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Pioneering use of genetic analysis for *CDH1* to identify candidates for prophylactic total gastrectomy to prevent hereditary diffuse gastric cancer

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Abstract

Worldwide, gastric cancer results in significant morbidity and mortality. Ten per cent of patients with gastric cancer have a strong family history of the disease. *CDH1* (E-cadherin) has been identified as a key gene whose mutation leads to hereditary diffuse gastric cancer. We overviewed 33 articles with prophylactic total gastrectomy and assessed the outcomes and benefits. Families with mutations in *CDH1* may benefit from early prophylactic total gastrectomy. Dr Mark Duncan has applied his experience as a high-volume gastric cancer surgeon to treat not only individual patients, but several generations of patients within a family. This use of prophylactic total gastrectomy is well tolerated by patients and prevents the future development of gastric cancer.

INTRODUCTION

Worldwide, gastric cancer accounts for 5.6% of all new cancers and 7.7% of all cancer-related deaths, ranking fifth for incidence and fourth for mortality globally.[1] Approximately 10% of all gastric cancers show familial aggregation, and in about 1–3% of cases, gene

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mutations can be detected. Mutations in *CDH1* are associated with hereditary diffuse gastric cancer (HDGC).[2 3]

Identification of a causative genetic driver for HDGC was first reported in 1998 in large kindred from New Zealand, with over 25 family members succumbing to HDGC over a 30-year period.[4] The most frequently implicated gene in HDGC is *CDH1* (E-cadherin), which was discovered by genetic linkage analysis employing microsatellite markers surrounding various portions of the genome. *CDH1* is localised on chromosome 16 (16q22.1). *CDH1* mutations have been identified throughout the gene, including 16 exons and introns. The most common types of mutations are missense mutations, splice site mutations and nonsense mutations.[5] Over 100 unique mutations of the *CDH1* gene have been identified, and it is the genetic driver in 40% of families affected by HDGC.[6]

As a tumour suppressor gene, *CDH1* requires the loss of function of both alleles to initiate the neoplastic process. Promoter hypermethylation, somatic mutation and loss of heterozygosity are the main mechanisms for gene inactivation. E-cadherin is *CDH1*'s gene product (figure 1). E-cadherin is a transmembrane glycoprotein and ubiquitous calcium-dependent cell–cell adhesion molecule in epithelial tissue.[7] E-cadherin protein contains three domains: intracellular cytoplasmic tail, transmembrane domain and extracellular domain, which are important for cell–cell adhesion and signal transduction. E-cadherin production dysregulation promotes tumour initiation through loss of cell adhesion.[8]

In addition, loss of E-cadherin function leads to the activation of oncogenic signalling pathways, such as the Wnt/β-catenin pathway which contributes to the uncontrolled growth and promotes tumourigenesis in HDGC (figure 1). Despite the extensive elucidation of the *CDH1* mutation, the pathological variant that produces cancer has not been identified and there is no explanation why some patients with *CDH1* variant develop HDGC whereas some patients do not.[9] The gene *CTNNA1* is the second most common genetic driver and encodes the protein α-E-cadherin, a *CDH1*-binding partner. Mutations in several other genes have also been associated with HDGC and include *MAP3K6, DOT1L, MSH2, BRCA1, PALB2, RAD51C, MET, CD44, INSR* and *FBXO24*.[10]

GENETIC SCREENING GUIDELINES

The most recent International Gastric Cancer Linkage Consortium (IGCLC) guidelines for the management of HDGC were published in 2020.[11] Genetic testing for mutations in *CDH1* and *CTNNA1* should be pursued in patients from families with any of the following histories: (a) two family members with HDGC diagnosed at any age; (b) one or more family member(s) with HDGC diagnosed at any age and one or more family member(s) with lobular breast cancer (LBC) diagnosed at <70 years of age; or (c) two or more family members with LBC diagnosed at <50 years of age. Furthermore, testing should be offered if an individual is diagnosed with HDGC at <50 years of age, has HDGC and is of Māori ethnicity, has HDGC diagnosed at any age with a personal or family history of cleft lip/palate, has a personal history of HDGC and LBC, each diagnosed at <70 years of age, has bilateral LBC diagnosed at <70 years of age or has gastric in situ signet ring cells identified at <50 years of age.

MANAGEMENT OF *CDH1*-POSITIVE INDIVIDUALS

In a recent review of 75 families, a germline mutation in *CDH1* was found to confer a roughly 42% and 33% lifetime risk of gastric cancer for men and women, respectively. In addition, there is a 55% cumulative incidence of LBC in women and a slightly elevated risk of colorectal cancer compared with the general population with lifetime incidences of 7% in men and 4% in women.[12 13] With increased access to genetic testing in patients with no family history of HDGC or LBC, *CDH1* variants of unknown significance are increasingly common, and these patients are advised to undergo annual to biannual endoscopy with expectant management based on pathological results.[11] Despite evaluating the correlation between gene mutation type and cancer phenotype in a recent study,[14] there is no guideline for classifying cancer risk based on genotype.

The First Workshop of the IGCLC developed guidelines for managing families with known *CDH1* mutations.[3] Prophylactic total gastrectomy (PTG) was proposed as a management option, but only after careful consideration of the morbidity associated with the procedure. Surveillance with endoscopy every 6–12 months was recommended for all individuals, as well as increased screening for breast and colon cancer.

CHALLENGE IN MANAGEMENT

Early foci of cancer in patients with HDGC are characterised by infiltrates of signet ring cells that underline normal-appearing mucosa, since screening endoscopy can only detect occult signet ring cells in up to 61% of patients, with a high false negative rate.[15 16] Surveillance endoscopy is not a trustworthy approach, and gastric cancer onset and progression before diagnosis are inevitable. In addition, 90% or more of those with the *CDH1* mutation have foci of diffuse gastric carcinoma on the specimen after PTG.[17]

Phenotype expression has not been shown to correlate with the type of mutation or its location in the *CDH1* gene. Despite these established mechanisms, an explanation for why some patients with *CDH1* variants will develop HDGC whereas others will not is not clear. Diffuse gastric carcinoma is very aggressive, and outcomes would be worse if the diagnosis were not made at an early stage.

Patients who decline surgical intervention should undergo surveillance endoscopy every 6 months or annually used the Cambridge protocol or something similar with extensive biopsies mapping the entire stomach. Also, individuals with mutations in *CTNNA1* should undergo annual endoscopy and be considered for PTG based on the penetrance of HDGC observed in their family.[18]

PROPHYLACTIC TOTAL GASTRECTOMY

The first use of PTG in asymptomatic individuals based on family pedigree and genetic analysis was described in 2001 in six patients from two separate families.[19] Pathological analysis of specimens confirmed microscopic foci of cancer in all subjects. Similar findings have been observed in other studies, and PTG in *CDH1*-mutant families became more widely adopted.[20 21]

Patients who meet criteria for genetic testing and are found to have a *CDH1* variant should undergo PTG. Surgery should be offered at a young age, preferably <30 years old, to minimise the development of invasive cancer and minimise perioperative morbidity.[21] For families in which a patient developed gastric cancer before age 30 years, PTG is offered sooner. The operative approach for PTG (open vs minimally invasive surgery) is dependent on the experience of the surgeons. It is also recommended to be pursued by a high-volume surgeon at a high-volume centre experienced in total gastrectomy specifically. Many surgeons prefer creation of an intestinal pouch for the oesophagojejunostomy with the belief that it may improve short-term and long-term food intake problems.[22]

ALTERNATIVE TREATMENT

Loss of E-cadherin liberates β-catenin into the cytoplasm and activates the Wnt/β-catenin pathway allowing β-catenin to translocate to the nucleus and promote tumourigenesis. Targeting genetic and epigenic aspects with their expected functional outcome is a promising future approach for treatment for gastric cancer.[23 24]

PTG FOR *CDH1*: WORLDWIDE RESULTS

To date, 33 articles have been published describing the surgical experience with prophylactic gastrectomy. After excluding patients with any positive preoperative endoscopic result on histology for gastric cancer, 299 individual patients were enrolled to assess for true PTG. Most patients came from the USA (142 patients) and Canada (51 patients). European countries accounted for a substantial number: Netherlands: 46, UK: 32, Germany: 8, Portugal: 6, Denmark: 4, Italy: 2. Additional patients came from Argentina: 6, Australia: 1 and Iran: 1 (table 1).[25–54]

Among the 268 patients from 32 articles with postoperative pathological results reported, 208 patients (78%) had T1N0M0, 30 patients (11%) had cancer in situ and 30 patients (11%) were free of tumour. These results demonstrate that, despite the fact that surveillancee can detect cancer in some patients with *CDH1* variants, for long-term surveillance of diffuse gastric cancer in this patient population, it is not adequate. Patients do not require the extended D2 lymphadenectomy used for clinical gastric cancer when total gastrectomy is performed in the prophylactic setting. Not a single nodal metastasis was found in the patients with PTG for *CDH1*. For the 165 patients from 14 articles for whom lymph node dissection was described, from 5 to 58 lymph nodes were resected, and all of them were negative. Considering these findings, and also since mucosal adenocarcinoma without submucosal invasion in patients with gastric cancer detected clinically has a very low risk of nodal metastases, only a D1 dissection which includes perigastric lymph node stations 1–6 is recommended. Surveillance for LBC is recommended with annual MRI from age 30 to 50 years together with annual mammography usually 6 months later, followed by standard-of-care mammography after age 50 years.[11] Prophylactic mastectomy should be considered on a case-by-case basis. Given small increase in risk of colorectal cancer, it is recommended that standard-of-care screening protocols are followed.

PTG has acceptably low morbidity in the hands of experienced surgeons. Among all 299 patients undergoing prophylactic surgery reported, there was only one case of 30-day surgical mortality, occurred in a patient with a history of kidney transplant who developed pneumonia and sepsis.[45] The surgical complications of 248 patients were described in 26 articles which included anastomotic leak (19 patients), dumping (16 patients), pulmonary complications and pneumonia (13 patients), anastomotic stricture (7 patients), surgical site infection (7 patients), intraoperative bleeding (5 patients) and pulmonary thromboembolism (5 patients). Reoperation was reported for six patients among all studies for anastomotic leakage (four cases), intra-abdominal haemorrhage (one case) and abdominal washout (one case).

Weight loss is an expected consequence of gastrectomy. DiBrito *et al* described eight patients with *CDH1* mutation without biopsy-proven HDGC preoperatively who underwent PTG.[50] At 1 year, patients experienced an average weight loss of 18% when compared with their preoperative weight. Forrester *et al* describe a 19-patient series of patients who underwent PTG.[54] They report no postoperative complications and 15 patients followed up long term with a median follow-up of 9 years. Most patients experience ~25% weight loss and ~50% of patients report bile reflux symptoms. In the biggest review study on prophylactic gastrectomy, Vos *et al*[52] found 10–28% weight loss during 1–2 years of follow-up.

CONCLUSION

Although PTG changes a diet, habit, and lifestyle and introduces short-term morbidity, it is ultimately the only method for definitive prevention of gastric cancer and is the preferred treatment for individuals with *CDH1* germline mutations and a family history of HDGC and LBC. In patients with known *CDH1* mutations, HDGC is a preventable condition. The important steps in the management of *CDH1* patients are good interaction between the surgeon and patient, evaluating all aspects of the patient's profile and discussion about outcomes.

FINAL THOUGHTS: PERSONAL STATEMENT OF DR MARK DUNCAN'S QUEST FOR IMPROVED RESULTS FOR STOMACH CANCER

I have spent much of a career chasing cancer. Stomach cancer has a poor prognosis, with less than one-third of patients cured despite therapy. This means many of the patients for whom we perform gastrectomy will still die from the disease. We always aim to catch the disease at an earlier stage, but that is rarely the case. Now, we have identified an at-risk population with a significant chance of getting a lethal cancer which can be difficult to detect even with endoscopic screening. We have a chance to get ahead of the disease. The initial cohorts of *CDH1* patients had up to 70% risk of developing gastric cancer. That estimate has decreased as more people are having genetic testing without having the family history of HDGC or LBC as the earlier cohorts. Still, if the risk of gastric cancer approaches 50%, it seems like too much of a gamble to not intervene. Total gastrectomy is a major undertaking, and when done prophylactically must have acceptably low morbidity and

negligible mortality. A high-volume surgeon in a high-volume setting, however, can prevent gastric cancer in these patients.[55]

One can take the view that we should have a better treatment plan than removing the stomach for everyone at risk—that surgery is too big a hammer if applied to all. This is similar to the notion that surgery is a gross approach to biology, and that perhaps in the future, instead of cutting out tumours, we would have chemotherapeutics or biological agents to modify the biology and nullify the protean manifestations of cancer and diminish the pathophysiological consequences so that cancer becomes a disease we can live with (think prostate cancer in older men, or some lymphomas, or some metastatic neuroendocrine tumours). But at present, we do not have these therapeutics, and evidence is only now emerging as to whether endoscopic screening is reasonable or adequate. If a few patients die from gastric cancer detected a year or years into a surveillance protocol, is that acceptable for a condition that could have been prevented? Of course, it is important to be studying the genetic profile of *CDH1* mutations to identify genetic abnormalities that drive carcinogenesis. If we can more accurately predict risk or biological behaviour for each mutation, we can better inform each patient in decision-making regarding the risks of observation and endoscopic surveillance versus the risks of surgery.

Until we have a better approach, we are left with this dilemma. When one sees a 20-year-old woman with advanced, stage IIIC gastric cancer which is treated with multidisciplinary care with neoadjuvant chemotherapy followed by radical total gastrectomy with intestinal pouch ‘new stomach’ reconstruction, and then adjuvant chemotherapy and radiation, it is hard to offer only surveillance endoscopy to her father, aunt, uncle and cousin who also tested positive for *CDH1*. If a mother has early gastric cancer and a Krukenberg tumour in the ovary, it is again hard to not intervene for her two daughters who tested positive for *CDH1*. In my practice, these families were offered PTG. When a mother and her son in his 20s come from out of state because they found you through the No Stomach for Cancer organisation, and were pleased to finally find a physician and high-volume surgeon who knew more about their disease, specifically *CDH1*, than they did; and the mom briefly had remorse when the pathological review of her stomach after gastrectomy failed to find an early cancer, but this remorse immediately vanished when the typical T1a early cancer was found in her son’s stomach after gastrectomy; when this is the case, it is hard not to think that prophylactic gastrectomy was the right move.

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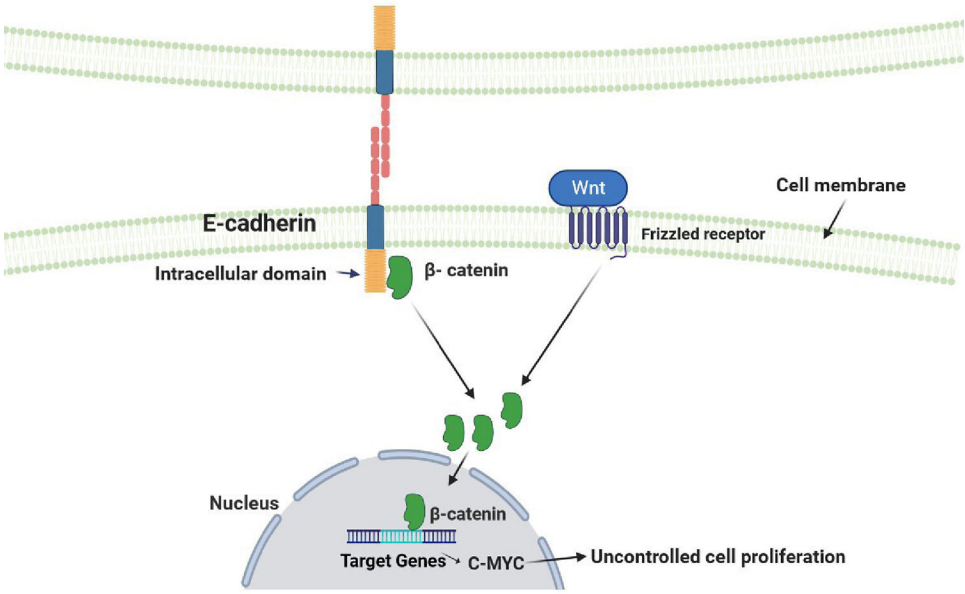

Figure 1.

Role of E-cadherin molecule as cell adhesion molecule and tumour suppressor gene. Mutation of *CDH1* gene results in dysfunction of E-cadherin and release of β-catenin to the cytoplasm. Wnt protein binds to cell surface frizzled receptor and leads to translocation of β-catenin from the cytoplasm to the nucleus. β-catenin promotes transcription of target genes which include C-MYC, an oncogene that promotes cell growth and cell proliferation (created by BioRender.com).

Table 1

Characteristics of the patients with *CDH1* mutation who underwent prophylactic total gastrectomy for hereditary diffuse gastric cancer

Authors (reference)	Patients (f/m)	Age (mean)	Surgical method	LND	Frozen section for margin	Postop weight loss	Mortality	Follow-up
Lewis *et al* (USA)[19]	6 (4/2)	22–40 (50)	O.PTG	N/A	67.00%	13%	0	3–12 months
Huntsman *et al* (Canada)[20]	5 (3/2)	22–40 (31)	PTG	26	100%	N/A	0	N/A
Chun *et al* (USA)[21]	5 (3/2)	37–47 (41)	PTG	7	100%	N/A	0	N/A
Newman and Mulholland (USA)[25]	2 (1/1)	28–35 (31.5)	PTG	N/A	N/A	20–24%	0	6 months
Norton *et al** (USA)[26]	6 (4/2)	51–57 (54)	PTG	24 (18–40)	100%	40 lbs	0	12 months
Francis *et al* (USA)[27]	1 (1/0)	53	PTG	N/A	100%	10–15%	0	12 months
Rogers *et al** (USA)[28]	7 (N/A)	N/A	PTG	N/A	100%	N/A	0	N/A
Hebbard *et al* (Canada)[29]	21 (13/8)	26–63 (45.7)	O.PTG	N/A	96%	N/A	0	3–36 months
Hackenson *et al* (USA)[30]	6 (3/3)	21–51 (38.2)	PTG	5–25 (12)	N/A	N/A	0	N/A
Pandalai *et al* (USA)[31]	9 (4/5)	26–51 (41.7)	O.PTG	12 (6–18)	100%	19%	0	12 months
Nasiri *et al* (Iran)[32]	1 (0/1)	27	PTG	N/A	100%	N/A	0	N/A
Chen *et al** (USA)[33]	11 (7/4)	18–70 (45.3)	O.TG	20–30	N/A	22–31 lbs	0	29 months
Kluijt *et al* (Netherlands)[34]	25 (13/12)	18–65 (35.2)	O.PTG (79%) L.PTG (21%)	N/A	100%	N/A	0	N/A
Onitilo *et al* (USA)[35]	2 (2/0)	26–26 (26)	PTG	2	N/A	N/A	0	1 month
Li *et al* (USA)[36]	2 (2/0)	32–38 (35)	PTG	N/A	100%	N/A	0	35 months
Wickremeratne *et al* (Australia)[37]	1 (1/0)	16	PTG	N/A	100%	N/A	0	18 months
Black *et al* (USA)[38]	1 (1/0)	22	N/A	15	100%	N/A	0	N/A
Bardram *et al* (Denmark)[39]	4 (2/2)	26–52 (40)	O.PTG	12–41 (20)	100%	12–25%	0	7 months
Worster *et al* (UK)[40]	32 (17/15)	16–64 (34.6)	O.PTG	N/A	N/A	18%	0	24 months
Haverkamp *et al* (Netherlands)[41]	11 (8/3)	22–61 (40)	PTG (91%) O.PTG (9%)	10 (1–15)	100%	N/A	0	2 months
Muir *et al* (Canada)[42]	11 (9/2)	23–63 (45.6)	PTG	9–58	100%	37 lbs	0	24 months
Pantelis *et al* (Germany)[43]	8 (5/3)	23–60 (41.6)	O.PTG	N/A	100%	N/A	0	8 months
Shepard *et al* (USA)[44]	1 (1/0)	37	PTG	6	100%	N/A	0	2 months

Authors (reference)	Patients (f/m)	Age (mean)	Surgical method	LND	Frozen section for margin	Postop weight loss	Mortality	Follow-up
Strong *et al** (USA)[45]	41 (27/14)	20–71 (47)	PTG (20%) PTG 20%) PTG (60%)	18 (1–54)	100%	15%	1	16 months
Feroce *et al* (Italy)[46]	2 (2/0)	30–63 (42.5)	N/A	N/A	100%	N/A	0	N/A
van der Kaaij *et al* (Netherlands)[47]	10 (N/A)	30–53 (41)	O.PTG	13–22	100%	15%	0	48 months
Gullo *et al* (Portugal)[48]	6 (4/2)	14–58 (35.6)	N/A	N/A	100%	N/A	0	N/A
Gjyshi *et al* (USA)[49]	2 (1/1)	23–34 (29.6)	N/A	23–30	100%	N/A	0	N/A
DiBrito *et al* (USA)[50]	8 (6/2)	21–60 (40.5)	O.PTG	6–18	50% R0 50% N/A	11%	0	19 months
McGarragle *et al* (Canada)[51]	14 (11/3)	19–63 (45)	N/A	N/A	N/A	N/A	0	N/A
Vos *et al** (USA)[52]	78 (N/A)	18–69 (44)	O.PTG L.PTG	9–34	52%	10–23%	0	6–43 (16) months
Ithurralde-Argerich *et al* (Argentina)[53]	6 (4/2)	17–42 (27)	PTG	N/A	100%	9%	0	28 months
Forrester *et al** (USA)[54]	19 (10/9)	27–71 (37)	PTG	20	100%	23%	0	5–17 years

* Only patients with proven prophylactic gastrectomy with preoperative normal biopsies were included in our analysis. When authors publish multiple reports, duplicate patients are not included in our analysis.

LND, lymph node dissection; L.PTG, laparoscopic PTG; N/A, not applicable; O.PTG, open PTG; O.TG, open total gastrectomy; PTG, prophylactic total gastrectomy.