 years post-
operatively, psychological health and body image was preserved
57 in all subjects. Patients who underwent PTG expressed little to
no regrets and all individuals reported low decisional conflict.³⁸
59 Since inclusions mostly occurred in surgical centers, we may
have missed some patients who declined surgery and con-
61 sequently underestimated this population. In addition, we cannot
pretend that our series was exhaustive since only 15 centers of the
63 FREGAT network responded. It remains, however, one of the
largest and rarest multicentric series yet published. Identification

of patients who will develop an invasive tumors would be crucial
to Taylor's indications of PTG but the present data cannot
answer this specific question.

In conclusion, among pCDH1vc, index cases with
symptomatic tumors carry a dismal prognosis. The risk of cancer
among asymptomatic patients undergoing PTG was high and
unpredictable and has to be balanced with the POM and func-
tional consequence of PTG. There is still much work to be done
to define genetic, endoscopic, surgical, pathological, and onco-
logical centers throughout the country that can manage this
challenging condition.

ACKNOWLEDGMENTS

The authors thank Dr Diana Enea, pathologist in the
Department of Pathology, Sorbonne Université, Hôpital Saint-
Antoine, AP-HP, Paris, France for her help in collecting the
data. They also thank Dr Alexandre Challine, surgeon in the
Department of Surgery Sorbonne Université, Hôpital Saint-
Antoine, AP-HP, Paris, France for his help in analyzing the
PMSI data. The authors also thank Stéphanie Devaux and
Elodie Tiertant for their help in analyzing the data of FREGAT
database.

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Giovanni De Manzoni (Verona, Italy)

This paper deals with an interesting topic. Its main strength is the effort that has been put in reporting CDH1-related gastric cancers on a national level. That is the fundamental step to start effective programs of early diagnosis of tumors associated with inheritance in relatives carrying the same mutation, as well as the application of strategies to reduce the risk of gastric and breast cancer development.

However, the main issue is the pathological handling of surgical specimen in this retrospective multicenter cohort: the authors added the levels of pathological examination in the manuscript that largely depended on the availability of resources. Considering this classification, most of the specimens have been analyzed to an insufficient level. This leads to an underestimation of the number of identified neoplastic foci or even to their non-identification. As such, the data in this study cannot be used to analyze the clinical, anamnestic, genetic (i.e., type of mutation) and pathological factors predicting neoplastic evolution in the carriers of germline mutations of CDH1; indeed, any analysis of this kind could lead to incorrect results. Could you please comment of this?

The indications for CDH1 pathogenetic mutations screening follow the IGCLC Guidelines, updated in the years since 1999. A stratification based on the change of indications (Caldas, *J Med Genet* 1999, Fitzgerald *J Med Genet* 2010; Van der Post 2015 ref;² Blair 2020 ref¹⁰) would have been useful to understand the impact that this change has had on the identification of subjects at risk. Do you think that this variation had a clinical impact? Do you think there was a difference in the identification of carriers between family and individual criteria?

Other weaknesses in handling these cases are the following:

First, regarding endoscopic management, the study reflects a lack of expertise. It is not specified whether a specific bioptic protocol (such as the Cambridge Protocol) was used and in which percentage. This emerges both in the group of patients receiving endoscopy soon after the diagnosis of CDH1 germline mutation, and in those who declined surgery and should, therefore, undergo annual endoscopic surveillance.

Second, we know that CDH1 germline mutations predispose to the onset of other cancers (lobular breast cancer, colon cancer). In the study, it is not indicated whether the germline mutation carriers undergo a complete breast examination, including a contrast-enhanced MR, and a colonoscopy, in cases with colon cancer among relatives. Are these exams routinely performed during Surveillance, too? In order to identify the centers of reference for this condition, it may be useful to indicate this aspect as well.

Third, regarding type and grade of complications, the authors added a Table underlining the percentage of complications in PTG according to International Consensus on Gastrectomy for Cancer (Baiocchi Gastric Cancer 2019; Baiocchi *Ann Surg* 2020) and the grade following Clavien-Dindo classification. From these data, 13% of patients who underwent PTG had an anastomotic leak, and 70% of them had a CD \geq 3a. Looking to the FREGAT database, it seems there are no differences with other patients who underwent gastrectomies for cancer. No significant differences were observed between Minimally Invasive and Open Approaches. What is the percentage of esophagojejunal leaks in prophylactic gastrectomies the same compared with clinical series, likely including bulky tumors

1 located at upper third of the stomach? In my opinion, a stratification by center could be useful to better understand this high
3 percentage of complications.

5 Precisely, on the basis of this evidence of inappropriateness, the main message of the present study is that a specific path
7 must be designed for CDH1 gastric cancer cases correlated with the identification of centers of reference that takes into account
9 the genetic, endoscopic, pathological and surgical expertise. Ultimately, can the authors plan a path based on the sometimes-
11 unsatisfactory results of this study?

Response From Guillaume Piessen (Lille, France)

13 Thank you for your interesting questions. First, I fully agree that there is an underestimation of the patient who had
15 SRC foci in the present study, and this is most probably related to the insufficient level of expertise in the pathological exami-
17 nation. When you perform a Level 3 pathological examination, 95% of the patients have SRC foci. Of note, nearly all patients in
19 those cases have noninvasive tumors.

21 The real problem is to identify which patients will present an invasive cancer and when they will present it. When patients
23 refuse surgery, most of them do so because they fear complications and for their quality of life. These two points are major, but
25 unfortunately, I agree with you that I am unable to answer them with the data that we analyzed in the present manuscript.

27 Second, regarding the time period of diagnosis, it was difficult to find the exact date of the offered diagnosis of mutation in
29 the different families. I think that the initial international criteria were very robust, so I would guess that it had a low impact, but
31 the difference between the varying periods could not be analyzed.

33 Third, regarding endoscopic management, it is the similar problem that we observed for pathological examination. The
35 median number of biopsies realized during endoscopy was 10, far from the 18-20 systematic biopsies currently recommended in
37 addition to targeted biopsies (Blair Lancet Oncol 2020). The centralization of endoscopy is, consequently, also essential.

39 Fourth, due to space limitations, we did not specify the modalities of surveillance for other cancers. The risk of breast
41 cancer is high in pCDH1vc (42%), justifying a yearly clinical examination and MRI from the age of 30. Colonoscopy was
43 only proposed in cases that had relatives with colon cancer. This surveillance is usually organized via geneticists who systemati-
45 cally see pCDH1vc.

47 Fifth, regarding the high rate of leakage, it's true that when compared to the FREGAT database, in which all patients
49 have an active cancer, we observed a similar leakage rate of 13%. We were also a bit disappointed with this. However, we looked
51 at the number of patients who were operated in the different centers, and using a cut-off of 25 total gastrectomies for cancer
53 per year in the 11 centers, we performed a stratification. We found a decrease in severe postoperative complication, reoper-
55 ation and fistula rates. I think it's an argument to operate these patients in highly experienced centers.

57 Finally, in answer to your last question, I fully agree that we still have some hard work to do in France, in order to
61 centralize these patients. I think that we will communicate the results of this study at the two national congresses, and we will

also improve information among general practitioners, who first see these patients, in order to better organize things.

Ronan P. O'Connell (Dublin, Ireland)

Just to follow-up on the morbidity, which is excessive for a prophylactic operation, can you speculate why? For example, if you were doing a sleeve gastrectomy for obesity, you would not accept leak rates of this amount. Is the addition of a lymphadenectomy D2 or D3 contributing to your complications, and is it necessary, in a prophylactic operation, where none of your patients had lymph node positive disease?

Response From Guillaume Piessen (Lille, France)

One of the challenges of this operation is that you have to cut the esophagus 2-3 cm above the esophago-gastric junction to be sure that you don't have any residual gastric mucosa. This probably partly explains this problem of leakage rate. The lymphadenectomy is probably not the explanation. Only 52% had a D2-modified lymphadenectomy, which is, I agree, probably not useful. A D1 lymphadenectomy would be sufficient in this context.

Christiane Bruns (Cologne, Germany)

Thank you for presenting such a great theory. I have the following question: regarding the prophylactic gastrectomy patient group, how many of them already had a history of breast cancer or any other previous surgery, due to diseases/malignancies based on this mutation? Would this be the reason why some patients refused surgery?

Response From Guillaume Piessen (Lille, France)

Out of 77 patients, I think only 1 patient had a prophylactic mastectomy. As such, I don't think this explains why some patients refused surgery.

Suzanne Gisbertz (Amsterdam, The Netherlands)

Thank you for your interesting presentation. First, was a frozen section of both the proximal and distal resection margin performed in all patients to assure resection of all gastric tissue, as is advised in the guidelines? The duodenal margin will be especially difficult to follow-up. Second, do we have data on the long-term follow-up. Were there any recurrences or cases of gastric cancer in the esophageal or duodenal resection plane?

Response From Guillaume Piessen (Lille, France)

With regards to your first question, in the manuscript, we show the rate of frozen section, which was not so high. It is true that the recommendations state that you must check that you removed all the gastric mucosa, and I know that there is a paper from your country showing that, even if we cut 2-3 cm above the esophago-gastric junction and you perform a frozen section, 34% of patients still have some gastric mucosa. However, I think that this should be done macroscopically, at least when opening the surgical specimen during resection, and probably adding frozen section is a good security for young patients, because if they must be reoperated for 2-3 cm, it is a shame.

Second, we have long-term data, and no recurrences were observed. Of note, in 90% of cases, the pathological report mentioned the presence of an esophageal cuff on the specimen.