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# Gastric Cancer: Local and Global Burden

*Lynne Lederman, PhD*

## Introduction and Epidemiology

Cancer is a leading cause of death worldwide in both developed and developing countries. In 2012, 14.1 million new cases of cancer were diagnosed and 8.2 million deaths were estimated to have occurred worldwide.<sup>1</sup> In the United States alone, 1,688,780 new cases of cancer and 600,920 deaths are estimated for 2017.<sup>2</sup> As populations grow and age, the burden of cancer will increase, particularly for less developed countries.<sup>1</sup>

Here, we will look at the changing burden of gastric cancer worldwide and in the United States. The incidence of some types of cancers, including gastric cancer, is different in developed versus developing countries; rates also vary between men and women and by ethnicity.<sup>1</sup> Gastric cancer occurs about twice as frequently in men than in women, and it leads to more deaths in men.<sup>1,2</sup> It is the third leading cause of cancer deaths in men worldwide, after lung cancer and liver cancer. In women, it is the fifth leading cause of cancer deaths, after breast, lung, colorectal, and cervical cancer.<sup>1</sup>

The estimated numbers of new cases, by sex, of gastric cancer and of gastric cancer deaths worldwide, in developed versus developing countries, and in the United States, are summarized in the [TABLE](#).<sup>1,2</sup>

The occurrence of gastric cancer is highest in Eastern Asia, especially in Korea, Mongolia, Japan, and China, as well as in Central and Eastern Europe, and South America. The lowest incidence is in North America and most of Africa.<sup>1</sup>

In the United States, the incidence of gastric cancer is highest in non-Hispanic blacks, individuals of Asian and Pacific Island descent, and Hispanic and Latino individuals; in these populations, the incidence is nearly twice that of non-Hispanic white individuals, who have the lowest incidence. Native American and Alaskan populations have an incidence of gastric cancer higher than that of non-Hispanic whites, but lower than that of other ethnic populations. Although death rates related to gastric cancer are similar among all ethnic populations, among non-Hispanic whites, rates of death related to gastric cancer occur at approximately half the rate observed in other ethnic populations.<sup>2</sup>

In general, staging of cancer is based on the size and location of the primary tumor, whether the tumor has spread locally or invaded adjacent structures, if local lymph nodes are involved, or if the tumor has spread distantly (ie, metastasized). Clinical staging is based on the results of physical examinations, imaging tests, and biopsies. The pathologic or surgical stage can be determined if surgery is performed to remove the tumor and/or lymph nodes, or to take a biopsy. When the clinical and pathologic stages differ, the pathologic stage is more accurate for determining treatment options and prognosis.<sup>3</sup>

Expected survival is related to the stage at diagnosis. The 5-year relative survival rates for all stages of gastric cancer at diagnosis were 30% over the last decade in the United States. For gastric cancer diagnosed as local (con-

**TABLE.** Estimated New Cases of Gastric Cancer and Deaths<sup>1,2</sup>

REGION	ESTIMATED NEW CASES		ESTIMATED DEATHS	
	MEN	WOMEN	MEN	WOMEN
Worldwide	631,300	320,300	469,000	254,100
Developed countries <sup>a</sup>	175,100	99,400	106,700	68,000
Developing countries	456,200	220,900	362,300	186,100
United States <sup>b</sup>	17,750	10,250	6720	4240

<sup>a</sup>Not including the United States.<sup>b</sup>Estimated for 2017.

financed entirely to the stomach), the 5-year relative survival rate is 67%; for gastric cancer diagnosed at a regional stage (because it has extended beyond the stomach into adjacent tissues, or involves regional lymph nodes, or both), or at a distant stage (having spread to sites distant from the stomach by extension or metastasis), the 5-year relative survival rates drop to 31% and 5%, respectively.<sup>2</sup>

The risk factor for gastric cancer that has been most clearly identified is chronic infection with *Helicobacter pylori* (*H. pylori*).<sup>1</sup> Other general risk factors for gastric cancer include being overweight or obese, heavy drinking, and cigarette smoking. Cigarette smoking is estimated to contribute to 20% of gastric cancer deaths.<sup>2</sup>

In the United States, the rate of gastric cancer has declined steadily since the 1930s. For all ethnicities, the 5-year relative survival rate has increased over the last 4 decades.<sup>2</sup> A steady decline in gastric cancer's incidence and mortality has also been observed in other parts of North America and in Europe. This decline is thought to be due to reduction in chronic infection with *H. pylori* as well as to the increased availability of fresh fruits and vegetables and decreased use of salt-preserved food.<sup>1</sup>

Strategies to prevent gastric cancer include increased intake of fresh fruits and vegetables; reduced intake of salted, smoked, or preserved foods; and reduction of *H. pylori* infection through improved sanitation and antibiotic use.<sup>1,2</sup> Clinical trials of screening for and treatment of *H. pylori* infection to prevent gastric cancer are ongoing. However, additional studies may be needed to determine how to best implement prevention programs, to establish which populations should be treated, and to identify possible negative effects of gastric cancer preventive measures. For instance, measures taken such as the elimination of *H. pylori* might result in the elimination of the possible protective effects of *H. pylori* against other health conditions. In addition, alteration of the gut microbiome could have unforeseen detrimental effects, and could result in proliferation of antibiotic-resistant strains of bacteria, and alteration of the gut microbiome.<sup>4</sup>

### Historical Perspectives on Treatment

Gastric cancer was first recognized millennia ago, as early as 1600 BC, but not until the late 1800s was surgery used to treat it. The first surgeries defined as successful, meaning survival of the patients past the perioperative period, were performed by 2 different surgeons; they included a subtotal resection with gastroduodenal anastomosis in 1881, and a total gastrectomy with an esophagojejunostomy for reconstruction in 1897. Although both patients subsequently died of recurrences, refinements of the surgical procedures led to the eventual adoption of surgery as an accepted treatment modality for gastric cancer.<sup>5</sup>

In the early 1950s, the chemotherapeutic agent nitro-min was used to treat advanced gastric cancer in Japan. Relatively primitive, nitro-min was a derivative of nitrogen mustard, a chemical weapon, and its use resulted in minimal therapeutic benefit and serious adverse events. The late 1950s saw the introduction of mitomycin C and 5-fluorouracil (5-FU),<sup>6</sup> agents still used today against advanced gastric cancer.<sup>7</sup> Agents introduced in the late 1960s include tegafur, the prodrug of fluorouracil, and adriamycin; these agents resulted in response rates of 20% with little survival benefit. However, the combination of 5-FU, adriamycin, and mitomycin C, used as a standard regimen in Western countries, resulted in response rates of 50%, although not in all settings.<sup>6</sup> In the late 1970s, the use of cisplatin in combination therapy resulted in improved responses. More recently, higher response rates and survival benefits have been obtained with combinations such as cisplatin plus 5-FU or irinotecan; and with tegafur, gimeracil, and oteracil, known as S-1. S-1 is approved and used in Japan and Europe, but in the United States it is still considered investigational and is not used.<sup>6,7</sup>

While chemotherapy was being introduced as a treatment regimen for advanced gastric cancer, it was also being investigated as adjuvant therapy after curative gastrectomy to prevent recurrence—mixed results occurred. As better chemotherapy agents for advanced gastric cancer were developed, they were also used for neoadjuvant therapy »

preoperatively as an alternative to surgery for patients with locally advanced gastric cancer. Chemotherapy agents were also used for those with inoperable advanced gastric cancer, with the goal of downstaging tumors to render them operable.<sup>6</sup>

### Modern Perspectives on Treatment

The modern recommended approach to treatment of gastric cancer considers the clinical and pathologic stage of the disease, the patient's fitness for surgery, and the presence of an actionable biomarker, human epidermal growth factor receptor 2 (*HER2*) overexpression, which may respond to anti-*HER2* monoclonal antibodies.<sup>8</sup>

Surgery remains the primary treatment for patients with early-stage gastric cancer. Clinical staging determines the extent of the disease before surgery, and the goal is complete resection with adequate margins. No consensus exists on the best type of resection (subtotal vs total gastrectomy) or the extent of lymph node dissection.<sup>7</sup>

In East Asia, treatment consists of gastrectomy with D2 lymph node resection (ie, removal of involved proximal or distal part of the stomach, or entire stomach, including the greater and lesser omental lymph nodes, plus removal of all the nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery). In Western countries, although extended lymph node dissection of distant lymph nodes allows accurate staging, it is associated with increased survival in some, but not all, clinical studies. D2 lymph node dissection is recommended, but not required. There is agreement that removal of 15 or more lymph nodes aids in staging.<sup>7</sup>

Newer surgical approaches that reduce morbidity compared with open surgery include laparoscopic resection and endoscopic therapies, including endoscopic mucosal resection and endoscopic submucosal dissection. Laparoscopic resection requires further study. The endoscopic approaches are major advances in the treatment of early-stage gastric cancer, and are therefore less applicable in the United States, where gastric cancers tend to be diagnosed in advanced stages.<sup>7</sup>

Radiation therapy has been used both presurgically and post surgically for patients with more advanced gastric cancer, and it may provide some benefit, including reduction of locoregional recurrence and higher resection rates, particularly if used in combination with chemotherapy (as chemoradiation) in resectable gastric cancer, either preoperatively or perioperatively.<sup>7,8</sup> Chemoradiation or chemotherapy is recommended for patients with surgically unresectable gastric cancer and for those who are not surgical candidates. Unresectable gastric cancers may become surgically resectable after treatment.<sup>8</sup>

Currently, chemotherapy regimens for gastric cancer are fluoropyrimidine-based (eg, fluorouracil or capecitabine)

or taxane-based. Postoperative treatment is determined by the stage, the completeness of the resection, the presence or absence of positive lymph nodes, and whether chemotherapy was received preoperatively. Patients who experience locoregional recurrence may be offered surgery; those with unresectable locoregional recurrence and those with metastatic disease at diagnosis or after initial therapy may be offered palliative management. For those with good performance status, palliative management may include systemic therapy, enrollment in a clinical trial, or palliative or best supportive care. Those with poor performance status should be offered palliative or best supportive care.<sup>8</sup>

Regimens in advanced gastric cancer may be described by treatment setting. Key treatment settings include preoperative chemoradiation, perioperative chemotherapy, postoperative chemoradiation, and postoperative chemotherapy for patients who have undergone primary D2 lymph node dissection. Preferred regimens for patients receiving preoperative chemoradiation include paclitaxel plus carboplatin, or fluorouracil used with either cisplatin or oxaliplatin (category 1 recommendation). Other regimens for patients receiving preoperative chemoradiation may include paclitaxel plus fluorouracil or capecitabine (category 2B recommendation).<sup>8</sup>

In the setting of perioperative chemotherapy, which includes 3 cycles of treatment preoperatively and 3 cycles of treatment postoperatively, treatments used include fluorouracil and cisplatin (category 1 recommendation); or epirubicin plus cisplatin or oxaliplatin plus fluorouracil or capecitabine (category 2B recommendation).<sup>8</sup>

In the setting of postoperative chemoradiation, treatments may include infused fluorouracil or capecitabine before and after fluoropyrimidine-based chemoradiation (category 2A evidence). For patients receiving postoperative chemotherapy who have previously undergone primary D2 lymph node dissection, treatment may consist of capecitabine plus either oxaliplatin or cisplatin (category 1 recommendation).<sup>8</sup>

Patient performance status and comorbidities and agent adverse effect profiles should be used to select therapies. For example, 2-drug regimens are less toxic than 3-drug regimens, and may be more appropriate for patients with lower performance status. Note that category 1 regimens are based on high-level evidence, and the National Comprehensive Cancer Network considers category 1 regimens to be appropriate for therapy. Category 2 interventions are based on lower-level evidence, with uniform consensus (category 2A) or merely consensus (category 2B) that the intervention is appropriate.<sup>8</sup>

Preferred regimens for second-line therapy for gastric cancer include the targeted agent ramucirumab (an anti-vascular endothelial growth factor-2 monoclonal anti-

body) alone or in combination with paclitaxel; docetaxel, paclitaxel, or irinotecan as single agents; and fluorouracil plus irinotecan if not previously used for first-line therapy. Another targeted agent, trastuzumab (an anti-HER2 monoclonal antibody for HER2-positive tumors in combination with chemotherapy for previously treated disease), is also approved for advanced or metastatic gastric cancer.<sup>7</sup>

Other targeted therapies have been investigated in advanced gastric cancer. Results have not been promising for nivolumab, an anti-programmed cell death 1 (PD-1) antibody as salvage therapy after failure of 2 or more prior standard chemotherapy regimens for advanced gastric or gastroesophageal junction cancer. Patients at this stage of the disease have few if any other treatment options. In a phase 3 randomized trial, although median overall survival (OS) and progression-free survival (PFS) were significantly longer for nivolumab versus placebo, the actual increase was only 1.18 months for OS (median OS: 5.32 months with nivolumab vs 4.15 months with placebo;  $P < .0001$ ) and 0.16 months for PFS in the nivolumab group (median PFS: 1.61 months with nivolumab vs 1.45 months with placebo;  $P < .0001$ ).<sup>9</sup>

In 2 phase 3 trials, treatment with ramucirumab resulted in significant survival benefits with manageable toxicity in patients with advanced gastric cancer in the second-line setting. Patients in 1 trial received best supportive care plus ramucirumab or placebo; patients in the other trial received paclitaxel plus ramucirumab or placebo. A pooled analysis of these 2 trials showed efficacy of ramucirumab in all age groups, with similar adverse event rates among age groups, supporting the use of ramucirumab to treat gastric cancer regardless of patient age.<sup>10</sup>

Some fluorouracil-based regimens require the administration of leucovorin. Leucovorin has been in short supply in the United States, requiring management strategies. Levo-leucovorin is an alternative agent used in Europe. Although leucovorin dose modifications are possible, specific supporting data are lacking.<sup>7</sup>

In addition to the use of tumor-specific therapy, management of gastric cancer requires supportive care for common complications of the disease and its therapy, including bleeding, obstruction, pain, and nausea and vomiting.<sup>7</sup>

### Looking Ahead

In the United States, a country where the incidence of gastric cancer is relatively low, the cost of treating this disease was estimated to be \$1.8 billion in 2010 and is predicted to increase over the following decade.<sup>11</sup> However, the National Cancer Institute spent less than \$12 million on gastric cancer research in 2014, the most recent year for which data are available; of this, only 12% was allocated to early detection, diagnosis, and prognosis, 10% to prevention, and 6% to treatment.<sup>12,13</sup> It is

difficult to predict the future of funding for research on gastric cancer in the United States and elsewhere.

The worldwide burden of gastric cancer is substantial. Survival remains poor and there is a dearth of therapeutic options after first-line therapy.<sup>14</sup> Although progress in the treatment of gastric cancer is continuing, unanswered questions and unmet needs remain. These include identification and implementation of population-specific strategies to prevent gastric cancer; strategies to identify it at earlier, treatable stages; the development of less invasive yet effective surgical procedures; and the evolution of more effective chemoradiation and chemotherapy regimens. ■

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