A multimodality approach to improve oesophageal and gastric cancer treatment
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OUTCOMES AFTER PROPHYLACTIC GASTRECTOMY FOR HEREDITARY DIFFUSE GASTRIC CANCER

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ABSTRACT

Background
Patients with hereditary diffuse gastric cancer (HDGC) and a CDH1 mutation have a 60–80% lifetime risk of developing diffuse gastric cancer. Total prophylactic gastrectomy eliminates this risk, but is associated with considerable morbidity. The effectiveness (removal of all gastric mucosa) and outcomes of this procedure were evaluated retrospectively.

Methods
All consecutive individuals undergoing a prophylactic gastrectomy for a CDH1 mutation or gastric signet ring cell foci at the authors’ institute between 2005 and 2017 were included.

Results
In 25 of 26 patients, intraoperative frozen-section examination (proximal resection margin) was used to verify complete removal of gastric mucosa. All definitive resection margins were free of gastric mucosa, but only after the proximal margin had been resected in nine patients. In the first year after surgery, five of the 26 patients underwent a relaparotomy for adhesiolysis (2 patients) or jejunostomy-related complications (3 patients). Six patients were readmitted to the hospital within 1 year for nutritional and/or psychosocial support (4 patients) or surgical reintervention (2 patients). Mean weight loss after 1 year was 15% (95% CI 12 to 18). For the 25 patients with a follow-up of 1 year or more, functional complaints were reported more frequently at 1 year than at 3 months after the operation: bile reflux (15 versus 11 patients respectively) and dumping (11 versus 7 patients). The majority of patients who worked or studied before surgery (15 of 19) had returned fully to these activities within 1 year.

Conclusion
The considerable morbidity and functional consequences of gastrectomy should be considered when counselling individuals with an inherited predisposition to diffuse gastric cancer. Intraoperative frozen-section examination is recommended to remove all risk-bearing gastric mucosa.

INTRODUCTION

Gastric cancer arises as a result of an inherited predisposition syndrome in 1–3% of the patients.1–3 Hereditary diffuse gastric cancer (HDGC) is one of the major familial gastric cancer syndromes. Genetic susceptibility in up to 20% of HDGC families is caused by truncating germline mutations in the CDH1 gene.4 This tumour suppressor gene encodes for E-cadherin, a cell–cell adhesion protein involved in the maintenance of epithelial integrity.4,5 Pathogenic mutations cause mucosal signet ring cell (SRC) growth which, possibly after a dormant period, leads to early-onset diffuse gastric cancer.6,7 Affected individuals have an up to 80% lifetime risk of developing gastric cancer (men: 60–80%; women: 45–70%).6 Affected women also have a 40% lifetime risk of developing lobular breast cancer.1,4 Table 1 provides a summary of the characteristics of HDGC.3,4,8–10

Endoscopic surveillance has a limited ability to detect diffuse gastric cancer at an early, curable stage.11–14 Therefore, in patients with a proven mutation, a total prophylactic gastrectomy is advised early in adult life to remove all risk-bearing gastric mucosa.3 The potential impact of surgery on the psychosocial and physiological wellbeing of these mainly young individuals emphasises the need for comprehensive counselling.6,8,15,16 To allow well informed counselling, the effectiveness of (removal of all gastric mucosa) and clinical outcomes following prophylactic gastrectomy were studied.

METHODS

Individuals who were under surveillance in the authors’ institute and who underwent a prophylactic gastrectomy for HDGC between January 2005 and February 2017 were included in the study. A prophylactic gastrectomy was offered to patients with a proven pathogenic CDH1 mutation, or when mucosal SRC foci were found during endoscopy in individuals participating in an HDGC screening programme.14 Patient characteristics, endoscopic data, surgical details, pathology data and clinical outcomes were collected from written and electronic medical records.

Preoperative investigation
Before surgery, all patients had at least one gastroscopy according to the consensus guideline for HDGC.9 This involves intensive inspection of the gastric mucosa, collecting biopsies from focally suspected lesions and random biopsies from all anatomical regions of the stomach (at least 6 per region): cardia, fundus, corpus, transitional zone and antrum.3 All individuals were discussed and counselled by a specialised multidisciplinary HDGC team.
Outcomes after prophylactic gastrectomy for hereditary diffuse gastric cancer

Chapter 07

Surgery
All patients underwent an open total gastrectomy with standard omentectomy and D1 lymphadenectomy under combined general and thoracic epidural anaesthesia. The oesophagus was resected 2–3 cm above the externally visible gastro-oesophageal junction. After removal of the complete stomach, the specimen was sent to pathology for frozen-section analysis of the proximal resection margin (this routine started after the first patient). When gastric mucosa was present in the frozen section, an additional short segment was resected from the distal oesophagus and also submitted for frozen-section examination. When complete removal of gastric mucosa was confirmed, Roux-en-Y reconstruction was performed. The definitive proximal resection margin – the oesophageal doughnut – was also sent for pathological assessment, but was not analysed by frozen-section examination. At the end of the operation, a jejunostomy was inserted in the proximal jejunum. Enteral feeding (by jejunostomy) started immediately after surgery. When contrast-swallowing X-ray 7 days after surgery showed no signs of anastomotic leakage, oral intake was started.

Pathology
Resection specimens were evaluated using the Swiss roll technique. For the purpose of this study, a dedicated gastrointestinal pathologist blindly reassessed all frozen sections (presence of gastric mucosa) and, if available, duodenal parts of the resection specimens (presence of ectopic gastric mucosa). Frozen sections were compared with the corresponding formalin-fixed paraffin-embedded (FFPE) slides of the frozen section, and the definitive resection margin (doughnut). Postoperative tumour stage was defined according to the seventh edition of the TNM classification.

Follow-up
The standard postoperative follow-up schedule was: every 3 months in the first year, twice in the second year, and once a year from the third year onwards. All patients received close and individualised dietary coaching. It was established whether common functional complaints, such as bile reflux, dumping and signs of pancreatic insufficiency requiring pancreatic enzyme supplementation (steatorrhoea, excessive weight loss), had been reported at 3 months and 1 year after surgery. Complaints were scored as present only when explicitly reported. All weight measurements were collected per patient from the medical records from day 14 after surgery onwards. Whether and when patients returned fully (100%) to work or study was also determined from the medical record.

Statistical analysis
Interobserver agreement between the original (intraoperative) assessment and the reassessment of frozen sections was measured with the \( \kappa \) statistic. Median follow-up was calculated using the Kaplan–Meier method from date of surgery to the last follow-up. Relative weight loss within 2 years after surgery was calculated using a mixed model. On the plot with individual profiles, weight loss over time appeared non-linear; a cubic time effect was therefore entered into the model. Confidence intervals were estimated.
using bootstrapping. Data were analysed using SPSS® version 22.0 for Windows® (IBM, Armonk, New York, USA) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). *P*<0.050 was considered statistically significant.

### RESULTS

In total, 26 patients underwent a prophylactic gastrectomy during the study interval. Their median length of follow-up was 48 (range 3–148) months. Patient characteristics are shown in Table 2. Two women had a history of lobular breast cancer (1 bilateral at age 52 years; 1 unilateral at age 58 years). Five of the 14 women had undergone a (prophylactic) bilateral mastectomy (before or after the gastrectomy). Preoperative endoscopic surveillance revealed mucosal SRC foci in 16 of the 26 patients. Before surgery, 23 patients had a proven pathogenic germline CDH1 mutation. The remaining three patients, all members of a single family, underwent a gastrectomy for SRC foci found during HDGC screening. In this pedigree, a germline mutation in the CTNNA1 gene was identified.²⁹

#### Surgical outcomes

There were no intraoperative complications. Postoperative outcomes are shown in Table 3. Median duration of surgery was 167 (IQR 147–194) min and median blood loss was 260 (150–510) ml. No blood transfusions were needed. During the gastrectomy procedure, one patient underwent a simultaneous unilateral mastectomy (after a previous contralateral mastectomy) and a bilateral oophorectomy (this patient was not included in the operating time and blood loss analyses).

Postoperative complications occurred in eight of the 26 patients, including pneumonia, radiological anastomotic leakage treated with antibiotics, and paralytic ileus in one patient each. Five patients needed a surgical reintervention within 1 year after surgery: two patients required adhesiolysis for an obstructive ileus, and three had a jejunostomy-related complication (torsion/small bowel perforation/ dislocation). One of these patients also required radiological drainage of an intra-abdominal fluid collection. In one patient with substantial weight loss (16% of preoperative bodyweight) 19 months after surgery, a jejunostomy was inserted radiologically; after dislocation, surgery was needed to replace it. In total, six of 25 patients were readmitted within the first year after surgery for nutritional and/or psychosocial support (4 patients) or a surgical reintervention (2 patients).

#### Pathology

SRC foci were found in the resection specimens of 23 of the 26 patients. Most foci were found in the corpus (17 patients) and fundus (9 patients). All patients with preoperative

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**Table 2.**


<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients * (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at operation (years) †</td>
<td>41 (30–53)</td>
</tr>
<tr>
<td>Sex ratio (M : F)</td>
<td>12 : 14</td>
</tr>
<tr>
<td>BMI at operation (kg/m²) †</td>
<td>25 (22–27)</td>
</tr>
<tr>
<td>ASA grade</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>21</td>
</tr>
<tr>
<td>II</td>
<td>5</td>
</tr>
<tr>
<td>Smoker ‡</td>
<td>7</td>
</tr>
<tr>
<td>Alcohol user</td>
<td>18</td>
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<tr>
<td>CCI score</td>
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<tr>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>≥ 3</td>
<td>1</td>
</tr>
<tr>
<td>Preoperatives SRC lesions</td>
<td>16</td>
</tr>
<tr>
<td>Type of mutation</td>
<td></td>
</tr>
<tr>
<td>CDH1 gene §</td>
<td>23</td>
</tr>
<tr>
<td>CTNNA1 gene §</td>
<td>3</td>
</tr>
</tbody>
</table>

* Unless specified otherwise; † values are median (i.q.r.). ‡ 10 pack-years or more. § Pathogenic mutation. CCI, Charlson co-morbidity index (without age factor); SRC, signet ring cell.

SRC foci had SRC foci in the resection specimen. In seven of the ten patients with no preoperative lesions, SRC foci were found in the resection specimen. Small foci of ectopic gastric mucosa were found in the duodenum of four of 23 available resection specimens. Mucosal SRCs were observed in one of these.³² Pathology results are shown in Table 3.

During surgery, the initial frozen-section examination of nine patients showed gastric mucosa in the specimen’s proximal resection margin. In these patients a second frozen-section analysis was done on an additionally resected short oesophageal segment. In total,
34 frozen sections were analysed in 25 patients. The interobserver agreement between the original examination (as performed during surgery) and the blinded reassessment of all 34 frozen sections was excellent ($\kappa = 0.93$, 95% CI 0.79 to 1.00). At reassessment, the result of one frozen section was different from that in the original report: a small focus of gastric mucosa was found in a frozen section that originally had been judged negative (Table 4). All definitive proximal resection margins (doughnuts) were free of gastric mucosa.

The concordance rate was 94% (32 of 34) between the frozen section (as initially assessed during surgery) and its corresponding FFPE slide (as initially assessed by the pathologist); in two of 34 frozen sections, gastric mucosa was found in the corresponding FFPE slides, whereas the frozen section itself showed none. In one of these (as indicated above), the focus of gastric mucosa was missed during initial assessment, but found during reassessment. The other frozen section was truly negative: gastric mucosa appeared only in the corresponding FFPE slide.

### Follow-up

For the 25 patients with a follow-up of 1 year or more, bile reflux, dumping, and the use of pancreatic enzyme supplementation were reported more frequently at 1 year than at 3 months after surgery (respectively: bile reflux, 15 versus 11 patients; complaints of dumping, 11 versus 7; pancreatic enzyme supplementation, 5 versus 2). Table 3 shows the total number of patients in whom these complaints were reported at least once during follow-up. All patients received vitamin B12 supplementation. Of 19 patients who had a job or studied before surgery and were followed up for more than 1 year, the majority (15 patients) had returned fully to work or study within 1 year. One patient had retired; the other three all started working again within 2.5 years.

All patients received postoperative enteral feeding via a nasojejunal tube (1 patient) or a jejunostomy (25), for a median of 65 (IQR 37–106) days. For all, relative weight loss was at its lowest point 1 year after surgery: mean weight loss 15% (95% CI 12 to 18) (Table 3 and Fig. 1).

### Table 3.

#### Postoperative outcomes and pathology results

<table>
<thead>
<tr>
<th>Surgical outcomes</th>
<th>No. of patients <em>(n = 26)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of hospital stay (days) †</strong></td>
<td>11 (9 - 12)</td>
</tr>
<tr>
<td><strong>Time spent in ICU (days) †</strong></td>
<td>1 (1 - 11)</td>
</tr>
<tr>
<td><strong>Hospital readmission</strong></td>
<td></td>
</tr>
<tr>
<td>Within 30 days</td>
<td>3</td>
</tr>
<tr>
<td>Within 1 year</td>
<td>6 of 25 ‡</td>
</tr>
<tr>
<td><strong>Postoperative reintervention ¶</strong></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>5</td>
</tr>
<tr>
<td>Radiological</td>
<td>5</td>
</tr>
<tr>
<td><strong>1-year mortality</strong></td>
<td>0</td>
</tr>
</tbody>
</table>

#### Resection specimen

| SRC foci found | 23 |
| No. of SRC foci per patient † | 6 (2 - 12) |
| pT category | |
| 0 | 3 |
| 1a | 21 |
| 1b | 2 |
| Ectopic gastric mucosa in duodenum | 4 of 23 |
| Resection margin free of gastric mucosa | 26 |
| **Lymph node yield †** | 19 (13 - 22) |

#### Follow-up

| Duration of enteral tube feeding (days) † | 65 (37 - 106) |
| Bile reflux # | 16 |
| Dumping syndrome # | 18 |
| Pancreatic enzyme supplementation # | 6 |
| Weight loss after surgery(%) ‱ | |
| 6 months | 12 (10, 15) |
| 12 months | 15 (12, 18) |
| 18 months | 13 (10, 17) |
| 24 months | 10 (4, 18) |

*Unless specified otherwise, values are † median (i.q.r.) and ‡ mean (95 per cent c.i.). ¶ One patient was followed up for only 3 months and was not taken into account for this variable. # Multiple complications and reinterventions were scored per individual patient. # Reported at least once during median follow-up of 48 months. SRC, signet ring cell.
This study demonstrates the impact of prophylactic gastrectomy in terms of surgical and functional outcomes and can help clinicians with preoperative counselling of individuals with a predisposition for early-onset diffuse gastric cancer.

In general, the patient population with surgical gastric cancer is predominated by older patients with comorbidity who receive extensive surgery (D2 lymphadenectomy), whereas the HDGC population is younger, healthier, and undergoes less extensive surgery (D1 lymphadenectomy). Nevertheless, the complication rates in the HDGC setting are high, considering that surgery is performed in ‘healthy’ individuals. In this study, grade II complications were seen less frequently than in the Dutch therapeutic setting: pulmonary complications 4% (1 of 26) versus 16%; anastomotic leakage 4% (1 of 26) versus 8%. In other prophylactic gastrectomy series21–23 (more than 10 patients), rates of pulmonary complications were 9–15% and anastomotic leakage rates were 7–18%. The number of patients needing a reintervention (5 of 26, 19%) was comparable to that in the therapeutic setting (15%)24 and to other risk-reducing patient series (14–18%)11,21–23.

Jejunostomy-related complications were the main reason for relaparotomy. In this series, the rate of such complications (3 of 26 patients, 12%) is at the top end of rates reported from other series (1–13%)25–30, the confidence interval, however is broad. The surgeons, their experience (no learning curve issues), type of procedure and tubes were the same over the years. Whether or not a feeding jejunostomy should be placed routinely is an ongoing debate in oesophagogastric cancer surgery.29,31,32 In the present series, patients needed their feeding tube for approximately 2 months. The favourable (less weight loss, which adversely affects quality of life) and unfavourable (high reintervention rate) factors associated with a feeding jejunostomy should be taken into full consideration when treating these patients.

The surgical removal of all gastric mucosa is challenging.11,33 In a previous prophylactic gastrectomy series, three of 29 patients required a reintervention because of incomplete removal of gastric mucosa. In the present study, gastric mucosa was found frequently (in 9 of 25 patients) in the frozen section at the proximal resection margin of the specimen, suggesting that a reintervention was prevented in one-third of patients. The good interobserver agreement proves that frozen-section analysis is a reliable method for assessing the presence of gastric mucosa in the proximal resection margin. Following presentation of the initial results at the HDGC consensus meeting in 2014, frozen-section analysis was incorporated in the international guideline8 to minimise the risk of the incomplete removal of all risk-bearing mucosa.
Ectopic gastric mucosa was detected in the resected part of the duodenum in four of 23 patients. The clinical importance of this finding is unclear. Gastric cancer arising in the residual stomach after a subtotal gastrectomy for HDGC has been described, as has gastric cancer arising from ectopic gastric mucosa in the upper oesophagus. Gastric cancer arising from ectopic gastric mucosa in CDH1 mutation carriers has not been described. Clinicians should, however, be aware of the possible presence of ectopic gastric mucosa in the remaining duodenum (and oesophagus), and the accompanying theoretical risk of gastric cancer arising in this mucosa.

Psychological and physiological recovery from a gastrectomy takes approximately 1 year. In the present series, weight loss and complaints of dumping persisted for more than 1 year. Comparable to other HDGC case series, maximum weight loss was 15% at 12 months (other series 18–24%). The predicted mean weight loss after 2 years was still 10% of the starting weight, despite close dietary monitoring. Weight loss appeared to stabilise after 1.5–2 years. Dumping syndrome – a combination of physical symptoms in reaction to the fast arrival of food in the small intestine – is common after total gastrectomy (43–73%), and may not fully recover. In the present series, complaints of dumping still persisted in 11 of 25 patients who had follow-up for 1 year or more after surgery. Furthermore, nutritional and accompanying psychological issues were the reason for hospital readmission in four of 25 patients (16%). These findings delineate the need for close, individualised and multidisciplinary monitoring of the physical and psychological impact of a prophylactic gastrectomy, not only in the immediate postoperative period.

The retrospective nature of this study meant that other common and highly individual postoperative problems, such as specific food intolerances, preferred eating habits and body composition, could not be assessed reliably. In addition, the reported rates of bile reflux and dumping, especially those early in follow-up, might be underestimated because they are overshadowed by other, more obvious, problems during consultation in the outpatient clinic. Prospective research is needed to gain more specific and reliable insight in the patients’ long-term experience.

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REFERENCES