6 Diffuse Gastric Cancer

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Diagnosis

History

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Introduction

Today, gastric cancer is still the fourth most common cancer and the second leading cause of cancer-related mortality worldwide (Jemal *et al.* 2004). Over the last few decades, there has been a decline in gastric cancer-related mortality, associated with a declining incidence worldwide and not due to improving cure rates.

Because of the morphologic heterogeneity of gastric carcinomas, many classification systems were designed to cover different aspects of this tumor. Of these, the Laurén classification (Laurén 1965), which is based on epidemiology, morphology and growth pattern, has clinicopathologic importance but no unequivocal prognostic value. The decreasing incidence rate is a result of environmental awareness (e.g. better food preservation) and is mainly observed in the intestinal-type gastric cancer (according to the Laurén classification) and not the diffuse-type gastric cancer. The latter type has shown a relative increase in incidence over the last few decades.

History

The acknowledged known risk factors for developing gastric cancer are summarized in Table 6.1. Initial symptoms are usually vague and non-specific, resulting in dyspeptic complaints sometimes mimicking ulcer disease. Because gastric cancer causes symptoms late in the course of the disease and symptoms respond to antiacid medication, H_2-blocking agents or proton pump inhibitors (PPIs), the diagnosis is usually made at an advanced stage. The lack of screening programs—not cost-effective in Western countries because of the low incidence—also contributes to diagnosis being mostly at an advanced stage. As the disease progresses, the symptoms become more specific: pain in the (epi)gastric region, dysphagia (obstructing proximal tumors), loss of appetite, fatigue, weight loss, vomiting (gastric outlet obstruction), indigestion, heartburn, rectal blood loss (melena), hematemesis, and epigastric/abdominal mass. If the disease has progressed even further with distant metastases, patients can present with an enlarged left supraclavicular nodule or mass (Virchow's nodule), an abdominal mass as a sign of metastasis to the ovaries (Krukenberg tumor) or a periumbilical mass (Sister Mary Joseph nodule), all signs of incurable (stage IV) disease stage. However, discrimination between diffuse- and intestinal-type gastric cancer cannot be made on the basis of history-taking.

Clinical

Annemieke Cats

A meticulous history and physical examination are unlikely to aid the early detection of gastric cancer, as the clinical features are generally vague and non-specific. This means that up to 50% of patients in Western countries are diagnosed with advanced gastric cancer, and less than about 25% present with early-stage gastric cancer. In Asia, and especially in Japan, gastric cancer is detected much earlier: more than 50% of all newly diagnosed gastric cancers are early-stage cancers (Inoue & Tsugame 2005). This difference may be explained by a higher prevalence of gastric cancer, a more liberal use of gastroduodenoscopy, and possibly by the existence of population-based screening programs and better endoscopic techniques.

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Table 6.1 Risk factors for gastric cancer (partly derived from Lynch *et al.* 2005).

Age
Mainly > 60 years

Sex
Male : female = 2 : 1

Sporadic
Chronic atrophic gastritis (CAG)

Hereditary
10% of gastric carcinomas are familial, while only 5% show a classical hereditary etiology

Family history of gastric cancer
Hereditary diffuse gastric cancer (HDGC): associated with CDH1 (E-cadherin) germline mutations in one-third of the families. Mutation carriers have a > 70% lifetime risk of developing diffuse-type gastric cancer; when symptomatic it is lethal in 80% of cases

Other autosomal dominant inherited gastric cancer predisposition syndromes
Hereditary non-polyposis colon cancer syndrome (HNPCC): gastric cancers arise in 11% of HNPCC families and 79% of gastric carcinoma is of the intestinal type
Lynch syndrome: increased risk of gastric cancer in endemic regions (Korea, Japan); not in the West
Peutz–Jeghers syndrome (PJS)
Familial adenomatous polyposis (FAP): gastric cancer occurs in excess in Japanese FAP families, but no increased risk is demonstrated in Western countries
Cowden syndrome
Li–Fraumeni syndrome (LFS): gastric cancers are both intestinal and diffuse type
Blood group type A: conflicting reports in literature concerning the association with gastric cancer

Geographic
More frequent in the far east (e.g. Japan, Korea) and South America

Environmental
Dietary: salted and smoked food (fish, meat); protective are fresh fruit, vegetables and milk
Helicobacter pylori: associated with both types of gastric cancer
Epstein–Barr virus (EBV): association with EBV may in fact be a reflection of epidemiologic factors and/or dietary habits
Tobacco smoking
Alcohol
Stress

Physical examination in relation to spreading

When patients present with gastric cancer, 40% already have liver and lung metastases and about 10% have bone metastases and peritoneal carcinomatosis. A palpable abdominal mass may be felt only after extensive enlargement of the liver, ventral peritoneal implants or the primary tumor.

In the diffuse type of gastric cancer, malignant cells that infiltrate the gastric wall can rapidly spread through the extensive intramural lymphatics and the stomach's rich blood supply, and into the subserosal layers. Although not unique to this type of cancer, this gives rise to a characteristic locoregional spreading pattern. Lateral local extension into the esophagus and duodenum is principally through direct penetration and submucosal lymphatic spread, and this may subsequently give rise to intraluminal obstruction.

Peritoneal carcinomatosis primarily originates from subserosal infiltration with subsequent cell shedding and distant peritoneal attachment, but may also occur without demonstrable histologic serosal involvement as a result of hematogenous spread. It is difficult to detect peritoneal tumor deposits either by physical examination or through currently available imaging techniques such as (endoscopic) ultrasonography and CT scan. However, the presence of ascites suggests such a diagnosis. Small amounts of ascites, however, can easily be missed as well. Peritoneal carcinomatosis often becomes apparent only during surgery or after cytologic evaluation of peroperative washings of the abdominal cavity. As peritoneal carcinomatosis progresses, slow colonic transit with symptoms of constipation develops, and eventually tumor obstruction of small and large bowel segments may occur. Large peritoneal implants beyond the abdominal wall may be palpated during physical examination, and drop metastases in the pouch of Douglas may be encountered during digital pelvic or rectal examination (Blumer's shelf).

Local extension of the primary tumor into adjacent structures may cause several problems. Proximal gastric cancer may directly penetrate the splenic hilum, pancreas, diaphragm, and lateral segment of the left lobe of the liver. Extensive diffuse infiltration into the porta hepatis, or enlarged hepatic hilar or peripancreatic lymph nodes—and to a lesser extent intrahepatic metastases—may cause jaundice. Distal gastric tumors may spread through the gastrocolic ligament and can lead to extraluminal impression or tumor growth into the transverse colon, and thus may cause obstruction or formation of a gastrocolic fistula. Ingrowth may be mistaken for primary transverse colon cancer. Transperitoneal or hematogenous spread in the ovaries is also known as a Krukenberg tumor and typically consists of mucinous, signet-ring carcinoma cells surrounded by non-neoplastic ovarian stroma. These tumors are usually quite bulky, and therefore may give rise to symptoms before the primary tumor has been detected. They often affect both ovaries but a unilateral presentation is possible as well. Besides extensive intramural lymphatics, a widespread locoregional perigastric lymph node system also exists. Clinically manifest metastatic lymph nodes in the left supraclavicular fossa (Virchow's node) and left axilla (Irish's node) are the result of extensive spread through intrathoracic lymph channels. A subcutaneous periumbilical tumor implant, the so-called Sister Mary Joseph's node, probably originates from the lymphatics in the hepatoduodenal ligament that extend into the falciform ligament

alongside the obliterated umbilical vein, although transperitoneal spread has also been described.

Subcutaneous or dermal nodules may occur at other sites on the trunk, and also on the scalp and extremities. They are usually non-tender, firm and sometimes ulcerated. A more cellulite-like lesion that presents as a warm, erythematous, edematous and slightly infiltrating plaque is rare, and preferentially associated with the diffuse type of gastric cancer (Fig. 6.1). Histologic examination reveals signet-ring cells diffusely infiltrating in the dermis, both with and without occlusion of dilated lymphatics by tumor cells (Han *et al.* 2000; Navarro *et al.* 2002). The pleura and pericardium may be involved via abdominal tumor implants penetrating the thorax, the lymphatics and, more rarely, the blood. This may lead to pleural effusion and cardiac tamponade.

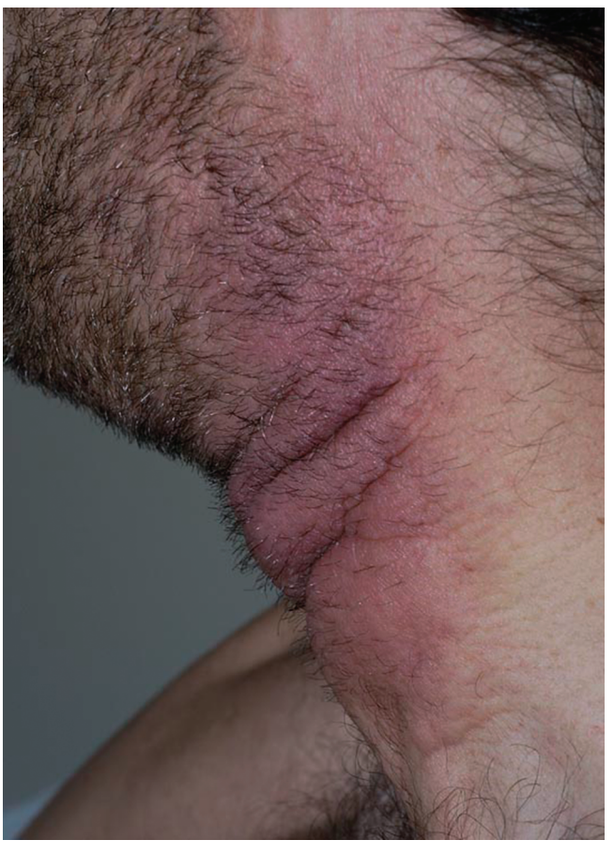
Gastric cancer is occasionally associated with paraneoplastic conditions. Acanthosis nigrans is a patchy velvety dark-brown hyperpigmentation and thickening that usually occurs in intertriginous zones and areas subjected to trauma such as knees and elbows. The Leser–Trélat sign (seborrheic keratoses) may occur in association with acanthosis nigrans in 35% of cases. Thrombophlebitis migrans (Trousseau's syndrome) is a prothrombotic state with poorly understood pathophysiology. It is best managed by anticancer treatment and the administration of low-molecular-weight heparins. Other rare paraneoplastic conditions associated with gastric cancer are membranous nephropathy, microangiopathic hemolytic anemia, dermatomyositis, palmar fasciitis and polyarthritis (flexion contractures of both hands and thickening of palmar fascia), and cerebellar degeneration.

Laboratory investigations

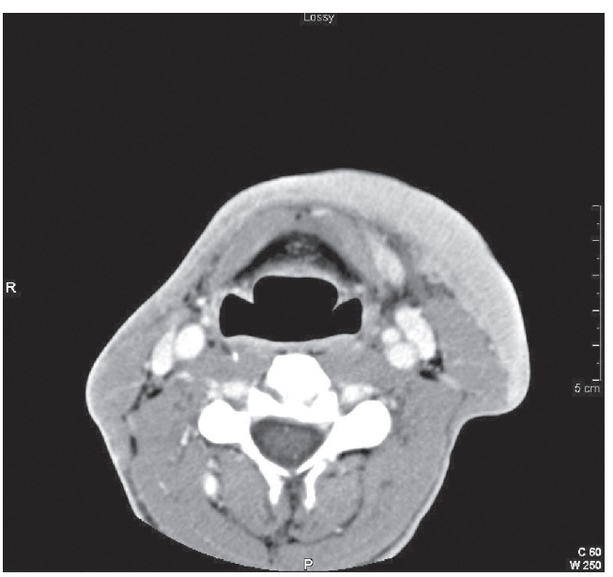
Anemia occurs in 50% of patients with gastric cancer and is usually microcytic, although it can be megaloblastic or mixed. Liver enzymes may be elevated in the presence of liver metastases. Several proteins and carbohydrates have been tested as diagnostic and prognostic markers for cancer. Carcinoembryonic antigen (CEA) is elevated in 15–30% of patients with gastric cancer and tends to indicate disseminated disease or, in the case of poorly differentiated or signet-ring cell carcinoma, massive local infiltration (Horrie *et al.* 1996). Its sensitivity and specificity for advanced disease increases when used in combination with other antigens, such as carbohydrate antigen 19-9 (CA 19-9) and CA 72-4, but it is still too low to merit routine clinical use for (early) detection of gastric cancer.

Endoscopy

The gold standard for the diagnosis of gastric cancer is endoscopy with biopsy specimens from areas suspected of tumor growth. The number of biopsies correlates with its diagnostic yield. In diffuse gastric cancer, however, it is less accurate. Endoscopy is not a suitable instrument for staging. Irrespective



(a)



(b)

Fig. 6.1 A 35-year-old male patient with pT3 N2 diffuse-type gastric cancer. Seven months after total gastrectomy with splenectomy he developed focal erythematous infiltration of the skin in his neck, which cytology showed to contain adenocarcinoma cells (a). As can be seen on the CT scan tumor infiltration was limited to the skin, without evidence of lymph node infiltration (b).

of this, determination of the location of the tumor within the stomach is essential for further surgical or palliative treatment planning.

Gastric cancers can be endoscopically classified according to the macroscopic presentation of their growth pattern. The Japanese classification divides early gastric cancer into three types: protruded (type I), superficial (type II), and excavated (type III). Type II is further subdivided into type IIa (elevated), type IIb (flat), and type IIc (depressed). Diffuse gastric cancers are usually types IIc and III, and account for less than 15% of early gastric cancers. Borrmann's classification for more advanced gastric cancers consists of four types: polypoid (type I), ulceration (type II), ulceration with border infiltration (type III), and diffuse infiltration (type IV). The latter represents about 50% of cases. Its superficial spread through the mucosa and submucosa produces thickening of the mucosal folds that develop into flat, plaque-like lesions with or without shallow ulcerations. When infiltration further progresses and involves the entire stomach, this results in linitis plastica or so-called 'leather bottle' stomach. This situation frequently coincides with retention of food due to decreased gastric peristalsis or gastric outlet obstruction, and is, therefore, often accompanied with endoscopic signs of reflux esophagitis. Further signs are diminished distensibility of the stomach and pain during air insufflation.

Even in early-stage gastric cancer, 5–15% of cancers are multifocal. However, the presence of satellite lesions is often only recognized after histopathologic examination of the resected stomach.

Both the importance of and the technical difficulties with early detection of diffuse gastric cancer are illustrated by the autosomal dominant predisposition to gastric cancer known as hereditary diffuse gastric cancer (HDGC). Patients with HDGC have a germline mutation in the *CDH1* gene, which causes impaired production and function of E-cadherin. This protein belongs to the family of cell–cell adhesion molecules and plays an important role in maintaining the normal architecture of epithelial tissues. Patients with HDGC develop diffuse, poorly differentiated infiltrative adenocarcinomas, often associated with signet-ring cells, at an early age (median age 37 years). A prophylactic total gastrectomy is currently the treatment of choice in patients with established *CDH1* gene mutations. Histopathologic examination of postgastrectomy specimens reveals tens to hundreds of intramucosal foci of malignant cells that cannot be recognized endoscopically (Shaw *et al.* 2005). Therefore, endoscopy does not seem to be a reliable tool for the detection of precursor lesions. Additional techniques such as chromoendoscopy have been tested to overcome this diagnostic shortcoming. Shaw *et al.* (2005) reintroduced a slightly modified chromodye enhanced endoscopy with methylene blue and congo red in 33 *CDH1* gene mutation carriers for whom total gastrectomy was not an acceptable treatment. In 24 of 93 chromoendoscopies 1–6 pale areas of 2–10 mm were detected per stomach. In 41% of biopsies taken from these lesions signet-ring cell carcinoma was detected. In patients subsequently undergoing surgery many more malignant foci were observed, and foci less than 4 mm in particular were missed during endoscopy. The technique may thus facilitate surveillance endoscopy in mutation carriers who decline gastrectomy or in subjects in whom a familial predisposition is suspected, but a genetic defect has not been demonstrated. In conjunction with chromoendoscopy, newly developed magnification and high-resolution endoscopes may offer better imaging. Other diagnostic modalities, such as (auto)fluorescence spectroscopy, narrow-band imaging and confocal endoscopy have also been tested. Their role remains to be established in the near future as well.

Histopathology and molecular pathology

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Several classification systems for gastric cancer have been described, of which the most widely accepted are the classifications by the World Health Organization (WHO) (Table 6.2) and Laurén (Laurén 1965; Hamilton & Aaltonen 2000). Gastric adenocarcinomas can be subdivided into intestinal-type and diffuse-type adenocarcinomas (Laurén 1965). These tumor types differ with respect to epidemiologic and clinicopathologic characteristics as well as the involvement of certain molecular pathways, such as E-cadherin (Carvalho *et al.* 2006).

For the intestinal-type adenocarcinoma a clear sequence of precursor lesions has been described by Correa: long-term *Helicobacter pylori* infection leads to chronic gastritis, mucosal atrophy, intestinal metaplasia, dysplasia, and finally adenocarcinoma (Correa *et al.* 1976). Macroscopically, intestinal-type adenocarcinomas form well-circumscribed tumor masses, sometimes with a central ulcer. The definitive diagnosis,

Table 6.2 World Health Organization classification of epithelial neoplasms of the stomach.

Intraepithelial neoplasia – adenoma
Carcinoma
Adenocarcinoma
Papillary adenocarcinoma
Tubular adenocarcinoma
Mucinous adenocarcinoma
Signet-ring cell carcinoma
Adenosquamous carcinoma
Squamous cell carcinoma
Small cell carcinoma
Undifferentiated carcinoma
Others
Carcinoid

however, should be made on histologic examination. Intestinal-type tumors consist of well-defined ducts or cords, surrounded by newly formed desmoplastic stroma, containing various amounts of a mixed inflammatory infiltrate. The tumor cells are large and have variable sizes and shapes. Nuclei are often hyperchromatic, with coarse chromatin, and mitotic figures are easy to find. Intestinal-type tumors are usually well or moderately differentiated (Fig. 6.2a,b).

In contrast to intestinal-type adenocarcinoma, there is no clear sequence of precursor lesions leading to diffuse-type adenocarcinomas. The only precursor described so far is carcinoma *in situ*. Carneiro *et al.* systematically screened complete prophylactic gastrectomy specimens from subjects with an E-cadherin germline mutation for foci of invasive adenocarcinoma and potential precursor lesions (Carneiro *et al.* 2006). In 7 out of 10 cases they found small foci of signet-ring cells lining foveolae and glands, sometimes forming two layers: an inner layer of benign cells and an outer layer of neoplastic cells. Intestinal metaplasia was found in none of the specimens. Macroscopically, the stomachs of patients with diffuse gastric adenocarcinomas often show a diffuse thickening of the gastric wall due to an extensive stroma reaction surrounding the diffusely invaded tumor cells, leading to a rigid gastric wall. This rigidity, also known as 'linitis plastica', often results in obstruction at the side of the pyloris. Malignant cells may extend submucosally under the normal-appearing mucosa, making it difficult for the clinician or endoscopist to establish the extent of the tumor. This is of clinical importance when making decisions about treatment options. Histologic type according to the Laurén classification is also a prognostic marker. Diffuse-type adenocarcinomas are associated with a significantly worse prognosis compared to the intestinal-type tumors. However, a paper by Kattan *et al.* (2003) weighted several survival-related parameters and showed that the number of positive lymph nodes and depth of invasion are far more important in predicting patient survival (Zhao *et al.* 2005). Diffuse-type tumors, however, are often associated with positive lymph nodes and deeper invasion.

The macroscopic appearances of diffuse adenocarcinomas are reflected microscopically in the typical discohesive growth pattern of this tumor, with solitary or small groups of tumor cells infiltrating the gastric wall. There is extensive formation of new stroma, often to such an extent that it is difficult to recognize the actual tumor cells on a standard H&E section, and the true numbers of tumor cells are only revealed by cytokeratin stains. Glandular formations are absent. Diffuse adenocarcinomas typically exist of cells with relatively uniform size and shape. They have round to oval nuclei with coarse chromatin (Fig. 6.2c). In some cases intracytoplasmic vacuoles can be seen. These mucus-containing vacuoles push the nucleus to the periphery of the cell, giving it a signet-ring appearance (Fig. 6.2d). If a tumor predominantly exists of such signet-ring cells, it should be classified as a signet-ring cell carcinoma (WHO). Although diffuse carcinomas often show less cytonuclear atypia, they should always be graded as poorly differentiated, because of their discohesive growth pattern. In some cases Indian files

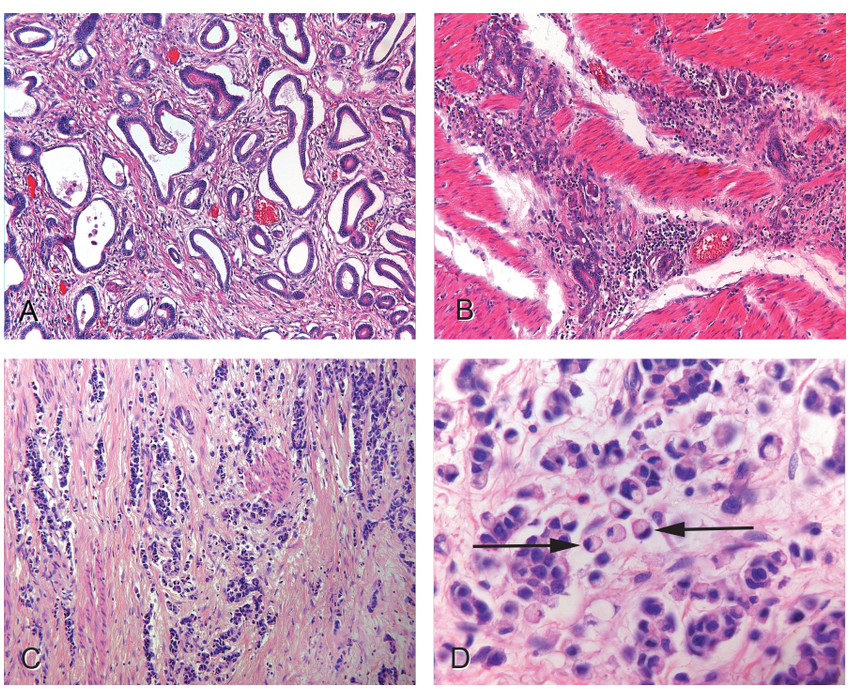

Fig. 6.2 Intestinal-type adenocarcinoma with irregularly shaped glandular structures surrounded by desmoplastic stroma (A). (B) shows the same intestinal-type tumor with neoplastic glands infiltrating the muscularis propria. Diffuse-type adenocarcinomas often show cords and small groups of tumor cells surrounded by extensive fibrosis (C). In some cases signet-ring cells can be detected (D, arrows).

can be seen. This growth pattern can also be seen in lobular carcinoma of the breast, a tumor that shares a particular biologic characteristic with diffuse gastric cancers, i.e. loss of function of the E-cadherin gene.

Histopathologically, gastric adenocarcinoma is usually diagnosed on endoscopically obtained biopsy specimens. Such biopsies are often small, and especially in the case of ulceration and extensive inflammation, it may be difficult to recognise single tumor cells infiltrating the lamina propria. For this reason, additional stainings can be used to detect tumor cells. Epithelial markers give a clear architectural overview, and mucin stains can be helpful in detecting single signet-ring cells that otherwise can be mistaken for histiocytes.

In the case of a mucin-producing tumor outside the stomach, such as in lymph nodes, ovary, mesenterium, omentum or peritoneum, immunohistochemistry may reveal the primary tumor of origin. Markers that are positive in up to 100% of gastric adenocarcinomas (irrespective of tumor type) are epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA). The majority of cases show cytokeratin 7 positivity, while a minority are positive for cytokeratin 20. A subset of cases, however, are positive for both CK7 and CK20. A combination of both these keratin markers may often differentiate between gastric and colorectal cancer, since the latter are usually CK20+ and CK7–. However, with immunohistochemical markers also, 100% specificity cannot be achieved. Loss of membranous E-cadherin expression, a cell–cell adhesion molecule, is seen more commonly but not exclusively in diffuse-type carcinomas as compared to intestinal-type carcinomas (Guilford *et al.* 1998).

Pathologic staging

Whereas preoperative clinical staging is based on physical examination, imaging, endoscopy and/or surgical exploration, pathologic staging is based on macroscopic and microscopic examination of a surgical gastrectomy specimen. For this purpose the most recent edition of the UICC pTNM classification is used (Sobin & Wittekind 2002). This classification includes depth of invasion (T), lymph node status (N) and presence of distant metastases (M).

Primary tumors restricted to the mucosa (lamina propria) or submucosa are T1. Tumors invading the muscularis propria or subserosa are T2a and T2b, respectively. If there is invasion of the visceral peritoneum the tumor is T3, and if adjacent structures are invaded by the tumor it is T4. Adjacent structures include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

Gastric adenocarcinomas primarily metastasize to the paragastric lymph nodes along the lesser and greater curvatures, the lymph nodes along the left gastric, common hepatic, splenic, and celiac arteries, and the hepatoduodenal lymph nodes. If the primary tumor is located at the gastroesophageal junction, regional lymph nodes include the paracardial, left gastric, celiac, diaphragmatic, and lower mediastinal paraesophageal lymph nodes. Lymph node metastases are scored from N0 to N3: N0 means no lymph node involvement, N1 involvement of 1–6 lymph nodes, N2 involvement of 7–15 lymph nodes and N3 involvement of more than 15 lymph nodes. Usually at least 15 lymph nodes can be found in a gastrectomy specimen. However, it should be noted that neoadjuvant therapy may decrease the number of lymph nodes.

The presence of pathologically confirmed distant metastases of the tumor is M1. However, distant metastases cannot usually be determined by the pathologist. In this case, the M stage should be reported as MX. As already mentioned, involvement of the adjacent organs does not influence M stage. On the other hand, metastases in distant intra-abdominal lymph nodes, such as retropancreatic, mesenteric and para-aortic lymph nodes, are classified as M1.

Molecular pathology

Most gastric adenocarcinomas are sporadic, i.e. non-hereditary, while about 10% of gastric cancers show familial clustering. This familial clustering can in part be explained by environmental factors, but germline mutations in several tumor suppressor genes have been associated with hereditary gastric cancer. As one allele is already missing or malfunctioning at birth, secondary loss or hypermethylation of the other allele results in gene silencing in a gastric epithelial cell, leading to cancer early in life. About 30% of hereditary gastric cancers are associated with germline mutations of E-cadherin, and consequently are diffuse gastric cancers. Other known germline mutations include mutation of *p53*, which is part of the Li–Fraumeni syndrome, and mutations of mismatch repair genes like *hMLH1*, *hMSH2*, *hMSH6*, and *hPMS2*. Li–Fraumeni syndrome is characterized by sarcomas of the soft tissues, bone and miscellaneous tumors of juvenile onset, and frequent occurrence of metachronous tumors. Germline mutations of mismatch repair genes are seen in hereditary non-polyposis colorectal cancer (HNPCC/Lynch syndrome). These patients have an increased risk of developing colorectal cancers, endometrial carcinoma, and gastric adenocarcinomas.

Sporadic gastric adenocarcinomas arise through a multistep process, in which accumulation of (epi)genetic changes that affect key biologic processes such as proliferation, apoptosis, cell cycle control, etc. ultimately lead to invasive cancer. For the necessary genetic alterations to be acquired, some form of genomic instability needs to occur. This can be genomic instability at the DNA level, such as failing DNA mismatch repair resulting in microsatellite instability, but most gastric carcinomas show genomic instability at the chromosomal level resulting in coarse genomic changes, like translocations, inversions and gains and losses of complete or parts of chromosome arms. A minority of sporadic gastric carcinomas show microsatellite instability (MSI); in a study by Vauhkonen *et al.* (2005)

MSI was found in 28% of sporadic diffuse gastric cancers. Loss of function of these genes leads to accumulation of mutations. In the following paragraphs some of the known genomic changes that occur frequently in gastric cancer are discussed. Given the enormous amount of reports and the rapid new developments in the field of molecular pathology, we obviously cannot give a complete overview.

E-cadherin (*CDH1*) is a protein involved in cellular adhesion. Loss of function of this gene, results in epithelial cells losing their adhesive properties so that they may easily migrate to and infiltrate other tissues. Germline mutations in this gene, mentioned above, account for 30% of hereditary gastric cancers, leading to diffuse-type carcinomas (Richards *et al.* 1999). Sporadic diffuse-type gastric cancers also show reduced or absent E-cadherin expression in about 50% of cases. In sporadic cases, the gene is silenced by somatic mutation and/or promoter hypermethylation (Guilford *et al.* 1998; Grady *et al.* 2000; Machado *et al.* 2001).

Another gene that is frequently involved in gastric carcinogenesis is *p53*. *p53* plays a critical role in cellular response to DNA damage, leading to cell cycle arrest in G1 or apoptosis. Loss of this gene, or loss of the short arm of chromosome 17 (locus of *p53*), is associated with 50% of gastric cancers of both types (Grieken *et al.* 2000). Accumulation of (mutated) *p53* has been found by immunohistochemical means in about 60% of diffuse-type gastric cancers without E-cadherin alterations (Fricke *et al.* 2003). Intestinal-type carcinomas show p53 expression in up to 60 % (Vollmers *et al.* 1997).

SMAD proteins play a role in signal transduction via the transforming growth factor beta (TGFβ) pathway. This pathway is involved in many cellular functions, including cell growth and differentiation, adhesion, migration, extracellular matrix formation, and immune function. In a series of 88 gastric adenocarcinomas (diffuse type, n = 39; intestinal type, n = 49), expression of *SMAD4* was significantly reduced in the diffuse-type carcinomas as compared to the intestinal-type tumors and gastric adenomas (Kim *et al.* 2005a). Furthermore, *SMAD4* expression has been claimed by some authors to have prognostic significance in advanced gastric carcinomas (without stratification for histologic type) (Xiangming *et al.* 2001).

Mutations of *APC*, known for its association with the development of colorectal adenomas in both familial adenomatous polyposis (FAP) and sporadic adenomas, have also been studied in gastric cancer. Absence of *APC* expression has been seen in up to 80% of gastric adenocarcinomas, independent of tumor type (Grace *et al.* 2002). Previously, only 4% of adenocarcinomas were found to harbor somatic mutations (Lee *et al.* 2002). However, the high frequency of absent expression can now be explained by frequent promoter hypermethylation (Sarbia *et al.* 2004).

About 70% of gastric carcinomas show loss of expression of fragile histidine triad (*FHIT*), more often in difuse-type (82%) than in intestinal-type (66%) carcinomas (Bragantini *et al.* 2006). Although in univariate analysis *FHIT* has been associated with higher clinical stage and poorer survival, multivariate analysis has shown that it is not an independent marker of prognosis (Zhao *et al.* 2005; Bragantini *et al.* 2006).

p16^{INK4A} is a cell-cycle regulatory gene involved in G1–S arrest. Germline mutations of this gene confer susceptibility to melanomas. Downregulation of *p16* by either mutation or loss of heterozygosity has previously been found in a small subset of diffuse-type adenocarcinomas (Gunther *et al.* 1998). However, recently hypermethylation of *p16* has been detected in about 30% of cases, irrespective of histologic type (Vo *et al.* 2002).

Her2/Neu overexpression by gene amplification has proven its clinical importance in breast carcinomas. Recently, in a large series of 131 cases, about 12% of gastric adenocarcinomas showed mutations of c-erbB-2, but in diffuse gastric cancers this was only 2% (Tanner *et al.* 2005). In other studies, however, no correlation between overexpression and histologic type could be detected.

K-ras mutations have been shown to occur not as frequently in gastric carcinomas as compared to colorectal carcinomas (10% vs 40%, respectively). However, it has been reported repeatedly that *K-ras* mutations in gastric cancer are mainly associated with the diffuse-type gastric adenocarcinomas (Kim *et al.* 1997; Arber *et al.* 2000).

Imaging and staging of gastric cancer

Regina G.H. Beets-Tan & Cornelius van de Velde

In patients who have suspected gastric cancer, early detection and accurate preoperative staging are important for determining the most suitable therapy modality. The delineation of tumor extent and local spread will influence the extent of surgery performed. The extent of nodal dissection is a major determining factor in staging and can influence stage-related outcome. Preoperative staging by imaging is necessary to determine the proportion of stomach involved by tumor, to assist in deciding the extent of gastric resection, to identify the presence of locoregional and distant nodal enlargement for determining the extent of lymphadenectomy, and to identify metastatic disease in the liver and peritoneum, including ovarian deposits.

The therapeutic spectrum for gastric cancer has been widely enlarged by both the introduction of preoperative chemotherapy and the possibility of endoscopic resection. Because treatment of gastric cancer is no longer exclusively surgical, precise preoperative staging by imaging has also become more important for selection of patients for different treatment strategies.

Tumor detection

Endoscopic examination is more reliable than double-contrast barium upper GI (UGI) studies in the diagnosis of gastric cancer, for it allows biopsies to be taken. However, for type IV

advanced gastric cancer—the diffuse-type infiltrating adenocarcinoma or scirrhous-type gastric carcinoma—endoscopy has been reported to have a sensitivity of only 33–73% (Levine *et al.* 1990), and UGI studies are known to be superior (Levine *et al.* 1990; Park *et al.* 2004). The main reason for the poor sensitivity of endoscopy is that these tumors are predominantly located in the submucosa, with the overlying mucosa often appearing normal. Therefore, the tumor extent is easily underestimated. On UGI studies, however, the presence of this diffuse-type gastric cancer can be suspected when there is typical loss of gastric distensibility, thickened or irregular folds and/or obliteration of the gastric folds.

Tumor staging

Endoscopic ultrasonography (EUS)

EUS is the most accurate method for evaluation of the depth of tumor ingrowth into the gastric wall. Furthermore, it has been reported that EUS can predict resectability with high sensitivity and specificity (Willis *et al.* 2000). Therefore EUS is valuable for selection of patients with early gastric cancer for local excision or (immediate) surgery.

The high accuracy of EUS for preoperative staging of T1 lesions has been reported in many studies (Botet *et al.* 1991) and was confirmed in a recent publication where the authors found an accuracy of 83% for T1, 60% for T2 and 100% for T3 respectively (Tsendsuren *et al.* 2006). Nevertheless, one must be aware of the relatively high rate of overstaging for the T1 and T2 stages, with 20–25% overstaging failures for T1 and 30% for T2 (Willis *et al.* 2000; Tsendsuren *et al.* 2006). Main reasons for overstaging are thickening of the gastric wall due to peritumoral inflammation and absence of the serosal layer in certain areas of the stomach. A systematic review of 13 EUS studies in gastric cancer showed a very high overall T staging performance, with an area under the receiver operating characteristic curve of 0.93 (Kelly *et al.* 2001). The articles included in this review, which compared EUS with CT, all suggested that the T staging performance of EUS was superior to that of conventional CT. Botet *et al.* for example, found an accuracy for T staging of 92% for EUS versus 42% for CT (Botet *et al.* 1991). Unlike CT, EUS can distinguish five layers within the gastric wall. Invasion of any of these layers by tumor can be more accurately assessed by EUS than by conventional CT.

The downside of EUS however is that, due to its limited range of view, EUS cannot provide information on distant staging.

Computed tomography (CT)

CT is a powerful tool in that it provides local and distant staging in one single examination. Conventional CT techniques, however, have been poor for T-stage determination. Although initial studies found good agreement between T stage as determined by CT and pathology (Balfe *et al.* 1981), many subsequent studies reported disappointing results. One of these studies involving 75 patients reported an accuracy of only 47% for conventional CT, with understaging in 31% and overstaging in 16% (Sussman *et al.* 1988). Recently, an advanced CT technique, multidetector row CT (MDCT), has been used for more accurate staging of gastric cancer (Fig. 6.3). MDCT has been reported to show promising results for T staging, comparable to those of EUS (D'Elia *et al.* 2000; Bhandari *et al.* 2004; Kim *et al.* 2005c). Bhandari *et al.* reported an overall accuracy for MDCT for detection of gastric lesions of 94%, with an accuracy of 97% for the detection of early gastric cancer and of 100% for the detection of advanced tumors. The overall accuracies for EUS and MDCT in the preoperative determination of depth of invasion (T stage) were similar at 88% and 82%, respectively; their sensitivities were 96% and 83%, respectively, and their specificities 69% and 94%, respectively (Bhandari *et al.* 2004). MDCT allows for thinner slices and faster scanning, and enables rapid and easy handling of image reconstruction to generate cross-sectional transverse and multiplanar reformation (MPR) images, which may contribute to the markedly improved results.

Nevertheless, some studies of MDCT have been less positive (D'Elia *et al.* 2000; Fukuya *et al.* 1997). According to Fukuya *et al.* CT with MPR images does not improve T staging (66%). D'Elia *et al.* also reported disappointing results for MDCT, with a far lower accuracy for the detection of early gastric cancer (20%) as compared to that of advanced gastric cancer (87%), and a tendency to overstage T1 tumors as T2 (D'Elia *et al.* 2000).

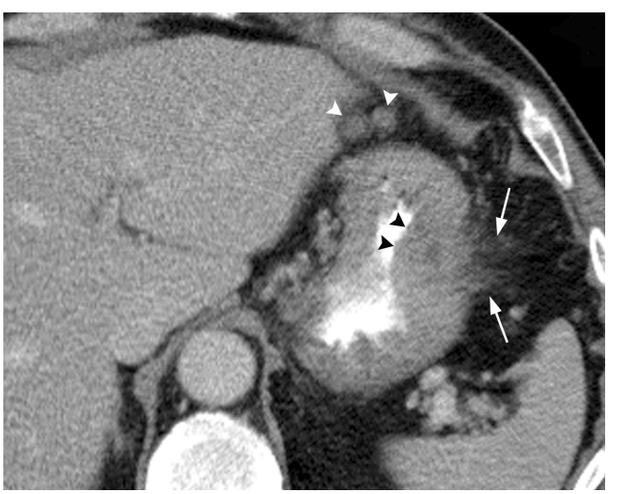

Fig. 6.3 Axial contrast-enhanced CT shows obliteration of the gastric folds and diffuse thickening of the wall of the gastric body (black arrowheads), blurring of the serosal contour, and tissue strands (white arrows) extending into the perigastric fat, due to a T3 gastric cancer. Two 8-mm large nodes are also seen in the perigastric fat, suspected to be involved nodes in compartment I (white arrowheads).

They found that the main causes of overstaging are due to the difficulty in observing the multilayered pattern of the gastric wall in the areas where the gastric wall is thinner (prepylorus) and where the obliquely scanned area (gastric angle) causes confounding partial volume effects.

Clearly there is a need for further improvement of planar imaging methods in the preoperative staging of stomach cancer. To improve tumor staging, exact tumor detection and location is essential. The detection of early gastric cancer in the absence of a thickened gastric wall remains very difficult even with MDCT. MDCT using volumetric data analysis might provide the solution. This so-called 'virtual gastroscopy' technique has been reported in some studies to increase the detection rate of early gastric cancer from 65 to 94% (Kim *et al.* 2005b). This technique, however, is limited to expert single centers and certainly not ready yet for general use.

Positron emission tomography (PET)

PET with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) has been recognized as a useful diagnostic technique in clinical oncology (Rohren *et al.* 2004), but experience of its use in evaluating stomach cancer is limited. FDG PET appears to be very accurate in detecting distant metastatic disease at the time of initial diagnosis, but it may be of limited use in locoregional staging (Kole *et al.* 1998). PET is not helpful in T staging because the FDG uptake can vary according to the histologic type of gastric cancer. Gastric adenocarcinomas, such as mucinous carcinoma, signet ring cell carcinoma and poorly differentiated adenocarcinomas, have been reported to show significantly lower FDG uptake than other histologic types of gastric cancer. PET, however, could play a significant role in monitoring treatment response. Recent reports involving patients with gastric cancer have demonstrated that response to preoperative chemotherapy can be predicted with FDG PET early in the course of therapy (Ott *et al.* 2003). Although further studies are needed to determine its efficacy, it is hoped that response to treatment will be apparent much earlier at PET than at CT, allowing early alteration of management in non-responders.

Nodal staging

The systematic review by Kelly *et al.* shows that EUS is not as effective for lymph node staging as it is for T staging, with an area under the receiver operating characteristic curve of 0.79 (Kelly *et al.* 2001). But a more accurate assessment of nodal disease can be obtained with EUS than with CT. An additional useful role of EUS in gastric nodal staging is the ability to take biopsies of suspected nodes. In the literature the accuracy figures of EUS for the determination of gastric nodal disease range from 66 to 77% (Botet *et al.* 1991; Willis *et al.* 2000; Tsendsuren *et al.* 2006).

N stage determination by EUS is not optimal and there are several reasons for this. Although the EUS criteria for malignant node prediction are very sensitive (size, shape, border, echogenicity and echo texture), they are less specific. Furthermore the para-aortic and celiac regions are often beyond the scope of the endosonography probe; consequently distant node metastases at these locations cannot be detected with EUS.

As already mentioned, alternative methods such as CT do not perform any better. Accuracies previously reported for prediction of gastric nodal metastases with CT have ranged between 51% and 76% (Kim *et al.* 2001). Although the use of MPR and volumetric imaging was expected to improve N staging, the results remained unsatisfactory. Kim *et al.* reported no improvement for nodal staging using these advanced CT tools, with an overall accuracy of only 64% (Kim *et al.* 2005c). These poor results are considered to be due to the lack of reliable CT criteria for metastatic lymph nodes. Regional lymph nodes are considered to be involved when the short-axis diameter is larger than 6 mm for perigastric lymph nodes and larger than 8 mm for extraperigastric lymph nodes (Balfe *et al.* 1981). Although there is a clear correlation between lymph node size and cancer involvement, CT, which is inherently low in contrast resolution, has significant limitations in nodal staging based on size criteria because of the high frequency of microscopic nodal invasion (involvement of normal-size nodes) and the poor differentiation between reactive and metastatic nodal enlargement. The wide ranges of sensitivity (48–91%) in the literature demonstrate this problem of CT in nodal staging (Sussman *et al.* 1988).

MRI with lymph node-specific iron oxide contrast agent has been reported by several investigators to be very effective for the detection of metastatic lymph nodes in various pelvic cancers. So far only one study has confirmed its efficacy in gastric cancer nodes, with 100% sensitivity, 93% specificity, 86% positive predictive value, and 100% negative predictive value (Tatsumi *et al.* 2006). It remains unclear though whether iron oxide MRI will work in gastric cancer because MRI of the gastric area is very susceptible to motion artefacts and because the contrast agent is not yet commercially available.

FDG PET as a metabolic imaging method could theoretically be used to overcome this limitation of anatomic imaging. PET is less sensitive than CT in the detection of locoregional lymph node metastasis mainly due to its poor spatial resolution, which makes it very difficult to distinguish between lymph nodes and the primary tumor (McAteer *et al.* 1999). However, the presence of these regional nodes may not be important in planning surgical extent, since these nodes would be removed at the time of surgery. Detection of nodal metastases distant from the tumor can change the extent of lymph node dissection or may preclude unnecessary surgery. Nodes at distant sites would theoretically be easier to identify at PET because they are remote from the hot spot of the primary tumor. Two recent studies on FDG PET have indeed shown its usefulness in nodal staging of gastric cancer (Yun *et al.* 2005; Kim *et al.* 2006). CT was superior to PET in terms of sensitivity but PET was superior to CT in terms of specificity for staging distant nodes in gastric cancer (Kim

et al. 2006). PET seems to complement CT and vice versa. Therefore the value of combined functional–anatomical techniques such as PET-CT should be further investigated for nodal staging.

Staging for distant metastasis

Hematogenous metastases from gastric cancer most commonly involve the liver. The optimal CT strategy is helical scanning during the portal venous phase of enhancement, because hepatic metastatic lesions are usually hypovascular. This technique improves lesion conspicuity by increasing the attenuation of normal liver tissue. CT staging for liver metastases is superior to abdominal ultrasound staging. Reported sensitivities for the CT detection of lesions larger than 9 mm vary between 64 and 85%, with the best results obtained by the newest-generation helical CT (Bipat *et al.* 2005). CT is therefore the preferred method for detection of liver metastases.

The advantage of helical CT is the 'one-stop shop' imaging evaluation of local and distant tumor spread in one single examination. Diffuse gastric carcinoma in particular tends to spread over the peritoneum with rapid growth and early metastasis. CT allows the determination of the presence of peritoneal metastases (Fig. 6.4) or Krukenberg tumors. Krukenberg tumors are readily detected on CT as often large and bilateral adnexal solid masses with heterogeneous contrast enhancement.

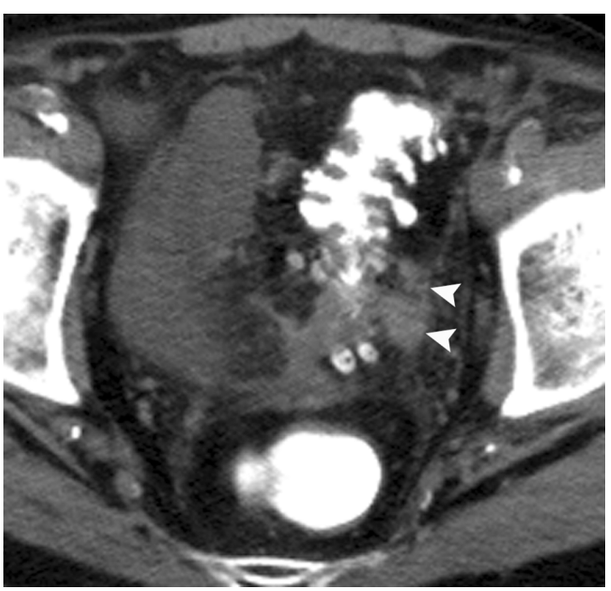

Fig. 6.4 Axial contrast-enhanced CT through the pelvis of a patient with advanced gastric cancer. Nodular deposits are seen on a thickened peritoneal surface (white arrowheads), suspicious of peritoneal metastases. Peritonitis carcinomatosa caused by the stomach cancer was confirmed at laparoscopy.

CT, although superior to all other imaging modalities, is not optimal for the preoperative diagnosis of peritoneal carcinomatosis, because it has a limited sensitivity for the detection of peritoneal nodules smaller than 1 cm, with reported figures ranging between 30 and 50% (D'Elia *et al.* 2000; Coakley *et al.* 2002). The identification of peritoneal metastases on CT strongly depends on factors such as size, location, the presence of ascites, the paucity of intra-abdominal fat and the adequacy of bowel enhancement.

FDG PET has been reported to be more sensitive than CT in the evaluation of peritoneal carcinomatosis. One report showed a sensitivities of 57% for PET, 42% for CT, and 78% for PET plus CT (Turlakow *et al.* 2003). A specific pattern of diffuse FDG uptake has been described to be a strong predictor for peritoneal carcinomatosis (Turlakow *et al.* 2003). However, the utility of PET for detection of peritoneal metastases remains controversial. Small peritoneal nodules may be missed because of the low spatial resolution of PET.

The major advantage of FDG PET in screening for distant metastases and peritoneal metastases is that it helps the CT radiologist to focus on and increase lesion conspicuity. Peritoneal deposits on bowel walls or small metastases in bones, adrenal glands, lungs, and ovaries can be easily overlooked on CT, but when suggested by PET are often detected on CT in retrospect. PET, which has low anatomic resolution but powerful contrast, undoubtedly helps CT, which has powerful anatomic resolution, to improve lesion detection. This valuable role of PET and CT being complementary tools to one another was confirmed by Turlakow's study where the combined use of PET and CT led to a major improvement in the detection rate (Turlakow *et al.* 2003).

Follow-up

CT is the primary tool for the investigation of a suspected recurrence and for evaluation of response to non-surgical treatment of recurrent disease. CT detection of recurrences is usually based on morphologic changes such as wall thickening and focal enhancement. However, treatment-induced bowel wall thickening caused by inflammation or fibrosis cannot be easily distinguished from wall thickening caused by residual tumor. These potential sources of erroneous interpretation are the reasons why it can be very difficult to detect early tumor recurrence on CT. For this reason CT at 3 months following surgery has been recommended as a baseline for further assessment. Equivocal CT findings that are suggestive of tumor recurrence can be further characterized with FDG PET, because tumor tissue shows uptake of FDG while scar tissue lacks uptake. However, PET is limited as a first-line screening tool in the follow-up of recurrent tumors because FDG PET may give false negative results in poorly differentiated gastric adenocarcinoma, and gastric cancer of the signet ring cell and mucinous types. Furthermore, the detection of recurrent gastric cancer

may be difficult with PET imaging alone, because of its lack of adequate spatial resolution (De Potter *et al.* 2002).

Conclusions

CT is the imaging modality of first choice for both the preoperative locoregional and the distant staging of gastric cancer. However, nodal staging remains a difficult issue, even with advanced MDCT techniques.

EUS is the most accurate method for evaluation of the exact depth of tumor growth into the gastric wall and therefore is preferred over CT when early gastric cancer has to be selected for local excision. Nodal staging with EUS, although better than with CT, remains suboptimal.

FDG PET is limited for locoregional staging but complementary to CT for accurate distant staging.

For *follow-up* CT is the modality of choice for the investigation of a suspected recurrence. Where CT findings are equivocal, FDG PET can be of value in distinguishing benign from malignant masses.

Treatment

Overview

Ilfet Songun & Cornelius van de Velde

In the 19th century, gastric cancer was the leading cause of cancer-related death, and many patients died of upper gastrointestinal obstruction. The first pylorus resection in a human being was performed by the French surgeon Péan in 1879 without success. The Polish surgeon Rydygier also operated unsuccessfully in 1880 (Polak & Vojtisek 1959). In 1881, Billroth was the first to perform a successful gastric resection. In fact, as he removed several enlarged lymph nodes, he performed a lymph node dissection as well (Wolfler 1881). The patient died 14 months later of recurrent disease. In 1898 Mikulicz advocated lymph node dissection in addition to gastrectomy, with removal of the tail of the pancreas if necessary (Mikulicz 1898).

After reviewing reports of 298 total gastrectomies, Pack and McNeer (1943) found a postoperative mortality rate of 37.6% and therefore rejected the use of total gastrectomy. From that time on, discussion was ongoing about what type of resection should be performed to achieve the best survival with the least morbidity and postoperative mortality. In a review of articles published in English since 1970, the proportion of patients undergoing resection (resectability rate), was found to increase from 37% in the series ending before 1970 to 48% in those ending before 1990 (Macintyre & Akoh 1991; Akoh & Macintyre 1992). The 5-year survival rate after all resections increased significantly from 21% in the series ending before 1970 to 28% in those ending before 1990, and the 5-year survival rate after curative resection rose from 38% to 55% over the same period (Akoh & Macintyre 1992). Reports from Japanese institutions have shown an even better prognosis: they have demonstrated an improvement in 5-year survival rates exceeding the decline in incidence, resulting in an improved overall cure rate (Kajitani 1981).

Surgery

The mainstay of treatment for both the diffuse and intestinal types of gastric cancer still consists of curative surgery (R0), because it is still at present the only treatment modality that offers the chance of a cure. A curative resection consists of gastrectomy with lymph node dissection. The extent of the gastrectomy (total or subtotal) depends on the extent of the tumor and its location in the stomach. In locally advanced disease with invasion of adjacent organs (T4), such as the colon, spleen, and pancreas, an en-bloc resection of the stomach with the invaded organ should be performed in addition to adequate lymph node dissection if the tumor is resectable. The most important current surgical controversy is the extent of lymphadenectomy (D classification), which the Japanese believe to be the most important explanation for the improved outlook for patients with gastric cancer. In 1997 the D classification was redefined according to the number of lymph nodes dissected, instead of their location.

The outcome of surgery depends on the quality of the resection performed. This means not only carefully selecting patients for surgery, but also performing radical surgery depending on the extent of the disease, because the outcome of inadequate surgery can never be compensated completely by additional radiotherapy and/or chemotherapy. Maruyama *et al.* (1987) have compiled a computer-based database which can be used to identify nodal stations at risk (pre- or peroperatively) to customize lymphadenectomy in order to perform an operation with a low MI (Maruyama Index), which is associated with better outcome. Since there is also substantial heterogeneity of risk within stages, there is also a validated gastric carcinoma nomogram available, which can be used for individual patient counseling and adjuvant therapy decision-making (Peeters *et al.* 2005b).

Surgical prognostic factors

As well as the issue of the extent of lymphadenectomy (D1 versus D2 dissections), other aspects of gastric surgery have generated controversies. These include the type of gastrectomy (subtotal vs total), pancreatectomy and/or splenectomy, patient selection, stage and stage migration, and the experience of the surgeon as a prognostic factor. The extent of the operation, in particular, has an influence on surgical complications and mor-

tality and a number of studies have addressed this topic. In particular, the resection of spleen or pancreas, or both, plays an important role in surgical complications. Most studies find a significant increase in morbidity and hospital mortality if a pancreaticosplenectomy is performed, without any beneficial effect on survival. The spleen should also preferably be spared as this may reduce concomitant morbidity, such as an increase in anastomotic leakage due to division of the vascularization, and immunologic factors associated with resection of the spleen itself and with immune suppression induced by blood transfusions.

Radiotherapy and chemotherapy

Gastric cancer is still mostly diagnosed at an advanced disease stage, except in some countries in the East, e.g. Japan. With surgery being the only curative treatment modality, the need has been felt to increase the number of patients having a curative resection (resectability rate). Screening has proven to be an option in Japan, where the incidence of gastric cancer is high. In Western countries, however, screening is not an option because of the relatively high cost involved because of the low incidence. Even though gastric cancer used to be known as a cancer notoriously resistant to radiation and chemotherapy, various (neo)adjuvant treatment regimens have been studied extensively. The MAGIC trial from the British Medical Research Council compared surgery alone with perioperative chemotherapy consisting of three courses of ECF (epirubicin, cisplatin, and 5-FU) preoperatively and three courses postoperatively in 503 randomized patients in the period between 1994 and 2002. This regimen resulted in downstaging, downsizing and an improved overall survival rate of 13% (Cunningham *et al.* 2006a). The other randomized trial comparing surgery alone with surgery and preoperative chemotherapy, the FAMTX (5-FU, adriamycin and methotrexate) trial from the Netherlands, was closed prematurely due to low accrual rate after 56 patients in the period between 1993 and 1996. There was no significant difference in overall survival rate (Hartgrink *et al.* 2004a). These two studies illustrate the importance of developing effective combination chemotherapy regimens.

Radiotherapy can be applied as palliative treatment for uncontrolled gastric bleeding and for irresectable tumors. In these cases radiation as a single modality did not result in a survival benefit, but locoregional control rates of 70% were reported. Due to the high incidence of locoregional failures after surgical treatment, radiotherapy has always been considered as an attractive modality in curative treatment of these tumors. Radiotherapy can be applied intra-, pre-, or postoperatively (with or without concurrent chemotherapy) using external-beam radiotherapy.

The US Intergroup study (INT 0116) in which 556 patients with completely resected stage IB–IV adenocarcinoma of the stomach or esophagogastric junction were randomized to either postoperative chemoradiotherapy or standard postoperative surveillance only, showed an improvement in overall and relapse-free survival (MacDonald *et al.* 2001). This study changed practise in most of the US. However, the majority of the benefit came from a reduction in the proportion of those with a locoregional relapse. As 54% of trial participants had a D0 dissection and only 10% had a D2 dissection, many have argued that the principal reason for an improvement in the survival was a countering of the effect of an inadequate operation. While the question of whether a D2 dissection is better than a D1 dissection is debated, most agree that a D0 procedure is inadequate. This study is a good example of the importance of interpreting data, before changing practise.

Considering both the MAGIC and the INT 0116 trials, the question that remains to be answered is whether postoperative radiochemotherapy improves survival and/or locoregional control in patients receiving neoadjuvant chemotherapy followed by D1+ gastric resection. Therefore, the so-called CRITICS trial (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) has been launched in the Netherlands. In this trial, quality control will be prospectively applied to standardize treatment and measured using the Maruyama Index of unresected lymph nodes.

Surgery

Ilfet Songun & Cornelius van de Velde

Introduction and background

As previously mentioned, the mainstay of treatment for gastric cancer is still curative surgery (R0). However, there have been changing trends in the treatment for gastric cancer, such as endoscopic mucosal or submucosal resection and minimally invasive surgery because the incidence of early-stage gastric cancer has greatly increased in Japan (Aikou *et al.* 2006). While standard uniform lymphadenectomy (D2) has been well accepted in Japan, in Western countries there is still no evidence that a D2 resection should be the standard. On the other hand, in Japan minimally invasive surgery has become the most common approach in early gastric cancer. The determination of the extent of lymphadenectomy in early gastric cancer has been controversial, because the incidence of micrometastasis in lymph nodes was nearly 20%, even if no lymph node metastasis was detected by routine histologic examination (Aikou *et al.* 2001).

The standard treatment of gastric cancer in the Western world for many years was a total or subtotal gastrectomy, with more or less complete removal of omentum and perigastric

lymph nodes (D1 dissection; see Fig. 6.5). Hospital mortality, most often defined as death within 30 days postoperatively, has decreased over the years. Before the 1970s a median mortality rate of 15% was reported, but in the decade before 1990 this rate had decreased to 4.6% (Macintyre & Akoh 1991). The 5-year survival rate in curative resections also improved from 38% before 1970 to 55% in the decade before 1990 (Macintyre & Akoh 1991; Akoh & Macintyre 1992). A survey by the American College of Surgeons showed a 77.1% resection rate in 18,365 patients, with a postoperative mortality of 7.2%, and a 5-year survival rate of 19%. Only 4.7% of these were D2 dissections (lymph node dissection of the N1 and the N2 tier; see Fig. 6.5). Stage-related 5-year survival was 50% for stage I, 29% for stage II, 13% for stage III, and 3% for stage IV (Wanebo *et al.* 1993). Japanese centers report 5-year overall survival rates above 50%, and above 70% for curative resections with hospital mortality rates of approximately 2% (Soga *et al.* 1979; Akoh & Macintyre 1992; Kinoshita *et al.* 1993). Japanese national stage-related 5-year survival is reported at 96.6% for stage I disease, 72% for stage II, 44.8% for stage III, and 7.7% for stage IV (Kinoshita *et al.* 1993). Differences in surgical techniques may in part be responsible for these better outcomes. In Japan a total gastrectomy in combination with en-bloc resection of adjacent organs, as well as a standard D2, is performed more often than in Western countries. This aggressive approach is thought by the Japanese to be the main explanation for the difference in stage-specific survival (Cuschieri 1989; Bonenkamp *et al.* 1993, 1999). Other factors may also contribute, however, such as the younger age of Japanese patients, the lower rates of systemic (such as cardiovascular) disease and obesity among gastric cancer patients, earlier diagnosis due to screening programs, stage migration, and the more aggressive chemotherapy policy in Japan. In a study by Schlemper *et al.* (1997) it was demonstrated that for high-grade adenoma/dysplasia according to most western pathologists, the Japanese gave the diagnosis of definite carcinoma. Therefore they concluded that this may also contintute to the relatively high incidence and good prognosis of gastric carcinoma in Japan as compoved to western countries (Schlemper *et al.* 1997). In the last decade D2 dissections have become more popular in Western countries as well. Non-randomized gastric cancer studies from Germany, England, Norway, and the United States have reported postoperative mortality of between 4% and 5%, morbidity of between 22% and 30.6%, and 5-year survival between 26.3% and 55% for patients undergoing D2 dissections (Siewert *et al.* 1993; Sue-Ling *et al.* 1993; Arak & Kull 1994; Wanebo *et al.* 1996). The variation in outcomes is substantial, because of the different definitions of D2 dissections in most series. Comparison (usually historical) of outcomes between a limited (D1) and D2 lymph node dissection showed better results for D2 dissection, although morbidity rates seemed to be higher. D2 dissection thus appears to improve survival even in Western countries, but results are still not near those reported by the Japanese.

Curative surgery (in intent)

A curative resection in intent (R0) consists of gastrectomy with lymph node dissection. The extent of the gastrectomy (total or subtotal) depends on the extent of the tumor and its location in the stomach. During resection a proximal tumor-free margin of 5 cm is required, and the perigastric lymph nodes, the N1 tier (D1 resection) should be dissected. In 1997 the D classification was redefined according to the number of lymph nodes dissected, instead of their location (Sobin & Wittekind 1997).

In locally advanced disease with invasion of adjacent organs (T4) such as the colon, spleen, and pancreas, an en-bloc resection of the stomach with the invaded organ should be performed in addition to adequate lymph node dissection if the tumor is resectable.

Based on retrospective data, four randomized studies comparing D1 and D2 dissections have been conducted. The first was by Dent *et al.* (1988), who described a selected group of only 43 patients. In 21 D2 dissections no hospital mortality was seen, but morbidity, hospital stay, and blood transfusion requirements were significantly higher than for those in the D1 dissection group. No difference in survival was noted between the two groups. A randomized study by Robertson *et al.* (1994) in 55 patients was set up to determine the difference in out-

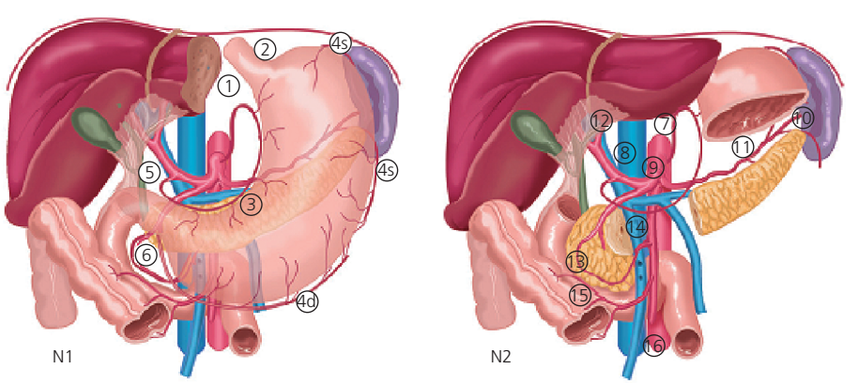

Fig. 6.5 Lymphatic drainage of the stomach (Japanese classification). 1, right cardial nodes; 2, left cardial nodes; 3, nodes along the lesser curvature; 4, nodes along the greater curvature; 5, suprapyloric nodes; 6, infrapyloric nodes; 7, nodes along the left gastric artery; 8, nodes along the common hepatic artery; 9, nodes along the celiac axis; 10, nodes at the splenic hilus; 11, nodes along the splenic artery; 12, nodes in the hepatoduodenal ligament; 13, nodes at the posterior aspect of the pancreas head; 14, nodes at the root of the mesentery; 15, nodes along middle colic vessels; 16, para-aortic nodes. N1, perigastric lymph nodes. N2, extra-perigastric regional lymph nodes.

comes between a D1 subtotal gastrectomy with omentectomy (n = 25) and a D3 total gastric resection including pancreaticosplenectomy (n = 30) in patients with adenocarcinoma of the gastric antrum. Postoperative death occurred only in one patient in the D3 group due to abdominal sepsis. Morbidity was significantly increased in patients undergoing extended resections, as half of the patients who had D3 dissections developed a subphrenic abscess. Survival was significantly better among patients undergoing a D1 dissection compared with those having D3 resection. In both studies no benefit was seen from more extended resections.

In the first large multicenter randomized study from the Netherlands (Dutch Gastric Cancer Trial, DGCT), 80 hospitals participated to compare morbidity, hospital mortality, survival, and cumulative relapse risk after D1 or D2 lymph node dissection for gastric cancer. Between 1989 and 1993, 996 patients were randomized; 711 patients underwent the allocated treatment (D1 or D2 resection defined according to the guidelines of the JRSGC) with curative intent, and 285 patients required palliative treatment. Continuous quality control was implemented to maintain the appropriate level of lymph node dissection. After curative resection, patients in the D2 arm had higher postoperative mortality compared with the D1 arm (10% vs 4%; $p = 0.004$), significantly more complications (43% vs 25%; $p < 0.001$) and significantly prolonged hospital stay. Hemorrhage (5% vs 2%), anastomotic leakage (9% vs 4%), and intraabdominal infection (17% vs 8%) were the most frequent complications (Bonenkamp *et al.* 1993). In the most recent evaluation with a median follow-up of 11 years for all eligible patients (range 6.8 to 13.1 years), survival rates were 30% and 35% for D1 and D2, respectively ($p = 0.53$). The risk of relapse is 70% for D1 and 65% for D2 ($p = 0.43$). When hospital deaths are excluded, survival rates are 32% for D1 (n = 365) and 39% for D2 (n = 299, $p = 0.10$). The relapse risk of these patients (n = 664) is in favor of the D2 dissection group ($p = 0.07$) (Hartgrink *et al.* 2004b).

In a univariate analysis of all 711 patients, no significant impact on survival rates was found for any of the subgroups based on the selected prognostic variables between D1 and D2 dissection. The only subgroup with a trend to benefit is the N2 tumor-positive group. When hospital mortality is excluded, there is a significant survival and relapse advantage for patients with N2 disease who had a D2 dissection ($p = 0.01$). Other stages show no significant difference. Furthermore, there is no difference in survival at 11 years whether fewer than 15 lymph nodes, between 15 and 25 lymph nodes, or more than 25 lymph nodes are harvested.

In the second large prospectively randomized multicenter trial, conducted by the British Medical Research Council (MRC), D1 dissection was compared with D2 dissection. Central randomization to treatment groups followed a staging laparotomy. Out of 737 patients with histologically proven gastric adenocarcinoma registered, 337 patients were judged ineligible by staging laparotomy because of advanced disease and 400 were randomly assigned to treatment (200 to D1 and 200 to D2 dissection). Postoperative mortality (13% vs 6.5%; $p = 0.04$) and postoperative complications were significantly higher in the D2 group (46% vs 28%; $p < 0.001$). In this study anastomotic leakage (26% for D2 vs 11% for D1), cardiac complications (8% for D2 vs 2% for D1), and respiratory complications (8% for D2 vs 5% for D1) were the most frequent complications. The 5-year survival rates were 35% and 33% for D1 and D2, respectively (Cuschieri *et al.* 1999).

These the only two major randomized studies, the MRC trial and the DGCT, obviously show the same tendency. The postoperative mortality and morbidity rates in both trials were significantly higher in the group undergoing D2 dissection, without a 5-year survival advantage for D2 dissections. The conclusion from these randomized studies was that generally no support exists for the standard use of D2 lymph node dissection in patients with gastric cancer in the West. There is also recent evidence from Japan that extending resection (beyond D2) with para-aortic lymph node dissection even in clinically M0 advanced gastric cancer (linitis plastica was excluded in this study) does not further improve survival (Sasako *et al.* 2006). The only study demonstrating a survival benefit from extended lymphadenectomy (D3) has recently been published by Wu *et al.* (2006). In this single-institution study from Taiwan, 221 patients were randomized: 110 were allocated to D1 and 111 to D3 surgery; 215 of them had an R0 resection. With a median follow-up of 94.5 months (range 62.9–135.1), the overall 5-year survival was significantly higher in patients having D3 resection compared with those having D1 resection (59.5% vs 53.6%; $p = 0.041$). At 5 years the recurrence rates were 50.6% for D1 and 40.3% for D1 ($p = 0.197$). They conclude that D3 offers a survival benefit over D1 surgery for patients with gastric cancer when done by well trained, experienced surgeons. This single-institution study reports an absolute overall survival advantage of 5.9%, which is statistically significant. However, it does not mean that this difference is clinically relevant and cannot be generalized. Moreover, there is no logical explanation for the survival advantage, which is not supported by, for example, significantly lower recurrence rates.

The success (outcome) of surgery depends on the quality of the resection performed, mandating surgery 'de necessité' instead of surgery 'de principe'. This means not only carefully selecting patients for surgery, but also performing radical surgery depending on the extent of the disease. Maruyama (1987) has compiled a computer-based database containing the pathologic data from 3040 patients. With the knowledge of tumor size, position, and depth of invasion (judged preoperatively by endoscopy and double-contrast barium meal or by endosonography), the likelihood of lymph node metastasis in each of the 16 lymph node stations can be predicted accurately. The applicability of this program to Western patients is shown by Peeters *et al.* (2005a) in a blinded, retrospective analysis of the DGCT data. Results indicate that low Maruyama Index (MI) surgery is associated with significantly increased survival.

Therefore we advocate using the Maruyama Program, a computerized tool based on patient experience, to identify nodal stations at risk (pre- or intraoperatively) in order to customize surgical lymphadenectomy and routinely generate a low MI operation, because the outcome of inadequate surgery can never be compensated for by additional radiotherapy and/or chemotherapy. Since there is also substantial heterogeneity of risk within stages, there is also a validated gastric carcinoma nomogram available, which can be used for individual patient counseling and adjuvant therapy decision-making. This nomogram provides a better prediction of outcome compared to the AJCC, regardless of the extent of lymphadenectomy (Peeters *et al.* 2005b).

Sentinel node mapping in gastric cancer

The sentinel lymph node (SLN) is defined as the first draining node from the primary lesion and has proven to be a good indicator of the metastatic status of regional lymph nodes in solid tumors. For gastric cancer, the combined method with dye and radio-guided method with lymphoscintigraphy using radioisotope (RI)-labeled colloid is recommended for stable and accurate sampling of SLNs in the laparoscopic setting for early-stage gastric cancer. Using a dual tracer method as the optimal procedure, the radio-guided method allows confirmation of the complete harvest of SLNs by gamma probing, while the dye procedure enables real-time observation of the lymphatic vessels. Clinically staged T1 N0 gastric cancer seems to be appropriate to try a therapy based on SN biopsy. At present, two large-scale prospective multicenter trials are ongoing in Japan. To overcome some remaining issues, such as limited sensitivity of intraoperative diagnosis of metastasis, and technical difficulty in laparoscopic SLN detection, further technical and instrumental developments will be required. The most common cause of a false-negative result from SLN mapping for gastric cancer is an obstructed lymphatic vessel caused by cancer invasion. In these cases, the tracer cannot migrate into the initial SLNs and will escape into the second echelon or false SLNs. Clinically positive node status and advanced tumors should therefore be excluded from SN procedures. Five to 10% of the SLNs in gastric cancer are located in the second compartment without distribution in the perigastric nodes (skip metastases). According to Kitagawa *et al.* (2005), during this transitional phase, focused lymph node dissection targeted to sentinel lymphatic basins and modified resection of the stomach is an acceptable approach.

Palliative surgery

In incurable cases, which usually need to be determined definitely by laparotomy, a palliative resection is indicated whenever the condition of the patient allows this, because resection offers the best palliative results. If there are gastric outlet obstruction symptoms (distal tumors) a gastroenterostomy should be performed; in cases of obstruction due to ingrowth of proximal tumors into the cardia and/or esophagus, palliative radiation therapy or endoscopic stent placement can be considered.

In a fit patient, chemotherapy should be considered: if there is an adequate response with significant tumor reduction, surgery could still be an option and deserves consideration.

Prophylactic surgery

Prophylactic gastrectomy is recommended in patients who are germline CDH1 mutation carriers. In a review Lynch *et al.* (2005) report that all prophylactic gastrectomies revealed multiple intramucosal diffuse gastric cancer, which were not visible at endoscopy. They recommend a total gastrectomy without lymphadenectomy when endoscopy is negative. If the surgical option is not taken, endoscopy with random biopsies every 6 months should be performed, because when diffuse gastric cancers (DGCs) become symptomatic, they will be lethal in 80% and mutation carriers have a greater than 70% chance of developing a clinically detectable DGC.

Chemotherapy

Christopher Jackson, Naureen Starling & David Cunningham

Early clinical trials which demonstrated that gastric cancer is sensitive to chemotherapy have led to research into the best regimen, the timing of chemotherapy with respect to surgery in resectable disease, and combination with radiotherapy, making the management of gastric cancer a model of the multidisciplinary approach.

Chemotherapy versus best supportive care in advanced gastric cancer

Four randomized controlled trials (Glimelius *et al.* 1997) and one meta-analysis (Wagner *et al.* 2006) address the issue of chemotherapy versus best supportive care (BSC) in metastatic gastric cancer. The regimens initially tested were FAMTX (5-fluorouracil [5-FU], adriamycin [doxorubicin], methotrexate), FEMTX (5-FU, epirubicin, methotrexate), and ELF (etoposide, leucovorin, 5-FU).

Median survival was increased in all of the studies in favor of treatment with chemotherapy by 3 to 9 months. Chemotherapy was generally well tolerated, and quality-of-life data reported in one trial favored the chemotherapy group. Response rates to chemotherapy were between 23 and 50%. The most common grade 3/4 side-effects were alopecia, hematological effects, nausea/vomiting (40% with FEMTX), stomatitis and diarrhea. The trial designs were flawed, with early termination or crossover from treatment to BSC arms.

Allowing for the design flaws, significant benefit is seen from the chemotherapy. This shifted the debate from whether chemotherapy is beneficial in the metastatic setting to which chemotherapy is most beneficial.

Selection of the most active regimen in advanced disease

The experimental arms of the chemotherapy versus BSC were adopted as the comparator arms in further trials in advanced disease. The European Organisation for Research and Treatment of Cancer (EORTC) group randomized 399 patients to 5-fluorouracil and cisplatin, ELF or FEMTX (Vanhoefer *et al.* 2000) (Table 6.3). With the broader inclusion criteria associated with a phase III trial compared to early phase trials, the results were disappointing. Progression-free survival was only 3.3 to 4.1 months. Median survival was 6.7 to 7.2 months, and was not significantly different between groups. In their final report the trialists concluded that none of these regimens should be the reference treatment.

In the 1990s the ECF regimen (epirubicin, cisplatin, and continuous intravenous infusion 5-FU) was developed. In phase II evaluation, response rates of 71% were seen, with 12% obtaining a complete response. Median survival was 8.2 months, and toxicity was not notably greater than with other regimens in historical trials. These results were sufficient to warrant direct comparison to other regimens in phase III trials.

In a head-to-head trial, 274 patients were randomized to receive either ECF or FAMTX (Webb *et al.* 1997). ECF outperformed FAMTX with a response rate (RR) of 45% versus 21%, and median survival of 8.9 versus 5.7 months (p = 0.0002).

Table 6.3 Summary of trials in advanced disease.

Author	Regimen	n	RR (%)	TTP (months)	MS (months)	1 year OS (%)	p (for OS)
Glimelius	ELF	31	23	5	8	NR	
et al. (1997)	BSC	30	–	2	5	NR	0.12
Murad *et al.*	FAMTX	30	50	NR	9	40	
(1993)	BSC	10	–	NR	3	0	0.001
Webb *et al.*	ECF	126	45	7.4*	8.9	36	
(1997)	FAMTX	130	21	3.4	5.7	21	
Vanhoefer	FAMTX	133	12	3.3†	6.7	28	
et al. (2000)	ELF	132	9	3.3	7.2	25	
	FUP	134	20	4.1	7.2	27	NS
Thuss-Patience	DF	45	37.8	5.5	9.5	NR	
et al. (2005)	ECF	45	35.6	5.3	9.7	NR	
Moiseyenko	TCF	227	36.7	5.6	9.2	40.2	
et al. (2005)	CF	230	25.4	3.7	8.6	31.6	0.0201
Dank *et al.*	IF	170	31.8	5.0	9.0	–	
(2005)	CF	163	25.8	4.2	8.7	–	
Cunningham	ECF	249	40.7	6.2†	9.9	37.3	
et al. (2006)	EOF	245	42.4	6.5	9.3		
	ECX	241	46.4	6.7	9.9		
	EOX	244	47.9	7.0	11.2	46.8	0.020
Kang *et al.*	XP	160	41	5.6†	10.5	–	0.003‡
(2006)	FP	156	29	5.0	9.3	–	
Al-Batran	FLO	112	34	5.7	–	–	
et al. (2006)	FLP	108	25	3.8	–	–	

* Failure-free survival.

† Progression-free survival.

‡ of non-inferiority for median survival.

A, adriamycin (doxorubicin); BSC, best supportive care; C/P, cisplatin; D/T, docetaxel (Taxotere); E, epirubicin; F/FU, 5-fluorouracil; I, irinotecan; L, leucovorin; MS, median survival; MTX, methotrexate; O, oxaliplatin; OS, overall survival; RR, relative risk; TTP, time to progression; X, Xeloda (capecitabine).

Quality-of-life data and improvement in symptoms all favored ECF. Line complications necessitated removal in 19% of trial patients. Patients in the ECF arm had more alopecia and nausea and vomiting, but less neutropenia and infection. Other toxicities were comparable between groups. In a separate randomized comparison between ECF and MCF, efficacy was similar but quality of life was greater with ECF.

Anthracyclines

In Europe cisplatin with 5-FU (CF) is used as the reference regimen and the value of adding an anthracycline is questioned. Two small trials have examined CF with and without an anthracycline and although each showed no additional benefit in terms of either median or overall survival, these were underpowered and the trends favored the anthracycline-based regimens. The recent Cochrane meta-analysis combined the data from these and one further trial. It concluded that there was a significant benefit in favor of the anthracycline/platinum-containing regimen in the order of an additional 2-month average survival, and that of the available regimens ECF appeared to be the best tolerated.

Taxanes

A randomized phase III trial presented at ASCO 2005 reported a study comparing CF to docetaxel (Taxotere, T) combined with CF (Moiseyenko *et al.* 2005): 457 patients were randomized to either CF or to TCF. Time to progression (TTP) was 5.6 versus 3.7 months favoring TCF ($p = 0.004$); RR was 36.7% compared to 25.4% ($p = 0.01$); median survival was 9.2 versus 8.6 months ($p = 0.02$); and 1-year overall survival was 40.2% compared to 31.6%, all in favor of TCF. However grade 3/4 neutropenia for TCF was 82.3% compared to 56.0%, and the rate of febrile neutropenia was 30 versus 13.5%, which highlights the intense myelotoxicity of this regimen. Taxanes are clearly active and further investigation is under way to identify the best-tolerated regimen.

Irinotecan

Irinotecan is highly active in advanced colorectal cancer, and has been trialled in gastric cancer. In a phase III study presented at the ASCO annual meeting in 2005, 337 patients were randomized to a regimen of either irinotecan, folinic acid and a 22-hour infusion of 5-FU (IF), or to cisplatin and a 5-day continuous infusion of 5-FU (Dank *et al.* 2005). The primary endpoint was TTP, and there was a non-significant trend in favor of the IF regimen (5.0 vs 4.2 months). Grade 3/4 diarrhea was higher in the IF group (21.6% vs 7.2%), but grade 3/4 stomatitis (2.4% vs 16.9%), neutropenia (25% vs 52%), and febrile neutropenia (4.8% vs 10.2%) were all lower in the IF compared to the CF group. This shows that the activity of the regimen is preserved when compared to CF, with a more favorable side-effect profile presenting an alternative regimen in selected patients.

Substitution of agents in the ECF regimen

The incidence of line complications as well as the inconvenience to the patient of protracted infusions of 5-FU have been noted. Additionally, cisplatin is contraindicated in patients with renal dysfunction or with hearing loss, both of which are common in the population affected by gastric cancer. In the REAL-2 trial presented at ASCO 2006 (Cunningham *et al.* 2006b), cisplatin and 5-FU were replaced with either oxaliplatin (O) or capecitabine (Xeloda, X), or both (Fig. 6.6). This trial included patients with advanced/non-resectable esophagogastric cancers.

The study randomized 1002 patients with advanced gastroesophageal cancer (40% with gastric cancer), had a two by two factorial design, and tested for non-inferiority of capecitabine over infusional 5-FU, and of oxaliplatin over cisplatin. Non-inferiority was demonstrated for both these agents, and in the individual arm comparisons 1-year and median survivals were highest for EOX (46.8% and 11.2 months) compared to ECF (37.7% and 9.9 months). Treatment was generally well tolerated in all the arms, with grade 3/4 peripheral neuropathy higher in the oxaliplatin arms and a slight increase in grade 3/4 diarrhea. Thrombotic events were highest in the ECF arm, significantly lower in the oxaliplatin arms, and mainly related to line thromboses. There were no significant differences in quality of life.

A further phase III trial presented at the same meeting randomized 316 chemotherapy-naive patients with advanced gastric cancer to receive either cisplatin and infused 5-FU (FP) or capecitabine with cisplatin (XP) (Kang *et al.* 2006). The study tested for non-inferiority in progression-free survival. With a median progression-free survival of 5.6 months with XP and 5.0 months for FP, non-inferiority was demonstrated. Objective response rates were greater with XP, but 1-year overall survival

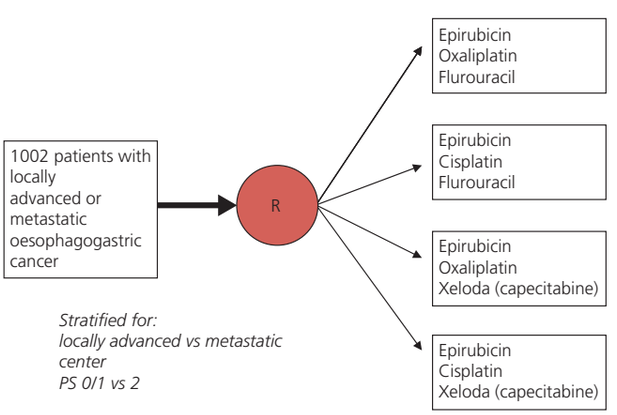

Fig. 6.6 The design of the REAL-2 trial. R, randomization; PS, performance scale/score.

was similar. Toxicities were comparable, with the exception of greater hand–foot syndrome in the XP group (22% vs 4%). Another trial that randomized 220 patients to receive either 5-FU, leucovorin and oxaliplatin (FLO), or 5-FU, leucovorin and cisplatin (FLP) showed a longer but non-significant TTP with FLO than with FLP (5.7 vs 3.8 months; $p = 0.081$) (Al-Batran *et al.* 2006). Other measures of efficacy such as time to treatment failure and response rates favored FLO, and severe toxicities were fewer. These two trials corroborate the findings of the REAL-2 trial.

Summary of advanced disease

ECF is a standard reference regimen in much of Europe, and recent data support the substitution of capecitabine over infused 5-FU. EOX has comparable, if not better, efficacy and is currently used in selected populations. Taxane-based regimens represent another promising area of investigation with superior efficacy compared to CF, another worldwide reference.

Localized disease

Several randomized controlled trials and five meta-analyses have examined the use of adjuvant chemotherapy, few showing a positive effect. In general, the trials are thwarted by small sample sizes, failure to specify a standard surgical technique, inclusion of patients with positive surgical margins, and lack of adequate randomization.

The first meta-analysis which found no benefit of adjuvant chemotherapy included trials with regimens including intraperitoneal chemotherapy, and older regimens such as semustine (MeCCNU), and FAM. The largest trial analysed included 281 patients, but most had under 90 patients in each arm. This analysis points out that to detect an increase in survival from 30% to 40% requires 500 patients in each arm—a hurdle not overcome by any of the included trials. A later meta-analysis found an overall survival benefit of approximately 4% in favor of adjuvant chemotherapy. When they analysed trials where more than two-thirds of the patients included were node positive, they found a non-significant trend towards greater benefit (Earle & Maroun 1999). A further meta-analysis confirmed this benefit, whist a fourth failed to do so.

Intraperitoneal chemotherapy regimens with 5-FU, mitomycin, and cisplatin individually or in combination have been trialled and have had no impact on recurrence, with one trial showing a greater number of postoperative complications.

Two recent trials have informed the current standards for the treatment of localized resectable disease. The first was a US Intergroup study where 556 patients with completely resected stage IB–IV adenocarcinoma of the stomach or esophagogastric junction were randomized to either postoperative chemoradiotherapy or standard postoperative surveillance only (MacDonald *et al.* 2001). The type of surgical procedure or degree of lymph node dissection (D0, D1, or D2) was not specified, although a D2 procedure was recommended (achieved in only 10% of participants).

Patients randomized to chemoradiotherapy had one cycle of 5-FU chemotherapy followed by chemoradiotherapy, then two further cycles of chemotherapy. With a median follow-up period of 5 years, the median survival was 36 months in the chemoradiotherapy group compared to 27 months in the surgery-only group. Relapse-free survival was 30 months versus 19 months respectively ($p < 0.001$), and 3-year overall survival was 50% versus 41% in favor of the adjuvant treatment arm ($p = 0.005$). Toxicity consisted of three (1%) treatment-related deaths, 54% grade 3–4 hematologic toxicity, and grade 3–4 gastrointestinal toxicity in 33%. These results were preserved when the 7-year follow-up was presented in 2004.

This impressive improvement in overall and relapse-free survival changed practice in most of the US, where the pattern of referral is postsurgical. However, the majority of the benefit came from a reduction in the proportion of those with a locoregional relapse. As 54% of trial participants had a D0 dissection, many have argued that the principal reason for an improvement in the survival was a countering of the effect of an inadequate operation. The data on whether a D2 operation is better than a D1 procedure are debated, but most agree that a D0 procedure is inadequate.

Another problem facing surgeons is that gastric cancers are often bulky and have margins that are difficult to clear. For this and other reasons, interest in a neoadjuvant approach has been stimulated. In the 2006 MRC 'MAGIC' trial, 503 patients with resectable adenocarcinoma of the stomach, esophagogastric junction or lower-third esophagus were randomized to either three cycles of preoperative ECF followed by surgery then three postoperative cycles, or to surgery alone (Cunningham *et al.* 2006c).

With a median follow-up of 4 years, the 5-year overall survival was 36.3% for the ECF group versus 23.0% for the surgery-only group ($HR = 0.75$, $p < 0.001$). Local recurrence was also less with chemotherapy (14.4% vs 20.6%) and tumors were smaller in the resected specimens of patients undergoing perioperative chemotherapy. Surgical complications were comparable (45.7% vs 45.3% in the surgery-only group). No patient had a D0 dissection, but a D1 versus D2 procedure was at the discretion of the surgeon.

Of those randomized to receive perioperative chemotherapy 54.8% received postoperative chemotherapy. The reasons for this included disease progression or early death (37 patients), patient choice (11), postoperative complications (10), and Hickman catheter problems (4). Only 5 patients did not complete treatment because of previous toxic effects or lack of response to preoperative treatment.

These results have introduced another standard of care into the UK and other parts of Europe. Subsequent research on this systemic approach has focused on replacing infusional 5-FU with the oral prodrug capecitabine, on substituting cisplatin with oxaliplatin, and incorporating targeted drugs.

The cross-study comparisons between the Intergroup and MAGIC trials are difficult as the patient populations are not comparable. The Intergroup patients were preselected to a degree by virtue of their ability to survive an operation, and the fact that complete resection had to be obtained before randomization into the trial, both factors biasing towards better outcome. MAGIC also contained a small number of patients with esophageal tumors, although their outcomes were similar. A current US Intergroup study is examining the issue of postoperative ECF with radiotherapy versus 5-FU with radiotherapy, but does not include any preoperative arm.

In summary, the pattern of referral essentially determines the type of treatment. When a patient has already received an operation at the time of referral, the US Intergroup study will have greater influence. However the MAGIC study and perioperative chemotherapy has gained greater influence in parts of the world where treatment decisions are made at the time of diagnosis and there is a greater MDT approach to the management of gastric cancer.

Radiotherapy

Edwin P.M. Jansen & Marcel Verheij

Radiotherapy can be applied as palliative treatment for uncontrolled gastric bleeding and for irresectable tumors. In such cases radiation as a single modality did not result in a survival benefit, but locoregional control rates of 70% were reported (Moertel *et al.* 1969; Henning *et al.* 2000a). Because of the high incidence of locoregional failures after surgical treatment, radiotherapy has always been considered as an attractive modality in curative treatment of these tumors (Gunderson & Sosin 1982; Landry *et al.* 1990; Henning *et al.* 2000a; Smalley *et al.* 2002; Jansen *et al.* 2005). Radiotherapy can be applied intraoperatively (intraoperative radiotherapy, IORT) or pre- or postoperatively (with or without concurrent chemotherapy) using external-beam radiotherapy (EBRT).

Intraoperative radiotherapy

In a prospective randomized trial by the National Cancer Institute 41 patients with non-metastatic disease at surgery were randomized to receive 20 Gy to the gastric bed intraoperatively or postoperative 50 Gy in 25 fractions in locally advanced cases (Sindelar *et al.* 1993). Median survival was the same in both groups, but locoregional disease failures were significantly less in the IORT group (44% and 92%, respectively), without a difference in toxicity. Although IORT has shown to favorably affect locoregional control, this technique has not gained wide acceptance in the radiation oncology community. This is most likely due to logistic reasons, an anticipated increased risk of late neurologic sequelae and because other, more conformal external-beam techniques have emerged.

Postoperative radiotherapy

Adjuvant radiotherapy in operable gastric cancer has been evaluated in several studies. In the British Stomach Cancer group study, 436 stage II and III patients were randomized to receive surgery only, surgery followed by 45–50-Gy radiotherapy or surgery plus eight courses of FAM (5-fluorouracil, adriamycin and mitomycin C) chemotherapy (Allum *et al.* 1989; Hallissey *et al.* 1994). Only 58% of patients in the chemotherapy group completed the recommended eight cycles, while 24% of patients failed to start radiotherapy. This phenomenon of noncompliance is frequently encountered after surgery of the upper abdomen and stresses the importance of less toxic adjuvant strategies, careful patient selection, and intensive clinical support. The differences in 5-year survival were statistically non-significant in the three arms, with 20% for surgery alone, 12% for surgery plus radiotherapy, and 19% for surgery plus chemotherapy. The EORTC randomized 115 patients after surgery into four arms: 55.5-Gy radiotherapy only; radiotherapy with short-term concurrent 5-FU chemotherapy; radiotherapy with long-term (1–18 months postoperatively) 5-FU; and combined short- and long-term chemotherapy (Bleiberg *et al.* 1989). After correction for prognostic factors such as T stage, age, and type of surgery, no differences between the four arms were found. In a retrospective study from Thomas Jefferson University, 70 patients were treated with surgery alone, while 50 had adjuvant therapy (chemotherapy in 17, radiotherapy in 13, both in 20). Patients with T3–4 N1–2 stage disease had a 5-year survival of 4% with surgery alone and 22% with adjuvant therapy ($p < 0.03$). In the surgery-alone group 45% developed a locoregional relapse, while this was only 19% after adjuvant chemotherapy and radiotherapy (Regine & Mohiuddin 1992). In summary, although postoperative radiotherapy seems to have a modest favorable impact on locoregional control, a survival benefit only appears achievable when concurrent chemotherapy is added.

Preoperative radiotherapy

Theoretically, preoperative radiotherapy is an interesting concept because: (i) no patients are lost to protracted postoperative recovery; (ii) the target volume is much easier to delineate because the tumor and stomach are still *in situ*; and (iii) tumor downsizing facilitates surgery. A disadvantage is that no pretreatment pathologic staging is available. However, since the majority of gastric cancer cases in the Western world present at advanced stages, overtreatment will occur in a minority, especially as pretreatment staging with modern CT scanning and endoscopic ultrasound is used. In Russia two trials have been performed since the 1970s in which 152 patients were randomized between surgery alone, or 20-Gy radiotherapy (5 fractions) using a cobalt source in the week before surgery, or the same regimen combined with radiosensitizing metronidazole (Skoropad *et al.* 2002, 2003). In the evaluable patients,

5-year overall survival was 39% after radiotherapy and surgery and 30% after surgery alone, which was not statistically significant. In the metronidazole arm 5-year overall survival was 46%. No increase in postoperative complications was found, but total radiation doses were rather modest. In China a large prospective trial was performed which randomized 370 patients between surgery only and surgery with preoperative 40-Gy radiotherapy (20 fractions in 4 weeks) (Zhang *et al.* 1998). Five-year overall survival was 19.8% with surgery only, and 30.1% with preoperative radiotherapy ($p < 0.01$). Resectability (79.4 vs 89.5%) and radical resection rates (61.8 vs 80.1%) also increased after preoperative radiotherapy. Perioperative mortality and anastomotic leakage rates were not significantly different between both arms. While this study demonstrates an advantage of this neoadjuvant strategy, a confirmatory study is unlikely to be conducted, because all efforts are currently directed towards perioperative chemotherapy and chemoradiotherapy (see below).

Postoperative chemoradiotherapy

Since the 1960s reports of randomized studies comparing surgery with surgery plus 5-FU-based chemoradiotherapy have appeared. The Gastrointestinal Tumor Study Group (GITSG) and Eastern Cooperative Oncology Group (ECOG) were among the first to randomize patients with residual or unresectable gastric cancer between chemotherapy and 5-FU-based chemoradiotherapy (GITSG 1982; Klaassen *et al.* 1985). Both studies showed no clear survival advantage but an increase in toxicity with chemoradiotherapy. These studies demonstrate the feasibility of concurrent chemoradiotherapy, but lack homogeneous treatment schedules and sufficient patient numbers (Dent *et al.* 1979; Moertel *et al.* 1984). A retrospective study from the Mayo Clinic showed that after 50.4-Gy radiotherapy combined with 5-FU, survival and locoregional control were greater in patients without residual disease (Henning *et al.* 2000b). In another study from Italy, postoperative 55-Gy radiation in 50 fractions of 1.1 Gy twice a day with continuous 5-FU infusion resulted in 36% 5-year overall survival and 43% cause-specific survival (Arcangeli *et al.* 2002). In 2001 the landmark SWOG/Intergroup 0116 trial was published, in which 556 patients were prospectively randomized between surgery only and surgery plus postoperative chemoradiotherapy (Macdonald *et al.* 2001). The adjuvant treatment consisted of 5-FU (425 mg/m^2) and leucovorin (20 mg/m^2) for 5 days, followed by 45 Gy of radiation at 1.8 Gy per day, given 5 days per week for 5 weeks, with modified doses of 5-FU and leucovorin on the first 4 and the last 3 days of radiotherapy. One month after the completion of radiotherapy, two 5-day cycles of 5-FU (425 mg/m^2) plus leucovorin (20 mg/m^2) were given 1 month apart. Although there was significant acute toxicity observed in the chemoradiotherapy arm (41% grade III; 4% grade IV), median overall survival was 27 months in the surgery-only group and 36 months after chemoradiotherapy ($p = 0.005$). Furthermore, relapse-free survival was prolonged from 19 months in the surgery-only arm to 30 months in the chemoradiotherapy arm ($p < 0.001$). Since the publication of these results, postoperative chemoradiotherapy has become standard treatment in the US. Nevertheless, many have criticized this study, mainly focusing on the suboptimal surgery. Indeed, 54% of all patients underwent a D0, instead of the prescribed D2 lymph node dissection, which could be a factor in undermining survival (Hundahl *et al.* 2002). However, an observational study from Korea showed that 544 patients who received chemoradiotherapy after a D2 resection had a 5-year overall survival of 57.1%, compared to 51.0% ($p = 0.02$) in 446 patients who did not receive adjuvant chemoradiotherapy. Locoregional failure rates in the radiation field were 14.9% and 21.7% respectively ($p = 0.005$) (Kim *et al.* 2005d). No details on late toxicity of combined treatment have been provided yet. Nevertheless, late progressive renal toxicity after chemoradiotherapy for gastric cancer with the use of common straightforward radiation techniques has been described. It can also be demonstrated that modern, sophisticated image-guided or intensity-modulated radiotherapy (IGRT/IMRT) techniques are able to spare the kidneys and prevent renal damage (Fig. 6.7) (Jansen *et al.* 2006; Verheij *et al.* 2006). However, a retrospective study from the Princess Margaret hospital showed that even with 5-field three-dimensional conformal radiotherapy and concurrent chemotherapy according to the Intergroup 0116 study, grade III or greater acute toxicity occurred in 57% of their patients. It is suggested that when individualized target volumes are defined, based on T and N stage and tumor location in the stomach, treatment volumes can be reduced and normal tissue toxicity minimized (Tepper & Gunderson 2002).

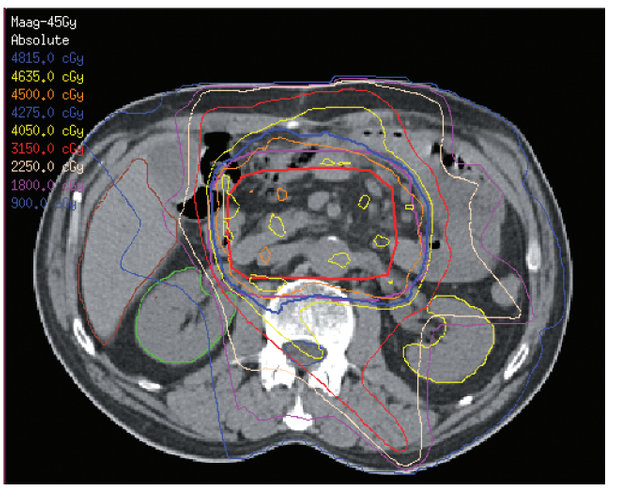

Fig. 6.7 Typical dose distribution of an intensity-modulated radiotherapy (IMRT) treatment plan in postoperative chemoradiotherapy for gastric cancer. It is clearly visible that IMRT is able to spare both kidneys. Green, right kidney; yellow, left kidney; purple, the planned target volume (PTV); blue, 95% isodose.

The Intergroup study was initiated at the beginning of the 1990s, when the concept of concurrent chemoradiotherapy was not yet widely accepted. Nowadays, regimens in which patients are exposed to radiation and radiosensitizing chemotherapy (cisplatin) on a daily and thus prolonged basis seem to have a beneficial effect. Paclitaxel is also reported to have favorable radiosensitizing properties, and when given concurrently with 45-Gy radiotherapy in inoperable gastric cancer, resulted in an overall response of 56% and complete resection rate of 40% (Safran *et al.* 2000). Postoperative chemoradiation has improved locoregional control, but the high incidence of systemic failures highlights the need for more effective systemic treatment. Studies that combine chemoradiation with epirubicin and paclitaxel-based chemotherapy show that these regimens are feasible, but effects on survival have to be awaited (Leong *et al.* 2003; Kollmannsberger *et al.* 2005). In conclusion, for the first time in the history of gastric cancer treatment, a survival benefit was demonstrated with adjuvant therapy in a prospective randomized trial. Although there are issues such as optimization of radiotherapy and chemotherapy and the value of chemoradiotherapy after an extended lymph node dissection that have to be resolved, postoperative chemoradiotherapy is a very promising concept that deserves further study.

Preoperative chemoradiotherapy

Since preoperative combined chemoradiotherapy has been shown to have a beneficial effect on surgical outcome in esophageal and rectal cancer, this is an attractive approach to explore in operable gastric cancer as well. The MD Anderson Cancer Center has reported a study in which 33 patients completed a preoperative regimen that started with two series of continuous infusion of 5-FU for 21 days, followed by 45-Gy radiotherapy in 25 fractions during 5 weeks which was combined on radiation days with continuous intravenous 5-FU (Ajani *et al.* 2004). In 28 (85%) of the patients a gastrectomy was performed and a D2 lymph node dissection was attempted. The median number of removed nodes was 16. Resection of spleen or other organs was performed only in cases of tumor invasion. Pathologic complete and partial response (pathCR; pathPR) was found in 54% of all operated patients. These patients showed a significant longer median survival of 64 months in comparison with 13 months in patients who did not reach pathCR or PR. In a study from the same center 41 patients with operable gastric cancer received two cycles of continuous 5-FU, paclitaxel and cisplatin followed by 45-Gy radiotherapy with concurrent 5-FU and paclitaxel (Ajani *et al.* 2005). An R0 resection was achieved in 78% of patients; pathCR and pathPR were found in 20% and 15% respectively. Median overall survival was more than 36 months. Pathologic response, R0 resection and postoperative T and N stage were correlated with overall and disease-free survival. In a Swiss study also, promising results with preoperative cisplatin and 5-FU-based chemoradiotherapy and hyperfractionated radiotherapy in doses of 31.2–45.6 Gy were found (Allal *et al.* 2005). Five-year locoregional control and overall survival were 85% and 35%, respectively. Thus, preoperative chemoradiotherapy theoretically combines the proven benefit of chemoradiotherapy with the advantages of a neoadjuvant approach, and therefore deserves further exploration in clinical trials.

Future developments

Further improvements in the treatment of gastric cancer are expected from technologic advances in radiotherapy allowing high-dose and high-precision irradiation, and from more effective systemic treatment, including novel biologic response modifiers. By applying several beams from different angles, each consisting of multiple smaller segments (IMRT), even complicated treatment volumes like the stomach and adjacent nodal areas can be irradiated with high precision. Consequently, this also allows delivery of the higher radiation doses necessary to obtain locoregional control of this relatively radioresistant tumor type, without an increase in normal tissue complications. In addition, better imaging techniques used both before and also during treatment (IGRT) contribute to improved tumor/target delineation and smaller treatment volumes.

More effective chemotherapy can be given sequentially or concurrently with radiation. In the latter setting the chemotherapeutic agents are used as radiosensitizers, mainly enhancing the locoregional cytotoxic effect of radiotherapy. 5-FU (and its oral derivative capecitabine) and cisplatin are well known potent radiosensitizers used in the treatment of a variety of gastrointestinal malignancies. Newer-generation cytotoxic agents such as oxaliplatin, irinotecan and the taxanes show also promising activity, and are combined with radiation on a limited scale (Safran *et al.* 2000; Ilson & Minsky 2003; Ajani *et al.* 2005). Recently, a variety of novel biologic agents with specific modes of action have become available for clinical use, including monoclonal antibodies, angiogenesis inhibitors and tyrosine kinase inhibitors. It is expected that these molecularly targeted agents will be incorporated into (neo)adjuvant treatment strategies for gastric cancer as well. In fact, accumulating data indicate that the anti-EGFR monoclonal antibody cetuximab can be safely combined with concurrent chemoradiation in gastric and esophageal cancer (Suntharalingam *et al.* 2006).

Novel agents

Annemieke Cats

Advances in combination chemotherapy have led to improved survival in patients with advanced gastric cancer. However, survival is still poor, with median progression-free survival and overall survival not exceeding 7 months and 11 months, respectively, in phase III studies. Therefore, new treatment strategies

with better outcomes, but without increased toxicity, are urgently required.

Over the last decade, major advances in molecular biology technology have identified many signal transduction pathways that regulate cellular processes essential for cell growth, proliferation, differentiation, migration, and apoptosis. Biologically based or targeted therapy aims to disrupt critical components in signal transduction networks unique to cancer cells and simultaneously leave normal cells unharmed, thus avoiding the toxic effects common with conventional chemotherapy and radiotherapy.

Such novel targeted agents have recently become available and their exploitation in clinical trials has now become a reality. While clinical data in gastric cancer patients are still limited, an overview will be given here focusing mainly on the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) pathways.

Epidermal growth factor receptor inhibitors

EGFR is a receptor tyrosine kinase of the erbB family that is abnormally activated in many epithelial tumors, including gastric cancer. This aberrant activation of EGFR occurs through its natural ligands and leads to homo- or heterodimerization of the receptor. As a consequence, the intracellular tyrosine kinase domain is autophosphorylated, and signal transduction cascades are initiated, leading to enhanced proliferation, cell motility and angiogenesis, and reduced apoptosis. EGFR levels have been found to be elevated in gastric carcinomas relative to adjacent mucosa. Such elevated EGFR levels have been found especially in more invasive T3–4 carcinomas, lymph node-positive tumors, and undifferentiated and diffuse-type carcinomas, and have been associated with poor prognosis (Kopp *et al.* 2002). Two classes of EGFR inhibitors exist: monoclonal antibodies (mAbs) that are directed at the extracellular receptor domain, and small molecules that compete with adenosine triphosphate binding to the intracellular tyrosine kinase domain of the receptor.

Monoclonal antibodies directed at the EGFR

Trastuzumab (Herceptin), a humanized mAb directed at the erbB2/HER-neu receptor, was the first anti-EGFR agent approved for use in solid tumors, i.e. breast cancer. Its use in gastric cancer has been discouraged because of an extremely low erbB2/HER-neu expression in distal gastric cancer.

Cetuximab (Erbitux) is a chimeric IgG2 mAb directed at erbB1/EGFR, and has been approved for the treatment of metastasized colorectal cancer. Cetuximab has been demonstrated to act in synergy with irinotecan, cisplatin, oxaliplatin and taxanes, which are all cytotoxic drugs with confirmed activity in advanced gastric cancer. Preliminary results in 25 patients with EGFR-positive, advanced gastric cancer have shown an objective response of 56% after treatment with weekly cetuximab in combination with biweekly irinotecan, 5-FU, and folinic acid (Pinto *et al.* 2006). In a small feasibility study, heavily pretreated metastasized gastric cancer patients received weekly cetuximab and irinotecan, and an impressive 5 out of 13 patients (38%) showed a partial response (Stein *et al.* 2007). These results should, of course, be confirmed in larger, randomized phase II and phase III studies. Cetuximab has demonstrated encouraging efficacy as a radiation sensitizer in esophageal cancer as well. In these studies gastric cancer patients were treated too, but their numbers were too small to draw any conclusion.

Another humanized EGFR mAb, matuzumab (EMD 72000), has been tested as first-line treatment in combination with fixed doses of epirubicine, cisplatin and capecitabine in 17 patients with EGFR-positive and advanced esophagogastric cancer (Rao *et al.* 2005). In this ongoing phase I study, the preliminary efficacy data are promising, with 7 partial responses.

Small molecule tyrosine kinase inhibitors

The number of agents of this class under development is rapidly increasing. They are differentiated mainly on their ability and potency in binding to and inhibiting the various erbB and other tyrosine kinase receptors. Probably due to their success in the treatment of patients with non-small-cell lung cancer (NSCLC), gefitinib (Iressa) and erlotinib (Tarceva) are the most extensively studied compounds in gastric cancer treatment as well.

In a randomized multicenter phase II study, gefitinib 250 mg/day or 500 mg/day was administered orally in 75 Japanese and non-Japanese patients with metastasized adenocarcinoma of the stomach (n = 54) and esophagogastric junction (n = 15). Patients were stratified according to ethnicity, and all patients had received prior chemotherapy. The preliminary safety and efficacy results showed good tolerability (grade 3/4 toxicity: rash 5.4%, diarrhea 4.1%, and anorexia 2.7%), but unfortunately only modest clinical activity (1 partial response and 12 stable disease) (Doi *et al.* 2003). In a pharmacodynamic side study, the biologic activity of gefitinib was investigated in available gastric tumor biopsy samples obtained at baseline and during therapy (Rojo *et al.* 2006). EGFR was detected in about 60% of baseline samples, and the degree of EGFR inhibition, measured as the amount of phosphorylated EGFR (pEGFR), was almost complete in these tumors during gefitinib treatment. However, reduction of pEGFR was not accompanied by abolition of the downstream signalling pathways, such as the mitogen-activated protein kinase (MAPK) and phosphatidyl-inositol-3-kinase (PI3K)/Akt survival pathways, although a subpopulation may benefit from EGFR inhibition as demonstrated by a decrease in proliferation and increase of apoptosis in some tumors. No differences in outcomes were detected according to ethnicity and efficacy parameters.

In a second multicenter phase II study, patients without prior chemotherapy for advanced or metastasized adenocarcinoma of the esophagogastric junction (n = 47) or stomach (n = 25) received 150 mg/day erlotinib orally as monotherapy

(Dragovich *et al.* 2006). Four patients in the esophagogastric junction cohort experienced a confirmed objective response (1 complete response, 3 PR), and although baseline characteristics were similar in the gastric cancer patients, none of these patients perceived any clinical benefit. Moreover, four of the gastric cancer patients discontinued erlotinib treatment because of toxicity or death (one each of anemia, fatigue, CNS hemorrhage, hepatic failure). Median overall survival was 6.7 months in the esophagogastric junction cohort and 3.5 months in the gastric cancer group.

Recently, somatic EGFR mutations in the region encoding for the tyrosine kinase domain (exons 18–21) and also EGFR amplification have been linked to responsiveness to monotherapy gefitinib and erlotinib in NSCLC. The fact that no such mutations and EGFR amplification have been detected in gastric cancer (Dragovich *et al.* 2006) may explain the disappointing results in the above-mentioned studies.

Angiogenesis inhibitors

The vascular endothelial growth factor (VEGF) pathway plays a critical role in the process of new blood vessel formation under normal and pathologic conditions, such as tumor growth and dissemination. Activation of the VEGF family of proteins and receptors triggers multiple signaling networks that result in endothelial cell survival, proliferation, invasion, migration, and vessel permeability. Overexpression of VEGF in gastric cancer has been associated with tumor progression, relapse following resection and poor clinical outcome (Maeda *et al.* 1996; Takahashi *et al.* 1996; Yoshikawa *et al.* 2000; Juttner *et al.* 2006). Such and other findings have stimulated interest in and efforts to develop drugs that may induce suppression or disruption of the VEGF/VEGFR axis. Several strategies have been developed for this, including neutralizing antibodies against VEGFs and VEGFRs, and VEGFR tyrosine kinase domain inhibitors. The humanized anti-VEGF antibody bevacizumab (Avastin) has been approved for fluoropyrimidine-based colorectal cancer therapy, and it has demonstrated efficacy in other tumor types as well.

In a recently published phase II study, the efficacy and safety of bevacizumab in combination with irinotecan and cisplatin in patients with advanced adenocarcinoma of the esophagogastric junction (n = 23) and stomach (n = 24) was tested (Shah *et al.* 2006). Prior adjuvant or neoadjuvant chemotherapy was allowed, as long as it did not consist of irinotecan or cisplatin. Results were compared with historical findings of three pooled studies with irinotecan- and cisplatin-containing regimens in gastric and esophageal cancer patients. The primary tumor was unresected in 40 patients. In 13 patients the tumor was assessable, but not measurable. The primary endpoint of the study was TTP, which was met at the number of 47 patients. In patients with measurable disease TTP was 9.2 months, whereas in patients with non-measurable disease this was 6.4 months, with an overall TTP of 8.3 months, which proves to be an increase of 75% over historical controls. Median overall survival was 12.3 months, and thus far is the highest ever reported. In 12 patients (26%) a thromboembolic (TE) event occurred; of these, eight pulmonary emboli were found incidentally during protocol-specified CT scans. The authors reported that the incidence of TE events was not higher than in the previously re-evaluated historical controls (30%) (Shah *et al.* 2005). After TE diagnosis, eight patients—all with their primary *in situ*—continued treatment while receiving anticoagulant agents. One of these patients subsequently had an episode of GI bleeding. Grade 3 hemorrhage was observed in one other patient. Other toxicities, possibly related to bevacizumab, consisted of grade 3 hypertension (28%), myocardial infarction (2%), and GI perforation (6%). The incidence of GI perforations in colorectal cancer patients while on fluoropyrimidine-based therapy with bevacizumab is about 1–2%. It has been suggested that in these patients GI perforations are related to the presence of the primary tumor, non-steroidal anti-inflammatory drug use, and peritoneal carcinomatosis. Notwithstanding the encouraging results of this study, larger randomized phase II and III studies are needed to confirm these findings and to evaluate its toxicity in this fragile patient population.

Other anti-angiogenetic agents targeting the VEGFR tyrosine domain have been tested in preclinical experimental and xenograft models, and these studies report a reduced proliferation and microvasculature density, and increased apoptosis. Clinical data are still awaited.

Besides the combination of targeted agents and conventional cytotoxic agents in these malignancies, another treatment strategy for the near future is the combination of multiple targeted agents in order to simultaneously inhibit multiple and 'cross-talking' pathways responsible for tumor growth and dissemination. Preclinical studies underscore this approach.

Gene therapy is another innovative therapeutic approach for cancer. Although few gene therapeutic approaches have demonstrated promising anti-tumor effects in preclinical studies, clinical trials have been disappointing. A major breakthrough is still needed. Hopefully, the introduction of new powerful molecular techniques such as RNA interference (RNAi) and detection of new target genes may improve gastric cancer therapy in the near future.

Conclusion

Clinical data on targeted therapy in advanced gastric cancer are limited. Despite the rational basis for these novel treatments, their identification and validation remains a challenge. For example, the inhibition of key processes in carcinogenesis has not always proved effective; nor have rationally assumed predictive markers helped to distinguish patients who are more or less likely to respond to targeted therapy.

In light of the rapidly changing landscape for cancer treatment, we are faced with the ongoing challenge of choosing from an ever-changing variety of agents, and identifying appropriate combinations and sequences of application, which may one day substantially improve survival rates.

Prognosis and follow-up

Ilfet Songun & Cornelius van de Velde

Cancer stage

Tumor stage is an important prognostic factor for survival in gastric cancer. A clear relation is seen between increasing depth of invasion and survival (Bonenkamp *et al.* 1993). With increasing depth of invasion a steady increase is seen in lymph node metastasis, from 45.7% when the tumor invades the muscularis propria, to 79.6% when adjacent organs are directly invaded. Also, the frequency with which the more distant tiers of nodes (second, third, and fourth) are involved rises steadily with depth of invasion (Sasako *et al.* 1995).

The incidence of metastasis and 5-year survival rate show a strong correlation. Moreover, with increasing distance between involved node and the primary tumor, the 5-year survival rate decreases. Involvement of node station 13 is associated with a zero 5-year survival rate. In the DGCT, surgery with an involved N4 node was regarded as a non-curative operation. Benefit from extended dissections (stations 7 to 12 and 16) in Japanese studies is estimated to be between 0% and 10.5% (Sasako *et al.* 1995), although this benefit was not found in randomized studies in the West (Cuschieri *et al.* 1996; Bonenkamp *et al.* 1999). In Japan, dissections even beyond the D2 level are now being studied in two randomized studies; one of them shows no survival benefit (Sasako *et al.* 2006) and the results of the second study are not expected before 2008 (Sano *et al.* 2004).

A survey by the American College of Surgeons showed a 77.1% resection rate in 18,365 patients, with a postoperative mortality of 7.2%, and 5-year survival of 19%. Only 4.7% of these were D2 dissections. Stage-related 5-year survival was 50% for stage I, 29% for stage II, 13% for stage III, and 3% for stage IV (Wanebo *et al.* 1993). Japanese national stage-related 5-year survival is reported at 96.6% for stage I disease, 72% for stage II, 44.8% for stage III, and 7.7% for stage IV (Kinoshita *et al.* 1993). Differences in surgical techniques may in part be responsible for these better outcomes. Non-randomized gastric cancer studies from Germany, England, Norway, and the United States have reported 5-year survival at between 26.3% and 55% for patients undergoing D2 dissections (Siewert *et al.* 1993; Sue-Ling *et al.* 1993; Arak & Kull 1994; Wanebo *et al.* 1996). The variability in outcomes is substantial, likely because of the different definitions of D2 dissections in most series.

Patterns of spread and recurrence

Understanding the patterns of spread of gastric cancer can help to direct therapeutic approaches, particularly those using systemic or regional (intraperitoneal) chemotherapy and radiation. Especially in more advanced stages in which the propensity for systemic metastasis is high, surgery alone (or any local treatment modality alone) is unlikely to offer long-term benefit.

Gastric cancer shows several patterns of recurrence: local recurrence in the gastric bed or regional lymph nodes, peritoneal metastasis, liver metastasis and distant metastasis. The pattern of spread has been evaluated both in patients with newly diagnosed cancer and in patients undergoing potentially curative surgical resection. In the West, the pattern of recurrence tends to be mainly local. In a study by Gunderson and Sosin (1982) of planned relaparotomy following curative resection, distant metastasis alone was found in 25.6%. Local recurrence and/or regional lymph node metastasis occurred as the only failure in 53.7% of the failure group if localized peritoneal failures were included, and as any component of failure in 87.8%. A similar high rate of local failure (54%) was reported by the British Stomach Cancer Group in patients undergoing operation alone (Allum *et al.* 1989). In an Italian study by Roviello *et al.* (2003) in 441 patients after curative resections for gastric cancer, recurrence was seen in 215 (49%) patients: peritoneal recurrence in 36%, locoregional recurrence in 45%, hepatic recurrence in 27%, and distant metastases in 9%. In the DGCT involving 1078 patients, death from recurrent disease was noted in a total of 289 patients: 30% of the patients had locoregional recurrence only, and 51% had locoregional and distant disease (Bonenkamp *et al.* 1999). In summary, patients with gastric cancer frequently have intraabdominal metastasis, even at the time of diagnosis. Sunderland and colleagues evaluated lymph node metastasis for proximal versus distal lesions (Sunderland 1967). Proximal tumors were much more likely to have lymph node involvement than were distal lesions. The extent of spread within the stomach also varies widely. Tumor invasion of intramural lymphatics may extend into the distal esophagus or the proximal duodenum. As mentioned earlier, inadequate resection margins resulting in an R1 resection (with a concomitant high likelihood of local failure) may occur because of lymphatic vessel invasion. Deep penetration of primary lesions may increase the risk of intraperitoneal contamination. Positive findings on cytologic examination of abdominal lavage fluid in gastric cancer are associated with a poor prognosis (Nakajima *et al.* 1978). In the DGCT, cytologic examination was performed in 535 patients: 457 (85%) after curative resection and 78 (15%) after palliative resection. A clear association was seen between positive cytologic findings and serosal invasion (12.4% positive cytology) and lymph node invasion (7.5% positive cytology). Survival was significantly lower in patients with positive cytology findings compared with those with negative cytology findings, irrespective of the procedure used (curative or palliative).

Some studies, especially those from Japan, have evaluated the lymph node drainage from various portions of the stomach to direct the extent of resection for tumors in relatively early stages. Maruyama *et al.* (1989) have extensively studied the incidence of metastasis to different lymph node groups. In their study, lymph node metastases were seen in 49% of patients. The likelihood of metastasis was analysed based on the location of the primary tumor within the stomach (proximal, middle, or distal third) and its location on the lesser or greater curvature

and anterior or posterior wall. Not surprisingly, metastases were considerably more likely in lymph node groups closest to the primary tumor and in the nodal chain immediately adjacent. The risk of metastasis to more distant lymph node sites could be predicted using this database. This type of data might direct the extent of resection. In a series from Korea examining 508 patients with recurrent gastric cancer from an initial 2328 operated patients, 425 had recurrence at only one site, 23% had local recurrence, 40% had peritoneal recurrence, 18% had hepatic metastasis and 19% had distant metastasis (Yoo *et al.* 2000). The lower local recurrence rates in the East seem to be related to the routine performance of D2 resection.

Because peritoneal recurrence is common, these data might influence the design of clinical trials by, for example, supporting the use of intraperitoneal chemotherapy in selected patients.

The type of adjuvant therapy that might be proposed (systemic vs locoregional) also depends, as noted above, on recurrence sites after potentially curative (R0) resection. Treatment failure patterns in patients who have undergone resection for primary gastric cancer have been evaluated by autopsy series, second-look laparotomy, and clinical evaluation. In one early study, McNeer and colleagues (1951) reviewed the autopsy results of 92 patients who had undergone potentially curative resections. In 50% of patients, local failure was noted, either in the gastric remnant or at the gastroenterostomy. An additional 21% of patients had recurrence in the gastric bed. Thirteen per cent of patients had distant failure only without any local component. Wisbeck *et al.* (1986) reviewed the autopsy data for 85 patients with primary gastric cancer. Only 16 of these patients had undergone potentially curative resections. For the group as a whole, peritoneal involvement was seen in 47% of patients. Hepatic metastases were also common, occurring in 39% of patients. Lung metastases occurred in 34% of patients.

Surgical prognostic factors

Besides the issue of the extent of lymph node dissection, other aspects of gastric cancer surgery have generated controversies. These include type of gastrectomy (subtotal vs total), pancreatectomy and/or splenectomy, patient selection, stage and stage migration, and the experience of the surgeon as a prognostic factor.

Surgical complications are influenced by the extent of the operation, and a number of studies have addressed this topic. In a Norwegian study (Viste *et al.* 1988) morbidity was significantly lower after subtotal resection (28%) than after total gastrectomy (38%), while proximal gastrectomy had the highest morbidity (52%). In a German study (Bottcher *et al.* 1994) these differences in morbidity were also found (23% for subtotal vs 48% for total gastrectomy). Gennari *et al.* (1986) also found a decreased morbidity for subtotal resections without any significant influence on survival. Comparison of their results with those of previous studies led to the conclusion that subtotal gastrectomy should be standard, provided that a safe proximal margin is guaranteed. In the DGCT and MRC trials, hospital mortality in the groups undergoing D1 dissection and D2 dissection was significantly lower for subtotal gastrectomy (3% and 7%, respectively) than for total gastrectomy (5% and 14%, respectively) (Cuschieri *et al.* 1996; Sasako 1997; Hartgrink *et al.* 2004). In both trials the complication rate was also lower after subtotal resections. In the DGCT this difference was statistically significant. The prognostic value of microscopic resection-line involvement in the DGCT was studied by Songun *et al.* (1996). Tumor-positive resection lines were seen in 5.9% of evaluable patients. Resection-line involvement was significantly associated with T stage, N stage, tumor location, and tumor differentiation. Presence of resection-line involvement was also associated with significantly worse survival. The conclusion from this study was that peroperative frozen-section examination is mandatory in patients undergoing a curative resection for gastric cancer, especially in those with poorly differentiated, signet-ring cell, or anaplastic tumors. In this context arguments can be made for performing a total gastrectomy in all patients with poor tumor differentiation.

Pancreatectomy and splenectomy

Resection of spleen or pancreas or both plays an important role in surgical complications. Most studies find a significant increase of morbidity and hospital mortality if a pancreaticosplenectomy is performed (Arak & Kull 1994; Griffith *et al.* 1995; Degliulie *et al.* 1997). Two studies in Japan did not show any beneficial effect on survival if pancreaticosplenectomy was combined with total gastrectomy, whereas morbidity was increased in these patients (Kodera *et al.* 1997; Kitamura *et al.* 1999). In the DGCT pancreatectomy and type of gastrectomy were the only factors significantly influencing the occurrence of major surgical complications. Although the number of dissected lymph nodes increases, septic complications occur more often due to anastomotic leakage, intraabdominal infections, and pancreatic fistula (Siewert *et al.* 1995).

The spleen should also preferably be spared as this may reduce concomitant morbidity (Brady *et al.* 1991; Sasako 1997). An increase of anastomotic leakage was seen, especially in subtotal D2 gastrectomies. The most likely explanation for this finding is that in D2 dissections the left gastric artery is divided at its origin and the rest of the stomach is dependent on the blood supply of its short gastric arteries. In D1 dissections, in which the left gastric artery is divided more peripherally, the vascularization of the rest of the stomach is probably less compromised. Immunologic factors may play a role in this as well, associated both with resection of the spleen itself (Meyers *et al.* 1987; Aldridge & Williamson 1991) and also with the immunosuppression induced by blood transfusions, which may be needed for increased hemorrhage (Kaneda *et al.* 1987; Kampschoer *et al.* 1989; Sugezawa *et al.* 1989).

Timeline of recurrence

With regard to the timeline over which the disease recurs, over two-thirds of recurrences are in the first 3 years and fewer than 10% occur after 5 years (Katai *et al.* 1994; Shiraishi *et al.* 2000; Kodera *et al.* 2003). Early gastric cancer (EGC) carries a very favorable prognosis, with a 1.4% recurrence rate in 1475 patients with EGC (Sano 1993). This study from NCC Tokyo reported that 40% of the deaths from recurrence occurred within the first 3 years and 23% after 5 years.

Adjuvant treatment after gastrectomy may alter patterns of recurrence; adjuvant chemoradiation reduced the proportion of local recurrences from 29% to 19% and regional recurrences from 72% to 65% as the first site of relapse compared with surgery alone (Macdonald *et al.* 2001).

Follow-up

Today, CT is the primary tool for the investigation of a suspected recurrence and for evaluation of response to non-surgical treatment of recurrent disease. CT detection of recurrences is usually based on morphologic changes such as wall thickening and focal enhancement. However treatment-induced bowel wall thickening caused by inflammation or fibrosis cannot be easily distinguished from wall thickening caused by residual tumor. For this reason a CT at 3 months following surgery has been recommended as a baseline for further assessment. However, PET is limited as a first-line screening tool in the follow-up of recurrent tumors because FDG PET may give false negative results in poorly differentiated gastric adenocarcinoma, and gastric cancers of the signet-ring cell and mucinous types. Furthermore the detection of recurrent gastric cancer may be difficult with PET imaging only.

Although there is broad agreement as to staging, classification, and surgery for gastric cancer, there is no consensus regarding follow-up after gastrectomy. Follow-up varies from investigations on the basis of clinical suspicion of relapse to intensive investigations to detect recurrences early, on the assumption that this improves survival and quality of life. For early gastric cancers, endoscopy can detect new primaries, but the incidence of these tumors is low, and many thousands of procedures are required to detect each operable case.

Advanced gastric cancers recur mainly locoregionally or as distant metastasis. Local recurrences detected at endoscopy or on CT are mainly incurable. CT is much better at detecting liver metastases, and although these are usually multiple and unresectable, there are several reports of good survival following liver resection for isolated metastasis.

Tumor markers have been used with some success to detect subclinical recurrences and could be used to target more invasive or expensive procedures. In chemotherapy, many newer agents are promising significantly improved survival, but again, the evidence for greater benefit when administered before the patient becomes symptomatic is lacking. Overall, it appears that follow-up policy is as much decided by the wealth and facilities of the institution as by any significant evidence base (Whiting *et al.* 2006). Although the early detection of recurrent cancer is an emotive issue for both patients and surgeons, considering the amount of time and money invested in follow-up, and the lack of evidence of efficacy, a randomized controlled trial of intensive follow-up is not cost-effective.

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