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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 technics (IET) (chromoendoscopy and more recently virtual chromoendoscopy) were also collected. Intraoperative 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-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)

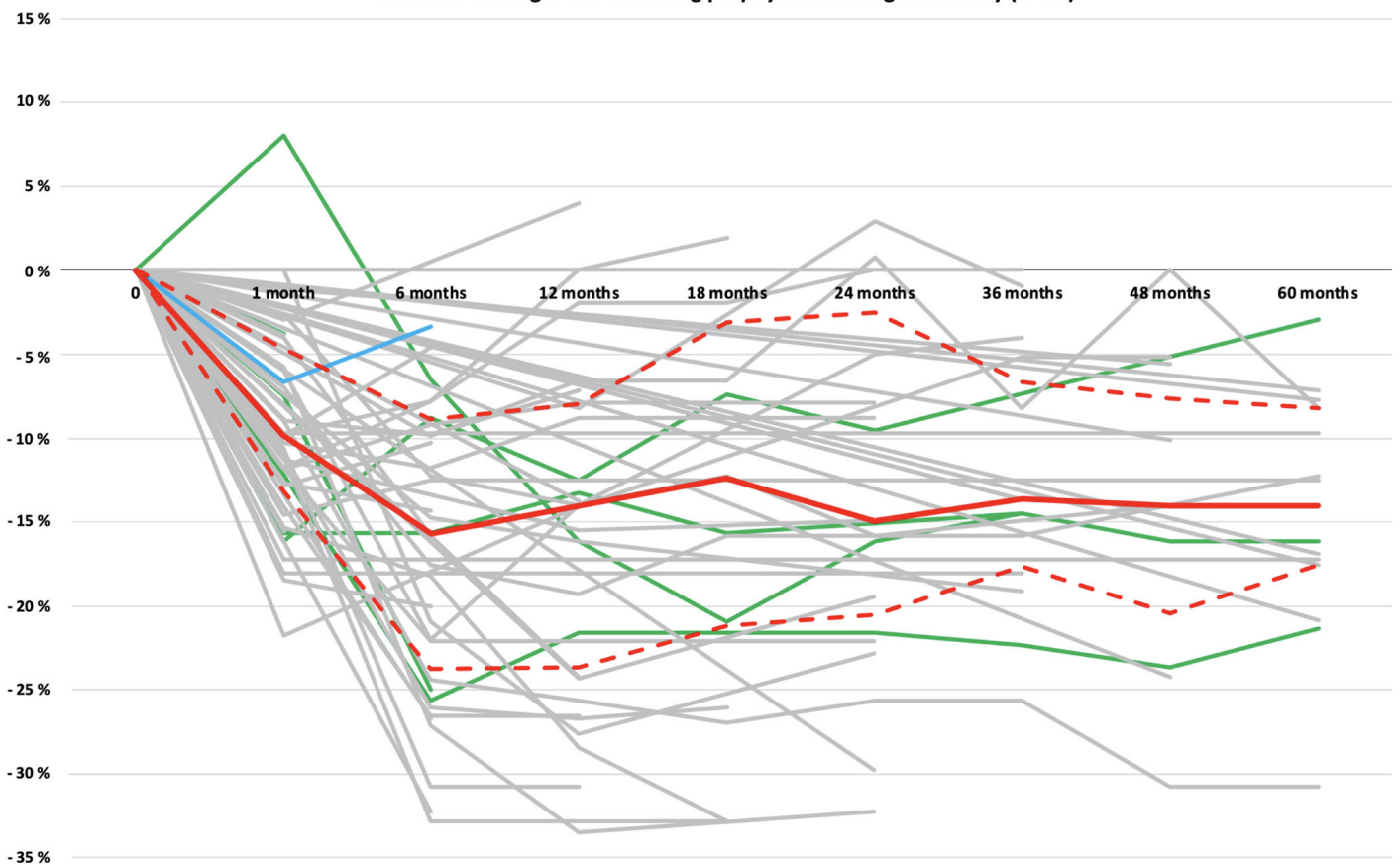


FIGURE 1. Weight loss after prophylactic gastrectomy (N=65). Green lines represent patients with jejunostomy. Blue line represents patient with jejunal pouch.

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
65 answer this specific question. 67

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

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394-424. 91
2. van der Post RS, Vogelaar IP, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J Med Genet.* 2015;52:361-374. 93
3. Guilford P, Hopkins J, Harraway J, et al. E-cadherin germline mutations in familial gastric cancer. *Nature.* 1998;392:402-405. 95
4. Pharoah PD, Guilford P, Caldas C, et al. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology.* 2001;121:1348-1353. 97
5. Hansford S, Kaurah P, Li-Chang H, et al. Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. *JAMA Oncol.* 2015;1:23-32. 99
6. Xicola RM, Li S, Rodriguez N, et al. Clinical features and cancer risk in families with pathogenic CDH1 variants irrespective of clinical criteria. *J Med Genet.* 2019;56:838-843. 101
7. Roberts ME, Ranola JMO, Marshall ML, et al. Comparison of CDH1 penetrance estimates in clinically ascertained families vs families ascertained for multiple gastric cancers. *JAMA Oncol.* 2019;5:1325-1331. 103
8. Park JC, Lee YC, Kim J-H, et al. Clinicopathological aspects and prognostic value with respect to age: an analysis of 3,362 consecutive gastric cancer patients. *J Surg Oncol.* 2009;99:395-401. 105
9. Voron T, Messenger M, Duhamel A, et al. Is signet-ring cell carcinoma a specific entity among gastric cancers? *Gastric Cancer.* 2016;19:1027-1040. 107
10. Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol.* 2020;21:e386-e397. 109
11. Strong VE, Gholami S, Shah MA, et al. Total gastrectomy for hereditary diffuse gastric cancer at a single center: postsurgical outcomes in 41 patients. *Ann Surg.* 2017;266:1006-1012. 111
12. Fujita H, Lennerz JKM, Chung DC, et al. Endoscopic surveillance of patients with hereditary diffuse gastric cancer: biopsy recommendations after topographic distribution of cancer foci in a series of 10 CDH1-mutated gastrectomies. *Am J Surg Pathol.* 2012;36:1709-1717. 113
13. Mi EZ, Mi EZ, di Pietro M, et al. Comparative study of endoscopic surveillance in hereditary diffuse gastric cancer according to CDH1 mutation status. *Gastrointest Endosc.* 2018;87:408-418. 115
14. Hebbard PC, Macmillan A, Huntsman D, et al. Prophylactic total gastrectomy (PTG) for hereditary diffuse gastric cancer (HDGC): the Newfoundland experience with 23 patients. *Ann Surg Oncol.* 2009;16:1890-1895. 117
15. Worster E, Liu X, Richardson S, et al. The impact of prophylactic total gastrectomy on health-related quality of life: a prospective cohort study. *Ann Surg.* 2014;260:87-93. 119

16. van der Kaaij RT, van Kessel JP, van Dieren JM, et al. Outcomes after prophylactic gastrectomy for hereditary diffuse gastric cancer. *Br J Surg*. 2018;105:e176–e182.
17. Kaurah P, Talhouk A, MacMillan A, et al. Hereditary diffuse gastric cancer: cancer risk and the personal cost of preventive surgery. *Fam Cancer*. 2019;18:429–438.
18. Benesch MGK, Bursey SR, O'Connell AC, et al. CDH1 gene mutation hereditary diffuse gastric cancer outcomes: analysis of a large cohort, systematic review of endoscopic surveillance, and secondary cancer risk postulation. *Cancers (Basel)*. 2021;13:2622.
19. Caldas C, Carneiro F, Lynch HT, et al. Familial gastric cancer: overview and guidelines for management. *J Med Genet*. 1999;36:873–880.
20. Fitzgerald RC, Hardwick R, Huntsman D, et al. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet*. 2010;47:436–444.
21. Keats AS. The ASA classification of physical status—a recapitulation. *Anesthesiology*. 1978;49:233–236.
22. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
23. Baiocchi GL, Giacomuzzi S, Marrelli D, et al. International consensus on a complications list after gastrectomy for cancer. *Gastric Cancer*. 2019;22:172–189.
24. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin*. 2017;67:93–99.
25. Oghuzka M, Orzechowska M, Jędraszka D, et al. Evaluate cutpoints: adaptable continuous data distribution system for determining survival in Kaplan-Meier estimator. *Comput Methods Programs Biomed*. 2019;177:133–139.
26. Challine A, Voron T, Dousset B, et al. Postoperative outcomes after laparoscopic or open gastrectomy. A national cohort study of 10,343 patients. *Eur J Surg Oncol*. 2021;47:1985–1995.
27. Goéré D, Gras-Chaput N, Aupérin A, et al. Treatment of gastric peritoneal carcinomatosis by combining complete surgical resection of lesions and intraperitoneal immunotherapy using catumaxomab. *BMC Cancer*. 2014;14:148.
28. Baiocchi GL, Giacomuzzi S, Reim D, et al. Incidence and grading of complications after gastrectomy for cancer using the GASTRODATA Registry: a European retrospective observational study. *Ann Surg*. 2020;272:807–813.
29. Davis JL, Selby LV, Chou JF, et al. Patterns and predictors of weight loss after gastrectomy for cancer. *Ann Surg Oncol*. 2016;23:1639–1645.
30. Brenkman HJF, Roelen SVS, Steenhagen E, et al. Postoperative complications and weight loss following jejunostomy tube feeding after total gastrectomy for advanced adenocarcinomas. *Chin J Cancer Res*. 2017;29:333–340.
31. Patel SH, Kooby DA, Staley CA, et al. An assessment of feeding jejunostomy tube placement at the time of resection for gastric adenocarcinoma. *J Surg Oncol*. 2013;107:728–734.
32. Syn NL, Wee I, Shabbir A, et al. Pouch versus no pouch following total gastrectomy: meta-analysis of randomized and non-randomized studies. *Ann Surg*. 2019;269:1041–1053.
33. Fujioka K. Follow-up of nutritional and metabolic problems after bariatric surgery. *Diabetes Care*. 2005;28:481–484.
34. Rocha JP, Gullo I, Wen X, et al. Pathological features of total gastrectomy specimens from asymptomatic hereditary diffuse gastric cancer patients and implications for clinical management. *Histopathology*. 2018;73:878–886.
35. Lynch HT, Kaurah P, Wirtzfeld D, et al. Hereditary diffuse gastric cancer: diagnosis, genetic counseling, and prophylactic total gastrectomy. *Cancer*. 2008;112:2655–2663.
36. Jacobs MF, Dust H, Koeppe E, et al. Outcomes of endoscopic surveillance in individuals with genetic predisposition to hereditary diffuse gastric cancer. *Gastroenterology*. 2019;157:87–96.
37. Chen Y, Kingham K, Ford JM, et al. A prospective study of total gastrectomy for CDH1-positive hereditary diffuse gastric cancer. *Ann Surg Oncol*. 2011;18:2594–2598.
38. Muir J, Aronson M, Esplen M-J, et al. Prophylactic total gastrectomy: a prospective cohort study of long-term impact on quality of life. *J Gastrointest Surg*. 2016;20:1950–1958.

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?

13 **Response From Guillaume Piessen (Lille, France)**

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

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

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

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

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

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

61 Finally, in answer to your last question, I fully agree that we still have some hard work to do in France, in order to
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.