

Gastric cancer: epidemiology, prevention, classification, and treatment

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Abstract: Gastric cancer is the second most common cause of cancer-related deaths in the world, the epidemiology of which has changed within last decades. A trend of steady decline in gastric cancer incidence rates is the effect of the increased standards of hygiene, conscious nutrition, and *Helicobacter pylori* eradication, which together constitute primary prevention. Avoidance of gastric cancer remains a priority. However, patients with higher risk should be screened for early detection and chemoprevention. Surgical resection enhanced by standardized lymphadenectomy remains the gold standard in gastric cancer therapy. This review briefly summarizes the most important aspects of gastric cancers, which include epidemiology, risk factors, classification, diagnosis, prevention, and treatment. The paper is mostly addressed to physicians who are interested in updating the state of art concerning gastric carcinoma from easily accessible and credible source.

Keywords: gastric cancer, epidemiology, classification, risk factors, treatment

Epidemiology

Gastric carcinoma (GC) is the fourth most common malignancy worldwide (989,600 new cases per year in 2008) and remains the second cause of death (738,000 deaths annually) of all malignancies worldwide.^{1,2} The disease becomes symptomatic in an advanced stage. Five-year survival rate is relatively good only in Japan, where it reaches 90%.³ In European countries, survival rates vary from ~10% to 30%.⁴ High survival rate in Japan is probably achieved by early diagnosis by endoscopic examinations and consecutive early tumor resection.

The incidence shows wide geographical variation. More than 50% of the new cases occur in developing countries. There is a 15–20-fold variation in risk between the highest- and the lowest-risk populations. The high-risk areas are East Asia (China and Japan), Eastern Europe, Central and South America. The low-risk areas are Southern Asia, North and East Africa, North America, Australia, and New Zealand.³

Steady declines in GC incidence rates have been observed worldwide in the last few decades.³ This trend applies particularly to young patients with noncardia, sporadic, intestinal type of GC, as reported in the Japanese analysis.^{5,6} On the other hand, the American study differentiates race and age subpopulations, as well as the anatomic subtype of corpus gastric cancer, which have an increasing tendency.⁷ Nevertheless, the general declining incidence of GC may be explained by higher standards of hygiene, improved food conservation, a high intake of fresh fruits and vegetables, and by *Helicobacter pylori* (*H. pylori*) eradication.⁸

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Conclusions relating to the epidemiology

- GC detected at the stage >T1N0 has a poor prognosis.
- The incidence of GC varies geographically.
- Within the last few decades, the incidence of GC has steadily declined.

Risk factors and prevention of gastric cancer

Gastric cancer results from a combination of environmental factors and accumulation of specific genetic alterations. Despite declining trends worldwide, prevention of GC should remain a priority. The primary prevention includes healthy diet, anti-*H. pylori* therapies, chemoprevention, and screening for early detection. Dietary factors have an important impact on gastric carcinogenesis, especially in case of intestinal adenocarcinoma. Healthy dietary habits, that is, high intake of fresh fruits and vegetables, Mediterranean diet, a low-sodium diet, salt-preserved food, red and high cured meat, sensible alcohol drinking, and maintaining a proper weight might be associated with a decreased risk of GC.^{9–11}

The protective role of fresh fruits and dark green, light green, and yellow vegetables rich in B carotene, vitamin C, E, and foliate is strongly emphasized, probably due to their antioxidant effect. B carotene seems to be the leading risk reducer.¹²

The beneficial influence of vitamin-rich diet seems to be particularly noticeable in case of earlier foliate and selenium deficiency.^{13,14}

Nevertheless, the outcomes of various studies about anti-cancer properties of carotenoids, tocopherols, and retinoids are not always coherent. Therefore, the issue requires further investigations.¹⁵

Many studies have confirmed that tobacco smoking increases the risk of GC, both cardia and noncardia subtypes.^{16,17} It has been shown that the risk of GC is increased by 60% in male and 20% in female smokers compared to nonsmokers. The risk of GC is lower in former smokers compared with occasional smokers, and smokers with higher consumption of cigarettes (>20 cigarettes per day) are at higher risk of GC.¹⁶

Alcohol consumption also predisposes to GC.¹⁸ The association between alcohol abuse and gastric cardia cancer was reported.¹⁹

GC has been found to be inversely related to socioeconomic status, so that high socioeconomic position is associated with a reduced risk of GC, particularly cardia and intestinal

subtypes.²⁰ Professions that are at higher risk of GC are minors, fishermen, machine operators, nurses, cooks, launderers, and dry cleaners as the main occupational exposures comprise dust, nitrogen oxides, N-nitroso compounds, and radiation.^{21–23}

Marshal and Warren discovered the association between *H. pylori* and gastritis in 1982.²⁴ In 1994, *H. pylori* was classified as a class I carcinogen by the International Agency for Research on Cancer.²⁵ Next, it has been accused of being the main environmental factor causing GC.^{26,27} *H. pylori* infection is a common cause of gastrointestinal problems, but only a few infected patients develop a severe disease such as peptic ulcer (10%–15%) or GC (1%–3%).²⁸

In the general population, *H. pylori* infection reaches ~60%, but in patients with GC, it is more common (84%) or even inevitable (noncardia GC).^{29,30} The correlation between *H. pylori* infection and GC relates also to younger age (<40 years)³¹ and is involved in both intestinal and diffuse types of noncardia GC. The latter is more common in early onset gastric cancer (EOGC).^{32,33}

Undoubtedly, the strong correlation between *H. pylori* infection and GC is a possible target of intervention.²⁵ The Maastricht III Guidelines recommend to treat the infection in peptic ulcer diseases, mucosa-associated lymphoid tissue lymphomas, atrophic gastritis, patients after resection of GC, first-degree relatives of GC patients, patients with unexplained iron deficiency anemia, patients with idiopathic thrombocytopenia purpura, patients who require long-term nonsteroidal anti-inflammatory drugs (NSAIDs), and in patients who just wish to be treated.³⁴ The first-line eradication treatment of *H. pylori* relies on proton pump inhibitors and combination of two antibiotics such as amoxicillin, clarithromycin, or metronidazole. If the first therapy does not succeed, then the proposed second-line treatment is bismuth salts, proton pump inhibitor, tetracycline, and metronidazole.³⁴

Epstein–Barr virus (EBV) is a human herpes virus for which a causal role in gastric carcinogenesis has been suggested.³⁵ The association between EBV and carcinogenesis varies from 4% in China, 7.7% in France, 8.1% in Russia, 12.5% in Poland, to 17.9% in Germany.^{36,37} EBV in carcinoma biopsies indicates that the tumor has been formed by the proliferation of a single infected cell.³⁷ In addition, EBV infection might be a late event in gastric carcinogenesis.³⁸ Interestingly, EBV is more common in carcinomas in post-surgical gastric remnant (27%) than in an intact stomach.³⁹

Aspirin and NSAID users are shown to be at a reduced risk of GC.⁴⁰ On the other hand, the side effects of these are bleeding, perforation, or gastric outlet obstruction,⁴¹ and therefore, these drugs are not recommended for patients with

a history of digestive complaints.⁴² In the late 1990s, there was an impermanent enthusiasm for the COX-2-selective NSAIDs, but shortly after, they were accused of increasing risk of myocardial infarction.⁴³

Familial clustering of GC has been reported for centuries and the world-famous example is the family of Napoleon Bonaparte.^{44–46} In 1998, truncating mutations of *CDHI* were described in the germline of three New Zealand Maori families predisposed to diffuse GC.⁴⁵ In general, the risk of developing GC is calculated to be 1.5–3 fold increased in individuals with a family history of GC.⁴⁴

Obesity is a risk factor for gastric cardia carcinomas.⁴⁷ Less common risk factors include pernicious anemia, blood type A.^{48,49} Gastrectomy is also a risk factor for gastric cancer, a long time after partial gastrectomy.⁵⁰

Endoscopy is the most sensitive and specific diagnostic screening method.⁵¹ However, mass screening for early detection of GC is expensive, and therefore, recommended only in regions with high incidence, such as East Asia, and senseless in low-incidence regions, such as North America.^{52,53}

Additionally, endoscopic surveillance should be performed one to two times per year in patients who are at higher risk of GC (history of GC in family, familial adenomatous polyposis, Li–Fraumeni syndrome, BRCA2 mutations, hereditary nonpolyposis colon cancer syndrome, Peutz–Jeghers syndrome, and Ménétrier disease, previous gastric surgery, gastric polyps).^{52,54}

Conclusions relating to risk factors and prevention

1. Early detection of both changeable and unchangeable GC risk factors is vital in primary prevention.
2. Changeable risk factors accounting for gastric cancer incidence are as follows:
 - a. Patient dependent: maintaining balanced diet, moderate alcohol intake, giving up smoking, and keeping normal weight.
 - b. Doctor dependent: *H. pylori* eradication, considering NSAIDs.
3. Unchangeable risk factors of GC are occupational exposures, family history of GC, comorbidities, and history of partial gastrectomy.

Classification of gastric cancer

Sporadic gastric cancer

The majority of GC occurs sporadically and mainly affects people over the age of 45 years. These carcinomas are termed as “sporadic gastric cancers” (SGCs) (Figure 1).⁵⁵ They are commonly caused by coincidence of many environmental

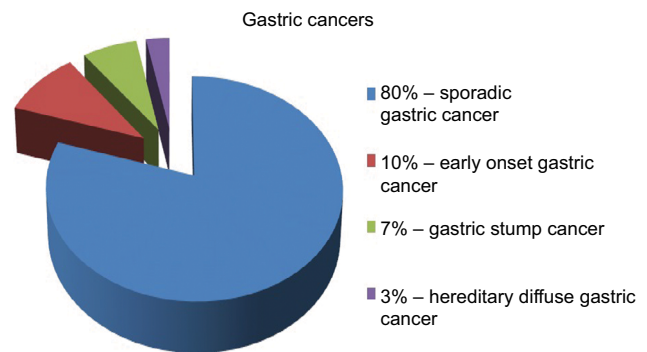


Figure 1 Classification of gastric cancers.

Notes: Adapted from Skierucha M, Milne AN, Offerhaus GJ, Polkowski WP, Maciejewski R, Sitarz R. Molecular alterations in gastric cancer with special reference to the early-onset subtype. *World J Gastroenterol.* 2016;22(8):2460–2474. Copyright ©The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.⁵⁵

factors.⁵⁶ They occur at the age of 60–80 years, and males are two times more often affected than females, particularly in high-risk countries.⁵⁷

Early onset gastric cancer

EOGC is defined as GC before the age of 45 years and encompasses about 10% of GCs (Figure 1).^{55,58} In EOGCs, genetic factors seem to play the causal role.⁵⁶ These cancers are often multifocal, diffuse, and are more frequently observed in females, probably because of hormonal factors.^{56,59–62} SGC and EOGC vary as well at the molecular level.^{55,63} Nevertheless, apart from the cases of hereditary GC, the pathogenesis of EOGC still remains unclear.

Gastric stump cancer

Gastric stump cancer (GSC) is a separate subtype of GC, defined as a carcinoma that occurs in the gastric remnant at least 5 years after the surgery for peptic ulcer.⁶⁴ GSC represents from 1.1% to 7% of all GCs (Figure 1), and males are more prone to them than woman.^{55,65,66} Gastrectomy is a well-established risk factor for GSC, even long time after the initial surgery.^{50,67} After 15 years from the gastrectomy, the risk of GSC is increased four- to sevenfold compared with the healthy population.^{50,68} EBV infection is more often in gastric remnants than in intact stomachs.³⁹ The virus may interact with the p53 protein.⁶⁹ In contrast, *H. pylori* infection in GSCs is less frequent.⁷⁰ GSCs are commonly preceded by well-defined precursor lesions, mostly by dysplasia, and therefore, endoscopic surveillance with multiple biopsies of the gastroenterostoma is recommended.⁷¹

Hereditary diffuse gastric cancer (HDGC)

Most cases of GCs appear sporadically, but in 5%–10% of cases, familial clustering is observed.⁴⁴ HDGC concerns

1%–3% of all GCs (Figure 1).^{55,72} HDGCs result from inherited syndromes, one of which are germline mutations in the *CDH1* gene that encodes E-cadherin. These are autosomal dominant conditions that cause diffuse, poorly differentiated GC, which infiltrates into stomach wall and causes thickening of the wall without forming a distinct mass.

Conclusions related to classification

- Eighty percent of GCs are SGCs. They occur mostly in elderly males, who come from high-risk area and have been exposed to environmental risk factors.
- Ten percent of gastric cancers are EOGCs. They occur at the age <45 years, more frequently in females.
- Seven percent of gastric cancers are GSCs. Most of them are preceded by dysplasia. The risk of them rises within time after gastrectomy.
- Three percent of gastric cancers are HGDCs. They are inherited by autosomal dominant mutation of *CDH1* gene.

Pathological classification

According to the World Health Organization guidelines, GC can be classified as adenocarcinoma, signet ring-cell carcinoma, and undifferentiated carcinoma. However, it is not as widely used as the Lauren classification, which distinguishes two major subtypes of GC, intestinal and diffuse types.⁷³ The Lauren classification contains microscopic and macroscopic differences.⁷³ It has been postulated that intestinal types of GC are associated with chronic atrophic gastritis and intestinal metaplasia, whereas diffuse types originate from normal gastric mucosa. The ratio of intestinal and diffuse types varies between countries and continents. In European countries, intestinal type is currently more common.^{74–78} It tends to occur more often in the distal stomach, in high-risk areas, and it is often preceded by a long-standing precancerous lesion.⁷⁵ The diffuse type prevails among young patients. The extent of the surgical resection depends on the Lauren's histological subtype of GCs.

Conclusions relating to the pathological classification

- GC is mostly divided into two subtypes: intestinal and diffuse ones.
- Extent of surgical resection depends on histopathological outcome.

Treatment

Multidisciplinary approach for the planning of the GC treatment is mandatory. The multidisciplinary team (MDT)

should include at least a surgeon, pathologist, gastroenterologist, medical and radiation oncologists.⁷⁹ In case of curative intention, the surgery involves complete resection with a standardized D2 lymphadenectomy.⁸⁰ In 1998, Japanese Gastric Cancer Association (JGCA) standardized the regional lymphadenectomy based on the location of the tumor and the respective regional node drainage. Sixteen different lymph node stations around the stomach have been recognized. The lymph node stations along the lesser curvature (stations 1, 3, and 5) and the greater curvature (stations 2, 4, and 6) of the stomach have been grouped as N1. The nodes along the left gastric artery (station 7), the common hepatic artery (station 8), the celiac artery (station 9), and the splenic artery (stations 10 and 11) have been grouped as N2. N3 group has encompassed the lymph nodes along the hepatoduodenal ligament (station 12), at the posterior site of the pancreas (station 13), and at the root of the mesentery (station 14). Finally, the lymph nodes around the middle colic artery (station 15) and lower paraesophageal lymph node and diaphragmatic lymph (station 16) have been grouped as N4.⁸¹ D1, D2, and D3 are the names given to the procedures that depend on the range of lymphadenectomy.⁸¹ However, the seventh edition of TNM classification and a new version of the JGCA classification cancer of the stomach changed the definitions of D1/D2 lymphadenectomy according to the extent of gastric resection (Table 1).⁸² Endoscopic mucosal resection (EMR) in early GC treatment (T1aN0M0) and in intraepithelial neoplasia can provide the same effect as traditional surgical resection.^{83,84} For well-differentiated types of mucosal tumors, endoscopic submucosal dissection (ESD) is often successful.^{84,85} Splenectomy is acceptable only in the case of the direct cancer infiltration of the splenic hilum.⁸⁶ Advanced gastric tumors with distant metastasis are usually incurable; however, it does not concern cases with solitary liver metastasis or peritoneal nodules invasion. For incurable GC patients, palliative resection may improve the quality of life, but it is not recommended in an asymptomatic patients.⁸⁷ Histological examination after regional lymphadenectomy should include more than 15 lymph nodes. Treatment recommendations of the JGCA (fourth edition from 2014) are presented in Table 2.⁸²

The high incidence of distant metastases and the local recurrence after have paved the way for systemic therapy, and recently in neo-adjuvant therapy.⁸⁸ The extensive treatment may include chemotherapy, radiation therapy or immunotherapy, either alone or in combinations. Adjuvant therapy has been shown to be beneficial in GC.^{89,90} Recent studies have revealed the superiority of the neoadjuvant therapy

Table 1 Extent of lymphadenectomy according to the type of gastric resection

Gastreotomy	D1	D1+	D2
Distal resection of the stomach	1, 3, 4, 5, 6, 7	(D1) +8, 9	(D1) +8, 9, 11, 12
Total gastrectomy	1–7 (2 included)	(D1) +8, 9, 11	(D1) +8, 9, 10, 11, 12

Note: Data from Japanese Gastric Cancer Association.⁸²

Abbreviations: D1, D1 lymphadenectomy; D1+, expanded D1 lymphadenectomy; D2, D2 lymphadenectomy.

	N0	N1 (1–2)	N2 (3–6)	N3 (>7)
T1a	ESD/EMR (G1, <2 cm, not ulcerated)	D2	D2 and ACT	D2 and ACT
T1b	D1+ and sentinel	D2	D2 and ACT	D2 and ACT
T2	D2	D2 and ACT	D2 and ACT	D2 and ACT
T3	D2 and ACT	D2 and ACT	D2 and ACT	D2 and ACT
T4a	D2 and ACT	D2 and ACT	D2 and ACT	D2 and ACT
T4b	D2 + extended resection + ACT	D2 + extended resection + ACT	D2 + extended resection + ACT	D2 + extended resection + ACT

Table 2 The JGCA cancer classification according to the extent of gastric resection and D1/D2 lymphadenectomy.

Notes: Recently, chemotherapeutic regimens for HER2-positive gastric cancer should include trastuzumab, and the efficacy of ramucirumab has proved as a second-line chemotherapy for recurrent or metastatic gastric cancers. Data from Japanese Gastric Cancer Association.⁸²

Abbreviations: ACT, adjuvant chemotherapy; D1, D1 lymphadenectomy; D1+, expanded D1 lymphadenectomy; D2, D2 lymphadenectomy; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; extended resection, extended resection of the adjacent organs; G1, grade 1; JGCA, Japanese Gastric Cancer Association; sentinel, sentinel lymph node mapping; N, extent of nodule invasion; T, tumor stage.

combined with surgery over the surgery alone, with 5-years progression-free rate at 23%–36%.⁹¹ Palliative chemotherapy or surgery is recommended in patients with metastases, but in a good general condition. In case of patients with poor performance status, the supportive treatment is the only recommendation.⁸⁶ Management algorithm for patients in a good general condition without distant metastases (M0) is shown in Figure 2.⁹²

Chemotherapy

Two randomized trials have shown an improvement in overall survival in patients receiving perioperative chemotherapy.^{91,93} Such a treatment is, therefore, routinely performed in Europe and includes three cycles of chemotherapy before surgery and three cycles after surgery.⁹⁴

Neo-adjuvant (chemo-)radiotherapy

The results of the INT 0116 trial have shown the effectiveness of adjuvant radiotherapy and chemotherapy compared with surgery alone. Three-year observation has shown an 11%

improvement in overall survival after combined treatment, with a median survival of 36 months. It has been compared with only 27 months of survival after surgery alone. The median recurrence-free survival time has been 30 months in the chemo-radiotherapy group and 19 months in the surgery alone group.⁹⁵

Although adjuvant radiotherapy and chemotherapy is recommended in the United States, in the European countries, the treatment has been limited to cases with suboptimal lymphadenectomy (removal of <15 lymph nodes) or irradical microscopic resection (R1) of the stomach.⁹⁶ Application of adjuvant chemo-radiotherapy after D1 lymphadenectomy reduces the incidence of local recurrence and improves survival of the patients.^{97,98}

The results of perioperative chemotherapy in patients with GC and gastro-esophageal junction are promising.^{91,93} A statistically significant improvement of overall survival and progression-free survival has been observed in 36% of patients with perioperative chemotherapy compared with 23% after the operation alone.⁹¹ Therefore, perioperative

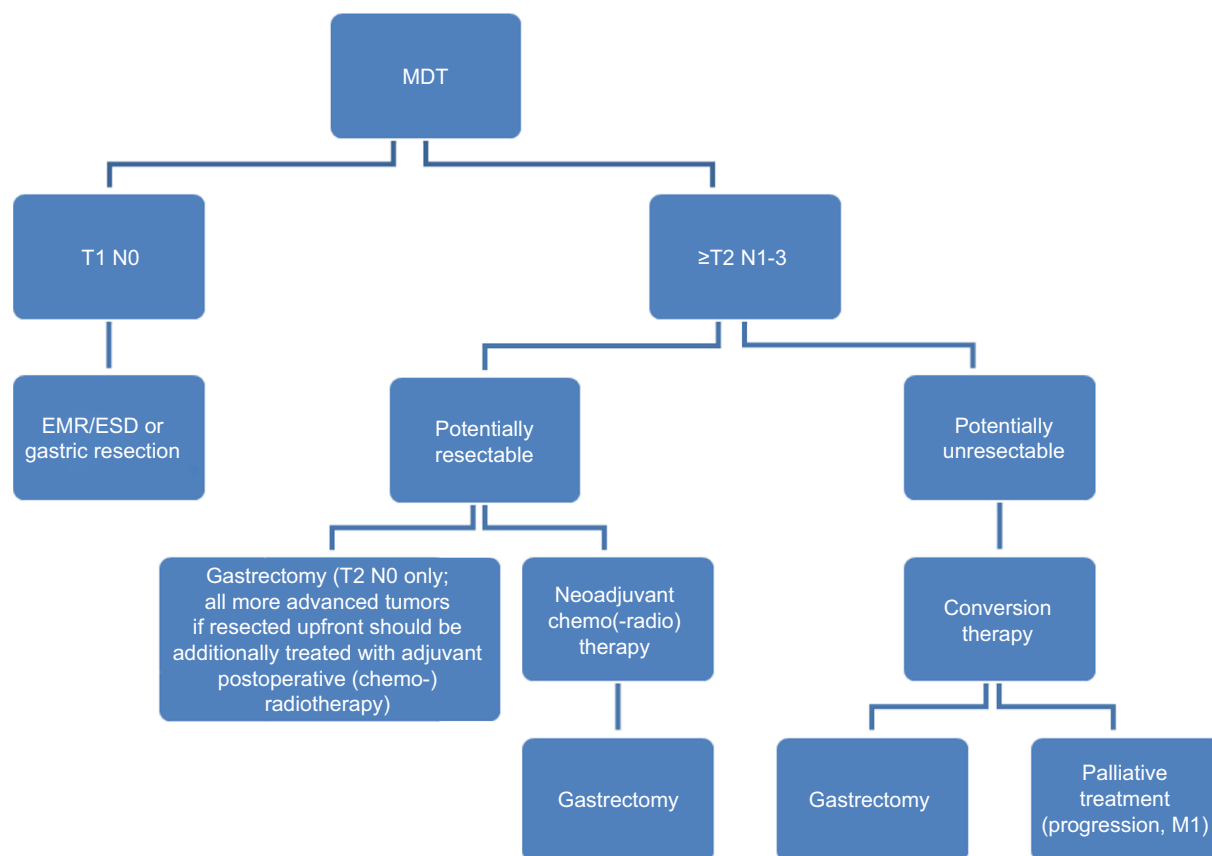


Figure 2 Management algorithm for patients in good performance status and without distant metastases (M0).

Notes: Modified with permission from Polkowski W, Łacko A, Guzel Z. Nowotwory żołądka [Gastric cancers]. In: Krzakowski M, Warzecha K, editors. *Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych – 2013 rok* [Recommendations for Diagnostics and Treatment of Malignant Neoplasms – 2013]. Gdansk: Via Medica; 2013:119. Copyright © 2013 Via Medica.⁹²

Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; MDT, multidisciplinary team.

chemotherapy plus radical surgery has been recommended as a standard treatment for locally advanced tumors.^{99,100}

Combination of regimens bases traditionally upon a platinum– fluoropyrimidine doublet, but adding an anthracycline has been shown to be beneficial.¹⁰¹ The most commonly used protocols are ECF (epirubicin, cisplatin, 5-FU), ECX (epirubicin, cisplatin, capecitabine), EOF (epirubicin, oxaliplatin, 5-FU), and EOX (epirubicin, oxaliplatin, capecitabine). Alternatively, chemo-naïve patients might be treated with taxane-based or irinotecan/5-fluorouracil regimens.^{94,102}

Second-line therapy bases on irinotecan, docetaxel, and paclitaxel.^{103–106} However, in case of late disease progression after first-line chemotherapy (after >3 months), it might be beneficial to try the same drugs again.⁹⁴

Despite the improvement in overall survival after neoadjuvant chemotherapy, high occurrence of relapses are still observed. Therefore, addition of radiotherapy in preoperative setting may be beneficial. Radiotherapy is well tolerated, improves the resectability of the tumor, and does not increase the frequency of surgical complications. Currently, adjuvant radio-chemotherapy is recommended in patients with

loco-regionally advanced carcinoma of the gastro-esophageal junction (T2N1-3M0 or T3N0-3M0).¹⁰⁷

Palliative radiotherapy

Radiotherapy is justified in cases of unresectable GC with anemia, and/or in the cases with pyloric or cardiac obstruction. The dose of 30 Gy in 10 fractions can be effective both in diminishing bleeding and in improving the food passage. The effect is usually short (3–6 months), but it is an easy therapeutic option.^{108,109}

Treatment of gastric cancer in the metastatic setting

Compared with symptomatic treatment, palliative chemotherapy for patients with inoperable GC prolongs survival and improves its quality. In 2010, the US Food and Drug Administration approved “trastuzumab”, a monoclonal antibody that interferes with the HER2 receptor, for the treatment of locally advanced and metastatic GC. Following the results of the ToGA trial, “trastuzumab” in combination with capecitabine or 5-FU and cisplatin is now the standard of care for HER2-positive GCs.^{82,110}

Second-line chemotherapies base on the regimens with a taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as single agent or in combination with paclitaxel. Ramucirumab is the anti-vascular endothelial growth factor receptor-2 monoclonal antibody that has been associated with a survival benefit compared with cytotoxic chemotherapy in the second-line setting. Ramucirumab in addition to paclitaxel has correlated with a survival benefit compared with paclitaxel alone.^{82,111,112}

However, chemotherapy may be used only in patients with good performance status (PS 0–1).⁸² Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival in a group of highly selected patients with limited peritoneal carcinomatosis of gastric origin (peritoneal cancer index <12).^{113,114}

Conclusions relating to treatment

- Operation range depends on the stage of the disease, and it is described in recommendations from 2010 (Figure 2).
- Systematic therapy improves long-term, progression-free survival rate in comparison with surgical treatment alone.
- Palliative chemotherapy in patients with inoperable gastric cancer prolongs survival and improves the quality of life.

Conclusion

GC is a malignant disease with a generally poor long-term prognosis. The majority of GCs are sporadic subtypes that are strongly associated with environmental risk factors. In the last decades, some mechanisms of gastric cancerogenesis have been elucidated, which has resulted in the primary and secondary prevention, such as healthy lifestyle and *H. pylori* eradication. Consequently, the incidence of gastric cancer has started to decline. This tendency does not concern the GC subtypes that result from genetic predisposition or comorbidities. Nevertheless, the endoscopic surveillance program is recommended for screening a group of patients with the highest risk of GC.

Every patient with GC needs to be treated according to the individual plan made by MDT. The planning strategy should consider: stage of the tumor, intention of the therapy, patient's performance status, and technical possibilities. Generally, the most beneficial approach seems to be surgery combined with chemotherapy and radiotherapy.

Disclosure

The authors report no conflicts of interest in this work.

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