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Stomach

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Neoplasms of the stomach encompass both benign and malignant tumors, with more than 95% of the latter consisting of adenocarcinomas. Until approximately 1980, gastric cancer was the most common solid organ tumor in the world, and today it is eclipsed only by lung cancer in incidence and mortality.[1]

This chapter addresses the classification, epidemiology, staging, and evidence-based treatment of gastric adenocarcinoma. Less-common gastric neoplasms, such as gastrointestinal stromal sarcomas (GIST), carcinoid tumors, and gastric lymphomas, are comprehensively reviewed in other chapters. Despite the necessary emphasis on new findings and improved treatments, background items of historical significance are also mentioned, lest we underappreciate previous work and the difficulty of progress.

Gastric Adenocarcinoma

Classification

Borrmann first characterized gastric carcinoma on the basis of gross characteristics in 1926, based on a review of 5,000 European cases.[2] He described four macroscopic tumor growth patterns: (1) type I, nodular polypoid tumor without ulceration and usually with a broad base; (2) type II, a fungating, exophytic, circumscribed tumor with defined sharp margins, devoid of ulceration except at its dome; (3) type III, an ulcerating tumor with a penetrating, infiltrating ulcer base; (4) type IV, a diffuse thickening of the gastric wall without a discretely marginated mass or ulceration, corresponding to the "leather bottle," nondistensible stomach termed linitis plastica. Still used today, the Borrmann classification has proved useful in guiding surgical treatment, especially the extent of gross tumor clearance necessary for reliable negative margin resection.

The histology of gastric adenocarcinoma falls into two distinct subtypes, first identified by the Finnish authors Jarvi and Lauren in 1951 and refined in 1965[3,4]: (1) intestinal type and (2) diffuse type. Intestinal-type cancers (Figure 41.1), often found in association with chronic atrophic gastritis and intestinal metaplasia, demonstrate gland formation and locally/progressively invade the gastric wall. Diffuse-type cancers (Figure 41.2) present as a sheet of discohesive individual cells that diffusely spread within the gastric wall, often spreading considerable distances from the site of origin. Diffuse tumors elicit a particularly brisk scirrhous proliferation of fibroblasts.

Histoepidemiologically, gastric adenocarcinomas generally sort into three broad patterns, based on simple combinations of Lauren type and location within the stomach.[5]

1. Intestinal-type tumors arising in the antrum or antral–corpus junction (*Helicobacter pylori* associated)
2. Diffuse-type cancers involving the corpus (*H. pylori* associated)
3. Intestinal-type cancers of the gastroesophageal junction

In regions of high gastric cancer incidence, approximately two-thirds of the incident cancers are of the intestinal-antral type associated with chronic *Helicobacter pylori* infection, multifocal atrophic gastritis, and intestinal metaplasia. This process usually begins at the lesser curve and the antral–corpus junction, and this is the most frequent site of cancer in high-incidence regions of the world. In such areas, most of the remaining cancers are also associated with *H. pylori* infection, but not intestinal metaplasia, and afflict younger age groups (usually those under 50 years). In this presentation, the cancer is of the diffuse type involving the body of the stomach and is associated with a brisk mucosal inflammatory infiltrate related to the *H. pylori* infection. *Helicobacter pylori* (see below) is therefore associated with both the antral-intestinal and the corpus-diffuse patterns.[6,7] Gastroesophageal junction (GE junction) tumors, on the other hand, tend to be associated with Barrett's metaplasia of the esophagus and are proportionately far less common in high-incidence regions but are an increasingly frequent subtype in low-incidence areas.

For the sake of completeness, a somewhat less common fourth subset of gastric cancer is also seen: intestinal-type cancers of the corpus associated with chronic autoimmune gastritis, G-cell hyperplasia, and achlorhidria. This less-common subtype is usually seen in Northern Europeans.[5]

Before the development of antral–intestinal-type adenocarcinoma, antecedent histologic changes occur that can be viewed as tissue markers along the multistep path to frank neoplasia. Multifocal atrophic gastritis, literally a thinning, chronic inflammation of the gastric mucosa, is generally thought to be the result of decades of superficial gastritis associated with *H. pylori* infection (Figure 41.3) and other factors. So-called intestinal metaplasia (Figure 41.4) is the characteristic histologic feature of atophic gastritis, and it occurs in two forms: (1) complete type intestinal metaplasia and (2) incomplete type intestinal metaplasia. Complete type intestinal metaplasia (Figure 41.4) closely duplicates the mucosa of the small intestine, with small intestine-like mucin-negative

M1

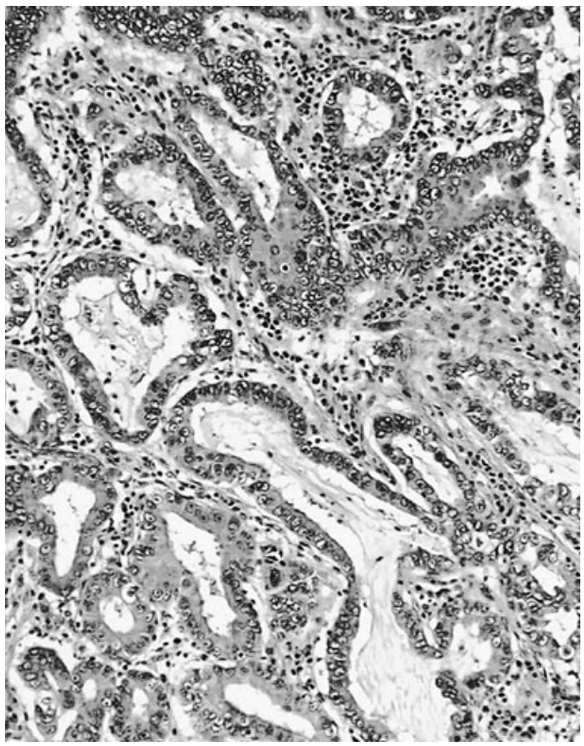

FIGURE 41.1. Intestinal-type cancer. Hematoxylin and eosin (H&E). (Courtesy of Alfredo Asuncion, M.D.)

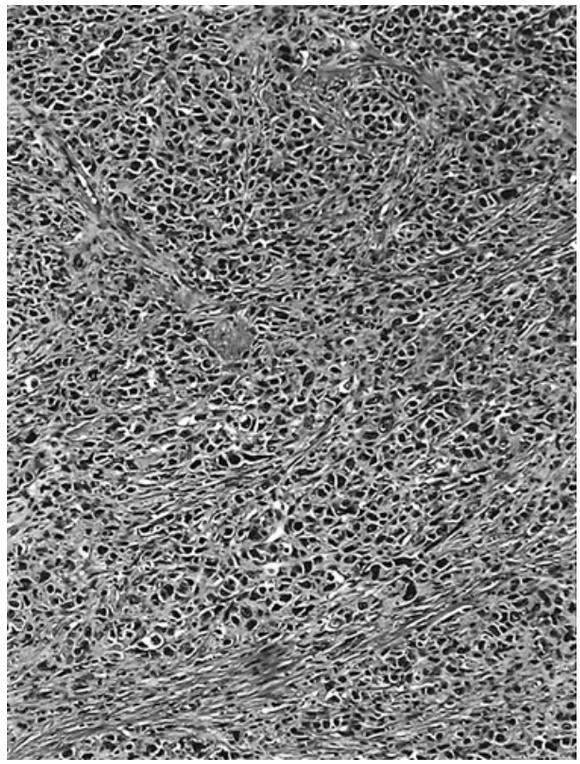

FIGURE 41.2. Diffuse-type cancer. H&E. (Courtesy of Alfredo Asuncion, M.D.)

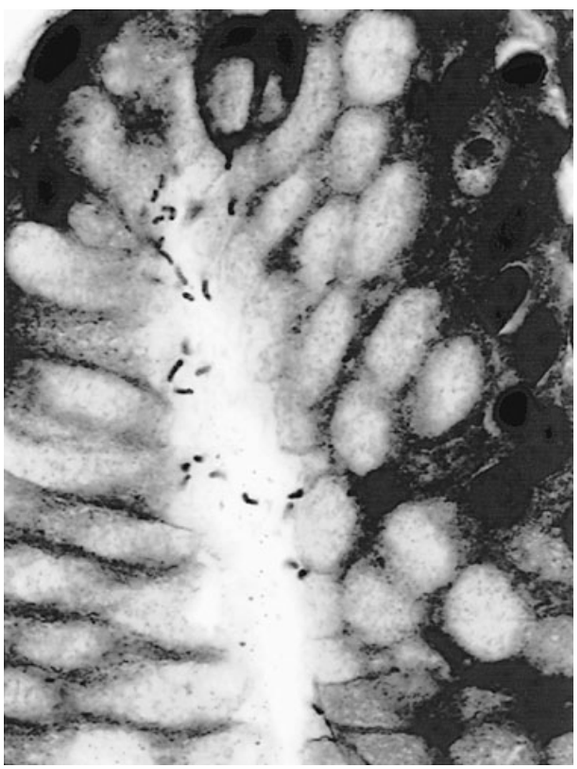

FIGURE 41.3. *Helicobacter pylori* (small rodlike organisms in crypt), Warthin–Starry stain. 100×. (Courtesy of Alfredo Asuncion, M.D.)

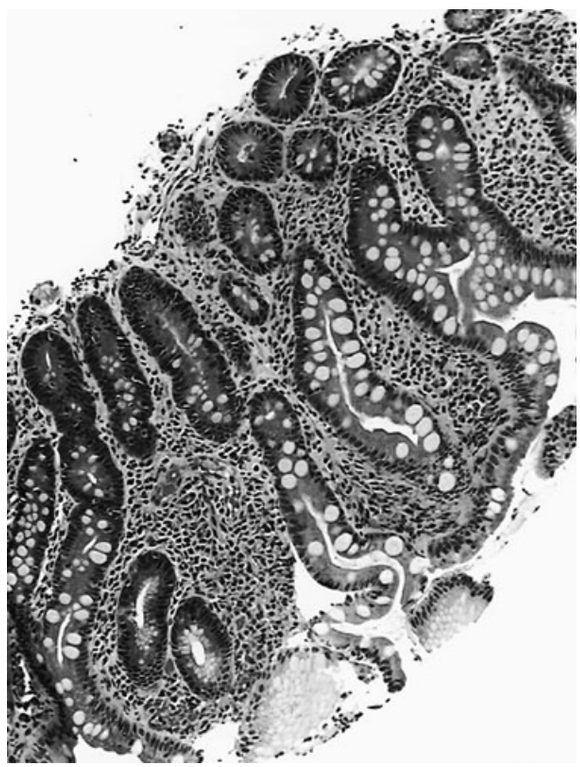

FIGURE 41.4. Intestinal metaplasia. H&E. Goblet cells, not normally seen in gastric mucosa, are numerous. (Courtesy of Alfredo Asuncion, M.D.)

absorptive cells and Alcian blue-positive, sialomucin-positive goblet cells. This process usually begins at the antral–corpus interface, especially along the lesser curve near the incisura.[8] When antral-intestinal metaplasia is still of limited area and spotty, and the remaining oxyntic gastric mucosa is still pumping out acid normally, peptic ulceration of affected areas is frequent, hence explaining the historical association between gastric ulcer and gastric cancer. Incomplete intestinal metaplasia represents a more-advanced process in which absorptive enterocytes disappear in favor of columnar, brush-border-free, colon-like cells with prominent mucous droplets and sulfomucins. Additionally, in incomplete intestinal metaplasia, Paneth cells are absent.[8] In both types of intestinal metaplasia, cells produce enzymes not normally present in the stomach, including sucrase, aminopeptidase, disaccharidases, and, most-importantly, alkaline phosphatase.[9] The latter enzyme may be used to grossly stain and map the distribution of intestinal metaplasia within the stomach ex vivo.[8]

Of the many alternative histologic gastric cancer classification schemes based on morphology, such as the World Health Organization Classification,[10] or histogenesis-based classifications such as that of Mulligan and Rember,[11] degree of differentiation such as Broder's classification[12] and the Nagayo–Komagome classification,[13] or classifications that include growth pattern such as the Ming classification,[14] none has proven of more "beyond-TNM" prognostic value than the Goseki classification.[15,16] In the Goseki scheme, degree of tubular differentiation (well versus poor) is combined with mucin staining pattern (mucin rich versus mucin poor) to divide gastric adenocarcinomas into four groups. Although of apparent prognostic value, it has yet to find widespread use.

Epidemiology

In incidence and mortality, gastric cancer ranks as the second in the world.[1] In raw numbers, it ranks third.[1,17] Of the estimated global cancer burden of 10 million cases in the year 2000, 876,000 are stomach cancers.[1,17] An estimated 38% of incident cases in the world occurs in China, where it is the most common cancer in both males and females.[18] In almost all registries, gastric cancer incidence for males is approximately twice that of females.[19]

Figure 41.5 depicts widespread variation in gastric cancer incidence in various population-based registries around the world. The registries selected for this figure reflect those with both high numbers of incident cases and relatively low death-certificate-only cases, which suggests good case-finding. The highest world standard incidence rate (91.3 cases per age-standardized 100,000) is reported from Yamagata, Japan. The lowest rates are reported from Bangkok, Thailand, as well as from England, Australia, and the United States.

Age-adjusted gastric cancer incidence rates are declining in most countries throughout the world.[18] The age adjustment of such rates tends to obscure the fact that, as a result of population growth and aging, the numerical burden of gastric cancer cases is actually expected to increase by 30% in 2010, to approximately 1 million cases.[18]

Unifying a vast body of epidemiologic, pathologic, and biologic research, Correa in 1975 proposed a multistep, multicausal model of gastric carcinogenesis, which he refined in 1988 and again in 1992.[20–22] Chronic gastric mucosal irritation, particularly that associated with the gastric mucosal bacterium *Helicobacter pylori*,[23–25] initiates a superficial gastritis, which, especially in a setting of a diet rich in salt-preserved foods and high NaCl intake,[26] progresses to atrophic gastritis and intestinal metaplasia (first the complete type and subsequently the higher-risk incomplete type). This transformation, and the subsequent march to dysplasia and cancer, is facilitated by diminished oxyntic acid output, increasing gastric pH, bacterial growth, and high-nitrate-containing diet. In such an intragastric environment, dietary nitrates are converted to carcinogenic *N*-nitroso compounds.[27–33] Many other carcinogenic compounds, such as polycyclic aromatic hydrocarbons, are also implicated. Certain ingested compounds, such as vitamin C, can interrupt this process.[34–36] Additional risk factors for epidemic gastric cancer include smoking and a diet deficient in fresh fruits, vegetables, and antioxidants.[26,37,38] Blood group A,[39] gastric ulcer,[40] ionizing radiation,[41,42] family history,[39,43–52] and previous gastric resection[53] are also associated risk factors.

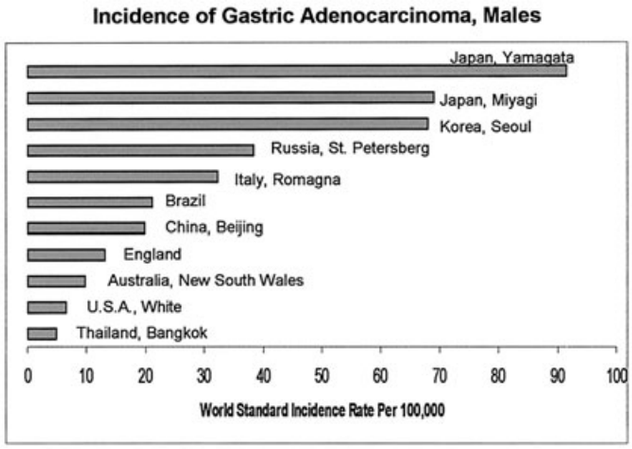

FIGURE 41.5. World Standard incidence of gastric adenocarcinoma (rate per 100,000 World Standard population, males). (Data from Cancer in Five Continents,[19] vol VIII.)

A vast body of data now supports *Helicobacter pylori* as a key factor in epidemic gastric cancer,[23–25] and the International Agency for Research on Cancer (IARC) has recognized it as a human carcinogen with both direct and indirect effects.[54] Strains containing the cagA gene appear more dangerous.[55–57] Summarizing a large body of surveillance data, Parkin and colleagues observe that more than 80% of individuals in developing countries are infected with *H. pylori*. The figure for developed countries is approximately 50%.[18,58] An odds ratio for *H. pylor*i and gastric cancer of 2.1 has been estimated.[18,58] Based on this, Parkin and colleagues estimate that 42% of the world total gastric cancer cases can be attributed to the impact of infection with this bacterium.[18]

Decades-long *H. pylori* infection, usually starting in childhood, begets superficial gastritis and chronic atrophic gastritis and intestinal metaplasia, which, once established, usually persists even after the *H. pylori* infection has disappeared because of the resulting achlohydric gastric luminal environment (the bacterium requires an acid environment to live). Atrophic gastritis and intestinal metaplasia were once believed to be irreversible. This does not appear to be entirely true, however. The pharmacologic elimination of *H. pylori*

TABLE 41.1. Hereditary Syndromes in Gastric Cancer.

Well-recognized association:
Hereditary diffuse gastric cancer syndrome
E-cadherin germ-line mutation syndrome
Hereditary non-polyposis colon cancer (HNPCC)
Li–Fraumeni syndrome (p53 mutations)
Possible, weak association:
Familial adenomatous polyposis (FAP) syndrome

along with favorable dietary intervention has led to documented regression of atrophic gastritis and intestinal metaplasia.[34,59–65] Unfortunately for the purpose of cancer prevention, however, a (somewhat underpowered) Chinese *H. pylori* elimination trial in Fujian Province has recently documented a significant decrease in gastric cancer incidence only in participants without preexisting intestinal metaplasia and no significant decrease when such metaplasia was already established.[66] Ongoing *Helicobacter* eradication trials include one in Venezuela,[64] and one in Japan, the Japanese Intervention Trial on *H. pylori*.[67]

Molecular Biology

The genetics and molecular biology of gastric cancer continue to be elucidated. With each clue to understanding the biology of gastric neoplasia, both targeted prevention and targeted therapy seem more and more feasible.

Between 8% and 10% of gastric cancer cases appear to be associated with a hereditary component, and these cases provide significant clues.[68] Dominant inheritance patterns and familial clusters have certainly been documented.[69–71] Notably, Napoleon Bonaparte's family was afflicted by hereditary gastric cancer, and this (rather than arsenic poisoning) appears to have caused his death.[72]

Table 41.1 summarizes recognized hereditary conditions associated with gastric cancer.[73] Perry Guilford and colleagues were among the first to describe germline E-cadherin mutations in a Maori kindred afflicted with diffuse-type gastric cancer,[52,74] and such mutations have also been described in African-American and European kindreds.[52,75] Gastric cancer is one of the neoplasms associated with the hereditary nonpolyposis colon cancer (HNPCC) syndrome, and such HNPCC-associated cancers are almost exclusively of the intestinal type.[43,76] It is also overrepresented in those afflicted with germline p53 mutations, Li–Fraumeni syndrome.[50,77] Asian reports of association of gastric cancer with familial polyposis coli (FAP) syndrome[78] have not been reported for other populations,[79] and the relationship remains controversial.

Table 41.2 summarizes genetic and molecular abnormalities frequently described in sporadic cases of gastric carcinoma. Immortalizing telomerase activity is commonly noted in advanced gastric cancers, but not in surrounding normal gastric mucosa,[80] and is associated with a poor prognosis.[81] Inactivation of the p53 gene and abnormal expression has been detected in more than 60% of gastric cancers.[82] In diffuse-type tumors, E-cadherin expression is reduced in as many as 92% of tumors, compared to adjacent normal tissue.[83] Reduced expression of alpha-catenin, which forms intracytoplasmic complexes with the cadherins, is noted in 56% of tumors.[84] Overexpression of the MET gene that encodes a tyrosine kinase receptor for hepatocyte growth factor (HGF) is seen in approximately half of gastric cancers and tends to be associated with poor prognosis.[85–87] Loss of trefoil peptide, the isomerization of which relates to repair of gut mucosa,[88] occurs in approximately half of gastric carcinomas, especially the intestinal type.[89–92] Proliferation of gastric cancer cell lines is decreased by this peptide.[93] Expression tends to be decreased in intestinal metaplasia.[94] This family of peptides appears to play a key role in the multistep progression to gastric cancer.[95] Epidermal growth factor (EGF) is detected in more than 50% of gastric cancers and epidermal growth factor receptor in approximately a third, and these have been associated with invasiveness and poor prognosis.[96–99] Subtypes c-erb-B1 and -B2 (HER-2/neu) have also been detected[100] in up to a third of cases, and the latter has similarly been associated with poor prognosis.[100–102] Similarly, fibroblast growth factor is expressed in 54% to 70% of gastric cancers.[103,104] Cyclin D is another protein variably overexpressed in gastric cancer, with incidence of overexpression approximately 20% to 30% in sporadic cases,[105–108] and possibly more in familial tumors.[109] COX-2 is not normally expressed in gastric mucosa but is in tumors,[110,111] precancerous lesions,[112] and inflammatory states (especially those induced by *H. pylori*).[113,114] In tumors, its presence seems to correlate with angiogenesis and invasiveness, and it tends to inhibit apoptosis.[115–117] For these reasons, and observational evidence of possible chemoprevention by aspirin,[118–121] COX-2 inhibitors have been proposed as chemopreventive agents in gastric cancer.[122]

Differences among molecular and genetic patterns for gastrointestinal cancers can also provide clues to etiology and therapy. Ras proto-oncogene mutations, which are frequent in colon cancer, are infrequent in gastric cancer.[123]

Paracrine-like interactions between gastric cancer and fibroblasts have also been reported, particularly those involv-

TABLE 41.2. Frequent genetic and molecular abnormalities in sporadic gastric cancer.

Telomerase expression	85% of advanced tumors, poor prognosis
E-cadherin	In 92%, downregulation or mutation
p53 mutations	More than 60% of tumors
Trefoil peptide, TFF-1 (sP2)	Loss in 50% of gastric tumors, and decrease in intestinal metaplasia
MET, c-*met*	Overexpression in approximately 50%, a marker for poor prognosis
Epidermal growth factor (EGF)	Expression in more than 50% of advanced cancers
Fibroblast growth factor	70% expression, especially undifferentiated tumors
Cyclooxygenase 2 (COX-2)	Expressed frequently in tumors and precancerous lesions, but not in normal mucosa

ing transforming growth factor-beta (TGF-β) and hepatocyte growth factor (HGF),[80,124] as well as other factors.[125] Such tissue interactions appear to impact on the proliferation of neoplastic and preneoplastic cells.

Diagnosis

Data from a registry-based American College of Surgeons Patient Care Evaluation Study nicely documents the presenting symptoms of patients with gastric cancer: weight loss in 62%, abdominal or epigastric pain in 52%, nausea in 34%, anorexia or early satiety in 32%, frank dysphagia in 26%, and melena in 18%.[126] Specific signs of gastric cancer are generally associated with more-advanced disease; these include palpable epigastric mass, ascites, left supraclavicular adenopathy, and Blummer's shelf palpable on rectal examination.

In low-incidence countries, fecal occult blood testing, when positive, triggers endoscopic investigation of both upper and lower gastrointestinal (GI) tract; this can lead to a diagnosis of early disease. Patients in defined higher-risk groups (e.g., positive family history or previously documented intestinal metaplasia) are increasingly being screened by surveillance endoscopy, and this, too, leads to diagnosis of more-localized disease. Overall in the United States and most low-incidence regions, stage IB or less (see following for staging) disease is detected in fewer than 23% of cases.[127]

In high-incidence countries, such as Japan, mass screening with upper GI contrast studies and endoscopy have proven successful in shifting stage distribution to lower stages, with measurable improvement in overall survival rates (level of evidence, II-1).[128–133] Pepsinogen I/II ratio of less than 2.0 (a marker of loss of oxyntic mucosa and the extent of intestinal metaplasia) has also been used as a mass screening tool.[134] In Japan, where mass screening has been established as national policy, the percentage of early gastric cancer cases among screening program participants is a staggering 74%.[135] Unfortunately, such mass screening is far less feasible in the poorer, less-developed nations of the world where gastric cancer tends to occur more frequently.[136]

Extent-of-Disease Evaluation

Most patients undergo upper endoscopy as part of their initial evaluation. Key information gleaned from this examination includes tumor location and extent of mucosal involvement, distance from the esophagogastric junction, and Borrmann type.

Endoscopic ultrasound examination (EUS), using a 7.5- to 12-MHz transducer at the end of an endoscope, offers a reliable means of preoperatively assessing the depth of tumor penetration of the wall and a fairly reliable means of assessing for gross lymph node enlargement.[137–139] Concordance of EUS and pathologic T stage in most series is 85% or better.[137,140] Endoscopic ultrasound examination appears more accurate than even helical computed tomography.[137,141]

CT scanning of the abdomen and chest should be performed in most cases. It is very helpful in detecting distant metastatic disease, extraregional adenopathy, and signs of locally-advanced disease unlikely to be removed to negative margins with up-front surgery. Helical CT, particularly if enhanced by the triphasic water-filling scanning technique, appears to be more sensitive than conventional CT.[142]

Positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) and PET-CT fusion scanning have enhanced detection of distant metastases in a variety of cancers. Unfortunately, gastric adenocarcinoma is not as suited for PET scanning as other tumors.[143] Primary tumor uptake is seen in only approximately 75% of cases, and the technique is less sensitive than CT for detecting nodal disease.[144] Neither mucus-containing tumors nor diffuse-type scirrhous tumors image well.[145] Furthermore, different regions of the normal stomach have different uptake of FDG,[146] thus complicating image interpretation. PET does appear to be somewhat helpful in detecting certain distant organ metastases, however.[147,148]

Laparoscopy and minilaparotomy represent invasive procedures, but can accurately detect serosal spread and small peritoneal implants, as well as extraregional nodal disease and small hepatic metastases.[149–151] In a recent large series, laparoscopy outperformed EUS and CT in detecting signs of unresectability and/or extraregional metastases.[152] It consistently outperforms CT.[153] In a recent series, laparoscopy proved more accurate than peritoneal fluid cytology in detecting peritoneal implants.[154] Lack of a prospective randomized trial showing resultant outcome differences makes inclusion of laparoscopy in pretreatment staging a level II-1 recommendation, however.[155]

Staging and Prognosis

Since 1987, the American Joint Committee on Cancer (AJCC) and the Union Internationale Contra le Cancer (UICC) systems for the staging of cancer have been identical.[156] Fifth and sixth edition UICC/AJCC TNM staging for adenocarcinoma of the stomach is summarized in Table 41.3.[157] This TNM staging system differs from previous versions with respect to nodal classification. Formerly, nodal classification was based on anatomic location of lymph nodes. In the current fifth–sixth edition system, nodal staging is based on the number of pathologically involved nodes, thus (at least partially) addressing the thorny issue of stage migration related to extent of lymphadenectomy.

The staging of tumor depth, or T staging, for this site has not changed since 1988. The reader should be aware that T staging for this site differs from that of colorectal cancer. Invasion of the lamina propria or submucosa, but not the muscularis propria of the gastric wall, is deemed T1 disease. Invasion of the muscularis propria or a breach of the muscularis propria without a serosal breach is deemed T2 disease. A tumor may extend into the lesser omentum or the greater omentum adjoining the stomach and, provided the serosa (i.e., visceral peritoneum) is not breached, the tumor is deemed T2. A T3 tumor breaches the serosa, thus placing the patient at increased risk of peritoneal dissemination. Microscopic breach of the serosa can be difficult for the pathologist to detect, but prognostically, presence or absence of such penetration has great impact (e.g., one recent study from Hong Kong reports 5-year survival of 64% versus 10% based on this feature alone).[158] A T4 tumor invades adjacent structures such as spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, or retroperitoneum. Intramural extension to the duodenum or the esophagus is not considered invasion of an adjacent structure, and a tumor exhibiting such intramural extension is

TABLE 41.3. UICC/AJCC Staging for Gastric Adenocarcinoma, 6th ed.

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	Invades muscularis propria or subserosa[a]
T2a	Tumor invades mucularis propria
T2b	Tumor invades subserosa
T3	Tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures[b,c]
T4	Tumor invades adjacent structures[b,c]
Regional lymph nodes (N)	
NX	*Regional lymph nodes* cannot be assessed
N0	No regional node metastasis[d]
N1	Metastasis in 1 to 6 regional lymph nodes
N2	Metastasis in 7 to 15 regional lymph nodes
N3	Metastasis in more than 15 regional lymph nodes
Distant metastasis (M)	
Mx	*Distant metastasis* cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

[a] 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.

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

[c] Intramural extension to the duodenum or esophagus is classified by the depth of the greatest invasion in any of these sites, including the stomach.

[d] A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.

Stage Grouping	
0	TisN0M0
IA	T1N0M0
IB	T1N1M0 T2a/bN0M0
II	T1N2M0 T2a/bN1M0 T3N0M0
IIIA	T2a/bN2M0 T3N1M0 T4N0M0
IIIB	T3N2M0
IV	T4N1-3M0 T1-3N3M0 Any T/Any N/M1

Source: Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, sixth edition (2002), published by Springer-Verlag New York, www.springer-ny.com.

staged based on the depth of greatest invasion, as described above.[157]

Nodal staging in the fifth and sixth edition UICC/AJCC system is by number of involved nodes. Absence of nodal metastasis is considered N0 disease. Nodal metastasis in 1 to 6 nodes is considered N1 disease and metastasis in 7 to 15 nodes is considered N2 disease. Metastasis to more than 15 lymph nodes is considered N3 disease, and most regard this extent of nodal disease as incompatible with survival following surgery treatment alone; hence, any N3 case is classified as stage IV.

Nodal data for prognostic estimates in large databases encompass hematoxylin and eosin (H&E) staining of nodes. Methods of nodal analysis such as immunohistochemistry or polymerase chain reaction analysis enhance sensitivity to a degree far beyond H&E analysis. Prognostic implications for nodes positive only by such methods are likely different, and to a degree that remains controversial.

Distant metastasis is scored as M1 disease and all such cases are deemed stage IV. Common sites of M1 disease include the peritoneal cavity, extraregional lymph nodes (e.g., paraaortic, retropancreatic, portal, retroperitoneal, and mesenteric lymph nodes), liver, ovaries, and, less commonly, lung and bone.[157]

The TNM staging matrix for stomach cancer is summarized in Table 41.3. If one creates a 2×2 table with T stages representing rows and N stages representing columns, stage categories generally map to the diagonals (i.e., if the sum of T and N is 1, stage IA; if the sum is 2, then stage IB; if the sum is 3, then stage II; if the sum is 4, then stage IIIA). Stage IIIB is reserved for stage T3N2M0 tumors. All cases with N3 disease, and all cases with a sum of T and N greater than 5, are considered stage IV.

Five-year and 10-year relative survival rates for U.S. cases treated by gastrectomy and pathologically staged according to the fifth–sixth edition UICC/AJCC system are depicted in Table 41.4.[127] Comparison of these rates suggests that 10-year relative survival (versus 5-year relative survival) should probably be considered as the preferred outcome standard for this cancer; in modern series, survival curves tend to plateau not at 5 years, but rather between 7 and 8 years.[127]

Clinicians in Japan and elsewhere often use an alternate staging system derived from a set of "General Rules for Gastric Cancer Study," first published in 1963 and revised many times since.[159] A complete version of the 12th edition of this staging system, usually referred to as the "General Rules," has been published in English, complete with color tables and diagrams.[159,160] The T stages in this system are similar to those in the UICC/AJCC system, but it is otherwise different. Nodal staging differs considerably, with node-level definitions ranging from (regional) N1 and N2 nodal levels to (generally considered extraregional) N3 and N4 levels. The specific definitions for such levels vary according to location of tumor within the stomach (e.g., proximal third, middle third, distal third). The system includes macroscopic

TABLE 41.4. TNM staging and relative survival for U.S. cases treated by gastrectomy, 1985–1996 (n = 50, 169).

6th edition UICC/AJCC 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%

Source: Data from Hundahl et al.[127]

M1

description of the tumor (e.g., early gastric carcinoma type or, if more advanced, Borrmann type), but such description does not directly impact on final stage assignment. Peritoneal metastases are described separately (e.g., P0–P3), as are liver metastases (e.g., H0–H3). Other sites are described conventionally (i.e., M0, M1). In the overall "General Rules" staging matrix, limited peritoneal or hepatic disease is lumped in stage IVA, and other distant metastatic disease is classified as stage IVB. In this Japanese system, nodal disease that one might term extraregional in the UICC/AJCC classification (e.g., General Rules N3 disease), is incorporated into stage IIIA or IIIB if the depth of invasion is T1 or T2. Fortunately, it is fairly easy to translate from the General Rules staging to UICC/AJCC staging, provided accurate node counts are also available.[159]

The Japanese General Rules system is of interest primarily because the extent of surgical lymphadenectomy in stomach cancer has been historically defined according to this system's lymph node classification. Before the mid-1990s, the Japanese described as an "R-level" the extent of lymphadenectomy according to the highest echelon of lymph node stations completely dissected by the surgeon. To avoid confusion with the UICC R-factor, which described completeness of resection, extent of lymphadenectomy was described as a "D-factor" after the 12th edition of the General Rules.[159,160] In reviewing earlier literature in gastric cancer, one should be aware of the dual use of "R" terminology. Also, one should remember that the D-level description for level of lymphadenectomy is based on the Japanese nodal classification system (e.g., a lymphadenectomy is classified as D4 if all Japanese General Rules N1–N4 nodes are surgically removed, D3 if all N1–N3 but not all N4 nodes are cleared, etc.).[159,160]

In the current AJCC/UICC staging system, the choice of numerical thresholds for nodal categories represents a point of ongoing controversy. A number of investigators have observed progressive decrease in survival with increasing number of involved nodes,[161–168] with an apparent dropoff in survival when more than 3 nodes are involved.[162–167,169] Another dropoff when more than 6 nodes are involved has been reported.[163,165,167,168,170,171] Involvement beyond 15 or 16 nodes has been observed to be largely incompatible with long-term survival.[161,169,171] UICC/AJCC cutoffs are based on these observations, but it must be recognized that differences in the pathologic analysis of surgical specimens and differences in the extent of surgical lymphadenectomy can alter thresholds. A National Cancer Data Base (NCDB) report of 50,169 cases, all treated by gastrectomy, from 1985 through 1995, has documented that only 18% of U.S. gastric cancer cases have more than 15 nodes analyzed by the pathologist,[127] as recommended by the AJCC for accurate nodal staging.[157] The study further documented that stage migration related to nodal analysis persists in the United States despite the move to the fifth edition AJCC staging system based on based on number of nodes positive. Inadequate nodal analysis generated observed survival differences within assigned stage levels of up to 20%, and this was clearly related to the number of nodes analyzed. Nodal analysis beyond 15 nodes failed to generate any measurable enhancement in stage-stratified survival rates. Overall, 5-year relative survival was 28% and 10-year relative survival was 20%. Of the 10-year survivors in this series, 67% were node negative and 98% had 8 or fewer nodes involved.[127] Despite documented variation in nodal sampling and analysis, however, assigning nodal stage categories based on the number of involved lymph nodes does appear to generate better prognostic estimates compared to previous versions of the UICC/AJCC system[172–174] and the Japanese General Rules.[173]

Recently, Kattan and colleagues at Memorial Sloan-Kettering Cancer Center in the United States have published a prognostic normogram based on multivariate analysis of 1,039 completely resected cases that somewhat corrects for inadequate nodal analysis in gastric cancer cases. Higher relapse risk is assigned when number of nodes analyzed is suboptimal.[175] This potentially useful prognostic tool awaits validation in a separate cohort.

Residual disease after surgical treatment is not included in the UICC/AJCC TNM stage grouping matrix. It nonetheless represents a powerful, significant, independent prognostic factor.[176] The UICC and AJCC code residual disease as R0 for none, R1 for microscopic residual, and R2 for macroscopic residual tumor.[157] The completeness of resection R-factor should be specifically assigned and recorded for all patients undergoing surgical treatment.

Surgical Treatment

Historical Overview

In the United States, increasingly radical surgical approaches for gastric cancer during the 1940s and 1950s[177–180] fell into disfavor in the late 1960s and 1970s with recognition of the sometimes considerable mortality such procedures entail, at least when performed on U.S. or European patients, given the level of patient selection and the level of postoperative care possible in that era.[181]

Encouraged by generally lower surgical mortality rates and favorable 5-year survival rates, Japanese surgeons, led principally by Kajitani and colleagues, adopted a related, but distinct, approach: negative-margin gastrectomy (with initial gross margins guided by the Borrmann type of the tumor: 2 cm for exophytic nodular tumors and 5+cm for ulcerated infiltrating tumors or linitis plastica) combined with aggressive removal of regional/extraregional lymph nodes, omentum, and en bloc removal of the peritoneum lining of the floor of the omental bursa along with the pancreatic capsule and associated fatty nodal tissue (i.e., omentobursectomy). Also, depending on tumor location, resection of contiguous organs such as tail of pancreas and spleen were advocated in an effort to better clear lymph node stations along the splenic artery and the splenic hilum.[182–185] Reports from large cancer hospitals in Japan emphasized increasingly favorable stage-stratified results with such techniques, multiplied by screening-driven trends to earlier-stage diagnosis and improvement in overall survival.[186–189]

Genuinely increased overall survival as a result of early diagnosis in Japan has been generally accepted as valid.[190–193] However, claims by Japanese surgeons that more-radical surgical treatment was simultaneously generating better stage-for-stage results[189,194–198] failed to uniformly win international acceptance, given the previous observation of high perioperative mortality accompanying U.S.-style radical surgery.[181] By the late 1980s, however, remarkably low 30-day postoperative mortality rates reported from major Japanese institutions (e.g., 0.6% for expert institutions such as the National Cancer

TABLE 41.5. Prospective, randomized surgical trials.

Lymphadenectomy trials	*Inclusion criteria*	*N*	*Mortality/survival*	*Mortality/ survival*	*P value (survival)*	*General comments*
			D1	**D2**		
Cape Town[209,210]	T1–3; N0–1; M0, age <75	43	0%/78% (3-year survival)	0%/76% (3-year survival)	n.s.	Solid design. Early closure due to poor accrual & inadequate power to detect.
British MRC[216–218]	Stage I–III, age >20	400	6%/35% (5-year survival)	13%/33% (5-year survival)	n.s.	Unique definition of "D1" and "D2". Skimpy quality control.
Dutch[219–220,222]	Stage I–II, age <85	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 effect of pancreaticosplenectomy.
			D2	**D4**		
Japanese D2 vs. D4 Trial[226]	Deep T2–T4		0.8%/–	0.8%/–	ongoing	Ongoing trial. Immature with respect to survival.
			Subtotal	**Total**		
French[211]	Antral tumor, M0		3%/48% (5-year survival)	1%/48% (5-year survival)	n.s.	Pioneering trial. Straightforward design.
Italian[213,214]	>6 cm proximal margin possible all, but not mandated M0		1%/65% (5-year survival)	2%/62% (5-year survival)	n.s.	D2 recommended all, but not mandated. Straightforward design.
			Subtotal + D1	**Total + D3**		
Hong Kong[215]	Antral >6 cm margin, M0, age <75		0%/1,511 median survival	3%/922 days median survival	0.04 days 0.07	Dual *P* values reported. Transfusion issue.

Center Hospital in Tokyo)[194] stimulated renewed interest in Japanese surgical methods. The much higher proportion of low-stage (early gastric cancer) patients in Japanese series, combined with marked differences between the Japanese staging system (see earlier) and the UICC/AJCC staging system, confounded direct international comparison of survival rates. The UICC and AJCC successfully standardized staging worldwide in 1987,[199,200] thus facilitating stage-stratified comparisons between Japanese and non-Japanese gastric cancer cohorts. Such comparisons revealed substantial stage-stratified survival differences,[126,201] prompting some to question whether gastric cancer in Japan was a "different disease" from that seen in Western industrial countries.[202] Several retrospective analyses from Japan and elsewhere suggested that Japanese-style surgical treatment generated higher stage-stratified survival.[203–207] With seemingly uniform UICC/AJCC staging, large apparent differences in stage-stratified survival rates were noted, with 5-year survival rates for each stage routinely much higher in the more radically treated Japanese cohorts.[126,208] Such observations set the stage for prospective, randomized clinical trials addressing the following two surgical questions: (1) What is the optimal extent of lymphadenectomy (i.e., Japanese D1 versus Japanese D2) in the treatment of gastric cancer? and (2) Is routine total gastrectomy with or without extended node dissection more effective than simple subtotal gastrectomy? Results of these trials are summarized next and in Table 41.5.

Prospective, Randomized Trials of Surgical Treatment

The Cape Town South Africa Trial (1982–1986)[209,210] of D1 Versus D2 Lymphadenectomy (termed Japanese R1 versus R2 at that time) was conducted between January 1982 and November 1986 by Dent and colleagues. Inclusion criteria included T1–T3, N0–N1 disease, no distant metastases, absence of significant comorbidity, and age less than 75 years. Patients from "remote areas" were excluded. For accurate staging, biopsies of celiac, common hepatic, hepatic nodes, and "any abnormal nodes" were taken for all patients. D2 (aka R2 dissection in the nomenclature of the time) was performed according to the Japanese methods described by Kajitani and Nakajima (i.e., removal of omentum, superior leaf of peritoneum on the transverse mesocolon, removal of the capsule of the pancreas, aka omentobursectomy, and celiac-based lymph node dissection).[182,185] For the gastric resection itself, gross proximal clearance of 5 cm was required in both arms, and reconstructive techniques were specified. Over the period of study, 608 cases were reportedly evaluated; 403 were deemed surgical candidates, but only 43 (7% overall and 11% at laparotomy) were deemed to meet all eligibility criteria. Following treatment and discharge, patients were followed by examination at 3-month intervals. No attempt was made to screen for recurrence.[209,210] No survival differences were noted. In-hospital mortality was zero for both groups. The trial did document increased operative time (*P* less than 0.005), increased blood transfusions (*P* less than 0.005), and longer hospital stay (*P* less than 0.05) for the D2 group. This single-institution trial was halted when single-institution accrual to adequate statistical power for the question was deemed unlikely.[209,210]

The French Subtotal Versus Total Gastrectomy Trial,[211] by the French Association for Surgical Research, was conducted between 1980 and 1985 to address the potential value of routine total gastrectomy versus the higher mortality and morbidity associated with this procedure, as documented by

McNeer and others.[180,212] Eligibility criteria included presence of an adenocarcinoma located in the distal half of the stomach, good organ function, and no evidence of nodal involvement higher than the gastroesophageal junction or in the splenopancreatic region. Cases of superficial carcinoma (in situ or early T1) were to be excluded, as were cases of obvious linitis plastica type extensive infiltration within the gastric wall. Extensive lymph node dissection was not mandated, but proximal ligation/resection of the left gastric artery was. A Billroth II gastrojejeunostomy reconstruction was used for all subtotal gastrectomy cases, reconstruction for all total gastrectomy cases consisted of Roux-en-Y esophagojejeunostomy, and 169 patients were randomized. Somewhat paradoxically, postoperative mortality was observed to be lower in the total gastrectomy group (1.3% versus 3.2%). Five-year survival rate for both groups was identical at 48%.[211]

The Italian Subtotal Versus Total Gastrectomy Trial[213,214] was conducted from April 1982 through December 1993. Six hundred eighteen patients with localized gastric adenocarcinoma of the antrum were randomized to subtotal gastrectomy versus total gastrectomy. A D2 lymphadenectomy and omentobursectomy was recommended for all patients but not mandated. Inclusion criteria included histologic confirmation of adenocarcinoma, age less than 75, absence of serious comorbid conditions, and no history of previous malignancy, gastric surgery, or chemotherapy. Additionally, during laparotomy, all patients were required to have a tumor-free proximal margin of 6 cm and absence of any extraregional nodes, hepatic metastases, peritoneal metastases, or unresectable infiltration of contiguous organs. Over this 1982–1993 period, 1,372 patients from 31 Italian institutions were evaluated and 648 randomized; after exclusions, 311 were left in the subtotal gastrectomy group and 296 in the total gastrectomy group.[213,214] With median 72-month follow-up, 5-year Kaplan–Meier survival was 65.3% for the subtotal gastrectomy group and 62.4% for the total gastrectomy group (P = n.s.).[213,214]

The Hong Kong Trial of D1 Subtotal Versus D3 Total Gastrectomy[215] was conducted between October 1987 and December 1991 by Robertson and colleagues at the Prince of Wales Hospital in Hong Kong. The trial was open to patients undergoing laparotomy for grossly localized antral tumors that could be cleared to a 6-cm proximal margin with subtotal gastrectomy. Additional entry criteria included negative distal margin, absence of liver metastases, absence of peritoneal metastases, age less than 75 years, and absence of serious comorbid conditions. Neither intraoperative cytologic nor histologic analyses were performed. In the D3 group, distal pancreatectomy and splenectomy and D3 lymph node dissection were routinely performed, but without omentobursectomy. The R1 subtotal group underwent simple distal gastrectomy with a 6-cm proximal margin, high ligation of the right and left gastric arteries, and simple omentectomy, but no other node dissection. Over the study period, 55 cases were randomized, 25 in the D1 subtotal group and 30 in the D3 total group.[215] In this trial, survival was actually better for the more simply treated D1 subtotal group (median survival, 1511 versus 922 days; P less than 0.05). The D3 total group had longer operative time (260 versus 140 minutes; P less than 0.05), more transfusions (P less than 0.05), and much longer hospital stay (16 versus 8 days; P less than 0.05). No patient in the D1 subtotal group died postoperatively in hospital, in contrast to 1 patient in the D3 total group (P = n.s.).[215]

The Medical Research Council (MRC) Trial of Modified "D1" Versus Modified "D2" Lymphadenectomy[216–218] was conducted in 1986 through 1995, by Cushieri, Fielding, Craven, Joypaul, and colleagues of the Surgical Co-operative Group. In this trial, a D1 procedure was defined in a manner at variance with the definition used by the JRSGC. For this trial, a D1 lymph node dissection was one in which only those lymph nodes within 3 cm of the tumor were removed (consistent with pre-1997 TNM definitions of N1 nodes). The D2 procedure was defined as one in which TNM N2 nodes (i.e., "celiac, hepatoduodenal, retroduodenal, splenic, and retropancreatic nodes, depending on location of the tumor," as well as perigastric nodes more than 3 cm from the tumor) were removed and the omental bursa resected (omentobursectomy). Distal pancreaticosplenectomy was performed almost exclusively in the D2 group, and splenectomy in both groups, but more frequently in the D2 group. Eligibility was assessed at staging laparotomy. Prelaparotomy exclusions included age less than 20 and those with serious comorbid disease. All patients were assessed, at laparotomy, for the presence of peritoneal implants, liver metastases, and extraregional/periaortic adenopathy, particularly in the area of the left renal vein. Those with disease in these sites were excluded. Intraoperative peritoneal cytology was not used. Eligible cases were deemed to have TNM stage I–III disease with negative margins of resection and a proximal margin of at least 2.5 cm free of gross disease. Of 737 cases registered, 337 were deemed ineligible at staging laparotomy because of advanced disease, leaving 400 cases for intraoperative randomization.[216–218] With median follow-up of 6.5 years, 5-year overall survival for the D1 group was 35% versus 33% for the D2 group (P = n.s.). Recurrence-free survival and disease-specific survival did not differ significantly. Unfortunately, splenic resection, performed more frequently in the D2 group, and pancreatic resection, performed almost exclusively in the D2 group, seriously impacted survival and proved to be independent predictors of poor survival. Complications and mortality were higher in the D2 group, and pancreaticosplenectomy appeared to be a powerful influence. The adverse impact of pancreaticosplenectomy, particularly pancreatectomy, somewhat confounded this trial with respect to the lymphadenectomy question.[216—218]

The Dutch Trial of D1 Versus D2 Lymphadenectomy[219,220] was conducted between August 1989 and July 1993 by surgeons participating in the Dutch Gastric Cancer Group. Eligibility criteria included age less than 85 years, adequate physical condition with no serious comorbid diseases, no previous cancer, no previous gastric surgery, and histologically confirmed gastric adenocarcinoma without evidence of distant metastases. Patients in both groups underwent distal or total gastrectomy according to the location of the tumor, with subtotal gastrectomy allowed if a proximal tumor-free margin of 5 cm could be achieved. At the onset of the trial, surgeons from 80 centers and 8 expert consulting surgeons were extensively instructed concerning Japanese-type surgical treatment according to Japan Research Society for Gastric Cancer (JRSGC) definitions and guidelines.[160,182,221] Patients were randomized preoperatively to arrange for the intraoperative presence of an expert consultant surgeon for all D2 cases. A Japanese expert surgeon attended every case during the first 4 months of the trial. The D1 procedure involved removal of all JRSGC-defined N1 nodes, generally the

M1

perigastric nodes at stations 1–6 along the greater and lesser curvatures of the stomach, along with removal of the lesser and greater omentum. The D2 procedure involved omentobursectomy (i.e., removal of greater and lesser omentum, the superior leaf of the transverse mesocolon and the capsule of the pancreas), frequent distal pancreatectomy and splenectomy (depending on tumor location), and removal of all JRSGC-defined N2 nodes at stations 7–12 (i.e., left gastric, celiac, common hepatic, proper hepatic, and splenic arteries and splenic hilar nodes). Reconstruction following completion of the D2 node dissection was left to the local institutional surgeon, as was the postoperative care of the patient[219,220]. Of the 1,078 cases randomized preoperatively, 82 (8%) were excluded for various reasons, most commonly, unavailability of a consultant reference surgeon (35 cases), poor physical condition, or lack of histologic confirmation of the diagnosis. Of the remaining 996 patients randomized and entered into the study, 285 had evidence of incurable/extraregional disease and were excluded; 711 deemed potentially curable underwent the randomly assigned treatment (i.e., D1 or D2 resection) with curative intent. The 380 cases in the D1 group and the 331 cases in the D2 group were well balanced with respect to age, gender, tumor location, and tumor depth. Eighty-nine percent of the cases in each group underwent apparent, pathologically confirmed, negative-margin resection. A slightly higher proportion of cases in the D2 group underwent total gastrectomy (38% versus 30% in the D1 group).[219,220]

Among randomized cases, morbidity (25% versus 43%; P less than 0.001) and in-hospital mortality (4% versus 10%; $P = 0.004$) were higher for the D2 group. With a median follow-up of 72 months, 5-year survival was 45% for the D1 group and 47% for the D2 group (P = n.s.). Pancreatic and splenic resection, performed mostly in the D2 group (and mandated for particular tumor subsites) were associated with significantly higher morbidity and mortality in this study. Restricting the 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 versus 71% for the D2 group; $P = 0.02$).[222] Overall, however, for those who indeed had a negative-margin resection deemed potentially curative, risk of relapse at 5 years was 43% for the D1 group versus 37% for the D2 group (difference between relapse rates was not significant). An 11-year follow-on report for this trial indicates that of the 89 cases with pathologic N2 disease, there were nine 10-year survivors, and 8 of the 9 were in the D2 group ($P = 0.01$ for this post hoc analysis of the N2 subgroup).[222] Overall survival at the 11-year mark is 31% versus 35% for D1 and D2, respectively ($P = 0.53$). Post hoc subset analysis notwithstanding, overall, this trial fails to support routine D2 lymphadenectomy.[219,220]

At the time, both the MRC trial and the Dutch Trial were initiated, pancreaticosplenectomy was still deemed a standard part of a Japanese-type operation for cancers involving the cardia. By the mid-1990s, Japanese recommendations with respect to pancreaticosplenectomy had shifted[223–225]; however, both trials were already well under way. Perhaps in response to MRC and Dutch Trial findings, pancreas-preserving D2 (or D2+) operations are now favored by the Japanese and others, unless resection of these organs is required to achieve negative margins.[223–225]

A multicenter Japanese Trial of D2 Versus D4 Lymphadenectomy,[226] initiated by Sasako, Sano, and colleagues, dwells on the potential value of paraaortic lymph node dissection for deep T2 (i.e., serosal invasion suspected) and T3–T4 proximal tumors. In both Japan and Italy, microscopic disease in such nodes is not infrequent, and resection of such diseased nodes can generate approximately 15% 5-year survival.[227–231] This trial has now completed accrual of 523 eligible cases. Thirty-day operative mortality for both D2 and D4 groups in this trial is 0.8%.[226] The trial remains immature with respect to survival.[226]

Summarizing results from all these surgical trials, neither routine D2 (or greater) lymphadenectomy with pancreatic-splenic resection nor routine total gastrectomy can be routinely recommended (level of evidence, I). Overall, the somewhat arbitrary D-level system for guiding lymphadenectomy has not proven helpful in increasing survival. However, the potential value of pancreas/spleen-preserving lymphadenectomy, particularly if performed in low-mortality centers (e.g., those in Japan and certain other expert centers) remains an open question.

In-Hospital Mortality Rates Associated with Gastrectomy for Cancer

In both the MRC trial (6.5% versus 13%, $P = 0.04$)[217] and the Dutch Trial (4% versus 10%, $P = 0.004$).[219,232] in-hospital mortality was significantly associated with pancreatic-splenic resection,[217,232] which, in turn, was far more frequent in the D2 group (mandated component of D2 for most nonantral tumors). Viewed critically, in-hospital mortality was also very high for the D1 groups. In the aforementioned Japanese multicenter D2 versus D4 trial, surgical mortality was only 0.8% for both groups.[226] Certainly, comorbid cardiovascular disease probably differs among international patient populations, but other factors such as surgical experience, technique, and variation in morbidity management can also play a role.[233] In U.S. studies, surgeon volume and hospital volume persistently impact on in-hospital mortality.[234–236] The mechanisms for the volume–mortality relationship have yet to be fully elucidated. Specialists, well-equipped and well-staffed operating rooms, and specialized services, including sophisticated ICU care, tend to be more available in larger hospitals.[237,238] Additionally, when surgeons have open access to various hospitals, high-volume surgeons might preferentially prefer to practice in such environments.[237,238] For a major procedure such as gastrectomy for cancer, there is evidence of both a learning curve[239] and value to volume. Referral to specialist centers has been proposed.[240,241]

Maruyama Index of Unresected Disease and Computer-Guided Lymphadenectomy

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, matching cases with similar characteristics to a given case. With seven demographic and clinical inputs (all identifiable preoperatively or intraoperatively), the program predicts the statistical likelihood of nodal disease for each of 16 (JRSGC-defined) nodal stations around the stomach (note that current JRSGC General Rules identify 33 nodal stations, substations,

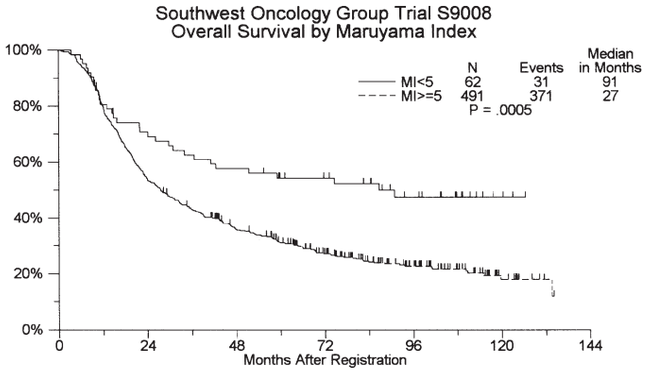

FIGURE 41.6. Impact of a surgical factor, Maruyama Index of Unresected Disease (MI), on overall survival for cases enrolled in SWOG 9008/INT 0116, a large U.S. adjuvant trial. (Updated data courtesy of Southwest Oncology Group.[246])

and optional sites). Maruyama Program predictions have been assessed in Japanese, German, and Italian populations and found to be highly accurate.[242–244] The tool is designed to be used by surgeons preoperatively or intraoperatively as a convenient means of rationally planning the optimal extent of lymphadenectomy for a given patient. Since the late 1980s, the program has been used in exactly this way by surgeons at the National Cancer Institute Hospital in Tokyo and 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 has been prepared.[245]

In a prospectively planned surgical analysis of a large multicenter U.S. trial of adjuvant postoperative chemoradiation in gastric cancer (SWOG 9008/Intergroup 0116; see following), the extent of surgical treatment was specifically assessed and prospectively coded through both detailed reporting forms and review of records (e.g., operative reports). The prospectively planned surgical analysis of survival in Intergroup 0116 made use of a novel means of quantifying the adequacy of lymphadenectomy relative to likely extent of nodal disease: the "Maruyama Index of Unresected Diease" (MI). The Maruyama Index of Unresected Diease was defined (by the author, S.H.) as the sum of Maruyama Program predictions for those Japanese-defined regional node stations (stations 1–12) left in situ by the surgeon.[246] Based on the Intergroup trial's entry criteria, and the definition of MI, every case registered to INT-0116 could have had an MI of 0; this variable was under the surgeon's control. Before any survival analysis in this trial, it was speculated that patients with MI less than 5 would have measurably superior survival. As shown in Figure 41.6, this indeed proved to be the case, with median overall survival for the MI less than 5 subgroup 91 months versus 27 months ($P = 0.005$). By multivariate analysis, adjusting for treatment, T stage, and number of nodes positive, MI proved an independent predictor of survival ($P = 0.0049$). Data for disease-free survival are similar.[246,247] The overall median Maruyama Index of Unresected Diease in this chemoradiation trial was 70 (range, 0–429), suggesting undertreatment. An effect for "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 $P = 0.002$).[246] In summary, by univariate analysis and by multivariate analysis, MI proved to be a strong and significant predictor of prognosis.[246,248]

To further assess of the utility of MI as a prognostic tool, the Dutch Trial has recently been reanalyzed. 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 and varied according to UICC stage, nodal stratum, T stage, D level, and tumor involvement of overlapping sites, in that order. In contrast to D level, MI less than 5 proved an independent predictor of both overall [$P = 0.016$, hazard ratio (HR) = 1.45, 95% confidence interval (CI) = 1.07–1.95] and relapse risk ($P = 0.010$, HR = 1.72, 95% CI = 1.14–2.60).[249] As shown in Figures 41.7 and 41.8, a dose–response effect was also evident.[249] This blinded

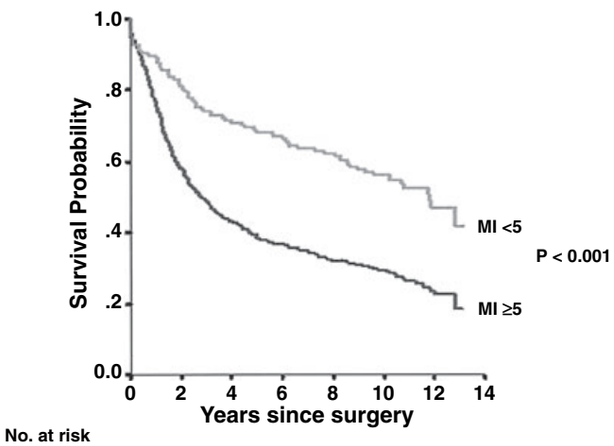

FIGURE 41.7. Reanalysis of the Dutch D1–D2 Trial. Maruyama Index of Unresected Disease (MI) is a major independent prognostic factor. Low MI is associated with superior survival. (From Peeters et al.,[249] by permission of *World Journal of Surgery*.)

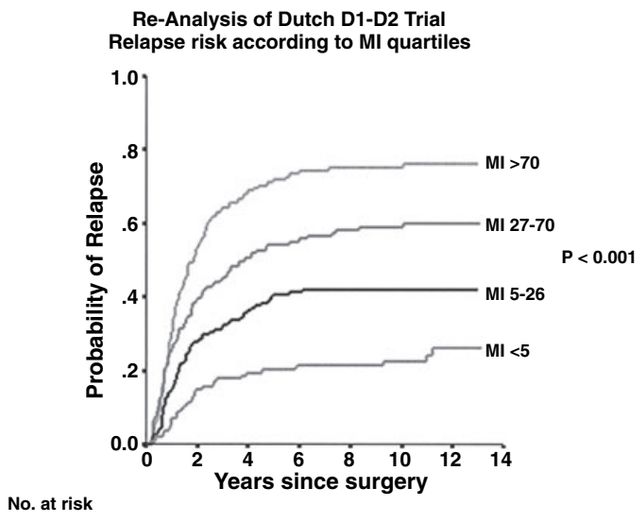

FIGURE 41.8. Dose–response effect for MI with respect to relapse in the Dutch D1–D2 Trial (data for survival similar, not shown). (From Peeters et al.,[249] by permission of *World Journal of Surgery*.)

reanalysis further supports the utility of the Maruyama computer program in customizing the extent of lymphadenectomy in individual gastric cancer cases according to the predicted extent of nodal disease. "Low Maruyama Index" surgery, which can easily be accomplished by using the Maruyama Program to prospectively plan lymphadenectomy for a given patient, appears to enhance survival (level II-1 evidence). This conclusion has yet to be validated in a prospective, randomized trial.

Endoscopic Mucosal Resection of Selected T1 Cancers

In countries such as Japan, where the incidence of early gastric cancer (i.e., T1 tumor) is high, endoscopic mucosal resection (EMR) has emerged as a reasonable option for selected cases.[250–255] In the traditional technique of endoscopic mucosal resection, submucosal injection of saline floats the small 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 use of incision endo-forceps,[256] aspiration mucosectomy,[257] use of a stabilizing distal magnetic anchor,[258] or use of the double endoscope resection technique[259] can facilitate its proper execution. Percutaneous traction assist techniques using small percutaneous ports and instrumentation can also facilitate the procedure,[260] but percutaneous violation of the gastric lumen in such cases can risk unnecessary intraabdominal or port site tumor implantation. For this reason, laparoscopic resection for superficial T1 tumors suitable for EMR has been viewed with caution.[255]

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 level II guidance.[261] For *intramucosal tumors*, none of 1,230 well-differentiated cancers of less than 30 mm diameter, regardless of ulceration findings, were associated with metastases (95% CI, 0%–0.3%). Regardless of tumor size, none of 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 and lymphatic-vascular involvement with an increased risk of nodal involvement. None of the 145 well-differentiated adenocarcinomas of less than 30 mm diameter without lymphatic or venous permeation were associated with nodal involvement, provided that the lesion had invaded less than 500 μm into the submucosa (95% CI, 0%–2.5%).[261]

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).[250] Although bleeding and perforation occurred in 5%, there were no treatment-related deaths.[250] For selected superficial T1 cancers, endoscopic mucosal resection performed by experienced personnel can generate superb results and can certainly be recommended, especially because local recurrences can be addressed with salvage gastrectomy (level II-2 evidence).

Adjuvant Treatments

Radiation and Chemoradiation

For locally advanced tumors deemed unresectable to negative margins, radiation and concomitant chemoradiation appear to make long-term disease-free survival possible for a small, but significant, subset of patients.[262] In a Mayo Clinic series published in 1969, Moertel and colleagues documented rare long-term survivals with regional chemoradiation.[263] In a follow-up prospective, randomized trial of radiation alone ($n = 23$) versus concomitant bolus 5-fluorouracil (5-FU) plus radiation ($n = 25$), mean survival was 13 months versus 6 months, favoring combined therapy (P less than 0.05) and 5-year survival was 12% versus 0%.[264] In a follow-up study, the Gastrointestinal Tumor Study Group randomized 90 eligible cases to receive either combination chemotherapy alone or concomitant chemoradiation with further, follow-on chemotherapy. Early nutritional and myelosuppressive complications rendered initial survival of the chemoradiation arm inferior, but with minimum 5-year follow-up, survival was significantly higher for the chemoradiation arm, with 16% alive disease free compared to 7% among those treated with chemotherapy alone (P less than 0.05).[265]

For cases treated surgically, historical pattern-of-failure data from clinical, operative second look, and autopsy sources document that approximately 60% of node-positive and/or transserosal cancers (T3 or more) recur in regional nodes, tumor bed, or anastomosis, with 20% of tumors recurring only locoregionally (Table 41.6).[262,266–270] Such data compellingly invited application of locoregional radiation or chemoradiation as an adjuvant to surgical treatment. Figure 41.9 depicts a early proposal by Gunderson and Sosin for a radiation treatment field encompassing frequent locoregional areas of failure, based on Wangensteen's University of Minnesota reoperative series.[271]

Between 1991 and 1998, the Southwest Oncology Group and the Gastric Intergroup conducted SWOG 9008/INT 0116, a two-armed prospective randomized trial of postoperative adjuvant chemoradiation versus surgery alone in patients with completely resected adenocarcinoma of the stomach and esophagogastric junction. Eligibility criteria for this trial specified complete negative-margin resection, registration 20–41 days postoperatively, adequate organ function, good performance status (i.e., Zubrod 1 or 2), postoperative caloric intake of more than 1,500 kcal per day, and fourth edition TNM stage IB or higher, distant-metastasis-negative, disease.[272] Of 603 cases accrued to the study, 46 (8%) were ineligible, leaving

TABLE 41.6. Patterns of failure after "curative" resection of gastric cancer.

Incidence in total patient group (%)			
Pattern of Failure	***Clinical***	***Reoperation***	***Autopsy***
A. Locoregional	38	67	80–93
B. Peritoneal seeding	23	41	30–50
—Localized		–19	
—Diffuse		–22	
C. Distant metastases	52	22	49

Modified from Smalley et al.,[262] by permission of *International Journal of Radiation Biology Oncology Physics.*

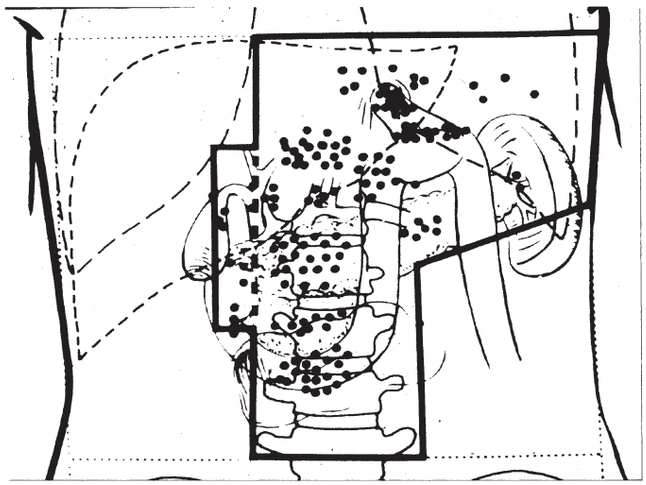

FIGURE 41.9. Early proposal by Gunderson and Sosin for a radiation treatment field encompassing frequent locoregional areas of failure, based on Wangensteen's University of Minnesota reoperative series. (From Gunderson and Sosin,[267] by permission of *International Journal of Radiation Oncology Biology Physics*.)

556 cases; 20% of eligible cases registered had disease of the cardia/gastroesophageal junction, and advanced-stage cases were overrepresented. Eighty-five percent of cases were node positive. Using AJCC/UICC fifth edition criteria, fully 69% of the cases had AJCC IIIA or IIIB disease (46% and 23%, respectively) and only 8% had stage IB disease.[272] Of the cases in this trial, 54% underwent D0 (i.e., less than D1 lymphadenectomy), a source of subsequent criticism. The treatment consisted of one cycle of 5-FU (425 mg/m^2) and leucovorin (LV, 20 mg/m^2) in a daily × 5 regimen followed by 4,500 cGy (180 cGy/day, M–F) given with 5-FU/LV (400 mg/m^2 and 20 mg/m^2) on days 1 through 4 and on the last 3 days of radiation. On completion of the radiation, two additional cycles of daily × 5% FU/LV were given at the original dose levels at monthly intervals.[272] Results for this trial were recently updated with more than 6 years of median follow-up (Figure 41.10).[273] Overall survival was 35 months median for chemoradiation versus 26 months for surgery alone [$P = 0.006$; hazard ratio, 1.31 (1.08–1.61)]. Disease-free survival was also significantly different at 30 months median for chemoradiation and 19 months for surgery alone [P less than 0.001; hazard ratio, 1.52 (1.75–1.85)].[273]

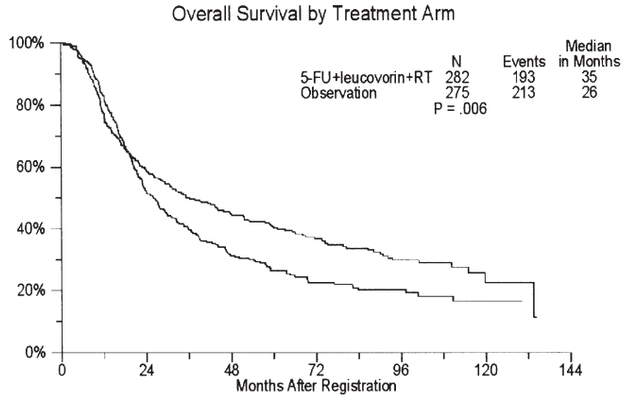

FIGURE 41.10. Updated survival with more than 6 years median follow-up for INT-0116, a trial of postoperative adjuvant chemoradiation (*upper curve*) versus postoperative observation (see text). (Updated data courtesy of Southwest Oncology Group.[272,273])

Exploratory subgroup analyses for INT-0116 were recently performed for six variables: gender, T stage, N stage, gastric subsite, D level of dissection, and diffuse versus intestinal histology. Positive treatment effects were seen in all subsets. A possible treatment interaction was seen, with diffuse-type histology cases doing poorly with therapy, but after adjusting for multiple testing, this result was not significant.[273]

The likely burden of unresected locoregional disease in this trial is problematic.[274] Less than D1 lymphadenectomy, considered suboptimal in the opinion of most experts, was performed in 54% of the cases.[246,272] As noted in the previous section, cases with Maruyama Index of Unresected Disease (MI) less than 5 enjoyed significantly greater survival (median overall survival for the MI less than 5 subgroup, 91 months versus 27 months; $P = 0.005$), and this was an independent predictor of survival.[246] By D level, median survival was 27 months for D0 lymphadenectomy and 48 months for D2 lymphadenectomy, but only 10% of cases registered to this trial underwent D2, and this difference was not significant.[246] Surgical undertreatment may have played a role in making this a positive trial.[274]

On the basis of INT 0116, adjuvant chemoradiation has been recommended in the United States for all patients with stage IB or greater, M0 disease (i.e., locoregional disease), *provided* they meet criteria for adequate caloric intake (more than 1,500 cal/day), good organ function, and good performance status.[272] Do all patient subgroups really benefit? The power to detect differing treatment effect in various subgroups in this trial (especially the stage IB subset) is low. Statistical tests of treatment interaction with pathology and surgical variables have been negative, however.[272] A cautionary note concerning the lower-risk, stage IB subgroup (i.e., patients with T2N0 or T1N1 disease) has been voiced.[274]

On the basis of this study, a new U.S. Intergroup trial, examining postoperative etoposide, cisplatin, and 5-FU (ECF) chemotherapy before and after radiation with continuous infusion 5-FU versus adjuvant treatment according to the INT-0116 protocol, is now under way, as well as other, similar trials in Europe.

Early Postoperative Intraperitoneal Chemotherapy

Japanese investigators have advocated intraperitoneal and intralymphatic installation of mitomycin C bound to microcarbon particles for some time.[275] This treatment has been tested in an Austrian prospective randomized trial with negative results.[276] Another Austrian prospective randomized trial of perioperative cisplatin has also been reported as negative.[277] A Japanese trial of intraperitoneal OK-432 in addition to systemic therapy has also been negative.[278] Phase II investigations of intraperitoneal therapy have also been conducted in the United States and elsewhere,[279,280] with some investigators enthusiastic[281] and some advising caution because of the associated morbidity.[282]

One positive prospective randomized clinical trial of perioperative intraperitoneal has been reported.[283] Between 1990 and 1995, 248 Korean patients with biopsy-proven gastric

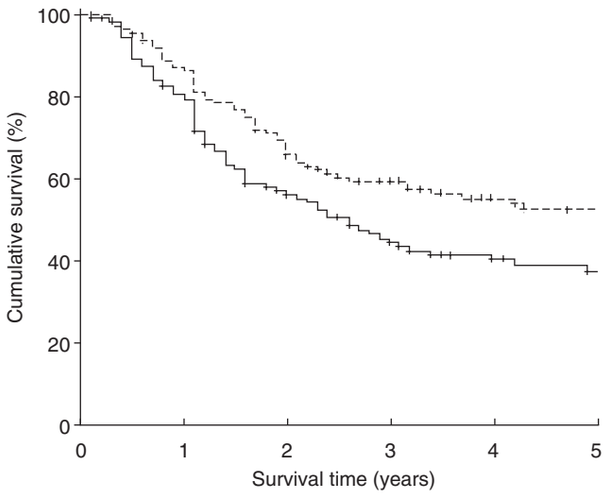

FIGURE 41.11. Kaplan–Meier overall survival for group treated with early postoperative intraperitoneal chemotherapy (mitomycin C on postoperative day 1 and 5-fluorouracil (5-FU) daily on postoperative days 2–5; *upper curve*) versus controls receiving surgery alone (*lower curve*). With mean follow-up of 36 months, survival difference is significant ($P = 0.0278$). (From Yu et al.,[283] by permission of *World Journal of Surgery*.)

cancer without intraoperatively detected distant organ metastases were randomized intraoperatively following complete resection and minimum D2 lymphadenectomy to receive postoperative intraperitoneal mitomycin C and 5-FU versus surgery alone (Figure 41.11). Stage I cases and those more than 70 years of age were excluded. Postoperative adjuvant treatment, delivered intraperitoneally through a Tenckhoff catheter, consisted of 10 mg/m^2 mitomycin C delivered at body temperature in 1 L dialysis solution on the first postoperative day, followed by 700 mg/m^2 5-FU plus 50 mEq sodium bicarbonate in 1 L dialysis solution daily on days 2 through 5. No further antitumor treatment was administered during the disease-free interval. In-hospital mortality was 6.4% in the treated group versus 1.6% in the surgery-only group (P = n.s.). Among morbidities, intraabdominal bleeding (10% versus 1%; $P = 0.002$) and intraabdominal abscess/peritonitis (14% versus 4%; $P = 0.008$) were more frequent among treated cases. Follow-up consisted of regular physical examinations, but CT scans, paracentesis, etc., were initiated only at the discretion of the surgeon to confirm clinical findings. The initial report of this trial in 1998 reported a significant positive effect on survival only for stage III cases.[284] A subsequent follow-up in 2001 reported significantly improved overall survival for the treatment group (54% versus 38%; $P = 0.0278$).[283] Subset analysis revealed the benefit was enjoyed predominantly by those with fifth–sixth edition UICC TNM stage III (57% versus 23%; $P = 0.0024$) and stage IV (28% versus 5%; $P = 0.0098$) disease.[283] Further subset analysis showed benefit for those with involved lymph nodes (46% versus 22%; $P = 0.0027$) and those with serosal invasion (52% versus 25%; $P = 0.0004$).[283] Although this trial has yet to be duplicated, and there are some methodological criticisms, it has encouraged continued investigation of both perioperative intraperitoneal therapy and methods to decrease the associated morbidity. In the view of advocates, this trial constitutes level I evidence in favor of such intraperitoneal therapy.[281]

Chemotherapy Without Radiation

A succession of meta-analyses concerning the value (or nonvalue) of systemic chemotherapy for gastric cancer have been conducted over the past decade. In 1993, Hermans et al. published a meta-analysis of 11 randomized trials of adjuvant chemotherapy, mostly involving treatment with 5-FU-based regimens, conducted over the previous decade. The odds ratio of 0.88 among treated patients was not significant.[285] A year later, in response to a journal letter,[286] two additional trials were added, and the addition of 318 cases from the two erroneously omitted trials lowered the odds ratio to 0.82; this was of borderline significance (CI, 0.68–0.98).[287] In 1999, Earle and Maroun published a 13-trial meta-analysis of non-Asian trials published between 1980 and 1996, with a similar odds ratio for death in the treated group of 0.80 (95% CI, 0.66–0.97).[288] In 2000, Mari et al. published a 20-article, 3,658 patient meta-analysis with an odds ratio for the treated group of 0.82; with the additional trials and patients, this was significant (95% CI, 0.75–0.89; P less than 0.001).[289] Nonetheless, even including subgroup analyses, only a few trials showed significant results favoring chemotherapy,[290–295] and the authors still considered adjuvant chemotherapy as investigational.[289] In 2002, Panzini et al., from Italy, restricted meta-analysis to those trials where all patients were treated with "radical" surgical techniques. Of the 17 papers eligible for inclusion, 3,118 patients were available for analysis. Odds ratio for death among the treated cases was 0.72 (95% CI, 0.62–0.84),[296] and on the basis of this, a large confirmatory randomized controlled trial of cisplatin-based chemotherapy was recommended.[296] In 2001, a less-selective, but more-comprehensive, meta-analysis was conducted by the Swedish Council of Technology Assessment in Health Care (SBU),[297] based on 153 scientific papers, 18 reviews, 60 randomized studies, and 57 prospective studies encompassing 12,367 patients. The authors' meta-analysis of 21 randomized adjuvant studies revealed a statistically significant survival benefit with odds ratio 0.84 (95% CI, 0.74–0.96); however, analyzing Western world and Asian studies separately, a statistically significant difference was noticed: Western world studies showed an odds ratio of 0.96 (95% CI, 0.83–1.12) and the Asian studies an odds ratio of 0.58 (95% CI, 0.44–0.76).[297] The authors concluded that adjuvant chemotherapy could not be recommended in Western patients, but that benefit in Japanese series was evident.[297] Overall, the benefit of adjuvant therapy in all these meta-analyses equates to an odds ratio of approximately 0.80 at best. The extent of surgical resection for patients entered into these adjuvant studies, and the consequent burden of residual locoregional microscopic disease, may, as Panzini et al. suggest, be the key confounding variable.[296] Nakajima et al., in a meta-analysis of 10 Japanese trials conducted at the Cancer Institute Hospital in Tokyo on radically treated surgical cases from 1959 to 1982 (n = 1,177 cases), noted a much better odds ratio of 0.63 favoring the treatment groups (P less than 0.01).[298]

As depicted in Table 41.7, most trials of adjuvant systemic chemotherapy versus surgery alone have been negative.[291,294,295,299–311] For the positive trials, unusually low control group survival,[295] or findings at odds with other trials,[294] undermine general applicability.

Following the aforementioned INT-0116 adjuvant chemoradiation trial, for patients with disease resectable to

TABLE 41.7. Prospective randomized trials of adjuvant systemic chemotherapy.

Author	*Year*	*Treatment group*	*N*	*Five-year survival*	*Survival Median survival*	*P value*
Nakajima et al.[299]	1984	MMC + 5-FU+araC →F	81	68%	>60 months	0.09
		MMC + ftorafur + araC→ftora	83	63%	>60 months	
		Surgery alone	79	51%	>60 months	
Engstrom et al.[300]	1985	5-FU + MeCCNU	91	—	36.6 months	0.73
		Surgery alone	89	—	32.7 months	
Coombes et al.[301]	1990	FAM (5-FU + Adria+MMC)	148	35%	36 months	0.17
		Surgery alone	133	46%	36 months	
Krook et al.[302]	1991	5-FU + Adria	64	33%	34 months	0.88
		Surgery alone	61	32%	36 months	
Grau et al.[291]	1993	MMC	68	41%	—	0.025*
		Surgery alone	66	26%	—	
Hallissey et al.[303]	1994	FAM	138	19%	17.3 months	0.14
		Postoperative radiotherapy alone	153	12%	12.9 months	
		Surgery alone	145	20%	14.7 months	
Macdonald et al.[304]	1995	FAM	93	—	32 months	0.57
		Surgery alone	100	—	28 months	
Tsavaris et al.[305]	1996	5-FU-epirub-MMC (FEM)	42	—	64 months	ns
		Surgery alone	42	—	81 months	
Neri et al.[295]	1996	5-FU-LV-epirub	48	25%	20.4 months	0.01*
		Surgery alone	55	13%	13.6 months	
Grau et al.[329]	1998	MMC-ftorafur	43	67%	—	0.04
		MMC	42	44%	—	
Nakajima et al.[306]	1999	MMC-5-FU-UFT	285	85.8%	>5 years	0.17
		Surgery alone	288	82.9%	>5 years	
Cirera et al.[294]	1999	MMC-tegafur	76	56%	74	0.04*
		Surgery alone	72	36%	29	
Langman et al.[307]	1999	Cimetidine	221	21%	13	0.42
		Surgery alone	221	18%	11	
Nashimoto et al.[308]	2003	MMC-5-FU-araC	126	91.2%	—	0.13
		Surgery alone	126	86.1%	—	
Chipponi et al.[309]	2004	5-FU-LV-CDDP	101	39%	—	ns
		Surgery alone	104	39%	—	
Sato et al.[310]	2004	5-DFUR	143	62.9%	—	0.79
		5-DFUR + OKT-432	144	63.8%		
Hartgrink et al.[311]	2004	Preop (neoadjuvant) FAMTX	29	—	18 months	0.17
		Surgery alone	30	—	30 months	

negative margins, clinical trials involving arms with only surgery or only postoperative adjuvant chemotherapy have become less feasible in the United States.[272,273]

To date, no neoadjuvant preoperative chemotherapy regimen has been shown superior to postoperative therapy or surgery alone in a Phase III prospective randomized trial, despite promising Phase II results.[312] Further, a recently reported trial of neoadjuvant FAMTX versus surgery alone showed median survival of 18 months for the treated group versus 30 months for the surgery-alone group ($P = 0.17$). On the basis of this result, the risk that neoadjuvant treatment with insufficiently effective chemotherapy might jeopardize survival must be considered.[311]

Advanced and Metastatic Disease

A variety of combination chemotherapy regimens have been used in the palliative management of patients with gastric cancer.[313–319] Although the EAP type regimens pioneered by Preusser, Wilke, and colleagues[317] led to a new era in combination chemotherapy, in which expectations of response rates in excess of 30%, and some complete tumor regressions, were possible, the EAP regimen is now utilized only rarely because of its significant toxicity.[320] There are now other regimens that are widely used. The major regimens of current interest include methotrexate-directed 5-FU combinations,[321] infusional 5-FU regimens,[37,314,322] and combinations containing taxanes[316] and irinotecan-based regimens.[315,323]

Over the past decade, there has been interest in the use of prolonged infusion of 5-FU as a part of the combination chemotherapy treatment for stomach cancer. Crookes and colleagues[314] used continuous infusion 5-FU as a major component of a neoadjuvant program described below. Webb and colleagues reported important results with a combination regimen designated ECF (epirubicin, cisplatin, and 5-FU).[322] Of note, ECF uses protracted infusion of 5-FU at a daily rate of 200 mg/m^2 with intermittent epirubicin and cisplatinum. Epirubicin is an anthracycline analogue available in Western Europe for several years and now commercially available in

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the United States (although its approval indication is for breast cancer, not gastrointestinal cancer, in the United States). ECF was tested in a major Phase III randomized trial reported in 1997.[322] This study compared ECF with FAMTX in patients with gastroesophageal adenocarcinoma. In this study, 274 patients with adenocarcinoma or undifferentiated cancer were randomized between FAMTX and ECF. The FAMTX regimen caused significant hematologic toxicity and was inferior in regard to response rate and survival when compared to ECF. The overall response rate for ECF was 45% versus 21% for FAMTX ($P = 0.002$). The median survival for ECF was 8.9 versus 5.7 months ($P = 0.0009$). At 1 year, 36% of ECF and 21% of FAMTX patients were alive. Webb and colleagues also assessed global quality of life scores in their study. The global quality of life was superior for ECF at 24 weeks. This advantage in quality of life, however, did not persist as patients were followed further on the study.[322] Of interest, Ross and colleagues performed a Phase III study of ECF versus a very similar regimen, MCF, that substituted mitomycin C (7 mg/m^2 every 6 weeks) for epirubicin and uses somewhat different doses of 5-FU (300 mg/m^2/day × 24 weeks) and cisplatin (50 mg/m^2 every 3 weeks).[324] The overall rates of survival were no different between the ECF and MCF regimens. This trial supports the use of MCF if either epirubicin is not available or a clinician would prefer not to use an anthracycline.[320]

Other, more-recent, regimens include the combination of docetaxel–cisplatin[316] and the regimen of irinotecan–cisplatin.[315] The irinotecan and cisplatin combination has been evaluated and shown to have good activity in gastroesophageal cancers. The response rate for adenocarcinoma with the regimen was 12 of 23 (57%), with excellent palliation of tumor-related symptoms.[315] Another regimen of interest recently is the combination of docetaxel and cisplatin.[316] In a European study of 85 patients with advanced gastric cancer, the overall response rate was 36%, and 7 of 85 (8%) had complete responses. The median survival in this study was 10 months, and grade IV toxicity was seen in only 4% of cases.[316]

Data on therapy of advanced gastric cancer allow one to draw some conclusions in regard to the standard recommendations for patients with metastatic stomach cancer. It is reasonable to assume that several approaches can be considered appropriate chemotherapeutic management for patients with advanced gastric cancer. FAMTX is well tolerated and can certainly result in some complete responses in patients with gastric cancer, but it is no longer considered a front-line regimen for advanced gastric cancer (level I evidence). More promising approaches entail the use of continuous infusions of fluorinated pyrimidines, such as 5-FU. The ECF regimen, along with similar regimens using alternate anthracyclines, continue to be investigated. Finally, taxane- and iritonecan-based regimens are also of interest and appropriate for use in patients with advanced gastric cancer (level IIc data). However, it is important to stress that none of these regimens results in long-term control of metastatic adenocarcinoma of the stomach.

For a subset of cases with advanced locoregional disease followed by major response to chemotherapy, eventual R0 surgical resection is sometimes possible, and occasional long-term disease-free survival can result.[325–327] It should also be noted that surgical resection of isolated hepatic metastases, before or after chemotherapy, can also result in occasional long-term disease-free survival.[328] In general, however, although some chemotherapy regimens produce major partial responses and complete response rates as high as 15%, such responses are usually not durable.

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