



# Advances in the Management of Gastric Cancer

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**Cover image:** CT Scan of the abdomen showing stomach cancer. The liver is seen in blue, the vertebrae of the spine is white. The stomach occupies the right part of the abdomen in green and black. The tumor appears as a whitish spot. Credit: AIRELLE-JOUBERT/Photo Researchers, Inc. All rights reserved.



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# Continuing Medical Education

## Textbook

Activity release date: December 1, 2006  
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### About the Activity

This activity is based on the book, *Advances in the Management of Gastric Cancer*. It was developed from an identified educational need for information about practical management issues in the practice of medical, surgical, and radiation oncology.

This activity has been developed and approved under the direction of Beam Institute.

### Activity Learning Objectives

After reading *Advances in the Management of Gastric Cancer*, participants should be able to:

- Discuss gastric cancer in terms of its epidemiology, risk factors, testing, and diagnosis.
- Review ways in which surgeons now offer patients data-driven, customized cancer treatment for gastric malignancy.
- Summarize the rationale for treating gastric cancer patients scheduled for surgery with adjuvant chemotherapy or neoadjuvant chemotherapy with or without radiotherapy and the results of studies using various regimens in this population.
- Contrast research results found with the use of single-agent chemotherapy and combination antineoplastic regimens in gastric cancer patients, and review supportive care measures available to quell symptoms and adverse effects.
- Describe progress made in treating stomach cancer and current directions in researching the disease and developing new therapies (e.g., cytotoxic combination therapy, targeted biologic therapy).

## Target Audience

This activity targets physicians in the fields of oncology and gastroenterology.

## Accreditation

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## Financial Disclosure

Dr. MacDonald serves on the speaker's bureau for Sanofi-Aventis, BMS and Imclone. Dr. Cunningham is a consultant and serves on the advisory board for Roche and Sanofi-Aventis; he also receives honoraria from Pfizer. The following contributors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in the article: Dr. Chua, Dr. Hundahl, Dr. Mahtani, Dr. O'Dea, Dr. Shah, Dr. Mitchell, and Dr. Waltzman.

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## Introduction

Gastric cancer remains a challenging problem in oncology. This book is designed to provide an updated summary of the current status of gastric cancer diagnosis and management and to show what the future possibilities in the management of stomach cancer might be. In their chapters, Dr. Hundahl provides an update on the role of surgery in gastric cancer, emphasizing that it is now possible to tailor surgical approaches to individual patients; Drs. Chua and Cunningham provide important information documenting the recently demonstrated benefits of perioperative chemotherapy in improving the outcome of patients with gastric cancer; Drs. Mahtani and Waltzman discuss the important gains in cure rates resulting from the use of post-gastrectomy chemoradiation, which has made this approach a standard of care in the view of many clinicians; Dr. Mitchell reviews the current status of cytotoxic chemotherapy in stomach cancer, emphasizing the many chemotherapeutic options available and the reasoning that clinicians use in choosing the right treatment option for the right patient; and Drs. Shah and Ilson share their views of the future directions that will be pursued in the management of this disease. These experienced clinicians provide a critical analysis of the roles of targeted therapies for patients with stomach cancer.

Although it is clear that in the past several decades some strides have been made in improving outcomes in gastric cancer, it is still a fact that too many patients diagnosed with gastric cancer will succumb to their disease. It is hoped that this book, which reviews the most recent management strategies and provides an informed glimpse of what the future approaches might be, will leave clinicians with a sense of optimism for what they may do now for their patients and what progress the future will undoubtedly hold.

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# Gastric Cancer Overview

Denise G. O’Dea, ANP, OCN, and

John S. Macdonald, MD, FACP

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## Epidemiology

Gastric cancer represents a challenging health problem around the world. It is the fourth most common cancer behind lung, breast, and colon and rectum cancers. The most recent analysis of the worldwide incidence and mortality from gastric cancer showed that 934,000 cases of gastric cancer occurred in 2002, and 700,000 patients die annually of this disease (1). In the United States, it is estimated that 22,280 new cases of gastric cancer will occur in 2006, and, as a result, 11,430 deaths are expected (2).

There are significant geographic variations in the incidence of gastric cancer. Most gastric cancers occur in developing countries. An estimated 42% of cases worldwide occur in China alone. This disease is far more common in geographic areas such as East Asia, Eastern Europe, Costa Rica, and parts of Central and South America than it is in the United States or Western Europe (1). In most countries, the incidence and death rates for men are twice as high as those for women. In high incidence countries (1,2), the intestinal form of gastric cancer associated with intestinal metaplasia and *Helicobacter pylori* (*H. pylori*)–mediated gastritis is significantly more common than the diffuse form.

Japan is the only country demonstrating a moderately good survival rate in patients diagnosed with stomach cancer. This finding is likely due to earlier diagnosis secondary to mass screening, including the use of newer endoscopic techniques such as photofluoroscopy (1). In North America, survival is improving secondary to greater numbers of endoscopic examinations for various upper abdominal symptoms, leading to earlier diagnosis of cancer.

A small percentage of gastric cancers are hereditary, but the vast majority are related to environmental, socio-economic, and dietary risk factors. In most economically developed countries, there has been a steady decline in the risk of gastric cancer incidence and mortality over several decades. The decline may be due to improvements in food storage and preservation as well as lifestyle changes. Changes in the prevalence of *H. pylori* may also play a role, and *H. pylori* infection is less prevalent in relatively wealthy western countries. If the decline continues, the expected number of cases in 2010 will be approximately 1.1 million (1).

## **Etiology**

The great majority of malignant tumors of the stomach are adenocarcinomas (3). The histology of gastric adenocarcinoma falls into two broad subtypes—the intestinal and diffuse types. The intestinal type is the form of gastric cancer seen in countries with high incidence rates, and it is also referred to as the *endemic form* of stomach cancer. The intestinal type arises in the antrum or antral-corporum junction. The histologic type varies with tumor location in the stomach. Diffuse-type cancers involve the corpus, and intestinal-type cancers may be seen in the gastroesophageal junction (4).

In high-incidence countries, the most common gastric cancers are the intestinal-antral types, which are usually associated with pre-existing intestinal metaplasia, atrophic gastritis, and chronic *H. pylori* infections. The remaining incidences of gastric cancer in high-incidence countries are diffuse type. Diffuse-type gastric cancers may also be associated with the presence of *H. pylori* but generally do not develop on the background of intestinal metaplasia. In high-incidence countries, these diffuse-type cancers occur in geographic locations where a high prevalence of *H. pylori* exists. The relationship of *H. pylori* infection to the etiology of diffuse-type cancers is not as clear as the bacteria's role in intestinal-type cancers. Diffuse-type cancers are more common in younger patients and may be associated with brisk mucosal inflammatory infiltrate that may be related to *H. pylori* infection (4).

Intestinal-type cancers of the gastroesophageal junction are less common in high-incidence countries. They are usually associated with gastroesophageal reflux disease (GERD). These tumors occur most commonly in middle-aged white men, and, although the distal esophagus is most commonly involved, the cardioesophageal junction also frequently exhibits tumors. It becomes difficult to determine whether these cancers are gastroesophageal junction stomach tumors or distal esophageal malignancies. The tumors associated with GERD also appear to be more common in obese men who drink alcohol and smoke cigarettes. It is considered possible that all three

factors (drinking, smoking, and obesity) decrease the tone of the gastroesophageal sphincter mechanism and thus favor GERD (1,3,5).

Gastric malignancies other than adenocarcinomas account for <10% of gastric cancers (6). These tumors of the stomach include undifferentiated gastric carcinomas with lymphoid stroma, hepatoid carcinomas, adenoacanthomas, adenosquamous and squamous cell carcinoma, parietal cell carcinoma, oncocytic gastric carcinoma, carcinoid tumors, and gastrointestinal stromal tumors (6). Choriocarcinomas, teratomas, and yolk sac tumors all occur as primary gastric tumors, although these neoplasms are rare. The stomach is the most common site of nongonadal, nongestational germ cell tumors (6). Lymphoma occurs in the gastrointestinal (GI) tract, and the stomach is the most common site for GI lymphomas. Most gastric lymphomas are of the non-Hodgkin's type, with the majority classified as B-cell lymphomas (6). Mucosa-associated lymphatic tissue (MALToma) neoplasms are low-grade neoplastic processes associated with *H. pylori* colonization. These neoplastic B-cell proliferations appear to initially develop as polyclonal proliferations, which may be successfully treated with antibiotic therapy directed at eradication of *H. pylori* before the MALToma has evolved to a monoclonal, truly malignant neoplasm (6–8).

## Staging

There are two major classification systems currently in use for gastric carcinoma. The Japanese classification system is based on the location of positive lymph nodes. The other staging system was developed jointly by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) and is used in countries in the western hemisphere (9). This system is based on tumor/node/metastasis classification (Table 1).

## Environmental Risks and Prevention

A number of epidemiologic studies have examined various factors associated with the development of gastric cancer. Low socioeconomic class and low education level have been associated with a higher incidence of gastric cancer. A higher incidence has also been seen in those who work in coal, nickel, and asbestos mining and in the processing of timber and rubber (10). Blood group A, gastric ulcer, ionizing radiation, and previous gastric resection are also associated risk factors (4).

Diet also plays a role in the development of gastric cancer. Diets with a high intake of smoked and cured meats, as well as diets with a high intake of

**Table 1.** Tumor/Node/Metastasis Staging for Gastric Cancer

**Primary tumor (T)**

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ; intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria or subserosa <sup>a</sup>
T2a	Tumor invades muscularis propria
T2b	Tumor invades subserosa
T3	Tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures
T4	Tumor invades adjacent structure <sup>b,c</sup>

**Lymph node involvement (N)**

NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis <sup>d</sup>
N1	Metastasis in 1–6 regional lymph nodes
N2	Metastasis in 7–15 regional lymph nodes
N3	Metastasis in >15 regional lymph nodes

**Distant metastasis (M)**

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

**Staging group**

Stage 0	Tis, N0, M0
Stage IA	T1, N0, M0
Stage IB	T1, N1, M0
	T2a/b, N0, M0
Stage II	T1, N2, M0
	T2a/b, N1, M0
Stage IIIA	T2a/b, N2, M0
	T3, N1, M0
Stage IIIB	T3, N2, M0

*(continued)*

**Table 1.** Tumor/Node/Metastasis Staging for Gastric Cancer (Continued)

Stage IV	T4, N1-3, M0
	T1-3, N3, M0
	Any T, Any N, M1

<sup>a</sup>A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified T2. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified T3.

<sup>b</sup>The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

<sup>c</sup>Intramural extension to the duodenum or esophagus is classified by the depth of greatest invasion in any of these sites, including the stomach.

<sup>d</sup>A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.

Data from Stomach Cancer Treatment, by the National Cancer Institute, 2006.

Retrieved March 16, 2006, from <http://www.cancer.gov/cancertopics/pdq/treatment/gastric/HealthProfessional/page3>

salt or salt-preserved foods, have been associated with gastric cancer (5). Diets deficient of raw vegetables and fruits, vitamin C, and antioxidants also are associated with gastric cancer. Obesity, smoking, and alcohol consumption have been associated with gastroesophageal junction tumors. Dietary and lifestyle changes may play a modest role in the prevention of gastric cancer (5).

Evidence linking *H. pylori* infection to gastric cancer was considered sufficient enough by the International Agency for Research on Cancer to classify it as carcinogenic in humans (1). The role of *H. pylori* infection carcinogenesis is probably indirect, with the bacteria serving as a factor in causing gastritis. This chronic gastritis may lead to dysplasia and eventually carcinoma. The infection is acquired in childhood, and prevalence is related to socioeconomic status. Prevention of *H. pylori* infection is a strategy that may reduce the incidence of gastric cancer.

## Genetic Risk

Hereditary diffuse gastric cancer (HDGC) is strongly associated with an autosomal dominant susceptibility to develop diffuse gastric cancer. These diffuse gastric cancers are poorly differentiated adenocarcinomas that infiltrate the stomach wall, causing thickening of the wall without forming a

**Table 2.** Criteria for Consideration of CDH1 Molecular Genetic Testing

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1. Two or more cases of gastric cancer in a family, with at least one diffuse gastric cancer diagnosed before age 50 years
  2. Three or more cases of gastric cancer in a family, diagnosed at any age, with at least one documented case of diffuse gastric cancer
  3. An individual diagnosed with diffuse gastric cancer before 45 years of age<sup>a</sup>
  4. An individual diagnosed with both diffuse gastric cancer and lobular breast cancer (no other criteria met)
  5. One family member diagnosed with diffuse gastric cancer and another family member diagnosed with lobular breast cancer (no other criteria met)
  6. One family member diagnosed with diffuse gastric cancer and another family member diagnosed with signet ring colon cancer (no other criteria met)
- 

<sup>a</sup>Criterion may be too inclusive.

Data from Hereditary Diffuse Gastric Cancer, by the University of Washington, Seattle, 2004. Retrieved July 1, 2006, from <http://www.genetests.org>.

distinct mass (11). Most cases of HDGC occur before age 40 years, with an average onset age of 38 years. Germline mutations in the E-cadherin gene, CDH1, have been identified in families with HDGC. The CDH1 gene is the only gene known to be associated with HDGC (11).

In 1999, the International Gastric Cancer Linkage Consortium defined HDGC as the presence of two or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least one case diagnosed before age 50 or three or more documented cases of diffuse gastric cancer in first- or second-degree relatives, regardless of age of onset (11). Genetic testing was recommended for individuals falling into these categories. In 2004, the criteria for consideration of genetic testing were revised. The six criteria for consideration of CDH1 molecular genetic testing are outlined in Table 2. Due to the broad nature of the recommendations, it may not be practical for use in regions of high gastric cancer incidence, such as Japan (11). Other cancers reported in family members are lobular breast cancer and colorectal cancer. Thus far, patients with these neoplasms have not been included as candidates for genetic testing (11).

Management options for carriers of CDH1 germline mutations include prophylactic gastrectomy or intensive surveillance for early detection and treatment of gastric cancer (12). Current methods of surveillance use chromogastrosocopy. The use of newer sophisticated endoscopic techniques (6), such as spectroscopy, confocal microscopy, and autofluorescence, has not been studied in HDGC. Small studies of prophylactic gastrectomy have shown that they can be performed safely and may be curative in carriers of CDH1 germ-

line mutations (13). Prophylactic gastrectomy and surveillance remain controversial and require further study to fully understand the risks and benefits of these approaches.

## Diagnosis and Workup

Initial diagnosis of gastric cancer often is delayed because patients are asymptomatic during early stages of gastric cancer. The symptoms of gastric cancer frequently are vague and nonspecific. They include complaints such as weight loss, epigastric discomfort, nausea, vomiting, fatigue, anorexia, and early satiety. In low-incidence countries, symptoms or positive fecal occult blood testing usually triggers endoscopic investigation. In Japan, mass screening with upper GI contrast studies and endoscopy has proven successful in obtaining early diagnosis (4). Mass screening is expensive and not practical in other high-risk countries without the resources to support the technology and logistics involved.

The double barium upper GI series still may be helpful in defining a gastric lesion; however, the most common diagnostic test used at initial evaluation is upper endoscopy. Endoscopy can be helpful in providing information about tumor location, distance from the esophagogastric junction, and extent of mucosal involvement. Biopsies for tissue diagnosis can be performed during this test. Endoscopic ultrasound examination is useful to evaluate depth of tumor, penetration of the wall, and assessment of gross lymph node enlargement. This is a reliable way of assessing patients preoperatively (4). Diagnostic/therapeutic laparoscopy is useful in identifying cases with disseminated and/or technically unresectable disease and, therefore, may spare patients full laparotomy. The extent of disease at laparotomy usually is greater than predicted preoperatively. Computed tomography (CT) scanning provides additional information for staging purposes before laparotomy and assists in decision making regarding curative versus palliative resections. CT scanning is helpful in detecting distant metastatic disease, extraregional adenopathy, and signs of locally advanced disease (4). Positron-emission tomography (PET) scanning is being used in patients receiving preoperative neoadjuvant therapy to indicate the possibility of disseminated cancers before curative resection is attempted. PET scanning is also being used to detect recurrent disease and distant organ metastases. However, PET scanning has not proven as useful in gastric cancers as in other tumors. Primary tumor uptake is only seen in approximately 75% of cases. Neither mucus-containing tumors nor diffuse-type tumors, particularly poorly differentiated scirrhous tumors, image well in PET scans (4). PET scanning, however, may be a useful means to assess the benefit of chemoradiation therapy in the management of well-differentiated

adenocarcinomas of the esophagus. Currently, no reliable serum tumor markers exist in gastric cancer. CEA and CA19-9 have been noted to be elevated in approximately 40%–50% of patients with disseminated disease (3).

Comprehensive physical examination is imperative in the workup of gastric cancer. Common physical findings in surgically incurable patients include palpable lymph node metastases in the left supraclavicular area (Virchow node) or left axilla (Irish node). Periumbilical nodules (Sister Joseph nodes) represent peritoneal dissemination of tumor. Hepatomegaly or ascites may be present. Epigastric mass or pelvic masses due to Krukenberg tumor (ovarian metastases) or pelvic peritoneal drop metastases (Blumer shelf) may be detected on physical examination, and a careful pelvic/rectal examination should be part of the initial evaluation of all gastric cancer cases.

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# **Data-Driven Surgical Treatment for Gastric Cancer**

Scott A. Hundahl, MD, FACS, FSSO, FAHNS

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## **A Customized Approach**

Mr. Ollie O., a figure from my early childhood on a Nebraska farm-ranch, had a way with tree stumps. Gauging his root work perfectly, he would invariably extend the perfect distance from the stump for complete root/stump removal. Considering the species of a tree, its size, the character of the ground, and recent weather conditions, he customized his approach. With an economy of action born of experience, arthritis, or both, he planned, selected his tools, and did the job with minimal trauma. Increasingly, the modern surgeon's treatment of gastric cancer reminds me of Mr. O. Consider the advent of endoscopic mucosal resection (EMR) for selected early cancers, the abandonment of routine total gastrectomy, the abandonment of routine pancreatic/splenic resections, and the emergence of customized lymphadenectomy. These developments represent a departure from the "mega-surgery-for-all" philosophy in favor of a more customized approach.

## **Endoscopic Mucosal Resection for Selected In Situ and T1 Cancers**

In countries such as Japan, where the incidence of "early gastric cancer" (i.e. T1 tumor) is high, EMR has emerged as a reasonable option for selected cases

(1–6). In the classic technique of endoscopic mucosal resection, a submucosal injection of saline floats the area of tumor-bearing mucosa off the underlying muscularis propria, and the lesion is resected with a special cautery snare with hooks to preserve specimen orientation for margin analysis. The procedure can be technically challenging, but innovations such as the use of incision endoforceps (7), aspiration mucosectomy (8), a stabilizing distal magnetic anchor (9), and double endoscope resection techniques (10) can facilitate it. Laparoscopic resection is another option, but the potential risk of intra-abdominal seeding and/or port site tumor implantation in node-negative T1 tumors otherwise suitable for EMR make EMR the appropriate choice for such lesions (6).

Selection of cases suitable for EMR hinges on the absence of disease in the regional lymphatics. A combined series of 5,265 surgically treated T1 cases from the National Cancer Center Hospital and the Cancer Institute Hospital in Tokyo offers unsurpassed guidance (11). For intramucosal tumors, none of the 1,230 well-differentiated cancers smaller than 30 mm diameter, regardless of ulceration findings, were associated with metastases (95% confidence interval [CI], 0–0.3). Regardless of tumor size, none of the 929 cancers without ulceration were associated with nodal metastases (95% CI, 0–0.4). For submucosal cancers, there was a significant correlation between tumor size larger than 30 mm in diameter and lymphatic-vascular involvement, with an increased risk of nodal involvement. None of the 145 well-differentiated adenocarcinomas with diameters smaller than 30 mm and without lymphatic or venous permeation were associated with nodal involvement, provided that the lesion had invaded less than 500 microns into the submucosa (95% CI, 0–2.5) (11).

In an 11-year, 445-case series by Ono and colleagues from the National Cancer Center Hospital in Tokyo, there were no gastric cancer-related deaths during a median follow-up period of 38 months (3–120 months) (1). Although bleeding and perforation occurred in 5% of patients, there were no treatment-related deaths (1). For selected superficial T1 cancers, EMR performed by experienced personnel can generate superb results and can certainly be recommended, especially as local recurrences can be addressed with salvage gastrectomy.

## **Prospective Randomized Trials: Total versus Subtotal Gastrectomy**

Table 1 summarizes prospective, randomized trials of routine total gastrectomy versus subtotal gastrectomy for lesions that can be successfully cleared to negative margins by either procedure (12–15). The Hong Kong trial (15) includes the addition of extended node dissection to the total gas-

**Table 1.** Total versus Subtotal Gastrectomy.<sup>1</sup>

<b>Total versus Subtotal Trials (References)</b>	<b>Inclusion Criteria</b>	<b>Subtotal</b>	<b>Total</b>	<b>P Value (Survival)</b>
French (12)	Antral tumor M0	3%/48% (5-y survival)	1%/48% (5-y survival)	n.s.
Italian (13,14)	>6 cm proximal margin possible M0	1%/65% (5-y survival)	2%/62% (5-y survival)	n.s.
Hong Kong (15)	Antral >6 cm margin M0, Age < 75	<b>Subtotal + D1</b> 0%/1,511 days median survival	<b>Total + D3</b> 3%/922 days median survival	.04 .07

n.s., not significant.

<sup>1</sup>Percentages reflect postoperative (30-day) mortality/survival as indicated.

trectomy arm. As seen in the table, routine total gastrectomy fails to generate a survival advantage, and, in the Hong Kong trial, the “subtotal + D1” group enjoyed superior survival compared to the “total + D3 group.”

### **The Difficult “D”: Changing Lymphadenectomy Definitions**

Lymphadenectomy in gastric cancer has been historically defined according to (several variations of) Japanese-defined nodal treatment. Such definitions reflect mandates contained in various editions of Japanese standardized treatment/staging rules dating from 1963 to the present (16–19). The Japanese treatment and classification system has, since its inception, included numeric designations for various lymph node stations and sub-stations around the stomach—31 at last count (19). Definitions for various nodal levels, originally N1 through N4, are expressed in terms of groupings of these numbered anatomically defined nodal stations for tumors in various positions within the stomach. The N groupings have changed considerably over time. Current definitions include only node levels from N1 through N3 (i.e., no N4). With the thirteenth edition of the Japanese classification system, circa 1997, which has been translated into English (20), several major changes were instituted. For example, one major change involves the designation of node involvement at perigastric, short gastric (No. 4a), and left paracardial (No. 2) sites as distant metastatic disease sites (M1) when they occur in the setting of an antral primary tumor. The same stations are N1 disease or N3 disease for other primary sites within the stomach. The reader should appreciate that the Japanese system bears scant relation to the more familiar International Union Against Cancer/American Joint Committee on Cancer tumor/node/metastasis system (21).

Japanese mandates for node dissection are classified according to the “D-level” system. Definitions for extent of lymphadenectomy in all but one of the trials discussed in the next sections follow the Japanese mandates. According to the Japanese system, a “D1 lymphadenectomy” encompasses all anatomically defined N1 node stations for a given location of tumor, a “D2” encompasses all N2 node stations, and a “D3” encompasses all N3 node stations. To make matters a bit more confusing, all but one of the trials discussed use D-level definitions based on pre-1997 editions.

### **Prospective Randomized Trials: D1 versus D2 or D2+**

Table 2 summarizes prospective randomized trials of various Japanese-defined lymphadenectomy schemes (22–30). Given the aforementioned

**Table 2.** Lymphadenectomy According to Japanese Treatment Methods (D level)<sup>1</sup>

<b>Lymphadenectomy Trials (References)</b>	<b>Inclusion Criteria</b>	<b>N</b>	<b>D1</b>	<b>D2</b>	<b>P Value (Survival)</b>
Cape Town (22,23)	T1-3, N0-1, M0 Age <75 y	43	0%/78% (3-y survival)	0%/76% (3-y survival)	n.s.
British Medical Research Council (24,25)	Stage I-III Age >20 y	400	6%/35% (5-y survival)	13%/33% (5-y survival)	n.s.
Dutch (26-28)	Stage I-II Age <85 y	711	Note: non-Japanese definition of "D1" and "D2" for this trial 4%/45% (5-y survival)	10%/47% (5-y survival)	n.s.
<b>D1</b>					
Taipei D1 versus D3 (29)	≥ T2, M0 Age <75 y No esophageal involvement	156	0%/45% OS 0%/49% DFS	0%/51% OS 0%/54% DFS	.056-borderline .15-n.s.
<b>D2</b>					
Japanese D2 versus D4 Trial (30)	Deep T2-T4 M0, age <76 y	523	0.8%/69% OS (5-y survival)	0.8%/70% OS (5-y survival)	n.s.

DFS, disease-free survival; n.s., not significant; OS, overall survival.

<sup>1</sup>Percentages reflect postoperative (30-day) mortality/survival as indicated.

changing definitions and resulting confusion, surgeons might consider themselves fortunate that the trials are all largely negative.

For the two large European trials, the British Medical Research Council (MRC) Trial (24,25) and the Dutch trial (26–28), in-hospital surgical mortality for the D2 groups was quite high: 13% and 10%, respectively. Both trials showed higher mortality rates when pancreatic-splenic resection was performed, and this somewhat confounded the D-level question as, at the time of these trials, these were mandated procedures for the D2 group when tumors were in the middle third or proximal third of the stomach. In the Dutch trial, which restricted subgroup analysis to patients who did not undergo pancreatic or splenic resection (a post-hoc, selected analysis), survival was higher for the D2 group (59% for the D1 group vs. 71% for the D2 group,  $P = .02$ ) (28). An 11-year follow-up report for this trial indicates that, of the 12% of patients with pathologic N2 disease ( $N = 89$  out of 711 total), there were nine 10-year survivors, and eight of the nine were in the D2 group ( $P = .01$  for this post-hoc analysis of the N2 subgroup) (28). Subgroup analysis notwithstanding, both European trials were negative. Whatever was supposedly gained as a result of D2 lymphadenectomy was lost as a result of higher surgical mortality.

In the mid-1990s, as a result of key works by Maruyama and others (31–33), the Japanese abandoned routine pancreatic-splenic resection unless required to achieve a negative-margin resection and changed published D2/D3 recommendations accordingly, but it was too late to affect the aforementioned trials. Both the British MRC and Dutch trials verified the wisdom of this change.

### **Maruyama Index of Unresected Disease: “Low Maruyama Index” Surgery Is Associated with Improved Survival**

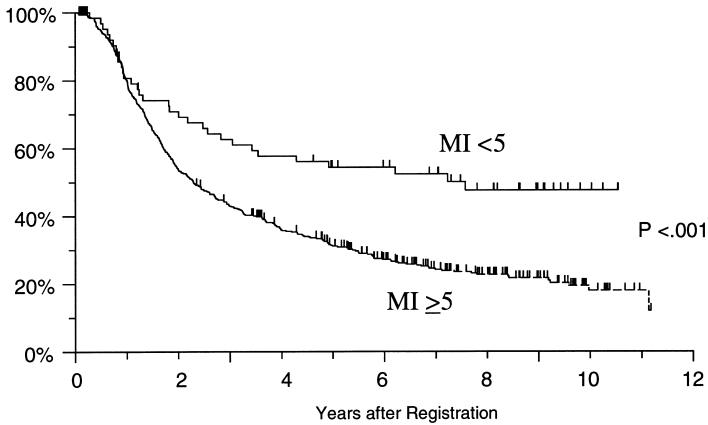
In the late 1980s, Keiichi Maruyama and colleagues at the National Cancer Center Hospital in Tokyo created a computer program (known as the “Maruyama Program”) that searched a meticulously maintained, 3,843-patient database of gastric cancer cases treated by extensive lymphadenectomy. The program is designed to match patients with characteristics similar to a given case and report observed nodal dissemination risk, survival, and other information. With seven demographic and clinical inputs, all identifiable preoperatively or intraoperatively, the program predicts the statistical likelihood of nodal disease for each of the 16 main nodal stations around the stomach. Maruyama Program predictions have been assessed in Japanese, German, and Italian populations and found to be highly accurate (34–36). The

Maruyama Program is designed to be used by surgeons preoperatively or intraoperatively as a convenient means of rationally planning a more data-driven extent of lymphadenectomy for a given patient. Since the late 1980s, the program has been used in exactly this way by many gastric cancer surgeons around the world. In an effort to expand use of this computerized tool, a CD-ROM with expanded case volume was prepared in 2000 (37).

In a prospectively planned surgical analysis of a large adjuvant chemoradiation trial in the United States (known as the “Macdonald Trial,” Southwest Oncology Group 9008, or Intergroup 0116), the extent of surgical treatment was specifically assessed and prospectively coded. The prospectively planned surgical analysis of survival made use of a novel means of quantifying the adequacy of lymphadenectomy relative to likely extent of nodal disease, the “Maruyama Index” (MI) of unresected disease. MI was defined as the sum of Maruyama Program predictions for those Japanese-defined regional node stations (stations 1–12) left in situ by the surgeon (38). Based on the trial’s entry criteria and the definition of MI, every case registered could have had an MI of zero; this variable was under the surgeon’s control. As depicted in Figure 1, the median overall survival for the MI <5 subgroup was 91 months, versus 27 months for other groups ( $P = .005$ ). By multivariate analysis, adjusting for treatment, T stage, and number of nodes positive, MI proved an independent predictor of survival ( $P = .0049$ ). Data for disease-free survival were similar (38,39). Some impact of “dose of surgery,” as measured by MI, was also evident; median survival was 20 months for the highest MI quartile and 46 months for the lowest MI quartile (treatment-adjusted  $P = .002$ ) (38).

To further assess the utility of MI as a prognostic tool, the Dutch D1 versus D2 trial has recently been re-analyzed (40). Blinded to survival, and eliminating cases with incomplete information, 648 of the 711 patients treated with curative intent had MI assigned. Median MI was 26 (versus median of 70 for the Macdonald trial). Overall trial findings with respect to D level were not affected by the absence of the 63 cases with incomplete data. In contrast to D level, MI <5 proved a strong predictor of survival by both univariate and multivariate analysis (Figure 2). MI was an independent predictor of both overall survival ( $P = .016$ , hazard ratio [HR] = 1.45, 95% CI, 1.07–1.95) and relapse risk ( $P = .010$ , HR = 1.72, 95% CI, 1.14–2.60). Strong dose response with respect to MI and survival was also observed (see Figure 2). Thus, the Dutch trial findings, with respect to MI, largely confirmed what was observed in the Macdonald trial.

Based on results from these two trials, it appears that surgeons might make a better impact on patient survival by pursuing a “low MI” operation instead of relying on D level guidance. By using the Maruyama Program to prospectively plan a given patient’s lymphadenectomy, achieving a “low MI” operation is relatively straightforward, and in the current era, what sur-



No. at Risk

MI <5	62	43	35	28	18	4	0
MI ≥5	491	263	166	103	55	13	0

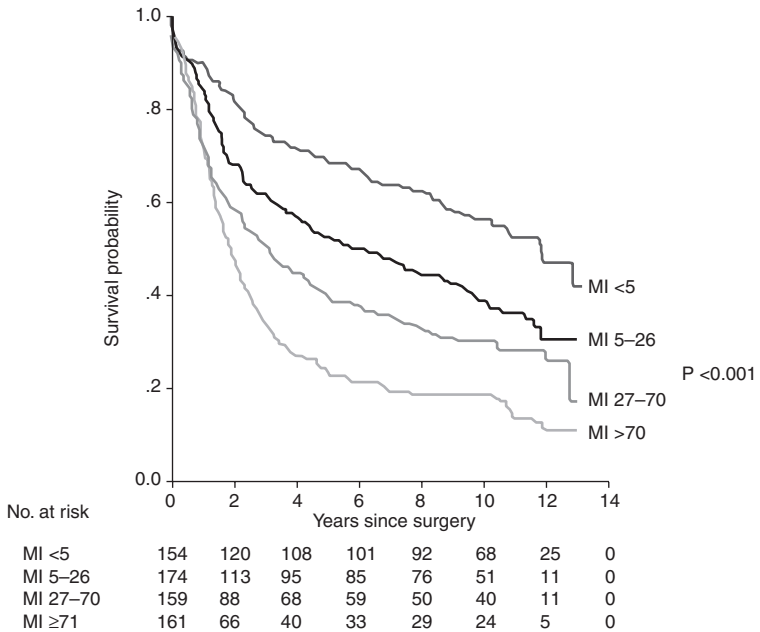
**Figure 1.** Updated overall survival curves for Maruyama Index (MI) <5 versus ≥ 5 in the Macdonald chemoradiation trial (Intergroup 0116). (Reprinted courtesy of Peeters KCMJ, Hundahl SA, Kranenbarg EK, et al. “Low-Maruyama-Index” Surgery For Gastric Cancer—A Blinded Re-analysis of the Dutch D1-D2 Trial. *World Journal of Surgery*. 2005;29:1576–1584. With kind permission of Springer Science and Business Media.)

geon or operating room does not have access to a laptop or personal computer to display the output?

The compelling dose-response effect for MI suggests that it can also be viewed as a quantitative yardstick for the adequacy of lymphadenectomy in a given case of gastric cancer. As such a quantitative yardstick, it might someday be used to identify patients at greater or lesser risk of locoregional recurrence, or it might influence decisions on postoperative adjuvant therapy. At a minimum, MI should be explicitly calculated and reported for every patient entered into a postoperative adjuvant trial.

## Conclusion

Surgeons treating gastric cancer can now offer their patients data-driven, customized cancer treatment. For selected favorable “early” T1 cancers, EMR offers a valuable, minimally invasive treatment option. For patients with



**Figure 2.** Overall survival for various Maruyama Index (MI) quartiles in the Dutch D1–D2 trial. (Reprinted courtesy of Peeters KCMJ, Hundahl SA, Kranenbarg EK, et al. “Low-Maruyama-Index” Surgery For Gastric Cancer—A Blinded Re-analysis of the Dutch D1-D2 Trial. *World Journal of Surgery*. 2005;29:1576–1584. With kind permission of Springer Science and Business Media.)

deeper cancers, subtotal distal gastrectomy should be offered whenever total gastrectomy is not required to secure a negative resection margin. Similarly, unless required for a negative-margin resection, the pancreas and spleen should be preserved. Lymphadenectomy can be customized by preoperative or intraoperative use of the Maruyama Program to generate a “low MI” operation, thus optimizing survival by restricting dissection to node stations at risk for disease. Such developments contrast with the “mega-surgery-for-all” philosophy once popular in surgical oncology.

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# Neoadjuvant Therapy for Resectable Gastric Cancer

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David Cunningham, MD, FRCP

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## Incidence and Outlook

Gastric cancer is one of the most common cancers worldwide and is one of the top causes of cancer-related deaths. There is significant geographical variation in the incidence of gastric cancer; for example, incidence is higher in the Far East than in the United States or Western Europe. The management of gastric cancer remains challenging. This is due to a combination of factors such as the relative resistance of disease to treatment, the frequent occurrence of symptomatic disease or impaired performance status of patients, and the propensity of gastric cancer to present when it has become locally advanced or metastatic.

Surgery is the only treatment modality that may potentially cure gastric cancer; however, the disease is localized and operable at the time of diagnosis in only 20%–30% of patients, and, of that group, those who proceed to complete surgical resections often experience recurrences of their disease, usually due to local or distal micrometastatic disease that was undetectable at the time of surgery. Without any additional treatment, patients with resected gastric cancer have a median survival of approximately 25 months and a 5-year survival rate of only about 20%–30%. Surgical trials, especially those done in Japan, have been able to improve on these outcomes with more extensive surgery and lymph node dissections, but these results have not been reproduced in Western patients.

This has led to various clinical trials of adjuvant treatment initiated either after surgery (postoperative approaches) or before surgery (either

neoadjuvant or perioperative approaches). This chapter focuses on the rationale and evidence for using neoadjuvant chemotherapy in patients with resectable gastric cancer, in particular the recently reported results of the United Kingdom National Cancer Research Institute (U.K. NCRI) Upper Gastrointestinal Cancer Clinical Studies Group MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) randomized trial (1).

## **Rationale for Neoadjuvant Treatment**

The potential benefits of using neoadjuvant treatment before surgery in patients with resectable cancer include rapidly improving tumor-related symptoms, eliminating micrometastases, increasing the likelihood of a curative resection by downsizing and/or downstaging effect, and determining the sensitivity of a particular patient's disease to treatment (Table 1). Preoperative treatment may also be better tolerated by patients than postoperative treatment, making patients more likely to complete the course of treatment before surgery. This is because recovery from upper gastrointestinal surgery may be prolonged, and patients are more likely to be weakened by surgery and more susceptible to treatment-related toxicity.

Patients presenting with gastric cancer often have symptoms such as epigastric pain or discomfort, anemia, and impaired nutrition due to anorexia or

**Table 1.** Advantages and Disadvantages of Neoadjuvant Treatment in Resectable Gastric Cancer

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### **Possible advantages of neoadjuvant treatment**

- Rapid improvement of tumor-related symptoms.
- Elimination of micrometastases and early systemic control of disease.
- Increased likelihood of curative surgery secondary to downsizing/downstaging effect.
- Demonstrates sensitivity of tumor to chemotherapy.
- May be better tolerated than postoperative treatment.

### **Possible disadvantages of neoadjuvant treatment**

- Risk of patient becoming inoperable with progression of disease on treatment; but, these patients may do poorly with surgery anyway.
  - Treatment-related toxicity may prevent surgery.
  - Possible increase in perioperative morbidity depending on treatment used.
-

luminal obstruction. These factors can contribute to impairment in performance status and an increased risk of complications from treatment. A response to neoadjuvant treatment may alleviate some of these symptoms and, therefore, improve a patient's condition before surgery.

Micrometastatic disease—cancer that is undetectable by the staging investigations in use—is the most likely source of relapse in patients who have had surgery in which all known tumors have been completely resected. A large proportion of the benefit from any adjuvant treatment may be due to either eliminating these tumor seedlings or delaying their regrowth to a clinically significant size. In theory, neoadjuvant treatment allows for early treatment and control of micrometastases compared to postoperative treatment because several weeks may have elapsed before treatment can be commenced after surgery, during which time any disease not resected would have time to progress. Achieving adequate surgical margins can also be more difficult in patients with larger or more locally advanced tumors, so that any shrinkage or regression of a tumor induced by preoperative treatment may make curative surgery more likely.

Without any measurable disease after surgery, a drawback of the routine use of postoperative adjuvant treatment is that the sensitivity of tumors to the chemotherapy used is difficult to assess. The response of a tumor to preoperative treatment is more easily evaluated by comparison between pretreatment and preoperative staging investigations. Patients with a documented benefit from the regimen used can then be re-treated with the same regimen postoperatively with a greater likelihood that the disease will be sensitive to treatment.

There is a risk that the cancer may progress during preoperative treatment, possibly to the extent that the patient may become inoperable; however, patients who have progressed during preoperative treatment have biologically aggressive chemorefractory disease, which most likely would have recurred soon after surgery. Proponents of neoadjuvant treatment often regard this as a means of sparing these patients who are unlikely to benefit from surgery from a radical operation with significant associated morbidity. There are also potential concerns that patients may experience toxicity from preoperative treatment that prevents them from proceeding to surgery, or that preoperative treatment may increase the risk of perioperative morbidity or mortality, but, at least in the MAGIC trial discussed in the following section, more than 90% of patients randomized to perioperative chemotherapy proceeded to surgery with no increase in perioperative morbidity or mortality compared to the surgery-alone arm (1).

An important factor that may influence the likelihood of a positive outcome from neoadjuvant treatment is the activity of a particular regimen in gastric cancer, particularly considering this disease's reputation for being

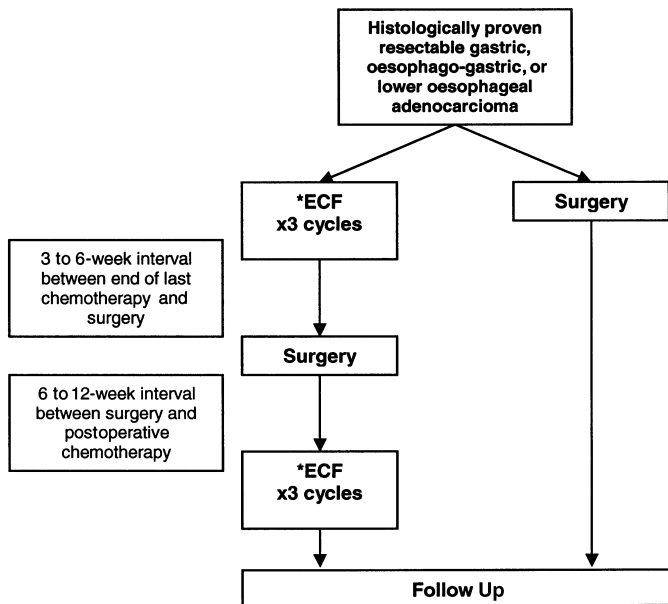
relatively chemoresistant. Neoadjuvant approaches will therefore probably become more attractive as more active combination treatments are developed, particularly with the addition of the novel targeted agents. Certainly, this was the rationale for using the epirubicin, cisplatin, 5-fluorouracil (ECF) regimen (50 mg/m<sup>2</sup> of epirubicin and 60 mg/m<sup>2</sup> of cisplatin given on day 1 and 200 mg/m<sup>2</sup> per day of 5-FU given by protracted venous infusion [PVI] over a 21-day cycle) popular in the United Kingdom and parts of Europe, in the MAGIC trial. High response rates have been observed with this regimen in earlier clinical trials, particularly in the subgroup of patients with locally advanced gastroesophageal cancer. This three-drug combination has repeatedly proven to be one of the most effective drugs for the treatment of patients with advanced gastroesophageal cancer (2,3) and is also supported by a Cochrane metaanalysis of chemotherapy for this disease setting (4).

## **Randomized Trials of Neoadjuvant Chemotherapy**

The two randomized trials that include preoperative chemotherapy in gastric cancer and have reported results are the U.K. NCRI MAGIC trial (1) and the Dutch Gastric Cancer Group study of preoperative FAMTX (5-FU, doxorubicin, and methotrexate) (5). Preliminary results are also available for a French trial of perioperative cisplatin and 5-FU (6).

It should be emphasized that MAGIC is not strictly a trial of neoadjuvant or perioperative treatment only, as patients in the study treatment arm received chemotherapy before and after surgery. Although the study only initially included patients with operable gastric adenocarcinoma of stage II or higher disease with no evidence of distal metastases, the eligibility criteria were later amended to allow the inclusion of patients with lower esophageal adenocarcinomas as well, coinciding with the completion of another U.K. national study of neoadjuvant chemotherapy in patients with esophageal cancer (the U.K. Medical Research Council OE02 trial). Patients had to be of adequate performance status (World Health Organization performance status 0 or 1), and they could not have any cardiac or renal contraindications to receiving the regimen (uncontrolled cardiac disease or creatinine clearance of 60 mL per minute or less).

A total of 503 patients were randomized to receive perioperative chemotherapy (N = 250) or surgery alone (N = 253). Patients in the perioperative chemotherapy arm received three cycles of ECF and were then scheduled to have surgery within 3 to 6 weeks of completing their third cycle of chemotherapy (Figure 1). Three further cycles of ECF were administered commencing 6–12 weeks after surgery. Patients in the surgery-only



**Figure 1.** Summary of study treatment in the United Kingdom National Cancer Research Institute MAGIC trial. ECF, epirubicin, cisplatin, and 5-fluorouracil. \*ECF regimen: epirubicin 50 mg/m<sup>2</sup> IV day 1, cisplatin 60 mg/m<sup>2</sup> IV day 1, and 5-fluorouracil 200 mg/m<sup>2</sup> per day by protracted venous infusion days 1–21, repeated every 21 days.

arm of the study had to proceed with surgery within 6 weeks of randomization. As there was no evidence at the time that the study was initiated to support recommending either so-called *D1* or *D2* surgery in this population, the extent of lymph node dissection was left to the discretion of the participating surgeon, although a minimal extent of dissection for each primary type was recommended in the study protocol.

Of the patients randomized to perioperative chemotherapy, 215 (86%) completed all three cycles of preoperative treatment, and 229 (92%) had surgery (209 of these had completed preoperative chemotherapy; in comparison, 244 patients in the surgery-only arm proceeded to surgery). After surgery, 137 (66% of those who completed preoperative chemotherapy and had surgery or 55% of those randomized to this arm) commenced postoperative treatment, with 103 completing protocol treatment (perioperative chemotherapy and surgery). The main reasons for not commencing postoperative treatment were disease progression, early death, patient choice, and postoperative complica-

**Table 2.** Tumor and Nodal Stage of Surgical Specimens of U.K. NCRI MAGIC Trial at Pathology Examination<sup>a</sup>

	Perioperative Chemotherapy Arm (%)	Surgery-Only Arm (%)
Tumor stage (all patients)		
T1/T2	52	37
T3/T4	48	63
Nodal stage (gastric cancers only)		
N0/N1 (<7 nodes involved)	84	71
N2/N3 (≥ 7 nodes involved)	16	29

<sup>a</sup>A significantly higher proportion of patients in the perioperative chemotherapy arm of the study had lower T stage (T1 or T2) and nodal stage (N0 or N1) tumors than the surgery-only arm ( $P = .002$  and  $P = .01$  for the respective comparison between arms). U.K. NCRI, United Kingdom National Cancer Research Institute. MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy.

tions. The incidence of adverse effects observed was as would be expected with this chemotherapy regimen, with no significant increase after surgery. In addition, the incidence of postoperative complications was similar between the two study arms, as was the number of deaths within 30 days.

During surgery, surgeons were asked to record whether the procedure performed was regarded as curative or palliative. Among patients who had radical surgery, resections were considered curative in 169 out of 213 patients (79%) in the perioperative chemotherapy arm and in 166 out of 236 patients (70%) in the surgery-only arm ( $P = .03$ ). On pathologic examination of the surgical specimens, tumors from the perioperative chemotherapy arm were significantly smaller (median of 3 cm vs. 5 cm,  $P < .001$ ; at baseline, maximum tumor diameters were the same in both arms) and of significantly less advanced tumor and nodal stages compared to the surgery-only arm (Table 2). These findings suggest that both downsizing and downstaging had occurred with neoadjuvant treatment.

Most important, this study was able to show that the use of perioperative ECF improved overall survival (the study primary end point), with a 25% reduction in the risk of death, corresponding to 5-year survival rates of 36% and 23% for the perioperative chemotherapy and surgery-only arms, respectively (Table 3, Figure 2). Progression-free survival was also significantly improved. These benefits were maintained after adjustment for stratification factors, and patients benefited from perioperative treat-

**Table 3.** Overall and Progression-Free Survival of the U.K. NCRI MAGIC Trial

	Hazard Ratio (95% Confidence Interval; P Value)	5-Year	
		Perioperative Chemotherapy Arm	Surgery-Only Arm
Overall survival	0.75 (0.60-0.93; $P = .009$ )	36%	23%
Progression-free survival	0.66 (0.53-0.81; $P < .001$ )		

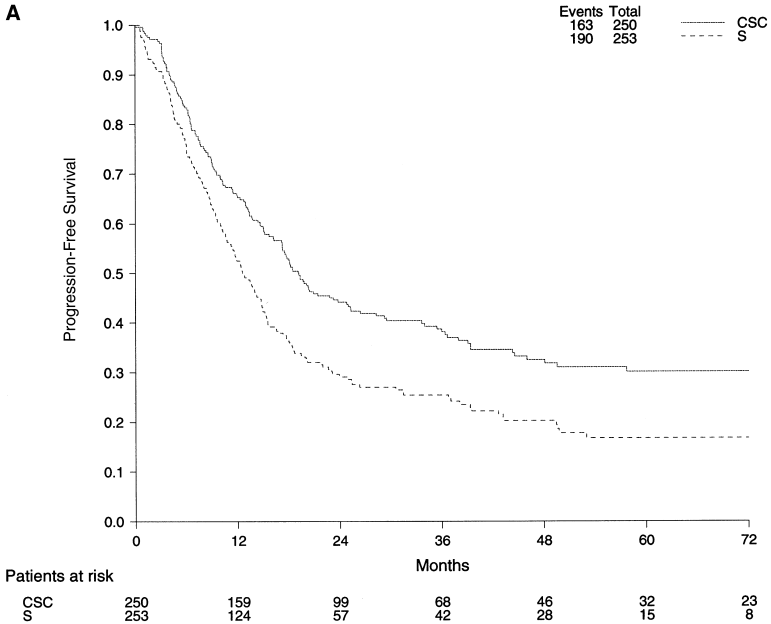
U.K. NCRI, United Kingdom National Cancer Research Institute.

MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy.

ment regardless of the site of the primary tumor (lower esophagus, esophagogastric junction, or stomach). These results are mature. The study was not designed to evaluate the relative contributions of the pre- and postoperative components of treatment to the survival benefit; therefore, it is not possible to determine the benefit of preoperative chemotherapy alone, which is tempting given the significant number of patients who did not commence or complete postoperative treatment.

The survival benefit observed in this trial is similar to that which has been reported by the U.S. Southwest Oncology Group Intergroup (SWOG 9008/INT-0116) which is discussed in detail in chapter 5 (7). The INT-0116 trial randomized patients to postoperative adjuvant chemoradiotherapy or surgery alone and reported median survivals of 36 months and 27 months for each arm, respectively, with a 26% reduction in the risk of death (hazard ratio 0.74; 95% confidence interval, 0.60–0.92;  $P = .005$ ). The positive results of this trial have significantly influenced standard practice in this disease, especially in the United States. However, the results of MAGIC and INT-0116 should not be directly compared because the patients enrolled in both studies at different points in their treatment; patients enrolled in MAGIC at the time of diagnosis and in INT-0116 after complete resection had been performed.

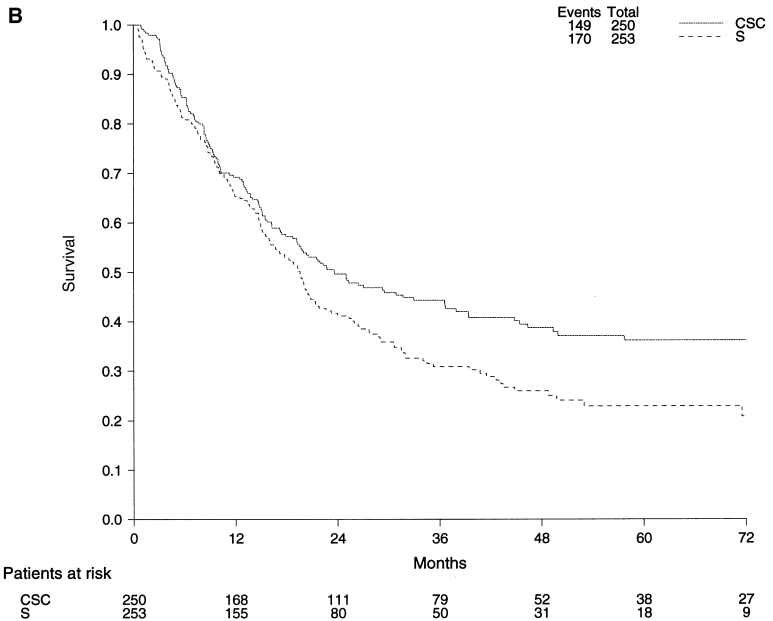
In the Dutch Gastric Cancer Group study, patients with resectable gastric cancer were randomized to receive four cycles of 5-FU, doxorubicin, methotrexate (FAMTX) chemotherapy followed by surgery, or surgery alone (5). Although the study planned to include a total recruitment of 450 patients, it was closed early after only 59 patients were enrolled because poor accrual prompted an early analysis of the curative resection rate (the study primary end point) of both arms, finding the rate to be lower in the chemotherapy arm. With further followup, the preoperative chemotherapy arm was also found to have inferior survival compared to the surgery-only arm. The



**Figure 2.** Kaplan-Meier estimates of progression-free survival (**A**) and overall survival (**B**) of the United Kingdom National Cancer Research Institute MAGIC trial. CSC, patients receiving perioperative chemotherapy; S, patients receiving surgery alone. (From Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355[1]:11–20. Copyright © 2006 Massachusetts Medical Society. All rights reserved.)

medial survival rates for the preoperative chemotherapy and surgery-only arms were 18.2 months and 30.3 months, respectively, with 5-year survival rates of 21% and 34%. These results may reflect the inferiority of the FAMTX regimen, and the fact that 44% of the patients randomized to this arm did not complete four courses of chemotherapy, either due to disease progression during treatment or toxicity, also suggests this inferiority. The ECF regimen used in MAGIC, on the other hand, has been shown to be more efficacious than FAMTX in the advanced disease setting (3).

Thus far, the French study, in which 224 patients with cancer of the stomach or lower esophagus were randomized to preoperative treatment with two to three cycles of cisplatin and 5-FU or surgery alone, has reported a statistically significant improvement in disease-free survival in favor of chemother-



**Figure 2.** (Continued)

apy (6). The study also observed a trend toward lower T and N staging in the study treatment arm, with significantly more patients in this arm having had complete (R0) resections (84% vs. 73%,  $P = .04$ ). Overall survival results of this study are not yet available, although, so far, these results support the benefits already observed in the MAGIC trial.

## Radiotherapy and Chemoradiotherapy

The use of radiotherapy-based treatment preoperatively is appealing, particularly because chemoradiotherapy with 5-FU has been shown to be beneficial in the postoperative setting in the U.S. INT-0116 trial (7) and has established benefit in other gastrointestinal tumors such as rectal cancer. In theory, radiosensitization may be enhanced preoperatively because of the increased oxygenation of the undisturbed tumor bed. A reduced volume of normal tissue may also be incorporated within the radiotherapy field. As with preoperative chemotherapy, radiotherapy before surgery may also be more tolerable to patients.

There is some evidence for the use of radiotherapy in the preoperative setting in gastric cancer from a Chinese trial that enrolled 360 patients (8). Although survival and resection rates were improved by preoperative radiotherapy and tumor downstaging was observed, these results have not influenced the treatment of this disease. Various phase II trials conducted by the M. D. Anderson Cancer Center have shown that preoperative chemoradiotherapy is feasible. As of this writing, there are no ongoing randomized trials evaluating preoperative chemoradiotherapy in this setting.

### **Future Directions**

Despite the survival improvements that are possible with either perioperative chemotherapy or postoperative chemoradiotherapy, there is a great need for further progress. In both trials, 5-year overall survival rates of the study treatment arms were still less than 40%, lagging far behind some other common cancers, such as colon cancer. As already alluded to, the efficacy of a particular chemotherapy regimen as neoadjuvant treatment may be influenced by the activity of that treatment combination in gastric cancer. Using newer, more effective agents in ECF-like combinations may therefore eventually lead to better neoadjuvant treatments. Developments in the treatment of advanced disease will certainly inform future trials and treatment in the neoadjuvant setting. For example, the recently reported U.K. NCRI REAL2 randomized multicenter trial had a 2 × 2 randomization designed to evaluate the substitution of capecitabine and oxaliplatin for 5-FU and cisplatin, respectively, in advanced esophagogastric cancer (9). This four-arm trial concluded that capecitabine could replace PVI 5-FU in triplet combinations, simplifying the administration of chemotherapy by obviating the need for long-term intravenous access (e.g., Hickman's catheters) and portable infusion pumps. This should reduce the incidence of line-related complications and improve the acceptability of treatment to patients. Other cytotoxic agents that may also eventually warrant evaluation in the neoadjuvant setting include oxaliplatin, docetaxel, and irinotecan.

The incremental gains from new chemotherapy combinations, however, are likely to be small, and the next major advances in the treatment of this disease will probably come from the addition of the novel targeted agents to combination chemotherapy. A hint of the potential benefit of these agents comes from a phase II study conducted by the Memorial Sloan-Kettering Cancer Center. This study shows promising response rates, and survival rates were reported from the addition of the anti-vascular endothelial growth factor monoclonal antibody, bevacizumab, to the irinotecan

and cisplatin combination. Indeed, in the U.K. NCRI MAGIC-B/ST-03 trial, expected to open to accrual late in 2006, patients will be randomized to receive ECX (epirubicin, cisplatin, and capecitabine) perioperative chemotherapy with or without bevacizumab.

As the preference for either perioperative chemotherapy or postoperative chemoradiotherapy is likely to remain polarized, it is unlikely that both approaches will ever be compared directly. It would be more useful to consider how lessons from one may inform the development of the other approach. For example, the results of the MAGIC trial support the use of postoperative ECF in the current U.S. INT randomized trial of adjuvant chemoradiotherapy (Cancer and Leukemia Group B 80101). Other possibilities that have been suggested include hybrid treatments consisting, for example, of neoadjuvant chemotherapy followed by surgery and postoperative adjuvant chemoradiotherapy.

Metabolic imaging, such as using fluorine-18 fluorodeoxyglucose (FDG-PET), may eventually have a role in neoadjuvant treatment strategies by predicting the likelihood of response ahead of anatomic imaging modalities that are more commonly in use. In the advanced disease setting, FDG-PET performed early after the initiation of treatment has already been prospectively shown to predict the likelihood of response to treatment. In the neoadjuvant setting, this may potentially be used to identify patients who are not going to benefit from the treatment used, so the neoadjuvant regimen can be changed, or the patient can proceed directly to surgery before the tumor becomes inoperable. A related area of research is that of identifying molecular factors that may predict the likelihood of response to treatment; this may eventually guide clinicians to the most appropriate treatment combination to use preoperatively.

## **Conclusion**

Based on the results of the U.K. NCRI MAGIC trial, perioperative chemotherapy with the ECF regimen should be considered one of the treatment options for patients with resectable gastric cancer (Figure 1) and is preferred in the United Kingdom and parts of Europe. As shown by the trial findings, in addition to improving overall survival and progression-free survival, the benefits include tumor downsizing and downstaging and an increased likelihood of a curative resection. So far, these benefits are also supported by the preliminary results of the French trial.

Although there is no direct evidence from clinical trials to suggest that either perioperative chemotherapy or postoperative chemoradiotherapy is superior, clinicians may take various factors into consideration when choos-

ing between them. Local referral pathways and practices are certainly an important factor. Routine preoperative treatment is only feasible if patients are referred for consideration of chemotherapy before surgery, rather than being referred from surgeon to oncologist only after a resection has been performed. Part of the reason for the success of preoperative adjuvant treatments in the United Kingdom is because all newly diagnosed patients have to be discussed in a multidisciplinary forum before the management plan is confirmed so that there is an opportunity for preoperative treatment to be considered. Because of procedural waiting lists, preoperative chemotherapy can often be commenced nearly immediately, whereas there may be a longer wait for surgical or radiotherapy time in some centers, so that earlier disease control can be achieved. Given the downstaging and downsizing demonstrated in the MAGIC trial, preoperative chemotherapy may also be more appealing for patients in whom such an effect may have a positive impact on the likelihood of a curative resection being performed.

Finally, patient preference may favor one approach over another. Patients may prefer to have their tumor resected as soon as possible and may not be willing to wait the 12 weeks between commencement of chemotherapy and surgery because of the associated risks of toxicity or progression of disease. Indeed, in patients who are assessed as being likely to experience significant chemotherapy-related toxicity, proceeding directly to surgery may be the appropriate solution.

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# Gastric Cancer: Adjuvant Therapy

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## Background

Although there has been a dramatic decline in the incidence of gastric cancer in the past century, the disease remains associated with substantial morbidity and mortality. There were 934,000 documented cases of gastric cancer in 2002 and 700,000 deaths (1). Surgery is the primary modality for managing early stage disease; however, a large percentage of patients treated with “curative resections” develop locoregional or distant recurrence. The rate of progress since the 1980s in improving survival rates has been disappointing. Five-year survival rates for gastric cancer treated with gastrectomy decrease substantially with advanced-stage disease. As shown in Table 1, those with early stage disease (stages IA and IB) have 5-year survival rates of 78% and 58%, respectively. For patients with stage II disease, 5-year survival is 34%, whereas for those with stage III disease, 5-year survival ranges from 8% to 20% (2).

Treatment failure can be both local and distant. Local sites of recurrence involve the gastric bed, anastomosis, and regional lymph nodes. Distant recurrence is most commonly detected in the liver, bones, and lungs. As shown in Table 2, 52% of recurrences occur with distant metastases, whereas approximately 60% of node-positive and/or transserosal ( $\geq T3$ ) cancers recur in the tumor bed, regional nodes, or anastomosis sites. In addition, 20% of tumors recur only locoregionally (3). This information has been gathered from historical pattern-of-failure data from clinical, operative second look, and autopsy sources and has provided the rationale for locoregional radiation therapy (RT) or chemoradiation as an adjuvant to surgical treatment.

**Table 1.** Tumor, Node, Metastasis Staging and Relative Survival for U.S. Cases Treated by Gastrectomy, 1985–1996 (N = 50,169)

6th Edition UICC/AJCC <sup>a</sup> Stage	Five-Year Relative Survival (%)	Ten-Year Relative Survival (%)
IA	78	65
IB	58	42
II	34	26
IIIA	20	14
IIIB	8	3
IV	7	5

<sup>a</sup>AJCC, American Joint Committee on Cancer; UICC, International Union Against Cancer. Data from Hundahl SA, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the “different disease” hypothesis. *Cancer*(Phila) 2000;88(4):921–932.

## Postoperative Radiation Therapy

There are limited data regarding the role of postoperative RT alone in patients with resected gastric cancer, as most RT trials incorporate low dose chemotherapy as a radiation sensitizer. In 1989, the British Stomach Cancer Group published a controlled prospective randomized trial of adjuvant chemotherapy or radiotherapy in resected gastric cancer (4). This trial included 298 patients with resected disease who were randomly assigned to surgery alone, surgery and postoperative RT, or surgery followed by chemotherapy. There was no statistically significant survival advantage shown for those patients

**Table 2.** Patterns of Failure after “Curative” Resection of Gastric Cancer

Pattern of Failure	Clinical (%)	Reoperation (%)	Autopsy (%)
Locoregional	38	67	80–93
Peritoneal seeding	23	41	30–50
Localized	—	19	—
Diffuse	—	22	—
Distant metastases	52	22	49

Modified from Smalley SR, Gunderson L, Tepper J, et al. Gastric surgical adjuvant radiotherapy consensus report: rationale and treatment implementation. *Int J Radiat Oncol Biol Phys* 2002;52(2):283–293, with permission.

who received either adjuvant therapy compared to those who had surgery alone. The 5-year survival for surgery alone was 20%, for surgery plus radiotherapy 12%, and for surgery plus chemotherapy 19%. However, RT was associated with a significantly lower local recurrence rate compared with surgery alone (32% vs. 54%).

In 1994, Budach published a comprehensive review of the currently available data for RT in the adjuvant treatment of gastric cancer. Again, there was no clear evidence that RT improved overall survival. As seen with prior studies, however, the data did highlight the importance of RT in improving locoregional recurrence rates (5).

### **Studies of the Effectiveness of Adjuvant Systemic Chemotherapy**

Adjuvant therapy of gastric cancer using systemic therapy alone or as part of combined modality therapy with curative intent has been widely evaluated since the 1980s (Table 3). Most trials have used 5-fluorouracil (5-FU)-based therapy, and only seven trials had at least 100 patients in each arm. Several metaanalyses of these data have been performed, which have shown that adjuvant systemic chemotherapy alone has no or borderline benefit after surgical resection of gastric cancer.

In 1993, Hermans et al. (6) published a metaanalysis of 11 randomized trials of adjuvant chemotherapy conducted over the previous decade. The odds ratio of 0.88 among treated patients was not significant. Two additional trials were incorporated into the analysis a year later, when it was discovered that they were erroneously omitted. The addition of 318 cases from these two trials lowered the odds ratio to 0.82; this was of borderline significance (95% confidence interval [CI], 0.68–0.98).

Earle and Maroun (7) published a 13-trial metaanalysis in 1999 of non-Asian trials published between 1980 and 1996. The odds ratio for death in the treated group was 0.80 (95% CI, 0.66–0.97), corresponding to a relative risk of 0.94 (95% CI, 0.89–1.00). Subgroup analyses showed a trend toward a larger magnitude of benefit when the analysis was restricted to trials in which at least two-thirds of patients had node-positive disease. These data suggested that adjuvant chemotherapy may produce a small survival benefit of borderline statistical significance in patients with resected disease.

In 2002, Panzini et al. (8) hypothesized that the existing metaanalyses of adjuvant gastric cancer trials were biased with respect to inclusion criteria. Therefore, a restricted metaanalysis was undertaken of those trials in which all patients were treated with “radical” surgical techniques. From the 17 trials eligible for inclusion, 3,118 patients were available for analysis. Odds

**Table 3.** Prospective Randomized Trials of Adjuvant Systemic Chemotherapy

<b>Author</b>	<b>Year</b>	<b>Treatment Group</b>	<b>N</b>	<b>Five-Year Survival (%)</b>	<b>Median Survival (mo)</b>	<b>P Value</b>
Nakajima et al. (27)	1984	MMC + 5-FU + araC → F	81	68	>60	.09
		MMC + fluorafur + araC → ftora	83	63	>60	—
Engstrom et al. (28)	1985	Surgery alone	79	51	>60	—
		5-FU + MeCCNU	91	—	36.6	.73
		Surgery alone	89	—	32.7	—
Coombes et al. (29)	1990	FAM (5-FU + Dox + MMC)	148	35	36	.17
		Surgery alone	133	46	36	—
Krook et al. (30)	1991	5-FU + Dox	64	33	34	.88
		Surgery alone	61	32	36	—
Grau et al. (31)	1993	MMC	68	41	—	.25
		Surgery alone	66	26	—	—
Hallsissey et al. (4)	1994	FAM	138	19	17.3	.14
		Postoperative radiotherapy alone	153	12	12.9	—
		Surgery alone	145	20	14.7	—
Macdonald et al. (10)	1995	FAM	93	—	32	.57
		Surgery alone	100	—	28	—
Tsavaris et al. (32)	1996	5-FU-epirub-MMC (FEM)	42	—	64	n.s.
		Surgery alone	42	—	81	—

Neri et al. (33)	1996	5-FU-LV-epirub	48	25	20.4	.01
		Surgery alone	55	13	13.6	—
Grau et al. (34)	1998	MMC-florafur	43	67	—	.04
		MMC	42	44	—	—
Nakajima et al. (35)	1999	MMC-5-FU-UFT	285	85.8	60	.17
		Surgery alone	288	82.9	60	—
Cirera et al. (36)	1999	MMC-tegafur	76	56	74	.04
		Surgery alone	72	36	29	—
Langman et al. (37)	1999	Cimetidine	221	21	13	.49
		Surgery alone	221	18	11	—
Nashimoto et al. (38)	2003	MMC-5-FU-araC	126	91.2	—	.13
		Surgery alone	126	86.1	—	—
Chippioni et al. (39)	2004	5-FU-LV-CDDP	101	39	—	—
		Surgery alone	104	39	—	—
Sato et al. (40)	2004	5-DFUR	143	62.9	—	.79
		5-DFUR + OKT-432	144	63.8	—	—
Hartgrink et al. (41)	2004	Preoperative (neoadjuvant) FAMTX	29	—	18	.17
		Surgery alone	30	—	30	—

araC, cytarabine; CDDP, cisplatin; DFUR, 5'-deoxy-5-fluorouridine; epirub, epirubicin; Dox, doxorubicin; FAMTX, 5-FU, doxorubicin, and methotrexate; 5-FU, 5-fluorouracil; LV, leucovorin; MeCCNU, methyl-lomustine; MMC, mitomycin C; UFT, tegafur-uracil; florafur, tegafur and uracil.

ratio for death among the treated cases was 0.72 (95% CI, 0.62–0.84), suggesting a significant survival advantage for adjuvant chemotherapy. On the basis of this analysis, a large confirmatory randomized controlled trial of cisplatin-based chemotherapy was recommended.

The Swedish Council of Technology Assessment in Health Care (9) conducted a comprehensive metaanalysis in 2001, including 21 randomized adjuvant trials. The analysis revealed a statistically significant survival benefit with an odds ratio of 0.84 (95% CI, 0.74–0.96). Both Western and Asian studies were included in the analysis. The authors noted a statistically significant difference: Western world studies revealed an odds ratio of 0.84 (95% CI, 0.83–1.12) whereas the Asian studies odds ratio was noted to be 0.58 (95% CI, 0.44–0.76). Based on this observation, the authors concluded that adjuvant chemotherapy could not be recommended in Western patients, but that the benefit in Japanese patients was evident. The authors did acknowledge, however, that flaws in the conduct of several trials made it difficult to draw firm conclusions, again highlighting the need for larger randomized trials.

In the United States, a randomized controlled clinical trial by the Southwest Oncology Group (SWOG) testing 5-FU, doxorubicin, and mitomycin C (FAM) chemotherapy did not demonstrate any benefit for adjuvant chemotherapy. In this study, 191 patients were randomized between 1 year of FAM after surgery or surgery alone. There was no benefit for chemotherapy, and the survival curves of treatment and control cases were overlapping. The overall survival at 5 years demonstrated in the study was approximately 35% for both surgery alone and for surgery followed by FAM chemotherapy (10).

Based on the trials and metaanalyses presented, the data for adjuvant chemotherapy alone are confounding. One caveat to the interpretation of these results is that adverse events such as hematologic toxicity, infection, nausea/vomiting, and stomatitis can be significant. This has resulted in the administration of less than 80% of planned doses of chemotherapy in many of these trials. It is possible that dose reductions and delays due to toxicities may have adversely affected efficacy end points.

## **Combination Regimens in Adjuvant Chemotherapy**

Until recently, combination regimens such as epirubicin, cisplatin, and 5-FU (ECF) and docetaxel, cisplatin, and 5-FU had not been tested as pure adjuvant therapy in patients with resected gastric cancer. In 2006, Cunningham et al. (11) reported the results of a phase III trial in which they evaluated the role of perioperative chemotherapy in the management of resectable gastric cancer. Patients with resectable adenocarcinoma of the stomach, gastroesophageal junction, or lower esophagus were randomly assigned to either

perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients). The patients in the chemotherapy group received both preoperative and postoperative therapy with ECF. Patients in the surgery-alone group underwent only gastrectomy and received no adjuvant therapy. Major end points were progression-free and overall survival. The results demonstrated a clear benefit from the use of the ECF regimen. Five-year overall survival was 36% in the perioperative-chemotherapy group and 23% in the surgery-only group, which was statistically significant ( $P = .008$  by the log-rank test). Progression-free survival was also superior in the chemotherapy group (hazard ratio for progression, 0.66; 95% CI 0.53–0.81;  $P < .001$ ). In addition, patients who underwent chemotherapy with ECF had acceptable rates of adverse events, with less than 12% of patients experiencing grade 3 or 4 toxic effects (excluding 23% of patients with neutropenia).

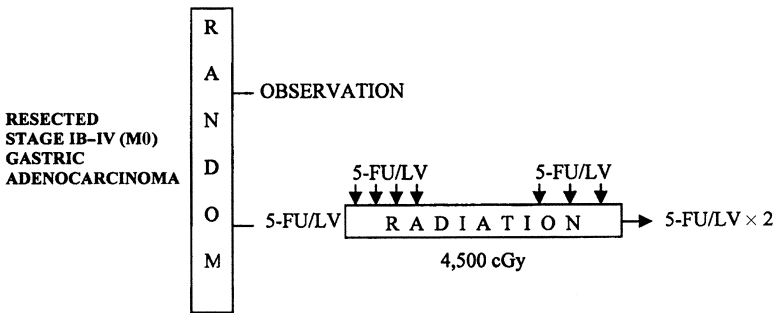
Although well designed and executed, the translation of the results of this trial into clinical practice is dependent on several factors. For example, it is useful to note that the ECF regimen was developed in the late 1980s. Currently, there are newer and less complex regimens with activity against gastric cancer. Newer regimens should be evaluated in a similar manner as the trial conducted by Cunningham et al. Another important factor concerns the timing of initial evaluation by an oncologist. Perioperative chemotherapy may be an option for patients who are evaluated before gastrectomy, but it is not unusual for patients to be seen after their surgical procedures. Patients who are evaluated after their surgical procedures are obviously not eligible for this treatment regimen. For the appropriate patient, however, the results of this study provide a new option for the use of adjuvant combination chemotherapy for localized, resectable gastric cancer. For the patient who is evaluated after a surgical procedure, treatment modalities other than adjuvant chemotherapy alone are warranted to decrease the risk of recurrent disease.

## Combined Modality Therapy in the Adjuvant Setting

An important therapeutic finding in gastric cancer relates to patients with known small amounts of residual or recurrent disease. Phase III trials have shown the combination of RT plus 5-FU used as a radiation sensitizer can result in complete control (apparent cure) in 12%–20% of patients (12,13). A controlled trial by the Gastrointestinal Tumor Study Group (13), published in 1982, compared survival in 90 patients with locally advanced gastric carcinoma treated with either chemotherapy alone (5-FU and methyl-CCNU) or external radiotherapy of 5,000 cGy combined with the same chemotherapy. Minimum follow-up was 4 years. During the initial 12 months, combined

modality therapy was associated with an increased number of early deaths (due to tumor progression, nutritional, or hematologic complications); however, patients followed during the second through fourth years who had received combined modality treatment had a significantly lower death rate compared to those treated with chemotherapy alone. Eight of 45 patients were alive and disease-free during this time period. In contrast, patients who had received only chemotherapy demonstrated a continued probability for tumor relapse and death. Only 3 of 45 patients in this group were alive at 4 years.

Based on this demonstrated benefit for combined chemoradiotherapy in this setting, the SWOG and the Gastric Intergroup conducted a trial (SWOG 9008/INT 0116) between 1991 and 1998 (14). This was the largest randomized trial ever to assess the efficacy of adjuvant postoperative chemoradiation in gastric cancer. This was a two-arm prospective randomized trial of postoperative adjuvant chemoradiation versus surgery alone in patients with completely resected adenocarcinoma of the stomach and gastroesophageal junction (Figure 1). A total of 603 patients accrued to the trial over 7 years, and results were reported initially in the spring of 2000 at the American Society of Clinical Oncology (ASCO) annual meeting, published in 2001, and updated in 2004. Eligibility criteria specified histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction, negative-margin resection, registration within 20–41 days postoperatively, usual adequate organ function, a performance status of Eastern Cooperative Oncology Group grade 2 or lower, and a postoperative caloric intake of at least 1,500 kcal per day by oral or enterostomal alimentation. Also required was tumor,



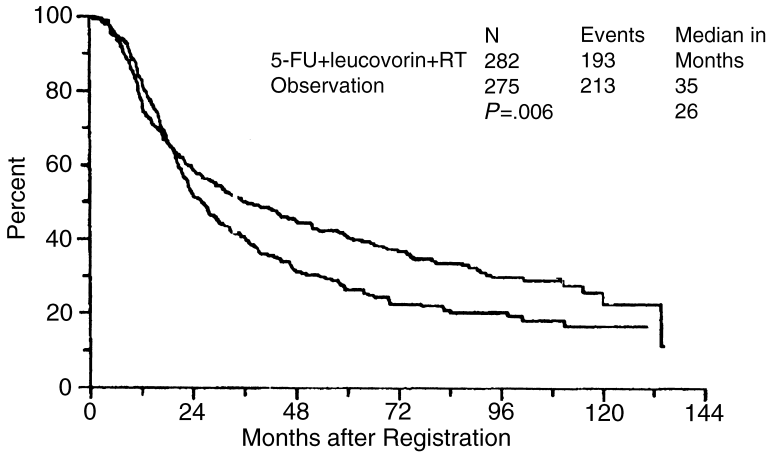
**Figure 1.** Schema for Southwest Oncology Group and Gastric Intergroup trial (SWOG 9008/INT 0116), patients with resected stage IB–IV (M0) gastric cancer are randomly allocated to either observation or postoperative chemoradiation. 5-FU, 5-fluorouracil; LV, leucovorin.

node, metastasis (TNM) stage IB or higher, but without distant metastasis. Of 603 patients initially accrued, 46 (8%) were ineligible based on the presence of positive surgical margins, disease other than adenocarcinoma on pathologic examination, or because they were registered after the specified time limit. Of the 556 remaining cases, 281 were assigned to the 5-FU/leucovorin (LV)/radiation arm, and 275 were assigned to the observation arm. Twenty percent of cases had disease of the cardia/gastroesophageal junction, and advanced-stage patients were overrepresented (85% of cases in both arms had node-positive carcinoma). Sixty-eight percent of patients had T3 or T4 disease. Sixty-nine percent were stage IIIA or IIIB (46% and 23%, respectively), whereas only 8% had stage IB disease. After undergoing gastrectomy, the treatment arm patients were given one cycle of 5-FU (425 mg/m<sup>2</sup>) and LV (20 mg/m<sup>2</sup>) daily for 5 days followed by 4,500 cGy (180 cGy per day) given with 5-FU/LV (400 mg/m<sup>2</sup> and 20 mg/m<sup>2</sup>) on days 1 through 4 and on the last 3 days of radiation. One month after the completion of radiotherapy, two 5-day cycles of 5-FU (425 mg/m<sup>2</sup>) plus LV (20 mg/m<sup>2</sup>) were given 1 month apart.

To ensure that combined modality therapy was given in a safe manner, radiation treatment plans were centrally reviewed and verified before the initiation of treatment. During this review, it was found that 34% of plans had major deviations. Two-thirds of these deviations would have resulted in under-treatment of patients, whereas one-third had the potential for delivering severely toxic doses of RT. Incorrect plans were modified before initiation of therapy.

Combined modality therapy as given in the INT 0116 trial was tolerable. Forty-one percent of patients experienced grade III toxicities, and 32% experienced grade IV toxicities. The most common grade III and IV toxicities were hematologic (54%) and gastrointestinal (33%) related. Leukopenia was most often observed, whereas severe thrombocytopenia was uncommon. Gastrointestinal toxic effects included nausea, vomiting, and diarrhea. Grade III/IV infections were seen in 6% of patients. Three patients (1%) died as a result of the administered treatment (pulmonary fibrosis in one patient, a cardiac event in another, and sepsis as a result of myelosuppression in the third).

Disease-free and overall survivals were significantly improved by combined modality 5-FU/LV/RT in the initial analysis presented in 2001. Average overall survival was 35 months in the treatment arm compared to 28 months in the control arm ( $P = .01$ , 2-sided  $P$  value). Average disease-free survival was 30 months in the treatment arm, compared to 19 months in the control arm ( $P < .0001$ , 2-sided  $P$  value). These improvements have been durable, with review of the updated data (2004), which was reported with more than 6 years median follow-up. Median overall survival for chemoradiation was 35 months versus 26 months for surgery alone ( $P = .006$ ; hazard ratio 1.31 [1.08–1.610]) (Figure 2). Average disease-free survival for chemoradiation was 30 months versus 19 months for surgery alone, which was



**Figure 2.** Updated survival by treatment arm with more than 6 years median follow-up for Intergroup 0116, a trial of postoperative adjuvant chemoradiation (*upper curve*) versus postoperative observation (see text). (Updated courtesy of Southwest Oncology Group. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345[10]:725–730.)

statistically significant ( $P < .001$ ; hazard ratio, 1.52 [1.75–1.85]). Table 4 compares the outcomes from the 2001 and 2004 analyses and demonstrates that the improvements in disease-free and overall survival do not dissipate over time. The 2004 analysis also showed that combined modality therapy did not result in late toxic events leading to treatment-related morbidity or mortality for the patients on the treatment arm.

Exploratory subset analyses for treatment interactions and prognostic factors were performed on the following six variables: sex, T stage, N stage, location, D level of dissection and diffuse versus intestinal histopathology. Positive treatment effects were seen in all of these subsets. Prognostic factors that were found to be significant included T stage, N stage, and D level of dissection. Initially, a possible treatment interaction was seen with diffuse pathology cases and poorer outcomes with therapy. After adjustment for multiple testing, however, this result was not significant.

The influence of the extent of surgical dissection on the outcomes of this trial has been the subject of much discussion. For potentially curable gastric cancer (stages 0–IV, M0) the surgical procedure involves a tumor resection entailing at least a partial gastrectomy with an en bloc dissection of lymphatic tissue. The extent of resection in gastric cancer is defined using a des-

**Table 4.** Southwest Oncology Group and Gastric Intergroup Trial SWOG 9008/INT 0116

<b>Source</b>	<b>Hazard Ratio</b>	<b>95% Confidence Interval</b>	<b>P Value</b>	<b>Median Observation (mo)</b>	<b>Median Treatment (mo)</b>
Overall Survival					
New England Journal of Medicine 2001	1.32	(1.06–1.64)	.005	27	36
Update 2004	1.31	(1.08–1.61)	.006	26	35
Disease-Free Survival					
New England Journal of Medicine 2001	1.52	(1.23–1.86)	<.001	19	30
Update 2004	1.52	(1.25–1.85)	<.001	19	30

Data from Macdonald,JS. Role of post-operative chemoradiation in resected gastric cancer. J Surg Oncol. 2005;90(3):171–173; discussion 173.

**Table 5.** Gastric Cancer: Extent of Surgery

<b>Resection</b>	<b>Definition</b>
D0	Incomplete resection of N1 nodes
D1	Complete resection of N1 nodes
D2	Complete resection of N1 + N2 nodes

ignation of D0, D1, or D2 (Table 5). A D1 dissection includes resection en bloc of the tumor plus N1 lymph nodes. If the N1 nodes are not taken, a D0 procedure has been performed. If the N2 nodes are resected, this is termed a *D2 dissection*. Fifty-four percent of patients in the INT 0116 trial underwent less than a D1 dissection, and only 10% underwent a D2 dissection. Median survival was 27 months for D0 lymphadenectomy and 48 months for D2 lymphadenectomy; however, because only 10% of patients underwent the more aggressive surgical approach, this difference was not statistically significant.

The need for more aggressive surgical resections has been the subject of international debate for many years. In the 1960s, radical surgical approaches for gastric cancer fell into disfavor in the United States. This approach arose from recognition of the considerable morbidity and mortality associated with these procedures. Encouraged by generally lower surgical mortality rates and improved stage-stratified survival, Japanese surgeons routinely performed more aggressive surgical dissections. Small phase II studies comparing D1 and D2 dissections were reported from South Africa and Hong Kong (15,16). The studies had small numbers of patients (less than 30 per arm) and, therefore, were underpowered. No survival benefit was demonstrated for D2 nodal dissections.

Several prospective randomized trials of D1 versus D2 lymphadenectomy have also been completed (Table 6). In 1988, Dent and colleagues (17) reported on 403 patients who had T1–T3 disease, N0–N1 disease, no distant metastases, absence of significant comorbidities, and were younger than 75 years of age. Patients were randomized to D1 versus D2 dissections. No survival difference was noted, but increased operative time, increased blood transfusions, and longer hospital stays were noted for the D2 group.

Similarly, a phase III trial conducted in the Netherlands (18) including 711 cases also evaluated D2 versus D1 dissections. Again, D2 dissections did not improve overall survival and were associated with higher operative morbidity and mortality.

Therefore, although the extent of surgical resection performed in the INT 0116 trial may be considered suboptimal by some, it is clear that there is no

**Table 6.** Prospective, Randomized Surgical Trials

<b>Lymphadenectomy Trials</b>	<b>Inclusion Criteria</b>	<b>N</b>	<b>Mortality/ Survival</b>	<b>Mortality/ Survival</b>	<b>P Value (Survival)</b>	<b>General Comments</b>
Cape Town	T1-3; N0-1; M0, age <75 y	43		<b>D2</b> 0%/76% (3-year survival)	n.s.	Solid design. Early closure due to poor accrual and inadequate power to detect.
British Medical Research Council	Stage I-II, age >20 y	400	6%/35% (5-year survival)	13%/33% (5-year survival)	n.s.	Unique definition of "D1" and "D2." Skippy quality control.
Dutch	Stage I-I, age <85 y	711	4%/45% (5-year survival)	10%/47% (5-year survival)	n.s.	Solid design. Despite superb quality control efforts, substantial protocol noncompliance. Trial question confounded by adverse effects of pancreaticosplenectomy.
Japanese D2 vs. D4 trial	Deep T2-T4		<b>D2</b> 0.8%/—	<b>D4</b> 0.8%/—	ongoing	Ongoing trial. Immature with respect to survival.
French	Antral tumor, M0		<b>Subtotal</b> 3%/48% (5-year survival)	<b>Total</b> 1%/48% (5-year survival)	n.s.	Pioneering trial. Straightforward design.

(continued)

**Table 6.** Prospective, Randomized Surgical Trials (Continued)

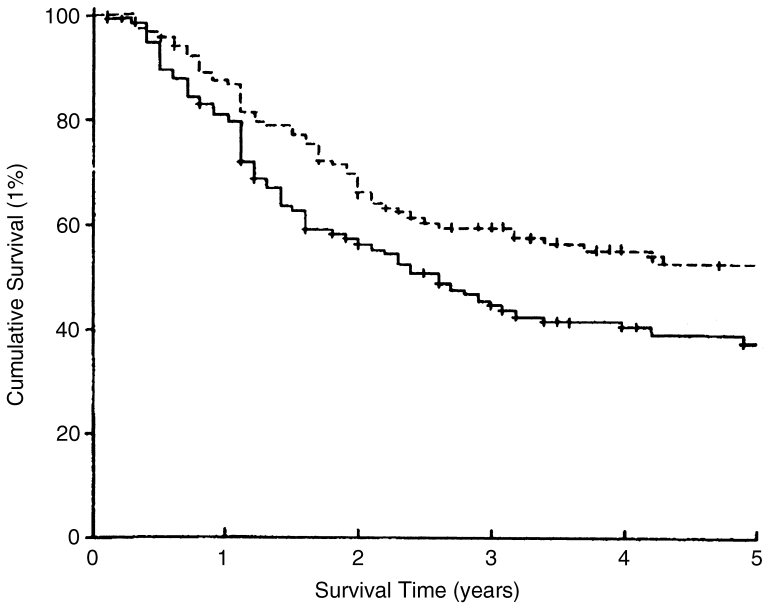
<b>Lymphadenectomy Trials</b>	<b>Inclusion Criteria</b>	<b>N</b>	<b>Mortality/Survival</b>	<b>Mortality/Survival</b>	<b>P Value (Survival)</b>	<b>General Comments</b>
Italian	>6 cm proximal marginal possible all, but not mandated M0		1%/65% (5-year survival)	2%/62% (5-year survival)	n.s.	D2 recommended all, but not mandated. Straight-forward design.
Hong Kong	Antral >6 cm margin, M0, age <75 y		<b>Subtotal + D1</b> 0%/4,511 days median survival	<b>Total + D3</b> 3%/922 days median survival	0.04 0.07	Dual P values reported. Transfusion issue.

definitive evidence that D2 dissection offers any survival advantage compared to less radical resections. In addition, the benefits achieved with postoperative chemoradiotherapy were not significantly different among patients who received a D0 resection compared to those who underwent a more radical surgical procedure. Thus, the trial did not demonstrate a causal relationship between inadequate surgical procedures and the benefit of postoperative chemoradiotherapy. Based on the results of INT 0116, adjuvant chemoradiotherapy has been recommended as the standard of care for all patients with gastric cancer stage IB or higher, but without distant metastatic disease. This recommendation should be made provided patients meet criteria for adequate caloric intake (more than 1,500 kcal per day), good organ function, and good performance status.

## Results of Recent Trials

In conclusion, the use of intraperitoneal chemotherapy is a rational approach to adjuvant therapy, given that the peritoneal cavity is a common site of recurrence for gastric cancer. Japanese investigators have advocated intraperitoneal installation of mitomycin for some time (19). There have been several negative prospective randomized trials reported (20–22). A positive trial was reported in 2001 by Yu et al. (23). This was a trial of 248 Korean patients with biopsy-proven gastric cancer without metastases who were randomized intraoperatively after complete resection and minimum D2 lymphadenectomy to receive postoperative intraperitoneal mitomycin C and 5-FU versus surgery alone. Results showed significantly improved overall survival for the treatment group (54% vs. 38%;  $P = .0278$ ) (Figure 3). Subset analyses demonstrated greater benefit for stage III and IV cases.

More recently, at ASCO 2006, Tsujitani et al. (24) reported results of a phase III randomized controlled trial in abstract form. This trial examined the use of hypotonic intraperitoneal cisplatin combined with 5-FU, tegafur, and uracil (UFT)/protein-bound polysaccharide (PSK) taken orally for the adjuvant treatment of gastric cancer invading the serosa. In this trial, 134 patients treated with curative resection for gastric cancer invading the serosa were randomized during surgery to one of two treatment arms: Arm 1 (54 patients) received hypotonic intraperitoneal cisplatin (100 mg/m<sup>2</sup>) during surgery and systemic UFT (300 mg per day) + PSK (3 g per day), whereas arm 2 (48 patients) received systemic UFT + PSK. Peritoneal recurrence rates were 26.9% in arm 1 and 40% in arm 2. Overall survival at 5 years was 62% (arm 1) and 31% (arm 2). The authors concluded that combining hypotonic intraperitoneal cisplatin and systemic oral chemotherapy improves the efficacy of oral chemotherapy after curative surgery



**Figure 3.** Kaplan-Meier overall survival for group treated with early postoperative intraperitoneal chemotherapy (mitomycin C on postoperative day 1 and 5-fluorouracil daily on postoperative days 2–5; *upper curve*) versus controls receiving surgery alone (*lower curve*). With mean follow-up of 36 months, survival difference is significant ( $P = .0278$ ). (From Yu W, Whang I, Chung HY, et al. Indications for early postoperative intraperitoneal chemotherapy of advanced gastric cancer: results of a prospective randomized trial. *World J Surg* 2001; 25[8]:985–990, with permission of World Journal of Surgery.)

for gastric cancer invading the serosa. The use of intraperitoneal therapy in the adjuvant treatment of gastric cancer, however, does not represent the standard of care.

Although increased RNA expression of dihydrofolate reductase and thymidylate synthase have been linked to poor outcomes in patients with recurrent or residual gastric cancer, measurement of these protein expressions is not yet in widespread use. Additionally, mutant dihydropyrimidine dehydrogenase and heterozygous expressions of cytidine deaminase are associated with poorer survival and greater toxicity to 5-FU-based chemotherapy. Although these studies provide thought-provoking potential for the utility of molecular markers, clinical treatment options have not evolved as yet to incorporate these findings in the selection of medical therapies (26,27).

## Conclusion

In summary, adjunctive therapy in addition to surgical resection of locally advanced gastric cancer has become a standard of care in many parts of the world. Purely postoperative chemotherapy as used in colon and breast cancer has not been accepted as a standard approach because no large well-powered phase III trial has demonstrated the usefulness of this approach; although, as described previously, metaanalyses suggest a trend toward its benefit. The recent publication of the perioperative chemotherapy trial by Cunningham et al. (11) demonstrated that this approach improves overall and disease-free survival in gastric cancer patients identified before gastric resection. In many instances, stomach cancer cases are only identified after a gastrectomy has been performed. In those cases at high risk for relapse, postoperative chemoradiation (14) is considered a standard of care and improves both overall and relapse-free survival. The roles of intraperitoneal and targeted or biologic therapies as adjuncts to gastric resection have yet to be defined.

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# Advances in Systemic Chemotherapy of Gastric Cancer

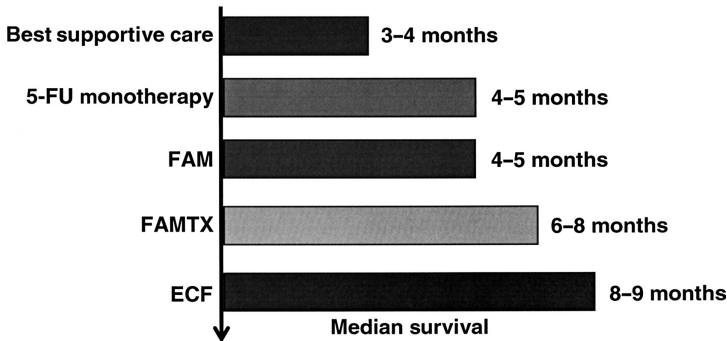
Edith P. Mitchell, MD, FACP

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## Advanced Gastric Cancer and Surgical Treatment

At the time of diagnosis, gastric cancers are localized in approximately 50% of patients, and primary management is based on surgical resection of the primary tumor. When the cancer is localized to the stomach, an early lesion with minimal invasion is detected with negative lymph nodes, and the cancer is confined to the mucosa or submucosa, surgical cure rates may exceed 80% (1,2); however, as few patients have symptoms, the detection of early gastric cancer is rare in the United States and other Western countries. Gastric cancer is more commonly locally advanced at diagnosis, with tumor extension through the gastric wall and direct extension into other organs, with or without metastatic involvement of perigastric lymph nodes (3–6). In these circumstances, fewer than 30% of patients are cured by surgical means.

Because many patients present with metastatic disease at the time of diagnosis, and this results in poor outcomes after surgery, with a significant number of patients having relapse of the disease, there has been interest in treating patients with systemic chemotherapy. In the setting of metastatic gastric cancer, many chemotherapeutic agents have resulted in positive response when used alone as monotherapy or in combination with other agents, that has resulted in improvement in overall survival rates, although the duration of response has remained limited (Figure 1). This chapter discusses the advances in systemic chemotherapy that may predict response and guide treatment in metastatic gastric cancer.



**Figure 1.** Progress in treatment of advanced gastric/esophagogastric cancer. FAM, 5-FU, doxorubicin, and mitomycin C; FAMTX, 5-FU, doxorubicin, leucovorin, and methotrexate; ECF, epirubicin, cisplatin, and 5-FU.

## Single-Agent Chemotherapy

Traditional chemotherapy agents used as monotherapy have resulted in variable response rates in patients with advanced or metastatic gastric cancer (Table 1). Single-agent chemotherapy has resulted in response rates from 10% to approximately 25% and included 5-fluorouracil (5-FU); mitomycin C, doxorubicin, epirubicin, cisplatin, and carmustine (BCNU); methotrexate; etoposide; chlorambucil; hydroxyurea; docetaxel; irinotecan; and paclitaxel.

5-FU has been the most extensively studied agent in metastatic gastric cancer. Reported response rates vary, but are up to 21%. Earlier trials used schedules with daily 5-FU administration by intravenous bolus injection for 5 consecutive days. Treatments using 5-FU by continuous infusion for several days up to several weeks have been reported. Although the response rates to infusional chemotherapy with 5-FU are similar to those of bolus 5-FU, the toxicity profiles are different. The major side effects of bolus 5-FU are neutropenia and diarrhea, whereas the major toxicities of infusional 5-FU are mucositis, diarrhea, and erythroderma of the palms and soles (hand-foot syndrome). The oral fluorinated pyrimidines ftorafur and uracil (UFT), S1, and capecitabine have also demonstrated significant efficacy as single agents in the treatment of metastatic gastric cancer.

## Combination Chemotherapy

Many phase II trials of combination chemotherapy were based on promising activity observed with a variety of single agents. Table 2 lists several combinations of recently published trials. Many of these regimens resulted in less activity and/or greater toxicities in subsequent phase II and phase III trials (Table 3).

**Table 1.** Response Rates to Single-Agent Chemotherapy in Patients with Advanced and Metastatic Gastric Adenocarcinoma

Drug	Number of Patients	Response Rate (%)
Antimetabolites		
Fluorouracil	416	21
Methotrexate	28	11
Gemcitabine hydrochloride	15	0
Oral antimetabolites		
UFT	188	28
S1	51	45
Capecitabine	31	28
Hydroxyurea (oral)	31	19
Tegafur (oral)	19	19
Antibiotics		
Mitomycin C	211	30
Doxorubicin hydrochloride	141	17
Epirubicin hydrochloride	80	19
Heavy metals		
Cisplatin	139	30
Carboplatin	41	17
Taxanes		
Paclitaxel	98	17
3 h	—	7
24 h	—	22
Docetaxel	123	21
Camptothecins		
Irinotecan hydrochloride	66	23
Topotecan hydrochloride	33	6
Targeted therapies		
Gefitinib	—	1.5
Erlotinib	—	5

UFT, uracil and tegafur.

**Table 2.** Phase II Trials of New Agents in Gastric Cancer

<b>Agents</b>	<b>Response Rate (%)</b>
Pac-5-FU	56
Pac-Cis-5-FU	53
CPT-Cis	50
UFT-Cis	51
Cape-Cis	55
5-FU-Oxal	48
FOLFOX-4	45
DCF	54

Cape, caffeic acid phenethyl ester; Cis, cisplatin; CPT, irinotecan; DCF, docetaxel, cisplatin, and 5-fluorouracil; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; 5-FU, 5-fluorouracil; Oxal, oxaliplatin; Pac, platinum, doxorubicin, and cyclophosphamide; UFT, tegafur and uracil.

### **Nitrosourea Combinations**

The combination of a nitrosourea, such as BCNU or methyl-CCNU (MeCCNU), with 5-FU represents one of the earlier approaches to combination chemotherapy in the treatment of metastatic gastric cancer. Although

**Table 3.** Phase III Trials in Gastric Cancer

<b>Agents</b>	<b>Response Rate</b>
ELF vs	9%
FAMTX vs	12%
Cis-5-FU	20%
FAMTX vs	21%
E-Cis-5-FU	45%
Mito-Cis-5-FU vs	44%
E-Cis-5-FU	43%
EAP vs	20%, more toxic
FAMTX	33%
DCF vs	36%
CF	26%

CF, cisplatin and fluorouracil; DCF, deoxycoformycin; Cis-5-FU, cisplatin and 5-fluorouracil; E, etoposide; EAP, etoposide, doxorubicin, cisplatin; ELF, etoposide, leucovorin, 5-fluorouracil; FAMTX, 5-fluorouracil, doxorubicin, and methotrexate; Mito, mitomycin.

earlier response rates, up to 41%, were promising, the median duration of survival for the combination was 7.7 months, which was not significantly improved over each of the drugs when used alone (7). Subsequent trials with combinations of BCNU and 5-FU showed lower response rates (8). MeCCNU was also evaluated with 5-FU. In a randomized study comparing MeCCNU combined with 5-FU to 5-FU alone, the combination produced a 40% response rate and superior survival (9), but subsequent studies with nitrosoureas failed to confirm these results (10).

### **Mitomycin Regimen**

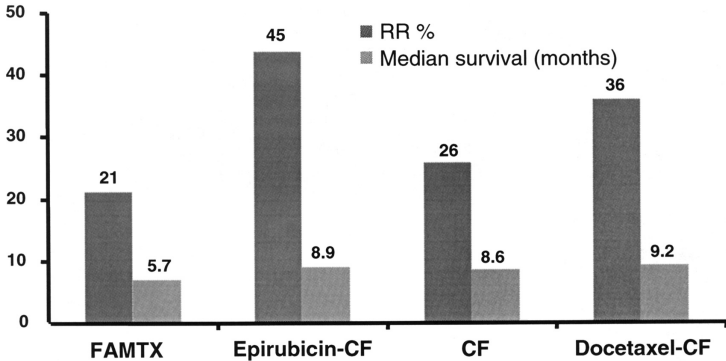
With single-agent therapy demonstrating activity of mitomycin C and doxorubicin, the triple drug combination of 5-FU, doxorubicin, and mitomycin C (FAM) underwent phase II and III evaluations (11). Initial studies demonstrated a 42% response rate; however, subsequent phase III trials failed to demonstrate the response rate or a survival benefit (12). In a randomized trial of 5-FU, 5-FU plus doxorubicin (FA), and FAM, 18% of patients responded to 5-FU, 27% to FA, and 38% to FAM. Survival among the groups was similar, with 27 weeks for FA and 30 weeks for the other two regimens (13).

### **5-Fluorouracil, Doxorubicin, Leucovorin, and Methotrexate**

Biochemical modulation of 5-FU by methotrexate and leucovorin led to the development of a regimen combining 5-FU, doxorubicin, leucovorin, and methotrexate (FAMTX). This combination was evaluated in metastatic gastric cancer, with responses exceeding 50% (14,15). When compared to FAM, FAMTX showed a superior response rate; however, the 2-year overall survival rate was no better than the expected rate with best supportive care (BSC) (13). Subsequently FAMTX was replaced by cisplatin-containing regimens.

### **Cisplatin-Based Combinations**

The *in vitro* synergy between cisplatin and 5-FU and the single-agent antitumor activity of cisplatin in metastatic gastric cancer led to the development of phase II studies of cisplatin-containing regimens (Figure 2). In a phase II study, the response rate of the combination of 5-FU, doxorubicin, and cisplatin (FAP) was 35% (16). A phase III study did not show an advantage of FAP compared to 5-FU (17). Cunningham et al. (18) utilized epirubicin, cisplatin, and 5-FU (ECF), with response rates in phase II trials of 37%–71%. In a ran-



**Figure 2.** Metastatic gastric cancer: phase III. Adding a third drug to 5-fluorouracil (F) and cisplatin (C). FAMTX, 5-FU, doxorubicin, leucovorin, and methotrexate.

domized trial, the response rate of ECF was superior to FAMTX (46% vs. 21%), and median survival was longer (8.7 months vs. 6.1 months) (18,19).

Etoposide was added to cisplatin and doxorubicin (EAP), with a response rate of approximately 50% but with a mortality rate in the range of 10%–14% (20). In a randomized study, similar response rates were demonstrated with FAMTX, but it also showed less toxicity (21). To decrease toxicity from the EAP regimen, this group developed a subsequent regimen of etoposide, leucovorin, and 5-FU (ELF), with a response rate of 53% and a median survival rate of 11 months (22).

In a phase III trial by the European Organization for Research and Treatment of Cancer, FAMTX was compared to ELF and to infusional 5-FU and cisplatin. There were differences in response rates and median survival rates (23).

### **Taxane-Based Regimen**

The combination of docetaxel, cisplatin, and 5-FU (DCF) has been compared to cisplatin/5-FU, with DCF demonstrating a significantly longer time to tumor progression (5.6 months vs. 3.7 months), higher response rate (36% vs. 26%), longer time on therapy (19 months vs. 16 months), and marginal, but significantly longer, overall survival, as well as greater 1- and 2-year survival. Toxicity, however, was also greater in the DCF group, with more neutropenia (82% vs. 57%) and neutropenic fever without granulocyte colony-stimulating factor (30% vs. 14%). The conclusion was that DCF improved clinical end points, but with greater toxicity (24).

## Irinotecan-Based Therapy

Multiple studies have demonstrated the activity of irinotecan with phase II response rates of irinotecan combinations in metastatic gastric cancer. The combination of irinotecan and bolus 5-FU demonstrated a response rate of 22% (25). The combination of irinotecan and cisplatin has been reported in several phase II studies, with responses ranging from 30%–60% (26–28). With infusional 5-FU, several phase II reports demonstrate responses of 35%–40% (29–31). A recent phase III trial randomized patients to irinotecan, weekly infusional 5-FU, and leucovorin (IF), or conventional cisplatin and 5-FU. Although the response rate, time to tumor progression, and overall survival were all improved in the IF group, statistical significance was not reached. Toxicity was likewise less in the IF arm except for diarrhea (32).

## Chemotherapy versus Best Supportive Care

Because of debate over whether chemotherapy offered any advantages for patients with advanced gastric cancer, randomized trials were conducted in which patients with metastatic gastric cancer were assigned to receive chemotherapy or BSC (Table 4). There was variability in when chemotherapy was initiated, with treatment beginning at the time of symptomatic or objective progression or at the discretion of the physician. Although the studies were different, results consistently showed that patients randomized to receive chemotherapy immediately had better survival than those randomized to BSC, even if they received chemotherapy later.

In a study of 40 patients with advanced gastric cancer, they received either BSC or an induction course of 5-FU, methotrexate, cyclophosphamide, and vincristine followed by weekly 5-FU and mitomycin C. The median survival in both groups was 2 months (33).

The West Midlands group reported on 193 patients randomized to 5-FU/MeCCNU or no treatment. For patients who received the minimum of one 6-week course of chemotherapy, the survival time was 25 weeks, compared to 22-week survival in control subjects. Median survival estimates for all patients, including early deaths, was in the 8- to 10-week range with no apparent difference between the two groups. A quality-of-life (QOL) analysis favored the patients treated with chemotherapy (34).

In a group of 76 patients with T4 or M1 disease who were randomized to no treatment, localized radiotherapy, and thiotepa, median survival for all three groups was approximately 19 weeks (35), whereas in another randomized trial, patients were assigned to treatment with a modified FAMTX regimen or supportive care. The trial was interrupted, and the remaining patients

**Table 4.** Chemotherapy for Advanced Gastric Cancer versus Best Supportive Care (BSC)

<b>Regimen</b>	<b>Median Survival (mo)</b>
FMCV/FM	2
BSC	2
FU/MeCCNU	25
BSC	22
Thiotepa	19
BSC	19
FAMTX	10
BSC	3
FEMTX	3.1
BSC	3.0
ELF/FU-LV	8
BSC	5
FAM	(1 yr = 34.1%)
BSC	(1 yr = 22.5%)

BSC, best supportive care; CV, cisplatin and vinorelbine; ELF, etoposide, leucovorin, 5-fluorouracil; FAM, 5-fluorouracil, doxorubicin, and mitomycin C; FAMTX, 5-fluorouracil, doxorubicin, and methotrexate; FEMTX 5-fluorouracil, epirubicin, and methotrexate; FM, fludarabine and mitoxantrone; FU, fluorouracil; LV, leucovorin; MeCCNU, Methyl-CCNU.

were assigned to treatment because of a significantly better outcome in those who received treatment. Median survival was 10 months for patients who were treated, versus 3 months for the untreated controls ( $P = .001$ ) (36).

In another trial, 41 patients were randomized to receive 5-FU, epirubicin, and methotrexate (FEMTX) plus vitamins A and E, versus the same vitamins and BSC. Median time to progression was 5.4 months and 1.7 months ( $P = .0013$ ), and median survival time was 3.1 months versus 3.0 months, favoring treatment with FEMTX (37).

In a group of 61 patients randomized between chemotherapy with lactoferrin or 5-FU/leucovorin compared to BSC, survival was superior in the treatment group, with 8 months median survival versus 5 months in the untreated patients ( $P = .003$ ), and QOL likewise favored the treated patients ( $P < .05$ ) (38).

In the final trial, a retrospective study of 409 patients treated with FAM and 207 patients untreated, the 1-year survival rate was 34.1% in the treated patients versus 22.5% in the untreated group (39).

## Targeted Therapy

Research into the properties that characterize gastric cancer cells has revealed genetic and molecular targets that are being evaluated as predictive and prognostic markers as well as the potential for strategies linked to the successful development of targeted therapeutic interventions.

### Monoclonal Antibodies and Tyrosine Kinase Inhibitors

Newer targeted therapies, such as the anti-HER2 monoclonal antibody, trastuzumab; the anti-vascular endothelial growth factor (VEGF) drug, bevacizumab; the anti-epidermal growth factor (EGF) receptor drugs, cetuximab and matuzumab; and signal transduction inhibitors, such as erlotinib and gefitinib, are currently being evaluated in gastric cancer. Cetuximab will be evaluated in the Cancer and Leukemia Group B 80403 trial, combining monoclonal antibody with chemotherapy as first-line treatment in a phase II trial of metastatic gastric cancer. As planned, this will be a randomized phase II trial of three different chemotherapy regimens combined with cetuximab: ECF; oxaliplatin, 5-FU, and leucovorin; and irinotecan with cisplatin (40) Multiple phase II trials of chemotherapy combined with targeted therapies are ongoing.

### Predictive Markers of Response

The development of methods for prospective selection of therapy by gene expression profiling or other techniques allows correlative analyses that may predict response to therapy. In studies conducted at the University of Southern California, an analysis of a subgroup of patients who received neoadjuvant cisplatin and 5-FU chemotherapy followed by resection and intraperitoneal floxuridine showed that response and survival were correlated with molecular markers assessed by reverse transcriptase-polymerase chain reaction for several genes. Patients whose tissues had low levels of expression of thymidylate synthase (TS) and excision repair cross-complementing gene (ERCC1) had significantly longer median survival and higher long-term survival than patients with high tissue levels of expression (41,42). The study utilized immunohistochemistry to measure TS, p53, VEGF, and glutathione transferase expression in 39 patients with unresectable gastric cancer who were treated with cisplatin and 5-FU combination chemotherapy, and showed that those tumors with a lower level of TS expression had a higher response rate. Improved clinical outcomes were similarly noted in patients whose tissues were negative for p53, BCL-2, and glutathione 5-transferase; in those patients, a higher expression of VEGF

demonstrated a higher response rate. In a multivariate analysis, a combination of favorable molecular features was more predictive of response than clinical parameters (43). Resistance to chemotherapy has been associated with p53 expression in locally advanced gastric cancer (44).

Another marker predicting fluoropyrimidine sensitivity is dihydropyrimidine dehydrogenase gene expression (DPD), a key enzyme in 5-FU degradation. In 53 patients with metastatic gastric cancer who received either S1 or S1 combined with irinotecan, TS and DPD expressions were evaluated. Results of this study showed no difference in DPD gene expression associated with response, but TS expression was predictive in patients receiving S1 as a single agent; the level of TS was lower in tumors of responding patients than in non-responding ones ( $P < .005$ ), and patients with low tumor expression had improved survival compared to those with high TS gene expression. Therefore, molecular markers may allow prediction of response to fluoropyrimidine therapy (45).

### **Surrogate Markers of Response**

Using immunohistochemistry techniques, assessing treatment response correlated best with p53, Ki-67, and EGF expression (46). Apoptosis has also correlated with histologic response and TUNEL assay (47,48).

Fluorodeoxyglucose positron emission tomography (FDG-PET) has also been used to predict response to therapy by using a 35% decline in standard uptake value (SUV) to distinguish responders versus nonresponders. A significant decrease in FDG-PET SUV on day 14 was associated with response and improved survival (49).

The use of surrogate methods to determine response to therapy is still experimental.

## **Supportive Care**

Because a large percentage of patients with metastatic gastric cancer have experienced significant weight loss, supportive care with attention to obstruction, nutrition support, and pain control are important to enhance the ability of the patient to undergo chemotherapy (Table 5). Gastric outlet obstruction can often be treated with endoluminal stent or with laser therapy for exophytic tumor masses. Nutritional support can be achieved through feeding jejunostomy or percutaneous endoscopic gastrostomy tube placement or through parenteral alimentation. Pain management, including selective use of palliative radiation for bone metastases or obstructing or bleeding tumors, may also be necessary.

**Table 5.** Supportive Care: Symptom Management

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**Obstruction**

Endoluminal stent

Endoscopic laser

**Nutritional support**

Feeding jejunostomy

Percutaneous endoscopic gastrostomy (PEG)

Parenteral alimentation

**Pain control****Palliative irradiation**

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## Conclusion

Gastric cancer is a common disease worldwide with an increasing incidence shift to more proximally located tumors in the cardia and gastroesophageal junction. Because many patients have advanced or metastatic disease at the time of diagnosis, and a significant percentage of those undergoing surgical resection later develop metastases, it is important to continue to develop effective systemic therapy. Treatment with systemic chemotherapy has resulted in response rates of approximately 50% in selected patients with metastatic gastric cancer. Chemotherapy has demonstrated prolonged survival in patients when compared to BSC. Cytotoxic combinations continue to develop, with results indicating that triplet combinations with epirubicin or docetaxel added to cisplatin and fluoropyrimidines result in improved outcomes but are also frequently associated with greater toxicities. Thus, careful patient selection, institution of supportive care measures before treatment, prevention of potential side effects when possible, and early intervention strategies for management of toxicities are essential components in the treatment of patients with metastatic gastric cancer. In the future, it is anticipated that molecular and gene profiling may allow for better patient selection and individualized therapy, and the integration of novel targeted therapies with more traditional cytotoxics will lead to continued positive treatment outcomes.

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# **Advances in Gastric Cancer: What Lies Ahead**

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## **Recent Progress in the Treatment of Gastric Cancer**

Adenocarcinoma of the stomach is a common worldwide malignancy that is associated with a high mortality rate, even for patients who are completely resected. Modest progress has been made in the treatment of gastric adenocarcinoma since the 1990s. In this time a uniform staging system based on the number of nodes involved rather than their location has gained favor. A standardized extent of minimal resection for localized disease has also been developed, and preoperative and postoperative chemotherapy and chemoradiation as an adjunct to surgery have begun to be incorporated in the routine management of locally advanced disease. For metastatic disease, additional drugs and drug classes have been incorporated in routine treatment (including docetaxel, irinotecan, and oxaliplatin), and more combination therapies have been developed resulting in more treatment options for patients. Despite these significant strides in staging, surgery, and treatment, however, median survival for metastatic disease remains less than 1 year. Future advances in the treatment of this disease will lie in continued improvements in the understanding of its pathogenesis and biology of metastatic disease, the use of biologically targeted therapies for treatment, and the improved selection of therapies (e.g., individualized therapy to minimize toxicity). This chapter highlights some of the expected advances that will guide management of this disease in the years to come.

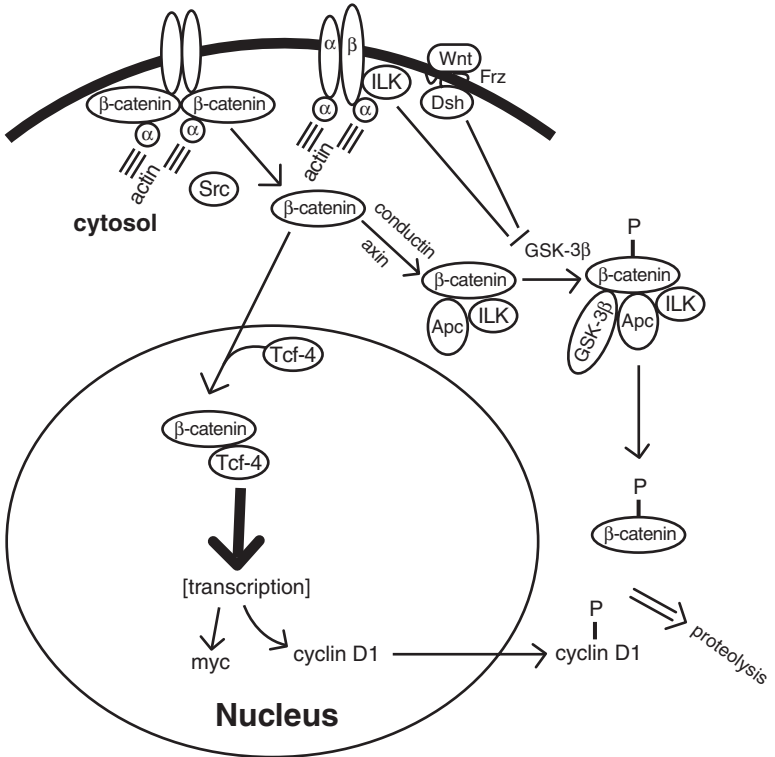
## **Emerging Biology of Gastric Cancer**

### **E-Cadherin and the Wnt Pathway: Implications in the Development of Diffuse and Intestinal Gastric Cancer**

At least part of the reason progress in the treatment of metastatic gastric cancer has been limited is the imperfect, but improving, understanding of the pathogenesis of this disease. As an example, virtually all stomach cancers are adenocarcinomas that can be pathologically distinguished according to the Lauren classification as intestinal or diffuse pathologic subtypes (1). Intestinal gastric cancers are generally well differentiated, with a glandular appearance, and tend to expand through the stomach wall, whereas diffuse gastric cancers are more commonly poorly differentiated and spread as single discohesive cells that infiltrate throughout the stomach wall. Intestinal gastric cancers are predominant in high-incidence areas and this histology is responsible for much of the ethnic variation across the globe (2). Despite the significant differences in the epidemiology of these two major types of gastric adenocarcinomas, the disease is generally treated uniformly with chemotherapy, independent of the histologic and biologic phenotype.

The Wnt signaling pathway is a central regulatory mechanism of gene expression that is present in vertebrates and invertebrates and is highly conserved in both; it may provide a biologic explanation of the pathogenesis of both diffuse and intestinal gastric cancer. This pathway plays an essential role in embryonic development and also functions in differentiated cells in a variety of processes, including cell cycle regulation. Central to the Wnt signaling pathway is the regulation of  $\beta$ -catenin, which has multiple cellular functions, from cell surface signaling with E-cadherin to nuclear translocation and transcription (Figure 1). Mutations in the gene's encoding Wnt components are associated with various cancers, including those of the gastrointestinal tract and, in particular, gastric cancer. Diffuse gastric cancer is associated with loss of E-cadherin function in approximately 50% of cases (3). Germline mutations in the E-cadherin gene (CDH1) are associated with loss of E-cadherin function and are associated with the familial form of diffuse gastric cancer, *hereditary diffuse gastric cancer* (4). Because E-cadherins are components of adherens junctions, this observation is consistent with the loose cell-to-cell attachment characteristic of the histology of diffuse-type gastric tumors.

In contrast to diffuse gastric cancer, intestinal gastric cancer is known as the "epidemic-type" of gastric cancer because of the high incidence of the intestinal histopathologic phenotype of gastric cancer in high-risk areas around the world. Intestinal gastric cancers have a defined pathologic carcinogenesis, beginning with multifocal atrophic gastritis followed by intestinal metaplasia and dysplasia, leading to adenocarcinoma (5). The Wnt signaling



**Figure 1.** The E-cadherin/β-catenin/Wnt signaling pathway. In the “canonical” pathway, activation is primarily mediated via the binding of soluble Wnt ligand(s) to Frizzled (Frz) and the low-density lipoprotein receptor-related coreceptors. This transduces an activating signal to Dishevelled (Dsh). On activation, Dsh is released from its complex with the cytosolic end of the Frz receptor and acts as an inhibitor of proteolytic degradation of β-catenin. Targeting of β-catenin for proteolysis is accomplished by axin-mediated phosphorylation (in association with a large complex that includes glycogen synthase kinase 3β [GSK-3β], adenomatous polyposis coli [APC], type 2 protein serine/threonine phosphatase) of serine and threonine residues on a region of β-catenin that is encoded by exon 3 of the β-catenin gene. Cytoplasmic levels of β-catenin are also regulated by cell-cell and/or cell-substrate interactions via E-cadherin and integrin cell surface receptors, respectively. α, alpha-catenin; ILK, integrin-linked kinase; Tcf-4, T cell factor 4.

pathway is also implicated in the development of intestinal gastric cancer. Whereas decreased E-cadherin expression is associated with diffuse gastric cancer, increased cytosolic expression of  $\beta$ -catenin and its nuclear translocation appear to be associated with the development of intestinal gastric cancer (6). Specifically, adenomatous polyposis coli (APC) gene mutations and mutations in the third exon of  $\beta$ -catenin lead to decreased phosphorylation of the  $\beta$ -catenin protein. Decreased  $\beta$ -catenin phosphorylation results in decreased  $\beta$ -catenin degradation by proteolysis. This results in the cytosolic accumulation of  $\beta$ -catenin, its nuclear translocation, and in malignant transformation of the cell (6,7). Somatic mutations in APC genes in gastric tumors have been reported and are thought to occur in approximately 30% of intestinal type gastric cancers (8). People with a germline mutation of the APC tumor suppressor gene are found to have a ten-fold increased risk of developing gastric cancer as compared with people who do not have this mutation (9).

### **Outlook for Biologically Directed Treatment**

The understanding of the biology of gastric cancer remains in its infancy. Recently, using the mouse equivalent of *Helicobacter pylori*-induced gastric cancer, bone marrow-derived stem cells were found to be the malignant cell in gastric cancer carcinogenesis (10). These findings have significant implications in understanding the development of the disease and, potentially, its treatment as well.

Clearly, the genetic determinants of the development of gastric cancer are just beginning to be better understood. With the explosion of new biologically directed therapies for the treatment of a variety of solid tumors since the 1990s, future treatment will clearly lie in a better understanding of the pathogenesis of this disease. As of this writing, a standard cytotoxic combination for the treatment of gastric cancer is still being defined. Understanding who, when, and how to administer future targeted therapies with standard cytotoxic therapies will undoubtedly have the greatest impact on future treatments.

## **Modern Cytotoxic Combination and Targeted Biologic Therapies**

### **Recent Advances in Cytotoxic Therapies**

Conventional chemotherapy for metastatic gastric cancer remains palliative, with few patients ever demonstrating long-term survival. Historically, most tumors develop rapid drug resistance and evidence of disease progression

within a few months of initiation of therapy. However, palliative chemotherapy has a proven survival advantage over best supportive care for gastric cancer. Modern combination therapies in the treatment of gastric cancer include various combinations of 5-fluorouracil (5-FU) infusion, cisplatin, oxaliplatin, docetaxel, irinotecan, and epirubicin. Table 1 provides a summary of several pertinent random assignment studies involving common combination regimens currently in use. The epirubicin, cisplatin, and 5-FU regimen (ECF) was compared to mitomycin, cisplatin, and infusional 5-FU (MCF) for the first-line treatment of metastatic or unresectable esophago-gastric cancer (11). This study randomly assigned 574 eligible patients with upper gastrointestinal malignancies and found that response to therapy was equivalent (42.4% for ECF vs. 44.1% for MCF), as was survival (median survival was 9.4 months for ECF vs. 8.7 months for MCF). Although ECF appeared to have greater toxicity, global quality-of-life scores were maintained in the ECF arm, whereas they fell in the MCF arm, suggesting that ECF was perhaps a subjectively more tolerable regimen (11).

Taxanes and taxane-containing combinations have considerable activity in the treatment of gastric cancer. Docetaxel was examined in combination with cisplatin and fluorouracil (DCF) and compared with the standard chemotherapy regimen of cisplatin and fluorouracil (CF) in a large random assignment phase III study (see Table 1) (12). The results reported at the American Society of Clinical Oncology 2005 meeting demonstrated a significant improvement in time-to-progression (TTP) (primary end point) with the docetaxel-containing combination (5.6 months vs. 3.7 months;  $P = .0004$ ) as well as an improvement in median and overall survival (median survival of 9.2 months vs. 8.6 months;  $P = .02$ ) with DCF when compared with CF alone. Notably, both DCF and CF were associated with significant toxicity. However, because the toxicity was generally equivalent in both arms, with the exception of increased myelosuppression with DCF, docetaxel has received U.S. Food and Drug Administration and European Union approval in combination with cisplatin and 5-FU for the first line treatment of gastric and gastroesophageal (GE) adenocarcinoma. As of this writing, the question remains whether the toxicity attributable to the addition of docetaxel to CF will outweigh the modest observed improvement in survival.

Finally, irinotecan was examined in a multicenter random assignment phase III study of irinotecan and 24-hour 5-FU (IF) infusion given weekly versus standard CF 5-day infusion (13). This was a 337-patient study that demonstrated no improvement in survival with IF compared with CF (hazard ratio [HR] 1.08; 95% confidence interval, 0.86–1.35); however, the IF arm did appear to have a reduction in grade 3–4 toxicity. This suggests that IF may be an adequate substitute for cisplatin-based therapy and may be particularly useful when there are contraindications to cisplatin use.

**Table 1.** Recent Pertinent Phase III Studies Using Modern Combination Regimens in the Treatment of Advanced Upper Gastrointestinal Malignancies

Reference	Disease	Rx	N	Response Rate (95% CI)	1-Year Survival (95% CI)	Median Survival (mo)	P Value
ECF-based phase III study							
Ross et al. (11)	Gastric + Esophageal	ECF MCF	289 285	42.4% (37%–48%) 44.1% (38%–50%)	40.2% (34%–46%) 37.7% (27%–38%)	9.4 8.7	n.s.
DCF versus CF phase III study							
Moiseyenko et al. (12)	Gastric + GE	DCF CF	221 224	36.7% (30.3%–43.4%) 25.4% (19.9%–31.7%)	40.2% 31.6%	9.2 (8.38–10.58) 8.6 (7.16–9.46)	.02
IF versus CF phase III study							
Dank et al. (13)	Gastric + GE	IF CF	170 165	31.8% 25.8%		9.0 (8.3–10.2) 8.7 (7.8–9.8)	.53

DCF, docetaxel, cisplatin, and 5-fluorouracil; CF, cisplatin and 5-fluorouracil; CI, confidence interval; ECF, epirubicin, cisplatin, and 5-fluorouracil; GE, gastroesophageal; IF, irinotecan and 5-fluorouracil; MCF, mitomycin, cisplatin, and infusional 5-fluorouracil; N, number of patients; n.s., not significant; Rx, treatment.

Oxaliplatin and capecitabine have just recently been shown to be adequate replacements for cisplatin and low-dose infusional 5-FU. The REAL-2 study involved 964 patients randomized to one of four treatment arms (ECF, epirubicin-cisplatin-capecitabine [ECX], epirubicin-oxaliplatin-5-FU infusion [EOF], and epirubicin-oxaliplatin-capecitabine [EOX]) (14). This study was a noninferiority study for survival, in which oxaliplatin-containing regimens (EOX and EOF) were compared with cisplatin-containing regimens (ECF and ECX), and the 5-FU containing regimens (ECF and EOF) were compared to the capecitabine-containing regimens (ECX and EOX). The respective substitutions were considered noninferior if the 1-year survival rate was within 23% of the control group. The study met both aims of noninferiority, with an HR for the 5-FU comparison of 0.86 (0.8–0.99) and 0.92 (0.8–1.1) for the platinum comparison (14). Thus, although this study demonstrated the activity of oxaliplatin and capecitabine and their relative equivalence to cisplatin and low-dose infusional 5-FU, respectively, it failed to show improved survival; median survival for all four arms in this nearly 1,000-patient random assignment clinical trial remained approximately 10 months.

S1 is a fluoropyrimidine derivative more commonly used in Japan, with response rates to single first-line therapy of approximately 44% (15,16). However, in a study by the European Organization for the Research and Treatment of Cancer, gastrointestinal toxicity was substantial, requiring a dose reduction, and the response rate appeared lower at 26% (17). Ajani and colleagues (18) recently reported their experience combining S1 with cisplatin in a phase I study in advanced gastric cancer. One of the main conclusions of this study was that the maximal tolerated dose of S1 with cisplatin in patients with gastric cancer from Western countries (specifically the United States) was 50 mg/m<sup>2</sup> per day in divided doses, whereas in patients from Japan, it was 80 mg/m<sup>2</sup> per day. A random assignment phase III study comparing cisplatin plus S1 versus CF infusion is under way.

## Biologically Targeted Therapies

A new targeted drug to be investigated in upper gastrointestinal malignancies is bevacizumab, a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF). When combined with irinotecan-based chemotherapy for colorectal cancer, this bevacizumab plus chemotherapy combination demonstrated significant antitumor activity over chemotherapy alone (19). Significantly, all measures of efficacy, including response rate, response duration, progression-free survival, and median survival, were improved with the addition of bevacizumab. With regard to

gastric carcinoma, VEGF expression or serum concentration has been positively correlated with vascular involvement and lymph node, liver, and peritoneal metastases (20,21). Bevacizumab has been evaluated in combination with irinotecan and cisplatin in gastric and GE cancers in a multicenter phase II study (22). Forty-seven patients with previously untreated metastatic gastric/GE adenocarcinoma were treated with bevacizumab, 15 mg/kg on day 1, and irinotecan, 65 mg/m<sup>2</sup>, and cisplatin, 30 mg/m<sup>2</sup>, on days 1 and 8 every 21 days. The primary end point was to demonstrate a 50% improvement in TTP over historical controls, which were estimated to be approximately 5 months with irinotecan and cisplatin alone, with the aim to improve TTP to approximately 7.5 months. With a median follow-up of 12.2 months, median TTP was improved to 8.3 months, and median survival improved to 12.3 months. Although there was no apparent increase in chemotherapy-related toxicity, including nausea, vomiting, diarrhea, and myelosuppression, there was a significant portion of patients with significant hypertension, two patients with a gastric perforation, and one near perforation (6%). This study demonstrates that the addition of bevacizumab to chemotherapy in the treatment of gastric and GE adenocarcinoma is associated with improved efficacy. What remains uncertain is whether the improved efficacy will be justified if the rate of perforation (4%–6%) demonstrated in this clinical trial is in fact a reality. Certainly, additional evaluation of antiangiogenic agents is warranted (22).

The epidermal growth factor (EGF) pathway has also been implicated in the pathogenesis of upper gastrointestinal malignancies (23–26). The EGF receptor inhibitor (Erb-B1), gefitinib (ZD1839), was examined as salvage therapy in 75 patients with gastric and GE tumors (27). Minimal antitumor activity was observed, with one patient achieving a partial response and 12 with disease stabilization. Notably, in 32 patients who underwent serial biopsies, the phosphorylation status of the EGF receptor was significantly reduced with gefitinib, but the inhibition of proliferation (in an *ex vivo* assay) was more dependent on levels of phosphorylated Akt (28), suggesting that resistance to EGF receptor inhibitors may be mediated downstream through the PI3-Akt pathway.

Evaluation of inhibitors of the EGF receptor pathway, both as single agents and in combination with cytotoxic agents, continues in upper gastrointestinal malignancies. Cetuximab and matuzumab are antibodies directed at the EGF receptor that are both under development in gastric cancer. The Cancer and Leukemia Group B is pursuing a random assignment phase II study comparing a combination of 5-FU, leucovorin (folinic acid), and oxaliplatin with irinotecan/cisplatin and ECF, all with cetuximab in a pick-the-winner phase II design. Matuzumab is another monoclonal antibody to the EGF receptor that has been evaluated in a phase I

clinical trial (29). This study defined the recommended phase II dose of this drug and also demonstrated inhibition of downstream targets of the EGF receptor, suggesting biologic efficacy. Matuzumab will also be examined in advanced studies in upper gastrointestinal malignancies.

Cytotoxic chemotherapy remains the mainstay for the palliative treatment of unresectable or metastatic disease. With increasing treatment options for patients, it is disappointing that median survival has not improved concurrently with the identification of more active therapeutics. Biologically targeted drugs appear promising in the treatment of this disease, particularly when given in combination with cytotoxic therapy. When to choose which agent and how to sequence these active therapies will be the next series of questions addressed by the academic medical community.

## Individualized Therapy

### **<sup>18</sup>F-Fluorodeoxyglucose-Positron Emission Tomography and Early Response Assessment**

With the recent increase in therapeutic options available to patients with gastric adenocarcinoma, efforts to better identify which patient will respond to which treatment will improve outcomes and reduce treatment-related toxicity. Functional imaging using <sup>18</sup>F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging is emerging as a technology that may allow the identification of treatment failure early in the treatment plan (30). This would then allow for early switching to alternative, potentially more active therapy. The early identification of treatment response has already been demonstrated in multiple tumor types, including non-Hodgkin's lymphoma (31,32), breast cancer (33), and tumors of the distal esophagus and GE junction (34).

In cancers of the esophagus and GE junction, Weber and colleagues (34) reported their experience in 40 patients who received preoperative chemotherapy with 5-FU given as a weekly 24-hour infusion and cisplatin administered every other week. They correlated the fall in FDG standard uptake value (SUV) at day 14 to histologic response to chemotherapy and found that patients with a response to preoperative chemotherapy experienced a drop in SUV of  $54\% \pm 17\%$  compared with baseline, and nonresponding patients had a drop in SUV of  $15\% \pm 21\%$  when comparing FDG-PET scans performed at baseline and at 2 weeks ( $P < .01$ ). According to this report, the optimal differentiation between responders and nonresponders can be achieved with an FDG SUV drop cut-off value of 35% (standard deviation of 20%). Applying

this cut-off value as a criterion for metabolic response, investigators were able to predict clinical response with a sensitivity of 93% (14 of 15 patients) and specificity of 95% (21 of 22 patients).

More recently, this group demonstrated similar results in a subsequent study for advanced proximal gastric and GE cancer (35). In this study, the positive and negative predictive values for FDG-PET for histologic response were 77% (10 of 13 patients) and 90% (18 of 20 patients), respectively. The 2-year survival rates for metabolically responding and nonresponding patients were 89% and 26%, respectively ( $P = .005$ ).

Building on this work of FDG-PET response predicting efficacy and survival, Ilson and colleagues (36) reported the use of FDG-PET scans to identify treatment failure to induction chemotherapy before the delivery of chemoradiation in the treatment of locally advanced esophageal cancer. They demonstrated that a PET response, defined as a drop in SUV of 22% or more from baseline, significantly correlated with TTP; PET responders had a median TTP of 18.5 months, whereas PET nonresponders had a median TTP of 5.5 months ( $P = .03$ ). Furthermore, and perhaps most important, four patients with PET progression were switched to alternative chemotherapy during radiation and achieved evidence of salvage, with one pathologic complete response, one radiographic complete response, and one partial response. These data support the potential utility of an early FDG-PET scan to identify response to therapy and, more important, allow nonresponding patients to switch therapy in the hopes of early salvage. Based on these and similar data in other malignancies, the Centers for Medicare and Medicaid Services has approved the routine use of FDG-PET scans for a variety of reasons included monitoring of the response to therapy (30).

### **Pharmacogenomics: Reducing Toxicity and Improving Efficacy**

Another emerging technology to reduce toxicity and improve efficacy is the selection of treatment based on the genetic profile of the individual patient, known as *pharmacogenomics*. One example of the utility of pharmacogenomics in oncology is the evaluation of polymorphisms in the UGT1A1 gene as a predictor for irinotecan-induced myelosuppression (37,38). A dinucleotide repeat polymorphism in the promoter of the UGT1A1 gene is closely related to Gilbert's syndrome (39). The wild-type number of TA repeats in the promoter region is six, whereas the presence of seven TA repeats results in the variant allele UGT1A1\*28. This allele is associated with reduced gene expression and reduced glucuronidation in human liver microsomes. The 7/7 UGT1A1\*28 genotype is associated

with reduced glucuronidation rates and with increased myelosuppression (38,40,41) and increased diarrhea (41).

Alternatively, in addition to predicting toxicity, pharmacogenomics can also be used to identify responsiveness to therapy. This has been examined in gastric cancer and sensitivity to cisplatin and 5-FU based therapy (42). In this study, chemotherapy responsiveness and survival were discriminated by examining polymorphisms in the thymidylate synthase untranslated region (5'-UTR) and glutathione-S-transferase gene family enzymes. Patients with one or both of these high-risk genotype polymorphisms had a significantly worse prognosis than patients with neither (42).

## Conclusion

Although median survival has made only marginal progress since the 1980s, there have been numerous areas of progress in the treatment of advanced gastric cancer. With the better understanding of the biology of disease and the biology of chemotherapy toxicity and sensitivity, the ability to better select a treatment plan for individual patients will improve substantially. With this better selection process, and individualization of therapy, the full complement of available drugs will afford patients a treatment care plan with a high rate of success and minimal toxicity. Coupled with this is the emerging increased utilization of targeted biologic therapies whose scope will only increase as the understanding of the pathophysiology and carcinogenesis of this disease improves. With these advances, it seems clear that the future of the treatment of advanced gastric cancer is bright.

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