

Gastric Cancer: Understanding its Burden, Treatment Strategies, and Uncertainties in Management

Michael R. Page, PharmD, RPh; and Shriya Patel, PharmD

GASTRIC CANCER IS ESTIMATED TO BE the fifth most frequently diagnosed cancer in the world, and the third leading cause of cancer-related death. In the United States alone, gastric cancer is responsible for more than 26,000 diagnoses and nearly 11,000 deaths each year. Both new diagnoses and deaths occur disproportionately in men, most often in older patients. The average age of diagnosis in patients with stomach cancer is 69 years, with more than half (60%) of diagnoses occurring in those 65 years or older. Although rates of gastric cancer have been declining around the world since the late 1930s, disparities in the incidence and prevalence of gastric cancer among countries indicate that there are potential important differences in genetics and lifestyle that may be contributing factors.^{1,3-5}

In the United States, gastric cancer is a relatively uncommon cancer type with the lifetime risk of developing stomach cancer estimated at less than 1%, far lower than in other countries.^{1,2} Of the more than 1.4 million new cancer cases that occur each year in the United States, gastric cancer accounts for approximately 1.5%.⁴ The United States incidence of gastric cancer has fallen dramatically since the

1930s, when the estimated incidence was 35 cases per 100,000 individuals in the population per year. By 2003, the incidence had fallen nearly 10-fold, with approximately 4 cases diagnosed per 100,000 individuals per year (FIGURE 1).^{2,5}

Although the factors behind the lowered gastric cancer risk are not fully understood, they may relate to an increased availability of refrigeration, which has both increased the availability of fruits and vegetables and reduced intake of salted or smoked foods. Other factors may include the use of antibiotics, which may kill *Helicobacter pylori* (*H. pylori*) bacteria in the stomach, a potential contributing factor in some stomach cancer cases.^{1,2,6}

The Heterogeneous Nature of Gastric Cancers

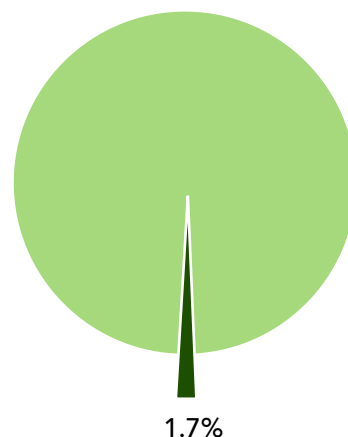
Understanding gastric cancer begins with knowledge of the stomach's 5 parts: cardia, fundus, corpus (or body), antrum, and pylorus. Together, the cardia, fundus, and corpus are known as the proximal stomach, located towards the top of the stomach, closest to the esophagus. These 3 stomach parts produce acid and digestive enzymes, as well as intrinsic factor, which is critical for absorption of vitamin B₁₂.

FIGURE 1. Estimated New Cases and Estimated Deaths by Type of Cancer⁴

Compared to other cancers, stomach cancer is relatively rare.

COMMON TYPES OF CANCER	ESTIMATED NEW CASES 2017	ESTIMATED DEATHS 2017
1. Breast Cancer (Female)	252,710	40,610
2. Lung and Bronchus Cancer	222,500	155,870
3. Prostate Cancer	161,360	26,730
4. Colon and Rectum Cancer	135,430	50,260
5. Melanoma of the Skin	87,110	9,730
6. Bladder Cancer	79,030	16,870
7. Non-Hodgkin Lymphoma	72,240	20,140
8. Kidney and Renal Pelvis Cancer	63,990	14,400
9. Leukemia	62,130	24,500
10. Endometrial Cancer	61,380	10,920
—	—	—
15. Stomach Cancer	28,000	10,960

Stomach cancer represents 1.7% of all new cancer cases in the United States



The 2 lower areas, the antrum and pylorus, are collectively known as the distal stomach (FIGURE 2^{2,7}).^{2,7}

The stomach's anatomy also includes its 5-layer wall. The mucosa is the innermost layer, followed by the submucosa, the muscularis propria, the subserosa, and then the outermost layer, the outer serosa. The outer serosa serves a protective function, and the muscularis propria mixes and agitates stomach contents. The mucosa produces digestive enzymes and acids, and this is where gastric cancers typically originate.^{2,8} As gastric cancer progresses, abnormal cells progress from inner layers of the stomach to outer layers of the stomach. As stomach cancer infiltrates the outer layers of the stomach, prognosis worsens.^{1,2}

Geographic Trends in Gastric Cancer

Examination of the age-adjusted death rate per 100,000 individuals in the population by country makes apparent that certain regions of the world—Russia, Eastern Europe, and parts of Asia—are more prone to a high incidence and prevalence of gastric cancer. Conversely, North America, Africa, the United Kingdom, Australia, and New Zealand have the lowest rates of gastric cancer.^{1,5,9}

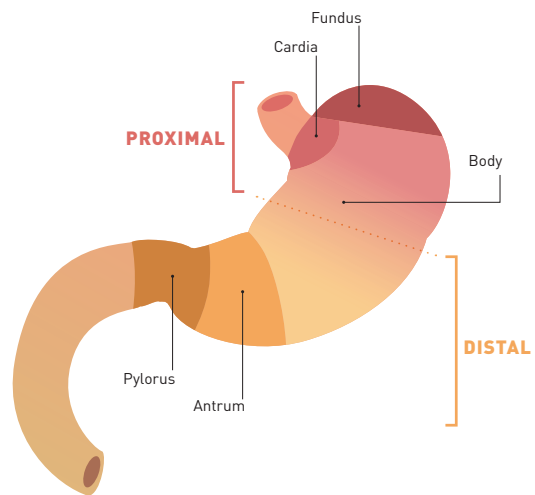
Japanese men have the highest incidence rate of gastric cancer in the world, with 116 cases occurring per 100,000 individuals. Of all new cancer diagnoses, nearly 1 in 5 new cancers diagnosed in Japan are gastric cancers.^{5,9} In considering incidence by country, including both genders, the overall incidence of gastric cancer is highest in China.¹ Gastric cancer is rarely diagnosed early in the disease, with most diagnoses occurring late, in the advanced stages of disease.¹

Just as the incidence and prevalence of gastric cancer vary regionally, rates of gastric cancer vary by ethnic population. For example, in the United States, the incidence of gastric cancer is 21.6 cases per 100,000 among those of Native American ancestry, and 20 cases per 100,000 in those of Asian background. However, the 5-year overall survival rate in patients of all ethnic backgrounds who develop gastric cancer does not vary substantially.^{4,5,10}

Although the incidence of gastric cancer varies internationally, incidence rates do not necessarily correlate to mortality. In European Union countries, for example, mortality rates are higher than in non-Western populations, because gastric cancer is encountered more commonly in non-Western populations and thus is often detected earlier in the disease process. Delayed diagnosis of gastric cancer in Western populations contributes to the presence of later-stage disease at initial diagnosis, resulting in increased rates of mortality, despite its lower incidence and prevalence.^{1,5,11}

Gastric cancers may also be classified by their histologic characteristics: undifferentiated (intestinal-type histology) or well differentiated and diffuse. Importantly, the

FIGURE 2. Areas of the Stomach^{2,7}



Adapted from American Cancer Society website. www.cancer.org/cancer/stomach-cancer/about/what-is-stomach-cancer.html. Updated February 10, 2017. Accessed May 22, 2017 and Barrett KE. *Gastrointestinal Physiology*. 2nd ed. New York, NY: McGraw-Hill Education; 2014: 147-164.

incidence of diffuse histologic cell types in gastric cancer is observed with approximately equal incidence and prevalence throughout the world, and is associated with diffuse gastritis without tissue atrophy. Gastric cancers with histologic characteristics of an intestinal type are observed more frequently in areas with abnormally high incidence and prevalence of gastric cancer. Gastric cancers of an intestinal subtype predictably progress from metaplasia to cancer in a well-characterized step-wise process.^{5,12}

Types of Gastric Cancer

There are 4 main types of gastric cancers, the most common by far of which is adenocarcinoma, diagnosed in 90% to 95% of cases. Adenocarcinomas typically develop in the mucosal layer and grow slowly.

The other gastric cancer types most often seen are lymphoma, gastrointestinal stromal tumors, and carcinoid tumors.^{2,13} Lymphomas account for approximately 4% of all gastric cancers. They have a heterogeneous pattern of pathogenesis and prognosis, with patient outcomes varying widely depending on the lymphoma's specific characteristics. Even rarer are gastrointestinal stromal tumors, which form in a set of cells located in the stomach wall known as the interstitial cells of Cajal, and carcinoid tumors, which occur in hormone-producing cells of the stomach. Other cancer types that occur exceedingly rarely in the stomach include squamous cell carcinoma, small cell carcinoma, and leiomyosarcoma.² »

Gastric Cancer and *H. Pylori*

Another factor associated with gastric cancer in certain populations is a high frequency of infection with *H. pylori*. Although it is not fully understood how *H. pylori* might increase the risk of gastric cancer, this rod-shaped helical bacterium has been classified since 1994 as a type I carcinogen by both the International Agency for Research on Cancer and the World Health Organization.^{11,14} Notably, *H. pylori* infection is most often associated with gastric cancers of the intestinal histologic subtype, which are observed more frequently in some areas of the world than others. Additionally, infection with *H. pylori* is not associated with all types of gastric cancer. *H. pylori* infection is only an independent risk factor for distal gastric cancer, and is not an independent risk factor for proximal forms of gastric cancer.⁵ Finally, although *H. pylori* infection is associated with 3- to 6-fold increase in the risk of developing gastric cancer, the vast majority of individuals infected with *H. pylori*—more than 99%—will never develop gastric cancer.⁵

The role of *H. pylori* in gastric cancer does not explain other epidemiologic factors and relationships. For example, risk factors for gastric cancer of the diffuse histologic subtype or of the cardia (a proximal form of gastric cancer) include higher socioeconomic class, obesity, and having type A blood.^{5,15} The complexity of gastric cancer epidemiologic factors point to an integrated understanding of the underlying causes.

Comorbidities associated with gastric cancer beyond *H. pylori* infection include adenomatous polyposis of the gastric tissue, chronic atrophic gastritis, intestinal metaplasia, and pernicious anemia. Other factors are related to diet, environment, occupation, and lifestyle. For example, frequent intake of heavily salted, smoked, and high-fat foods, in combination with low fruit and vegetable consumption, is a characteristic dietary pattern associated with gastric cancer. Smoking and frequent consumption of alcohol may also be related.^{1,5,10}

Other Risk Factors for Gastric Cancer

Environmental factors—such as acidic agricultural soil; use of nitrate fertilizers; and increases in water-supply levels of nitrates, lead, or zinc—may also be associated with increased risk for gastric cancer. Workers in certain occupations, too, including mining and metallurgical work, may be at increased risk.^{5,10}

Certain genetic factors increase risk. Specific mutated genes, such as *MCC*, *APC*, and *p53*, are found in a significant percentage of gastric cancer tumors. Another gene whose presence increases risk is *cadherin-1 (CDH1)*, which is an adhesion molecule that depends on calcium and serves to facilitate binding of adjacent cells. The genetic locus that encodes E-cadherin, *CDH1*, is often mutated in families that have increased susceptibility to gastric cancer,

possibly due to the *CDH1* mutations causing increased permeability of cells.^{1,5,15}

Other syndromes associated with gastric cancer include familial adenomatous polyposis, Cowden disease, hereditary diffuse gastric carcinoma, Li-Fraumeni syndrome, and hereditary nonpolyposis colorectal cancer syndrome. Many other genetic alterations are also often identified in gastric cancer with varying frequency.⁵

Signs and Symptoms of Gastric Cancer

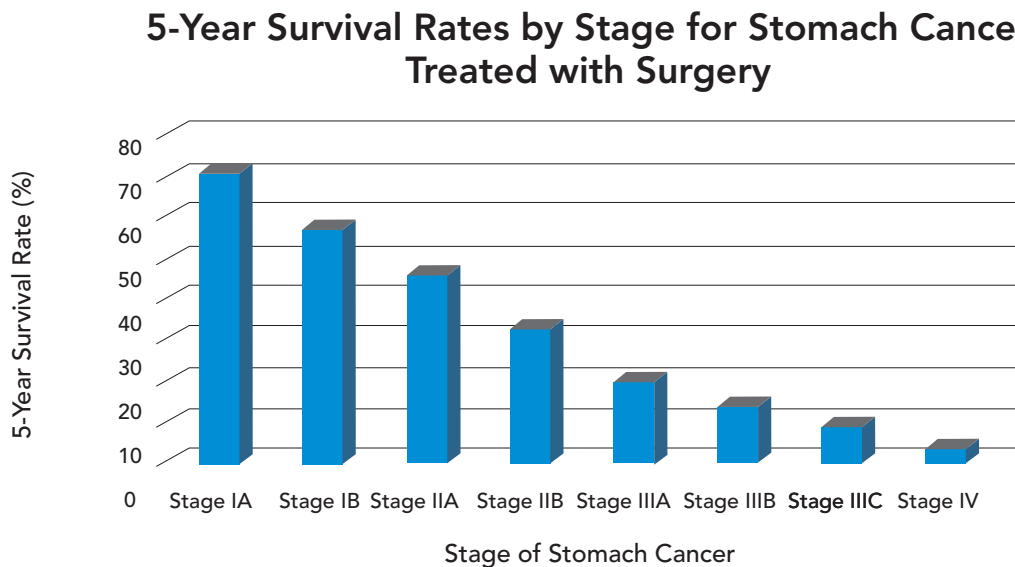
In most cases, stomach cancer in its early stages has few signs and symptoms. What symptoms there are may be nonspecific, contributing to difficulties in early detection and diagnosis. Patients with stomach cancer may experience poor appetite, involuntary weight loss, abdominal pain, abdominal discomfort (typically above the navel), a sense of fullness of the upper abdomen after eating a small meal, nausea, heartburn, indigestion, vomiting, anemia, or fluid buildup in the abdomen. Although these symptoms are more commonly related to other conditions, such as ulcers or viral infections of the stomach, symptoms that persist may more likely be associated with stomach cancer. Unfortunately, due to the symptoms' nonspecific nature, only about 20% of US stomach cancers are detected in their early stages, prior to metastasis.²

The diagnosis of stomach cancer is typically initiated following signs or symptoms that may be suggestive of the condition. Diagnostic tests beyond a medical history and physical may include upper endoscopy, endoscopic ultrasound, biopsy, and imaging, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), x-ray, laparoscopy, and other laboratory testing.²

The most common initial step in diagnostic testing for gastric cancer is an upper endoscopy or esophagogastroduodenoscopy (EGD). In this test, an endoscope is used to visually examine the lining of the esophagus, the stomach, and the upper portion of the small intestine. Visual abnormalities of these areas may result in further investigation through biopsy and histologic examination of tissue.²

In some cases, EGD is followed by an endoscopic ultrasound, in which an ultrasound transducer on the interior of the stomach examines the characteristics of stomach layers and the lymph nodes surrounding the stomach. This procedure may be helpful in guiding a biopsy of abnormal areas within or near the stomach. Tissue samples obtained through biopsy are examined histologically under a microscope, and may be tested for the presence of the *HER2* gene. Presence of this gene indicates that targeted therapies such as trastuzumab may be useful in treatment.²

Other imaging tests include x-rays of the inner lining of the esophagus, stomach, or small intestine with the aid of

FIGURE 3. 5-year Survival Rates by Stage for Stomach Cancer Treated With Surgery In the United States²

Adapted from American Cancer Society website. www.cancer.org/cancer/stomach-cancer/about/what-is-stomach-cancer.html. Updated February 10, 2017. Accessed May 22, 2017.

a barium swallow. CT scanning may also help characterize the structure of the stomach's affected areas, which is helpful to guide a needle biopsy. For more detail, MRI may be used, although CT is the preferred method of examining the stomach. PET can help determine whether the cancer has metastasized beyond the stomach by examining metabolically active areas through uptake of fluorodeoxyglucose (a radiolabeled glucose analog). Treatment options vary by presence and degree of metastasis.²

Staging of Stomach Cancer

The clinical and pathological staging of stomach cancer help determine the appropriate course of treatment. The determination of the clinical stage is based primarily on the physician's understanding of the extent of the cancer's progression based on the results of physical exams, endoscopies, imaging, and biopsies, and through direct surgical sampling of a tumor. Pathologic staging helps to further understand the extent of cancer severity.²

The staging system commonly used is the tumor nodes metastases (TNM) system designed by the American Joint Commission on Cancer. It is used for many cancer types to characterize the extent of a primary tumor, the number of nearby lymph nodes affected, and whether or not a tumor has metastasized to other parts of the body.² Through TNM scoring, gastric cancer may be characterized as stage 0, I, II, III, or IV, with substages denoted by the letters A, B, and C.²

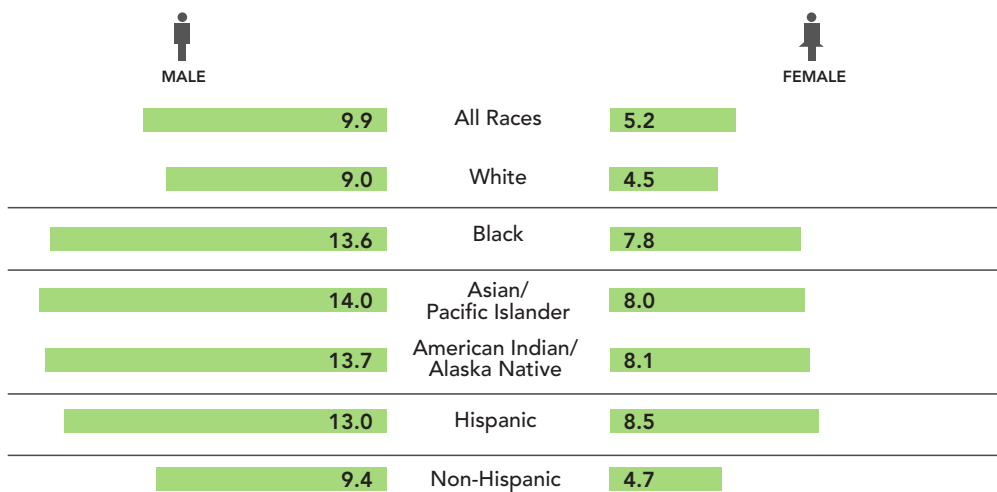
The 5-year survival rate of stomach cancer depends on the stage of cancer at diagnosis: It ranges from 71% in stage IA cancers to 4% in stage IV gastric cancers. Overall, the 5-year survival rate of all US patients with gastric cancer is approximately 29% (FIGURE 3).² Although this survival rate has gradually improved over the past 3 decades, the vast majority of US stomach cancers are diagnosed when patients already have late-stage disease.^{2,4} Characteristics of patients by age of diagnosis and mortality rates are detailed in FIGURE 4⁴ and FIGURE 5⁴.

Treatment of Gastric Cancer

The general treatment options in stomach cancer include surgery, chemotherapy, targeted therapy, and radiation therapy. However, their application may include choosing among hundreds of possible pathways and methods of treatment that vary by gastric cancer subtype and the extent and severity of disease. A physician will consider both the potential benefits and risks of a treatment in selecting therapy, with treatment decisions based largely on the tumor stage at baseline and the patient's age, health status, and treatment goals.² As with any cancer, clinical trial results should also be considered.²

Physician specialists involved in the treatment of gastric cancer include gastroenterologists, surgical oncologists, medical oncologists, and radiation oncologists. Many other professionals participate as well, including nurse »

FIGURE 4. Number of New Cases Per 100,000 Persons with Gastric Cancer by Race/Ethnicity and Sex, US, 2010-2014⁴



SEER 18 2010-2014, Age-Adjusted

practitioners, nutrition specialists, social workers, nurses, and pharmacists. Given the many combinations of treatment available for gastric cancer and uncertainties about optimal management, multidisciplinary care of patients with gastric cancer is an important priority.^{1,2,16}

Surgery

The option of surgery is generally limited to patients with stage 0, I, II, or III gastric cancer who are healthy enough to undergo surgery. Most often, surgical management includes the removal of the primary tumor and proximal lymph nodes. Surgical removal of early-stage cancers may, in some cases, be accomplished through endoscopic surgery. However, endoscopic surgery is less common in the United States than in other countries such as Japan, where diagnoses of early-stage gastric cancer are more common.^{1,2,11}

Non-endoscopic surgical options for more advanced gastric cancer include subtotal gastrectomy, the excision of either the lower or upper portion of the stomach, typically used when the cancer is localized either proximally or distally. When cancer is present in both the upper and lower stomach, total gastrectomy may be necessary. This involves excision of the entire stomach as well as surrounding lymph nodes, and, in some cases, the spleen, parts of the esophagus, sections of the intestine, and the pancreas. Patients who undergo subtotal gastrectomy are more able to consume food than patients who undergo total gastrectomy.²

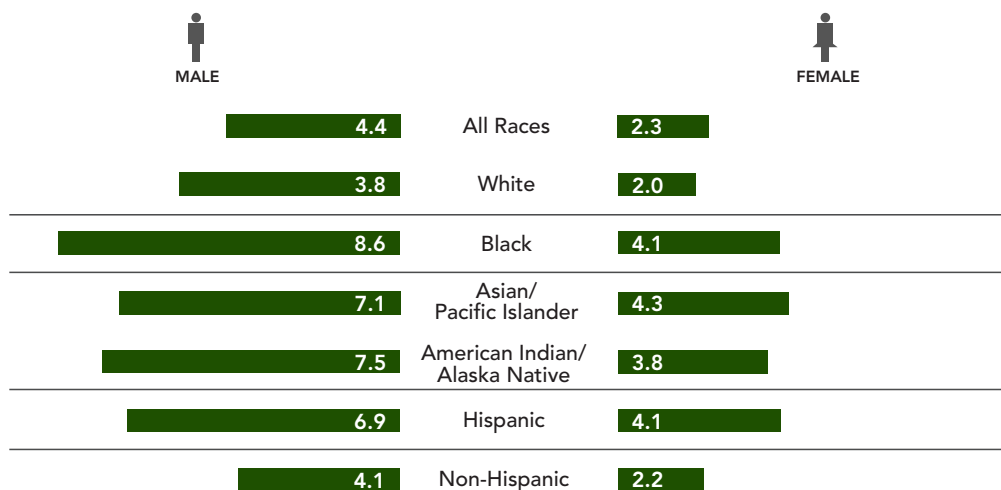
Following surgery, tube feeding is frequently the only mode of nutritional support, with more frequent administrations of enteral nutrition necessary in patients who have undergone total versus subtotal gastrectomy.²

In gastrectomy, extensive excision of lymph nodes may be related to outcomes. With removal of at least 15 lymph nodes, the subtotal or total gastrectomy may be known as a D1 lymphadenectomy, whereas removal of additional lymph nodes is known as a D2 lymphadenectomy. While D1 lymphadenectomy is typically performed in the United States, D2 lymphadenectomy has been performed with greater success in Japan.^{1,2,17}

In some patients, surgery is a palliative rather than a curative strategy. Palliative surgical options in patients with unresectable gastric cancer include subtotal gastrectomy, gastric bypass, endoscopic tumor ablation, stent placement, and surgical feeding tube placement with either a gastrostomy tube or a jejunostomy tube.^{1,2} Patients must be carefully selected for surgery, as complications of surgery may include bleeding, thromboembolism, and damage to surrounding organs. Although improvements in surgical techniques have reduced surgical mortality rates to 1% to 2%, the mortality outcome of any particular surgery is related to the skill of the surgeon as well as to the extent of lymph node removal.²

Chemotherapy

Chemotherapy for stomach cancer may include neoadjuvant treatment (chemotherapy administered before surgery) or adjuvant therapy (chemotherapy administered

FIGURE 5. Number of Deaths Per 100,000 Persons with Gastric Cancer by Race/Ethnicity and Sex, US, 2010-2014⁴

US 2010-2014, Age-Adjusted

after surgery). The goal of neoadjuvant treatment is to reduce the size of a tumor to enable surgical resection, while adjuvant therapy is intended to eliminate any remaining tumor after an initial surgical procedure. In some cases, radiation therapy may also be used after surgery. In metastatic disease, surgical therapy may not be possible, and chemotherapy may be the only treatment used. In this case, chemotherapy is typically palliative, not curative, used to relieve symptoms and increase lifespan.^{1,2}

The various chemotherapeutic agents that may be used to treat gastric cancer include the orally administered antimetabolite capecitabine (similar to 5-fluorouracil), which is often used with leucovorin. Others include platinum agents such as carboplatin, cisplatin, and oxaliplatin; taxanes such as docetaxel and paclitaxel; the anthracyclines epirubicin or daunorubicin; and the topoisomerase I inhibitor, irinotecan.^{1,2,18}

Chemotherapeutic agents are often used in combination, 2- or 3-drug regimens administered in multiple treatment cycles. Many regimens are designed for the management of gastric cancer, but the lack of standardization of therapy remains a challenge for treatment selection and optimization. One common 3-drug regimen combines epirubicin, cisplatin, and 5-fluorouracil; another includes docetaxel, cisplatin, and 5-fluorouracil. Although most regimens contain 2 or 3 chemotherapeutic medications, 2-drug combinations are generally preferred over 3-drug regimens for palliative (rather than curative) treatment.^{1,2,19}

Radiation Treatment and Other Therapies

Radiation therapy is often combined with chemotherapeutic medications for gastric cancer treatment. It may be used before or after surgery, or as a palliative option to allay the symptoms of advanced gastric cancer. Options include external beam radiation therapy, 3-dimensional conformal radiation therapy, and intensity-modulated radiation therapy. All are designed to tackle the cancer while minimizing potential damage to tissues near the sites of primary tumors. Adverse events related to radiation therapy may include blistering or peeling of the skin, nausea and vomiting, diarrhea, fatigue, and blood dyscrasias.²

Targeted Therapy

Targeted therapies tend to be better tolerated than chemotherapy. The 2 targeted treatments available in management of gastric cancer are the *HER2* targeting agent trastuzumab, and the vascular endothelial growth factor inhibitor ramucirumab. While trastuzumab may be used in the approximately 20% of gastric cancers that express *HER2* to improve survival duration versus chemotherapy alone, it may increase the risk of cardiac side effects if used in combination with anthracyclines.^{1,2}

The antiangiogenic therapy of ramucirumab inhibits the formation of new blood vessels in tumors to help slow the advance of stomach cancer throughout the body. Treatment may affect blood pressure and may be associated with adverse effects (headache, diarrhea, blood clots, bleeding, perforations of the stomach or intestine, and impaired wound healing).² »

Conclusions

The management of gastric cancer is challenging due to frequent late-stage diagnoses; the varying types, presentations, and histologic subtypes; and the lack of standardization of care. Since most US patients are diagnosed with gastric cancer at a late rather than earlier stage, oncologists should select therapy based on patient-specific factors, including patient fitness for surgical procedures, the tolerability and adherence characteristics of chemotherapeutic medications, and the patient's goals for treatment. Managing lines of therapy throughout the disease process and ensuring optimal use of available treatments must be priorities to improve outcomes for patients with this disease. ■

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