The Impact of Prophylactic Total Gastrectomy on Health-Related Quality of Life

A Prospective Cohort Study

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Background: The advice to individuals with identified CDH1 mutations is generally to undertake prophylactic total gastrectomy (PTG). This study evaluated the effect of PTG on health-related quality of life (HRQL) in asymptomatic individuals with identified CDH1 mutations at high risk for gastric cancer.

Methods: Individuals with hereditary diffuse gastric cancer (HDGC) were recruited to a prospective, multicenter UK study. Questionnaires, including the European Organization for Research and Treatment for Cancer core Quality-of-Life Questionnaire (EORTC QLQ C30); the gastric cancer specific module (EORTC QLQ STO22); and the 36-item short form health survey version 2.0, were completed before and at regular intervals after surgery.

Results: Sixty individuals fulfilled HDGC criteria; 38 (63%) had a CDH1 mutation and 32 (53%) underwent PTG. At baseline, there was no significant difference in mental health depending on CDH1 mutation status and treatment preference. Physical functioning reduced in the first month after surgery but recovered to baseline by 12 months. Similarly mental functioning reduced in the first month after surgery but recovered by 3 to 9 months. However, specific symptoms were identified, such as diarrhoea (70%), fatigue (63%), discomfort when eating (81%), reflux (63%), eating restrictions (45%), and body image (44%), which persisted after PTG.

Conclusions: Patients contemplating prophylactic gastrectomy can be reassured about the long-term HRQL outcomes, but some residual symptoms require adjustment.

Keywords: e-cadherin, health-related quality of life, hereditary diffuse gastric cancer

(*Ann Surg* 2014;260:87–93)

Gastric cancer accounts for approximately 9.7% of cancer deaths worldwide, estimated as the second most common cause of cancer mortality.[1] One percent to 3% of gastric cancers arise from a hereditary predisposition syndrome,[2–4] for example, hereditary diffuse gastric cancer (HDGC). The criteria used for a family to be diagnosed with HDGC are[5]

(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 years, or
(2) 3 or more cases of documented diffuse gastric cancer in first- or second-degree relatives, independent of age of onset.

And a broader inclusion of

(3) individuals with diffuse gastric cancer before the age of 40 years without a family history, and
(4) individuals and families with diagnoses of both diffuse gastric cancer (including 1 patient younger than 50 years) and lobular breast cancer.

Genetic testing is recommended on germline DNA from affected individuals with a strong family history of diffuse gastric cancer,[5,6] with 25% to 30% estimated to have a germline truncating mutation in the tumour suppressor gene E-cadherin (CDH1).[7–11] Owing to the high penetrance for gastric cancer, estimated at 80%,[8,12] clinical silence of the disease in early stages[13] and early age of onset,[14] identification of this mutation leads to referral to a multidisciplinary team.[15] Taking into account the age, fitness, and preferences of the individual, the advice is generally to undertake prophylactic total gastrectomy (PTG) rather than the alternative of annual endoscopic surveillance.[10,16–22]

The effect of PTG on the health-related quality of life (HRQL) of healthy individuals is largely undocumented, although recovery of cancer patients from therapeutic gastrectomy leads to significant comorbidity of up to 100% including diarrhoea, dumping syndrome, and loss of approximately 10% to 20% of original body weight.[23–25] Observation of the effects of PTG on HRQL will allow greater insight into the consequences of gastrectomy, and the information may be used to inform patients and aid decision making. The physiological consequences of gastrectomy may also help to inform clinicians and further understanding of the function of the stomach. With advances in cancer genetics, it is likely that germline mutations responsible for HDGC-in CDH1-negative individuals and mutations for familial intestinal type gastric cancer syndromes will be identified and hence decisions concerning prophylactic gastrectomy will become increasingly important beyond CDH1 mutation carriers.

This prospective, multicentre study aimed to assess the impact of PTG by quantifying the physical and mental effects on asymptomatic individuals harboring CDH1 mutations.

METHODS

Study Design

A prospective, multicenter UK study was performed in individuals fulfilling HDGC criteria. The study was originally approved by the Anglia and Oxford Medical Research Ethics Committee (Rec. number 97/5/32) and any amendments approved by the Cambridgeshire Research Ethics Committee. All individuals who

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Disclosure: The authors have nothing to declare. The research was supported by a Cancer Research UK grant to Carlos Caldas and Medical Research Council Programmatic funding to Rebecca Fitzgerald. Elizabeth Worster was an undergraduate summer student working with Rebecca Fitzgerald. Infrastructure support is received from the National Institute for Health Research (NIHR)–funded Biomedical Research Centre and the Cambridge Experimental Medicine Centre.

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ISSN: 0003-4932/14/26001-0087
DOI: 10.1097/SLA.0000000000000446

underwent genetic testing, and were notified to our group, completed HRQL assessments regardless of their clinical course (CDH1 negative, CDH1 positive opting for surveillance and CDH1 positive opting for surgery). Patients who underwent PTG between 2003 and 2011 and gave informed consent were followed up at 1, 3, and 12 months postsurgery and annually thereafter where written informed consent was given. Those who tested negative were assessed postgenetic testing and those having endoscopic surveillance were followed up annually, but insufficient patients in this group participated in the HRQL study.

Surgery was undertaken in 4 UK high-volume esophagogastric centers. All vagal sparing PTG's were performed in 1 center by a single surgeon. All patients had a standard total gastrectomy with stapled esophagojejunal anastomosis and Roux-en-Y reconstruction.

HRQL Assessment

Patients were asked to complete the EORTC QLQ C30, the EORTC QLQ STO22, and the 36-item short form health survey version 2.0 (SF-36v2). The EORTC QLQ C30 is a generic cancer tool that is widely validated[26] and was used here in line with previous research into HRQL of therapeutic gastrectomy patients. It is a 30-question questionnaire, with 5 functional scales: physical, role, emotional, cognitive, and social functioning. It also has 3 symptom scales (fatigue, nausea and vomiting, and pain) as well as 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) and assessment of global health status.

The EORTC disease-specific module for gastric cancer (EORTC QLQ STO22)[27,28] is aimed specifically at gastrectomy patients and addresses additional factors such as eating restrictions, dysphagia, stomach pain, reflux, and anxiety.[29]

In the EORTC questionnaires, the response categories range from *not at all*, *a little*, *quite a bit*, and *very much* and are scored 1 to 4, respectively. The global health scale has 7 response options ranging from *very poor* to *excellent*.

The short form (SF-36v2) is a generic tool,[30,31] which was used because the patients in this study are asymptomatic. The SF-36v2 has 2 summary measures: physical health, which includes physical functioning, role-physical, bodily pain, and general health, and mental health, which includes vitality, social functioning, mental health, and role-emotional. Role-physical and role-emotional encompass the effect of physical and emotional state on daily functioning, such as limitations in participating in working or social activities. The SF-36v2 has a range of response options, with the majority being 5-point scales ranging from, for example, "all of the time" to "none of the time." There is also a range of negatively and positively scored questions, meaning that higher scores correspond to lower or higher HRQL, respectively.

All questionnaires were sent by post and completed at home by the patients. If a patient did not return a questionnaire they were reminded approximately 2 months later, and if there was still no return they were marked as having not responded. They were still followed up a year after that. All patients were included in the analysis and any missing time points were excluded.

A research nurse based in Cambridge collected all questionnaire responses from patients across the United Kingdom as well as clinical information involving age, sex, weight, and any postoperative complications and medications required. Individual body mass index (BMI) was calculated and all data were stored in a customized dataase.

Statistical Analysis

The analysis included all responses to present from the 3 questionnaires individually and any missing data were excluded from analysis. All responses were linearly transformed to a 0 to 100 scale, whereby a score of 100 represents the highest HRQL and 0 represents the lowest, and then grouped into categories, according to the developers instructions for both the EORTC and SF-36v2.[31,32] The mean, median, and standard deviation for all scales were calculated for all time points and compared using an analysis of variance Kruskal-Wallis test and Dunn's multiple comparison post hoc test. The mean change in BMI was calculated, and weight loss was plotted against preoperation weight to determine any correlation.

All analyses were performed using SPSS or Graphpad Prism, with the majority of transformations of data performed in SPSS (SPSS Inc, Chicago, IL). The significance level for all statistical tests was set to $P < 0.05$.

RESULTS

Patients

Of 60 individuals fulfilling HDGC criteria, 38 (63%) tested positive for a germline CDH1 gene mutation of pathogenic significance. Of those who tested positive, 32 (84%) undertook PTG between 2003 and 2011 and half of these (15, 47%) had vagal-sparing surgery. The median follow-up time of this cohort was 2 years. Among these 32 patients, 28 had data available describing the pathological results following examination of the entire gastrectomy specimen and of these 27 patients had signet ring cells identified. A baseline comparison was made for the mental health scores on the SF-36v2 and EORTC QLQ C30 between those who tested positive for the CDH1 gene mutation, both those who undertook surgery or surveillance and those individuals in mutation-positive families who tested negative. The results displayed in Figure 1 show no significant difference between the groups in mental health scores found using the EORTC QLQ C30 ($P = 0.93$) and SF-36v2 ($P = 0.89$). The SF-36v2 scores correspond to "normal" population scores, suggesting that individuals are not significantly affected by results of genetic testing.

Because insufficient patients with CDH1 mutation undergoing surveillance responded to the questionnaires to enable a meaningful analysis, we focus on those CDH1-positive patients opting for PTG. The male-to-female ratio of patients undergoing surgery was 15:17 and they had a median age of 35, ranging from 16 to 64. We generally recommend PTG for patients older than 20 years who can give informed consent.[5] In our study, the patient aged 16 is an exceptional case, but we did find signet ring cancer cells after PTG. There were no postoperative deaths, but there was 1 anastomotic leak requiring reoperation and a bleed managed conservatively. Two related patients have had unexplained seizures, and 2 have required simple endoscopic balloon dilatation for anastomotic strictures. One patient has developed adhesions (Table 1).

Physical Functioning

For PTG patients, weight-loss-over-time and physical-functioning scores from both questionnaires are depicted in Figure 2. After surgery, there was a significant reduction in median and mean weight over time ($P = 0.04$), corresponding to a loss of approximately 18% of the starting weight, or a mean BMI loss of 3.77 (Figs. 2A, B).

Results of the SF-36v2 and the EORTC QLQ C30 regarding physical functioning demonstrated a drop in scores at 1 month postsurgery with difficulties with tasks such as carrying bags, taking long walks, and eating. However, these scores recovered by 12 months to a level that is not significantly different from presurgery levels (EORTC: $P > 0.05$, SF-36v2: $P > 0.05$), (Figs. 2C, D).

Mental and Emotional Functioning

After a significant drop in scores at 1-month postsurgery, mental functioning recovered faster (3–9 months) than physical

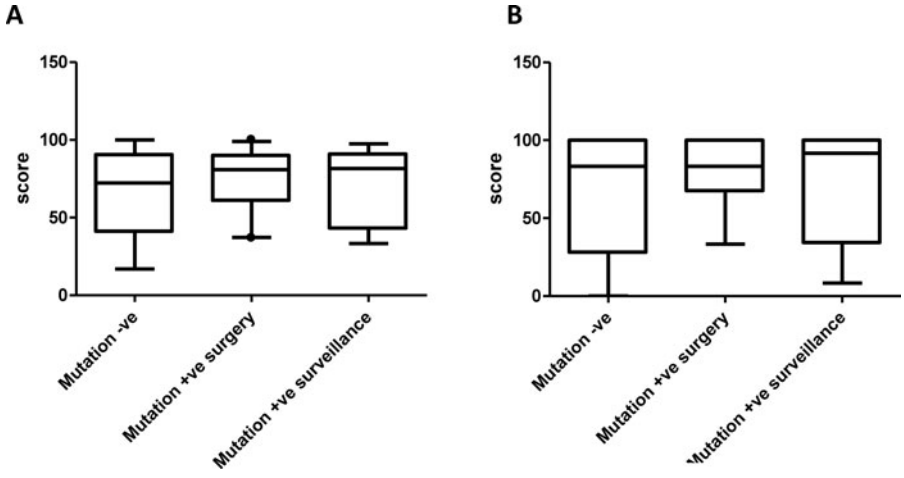

FIGURE 1. Comparison between mental health baseline scores of those with different outcomes of genetic testing and posttesting decisions: Mutation negative (n = 22), mutation positive opting for surveillance (n = 6) and mutation positive opting for surgery (n = 32). (A) Mental health summary measure from SF-36v2. (B) Emotional functioning scale from the EORTC QLQ C30.

functioning (12 months) according to the SF-36v2 (Fig. 3), whereas the EORTC does not have an overall assessment of mental health.

The emotional functioning scale measured by EORTC reveals no significant difference between presurgery scores and any time point postsurgery ($P = 0.51$).

Individual Symptoms

The mean and standard deviations for all the scales of the EORTC QLQ C30 are displayed in Table 2, which shows the effect of total gastrectomy on daily functioning, both physical and mental. All scales are either recovered by 12 months or are unaffected by surgery.

There are also individual symptoms, which do not show this pattern of recovery from both the EORTC QLQ C30 (2 of 9) and its extension, the STO22 (4 of 9 items) (Table 2). Many of these are components of dumping syndrome, which is commonly observed in therapeutic gastrectomy patients. Diarrhoea, an aspect of dumping syndrome, is one such symptom, which is not significantly different from presurgery levels up to 12 months postsurgery but then increases to a degree which is statistically significant (24 months: $P < 0.05$). Fatigue, reflux, and pain, referring to discomfort when eating, are also all symptoms of dumping syndrome that are not fully recovered, remaining at significantly higher levels than presurgery for all time points postsurgery. Extending beyond dumping syndrome, eating restrictions, and body image are identified by the STO22 as not fully recovering. The proportion of patients with persistent symptoms was 70% for diarrhoea, 63% for fatigue, 81% for discomfort when eating, 63% for reflux, 45% for eating restrictions, and 44% for body image.

There is no significant difference in recovery between men and women and no significant difference according to patient age at any time point revealed by any of the questionnaires.

Correlation Between Physical and Mental Functioning

There was strong correlation between mental and physical functioning as assessed by the SF-36v2 a Spearman *r* value of 0.85 (Fig. 4).

DISCUSSION

This prospective study demonstrates that the mental health of individuals is not significantly different at baseline between those who have positive or negative testing for CDH1 mutations or for those who opt for surgery or surveillance, suggesting that knowledge of mutation does not have a significant effect on mental health. Prophylactic gastrectomy initially causes significant morbidity in terms of physical and mental well-being but, in most cases, this is recovered by around 1 year postsurgery. Overall mental health is recovered faster than physical health after PTG and there is a strong positive correlation between the two. However, it should be noted that although the overall scales of global quality of life suggest full recovery, there remain some specific aspects of both physical and mental health, including symptoms of dumping syndrome, eating restrictions, and body image that have a delayed onset of recovery or are not recovered. The full effect of these symptoms on overall quality of life is not evident from the questionnaires and further investigation with qualitative methods may further clarify patients' experience after gastrectomy.

Unlike previous studies in symptomatic gastric cancer patients,[23,33–35] this study focuses on prophylactic surgery and thus allows insight into the effect of gastrectomy on healthy or asymptomatic individuals. It is the first quantitative, in-depth assessment of the physical and psychological effects of this type of surgery on asymptomatic individuals and reveals the time taken and correlation between physical and mental recovery. This extends findings in other studies, which have a larger focus on clinical symptoms such as weight loss and the symptoms of dumping syndrome.[12,24,36] The time taken for most recovery of physical health, approximately 1 year later, supports impressions gained by clinicians after PTG[5] and observations of recovery of gastric cancer patients.[37]

Many of the specific morbidities identified also support previous findings from curative gastrectomy in cancer patients. Eating restrictions are often observed but patients are able to eat normally with smaller and more frequent meals.[12,24,33,38] The significant increase in diarrhoea and symptoms of dumping syndrome, are long identified issues with gastrectomy patients,[12,24,34,39] as is the level of fatigue and abdominal pain.[34] Although it varies,[12,23] the loss of around 18% of the original weight is also previously observed[12,23,24,39] and is thought to be associated with increased diarrhoea[23] and change in eating pattern.[38] However, previous studies have suggested that weight loss stabilizes more quickly than is indicated here.[35,40] Patients are given dietetic advice before surgery and postoperatively both as an in-patient and then telephone follow-up once discharged. Overall, physical recovery appears to be similar to that observed in previous studies of cancer patients as well as asymptomatic patients.[41]

In contrast, recovery of mental health is less comparable, as those having curative gastrectomy often have lower mental health scores at the time of surgery,[40] which increases afterwards with the hope of being cured.[42,43] PTG patients in comparison are asymptomatic beforehand, remain at risk of other cancers, and must implement several long-term lifestyle changes[12,24,33,38] each of which may

TABLE 1. Summary of the Study Participants

Patient	Age at Surgery	Sex	Year of Diagnosis	Year of Surgery	Hospital	Vagal Sparing	Years of Follow-up	Mutation Type	Any Complications
ST001V.404	24	F	2006	2009	B	No	0.25	Exon6 (c.832G>A)	—
ST001V.405	22	M	2008	2009	C	No	2	Exon6 (c.832G>A)	—
ST001V.418	27	M	2007	2008	A	Yes	2	Exon6 (c.832G>A)	Postoperation bleed 9 units
ST035P.304	64	M	2002	2003	D	No	8	Exon1 (45^46ins T)	—
ST035P.402	29	F	2003	2004	E	No	5	Exon1 (45^46ins T)	Seizures—9/12 post.
ST035P.403	35	M	2006	2005	D	Yes	6	Exon1 (45^46ins T)	Seizures—10/12 post.
ST035P.404	37	M	2005	2009	A	Yes	1	Exon1 (45^46ins T)	—
ST098X.309	51	F	2008	2008	A	Yes	2	Deletion 828bp	—
ST122.301	16	F	Not tested	2007	F	No	1	Not tested	—
ST139.406	45	M	2003	2009	G	No	2	Exon10 (1472^1473insA)	—
ST139.408	40	M	Not known	2009	H	No	1	Exon10 (1472^1473insA)	—
ST198.401	36	F	2008	2007	D	No	4	Exon13 1bp deletion (c2100delT)	—
ST243.402	44	F	2006	2007	A	Yes	5	Exon2 c.67c> (p.Gin23X)	Nausea, vomiting, and dumping in first 18/12.
ST287.301	48	M	2004	2005	A	Yes	6	Exon 10 1466-1467insc	Dysphagia 3/12. Endoscopy and dilatation.
ST287.404	23	F	2005	2006	A	Yes	5	Exon 10 1466-1467insc	Dysphagia—6/12. Stricture dilated.
ST298.301	52	M	2003	2003	J	No	8	Exon2 49.2a>g	Dumping/ diarrhoea
ST298.402	26	F	2005	2006	J	No	5	Exon2 49.2a>g	Post operation adhesions.
ST312.401	21	F	2005	2005	K	No	5	Exon2 G>A59(c.59G>A)	Endoscopic dilatation at 5/52 and 3 /12 post.
ST318.308	48	F	2008	2009	A	Yes	2	deletion 828bp	—
ST336.301	23	F	2006	2006	A	Yes	4	Exon5.641T>C	—
ST336.302	20	F	2006	2006	A	Yes	4	Exon5.641T>C	—
ST336.304	36	M	2008	2008	A	No	2	Exon5.641T>C	—
ST348.407	28	F	2008	2009	J	No	0	c1565+2dupT Exon10	
ST348.408	25	F	2008	2009	J	No	2	c1565+2dupT Exon10	
ST349.302	26	F	—	2009	A	Yes	3	No mutation detected	Anastomotic leak, reoperated.
ST349.303	22	M	—	2009	A	Yes	2	No mutation detected	—
ST395.301	32	F	2009	2009	A	Yes	2	Exon7c.1008+2T>G	—
ST395.303	41	M	2010	2011	A	Yes	1	Exon7c.1008+2T>G	—
ST395.305	35	F	2010	2010	L	No	1	Exon7c.1008+2T>G	—
ST398.301	58	M	2009	2009	F	No		c.2154delT(p.Alc719LeufsX3) in Exon 13	—
ST398.409	32	M	Not known	2009	F	No	2	c.2154delT(p.Alc719LeufsX3) in Exon 13	—
ST403.301	42	M	2009	2010	A	Yes	1	c59G>A:p.Trp20X in Exon 2	—

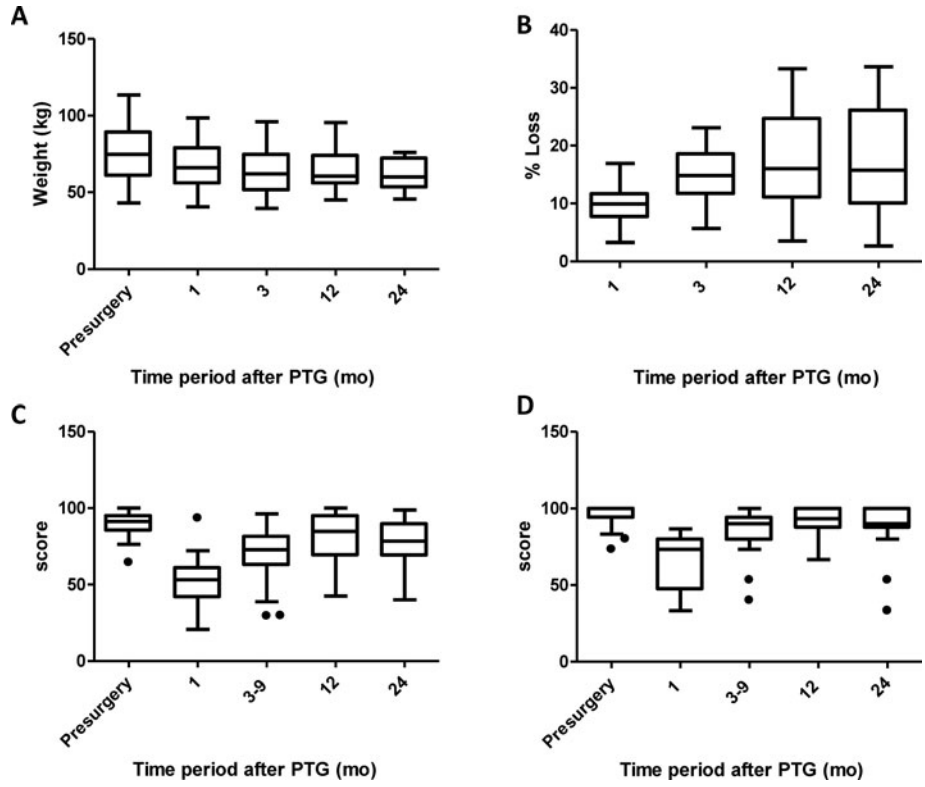

FIGURE 2. Development of weight loss and physical functioning presurgery and over time after total gastrectomy as assessed by the SF-36v2 and the EORTC QLQ C30. A, Weight change. B, Percentage loss of body weight. C, Physical health summary measure from SF-36v2. D, Physical functioning scale from EORTC QLQ C30.

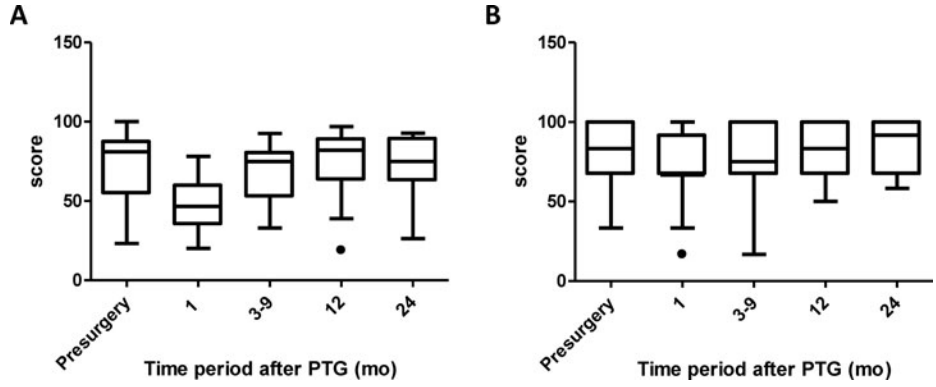

FIGURE 3. Changes in mental functioning after total gastrectomy as assessed by the SF-36v2 and the EORTC QLQ C30 presurgery and over time postgastrectomy. A, Mental health summary measure from SF-36v2. B, Emotional functioning from EORTC QLQ C30.

affect their mental health. Again, a qualitative assessment of their experience before and after surgery would allow for further insight into this recovery.

The number of years of follow-up of patients undergoing PTG means that, although there is the usual drop out of patients over time, there is still substantial data to follow up recovery up to a year after surgery. The use of 3 questionnaires that address similar aspects of physical and mental functioning is another strength of this study, as it allows cross-referencing of our results. Despite different approaches adopted in each questionnaire, they produce corresponding results. The use of the extension STO22 is also a methodological advantage as it complements the other, more general, questionnaires, approaching the effects of gastrectomy specifically and identifying individual symptoms to address. We are currently undertaking qualitative interviews to provide additional information about the impact of PTG on quality of life including perception of body image and effects on relationships, which are not reflected in the questionnaires. We believe that these 2 approaches will be complementary and taken together these data may help to inform the requirements for any more formal psychological counselling, which should be included in the clinical management of patients.

There are several limitations to this study. Because of the rare nature of the syndrome, the number of patients is limited even in data from a national register. The data are not yet at the stage to assess longer term recovery (>5 years) after PTG, which may reveal more negative effects. In addition, there were insufficient patents to carry out a full comparison over time of the HRQL between those who opted for surveillance and those who undertook PTG.

Therefore, as this is an ongoing study, future reflection on patients' long-term development after PTG would be valuable. To

TABLE 2. Scores for All Functional Scales of the EORTC QLQ C30 and Selected Symptoms for the EORTC QLQ C30 and STO22 Extension Before and AFTER SURGERY

			Postsurgery								
	Presurgery		1 mo		3 mo		12 mo		24 mo		
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P**
Functional scales											
Physical	96.09	7.70	66.35	17.95	85.83	14.60	93.33	9.04	86.67	18.54	<0.01
Role	93.55	13.75	50.00	18.90	68.00	23.03	80.77	18.07	77.08	24.25	<0.01
Emotional	79.49	18.66	71.03	22.15	77.56	21.57	83.01	15.00	84.38	16.91	0.51
Cognitive	91.74	12.82	79.37	25.22	80.77	22.94	89.10	14.86	91.67	16.10	0.16
Social	91.23	15.18	55.00	20.30	71.47	22.87	83.33	15.63	76.04	25.80	<0.01
Symptoms (2/9)											
Diarrhoea	5.073	12.75	19.05	22.54	22.44	27.87	23.08	29.47	39.58	36.96	<0.01
Fatigue	10.91	13.31	53.44	21.84	39.10	22.47	29.06	19.14	31.60	18.56	<0.01
STO22 extension symptoms (4/9)											
Pain	1.19	0.30	2.37	0.59	2.03	0.61	1.79	0.53	1.99	0.74	<0.01
Reflux	1.17	0.24	1.94	0.67	1.67	0.62	1.62	0.66	1.73	0.78	<0.01
Eating restrictions	1.21	0.52	2.71	0.66	2.35	0.78	1.97	0.62	1.93	0.75	<0.01
Body Image	1.07	0.23	1.76	0.89	1.92	1.09	1.65	0.77	1.72	0.21	0.02

*The *P* values are for the comparison of the 5 time points at presurgery, 1 month, 3 months, 12 months and 24 months after surgery.

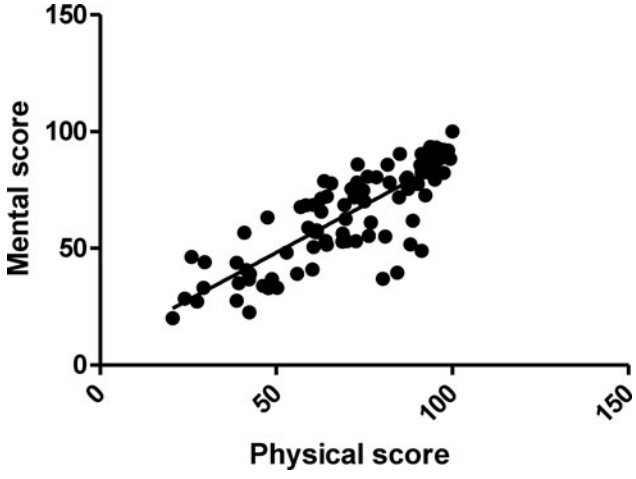

FIGURE 4. Correlation between mental and physical functioning summary measures from the SF-36v2.

further inform those considering PTG, it may also be possible for further follow up of patients who chose to have surveillance and to compare their HRQL with those who had PTG. To do so, additional strategies may need to be implemented, such as more regular reminders and telephone questionnaires, to increase the likelihood of nonsurgery patients returning questionnaires.

This study increases our understanding of the consequences of PTG and will hopefully reassure patients that it can be done safely in specialist high volume centers with acceptable outcomes. Identification of individual symptoms will allow them to be targeted specifically to improve overall HRQL and recovery postsurgery. Challenges remain, however, including life-long follow up of PTG patients and the evaluation of modifications to the surgery such as a laparoscopic approach and small bowel pouch formation. Until there is a breakthrough in gene therapy, surgery will remain the primary treatment for this condition and it is essential that we optimize the quality of life for patients undergoing PTG.

ACKNOWLEDGMENTS

The authors thank Professor Jane Blazeby for her helpful advice throughout the study and for her review of the manuscript. They are grateful to the all patients and clinicians who have contributed data to the Familial Gastric Cancer Registry. E.W., S.R., C.C., and R.C.F. designed and conducted the study. E.W. and X.L. analyzed the results. S.R., R.H.H., and S.D. managed patient recruitment. E.W., X.L., and R.C.F. wrote the manuscript, which was critically reviewed by all authors.

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