

Gastric Cancer Arises as a Result of a Complex Mechanism of Numerous Risk Factors

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Abstract

Gastric cancer is a serious condition that arises when cancerous cells develop in the stomach lining. It is frequently identified at an advanced stage because initial signs are often absent. Common symptoms include stomach pain, unexpected weight loss, nausea, low blood counts, and a quick feeling of fullness. Treatments available usually involve surgery, chemotherapy, and targeted treatments. Factors that increase risk include *Helicobacter pylori* infection, a diet high in processed foods, and smoking habits.

Keywords: gastric cancer; stomach; apoptosis; polyps; health

Introduction

Gastric cancer continues to be a significant health issue, being one of the most aggressive forms of cancer with a high mortality rate worldwide [1]. While its occurrence has declined in countries like the United States and regions of Western Europe, it still ranks as the fifth most prevalent cancer and the third top cause of cancer-related deaths globally. This situation arises mainly from late-stage presentations where the cancer is either unremovable or has spread, generally leading to a poor outcome. The rates of gastric cancer vary greatly across different nations, with a remarkable disparity in five-year survival rates; for instance, Japan achieves a survival rate of 90%, while Europe sees only a 30% rate. The higher rate in Japan can be attributed to routine early screening through endoscopic procedures. In the initial stages, gastric cancer is primarily found in the lower part of the stomach, where it accounts for 57.5% of cases, while the lesser curvature is involved in 37.8%. Several factors can lead to gastric cancer, particularly when combined, including genetic disorders that constitute about 3 to 5 percent of cases, such as hereditary diffuse gastric cancer linked to mutations in the CDH1 gene, Lynch syndrome, and other genetic issues. In developed countries, the occurrence of gastric cancer has declined, potentially due to improved food preservation techniques [2]. It is more prevalent among individuals with blood type A, facing a 20% higher risk. The incidence varies greatly by region; for example, 40% of cases are reported in China, making it the most frequent type of cancer there, while Japan has the highest age-adjusted incidence rates attributed to dietary factors. Certain dietary cancer-causing substances, especially nitrosamines and salty foods, can increase the likelihood of gastric cancer, particularly in Japan. *Helicobacter pylori* has

been associated with the development of cancers in patients suffering from atrophic gastritis, with a higher occurrence in those diagnosed with gastric cancer. Additionally, chronic atrophic gastritis reduces acid production, leading to an overgrowth of bacteria and an increase in nitrates, which triples the risk of developing gastric cancer. Genetic mutations in the cadherin-1 gene (CDH1) also raise the risk. Using proton-pump inhibitors regularly without thorough endoscopic investigation may result in delayed diagnosis. Moreover, vagotomy and partial gastrectomy performed two decades earlier raise the probability of gastric cancer. Other contributing factors include family history, being overweight, exposure to radiation, and belonging to a lower socioeconomic class.

Symptoms

Over 95% of stomach cancers are classified as adenocarcinoma and can be divided into two types: intestinal and diffuse adenocarcinoma [2]. The intestinal type tends to have a more favorable outcome and is typically found in older patients, often developing in the lower part of the stomach. In contrast, diffuse adenocarcinoma is found more frequently and generally has a poorer prognosis. Other uncommon types of tumors include squamous cell carcinoma, which accounts for 4%, as well as lymphoma, gastrointestinal stromal tumors (GIST), and neuroendocrine tumors. In the early stages, stomach cancer might not show any symptoms, or it could present with vague and non-specific signs like upset stomach, fatigue, or lack of appetite. Most individuals experience general discomfort in the upper abdomen that worsens after eating, along with

weight loss, feeling full quickly, loss of appetite, trouble swallowing, or vomiting. Symptoms of advanced disease include fluid accumulation in the abdomen, yellowing of the skin and eyes, black stools, liver enlargement (with 25% of patients having spread to the liver), and swollen lymph nodes (such as Virchow's node in the left supraclavicular area), which may be felt in one-third of patients upon diagnosis. Additionally, spreading to the ovaries (known as Krukenberg tumor) is a rare but serious complication.

Investigation

Patients aged 55 and older who show symptoms of dyspepsia alone or those with issues like swallowing difficulties, vomiting, lack of appetite, weight loss, or signs of gastrointestinal bleeding (for instance, shortness of breath or fatigue) should be urgently referred to a specialist for an endoscopy and evaluation [2]. A complete blood count could indicate microcytic anemia caused by blood loss and iron deficiency. Liver function tests might show abnormalities due to liver metastasis. An endoscopy with biopsy is crucial, and if a gastric ulcer is found, a follow-up endoscopy is necessary to verify if it has healed. An ulcer that does not heal may indicate a potential cancer presence. Barium studies can be useful for patients who cannot tolerate endoscopy; however, they do not allow for tissue biopsy for further examination. Ultrasound of the liver and chest X-ray are effective for checking for metastases, but many patients with advanced disease may need more detailed imaging. CT scans of the chest and abdomen can reveal local lymph node involvement and detect metastasis. PET scans are becoming more common for identifying the spread of the disease to assist in making surgical decisions.

Apoptosis

The ability of tumor cells to resist apoptosis is a significant factor in tumor development [3]. As a result, various genes have been researched for their role in promoting apoptosis in cancerous cells. TRAIL (TNF-related apoptosis-inducing ligand) is a powerful agent that induces apoptosis in these cells. TRAIL works by interacting with four different receptors, with TRAIL-R1 and TRAIL-R2 containing crucial death domains. The complex interactions that follow the activation of these death domains trigger caspase activation and, ultimately, apoptosis. Because of its targeted effect and high expression levels, TRAIL is being utilized in gene therapy. Studies have examined adenoviral TRAIL gene therapy for prostate cancer. Adipose-derived mesenchymal stromal/stem cells (AD-MS) are considered as potential carriers for cancer treatment because they can remain in the tumor environment after being injected locally. The suppression of the mitochondrial apoptotic pathway significantly contributes to the resistance of tumor cells to chemotherapy treatments. Research was conducted on targeting the intrinsic apoptosis pathway using a BAX adenovirus in gastric cancer cases. Nevertheless, it caused harm to normal cells. Blocking antiapoptotic elements is another promising strategy for cancer treatment. The use of miR-195, miR-24-2, and miR-365-2 showed encouraging results in reducing BCL2 levels and promoting apoptosis in MCF-7 breast cancer cells. The X-linked inhibitor of apoptosis (XIAP) specifically blocks the mitochondrial apoptotic route, which is activated by caspases 3, 7, and 9. By directly lowering XIAP through antisense RNA, there was an increase in apoptosis in human gastric cancer studied in the laboratory. E3 ubiquitin ligase is capable of binding to numerous mRNAs and enhancing their expression, such as that of XIAP. Using E3 ubiquitin ligase-specific siRNA in a dual inhibition strategy led to a decrease in XIAP levels and subsequent promotion of apoptosis. The melanoma differentiation-associated gene-7 (MDA7) or

IL-24 has various antitumor effects, including suppressing tumors, preventing the formation of new blood vessels, and inducing apoptosis. The transfection of MDA7 showed positive results in cases of HER2+ breast cancer, laryngeal carcinoma, and osteosarcoma.

Polyps

Gastric polyps are benign growths that can appear as single or multiple tumors, primarily seen in older individuals [4]. Polyps located at the distal part of the stomach are more likely to result in symptoms. When gastric polyps are found, it is crucial to eliminate the possibility of gastric cancer.

Histologically, gastric polyps can be divided into hyperplastic, adenomatous, or inflammatory types.

Among these, hyperplastic polyps account for 80% of cases, featuring an excessive growth of normal tissue; they are not considered true neoplasms and do not correlate with gastric cancer. Approximately 30% of adenomatous polyps have areas of adenocarcinoma, and 20% of patients with benign adenomatous polyps may have adenocarcinoma present elsewhere in the stomach. The risk of cancer in an adenomatous polyp increases as the size grows. Lesions with a stalk or those measuring under 2 cm in diameter are typically non-cancerous. About 10% of benign adenomatous polyps may turn malignant with extended monitoring. Anemia may arise due to ongoing blood loss or insufficient iron absorption. More than 90% of affected patients exhibit achlorhydria after maximum stimulation. Deficiency in vitamin B12 absorption is noted in 25% of cases, yet megaloblastic anemia is only found in a small fraction. Most polyps can be safely removed via snare excision using an endoscope. Surgical removal is necessary for polyps larger than 1 cm or when cancer is suspected. Single polyps might be taken out through a gastrotomy with a frozen section analyzed. If carcinoma is detected, the correct type of gastrectomy is necessary. A partial gastrectomy is advised for multiple polyps located in the distal stomach. If there are 10 to 20 polyps spread throughout the stomach, the antrum should be resected, and the fundic polyps should be excised. In cases of symptomatic diffuse multiple polyposis, a total gastrectomy may be required. These patients need ongoing monitoring due to their heightened risk of developing pernicious anemia or gastric cancer later on. Recurrence of polyps is rare.

Screening

Due to the increased rates of stomach cancer in East Asia, South Korea and Japan have started nationwide screening using upper endoscopy [5]. In the United States and other nations where stomach cancer rates are relatively low, regular screening is not generally advised, but it may be an option for individuals aged 50 and above who are first-generation immigrants from regions with higher rates of the disease, as well as for certain racial or ethnic groups that face a greater risk. Screening and treatment for H pylori infection is not advised for preventing stomach cancer in asymptomatic adults in the US, due to questions about its effectiveness and cost. However, it's suggested for those who have moved from areas where stomach cancer is more common or who have a family history of the disease. A retrospective study in 2023 involving over 716,000 patients with H pylori found a significant decrease in the risk of gastric adenocarcinoma after eight years in people who received treatment compared to those who did not.

Diagnosis

Every year, around 1 million new cases of stomach cancer are identified, with 720,000 deaths attributed to the disease [6]. The outlook for stomach

cancer patients is poor because early tumors, which have better survival rates, often do not show symptoms and are difficult to find. Most stomach cancers are diagnosed in advanced stages, where the five-year survival rate is only 10%. To enhance outcomes for stomach cancer, significant challenges must be addressed. Firstly, new methods for prevention and early detection need to be created, such as identifying genes that make individuals more susceptible to the disease. Until recently, E-cadherin, known as CDH1, was the sole recognized gene linked to stomach cancer; it is responsible for about 40% of hereditary diffuse gastric cancer cases and a very small percentage of non-hereditary cases. We have recently recognized a second type of familial stomach cancer related to mutations in DNA repair genes, which make up about 2-6% of all cases. Although this finding is a significant step forward, few people are currently taking advantage of prevention strategies that rely on genetic information. Another critical need is to develop more effective treatments to enhance outcomes for stomach cancer. Research from The Cancer Genome Atlas study indicated that 70% of stomach cancers possess mutations that existing medications can target. Despite this large percentage of treatable mutations, only two therapies aimed at stomach cancer have received approval from the Food and Drug Administration. Therefore, significant progress in research concerning the causes and translation of findings into practice is crucial for improving outcomes in stomach cancer through prevention, early identification, and better treatment options.

DC

Dendritic cells (DCs) are among the key antigen-presenting cells (APCs), and various studies have highlighted their ability to combat tumors [7]. In cases of gastric cancer, a significant presence of DCs within the tumor tissue correlates with a lower chance of invasion and metastasis, as well as improved five-year survival rates. An analysis of the immune profile of four gastric cancer patients revealed that the DCs derived from monocytes showed a high expression of CD1a, CD40, CD86, HLA-DR, and CCR7 on their surfaces. They exhibited a medium expression level of CD83 and CD80, and a low level of CD14. Using DC vaccination aimed at specific tumor-associated antigens (TAAs) presents a hopeful immunotherapy option in various types of cancer. DCs can be loaded with different types of antigens, the most frequent being synthetic peptides introduced to the DCs. Other methods include the use of DC-tumor fusion vaccines, combining immature DCs with tumor cell lysate, and introducing DNA/RNA into DCs. Choosing the right approach and the specific synthesized TAAs is essential for enhancing the success of DC-based vaccination. Numerous clinical trials have confirmed the safety of DC vaccination alongside a heightened immune response against tumors in patients with esophageal and gastric cancers. In a study, nine gastric cancer patients with HER-2 overexpression were vaccinated with HER-2 peptide-pulsed DCs, leading to a specific cytotoxic T lymphocyte (CTL) response in six patients with no adverse effects. Among them, one patient maintained stable disease for three months, and another showed decreased tumor markers. In another case study, a gastric cancer patient was chosen to receive DC vaccination after experiencing negative side effects post-chemotherapy. This patient underwent seven cycles of DC targeting synthesized peptides of WT1 and MUC1. A month after receiving DC vaccination, no tumor lesions were observed, and the patient remained disease-free for 30 months. Similarly, a recent phase I/II clinical trial showed that three gastric cancer patients vaccinated with WT1 peptide-pulsed DCs experienced a stronger immune response along with a reduction in myeloid-derived suppressor cells. A comparable encouraging outcome was reported among advanced esophageal cancer patients, where

67% had a positive immune response after receiving WT1 peptide-pulsed DC vaccination combined with docetaxel. Nonetheless, out of ten patients, nine showed disease progression, and one patient died during the second vaccination cycle.

CI

Over the past ten years, computational intelligence (CI) systems have been effectively utilized to discover specific anticancer drugs or have been adeptly employed in the design and development of these medications [8]. Different cancers may respond to the same drugs, but their mechanisms can vary across different cancer types. A model based on machine learning called Elastic Net Regression (ENR) was created to predict drug sensitivity. CI learning systems have also been applied to determine drug effectiveness for ovarian cancers as well as gastric and endometrial cancers. The CI models for ovarian cancer suggested that patients should receive tamoxifen treatments, whereas for gastric cancer, the recommendation was for 5-FU. In the case of endometrial cancer, the CI prediction indicated that treatment with paclitaxel would be beneficial.

Management

Surgery involving a laparotomy stands as the primary effective treatment option, usually followed by laparoscopic staging [2]. Nonetheless, just half of the patients can undergo surgery. The Japanese have played a key role in advancing surgical techniques, and there's ongoing discussion regarding the best surgical methods. In cases of antral cancers, performing a subtotal gastrectomy is associated with fewer risks than carrying out a total gastrectomy. A thorough lymph node removal along the coeliac axis, and the hepatic and splenic arteries aids in better staging and seems to enhance chances of survival. Patients with tumors located in the mid-gastric area must undergo a total gastrectomy, while those with tumors at the gastro-oesophageal junction need a subtotal resection that includes the oesophagus, cardia, and gastric fundus. For cancers identified at an early stage, an endoscopic mucosal resection can effectively treat the disease, leading to much lower rates of complications. Chemotherapy administered around the time of surgery, particularly using platinum, fluorouracil, and docetaxel, has been demonstrated to enhance long-term survival. This approach is advisable for patients in good health, similar to the treatment for oesophageal cancer. Patients facing locally advanced diseases might become eligible for surgery following neoadjuvant chemotherapy or chemoradiation. Those with metastatic disease can be treated with combination chemotherapy based on fluoropyrimidine. These treatments have around a 35% success rate but don't significantly extend survival. Such patients are often considered for clinical trials that focus on new targeted medications and biological treatments. Individuals with HER2 overexpressing metastatic gastric or gastro-oesophageal junction adenocarcinoma, who have not had previous treatment for their metastasis, can receive trastuzumab combined with platinum-based chemotherapy and fluoropyrimidine. The usage of immunotherapy, such as nivolumab or pembrolizumab, has become more common in palliative care. Additional palliative measures may be necessary to alleviate symptoms. Endoscopic laser therapy can help minimize bleeding caused by intraluminal tumors, while rigid or expandable metallic stents can assist in relieving swallowing difficulties due to tumors at the oesophagogastric junction and stomach cardia.

Conclusion

Gastric cancer is a form of cancer that develops when harmful cells grow in the stomach. Initial signs can include weight loss and discomfort in the

stomach area. If the condition is not addressed, a tumor can develop that invades the stomach wall and may spread to nearby organs, including the liver and pancreas. The approach to treatment varies based on how far the cancer has advanced, the overall health of the patient, and personal treatment choices. Adenocarcinoma accounts for 90% of gastric cancer cases. When people talk about gastric cancer, they typically refer to the type that forms from cells lining the stomach's interior. Lymphoma, a different kind of cancer, starts in the lymph nodes but can also appear in the stomach, though this is less common. Even more infrequently, tumors that develop from hormone-releasing cells and gastrointestinal stromal tumors from the stomach wall can be found in the stomach area. Gastric cancer results from a complicated interaction of various environmental risk factors, including diet and smoking, alongside genetic risks. Approximately 70% of gastric cancer cases occur in developing nations, with a decline in these rates due to increased awareness of the disease's risk factors. It is more prevalent among men, and families with certain genetic traits show a higher likelihood of developing it. Besides genetic influences, environmental risk factors play a crucial role in the disease's progression.

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