

# Total Gastrectomy for Hereditary Diffuse Gastric Cancer at a Single Center

## Postsurgical Outcomes in 41 Patients

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**Objective:** The aim of this study was to describe postoperative outcomes of total gastrectomy at our institution for patients with hereditary diffuse gastric cancer (HDGC).

**Background:** HDGC, which is mainly caused by germline mutations in the E-cadherin gene (*CDH1*), renders a lifetime risk of gastric cancer of up to 70%, prompting a recommendation for prophylactic total gastrectomy.

**Methods:** A prospective gastric cancer database identified 41 patients with *CDH1* mutation who underwent total gastrectomy during 2005 to 2015. Perioperative, histopathologic, and long-term data were collected.

**Results:** Of the 41 patients undergoing total gastrectomy, median age was 47 years (range 20 to 71). There were 14 men and 27 women, with 25 open operations and 16 minimally invasive operations. Median length of stay was 7 days (range 4 to 50). In total, 11 patients (27%) experienced a complication requiring intervention, and there was 1 peri-operative mortality (2.5%). Thirty-five patients (85%) demonstrated 1 or more foci of intramucosal signet ring cell gastric cancer in the examined specimen. At 16 months median follow-up, the median weight loss was 4.7 kg (15% of preoperative weight). By 6 to 12 months postoperatively, weight patterns stabilized. Overall outcome was reported to be “as expected” by 40% of patients and “better than expected” by 45%. Patient-reported outcomes were similar to those of other patients undergoing total gastrectomy.

**Conclusion:** Total gastrectomy should be considered for all *CDH1* mutation carriers because of the high risk of invasive diffuse-type gastric cancer and lack of reliable surveillance options. Although most patients have durable weight loss after total gastrectomy, weights stabilize at about 6 to 12 months postoperatively, and patients report outcomes as being good to better than their preoperative expectations. No patients have developed gastric cancer recurrence after resections.

**Keywords:** gastrectomy, gastric cancer, postoperative weight loss, prophylactic surgery

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Gastric cancer is the third leading cause of cancer deaths worldwide, with approximately 1 million new cases and 700,000 deaths annually worldwide.<sup>1</sup> Although the majority of gastric cancers are sporadic, up to 10% demonstrate some familial clustering.<sup>2,3</sup> Among these, approximately 1% to 3% arise from inherited cancer syndromes. Hereditary diffuse gastric cancer (HDGC) was first described in 1964 in 3 Maori families from New Zealand.<sup>4</sup> In 1998, Guilford et al<sup>5</sup> discovered that these families carry a germline mutation in the tumor suppressor gene *CDH1*, encoding E-cadherin. E-cadherin is a transmembrane glycoprotein that mediates calcium-dependent cell-cell adhesion and is important for cell polarity and epithelial differentiation during development.<sup>6,7</sup> Germline loss of E-cadherin expression increases the lifetime risk of developing diffuse gastric cancer and lobular breast cancer.<sup>8,9</sup> Criteria for identifying families that should be tested for *CDH1* mutations were established in 1999 by the International Gastric Cancer Linkage Consortium (IGCLC) and updated in 2014.<sup>10–12</sup> These criteria include (1) 2 or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least 1 diagnosed before the age of 50; or (2) 3 or more cases of documented diffuse gastric cancer in first- or second-degree relatives, independent of age of onset.<sup>10</sup> Genetic testing for germline *CDH1* mutations is available and recommended for any individual fulfilling either criterion.

The cumulative risk of diffuse gastric cancer for *CDH1* mutation carriers by age 80 is estimated to be 70% for men and 56% for women.<sup>13,14</sup> In families with *CDH1* mutations, women have an additional 42% risk of developing lobular breast cancer by the age 80.<sup>13</sup> Although the average age of onset of clinically evident invasive HDGC is 38 years, this age varies considerably even within kindreds.<sup>15</sup>

Due to the highly penetrant and aggressive nature of HDGC, at risk individuals should undergo annual endoscopic surveillance with multiple random biopsies starting in their twenties or at an age 5 to 10 years younger than the earliest age of diagnosis of gastric cancer within the kindred.<sup>16,17</sup> Multiple series, however, have shown that current endoscopic screening and biopsy techniques do not adequately identify early (ie, T1a) diffuse gastric cancer. In over a dozen series, 90% of patients undergoing prophylactic gastrectomy had occult gastric cancer on their final pathology after a normal preoperative upper endoscopy.<sup>17–28</sup> The lack of effective screening options prompts recommendations for a prophylactic total gastrectomy in this population. However, because total gastrectomy is associated with weight loss and increased risk of malnutrition, risk-reducing prophylactic gastrectomy should be carefully considered and is generally recommended only after the patient's growth period is completed.

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The complexities of HDGC (incomplete penetrance, variable age of gastric cancer onset) call for a multidisciplinary approach to patients at risk. This approach should include addressing aspects of genetic testing and counseling, options for prophylactic gastrectomy, and nutrition. A major challenge in addressing these concerns is discussing and setting expectations regarding long-term quality of life (QOL) after gastrectomy. Gastrectomy leads to changes in overall weight and changes in eating habits in terms of portion size, frequency of meals, and time taken to eat meals. It is important to thoroughly counsel patients regarding expectations about postoperative recovery and the long-term impact of gastrectomy. Although prophylactic gastrectomy carries its own morbidity and mortality, it is the only effective intervention to obviate the risk of invasive diffuse gastric cancer. Therefore, our objective is to report our experience with the specialized care of patients with *CDH1* mutation and to describe postoperative surgical outcomes for 41 patients identified with the *CDH1* mutation who underwent total gastrectomy at our institution.

## METHODS

This study was undertaken after approval from our Institutional Review Board. Using our prospective gastric cancer database, we identified 41 patients with a documented *CDH1* mutation who were evaluated, counseled, or treated at Memorial Sloan Kettering Cancer Center between January 2005 and November 2015. All patients underwent formal genetic counseling. Genetic counseling was performed by a clinical genetic counselor and attending physician; counseling was performed both before and after *CDH1* germline genetic testing.

Following genetic counseling, *CDH1* mutation-positive patients were referred for consultations with a surgeon, gastroenterologist, nutritionist, and psychologist as necessary. These consultations were to educate the patient regarding the *CDH1* mutation and potential lifetime risk of gastric cancer and other cancers, to discuss the option of prophylactic gastrectomy, the subsequent change in lifestyle, as well as the potential for no evidence of cancer being identified in their pathologic specimen. Every effort was made to ensure that each patient was fully informed of the facts and was requesting that the procedures be performed. Prophylactic gastrectomy was generally discouraged for patients under the age of 21, and those without adequate social infrastructure. The procedure was actively discouraged in *CDH1*-mutated patients with significant medical comorbidities, and especially in those under active treatment for metastatic lobular breast cancer.

Charts were reviewed for baseline patient demographics, family history of gastric and breast cancer, and any other types of cancer. The specific subtype of *CDH1* mutation was noted. Perioperative factors were recorded, including operative approach (open or minimally invasive), operative time, length of stay, and complications. Postoperative complications were prospectively graded using our previously described modification of the Clavien-Dindo classification.<sup>29</sup> Grades 1 (an event requiring oral medication) and 2 [an event requiring intravenous (IV) medication or a bedside procedure] were classified as minor events; grades 3 (an event requiring intubation or operative, endoscopic, or radiologic intervention), 4 (an event resulting in prolonged disability or organ resection), and 5 (death) were classified as major events.

Four experienced surgeons performed all of the procedures. Laparoscopic total gastrectomies were performed as previously described.<sup>30</sup> Extent of lymphadenectomy (D1 vs D2) was decided by each surgeon individually. Robotic gastrectomies were performed in a similar fashion on the da Vinci Si or Xi system (Intuitive Surgical, Inc., Sunnyvale, CA, USA). Complete total gastrectomy was confirmed by intraoperative frozen section analysis of the proximal and distal margins of the specimen, confirming esophageal squamous mucosa

**TABLE 1.** Patient Characteristics and Perioperative Outcomes—All Patients (n = 41)

Characteristic	Value (%)
Age, median (range)	47 (20–71)
Sex	
Male	14 (34)
Female	27 (66)
Breast cancer family history	15 (37)
Breast findings	
Invasive lobular breast cancer	4 (10)
Lobular carcinoma in situ	3 (7.1)
Atypical ductal hyperplasia	1 (2.3)
Breast procedures	
Prophylactic bilateral mastectomies	2 (4.9)
Therapeutic mastectomy	4 (9.8)
Therapeutic lumpectomy	2 (4.9)
Operative approach for gastrectomy	
Open	25 (61)
Minimally invasive	16 (39)
Operative time, min	
Open, median (range)	174 (115–296)
Minimally invasive, median (range)	220 (186–356)
Length of hospital stay, days, median (range)	7 (4–50)

and duodenal mucosa, respectively. Once specimens were removed, detailed pathologic analysis was undertaken to identify occult foci intramucosal diffuse cancer by a dedicated GI pathologist (L.H.T.). This was accomplished according to a specially designed protocol<sup>31</sup> for assessment of the location and multicentricity of occult cancer foci. In most cases, if cancer foci were not identified in the initial histologic sections, the entire stomach was ultimately submitted for the examination. Retrieved lymph nodes were subjected to pathologic analysis as well, although no metastases were identified in these early cancers.

Patients were evaluated by an institutionally developed set of questions on lifestyle changes, which was administered to patients during follow-up visits or, if consent was given, in a phone interview a minimum of 6 months after gastrectomy (range 6 months to 3 years). This series of questions is administered as a standard practice to our postgastrectomy patients, and results from 35 of our non-*CDH1* total gastrectomy patients were compared with answers from our *CDH1* patients. Patients' postoperative weights (as a percentage of preoperative weight) were subjected to linear regression with quadratic terms, using Stata 12 (StataCorp LP, College Station, TX).

## RESULTS

Forty-one patients (14 male, 27 female) with a known *CDH1* mutation elected to undergo total gastrectomy after comprehensive multidisciplinary evaluation. Their median age at operation was 47 years (range 20 to 71). Of the 27 women, 8 (30%) had coincident breast pathology (4 lobular cancer, 3 lobular carcinoma in situ, 1 atypical ductal hyperplasia). Fifteen of 41 patients in the cohort (37%) had a family history of breast cancer in first- or second-degree relatives. Table 1 summarizes patient characteristics in this group.

Eight of the total gastrectomies were performed laparoscopically and 8 were performed robotically. The median operative time for all patients was 199 minutes (225 minutes for the laparoscopic, 220 minutes for the robotic, and 174 minutes for the open approach). The median length of stay was 7 days. Thirty-five patients (85%) were found to have cancer in their specimen (Table 2). Of those with cancer, all had diffuse-type signet ring histology. The median number of lymph nodes retrieved was 18. No patient developed recurrent

**TABLE 2.** Pathologic Outcomes After Total Gastrectomy for *CDH1* Mutation at MSKCC

Variable	Number (%) or Median (Range)
Cancer in specimen	35 (85)
Number of microscopic foci	
<3	15 (37)
≥3	20 (49)
Stage	
IA	35
IB	0
IIA	0
IIB	0
IIIA	0
IIIB	0
IV	0
Number of lymph nodes harvested, median (range)	18 (1–54)
Number of positive lymph nodes in specimen, median (range)	0 (0)
Follow-up, months, median (range)	16 (1–96)
Disease status	
Alive without evidence of disease	38 (93)
Dead of other cause	3 (7)

gastric cancer, at a median follow-up of 16 months (range, 1 to 96 months) (Table 2).

The overall complication rate and 30-day mortality were similar to those in our prior series,<sup>32</sup> and pulmonary complications, wound infections, and anastomotic leaks were common (Table 3). The majority of pulmonary complications (a composite category of pulmonary effusion, hypoxia, atelectasis, and pneumonia) and wound infections were handled nonoperatively. Of the 3 patients with an esophageal anastomotic leak, only 1 patient required invasive intervention as part of their treatments. Both patients with a duodenal stump leak required invasive intervention: 1 undergoing early abdominal washout, while the other was treated with a percutaneous drain. This patient later developed gastrointestinal bleeding from the gastro-duodenal artery, which was managed with reoperation. Our perioperative death (1 patient of the 41; 2.5%) occurred in a patient with a history of kidney transplant and hepatitis who developed pneumonia and sepsis and died secondary to multiorgan failure, although the patient's water-soluble swallow study had been negative for an esophagojejunal leak.

Delayed complications included 2 patients who presented with an internal hernia through Petersen space (1 after an open and 1 after a laparoscopic approach), 1 at 7 weeks postoperatively, and one 3.5 years postoperatively.<sup>33</sup> Both patients underwent laparoscopic reduction and repair and were discharged home several days

later without further sequelae. Two patients developed Roux limb syndrome, requiring temporary placement of a percutaneous jejunostomy tube for nutritional support and small bowel resection with a distal anastomosis. The final gastrointestinal complications were anastomotic strictures, which developed in 2 patients (1 of whom underwent an endoscopic dilation).

There were 3 nongastrointestinal-related postoperative events. The first was pleural effusion that was sterile for organisms; a formal swallow study confirmed no anastomotic leak and it resolved after percutaneous drainage. The second patient was readmitted for shortness of breath a week after discharge; small bilateral pulmonary emboli were discovered, for which anticoagulation was initiated without further sequelae.

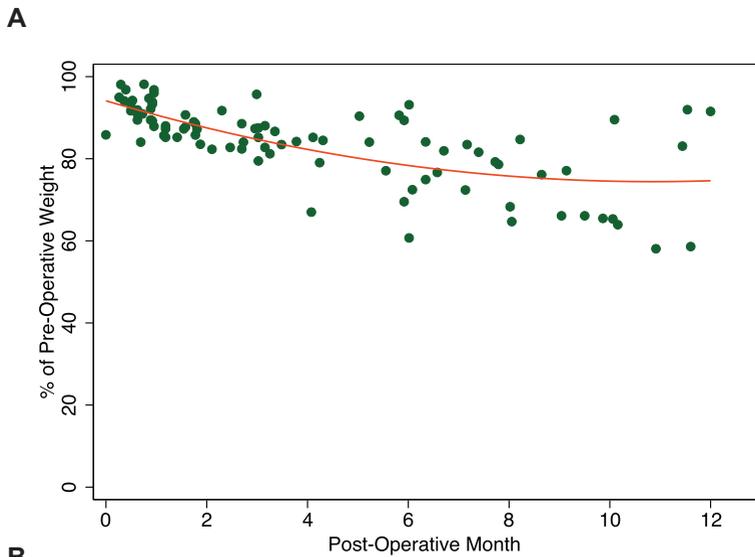
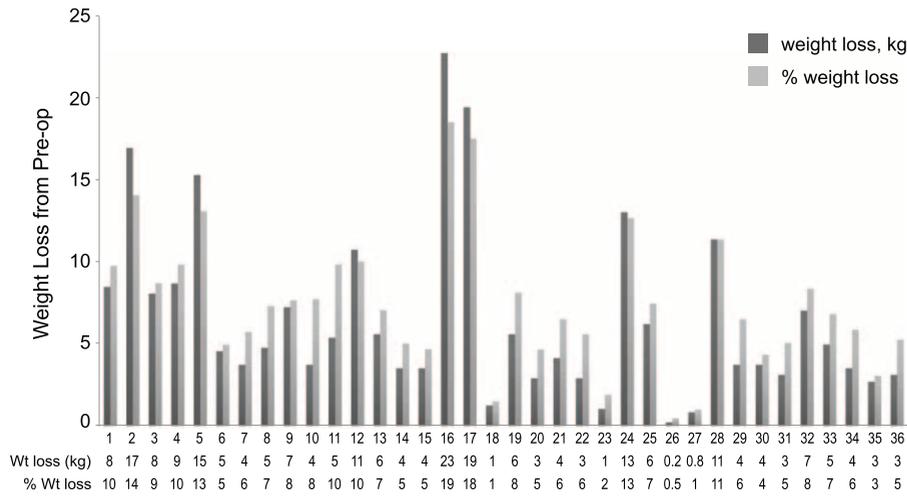
Sufficient follow-up data with postoperative weights (at a minimum of 6 months) were available in a total of 36 of 41 patients. These postoperative weights at 6-month follow-up visit are depicted in Fig. 1A. Body weight dropped during the first few months after surgery and then stabilized at around 6 to 12 months (Fig. 1B), in keeping with the trend seen in previous work from our institution.<sup>34</sup> Median weight loss was 4.7 kg (15% of preoperative weight). Figure 2 compares patients' pre-operative body mass index (BMI) to their BMI at 6 months or later after gastrectomy. Four patients (9.5%) became underweight (BMI <18.5 kg/m<sup>2</sup>), and all other patients were normal weight or remained overweight by 12 months after surgery.

Table 4 summarizes patient-reported postoperative outcomes that were collected from 20 of the 41 patients at a minimum of 6 months after total gastrectomy (range 6 months to 3 years). These data are compared with data for 35 total gastrectomy patients who were evaluated after gastrectomy for nonhereditary gastric adenocarcinoma at our institution. In both groups, more than 65% of patients reported that they could not eat as much per meal as they could before the operation. More than 40% of patients in both groups reported not being able to tolerate certain foods after gastrectomy, such as carbonated drinks, spicy foods, bread, or sweets. In both groups, patients reported needing to eat smaller portions and more meals per day, with a median of 5 meals per day (range 4 to 7). Regarding patients' perception of their weight, most patients reported having a lower weight than pre-operative baseline levels. Most patients reported some symptoms with eating: sweating or weakness for six, abdominal discomfort (not pain) for 9, flushing for 2 patients, and diarrhea occasionally for 3 patients. Two patients underwent anastomotic dilation, and, although 4 patients developed other medical problems, these were not related to the gastrectomy. All patients who completed the questionnaire who were working before the gastrectomy were able to return to work after gastrectomy. Almost all patients polled reported overall outcomes to be as or better than expected (Table 4).

**TABLE 3.** Postoperative Complications Following Prophylactic Total Gastrectomy for Hereditary Diffuse Gastric Cancer

30-day Postoperative Complications	Frequency	Patients (%)	Grade 3+ (%)
Pulmonary complication*	6	14.6	50.0
Anastomotic leak, esophagus	3	7.3	33.3
Wound infection	3	7.3	0.0
Duodenal stump leak	2	4.9	100.0
Gastrointestinal bleeding	2	4.9	100.0
Urinary tract infection	1	2.4	0.0
Supraventricular arrhythmia	1	2.4	0.0
Pulmonary embolus	1	2.4	0.0
Multiple organ system failure	1	2.4	100.0

\*Pulmonary complications include pleural effusion, hypoxia, pneumonia, and atelectasis.



**FIGURE 1.** A, Absolute and percentage weight loss for 36 *CDH1* mutation-positive patients. B, Changes in weight over time. The graph shows all weights recorded within the first year after surgery for the 36 patients with at least 1 recorded weight. Weights are expressed as the percentage of pre-operative weight, and the curve shows average weight loss as estimated using a linear regression model with quadratic terms.

**DISCUSSION**

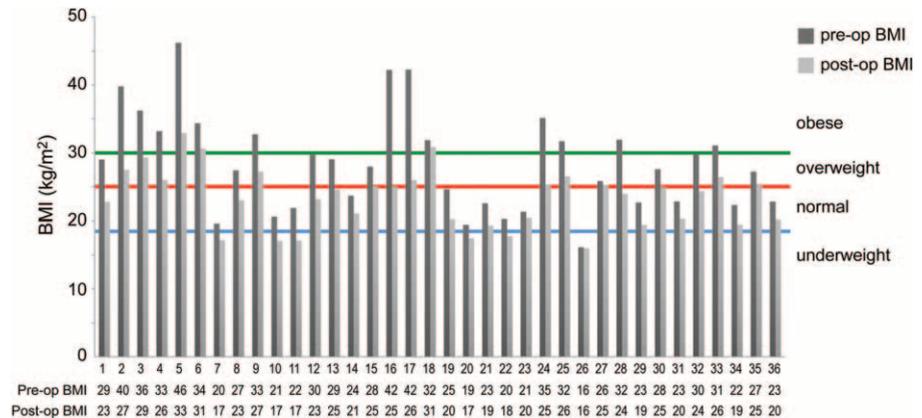
As little has been reported on postoperative outcomes of prophylactic total gastrectomy, in this study, we analyzed results for 41 patients who underwent the procedure because of *CDH1* mutation. A large majority of patients (85%) had microscopic foci of cancer, only 1 of whom had been detected by preoperative endoscopy. After surgery, all patients lost weight, but weights tended to stabilize by 6 to 12 months after surgery, and most patients’ post-operative BMIs stabilized in the normal range or remained in the overweight range. Patients commonly reported changes in eating habits and symptoms after eating. Nevertheless, most patients described their quality of postoperative eating patterns to be equal to or better than what they had expected before surgery.

Risk-reducing surgery is well established for patients with several genetic syndromes. Patients with *BRCA1* or *BRCA2* mutation, for example, harbor a 56% to 87% lifetime risk of breast cancer,<sup>35</sup> and prophylactic mastectomy in this high-risk group is considered a recommended risk-reducing procedure by greater than 90%.<sup>36,37</sup> Patients with these mutations are also at risk for ovarian

cancer and are strongly recommended to pursue prophylactic salpingo-oophorectomy, which can also decrease their risk by 90%. Oophorectomy alone can also offer a 50% reduction in breast cancer risk when performed in pre-menopausal women.<sup>37,38</sup> A third option in this population is chemoprevention with tamoxifen that has been proven to reduce the risk of developing breast cancer by 50%.<sup>39</sup> Similarly, in patients with familial adenomatous polyposis (FAP), inherited colorectal cancer risk is frequently mitigated by proctocolectomy to remove the organ at risk.<sup>40</sup> In multiple endocrine neoplasia type 2 (MEN-2), patients are at a risk for medullary thyroid cancer and are offered thyroidectomy often during childhood,<sup>39</sup> with exact timing of the surgery guided by the specific mutation in the family.

Over 100 pathogenic *CDH1* germline mutations have been identified internationally.<sup>15</sup> The timing for genetic testing and for surgery is based on the age of onset of gastric cancer in this population and on the individual’s family history. Very few cases of *CDH1* mutation mediated gastric cancer have been documented for individuals under the age of 20, and some of the larger series have documented the average age of onset at 38 years.<sup>24</sup> As a bridge to

**FIGURE 2.** Preoperative and postoperative body mass index (BMI) for 36 CDH1 mutation—positive patients who underwent total gastrectomy. Postoperative BMIs were recorded at a minimum of 6 months after total gastrectomy (range, 6 months to 3 years). The horizontal bars mark the boundaries of the reference ranges for BMI (<18.5 kg/m<sup>2</sup>, underweight, 18.5 to 25 kg/m<sup>2</sup> normal, 25 to 30 kg/m<sup>2</sup> overweight, >30 kg/m<sup>2</sup> obese).



prophylactic surgery, some patients with a *CDH1* mutation may elect for surveillance endoscopies, although debate exists to whether this is an adequate approach.<sup>41</sup> Of the 41 *CDH1* patients who underwent total gastrectomy at our institution, 35 patients (85%) were found, upon extensive pathologic evaluation, to harbor occult gastric cancer. These findings are commensurate with other published series, wherein the occult malignancy rate has been as high as 92%. Only 1 patient in our series had evidence of malignancy on preoperative endoscopy, on random preoperative EGD biopsy. In all other 34 patients with malignancy in their gastrectomy specimen, endoscopy missed the early diffuse gastric cancer. This high frequency of missed diagnoses is similar to that reported in other studies.<sup>42–44</sup> Some progress in endoscopic screening has been reported with the development of chromoendoscopy, which uses topical dye to improve the tissue diagnosis. But even with that technique, Shaw et al<sup>45</sup> demonstrated that only 6% of microscopic foci of cancer larger than 4 mm were detected in *CDH1* patients undergoing surveillance. In our series, no patients underwent chromoendoscopy, so we cannot

comment regarding the utility of this technique. The presence of occult gastric cancer in the majority of *CDH1* patients and the inability to detect early gastric cancer reliably by endoscopic means has made consideration for prophylactic total gastrectomy a standard for patients who have reached the age of 21.<sup>11,46</sup>

It is important that patients with hereditary cancer syndromes receive a multidisciplinary approach to decision-making and clinical care. For patients with the *CDH1* mutation, the decision-making does not stop with genetic testing. At our center, we have an established system whereby patients at risk initially meet with the genetics team and obtain testing and counseling. Subsequently, they meet with a surgeon experienced with the care of *CDH1* patients and familiar with the recommendations for their treatment. The initial discussion focuses on the patient’s individual risk and on the appropriateness of total gastrectomy. If a decision is made for surgery, patients are offered psychological counseling on the anticipated changes in eating habits, on nutritional deficiencies, and on the possibility of finding no microscopic foci of cancer in the resected stomach.

**TABLE 4.** Quality of Life Questions Asked of Patients at MSKCC Undergoing All Types of Total Gastrectomy for Cancer Versus Those Undergoing Total Gastrectomy for *CDH1* Mutation

MSKCC-10 Questions	Total Gastrectomy for Cancer (n = 35)	Total Gastrectomy for <i>CDH1</i> Patients (n = 20)
1. Can you eat as much in a single meal as compared to before your surgery? (YES)	5 (14%)	7 (35%)
2. Are there any foods you can no longer tolerate? (YES)	17 (49%)	8 (40%)
3. Approximately how many times per day do you eat? (Median and range in times/day)	5 (3–8)	5 (3–8)
4. What is your weight now relative to pre-op. weight?		
I. Higher	2 (6%)	2 (10%)
II. Same	4 (11%)	6 (30%)
III. Lower	29 (83%)	12 (60%)
5. After eating, do you experience any of the following symptoms?		
I. Sweating and/or weakness	10 (29%)	6 (30%)
II. Abdominal discomfort and/or cramping	18 (51%)	9 (45%)
III. Flushing	8 (23%)	2 (10%)
IV. Diarrhea	18 (51%)	3 (10%)
Patients reporting 1 or more symptoms:	27 (77%)	14 (70%)
6. Have you ever had a dilatation? (YES)	3 (9%)	2 (10%)
7. Have you developed any other types of cancer or significant medical problems? (YES)	10 (29%)	4 (20%)
8. Were you employed/working before you had your surgery? (YES)	18 (51%)	18 (90%)
If yes: Did you return to work after your surgery (YES)	13 (72%)	18 (100%)
If yes: Are you currently working? (YES)	7 (54%)	18 (100%)
9. How does your overall QOL now measure up to your expectations before surgery?		
Better	22 (63%)	9 (45%)
As expected	10 (29%)	8 (40%)
Worse	3 (9%)	1 (10%)
Had no expectations before surgery	0	2 (20%)

Once the decision for surgery has been made, there are important technical considerations to the prophylactic gastrectomy. The most important are the confirmation that both proximal and distal margins are tumor free and confirmation of squamous and duodenal mucosa by intraoperative frozen section (to confirm complete removal of all at-risk gastric mucosa). The operation typically includes regional lymphadenectomy, such as a D1 lymphadenectomy; however, in the absence of clinically identifiable tumor, microscopic foci of gastric cancer have not been shown to metastasize to the lymph nodes in this population. In 2009, Holscher et al<sup>47</sup> evaluated the frequency of lymph node metastases in patients who underwent surgery for T1 gastric cancer. They demonstrated that patients with a tumor infiltrating into the lower one-third of the mucosal layer had a 13% chance of having positive lymph nodes, and those with tumors infiltrating into the lower one-third of the submucosal layer had a chance as high as 40%. The same issue was also addressed by Hochwald et al,<sup>48</sup> who showed that among 168 patients, those with tumors of less than 4.5 cm that involved only the mucosa had a 4% chance of positive nodes, whereas patients with tumors which were larger than 4.5 cm and penetrated to the submucosa had a 56% chance of positive nodes. These data, however, may not apply to the *CDH1* population, as most patients with *CDH1* mutation have only microscopic foci of cancer confined in the superficial lamina propria (pT1a). In our cohort, where the median lymph node count was 18, none of the patients undergoing prophylactic gastrectomy had a positive lymph node. As per current international consortium guidelines, there is no need for a radical lymph node dissection with prophylactic gastrectomy, as mucosal adenocarcinoma without submucosal invasion has a very low risk indeed of lymph node metastases.<sup>11</sup>

Another technical consideration in prophylactic gastrectomy is the surgical approach: minimally invasive versus open. The majority of these patients are considering surgery in the semi-elective setting, and many are interested in the minimally invasive approach. Given recent advances and well-described randomized, prospective studies that have demonstrated advantages to the minimally invasive approach and its oncologic adequacy,<sup>49–51</sup> this approach is a viable option for surgeons with advanced training in the minimally invasive approach. We have previously demonstrated that laparoscopic subtotal gastrectomy for adenocarcinoma is similar to the open approach with regard to oncologic outcomes, with equivalent margin status and adequate lymph node retrieval.<sup>30</sup> In our previous study, the median operative time was slightly longer with the laparoscopic approach, but the length of stay, postoperative pain, and late complications were lower in these cases. Usui et al<sup>52</sup> have reported similar findings, with a shorter time for return of bowel function and oral intake and shorter length of stay. These findings make the laparoscopic approach attractive for patients with a *CDH1* mutation who wish to pursue prophylactic total gastrectomy.

The last technical question is the method of reconstruction after total gastrectomy. We have conventionally performed Roux-en-Y esophagojejunostomy; however, some reports have suggested that creation of an intestinal pouch yields similar perioperative outcomes with fewer symptoms of dumping and heartburn and some improvement in health-related QOL.<sup>53</sup> The optimal method of reconstruction has not yet been fully determined, and is usually selected as a matter of individual surgeon preference.

QOL following gastric resection has been formally examined in prior studies, the largest of which have assessed QOL from 6 months to 5 years following gastrectomy.<sup>54–57</sup> These studies found some aspects of QOL to be impaired after gastrectomy, largely dependent on extent of gastric resection. Two recent studies prospectively assessed QOL in patients before and after gastrectomy for cancer using the EORTC QOL modules. Kobayashi et al<sup>58</sup> reported results from 98 patients 1 year after gastrectomy. The authors concluded that QOL worsened in the immediate postoperative

period, but approached baseline by approximately 6 months following operation. The majority of procedures in this study were distal gastrectomies, with only 8 patients undergoing total gastrectomy, so the authors were unable to make strong conclusions regarding the impact of extent of resection on QOL. In another study, Avery et al<sup>59</sup> followed 58 patients who underwent total or subtotal gastrectomy for 2 years finding an initial decline in QOL that mostly returned to baseline by 6 months following operation. Similarly, in our analysis, patients experienced the majority of weight loss within 6 to 12 months after total gastrectomy and, for most, weight patterns stabilized and/or improved after that time. Although we did not measure formal validated QOL parameters, our postoperative questionnaire demonstrated that after operation, most patients noted several differences in the way they eat (ie, number of meals, symptoms such as cramping or diarrhea), but 85% of respondents noted that their outcome was “as expected” or “better than expected” compared with their expectations before surgery. These results are concordant with larger-scale assessments made for patients undergoing total gastrectomy for cancer indications (ie, not for *CDH1* mutation).

We recommend that patients being considered for prophylactic total gastrectomy because of germline *CDH1* mutation undergo evaluation by a multidisciplinary team experienced with genetic screening, nutrition, psychosocial support, and gastric surgery to ensure a safe and oncologically sound outcome. There are real and durable changes after total gastrectomy, but this study demonstrates that most changes in weight occur during the first 6 to 12 months, then stabilize or improve thereafter. Patients can expect to maintain a normal or above normal BMI after surgery, and the majority of patients report expected or higher-than expected outcomes after operation.

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