

# Adenocarcinoma of the stomach: a review

JAMES M. MCLOUGHLIN, MD

On January 29, 1881, in Vienna, Austria, Dr. Theodor Billroth performed the first successful operation for gastric cancer. Two previous attempts by other surgeons had resulted in early postoperative deaths; Dr. Billroth's patient survived the surgery but died a few months later from metastatic disease (1). Today surgeons are still challenged by similar obstacles in gastric cancer, notably the dismal result of incomplete resection.

## INCIDENCE AND ETIOLOGY

Worldwide, gastric cancer is the fourth most common cancer (2). In the West, the incidence of gastric cancer has steadily decreased since the 1930s due to better living conditions and dietary changes. It is now the eighth most common cause of cancer death (Figure 1). The incidence in the USA is 5.2 per 100,000 vs 12 to 15 per 100,000 in Europe and 93 per 100,000 in Japan (3–5). In 2002, there were 21,600 newly diagnosed gastric cancers and 12,400 deaths due to gastric cancer in the USA (6, 7). The median age of diagnosis is 70 years for men and 74 years for women (3, 8). The incidence is twice as high in men as in women and increases with age (9).

The vast majority of gastric cancers are attributed to environmental factors, the most common being infection with *Helicobacter pylori*. *H. pylori* was discovered in 1984 by Drs. Marshall and Warren as an inciting cause for peptic ulcer disease and has since been linked to gastric cancer (10). This organism is found in 72% of antral gastric cancers and results in a 9-fold increased risk of developing cancer. Inoculation most likely occurs in childhood through the oral-fecal pathway and is transmitted person to person (11), which partially explains why the incidence decreases as countries become more developed. Palayo Correa theorizes that preexisting infection with *H. pylori* causes inflammation and atrophy, leading to reduced acid and bacterial overgrowth. Chronic atrophic gastritis can progress to metaplasia, then to dysplasia, and finally to carcinoma (12–14). It is also possible that more virulent strains of *H. pylori* (i.e., the Cag A strain) may cause cancer (15). This mechanism is more likely to apply to distal cancers compared with more proximal cancers. Food intake is thought to be con-

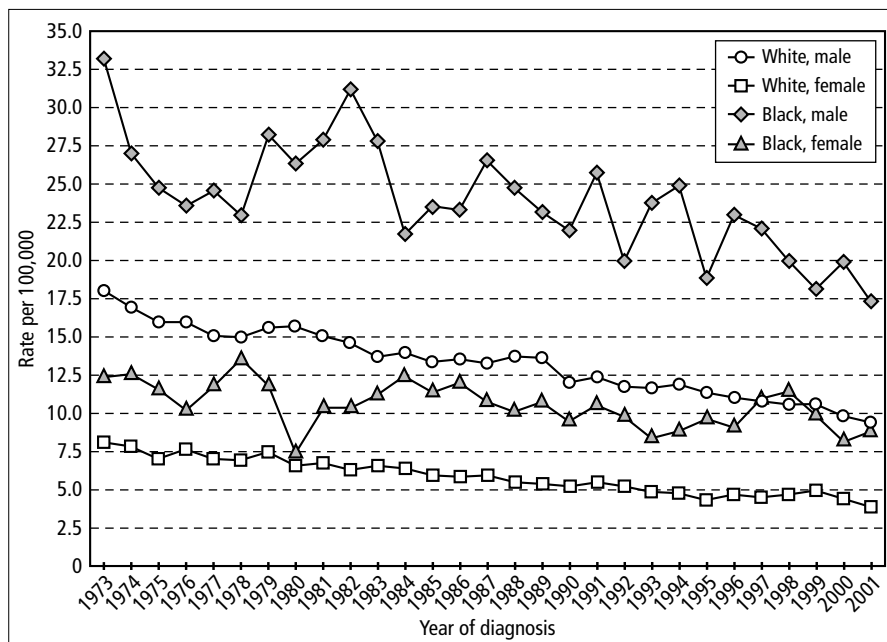


Figure 1. Incidence of gastric cancer according to race and gender, 1973–2001. Source: National Cancer Institute (reference 7).

tributary as well; diets high in salt and preserved, smoked foods as well as low in fresh fruits and vegetables appear to be a risk factor. A Swedish population-based case-control study evaluated the absolute risk reduction from changes in diet. It was estimated that 25,000 people would have to eat a high-fruit diet to prevent one gastric cancer (16). However, certain carcinogens in foods, such as nitrosamines and nitrosamides, in the presence of achlorhydria along with the decreased antioxidant effect of fruits and vegetables may enhance the risk of developing chronic atrophic gastritis. Proximal tumors, however, appear to have a different mechanism, as many pathology specimens fail to demonstrate dysplasia or metaplasia (17, 18).

Genetic factors have been difficult to prove. Although many molecular studies have been and are being performed to uncover the genetic basis for gastric cancer formation, no causal

From the Department of Surgery, Baylor University Medical Center, Dallas, Texas. Presented February 18, 2004, at surgical grand rounds, Baylor University Medical Center, Dallas, Texas.

Corresponding author: James M. McLoughlin, MD, Department of Surgery, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246.

relationships have been proven. Gastric cancer is part of several inherited disorders, including Lynch syndrome and Peutz-Jeghers syndrome (19). A directly inherited tendency was described in the family of Napoleon Bonaparte (1). More recently, the Maori tribe in New Zealand has demonstrated a hereditary inheritance with mutations in the E-cadherin/*CDH1* gene that regulates cell adherence. Several recent studies have further supported the role of E-cadherin mutations in familial gastric cancer (20–23). The lack of E-cadherin prevents binding to alpha-, beta-, or gamma-catenins by preventing normal cell-to-cell adhesion (24). The loss of normal adhesion may allow cells to detach and invade locally more easily. Abnormal cellular adhesions contribute to the raised, irregular edges seen in many tumors. Decreased expression of E-cadherin is noted more commonly in signet ring and mucinous adenocarcinomas. Loss of heterozygosity in the p53 gene also appears to be quite high in gastric cancer. Inactivation of p53 may be important in the late pathogenesis of gastric cancer (25, 26). Microsatellite instability is found in approximately 16% to 36% of gastric cancers. Adenomatous polyposis coli (*APC*) gene mutations are also found in approximately 30% of gastric cancers. The loss of *APC* function allows for increased levels of beta-catenins, which bind with lymphoid-enhancer factor 1 and become a growth-promoting transcription factor that modulates gene expression and stimulates cancer formation (27–30). Several studies are currently looking at alterations in growth factors such as bcl-2, c-met, K-sam, and c-erbB2 as markers for advanced disease and possible sources for immunotherapy (31–33). Elevated levels of vascular endothelial growth factor also appear to portend a worse prognosis. The ultimate goal for this genetic research is to uncover a more complete understanding of gastric cancer, allowing the development of specific therapy such as monoclonal antibodies to specific abnormal proteins.

Histologically, the Lauren classification scheme denotes two main subgroups for gastric cancer. The intestinal type is more commonly seen in Asian patients and the elderly. It typically involves the distal stomach and has glandlike structures that mimic intestinal glands. The diffuse or signet ring type is more common in Western cultures, younger patients, and individuals with blood type A. It is more frequently found in the proximal stomach, and the tumors are more poorly differentiated and lack glandular structures (9, 34, 35).

The anatomic location of gastric cancer is changing. In recently published European epidemiologic data, a 4% to 5% increase per year in proximal or cardiac cancers has been noted (3, 36). This rate parallels the increase in distal esophageal adenocarcinomas, suggesting a relationship to bile or alkaline reflux (37, 38). Proximal gastric cancers, referred to as esophagogastric junction cancers or cardiac cancers, have increased in the USA from 29% in 1984 to 52% in 1993 (39, 40). These cancers tend to have a worse prognosis secondary to the later onset of diagnosis and the more extensive lymph node drainage that involves the mediastinal, abdominal, and retroperitoneal lymphatics (41, 42).

Proximal cancers have been subclassified by Siewert and Stein based on location of the majority of tumor mass (43). A type I esophagogastric junction tumor is >2.5 cm above the cardia and is treated as an esophageal tumor. A type II tumor is located from about 2.5 cm above cardia to 2 cm be-

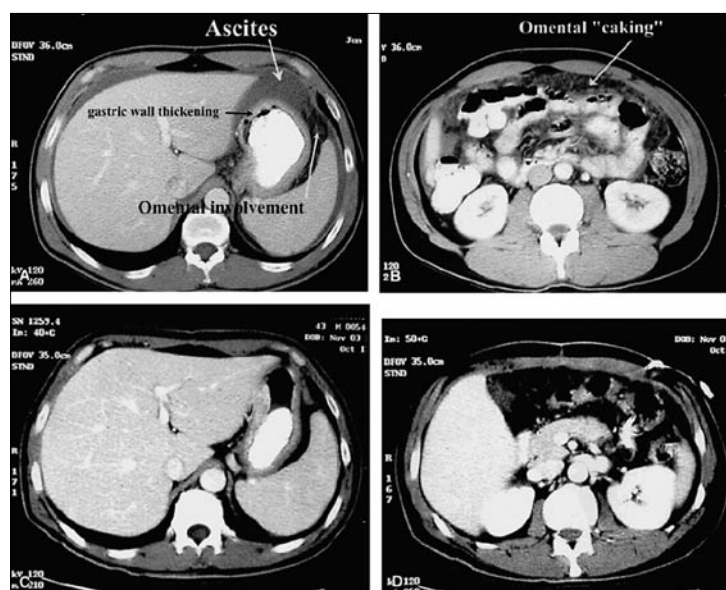
low cardia. The presence of goblet cells is suggestive of Barrett's esophagus and not of stomach origin (44). Type III tumors are >2.5 cm below the cardia. A proximal negative margin is required for complete tumor excision. Of note, patients with proximal cancers have survival rates similar to those of patients with distal esophageal adenocarcinomas, comparing stage for stage (45). Several studies have shown similar genetic abnormalities for proximal cancers and esophageal adenocarcinoma, including loss of the Y chromosome, gain of chromosome 20, loss of chromosome 5, p53 mutations, and microsatellite instability; these abnormalities can make determining the true organ of origin difficult (46–50). Several studies have also noted differences between esophageal and proximal gastric cancer. Proximal gastric cancers are associated with *H. pylori* infections and often have inflammation, whereas esophageal cancers are rarely associated with *H. pylori* and have much less inflammation (51, 52).

Distal gastric cancers, on the other hand, have continued to decrease in incidence. This decrease may be due to better living conditions, better dietary habits, and eradication of *H. pylori* with antibiotics. Distal cancers are seen most commonly in Asia (51).

## DIAGNOSIS AND STAGING

In the pursuit of cure, attempts have been made to diagnose gastric cancer in its early stage. Tumors confined to the mucosa and submucosa are termed early gastric cancer, which is discussed separately from most gastric cancer due to its overall favorable prognosis; the 5-year survival is >90% (53). Most cases of early gastric cancer in the USA are diagnosed outside of a formal screening program and are found during evaluations for symptoms. Early gastric cancer is more frequently encountered in Asian countries where screening for gastric cancer occurs. In the USA, it accounts for <10% of gastric cancers (54–56).

Gastric cancer spreads fairly predictably in a local fashion within the gastric wall and then to adjacent lymph nodes. Once it does reach the serosa, it can spread into the peritoneal cavity and then spread distantly. This sequential manner of spread has



**Figure 2.** Computed tomography findings in advanced unresectable gastric cancer before (upper panels) and after (lower panels) chemotherapy. Note the disappearance of ascites and omental thickening. Reprinted with permission from reference 1.

**Table 1. American Joint Committee on Cancer staging system for gastric cancer**

Primary tumor (T)		Distant metastasis (M)	
TX	Primary tumor cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumor	M0	No distant metastasis
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria	M1	Distant metastasis
T1	Tumor invades lamina propria or submucosa	<b>Stage grouping</b>	
T2	Tumor invades muscularis propria or subserosa*	0	Tis, N0, M0
T2a	Tumor invades muscularis propria	IA	T1, N0, M0
T2b	Tumor invades subserosa	IB	T1, N1, M0
T3	Tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures†‡		T2a/b, N0, M0
T4	Tumor invades adjacent structures†‡	II	T1, N2, M0
			T2a/b, N1, M0
			T3, N0, M0
		IIIA	T2a/b, N2, M0
			T3, N1, M0
			T4, N0, M0
		IIIB	T3, N2, M0
		IV	T4, N1-3, M0
			T1-3, N3, M0
			Any T, Any N, M1
Regional lymph nodes (N)			
NX	Regional lymph node(s) cannot be assessed		
N0	No regional lymph node metastasis§		
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		

\*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.

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

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

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

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*, 6th ed. (2002) published by Springer-Verlag New York, www.springer-ny.com.

encouraged the surgical pursuit of extensive local and lymph node resections. Even if lymph node biopsy results are negative, several factors are diagnostic of more aggressive disease. Investigators from Memorial Sloan-Kettering demonstrated predictors of poor survival in lymph node-negative patients, including male gender, serosal invasion, presence of vascular invasion, and neural invasion. Age, tumor location, Lauren histologic classification, and extent of lymphadenectomy had no effect on survival. Vascular invasion portends a more aggressive tumor, a poorer survival rate, and a higher likelihood of metastasis for equal size and location. A T1 lesion with vascular invasion was associated with a 5-year survival of 57% compared with 97% for a T1 lesion without vascular invasion (57).

Symptomatic findings in early stage disease are relatively vague and nonspecific, often mimicking peptic ulcer disease. Most commonly, patients complain of epigastric discomfort. Patients may also present with anemia, weight loss, early satiety, anorexia, and, rarely, an upper gastrointestinal bleed (1). The increased use of proton pump inhibitors and antiulcer therapy may contribute to later time of diagnosis due to resolution of common vague symptoms (58). One study suggested that 30% of gastric cancer patients were treated with proton pump inhibitors for their symptoms (59).

Physical examination findings, if present, portend more advanced disease. In general, patients may appear cachectic or jaundiced from obstruction by lymph nodes surrounding the com-

mon bile duct. The presence of disease in several lymph nodes is attributed to metastatic spread of gastric cancer. Virchow's node is a hard lymph node in the left supraclavicular fossa. The Sister Mary Joseph lymph node is a firm nodule in the umbilicus, often from tumor extending down the falciform ligament, and may cause a bloodstained discharge from the umbilicus. Irish's node is an enlarged left axillary lymph node. A Krukenberg tumor is gastric cancer metastatic to the ovary. A positive Blumer's shelf finding may indicate metastatic tumor high on the anterior rectal wall on rectal examination. Some patients may have a firm, palpable abdominal mass or present with malignant ascites (1, 60).

Early endoscopy should be considered in patients of recent Asian emigration as well as patients who have had previous gastric surgery or who have a positive family history or concerning symptoms. Patients with previous gastric surgery for ulcer disease are 2.4 times more likely to develop gastric cancer (60). Because of the low incidence of gastric cancer in the USA, no formal program is in place for screening, unlike in Japan and other Asian countries. A patient with a history of chronic atrophic gastritis or intestinal metaplasia also needs to be considered

for annual surveillance, as there is an 8% to 10% risk of developing cancer over a 10-year period (61).

Definitive diagnostic investigation begins with upper endoscopy, as >90% of cases will be diagnosed in this manner. Typical gastric cancer appears as an irregular ulcer with raised edges or an ulcer that is polypoid and fungating. Multiple biopsies, usually 6 or more, are required to minimize the false-negative rate. Even patients with gastric ulcers that appear benign should undergo endoscopy again after 6 weeks of medical treatment. Gastric ulcers need to be biopsied until they are completely healed (60). If the stomach appears undistensible, a barium upper gastrointestinal series may be more diagnostic of linitis plastica than esophagogastroduodenoscopy with biopsies, as the tumor diffusely infiltrates the submucosa of the stomach. If an upper gastrointestinal series is ordered, gastric cancer often appears elevated and irregular with nonradiating rugal folds. Once the diagnosis is made, a computed tomography (CT) scan is required to stage the cancer and evaluate for metastatic disease. Bulky adjacent lymphadenopathy in the periaortic region, ascites, and a thickened omentum can be evaluated on CT and suggest metastatic disease. Obliteration of the lesser sac and invasion to surrounding vessels can also be visualized (1) (Figure 2). Endoscopic ultrasound can be used to assess the tumor depth and to further evaluate adjacent lymphadenopathy. Endoscopic ultrasound-guided fine-needle aspiration of adjacent lymph nodes can also be performed. Staging laparoscopy may be required to assess for unresectability. Positron emission

tomography scans can also be used to assist in staging. Laparotomy, however, is still the gold standard for staging (60).

Gastric cancer is staged using the TNM staging system (3, 6) (Table 1). The most important prognostic indicators are lymph node involvement followed by tumor depth. The number of positive nodes is more important than the location of the nodes in determining survival (57, 62–64). Risk of lymph node spread can be predicted by tumor depth. The chance of positive nodes is <4% for a T1a (mucosal) lesion, 23% for a T1b (submucosal) lesion, 44% to 50% for a T2 (muscularis propria) lesion, and 64% for a T3 (to serosa) lesion (9, 57, 63).

### SURGICAL TREATMENT

The primary successful treatment is still surgical resection. It is the only single-modality treatment capable of curing gastric cancer. The goal of a surgical cure requires complete resection to an R0 status (no residual tumor), as the stage of disease is the most important predictor of outcome. On average in Western cultures, 20% to 30% of patients present with inoperable cancer secondary to metastatic disease. Of the remaining 75% progressing to surgery, 20% of patients have unresectable cancer at the time of surgery, 25% have cancer with positive microscopic margins and are thus not cured, and 30% have a curative procedure performed (60).

The approach to surgery is determined by 1) the incision(s) needed, 2) the extent of gastric/esophageal resection needed, and 3) the extent of lymph node dissection needed. Surgery may of course be required for palliation secondary to bleeding and obstruction and may even be offered as an option in prolonging life.

Controversy remains over the extent of lymph node dissection required with gastric resection. The great majority of gastric cancers that recur and metastasize do so first in the regional lymph nodes before spreading to the peritoneum, liver, or lung. The standard of care varies worldwide, with most Asian countries encouraging extended lymphadenectomy. The majority of surgeons in the USA, on the other hand, excise the N1 lymph nodes, which are in the immediate perigastric region. This resection is called a D1 resection. A D2 resection, as described in the 2002 American Joint Committee on Cancer manual, includes nodes along the celiac axis and its named branches and along the middle colic, superior mesenteric artery, and periaortic nodes (65–67). Asian studies suggest that a minimum of 15 nodes are required to adequately stage the disease and to truly declare a patient node negative (68). Several studies in Europe and the USA, however, have failed to show any significance in survival and even have shown an increase in perioperative morbidity and mortality with more extensive lymph node resections (65, 66, 69–71) (Table 2). A recent Dutch trial performed with Japanese moderators present showed no difference in survival and an increase in perioperative morbidity and mortality with extended lymphadenectomy (66). However, in a recent paper from Memorial Sloan-Kettering Cancer Center, a D2 resection was still recommended due to identification of 20% incidence of skip metastasis to D2 nodes.

**Table 2. Results of studies comparing D1 and D2 lymph node dissection**

First author (reference)	Patients D1/D2	Morbidity (%) D1/D2	Mortality (%) D1/D2	5-Year survival (%) D1/D2
Bonenkamp (66)	380/331	25/43	4/10	45/47
Cuschieri (69)	200/200	28/46	6.5/13	35/33
Dent (71)	22/21	15/30	0/0	78/76 (3 yrs)

**Table 3. Comparison of sentinel lymph node studies**

First author (reference)	Number of patients/ T category	Method	Detection rate (%)	Sensitivity (%)	Node-positive patients (%)
Kitagawa (76)	127/T1 18/T2	Tc-99m sulfur colloid	95	92	17
Ichikura (77)	62/T1,2	Dye, ICG	100	87	24
Hiratsuka (78)	44/T1 30/T2	Dye, ICG	99	90	14

Tc-99m indicates technetium 99m; ICG, indocyanine green.

Survival was slightly improved only for patients who had T3 disease and were node negative (9, 57, 63, 71).

In Japan, improvement in survival has been shown with more extensive lymphadenectomy. This has been attributed to more intense pathologic assessment of specimen lymph nodes, leading to up-staging, and possibly a difference in biology. Distal cancers are more common in Japan, whereas proximal cancers are more common in the USA. Also, there may be a difference in interpreting pathology and intraoperative findings, as many Western patients may be understaged (1, 72, 73).

At present, a computer database of >8000 patients, called the Maruyama program, is being compiled in Japan to help predict the most likely spread of tumor based on 7 variables, including tumor size, depth, and grade. These data may help guide the extent of dissection and improve the accuracy of removing involved nodes (74, 75).

In contrast to the emphasis on extensive lymphadenectomy, there is an interest in performing a more limited node dissection with sentinel node biopsy. This technique generally relies on intraoperative injection of isosulfan blue dye with direct visualization of the first node or nodes. This technique has been proposed for early gastric cancer when a local excision may be performed. Even when a complete lymphadenectomy is anticipated, some have proposed that the sentinel node technique should be performed to identify unsuspected patterns of drainage and to allow for a more thorough pathologic assessment of the first sentinel node, including serial sectioning and immunohistochemistry. Comparative studies in Japan demonstrate a detection rate of >95% and a sensitivity of 90% for sentinel lymph node biopsy vs a D2 dissection (Table 3). No clinical trials have been performed to give a definitive recommendation. Critics of this technique note the extensive drainage to the celiac axis, liver, mediastinum, and retroperitoneal basins (9).

The removal of the spleen and distal pancreas to achieve adequate lymphadenectomy has largely been abandoned because

several studies demonstrated that survival is worse with resection. This result may be secondary to a more advanced tumor or to the immunomodulatory effects of splenectomy on cancer recurrence as well as an increased risk of infection (79). If tumor is grossly invading the spleen or the tail of the pancreas, resection should be performed for tumor reduction. No tumor should purposefully be left behind if a curative resection is being attempted.

Gastric resections are determined by tumor location. Proximal cancers are further subcategorized according to type of tumor. A type I tumor is considered an esophageal cancer and treated with an esophagogastrectomy, usually requiring both an abdominal and thoracic approach. A type II tumor usually requires an esophagogastrectomy to achieve 6- to 7-cm proximal margins. A type III proximal gastric tumor can be treated with either a total or proximal subtotal resection. Several studies have demonstrated no survival difference in type of resection as long as margins are negative (80–86). Body and midstomach tumors typically require a total resection to gain adequate margins of at least 6 cm (87). Pylorus-preserving distal gastrectomies are often done for early gastric cancers or more proximal tumors. Total gastrectomy should be considered for T3 disease. Tomita et al monitored 32 patients over 5 years to compare pylorus-preserving vs traditional resections and concluded that pylorus-preserving resections decrease reflux, dumping, and gastritis, but patients have increased sensation of fullness and early satiety secondary to gastric atony. Symptoms can be reduced with preservation of hepatic and pyloric branches of the vagus nerve (88). Local excision of gastric cancer has been proposed for early gastric cancer (T1 mucosal disease). This stage of cancer is rarely seen in the USA. However, the Japanese have reported good results from treating the lesion endoscopically with local resection or with more limited open or laparoscopic gastric resections.

Reconstruction can be performed using a Roux-en-Y, Billroth I, or Billroth II anastomosis. A Roux-en-Y anastomosis tends to eliminate troublesome bile reflux. Long-term follow-up studies demonstrate no nutritional difference in reconstruction choices; however, short-term function is better with a Tanner 19 anastomosis (similar to a J-pouch) vs a straight gastrojejunostomy anastomosis (89, 90). A feeding jejunostomy is commonly placed to allow for nutritional replacement, especially during postoperative chemotherapy and radiation.

## SURGICAL COMPLICATIONS

The major postoperative complications include anastomotic leak, aspiration, hemorrhage, infection, thromboembolism, and pneumonia. Infection rates increase with splenectomy. Most often patients with a leak will present with tachycardia, hypotension, a decrease in hematocrit, and a left pleural effusion.

Long-term complications are related to loss of receptive relaxation, antral contraction, and secretory function, especially with a total gastrectomy. Patients may complain of early satiety and may have weight loss and nutritional deficits (i.e., B<sub>12</sub> from loss of intrinsic factor; iron and calcium if there is bypass of the duodenum). Dumping syndrome, which may include bloating, epigastric pain, diarrhea, and fainting, is related to rapid entry of osmotically active material into the small intestine. This rapid entry causes a shift of fluid from the intravascular space and results in symptoms of hypovolemia. Late dumping may produce fainting

**Table 4. Neoadjuvant treatment trials**

First author (reference)	Number of patients	Regimen	R0 resection rate (%)	Survival (months)
Ajani (91)	104	Preop FAMTX, postop 5-FU/CDDP vs preop and postop EAP	61 vs 77	15 vs 16
Ott (92)	49	Preop PLF	76	32
Kang (93)	107	Surgery vs PEF and surgery	61 vs 78 ( <i>P</i> = 0.049)	30 vs 42 ( <i>P</i> = 0.11)
Songun (94)	56	Surgery vs preop FAMTX and surgery	62 vs 56 (NS)	13.1 vs 12.8 (NS)
Skoropad (95)	78	Surgery vs preop RT 20 Gy IORT and surgery	(Data not shown)	9 vs 21 (NS)
Zhang (96)	370	Surgery vs 40 Gy and surgery	79 vs 89 ( <i>P</i> = 0.01)	20 vs 30 ( <i>P</i> = 0.0094)

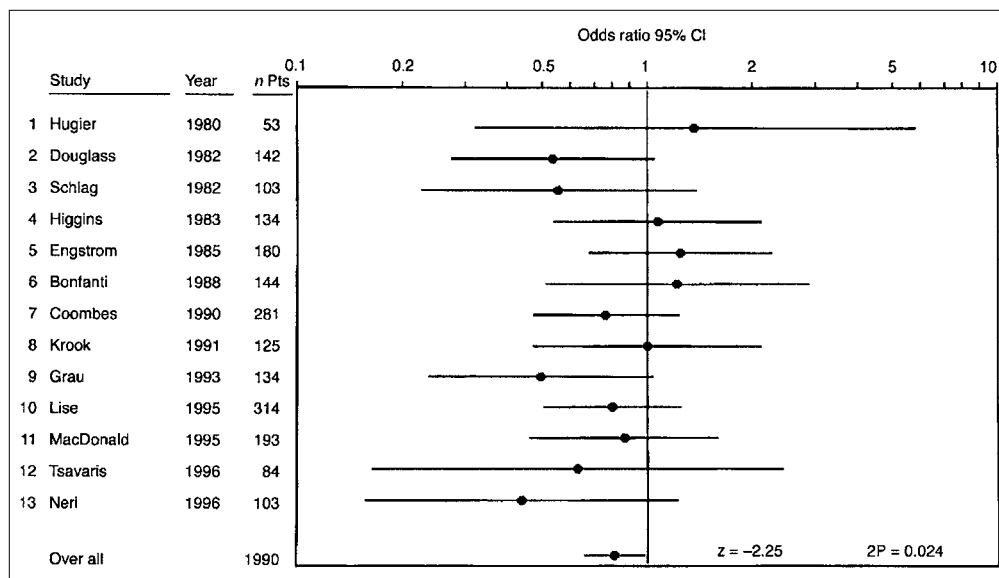
FAMTX indicates 5-FU, doxorubicin, methotrexate; CDDP, cisplatin; EAP, etoposide, doxorubicin, cisplatin; PLF, cisplatin, 5-FU/leucovorin; PEF, cisplatin, etoposide, 5-FU; NS, not significant; RT, radiotherapy; IORT, intraoperative radiotherapy.

symptoms, but these typically occur a few hours postprandial and are secondary to an excessive rise in insulin due to the rapidity of intestinal carbohydrate load and a resulting hypoglycemia.

## NEOADJUVANT THERAPY

Preoperative, or neoadjuvant, therapy is another controversial issue. Most trials have not demonstrated a significant benefit in overall survival (91–96) (Table 4). A recently published European study, designated as the MAGIC trial, involved 503 patients treated with pre- and postoperative epirubicin/cisplatinum/5-fluorouracil (5-FU) vs surgery alone. Treated patients showed improved survival, but the trend was not statistically significant. Tumors in treated patients were significantly smaller, allowing for a better rate of curative resection (79% vs 69% of patients receiving surgery alone), but again, survival was not significantly improved (89, 90). Preoperative chemoradiation at present is considered investigational as no phase III trials have demonstrated a survival advantage (9, 94, 101). Preoperative external-beam irradiation has been evaluated—especially for stage III and stage IV disease—as the tumor may be downsized, allowing for a better chance of curative resection (60, 96).

Multiple trials have been performed evaluating multiple drug combinations postoperatively over the past 20 years. No clear treatment option has been shown to make a significant overall survival difference. A recent Intergroup trial by Macdonald et al evaluated postoperative therapy with 5-FU/leucovorin and radiation vs surgery alone. A significant benefit from postoperative treatment was noted in patient survival (from 26 to 35 months) and relapse-free interval (from 19 to 30 months). This study was criticized for poor surgical technique; lymph nodes were removed in <40% of the procedures (99–101). A recent metaanalysis of multiple adjuvant trials suggested a small benefit from treatment (relative risk 0.94, 95% confidence interval [CI] 0.89–1.00) (98) (Figure 3). Trials in which most patients had node-positive disease demonstrated the greatest benefit (relative risk 0.91, 95% CI 0.85–0.99) compared with trials in which most



**Figure 3.** Metaanalysis of randomized trials that compared adjuvant chemotherapy with observation after curative resection of gastric cancer. CI indicates confidence interval. Reprinted from reference 98 with permission from Elsevier.

patients had node-negative disease (relative risk 1.00, 95% CI 0.90–1.11). At present, studies are comparing surgery with epirubicin, cisplatinum, and 5-FU pre- and postoperatively because this therapy appears to be more effective than 5-FU/leucovorin alone (99). Current treatment options are multiple, and most are in clinical trials. Epirubicin/cisplatinum/5-FU protocol vs docetaxel/cisplatinum/5-FU are options also being compared (98, 99, 101–103).

Survival data are varied in the literature based on country of origin and extent of resection. The following data are based on studies performed in the USA and Europe. Most Asian survival rates are significantly better. According to Kooby et al (59), the 5- and 10-year survival rates for patients with node-negative disease are 79% and 66%. The survival rate at 5 years for T1 with no positive nodes was 93%; for T2, 84%; and for T3, 52%. According to the National Cancer Data Bank, overall survival for stage IA is 78%; for stage IB, 58%; for stage II, 34%; for stage IIIA, 20%; for stage IIIB, 18%; and for stage IV, 7% over 5 years. Survival for R0 is 35% and increases to 79% if the cancer is node negative (Table 5). The presence of carcinomatosis indicates a survival of <6 months (57, 63, 104).

Many new therapies are being assessed as alternatives to current postoperative treatments. Immunotherapy options such as tumor vaccines and specific tumor protein antibodies are being examined. Photodynamic therapy is still being evaluated, but no completed studies have been reported (1, 60).

Intraperitoneal hyperthermic chemotherapy using mitomycin C is also being used at some centers to treat locally advanced gastric cancer. The effectiveness of intraperitoneal chemotherapy could be due to the high rate of local recurrence in the gastric bed. Surgical intervention may cause tumor spillage at the time of surgery and may further stimulate proliferation by releasing growth factors secondary to the surgical intervention itself. Surgery will stimulate a fibrous reaction that can compromise systemic delivery of chemotherapy and may trap and protect tumor cells from chemotherapeutic exposure (105–110). In this approach, the cancer is debulked as thoroughly as possible, and intraperitoneal hyper-

**Table 5. Five-year survival\***

Node negative  
 T1 93%  
 T2 84%  
 T3 52%  
 R0 79%

Overall survival  
 Stage IA 78%  
 Stage IB 58%  
 Stage II 34%  
 Stage IIIA 20%  
 Stage IIIB 18%  
 Stage IV 7%

\*Data from references 7 and 57.

thermic mitomycin C is circulated in the peritoneal cavity for 2 hours.

The addition of hyperthermia to the residual tumor from 100 to 1000  $\mu\text{m}$  at normothermic temperatures to 3000  $\mu\text{m}$  at hyperthermic temperatures (111–113). These patients then undergo standard postoperative chemotherapy and radiation regimens. In several Japanese, French, and US studies, significant survival and relapse-free improvements have been reported for patients treated with postoperative intraperitoneal mitomycin C and hyperthermia (105, 114, 116–118). Yu et al specifically evaluated 248 patients treated for curative gastric resection with and without intraoperative chemotherapy. They noted a 5-year survival of 54.1% with treatment vs 38.1% with no treatment ( $P = 0.0278$ ) (115, 118).

### CONCLUSION

In summary, distal gastric cancers are decreasing in incidence worldwide, but proximal cancers are becoming more common. The only chance of curing gastric cancer is surgical resection with R0 status. Postoperative chemotherapy and radiation offer some survival benefit, but more successful therapeutic options are needed. Intraperitoneal chemotherapy at the time of surgery may be effective in reducing local recurrence.

The pathophysiology, surgical options, and therapeutic challenges are changing and expanding in breadth and complexity. Continued pursuits hold promise for a better century for successful cures of gastric cancer.

1. Crookes PF. Gastric cancer. *Clin Obstet Gynecol* 2002;45:892–903.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: GLOBOCAN 2000. *Int J Cancer* 2001;94:153–156.
3. Wayman J, Forman D, Griffin SM. Monitoring the changing pattern of esophago-gastric cancer: data from a UK regional cancer registry. *Cancer Causes Control* 2001;12:943–949.
4. Terry MB, Gaudet MM, Gammon MD. The epidemiology of gastric cancer. *Semin Radiat Oncol* 2002;12:111–127.
5. WHO. *WHO World Health Report*. Geneva: World Health Organization, 2002.
6. Allum WH, Griffin SM, Watson A, Colin-Jones D; Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland; British Society of

- Gastroenterology; British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2002;50(Suppl 5):v1-v23.
7. National Cancer Institute. Surveillance, epidemiology, and end results: incidence, stomach cancer. Available at [http://www.seer.cancer.gov/faststats/html/inc\\_stomach.html](http://www.seer.cancer.gov/faststats/html/inc_stomach.html); accessed June 10, 2004.
  8. Kranenbarg EK, van de Velde CJ. Gastric cancer in the elderly. *Eur J Surg Oncol* 1998;24:384-390.
  9. Hohenberger P, Gretschel S. Gastric cancer. *Lancet* 2003;362:305-315.
  10. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984;1:1311-1315.
  11. Miyaji H, Azuma T, Ito S, Abe Y, Gejyo F, Hashimoto N, Sugimoto H, Suto H, Ito Y, Yamazaki Y, Kohli Y, Kuriyama M. *Helicobacter pylori* infection occurs via close contact with infected individuals in early childhood. *J Gastroenterol Hepatol* 2000;15:257-262.
  12. Correa P, Fontham ET, Bravo JC, Bravo LE, Ruiz B, Zarama G, Realpe JL, Malcom GT, Li D, Johnson WD, Mera R. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-*Helicobacter pylori* therapy. *J Natl Cancer Inst* 2000;92:1881-1888.
  13. Forman D, Webb P, Parsonnet J. *H pylori* and gastric cancer. *Lancet* 1994;343:243-244.
  14. Correa P, Malcom G, Schmidt B, Fontham E, Ruiz B, Bravo JC, Bravo LE, Zarama G, Realpe JL. Review article: Antioxidant micronutrients and gastric cancer. *Aliment Pharmacol Ther* 1998;12(Suppl 1):73-82.
  15. Kashiwagi H. Ulcers and gastritis. *Endoscopy* 2003;35:9-14.
  16. Terry P, Lagergren J, Hansen H, Wolk A, Nyren O. Fruit and vegetable consumption in the prevention of oesophageal and cardia cancers. *Eur J Cancer Prev* 2001;10:365-369.
  17. Meining A, Morgner A, Miehke S, Bayerdorffer E, Stolte M. Atrophy-metaplasia-dysplasia-carcinoma sequence in the stomach: a reality or merely an hypothesis? *Best Pract Res Clin Gastroenterol* 2001;15:983-998.
  18. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992;52:6735-6740.
  19. Becker KF, Keller G, Hoefler H. The use of molecular biology in diagnosis and prognosis of gastric cancer. *Surg Oncol* 2000;9:5-11.
  20. Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, Taite H, Scouler R, Miller A, Reeve AE. E-cadherin germline mutations in familial gastric cancer. *Nature* 1998;392:402-405.
  21. Chen HC, Chu RY, Hsu PN, Hsu PI, Lu JY, Lai KH, Tseng HH, Chou NH, Huang MS, Tseng CJ, Hsiao M. Loss of E-cadherin expression correlates with poor differentiation and invasion into adjacent organs in gastric adenocarcinomas. *Cancer Lett* 2003;201:97-106.
  22. Jones EG. Familial gastric cancer. *N Z Med J* 1964;63:287-296.
  23. Caldas C, Carneiro F, Lynch HT, Yokota J, Wiesner GL, Powell SM, Lewis FR, Huntsman DG, Pharoah PD, Jankowski JA, MacLeod P, Vogelsang H, Keller G, Park KG, Richards FM, Maher ER, Gayther SA, Oliveira C, Grehan N, Wight D, Seruca R, Roviello F, Ponder BA, Jackson CE. Familial gastric cancer: overview and guidelines for management. *J Med Genet* 1999;36:873-880.
  24. Handschuh G, Candidus S, Lubert B, Reich U, Schott C, Oswald S, Becke H, Hutzler P, Birchmeier W, Hoefler H, Becker KF. Tumour-associated E-cadherin mutations alter cellular morphology, decrease cellular adhesion and increase cellular motility. *Oncogene* 1999;18:4301-4312.
  25. Kim JH, Takahashi T, Chiba I, Park JG, Birrer MJ, Roh JK, De Lee H, Kim JP, Minna JD, Gazdar AF. Occurrence of p53 gene abnormalities in gastric carcinoma tumors and cell lines. *J Natl Cancer Inst* 1991;83:938-943.
  26. Yamada Y, Yoshida T, Hayashi K, Sekiya T, Yokota J, Hirohashi S, Nakatani K, Nakano H, Sugimura T, Terada M. p53 gene mutations in gastric cancer metastases and in gastric cancer cell lines derived from metastases. *Cancer Res* 1991;51:5800-5805.
  27. Peifer M. Signal transduction. Neither straight nor narrow. *Nature* 1999;400:213-215.
  28. Park WS, Oh RR, Park JY, Lee SH, Shin MS, Kim YS, Kim SY, Lee HK, Kim PJ, Oh ST, Yoo NJ, Lee JY. Frequent somatic mutations of the beta-catenin gene in intestinal-type gastric cancer. *Cancer Res* 1999;59:4257-4260.
  29. Candidus S, Bischoff P, Becker KF, Hoefler H. No evidence for mutations in the alpha- and beta-catenin genes in human gastric and breast carcinomas. *Cancer Res* 1996;56:49-52.
  30. Uchino S, Tsuda H, Noguchi M, Yokota J, Terada M, Saito T, Kobayashi M, Sugimura T, Hirohashi S. Frequent loss of heterozygosity at the DCC locus in gastric cancer. *Cancer Res* 1992;52:3099-3102.
  31. Tahara E. Molecular mechanism of stomach carcinogenesis. *J Cancer Res Clin Oncol* 1993;119:265-272.
  32. Klein RF, Vollmers HP, Muller-Hermelink HK. Different expression of bcl-2 in diffuse and intestinal type stomach carcinomas. *Oncology Reports* 1994;69:943-946.
  33. Ayhan A, Yasui W, Yokozaki H, Seto M, Ueda R, Tahara E. Loss of heterozygosity at the bcl-2 gene locus and expression of bcl-2 in human gastric and colorectal carcinomas. *Jpn J Cancer Res* 1994;85:584-591.
  34. La Vecchia CL, Negri E, Franceschi S, Gentile A. Family history and the risk of stomach and colorectal cancer. *Cancer* 1992;70:50-55.
  35. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at histo-clinical classification. *Acta Pathol Microbiol Scand* 1965;64:31-49.
  36. Dolan K, Sutton R, Walker SJ, Morris AI, Campbell F, Williams EM. New classification of oesophageal and gastric carcinomas derived from changing patterns in epidemiology. *Br J Cancer* 1999;80:834-842.
  37. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991;265:1287-1289.
  38. DeMeester TR. Esophageal carcinoma: current controversies. *Semin Surg Oncol* 1997;13:217-233.
  39. Kocher HM, Linklater K, Patel S, Ellul JP. Epidemiological study of oesophageal and gastric cancer in south-east England. *Br J Surg* 2001;88:1249-1257.
  40. Corley DA, Buffler PA. Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the Cancer Incidence in Five Continents database. *Int J Epidemiol* 2001;30:1415-1425.
  41. Aikou T, Natugoe S, Tenabe G, Baba M, Shimazu H. Lymph drainage originating from the lower esophagus and gastric cardia as measured by radioisotope uptake in the regional lymph nodes following lymphoscintigraphy. *Lymphology* 1987;20:145-151.
  42. de Manzoni G, Pedrazzani C, Di Leo A, Bonfiglio M, Tasselli S, Guglielmi A, Cordiano C. Metastases to the para-aortic lymph nodes in adenocarcinoma of the cardia. *Eur J Surg* 2001;167:413-418.
  43. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophago-gastric junction. *Br J Surg* 1998;85:1457-1459.
  44. Wittekind C, Henson DE, Hutter RVP, Sobin LH. *TNM Supplement: A Commentary on Uniform Use*, 2nd ed. New York: Wiley-Liss, 2001.
  45. Clark GW, Smyrk TC, Burdiles P, Hoefler SE, Peters JH, Kiyabu M, Hinder RA, Bremner CG, DeMeester TR. Is Barrett's metaplasia the source of adenocarcinomas of the cardia? *Arch Surg* 1994;129:609-614.
  46. Moskaluk CA, Ju J, Perlman EJ. Comparative genomic hybridization of esophageal and gastroesophageal adenocarcinomas shows consensus areas of DNA gain and loss. *Genes Chromosomes Cancer* 1998;22:305-311.
  47. van Dekken H, Alers JC, Riegman PH, Rosenberg C, Tilanus HW, Vissers K. Molecular cytogenetic evaluation of gastric cardia adenocarcinoma and precursor lesions. *Am J Pathol* 2001;158:1961-1967.
  48. Walch AK, Zitzelsberger HF, Bruch J, Keller G, Angermeier D, Aubele MM, Mueller J, Stein H, Braselmann H, Siewert JR, Hoefler H, Werner M. Chromosomal imbalances in Barrett's adenocarcinoma and the metaplasia-dysplasia-carcinoma sequence. *Am J Pathol* 2000;156:555-566.
  49. Ottini L, Palli D. Microsatellite instability in gastric cancer is associated with tumor location and family history in a high-risk population from Tuscany. *Cancer Res* 1997;57:4523-4529.
  50. Yamamoto H, Perez-Piteira J, Yoshida T, Terada M, Itoh F, Imai K, Peruchio M. Gastric cancers of the microsatellite mutator phenotype display characteristic genetic and clinical features. *Gastroenterology* 1999;116:1348-1357.
  51. Driessen A, Van Raemdonck D, De Leyn P, Filez L, Peeters M, Winpenning V, Penninx F, Lerut T, Ectors N; H.P. Belgian Contact Group. Are carcinomas of the cardia oesophageal or gastric adenocarcinomas? *Eur J Cancer* 2003;39:2487-2494.
  52. Parsonnet J. The incidence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1995;9(Suppl 2):45-51.
  53. Oliveira FJ, Ferrao H, Furtado E, Batista H, Conceicao L. Early gastric cancer: report of 58 cases. *Gastric Cancer* 1998;1:51-56.

54. Shimoyama S, Yasuda H, Mafune K, Kaminishi M. Indications of a minimized scope of lymphadenectomy for submucosal gastric cancer. *Ann Surg Oncol* 2002;9:625–631.
55. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000;3:219–225.
56. Sano T, Katai H, Sasako M, Maruyama K. The management of early gastric cancer. *Surg Oncol* 2000;9:17–22.
57. Kooby DA, Suriawinata A, Klimstra DS, Brennan MF, Karpeh MS. Biologic predictors of survival in node-negative gastric cancer. *Ann Surg* 2003;237:828–835; discussion 835–837.
58. Wayman J, Hayes N, Raimes SA, Griffin MS. Prescription of proton pump inhibitors before endoscopy. A potential cause of missed diagnosis of early gastric cancers. *Arch Fam Med* 2000;9:385–388.
59. Harris AW, Beveridge I, Dove-Edwin I, Keen J, Silk DBA. Audit of the use of anti-secretory drugs [abstract]. *Gut* 1997;40(Suppl 1):A59.
60. Rubin P. *Clinical Oncology: A Multidisciplinary Approach for Physicians and Students*, 8th ed. New York: WB Saunders, 2001.
61. Whiting JL, Sigurdsson A, Rowlands DC, Hallissey MT, Fielding JW. The long term results of endoscopic surveillance of premalignant gastric lesions. *Gut* 2002;50:378–381.
62. D'Ugo D, Pacelli F, Persiani R, Pende V, Ianni A, Papa V, Battista Doglietto G, Picciocchi A. Impact of the latest TNM classification for gastric cancer: retrospective analysis on 94 D2 gastrectomies. *World J Surg* 2002;26:672–677.
63. Siewert JR, Bottcher K, Stein HJ, Roder JD. Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. *Ann Surg* 1998;228:449–461.
64. Kim JP, Kim YW, Yang HK, Noh DY. Significant prognostic factors by multivariate analysis of 3926 gastric cancer patients. *World J Surg* 1994;18:872–877; discussion 877–878.
65. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, van Elk P, Obertop H, Gouma DJ, Taat CW, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995;345:745–748.
66. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJH. Extended lymph-node dissection for gastric cancer. Dutch Gastric Cancer Group. *N Engl J Med* 1999;340:908–914.
67. *AJCC Cancer Staging Manual*, 6th ed. New York: Springer-Verlag, 2002.
68. Dhar DK, Kubota H, Kinukawa N, Maruyama R, Kyriazanos ID, Ohno S, Nagasue N. Prognostic significance of metastatic lymph node size in patients with gastric cancer. *Br J Surg* 2003;90:1522–1530.
69. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, Sydes M, Fayers P. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999;79:1522–1530.
70. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet* 1996;347:995–999.
71. Dent DM, Madden MV, Price SK. Randomized comparison of R1 and R2 gastrectomy for gastric carcinoma. *Br J Surg* 1988;75:110–112.
72. Schlemper RJ, Dawsey SM, Itabashi M, Iwashita A, Kato Y, Koike M, Lewin KJ, Riddell RH, Shimoda T, Sipponen P, Stolte M, Watanabe H. Differences in diagnostic criteria for esophageal squamous cell carcinoma between Japanese and Western pathologists. *Cancer* 2000;88:996–1006.
73. Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, Dixon MF, Fenoglio-Preiser CM, Flejou JF, Geboes K, Hattori T, Hirota T, Itabashi M, Iwafuchi M, Iwashita A, Kim YI, Kirchner T, Klimpfinger M, Koike M, Lauwers GY, Lewin KJ, Oberhuber G, Offner F, Price AB, Rubio CA, Shimizu M, Shimoda T, Sipponen P, Solcia E, Stolte M, Watanabe H, Yamabe H. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000;47:251–255.
74. Kampschoer GH, Maruyama K, van de Velde CJ, Sasako M, Kinoshita T, Okabayashi K. Computer analysis in making preoperative decisions: a rational approach to lymph node dissection in gastric cancer patients. *Br J Surg* 1989;76:905–908.
75. Bollschweiler E, Boettcher K, Hoelscher AH, Sasako M, Kinoshita T, Maruyama K, Siewert JR. Preoperative assessment of lymph node metastases in patients with gastric cancer: evaluation of the Maruyama computer program. *Br J Surg* 1992;79:156–160.
76. Kitagawa Y, Fujii H, Mukai M, Kubota T, Otani Y, Kitajima M. Radio-guided sentinel node detection for gastric cancer. *Br J Surg* 2002;89:604–608.
77. Ichikura T, Morita D, Uchida T, Okura E, Majima T, Ogawa T, Mochizuki H. Sentinel node concept in gastric carcinoma. *World J Surg* 2002;26:318–322.
78. Hiratsuka M, Miyashiro I, Ishikawa O, Furukawa H, Motomura K, Ohgashi H, Kameyama M, Sasaki Y, Kabuto T, Ishiguro S, Imaoka S, Koyama H. Application of sentinel node biopsy to gastric cancer surgery. *Surgery* 2001;129:335–340.
79. Wolf HM, Eibl MM, Georgi E, Samstag A, Spatz M, Uranus S, Passl R. Long-term decrease of CD4+CD45RA+ T cells and impaired primary immune response after post-traumatic splenectomy. *Br J Haematol* 1999;107:55–56.
80. Stein HJ, Feith M, Siewert JR. Cancer of the esophagogastric junction. *Surg Oncol* 2000;9:35–41.
81. de Manzoni G, Pedrazzani C, Pasini F, Di Leo A, Durante E, Castaldini G, Cordiano C. Results of surgical treatment of adenocarcinoma of the gastric cardia. *Ann Thorac Surg* 2002;73:1035–1040.
82. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Crose N, Gennari L. Total versus subtotal gastrectomy: surgical morbidity and mortality rates in a multicenter Italian randomized trial. The Italian Gastrointestinal Tumor Study Group. *Ann Surg* 1997;226:613–620.
83. Katai H, Sano T, Fukagawa T, Shinohara H, Sasako M. Prospective study of proximal gastrectomy for early gastric cancer in the upper third of the stomach. *Br J Surg* 2003;90:850–853.
84. Steup WH, De Leyn P, Deneffe G, Van Raemdonck D, Coosemans W, Lerut T. Tumors of the esophagogastric junction. Long-term survival in relation to the pattern of lymph node metastasis and a critical analysis of the accuracy or inaccuracy of pTNM classification. *J Thorac Cardiovasc Surg* 1996;111:85–94; discussion 94–95.
85. Ellis FH Jr, Heatley GJ, Krasna MJ, Williamson WA, Balogh K. Esophagogastrectomy for carcinoma of the esophagus and cardia: a comparison of findings and results after standard resection in three consecutive eight-year intervals with improved staging criteria. *J Thorac Cardiovasc Surg* 1997;113:836–846; discussion 846–848.
86. Mariette C, Castel B, Balon JM, Van Seuningen I, Triboulet JP. Extent of oesophageal resection for adenocarcinoma of the esophagogastric junction. *Eur J Surg Oncol* 2003;29:588–593.
87. Bozzetti F, Bonfanti G, Regalia E, Andreola S, Doci R, La Malfa G, Gennari L. How long is a 6 cm margin of resection in the stomach? *Eur J Surg Oncol* 1992;18:481–483.
88. Tomita R, Fujisaki S, Tanjoh K. Pathophysiological studies on the relationship between postgastrectomy syndrome and gastric emptying function at 5 years after pylorus-preserving distal gastrectomy for early gastric cancer. *World J Surg* 2003;27:725–733.
89. Troild H, Kusche J, Vestweber KH, Eypasch E, Maul U. Pouch versus esophagojejunostomy after total gastrectomy: a randomized clinical trial. *World J Surg* 1987;11:699–712.
90. Schwarz A, Buchler M, Usinger K, Rieger H, Glasbrenner B, Friess H, Kunz R, Beger HG. Importance of the duodenal passage and pouch volume after total gastrectomy and reconstruction with the Ulm pouch: prospective randomized clinical study. *World J Surg* 1996;20:60–66; discussion 66–67.
91. Ajani JA, Mansfield PF, Lynch PM, Pisters PW, Feig B, Dumas P, Evans DB, Raijman I, Hargraves K, Curley S, Ota DM. Enhanced staging and all chemotherapy preoperatively in patients with potentially resectable gastric carcinoma. *J Clin Oncol* 1999;17:2403–2411.
92. Ott K, Sandler A, Becker K, Dittler HJ, Helmlinger H, Busch R, Kollmannsberger C, Siewert JR, Fink U. Neoadjuvant chemotherapy with cisplatin, 5-FU, and leucovorin (PLF) in locally advanced gastric cancer: a prospective phase II study. *Gastric Cancer* 2003;6:159–167.
93. Kang Y, Choi D, Im Y. A phase III randomized comparison of neoadjuvant chemotherapy followed by surgery versus surgery for locally advanced stomach cancer. *Proc Am Soc Clin Oncol* 1996;15:215.
94. Songun I, Keizer HJ, Hermans J, Klementsitsch P, de Vries JE, Wils JA, van der Bijl J, van Krieken JH, van de Velde CJ. Chemotherapy for operable gastric cancer: results of the Dutch randomised FAMTX trial. The Dutch Gastric Cancer Group (DGCG). *Eur J Cancer* 1999;35:558–562.

95. Skoropad VY, Berdov BA, Mardynski YS, Titova LN. A prospective, randomized trial of pre-operative and intraoperative radiotherapy versus surgery alone in resectable gastric cancer. *Eur J Surg Oncol* 2000;26:773-779.
96. Zhang ZX, Gu XZ, Yin WB, Huang GJ, Zhang DW, Zhang RG. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC)—report on 370 patients. *Int J Radiat Oncol Biol Phys* 1998;42:929-934.
97. Allum W, Cunningham D, Weeden S. UK NCRI Upper GI Clinical Studies Group. Perioperative chemotherapy in operable gastric and lower oesophageal cancer: randomized controlled trial (the MAGIC Trial). *Proc Am Soc Clin Oncol* 2003;22:A998.
98. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. *Eur J Cancer* 1999;35:1059-1064.
99. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725-730.
100. Peeters KC, van de Velde CJH. Improving treatment outcome for gastric cancer: the role of surgery and adjuvant therapy. *J Clin Oncol* 2003;21(23 Suppl):272s-273s.
101. Sasako M. Principles of surgical treatment for curable gastric cancer. *J Clin Oncol* 2003;21(23 Suppl):274s-275s.
102. Macdonald JS. Chemotherapy in the management of gastric cancer. *J Clin Oncol* 2003;21(23 Suppl):276s-279s.
103. Mari E, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, Cascinu S, Barni S, Labianca R, Torri V. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). *Ann Oncol* 2000;11:837-843.
104. Shiu MH, Perrotti M, Brennan MF. Adenocarcinoma of the stomach: a multivariate analysis of clinical, pathologic and treatment factors. *Hepato-gastroenterology* 1989;36:7-12.
105. Sugarbaker PH. Managing the peritoneal surface component of gastrointestinal cancer. Part 1. Patterns of dissemination and treatment options. *Oncology (Huntingt)* 2004;18:51-59.
106. Sendler A, Dittler HJ, Feussner H, Nekarda H, Bollschweiler E, Fink U, Helmberger H, Hofer H, Siewert JR. Preoperative staging of gastric cancer as precondition for multimodal treatment. *World J Surg* 1995;19:501-508.
107. Hansen E, Wolff N, Knuechel R, Ruschhoff J, Hofstaedter F, Taeger K. Tumor cells in blood shed from the surgical field. *Arch Surg* 1995;130:387-393.
108. Sugarbaker PH, Cunliffe WJ, Belliveau J, de Bruijn EA, Graves T, Mullins RE, Schlag P. Rationale for integrating early postoperative intraperitoneal chemotherapy into the surgical treatment of gastrointestinal cancer. *Semin Oncol* 1989;16(4 Suppl 6):83-97.
109. Fink U, Stein HJ, Schuhmacher C, Wilke HJ. Neoadjuvant chemotherapy for gastric cancer: update. *World J Surg* 1995;19:509-516.
110. Kelsen DP. Adjuvant and neoadjuvant therapy for gastric cancer. *Semin Oncol* 1996;23:379-389.
111. Douglass HO Jr. Gastric cancer: overview of current therapies. *Semin Oncol* 1985;12(3 Suppl 4):57-62.
112. Hagiwara A, Takahashi T, Kojima O, Sawai K, Yamaguchi T. Prophylaxis with carbon-adsorbed mitomycin against peritoneal recurrence of gastric cancer. *Lancet* 1992;339:629-631.
113. Hagiwara A, Takahashi T, Kojima O, Sawai K, Yamaguchi T, Yamane T, Taniguchi H, Kitamura K, Noguchi A, Seiki K, et al. Adjuvant intraperitoneal chemotherapy with carbon-adsorbed mitomycin in patients with gastric cancer: results of a randomized multicenter trial of the Austrian Working Group for Surgical Oncology. *J Clin Oncol* 1998;16:2733-2738.
114. Sugarbaker PH. Managing the peritoneal surface component of gastrointestinal cancer. Part 2. Perioperative intraperitoneal chemotherapy. *Oncology (Huntingt)* 2004;18:207-219; discussion 220-222, 227-228, 230.
115. Yu W. Impact of perioperative intraperitoneal chemotherapy on the treatment of primary gastric cancer. *Surg Oncol Clin N Am* 2003;12:623-634.
116. Ikeguchi M, Kondou A, Oka A, Tsujitani S, Maeta M, Kaibara N. Effects of continuous hyperthermic peritoneal perfusion on prognosis of gastric cancer with serosal invasion. *Eur J Surg* 1995;161:581-586.
117. Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa T. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. *Cancer* 1999;85:529-534.
118. Yu W, Whang I, Chung HY, Averbach A, Sugarbaker PH. Indications for early postoperative intraperitoneal chemotherapy of advanced gastric cancer: results of a prospective randomized trial. *World J Surg* 2001;25:985-990.