

Gastric carcinoma: Insights into risk factors, methods of diagnosis, possible lines of management, and the role of primary care

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ABSTRACT

Gastric carcinoma represents the second most common type of malignancy that contributes to cancer-related mortality worldwide. However, the geographic incidence of gastric carcinoma had changed over the last few decades, possibly due to increased hygiene, increased awareness of the importance of healthy nutrition, and increased rates of eradication of *Helicobacter pylori* infection. Gastric carcinoma consists of two pathological variants, intestinal and diffuse. Early cases of gastric carcinoma may be asymptomatic. However, advanced cases may present with significant weight loss, dysphagia, abdominal pain, vomiting, and even severe upper gastrointestinal bleeding. Patients at high risk of developing gastric carcinoma should be adequately screened at primary healthcare centers for early detection and effective management. Lines of treatment vary according to the stage of the disease but surgical resection of the tumor with regional lymphadenectomy remains the gold standard of therapy. This review sheds light on gastric carcinoma given the recent trends regarding its prevalence, risk factors, types, clinical picture, methods of diagnosis, possible lines of management, and the role of primary care.

Keywords: Carcinoma, diagnosis, management, primary care, stomach

Introduction

Gastric carcinoma is one of the common malignancies that have an impact on the various aspects of life.^[1] It is considered the fourth most common type of cancer and is the second leading cause of cancer-related mortality all over the world. Predisposing factors of this type of malignancy include consumption of salt and salt-preserved food, tobacco smoking, alcohol consumption, and *Helicobacter pylori* infection.^[2] Despite the declining rate of

incidence of gastric carcinoma owing to better prevention of the predisposing factors, earlier diagnosis and effective management, the prognosis of gastric carcinoma is still poor.^[3]

Gastric carcinoma has two main histologic subtypes; the intestinal and diffuse-type that have different prevalence, predisposing factors, pathogenesis, and management.^[4] Despite the gradual decline in the incidence of gastric carcinoma in the different areas of the world in the last decades, tumors of the gastric cardia and gastroesophageal junction are becoming more frequent with an increased incidence of complications including gastric outlet obstruction.^[1]

Most cases of gastric carcinoma are often diagnosed at an advanced stage, which may limit the lines of management.^[5] The

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mainstay of therapy of gastric carcinoma is surgical resection with adjuvant chemotherapy, with or without radiotherapy according to the stage of the disease.^[6] However, cases with distant metastasis still have a poor prognosis and the median overall survival rate of these cases is less than 1 year.^[1] Hence, studies on gastric carcinoma are vitally needed for a better understanding of the pathogenesis of the disease, to improve the prevention strategies, and to develop new methods for early detection and better management of this disease.^[7] Since early cases of gastric carcinoma are usually asymptomatic, the role of the primary care physicians in early detection of patients with gastric carcinoma has emerged in recent years and represents an important clue for the improvement of the therapeutic outcomes of this disease.^[4,6] This review sheds light on gastric carcinoma given the recent trends regarding its prevalence, risk factors, types, clinical picture, methods of diagnosis, possible lines of management, and the role of primary care.

Prevalence of Gastric Carcinoma

The recent epidemiological studies reported that gastric carcinoma is the fourth most common type of malignancy worldwide and is considered as the second cause of death of all malignancies all over the world.^[8] The 5-year survival rate of this disease is relatively good only in Japan, where it reaches 90% while it ranges from 10–30% in the European countries. This may be attributed to early diagnosis by endoscopic measures with early tumor resection in most cases in Japan.^[9]

In the last decades, more than 50% of the reported cases were from developing countries. The high-risk areas include Central and South America, East Asia, and Eastern Europe. Southern Asia, North America, North and East Africa, Australia, and New Zealand are classified as low-risk areas.^[10] There is a steady decline in the rate of incidence of gastric carcinoma worldwide. This might be explained by the improved food conservation, a high intake of fresh fruits and vegetables, following high hygienic standards, and the rapid progress in *Helicobacter pylori* eradication.^[11]

Risk Factors of Gastric Carcinoma

The risk factors for gastric carcinoma include a combination of environmental and genetic factors that contribute together to the pathogenesis of the disease.^[8] *Helicobacter pylori* infection is considered as one of the etiological factors that may predispose to gastric carcinoma.^[12] Laird-Fick *et al.*^[13] reported that *Helicobacter pylori* infection is the direct cause of at least 75% of gastric carcinoma worldwide. *Helicobacter pylori* was proven to disrupt the tight junctions between gastric cells, insert genetic material into them, and suppress the host immune responses.^[14] Two key pathogenic proteins were identified and proven to play the major role in *Helicobacter pylori*-induced gastric carcinogenesis; a vacuolization protein (VacA) and a cytotoxic antigen (CagA). Both proteins were proven to help *Helicobacter pylori* to extrude small packets of genetic and intracellular material out of the

affected cells.^[15] Moreover, *Helicobacter pylori* infection was reported to induce DNA methylation and histone modification in the gastric epithelial cells with the final result of the development of gastric carcinoma.^[13]

Dietary factors may play an important role in the pathogenesis of gastric carcinoma.^[16] Low intake of fresh fruits and vegetables, high-salt diet, poorly preserved food, excess alcohol intake, and obesity may be associated with an increased risk of gastric carcinoma.^[17] Recent studies tried to verify the possible ameliorative effect of fresh fruits and vegetables rich in beta carotenes, vitamin C, vitamin D, and tocopherols on gastric carcinogenesis.^[18]

Tobacco smoking was proven to increase the possibility of the development of various types of gastric carcinoma.^[17] The risk of gastric carcinoma was reported to increase by 60% in males and 20% in female smokers compared to nonsmokers. Besides, those with high consumption of cigarettes (more than 20 cigarettes per day) are at higher risk of developing gastric carcinoma.^[19]

The low socioeconomic status was found to be an important risk factor for gastric carcinoma, possibly due to the associated poor sanitation and unhealthy dietary habits. Besides, occupational exposure to dust, nitrogen oxide, N-nitroso compounds, and radiation may represent a crucial risk factor.^[20]

Infection with Epstein–Barr virus (EBV) was suggested to create a gastric microenvironment that is suitable for carcinogenesis. The frequent presence of EBV in biopsies from gastric carcinoma might indicate that the tumor may be caused by the proliferation of a single infected cell.^[21] Furthermore, recent reports suggested that there is an increased risk for gastric carcinoma after gastric surgery. Gastrojejunostomy was found to carry a higher risk than gastroduodenostomy. Although the latent period between the initial gastric surgery done for benign lesions and the development of gastric carcinoma is about 30 years, this interval may be reduced to 12 years if surgery was performed for prior gastric carcinoma.^[11] Besides, the risk of developing gastric carcinoma may be up to 2–3 folds in patients with a positive family history of gastric carcinoma compared to persons with negative family history for this type of cancer.^[14]

Classification of Gastric Carcinoma

Sporadic gastric carcinoma

Most cases of gastric carcinoma occur sporadically and affect patients older than 50 years. This type of carcinomas occurs most frequently due to a combination of environmental and dietary factors and affects males two times more than females, particularly in high-risk countries.^[11]

Early onset gastric cancer

This type usually occurs before the age of 50 years and represents about 10% of gastric carcinomas. This type is usually associated

with genetic factors and most cases are multifocal, diffuse, and more common in females than males.^[22]

Hereditary diffuse gastric carcinoma

This is a rare type of gastric carcinoma, accounting for about 1–3% of cases. It is the result of inherited mutations in the *CDH1* gene that encodes E-cadherin.^[23] These are autosomal dominant conditions that may cause a diffuse, poorly differentiated type of gastric carcinoma that infiltrates the entire thickness of the wall of the stomach causing its thickening without forming a distinct mass.^[11]

Gastric stump carcinoma

This is a subtype of gastric carcinoma that occurs in the gastric remnant about 5 to 10 years after the surgery for the treatment of peptic ulcers. It represents up to 7% of all cases of gastric carcinoma with increased incidence in males than females. Infection with EBV is more common in gastric remnants than in intact gastric epithelium.^[21] This type of carcinoma is usually preceded by premalignant changes such as metaplasia and dysplasia of the gastric epithelium.^[11]

Pathological classification of gastric carcinoma

Lauren classification is the most widely used histologic classification of gastric carcinomas which distinguishes two major subtypes, intestinal and diffuse forms. The Lauren classification contains microscopic and macroscopic differences.^[24] The intestinal form of gastric carcinoma is associated with chronic atrophic gastritis and intestinal metaplasia while the diffuse form originates from the normal gastric mucosa. The intestinal type occurs more frequently in old people and is usually located in the distal part of the stomach while the diffuse type is more prevalent among young patients. This classification is essential in determining the extent of the surgical resection of gastric carcinoma.^[25]

Primary Care and Diagnosis of Gastric Carcinoma

The accurate diagnosis of gastric carcinoma needs collaboration between careful history taking, thorough physical examination and genetic, radiologic, and endoscopic investigations. Anemia, unexplained weight loss, and the presence of occult blood in stool are suggestive but not conclusive manifestations of malignancy.^[26] The presence of epigastric mass or nodular liver on abdominal palpation may help in diagnosis. Early cases may be asymptomatic. However, advanced cases with distant metastases may present with an abdominal mass, abdominal distention, supraclavicular lymphadenopathy, rectal mass, splenomegaly, obstructive jaundice, ascites, enlarged ovary, or umbilical metastases.^[27]

Abdominal computerized tomography (CT) may be a useful aid in the staging of gastric carcinoma. CT scan can determine the site and size of the tumor, gastric wall thickness, and the

extent of spread of the tumor.^[28] However, CT scans cannot differentiate early from more advanced carcinoma. Moreover, the CT scan does not provide tissue confirmation for grading and typing. Abdominal ultrasonography may provide valuable data about the extent of the metastatic spread of the tumor inside the abdomen.^[26]

Currently, upper gastrointestinal endoscopy is considered the most specific and sensitive method of diagnosis and staging of gastric carcinoma. Gastrointestinal endoscopy allows the physician to visualize and take biopsies from the esophageal, gastric, and duodenal mucosa.^[29] Moreover, endoscopy facilitates accurate visualization, histological confirmation, and typing of the tumor. Endoscopy also plays a critical role in the diagnosis of gastric lymphoma. However, radiologic and endoscopic studies may understage primary gastric lymphoma when compared to surgery.^[30]

Genetic screening for the presence of *CDH1* mutations is essential for family members of young patients with diffuse gastric carcinoma. Carriers of germline *CDH1* mutations should undergo prophylactic gastrectomy.^[31] Genetic counseling is vitally important for all family members considering genetic testing and prophylactic gastrectomy. Women in these families who have a germline mutation of *CDH1* should be regularly examined for the high possibility of future development of lobular breast cancer.^[32]

Treatment of Gastric Carcinoma

The successful management of gastric carcinoma needs collaboration of members of a multidisciplinary team which should include at least a surgeon, gastroenterologist, pathologist, medical, and radiation oncologists.^[1] Lines of treatment include gastric resection, radiotherapy, chemotherapy, and biologic therapy.^[6]

In the case of curative intention, surgery involves complete resection of the tumor with a standardized D2 regional lymphadenectomy.^[2] Endoscopic mucosal resection in early cases of gastric carcinoma and intraepithelial neoplasia can yield the same therapeutic outcomes as traditional surgical resection.^[33] Splenectomy may be required in cases of direct cancer infiltration of the splenic hilum. Advanced gastric tumors with distant metastasis are usually incurable. However, palliative resection of solitary metastasis may improve the quality of life. Preoperative chemotherapy (neoadjuvant therapy) may be needed to decrease the size of the tumor and make it respectable.^[34]

Chemotherapy based upon platinum compounds, fluoropyrimidines, and anthracyclines has been effective for the improvement of the 5-years survival rate of advanced cases of gastric carcinoma.^[35] The most commonly used regimens are ECF (epirubicin, cisplatin, 5-fluorouracil), EOF (epirubicin, oxaliplatin, 5-FU), ECX (epirubicin, cisplatin, capecitabine), and EOX (epirubicin, oxaliplatin, capecitabine). Alternatively, patients

unresponsive to these regimens may be treated with taxane-based or irinotecan/5-fluorouracil protocols.^[36]

Despite the improvement in the overall survival rate after chemotherapy, the high possibility of recurrence is still documented. Therefore, the addition of radiotherapy preoperatively may be beneficial. Radiotherapy is well-tolerated, improves the resectability of the tumor, and does not increase the possibility of surgical complications.^[37] Currently, adjuvant radio-chemotherapy is recommended in patients with advanced carcinoma of the gastroesophageal junction. Besides, radiotherapy may be useful in advanced non-resectable cases of gastric carcinoma and cases of pyloric or cardiac obstruction.^[38]

In the last years, biologic therapy has emerged as an effective adjuvant line of therapy of gastric carcinoma.^[39] Trastuzumab is a monoclonal antibody that interferes with HER2 receptors and was largely used for the treatment of locally advanced and metastatic cases of gastric carcinoma. Several clinical trials have proven that trastuzumab in combination with capecitabine or 5-FU can be considered as the standard line of care for HER2-positive cases of gastric carcinomas.^[40] Furthermore, ramucirumab is an anti-vascular endothelial growth factor receptor-2 monoclonal antibody that can be used in combination with paclitaxel to improve the survival rate of patients with advanced gastric carcinoma.^[41]

Prognosis of Gastric Carcinoma

The 5-years survival rates for patients with gastric carcinoma vary greatly according to the stage of the disease, race, and general health of the individuals. According to Rawla and Barsouk,^[42] the 5-years survival rate for nonmetastatic cases is about 67%. The 5-years survival rate for stage IA and IB tumors treated with surgery is 94% and 88%, respectively. However, the 5-years survival rate is 18% for cases with stage IIIC treated with surgery. Asian patients in the United States have a better prognosis than Caucasians. Asians may be diagnosed earlier, have more lymph nodes examined, and more of their lymph nodes test positive and early treated with surgery.^[43]

Conclusion

Gastric carcinoma is one of the malignant conditions responsible for a vast majority of cancer-related deaths worldwide. It is predisposed by several risk factors such as *Helicobacter pylori* infection, environmental factors, gastric polyps, gastric surgery, and genetic mutations. Types of gastric carcinoma include adenocarcinoma, hereditary (familial) gastric cancer, early gastric cancer, and lymphoma. The goal of primary care is early detection of risk factors and proper diagnosis of this type of cancer. The therapeutic strategies for gastric carcinoma depend on the severity of the disease, the patient's general health, and the patient's preferences. Lines of treatment include surgical resection of the tumor with regional lymphadenectomy, chemotherapy, radiotherapy, and biologic therapy. After treatment, healthy

nutrition with regular follow-up is recommended to achieve a better prognosis of the disease. Besides, improvement of the skills of the primary care physicians for early diagnosis of this type of cancer may efficiently help in the reduction of morbidity and mortality rates.

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Conflicts of interest

There are no conflicts of interest.

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