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

According to the updated clinical practice published in 2020, pCDH1vc from families with confirmed HDGC should be advised to consider a prophylactic total gastrectomy (PTG), irrespective of endoscopic findings.¹⁰ When possible, surgery is recommended in early adulthood, generally between the age of 20 and 30 years old, preferably when growth is completed to avoid malnutrition consequences.^{2,11} Because of the risk of postoperative morbidity (POM) and mortality associated with PTG and the risk of malnutrition along with a decrease in quality of life, some patients, and even physicians, may be reluctant to consider this major procedure. If PTG is declined or delayed, annual endoscopic surveillance can be proposed but, even when meticulously performed, the effectiveness is uncertain.^{10,12} Although surveillance in expert centers suggests that superficial SRC carcinoma lesions can be indolent for several years, the rate of progression is unpredictable.¹³ Consequently, patients must be informed that endoscopic surveillance could delay the identification and treatment of GC. Thus, the timing of PTG before the onset of cancer remains difficult to evaluate and data in recent literature regarding the best strategy for pCDH1vc are scarce. So far, few large surgical series (>20 patients) of PTG have been published.^{11,14-18} Most of them were monocentric and did not analyze index patients nor patients declining surgery.

The aim of our study was to describe the management of pCDH1vc within the FREGAT (French Eso-GasTric tumor) network. The primary objective focused on clinical outcomes and pathological findings. A secondary objective was to identify risk factors predicting POM.

METHODS

Population of the Study

The survey was conducted within the FREGAT (French Eso-GAsTric tumor) network. The 38 centers were solicited by e-mail to clinicians with 2 reminders. Inclusion criteria was pCDH1vc followed-up between September 2003 and December 2021. We defined index cases as patients with HDGC in which pathogenic *CDH1* variant was previously unknown in the family and newly identified. Known pCDH1vc were separated into PTG, and endoscopic surveillance groups. Screening of patients

was performed following the recommendations of the IGCLC that have been regularly updated since 1999 and mostly concerned patients with familial history of diffuse GC or lobular breast cancer and more recently cleft lip/palate.^{2,10,19,20}

Management of Patients and Data Collection

Data collection included baseline characteristics: sex, age and body mass index at the time of surgery, American Society of Anesthesiologists (ASA) grade score,²¹ smoking habits, personal and family history of cancer, including breast cancer and/or GC with histological type. Weight loss and potential accompanying symptoms were also recorded. Data regarding preoperative endoscopy (macroscopic abnormalities, number and characteristics of biopsies (positivity, location, targeted vs random), use of image enhancing techniques (IET) (chromoendoscopy and more recently virtual chromoendoscopy) were also collected. Intra-operative data collection included surgical approach (open, laparoscopic or robotic and/or converted), extent of lymphadenectomy, type of anastomosis, creation of a jejunal pouch, associated procedure, occurrence of intraoperative complication, and length of procedure.

In-hospital mortality and POM were defined as death or complications during the same hospital admission or before postoperative day 30. Ninety-day mortality was reported. Complications were graded according to Clavien-Dindo classification²² and classified according to the Gastrectomy Complications Consensus Group.²³ Length of hospital stay and the need for readmission were also recorded as well as oncological data.

In this retrospective multicentric study, there was no standardized histological protocol for the management of the specimen. We retrospectively classified the level of pathological examination into 3 levels in accordance with the recently updated clinical practice (1: minimal examination for patient care, 2: intermediate, 3: total gastric embedding and mapping).¹⁰ The number of histological blocks was recorded. Histopathological analysis included the presence of SRC foci in PTG specimens and the number and positivity rate of lymph nodes retrieved. All cases of adenocarcinoma were classified according to the eighth International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) classification.²⁴

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

Statistical Analysis

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

1 using the R-package Evaluate cutpoints.²⁵ Survival and follow- 65
 up were calculated according to Kaplan-Meier and Shempers 67
 3 methods, respectively. All tests were 2 sided at a 0.05 significance 69
 5 level. All statistical analyses were otherwise performed using 71
 7 SPSS, version 22.0 (IBM Corp., Armonk, NY).

RESULTS

Overall Population

11 Among the 15 centers that responded to the survey, 75
 4 declared that they had no patients that met the inclusion cri- 77
 13 teria. Ninety-nine pCDH1vc from were identified in 11 centers 79
 15 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.

Index Patients

23 Considering the 14 index cases, 9 of them were men. 81
 25 Median age was 41 (31.6–48.4) years. All of them were ASA 1 or 83
 27 2. The median weight lost observed at the time of diagnosis was 85
 29 8.5%. Overall, 71.4% had peritoneal carcinomatosis. Seven 87
 patients had diffuse peritoneal carcinomatosis at the time of 89
 diagnosis and exclusively received palliative chemotherapy and/ 91
 or best supportive care. Among the 7 patients that underwent 93
 resection, 4 had preoperative chemotherapy. Three of them had 95
 localized peritoneal carcinomatosis that was resected during 97
 gastrectomy [cytoreduction alone (n=1): recurrence at 5 99
 35 months, died at 8.9 months; cytoreduction+hyperthermic
 intraperitoneal chemotherapy (n=1): no recurrence after
 27.7 months; cytoreduction+immunotherapy with catumax-
 omab 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.

TABLE 1. CDH1 Variants Identified in 15 Families

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

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

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.

Patients Undergoing PTG

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%).

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%.

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).

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.

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)
Jejunal 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 metaanalysis, 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	<i>P</i>	Severe Complication	No Severe Complication	<i>P</i>
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,

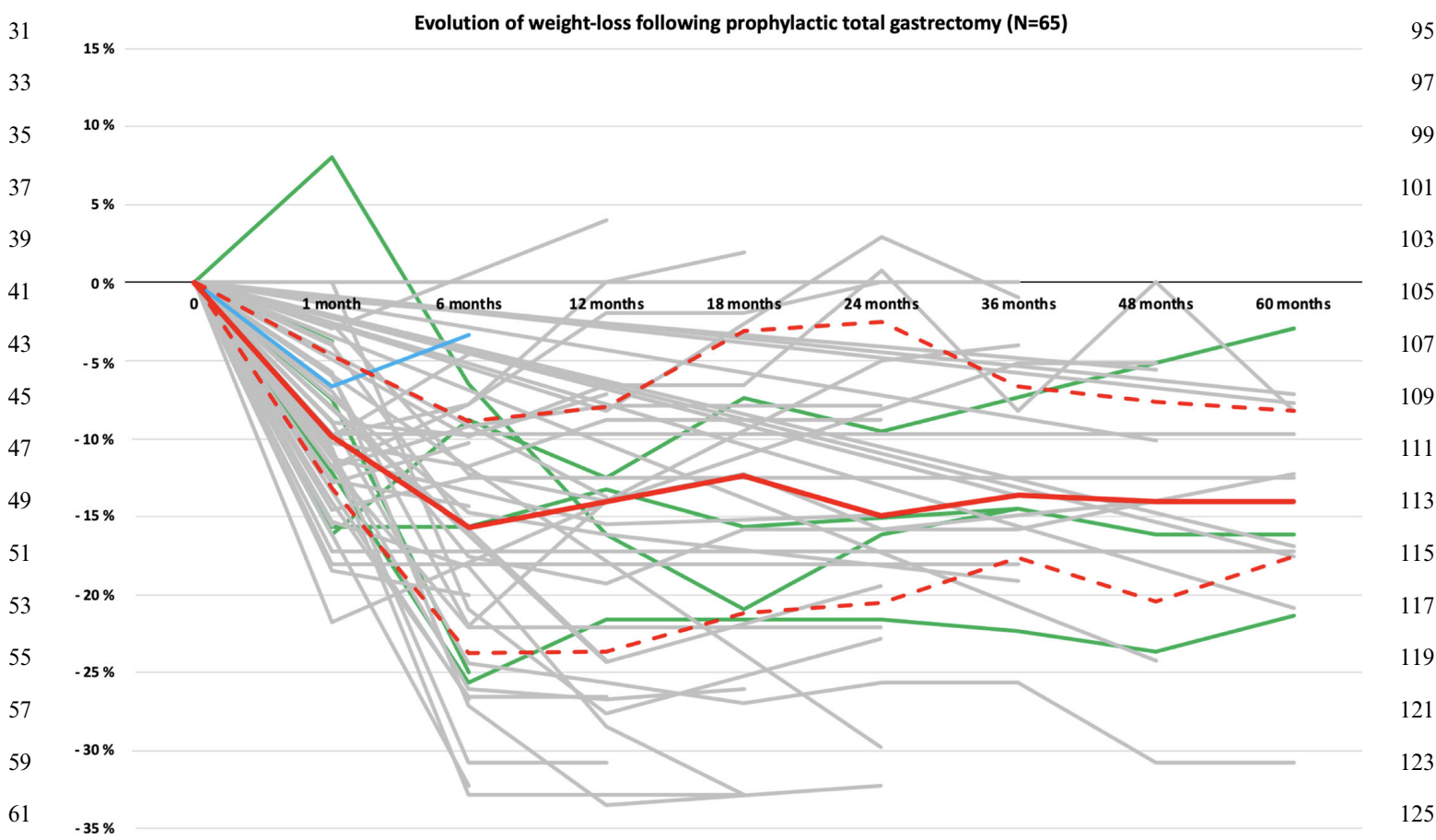


FIGURE 1. Weight loss after prophylactic gastrectomy (N=65). Green lines represent patients with jejunostomy. Blue line represents patient with jejunal pouch.

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

Despite these short-term and long-term concerns, pCDH1vc from families with confirmed HDGC remain advised to consider PTG, irrespective of endoscopic findings¹⁰ In the present cohort, only 19.1% of patients who had random or targeted biopsies had positive biopsies, whereas 54.5% exhibited SRC foci on PTG specimen. This discrepancy between endoscopic findings and pathological results on the PTG specimen is well known.^{14,18,34} These findings emphasize how much endoscopic surveillance is likely to miss preclinical lesions and tend to favor PTG. In a previous study focusing on endoscopic surveillance among pCDH1vc, Fujita et al¹² estimated that 1768 biopsies per patient would be necessary to obtain a 90% detection rate. Current recommendations state that, in patients declining or wishing to postpone surgery, a specific endoscopic surveillance protocol should be proposed in an expert center.¹⁰ Rates of SRC foci on specimens are usually as high as 75% to 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 significant correlation between age and sex and findings of SRC foci. We hypothesize that our lower rate of SRC foci may be due to the multicentric nature of our series within a context of real-life practice conditions including variable pathological expertise as well as a problem of resources which is well discussed in the recent recommendations describing 3 different levels of pathological examinations.¹⁰ Systematic use of a specific protocol for the assessment of the totality of gastric mucosa showed to significantly increase the rate of SRC foci on PTG specimen (62.3% vs 95.4%, $P < 0.001$).³⁴ The hypothesis of variants of uncertain significance to explain this low rate of SRC foci is unlikely since patients in the present study fulfilled all of the criteria of the IGCLC.^{2,10,19,20}

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

Our study has several limitations. Due to its retrospective nature, we could not evaluate impact of PTG on Quality of life. In a large prospective cohort study, physical and mental functioning was reduced in the first month after surgery but recovered to baseline by 12 months and 3 to 9 months, respectively.¹⁵ Residual symptoms including diarrhea, fatigue, discomfort when eating, and reflux remained present in more than half of patients. Another prospective study showed that at 2 years post-operatively, psychological health and body image was preserved in all subjects. Patients who underwent PTG expressed little to no regrets and all individuals reported low decisional conflict.³⁸ Since inclusions mostly occurred in surgical centers, we may have missed some patients who declined surgery and consequently underestimated this population. In addition, we cannot pretend that our series was exhaustive since only 15 centers of the 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 functional consequence of PTG. There is still much work to be done to define genetic, endoscopic, surgical, pathological, and oncological centers throughout the country that can manage this challenging condition.

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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 strat-	also improve information among general practitioners, who first	63
3	percentage of complications.	see these patients, in order to better organize things.	
5	Precisely, on the basis of this evidence of inappropriate-	Ronan P. O'Connell (Dublin, Ireland)	65
7	ness, the main message of the present study is that a specific path	Just to follow-up on the morbidity, which is excessive for a	67
9	must be designed for CDH1 gastric cancer cases correlated with	prophylactic operation, can you speculate why? For example, if	69
11	the identification of centers of reference that takes into account	you were doing a sleeve gastrectomy for obesity, you would not	71
13	the genetic, endoscopic, pathological and surgical expertise.	accept leak rates of this amount. Is the addition of a lymph-	73
15	Ultimately, can the authors plan a path based on the sometimes-	adenectomy D2 or D3 contributing to your complications, and is	75
17	unsatisfactory results of this study?	it necessary, in a prophylactic operation, where none of your	77
19		patients had lymph node positive disease?	79
21	Response From Guillaume Piessen (Lille, France)		81
23	Thank you for your interesting questions. First, I fully	Response From Guillaume Piessen (Lille, France)	83
25	agree that there is an underestimation of the patient who had	One of the challenges of this operation is that you have to	85
27	SRC foci in the present study, and this is most probably related	cut the esophagus 2-3 cm above the esophago-gastric junction to	87
29	to the insufficient level of expertise in the pathological exami-	be sure that you don't have any residual gastric mucosa. This	89
31	nation. When you perform a Level 3 pathological examination,	probably partly explains this problem of leakage rate. The	91
33	95% of the patients have SRC foci. Of note, nearly all patients in	lymphadenectomy is probably not the explanation. Only 52%	93
35	those cases have noninvasive tumors.	had a D2-modified lymphadenectomy, which is, I agree, prob-	95
37	The real problem is to identify which patients will present	ably not useful. A D1 lymphadenectomy would be sufficient in	97
39	an invasive cancer and when they will present it. When patients	this context.	99
41	refuse surgery, most of them do so because they fear complica-	Christiane Bruns (Cologne, Germany)	101
43	tions and for their quality of life. These two points are major, but	Thank you for presenting such a great theory. I have the	103
45	unfortunately, I agree with you that I am unable to answer them	following question: regarding the prophylactic gastrectomy	105
47	with the data that we analyzed in the present manuscript.	patient group, how many of them already had a history of breast	107
49	Second, regarding the time period of diagnosis, it was dif-	cancer or any other previous surgery, due to diseases/malign-	109
51	ficult to find the exact date of the offered diagnosis of mutation in	ancies based on this mutation? Would this be the reason why	111
53	the different families. I think that the initial international criteria	some patients refused surgery?	113
55	were very robust, so I would guess that it had a low impact, but		115
57	the difference between the varying periods could not be analyzed.	Response From Guillaume Piessen (Lille, France)	117
59	Third, regarding endoscopic management, it is the similar	Out of 77 patients, I think only 1 patient had a prophy-	119
61	problem that we observed for pathological examination. The	lactic mastectomy. As such, I don't think this explains why some	121