



## Review Article

# Contemporary paradigm for the evaluation and treatment of hereditary gastric cancer

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**Abstract:** Gastric cancer is the third leading cause of cancer mortality worldwide. Survival is linked to stage at diagnosis and tolerance to surgery and adjuvant therapy. The emergence of sophisticated methods to identify patients at high risk for the development of gastric cancer has given us an opportunity to eliminate a lethal disease in an identifiable patient population. Guidelines and recommendations have been established and prophylactic total gastrectomy is considered the most effective treatment. However, this requires substantial physical and emotional investment. It is imperative that patients and families are supported by genetic counseling, ongoing surveillance, and survivorship studies.

**Keywords:** Hereditary diffuse gastric cancer (HDGC); CDH-1; genetic counseling; quality of life; prophylactic total gastrectomy

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It is a philosophical dilemma whether knowing one's cancer risk makes it easier or more difficult to navigate the complexity of medical decision making (1,2). The emergence of genetic testing of known associations between certain mutations and the development of cancer over one's lifetime is as close to the "crystal ball" analogy as we have, yet understanding one's risk and acting on the information by undergoing more aggressive screening, diagnostic interventions, or preventative surgery can contribute to physical and psychological stressors that are not easily addressed in an outpatient clinic setting (3). Survivorship programs for patients undergoing prophylactic bilateral mastectomy for BRCA1–2 mutations, early and acute menopausal symptoms after, or bowel issues after familial adenomatous polyposis (FAP) have attempted to address the unique issues that are involved in making the decision to undergo prophylactic intervention and recovering from surgery short and long term (4–6). A paucity of programs targeting familial gastric cancer puts survivorship issues well behind what is required to address the particular needs of

this patient population.

Gastric cancer is the third leading cause of cancer mortality worldwide and survival after diagnosis is low (7–9). Most patients continue to present with locally advanced disease where long term survival is linked to the patient's ability to tolerate both surgery and adjuvant therapy (10–12). The morbidity of the surgery directly impacts their ability to tolerate adjuvant chemotherapy (13), contributing to both the quality and the quantity of life (14). Therefore, the ability to identify patients at highest risk would allow for prophylactic intervention with the goal of eliminating this as a life limiting possibility. With the identification of germline e-Cadherin mutations as a strong risk factor for diffuse gastric cancer, we are obligated to establish the infrastructure for surveillance and genetic counseling that address the unique needs of this subset of patients (15,16).

## Diagnosis

Guidelines to diagnose gastric cancer are well established,

but less relevant to familial gastric cancer (17). In most cases of gastric cancer, patients present with upper gastrointestinal symptoms of early satiety, pain, and/or anemia associated with bleeding (18,19). This prompts an upper endoscopy (20). Biopsies are taken of any abnormality as well as the background stomach. Four quadrant sampling of a gastric ulcer, cold forceps biopsy of a mucosal mass, and random biopsies of the background stomach to look for H Pylori infection are all used to increase the likelihood of getting an accurate diagnosis without the need for additional intervention. The major problem with this current diagnostic paradigm is that the diagnosis is made after symptoms have developed, the cancer is more advanced, and few patients survive long-term (21,22).

With a better understanding of germline mutations associated with the development of cancer we are given the foresight to identify vulnerable patients, provide intervention prior to the development of cancer and break the cycle of premature death for families at risk (23). The objective of this project is to review the unique aspects of the diagnosis, surveillance, management, and survivorship in hereditary gastric cancer.

### Hereditary gastric cancer

Independent of epidemiologic trends is a population of patients with hereditary gastric cancer syndromes (24,25). Recent improvement in molecular genetics has refined our understanding of the mutations causing hereditary gastric cancer (26). Since these patients are most often asymptomatic, guidelines for surveillance, indications for intervention, and long-term quality of life studies are in the medical literature (27). To date, the main gene implicated in hereditary diffuse gastric cancer (HDGC) syndrome is CDH-1 (27). This encodes E-cadherin, a protein that is integral to cell-cell adhesions and has been implicated in other cancer subtypes, like colorectal cancer (28). The International Gastric Cancer Linkage Consortium (IGL) developed diagnostic criteria for HDGC that includes at least two cases of cancer in first- or second- degree relatives, one of which is prior to the age 50, three documented cases of gastric cancer regardless of age, diffuse gastric cancer in individuals under 40, or individuals with gastric cancer and lobular breast cancer in which one cancer is diagnosed under the age of 50. The presence of bilateral lobular breast cancer may also justify CDH-1 testing. HDGC represents 1–2% of all gastric cancer with 37% associated with a mutation in CDH-1 (29-32).

### Genetic counseling

Genetic counseling is an important component in the management of families with a probable inheritable risk of any cancer (33). For many families, the knowledge of linkage between their “genetics” and cancer(s) that have taken the lives of loved ones is bittersweet. The reaction to the realization that cancer is likely to occur in them and/or another family member in a particular timeframe can lead to several emotions, including anger, helplessness, sadness, anxiety, and fear (34). The role of the genetic counselor is central to both an understanding of the risk and to establishing relationships between effected family members and medical professionals who will help navigate them through years of intervention and surveillance (35). These relationships, when they work well, become the foundation of survivorship.

Patients surveyed on their confidence in endoscopic surveillance prior to prophylactic gastrectomy, reported a moderate to high level of confidence that if they continued to be followed closely, it would increase the chances of finding cancer at an earlier and curable stage (36). This is contrary to the established evidence of the impact of endoscopic surveillance in the setting of HDGC (37,38).

There are two unresolved issues with respect to counseling and management of patients with a familial predisposition to gastric cancer:

- (I). How do we manage families who meet criteria for HDGC, but do not harbor a CDH-1 mutation or have variant mutations that are of unclear clinical significance? The current recommendation is ongoing endoscopic surveillance.
- (II). How do we counsel families that harbor the CDH-1 mutation, but have no established gastric or lobular breast cancer in their family history? These mutations are most commonly picked up in multigene panels evaluating a broader cancer risk, mostly in the context of breast cancer risk (39,40). There are currently no established guidelines for this patient population.

### Screening and surveillance

Annual endoscopy is recommended in all patients with a documented CDH-1 mutation despite the low likelihood of small cancers being discovered by random biopsies of otherwise normal looking mucosa (41,42). Chemo endoscopy using the application of 0.4% indigo carmine dye

to enhance contrast and help locate possible lesions was not associated with an improvement in detection of subclinical cancers in patients with CDH-1 mutations (43,44). On the other hand, it is extremely common to find multifocal intramucosal signet ring cell cancer within the gastric specimen after prophylactic gastrectomy further calling into question the “value” of routine endoscopic surveillance in an era of cost containment in healthcare (45,46). As unsettling as this finding is for a young patient, the natural history of what are most often T1N0 tumors suggests that it is rare to develop tumor recurrence or metastases.

### Lobular breast cancer

Guidelines for the screening and surveillance of breast cancer are rooted in the BRCA1/2 families and mammograms +/- breast MRI depending on the density of the breast tissue in younger women (47). In contrast to invasive ductal carcinoma that arises in the setting of BRCA1/2 carriers, the invasive lobular carcinoma associated with the loss of e-cadherin in CDH-1 deficient families is more difficult to pick up on mammograms (15,48-50). The tumor cells grow in sheets and cords and are less likely to form a mass or have associated calcifications (49). The current recommendation for screening and surveillance of female CDH-1 mutation carriers is bilateral breast MRI beginning at 30 (51). The potential value of bilateral prophylactic mastectomy has not been established and therefore no guideline or recommendation currently exists (4). An established relationship with a breast oncologist or breast surgeon is important to provide comprehensive annual breast examinations, routine discussions on breast awareness, and adequate interpretation of breast imaging over what is often years of follow-up on a case by case basis (52,53).

### Prophylactic gastrectomy for hereditary gastric cancer

The cumulative risk for diffuse gastric cancer in CDH-1 mutation carriers is approximately 67% for men and 83% for women, and in women there is a 42% risk of lobular breast cancer (41). Given this high life-time risk of developing gastric cancer combined with the high mortality associated with established gastric cancer and the lack of effective screening, 2016 guidelines issued by the international gastric cancer linkage consortium recommended that individuals over the age of 20 who

harbor the CDH-1 mutation undergo prophylactic total gastrectomy (54). The NCCN guidelines recommend consideration of surgery in affected patients between 18–40 taking into consideration the age(s) of family members who have been treated for gastric cancer (54). Taking age at diagnosis into consideration, a conservative recommendation is to discuss prophylactic gastrectomy 5 years earlier than the youngest cancer diagnosis within the family.

The major shift toward recommending early and prophylactic gastrectomy is born out of the following realities:

- (I). HDGC that is diagnosed in the context of symptoms is rarely cured.
- (II). If gastrectomy is performed in CDH-1 patients over the age of 40, there is only a 10% chance of cure.
- (III). Preoperative endoscopies are insufficient to find indolent cancers in HDGC patients. In gastrectomy specimens, done in the prophylactic setting, 27% had evidence of diffuse cancer despite a negative surveillance endoscopy.

Since patients are often asymptomatic, the decision to undergo total gastrectomy is difficult. Total gastrectomy, even when performed in younger and healthier patients, is associated with a moderate risk of perioperative morbidity as well as long term behavior and dietary modification to minimize post gastrectomy symptoms of diarrhea, dumping syndrome, weight loss, dysphagia, and reflux (46,55). For this reason, it is important for multidisciplinary gastric cancer programs to develop the infrastructure to address the broader needs of this patient population as they navigate the decision-making process, treatment, and survivorship.

### Quality of life considerations after total gastrectomy

With the introduction of prophylactic surgery for familial cancer syndromes, there is increasing attention on the long-term sequelae of preventative surgery, including quality of life studies that cover both the physical and psychosocial outcomes for patients after total gastrectomy. Patients considering gastrectomy should be given educational materials that will put the short term and long-term quality of life issues in perspective, namely:

- (I). Global quality of life scores, measured on the EORTC-QLQ-C30, declined immediately post-surgery and returned to baseline by 12 months in

most patients (56). The majority of issues describe by patients were included in the established post gastrectomy guidelines and included the dietary and behavior modifications recommended to minimize intestinal symptoms (51).

- (II). Quality of life scores declined again at 24 months and the issues that patients encounter are less likely to be addressed within the context of an outpatient oncology clinic and are often put onto the shoulders of community based primary medical doctors. At 24-months, most patients reported 2–3 single item symptoms including insomnia, appetite loss, dyspnea, and diarrhea (38%) (56). Gastrectomy related symptoms experienced by patients 2 years after surgery included eating restrictions, pain with eating, reflux, dysphagia, and dry mouth (56). With this information at hand, multi-provider gastric programs should include survivorship programs that set short term and longer-term expectations preoperatively, develop the infrastructure to address quality issues peri-operatively, and establish community-based partnerships that will ensure that we identify and address long term quality of life concerns.
- (III). One-half of patients express some degree of regret 2–4 weeks postoperatively. However, most patients who expressed regret had these feelings decrease to zero or near zero over time (57).

As difficult as it is to digest the inevitability of developing cancer, identification of genetic mutations associated with familial cancers is actually a blessing to many patients who have seen generations of loved ones die prematurely of gastric cancer. Our understanding of the natural history of this disease and our acceptance of the limitations of our surveillance methods has made recommendations far less debatable. With our ability to establish risk in an identifiable patient population comes opportunity to investigate methods to delay or prevent the disease, improve methods of surveillance in high risk families, and develop far better infrastructure for survivorship in patients after gastrectomy.

## Conclusions

The emergence of sophisticated methods to identify patients at high risk for the development of gastric cancer has given us an opportunity to eliminate a lethal disease in an identifiable patient population. Like many familial cancer syndromes, the discovery of a CDH-1 mutation in one's

family is bittersweet. Guidelines and recommendations have been established and prophylactic total gastrectomy is considered the most effective treatment. This requires substantial physical and emotional investment and lifelong dietary and behavior modification. It is imperative that patients and their relatives are rooted in programs that can address genetic counseling, ongoing surveillance, and survivorship.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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