Gastric cancer: epidemiology, pathology and treatment

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Gastric cancer incidence and mortality has fallen dramatically over the last 50 years in many regions, but remains the second most common cancer worldwide. Despite a marked decline in fundic and distal tumors, there is a rising incidence of adenocarcinomas of the gastroesophageal junction and gastric cardia, particularly in Western nations. This may imply that there are in fact two diseases differing from each other in epidemiology, etiology, pathology and clinical expression. While surgical resection remains the cornerstone of gastric cancer treatment, the optimum extent of nodal resection remains controversial, with randomized studies failing to show that the D2 procedure improves survival when compared with D1 dissection. The high rate of recurrence and poor survival following surgery provides a rationale for the early use of adjuvant treatment. Adjuvant chemotherapy or adjuvant radiotherapy, when used alone, do not improve survival following resection. However, the results of the recent Intergroup 0116 study are promising in showing that the combination of 5-fluorouracil (5-FU)-based chemotherapy with radiotherapy significantly prolongs disease-free and overall survival when compared with no adjuvant treatment. In advanced gastric cancer, chemotherapy enhances quality of life and prolongs survival when compared with best supportive care. There is no agreed standard of treatment in this setting. Of the commonly used regimens, epirubicin plus cisplatin and 5-FU (ECF) probably has the strongest claim to this role. However, there is a pressing need for new agents, both cytotoxic and molecularly targeted, to be assessed in both the advanced and adjuvant settings.

Epidemiology and pathology

Over the past five decades or more, the mortality associated with gastric cancer has decreased markedly in most areas of the world [1–6]. Among males living in the USA, for example, the age-adjusted death rate has fallen from ∼35 per 100 000 population in 1930 to ∼10 per 100 000 today [2]. However, in the individual case, the chances of a patient surviving 5 years after diagnosis of gastric cancer are still low [7–9].

Despite the reduced incidence and mortality, gastric cancer remains the second leading cause of cancer death worldwide [2, 3, 10]. It is expected that nearly 800 000 people will be diagnosed with gastric cancer in 2002 and that 500 000 will die of the disease [2, 3, 11]. In the USA, cancers of the stomach account for 2% of cancer deaths [2].

Risk factors

Across the world, there are intriguing regional variations [7, 12, 13]. Gastric cancer has a lower incidence in economically developed Western countries, and reductions in risk are reported in people who migrate from high-incidence areas such as Japan and Korea to low-incidence regions such as the USA.

In every region of the globe, gastric cancer has a higher incidence in males than females (ratio of 1.5–2.5:1) [7, 12, 13]. It is also more frequent in older populations (in the European Union, the median age at diagnosis is 62 years), and in lower socioeconomic groups [7, 12].

The reductions seen in gastric cancer mortality can be attributed to a number of factors [7, 13–16]. These include a decrease in the intake of salted, pickled, smoked and chemically preserved foods (including use of nitrates), and an increased consumption of fresh fruit and vegetables. Improved housing and living standards, with a resulting reduction in Helicobacter pylori infection, may also have played a part, as has earlier detection of gastric tumors.

Several genetic risk factors have been identified [7, 13, 14, 17]. These include type A blood, pernicious anemia, family history, hereditary nonpolyposis colon cancer and Li–Fraumeni syndrome. Little can be done to modify these risk factors, and the incidence of precursor lesions (chronic atrophic gastritis and adenomatous gastric polyps) is low [18]. However, a number of modifiable factors also increase risk, particularly of the classical distal form of gastric cancer. These include a high salt and nitrate consumption and low intake of vitamins A and C, cigarette smoking, and infection with Helicobacter. A series of steps has recently been proposed to explain the pathogenesis of Helicobacter-associated gastric cancer. This suggests that mucosal atrophy and increased gastric pH lead to bacterial overgrowth. Intestinal metaplasia then follows as a direct result of injury by the bacteria, possibly compounded by increased production of nitrites and N-nitroso compounds.

Recent evidence for the presence of genes from the Epstein–Barr virus implicates this organism in gastric cancer. Prior surgery for gastric ulcer and exposure to radiation also increase risk [18, 19].

Changing patterns of disease

While the incidence of ‘endemic’ gastric cancer, with intestinal pathology and located in the corpus of the stomach, has undoubt-

<table>
<thead>
<tr>
<th>Spread</th>
<th>Early hematogenous</th>
<th>Late locoregional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social status</td>
<td>Upper</td>
<td>Lower</td>
</tr>
<tr>
<td>Histology</td>
<td>Diffuse</td>
<td>Intestinal</td>
</tr>
<tr>
<td>DNA content</td>
<td>Aneuploidy high S-phase</td>
<td>Diploid</td>
</tr>
<tr>
<td>Spread</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+, weak association; ++++, strong association.

edly fallen, there are recent reports that tumors of the cardia are on the rise, especially among males and notably in the UK, Ireland, Northern Europe, Australia and New Zealand, China, and North America [7, 12, 13, 20, 21]. Among UK males with gastric cancer, for example, 54% of cases diagnosed in 1990 were tumors of the cardia [12]. There also appears to be a rising trend in adenocarcinomas of the lower esophagus, in which hyperacidity, reflux esophagitis, Barrett’s esophagus and obesity are possible etiological factors. The rate at which the incidence of proximal stomach cancers has risen exceeds that of any other cancer [21, 22].

The increase in tumors of the cardia is taking place principally in countries with relatively low overall rates of gastric cancer. In contrast to cancer of the corpus of the stomach, proximal tumors are associated with higher social class, and Helicobacter seems to play a smaller role (Table 1). The histology of gastric cardia tumors shows frequent aneuploidy and a high S-phase fraction. Spread is early and hematogenous, rather than locoregional and late.

The role of surgery

Approximately one-third of gastric cancer patients have stage I or II disease at the time of diagnosis. One-quarter have stage III disease, and the remaining 40% or so stage IV disease [23]. As with other tumors, prognosis is clearly related to stage: according to one series, estimated adjusted survival 5 years after surgery is 82.9% for stage I, 62.8% for stage II, 17.8% for stage III and 3.3% for stage IV [24].

The development of endoscopic techniques has improved the proportion of gastric cancers detected at an early stage, particularly in Japan, which has the highest incidence of the disease and the most developed programs for screening. Compared with other regions, oncology centers in Japan report higher 5 year survival rates at all stages of disease [25]. Among 1453 Japanese stage I patients operated on in the period 1971–1985 (who accounted for 46% of all gastric cancer diagnoses in that time), the 5 year survival rate was 91%. This compares with 50% survival among 2004 stage I patients treated in US centers, where stage I disease accounted for only 18% of diagnoses (Table 2). Among stage II patients, the corresponding survival figures were 72% in Japan and 29% in the US, and in stage III patients 44% and 13%.

Gunderson et al. [1] found that 53% of patients who failed following surgery had only locoregional recurrence. Gastric cancer is therefore clearly a difficult disease in which to achieve local control. The Japanese group of Maruyama et al. [25] has published data suggesting that the rate of local recurrence can be reduced from 38% to 12% with a more aggressive approach.

However, the most appropriate extent of resection is still debated, since more radical surgery has not been proven to improve outcome. The question of whether the routine use of D2–D4 resection (with extensive en-bloc removal of second echelon lymph nodes) increases cure rate when compared with limited lymphadenectomy of the perigastric nodes (D1 resection) remains open.

Bunt et al. [26] investigated the effect of more radical lymphadenectomy on stage migration. They reported that up to 75% of patients classified as stage IIIB on D1 dissection were reclassified as stage IV on D2 dissection (Table 3). This suggests that any effect of more radical surgery on survival could be confounded with that on staging.

The Dutch randomized study of D1 versus D2 dissection

Following extensive discussion with Japanese colleagues, a nationwide prospective study was designed by the Dutch Gastric Cancer Group [27, 28]. Over the period 1989–1993, 996 patients from 80 participating hospitals were randomized to either limited D1 lymph node dissections performed by local surgeons or extensive D2 dissections supervised by one of 12 reference surgeons with considerable experience (having performed an average of 41 radical procedures).

All operations were conducted according to protocol, videotaped and supervised; and pathology was reviewed. The aim of the study was to detect a 12% improvement in 5-year survival in patients in whom curative surgery had been attempted.

Table 1. Differences between cardias or corporal location of gastric cancer [7, 12, 13, 20, 21]

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Cardias</th>
<th>Corpus</th>
<th>Helicobacter</th>
<th>Social status</th>
<th>Histology</th>
<th>DNA content</th>
<th>Spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rising</td>
<td>Decreas</td>
<td>+</td>
<td>Upper</td>
<td>Upper</td>
<td>Diffuse</td>
<td>Aneuploidy</td>
<td>Early</td>
</tr>
<tr>
<td>Decreasing</td>
<td>+++++</td>
<td>Lower</td>
<td>Lower</td>
<td>Lower</td>
<td>Intestinal</td>
<td>Diploid</td>
<td>Late</td>
</tr>
</tbody>
</table>

Table 2. Survival with gastric cancer surgery: US versus Japanese centers [25, 26]

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients [n (%)]</td>
<td>5-year survival (%)</td>
</tr>
<tr>
<td>I</td>
<td>2004 (17.8)</td>
<td>50</td>
</tr>
<tr>
<td>II</td>
<td>1976 (17.5)</td>
<td>29</td>
</tr>
<tr>
<td>III</td>
<td>3945 (35.0)</td>
<td>13</td>
</tr>
<tr>
<td>IV</td>
<td>3342 (29.7)</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 3. Surgical/pathological-stage migration and comparisons of gastric cancer survival rates [26]

<table>
<thead>
<tr>
<th>D1 TNM</th>
<th>D2 TNM</th>
<th>Stage</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>30</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>IIIA</td>
<td>19</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>IIIB</td>
<td>6</td>
<td>18</td>
<td>75</td>
</tr>
</tbody>
</table>
Care was taken not to minimize any effect of more radical surgery: an attempt was made to exclude D2 dissections in patients randomized to the D1 group, and actually to carry out D2 dissections where patients had been assigned to them. Of the 996 patients randomized, 711 underwent the allocated treatment. In 42% of the 82 patients who were subsequently judged ineligible for the D2 procedure, the reason was lack of availability of the designated surgeon.

**Results**

The D1/D2 groups were well matched in age (median 63–65 years), male:female ratio and site of disease. The incidence of splenectomy and pancreatectomy was substantially higher in the D2 than in the D1 group (Table 4). The 10% incidence of perioperative death was higher than in the D1 group, the rate of complications and re-interventions was significantly higher, and hospital stay was longer.

In patients under 65 years of age (there was no upper age limit in the study), there was no significant difference between the perioperative mortality with D1 and with D2 dissections. The 6.6% perioperative mortality in the D2 group is not high compared with the nationwide 9.3% figure reported in the *British Journal of Surgery* for the period 1980–1990 [29]. The Dutch trial is compatible with work from Germany (Table 5) in suggesting that surgeons’ experience is an important determinant of postoperative mortality in patients with gastric cancer [30].

The 47% 5-year survival rate for patients undergoing a D2 resection was not significantly different from the 45% rate seen in the D1 group. The survival curves out to 10 years now confirm that extent of surgery did not affect outcome in N1 patients with 1–6 positive nodes (D1 versus D2, \( P = 0.9 \)). However, from 3.5 years after surgery onwards, patients undergoing D2 resections were less likely than those in the D1 group to experience recurrence.

**Implications**

The optimum extent of nodal dissection remains controversial despite randomized trials such as those of the Dutch group and the UK MRC, although data suggest that a D1 procedure at least should be undertaken [27, 28, 31–33]. In this context, the results of a Japanese study in which 530 patients with advanced gastric cancer were randomized to D2/3 or D4 dissections is awaited with interest. The postoperative mortality of 1% in both arms was low, but the more extensive procedure necessitated an average hospital stay of 6 weeks.

The high risk of locoregional failure, metastatic spread and death following even a D2 dissection provides a powerful rationale for the early use of systemic therapy. The nature of this systemic treatment remains unclear. In a recent study conducted in The Netherlands, for example, patients randomized to four courses of 5-fluorouracil (5-FU), doxorubicin and methotrexate (FAMTX) prior to surgery survived no longer than patients undergoing adequate D2 dissection alone. The question of whether chemotherapy or radiotherapy are at the moment doing little more than compensate for inadequate surgery remains open.

In the study by Macdonald et al. [34] (considered in greater detail below), and despite protocol advice, only 10% of patients underwent D2 dissections. D1 procedure was performed in 36% and D0 in 54%. It may be this factor, as much as any other, that accounts for the 64% recurrence rate in the surgery alone arm (compared with 43% among patients receiving surgery followed by chemotherapy and radiotherapy).

**The role of chemotherapy**

The majority of gastric cancer patients have stage III or IV disease at presentation and are therefore candidates for some form of chemotherapy [23]. Currently, 1-year survival rates are ~50% in stage IIIA and B disease, and <25% in stage IV disease. As has already been noted, a rising proportion of patients now present with tumors of the upper stomach, particularly of the gastro-esophageal junction [12, 21, 22]. This changing epidemiology has implications for treatment since 5-year survival following resection is approximately 45%. Five-year survival for patients with resected cardia or gastro-esophageal junction appears to be in the range of 10%.

A recent investigation into patterns of care indicated that many gastric cancer patients, even those with relatively early stage disease, are not receiving chemotherapy [23]. This appears to reflect a perception that systemic treatment has little effect, which is not in fact the case.

**Advanced disease**

On the evidence of four randomized trials of chemotherapy versus best supportive care, chemotherapy confers benefits both

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**Table 4.** The D1 versus D2 trial of the Dutch Gastric Cancer Group [27, 28]

<table>
<thead>
<tr>
<th>Dissection</th>
<th>D1</th>
<th>D2</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients operated on</td>
<td>380</td>
<td>331</td>
<td></td>
</tr>
<tr>
<td>Splenectomies</td>
<td>41</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Pancreatectomies</td>
<td>10</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Number of patients (intention-to-treat)</td>
<td>513</td>
<td>483</td>
<td></td>
</tr>
<tr>
<td>Perioperative deaths (%)</td>
<td>6</td>
<td>10</td>
<td>0.06</td>
</tr>
<tr>
<td>Complications (%)</td>
<td>25</td>
<td>38</td>
<td>0.001</td>
</tr>
<tr>
<td>Interventions (%)</td>
<td>8</td>
<td>16</td>
<td>0.001</td>
</tr>
<tr>
<td>Days in hospital (%)</td>
<td>18</td>
<td>22</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Table 5.** Risk factors for postoperative mortality in surgery for gastric cancer [30]

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnofsky index</td>
<td>0.0001</td>
</tr>
<tr>
<td>Concomitant diseases</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td>0.001</td>
</tr>
<tr>
<td>Tumor diameter</td>
<td>0.001</td>
</tr>
<tr>
<td>Experience of surgical department</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.026</td>
</tr>
</tbody>
</table>
in quality of life and in survival. These trials showed survival of 7.5–12 months with chemotherapy and only 3–4 months without it [35, 36]. However, there is no clear standard of treatment in gastric cancer. Many single-agent or combination chemotherapy regimens have been used. The drug 5-FU remains one of the most popular chemotherapy agents for gastric cancer, and has been the cornerstone of combination regimens such as FAMTX, ELF (etoposide, leucovorin and 5-FU) and ECF (epirubicin, cisplatin and continuous infusion 5-FU).

Typically, response rates (RRs) with chemotherapy are in the region of 20% to 30%. The highest recorded RR is the 45% seen with ECF in the randomized trial versus FAMTX, which had a significantly lower 21% RR [37]. In this study, epirubicin was given at 50 mg/m² and cisplatin at 60 mg/m² on day 1, and 5-FU 225 mg/m² on days 1–21. The median survival was longer with ECF (9 months) than with FAMTX (6 months). Of patients treated with ECF, 14% were alive at 2 years, compared with only 5% of FAMTX-treated patients. This difference was significant at \( P = 0.03 \). ECF was less toxic than FAMTX, and its use conferred superior quality of life.

This finding of a significant difference between regimens contrasts with that of an older NCCTG study which randomized 256 advanced gastric cancer patients to either 5-FU alone or a series of combination regimens (FAMVe, FAP and FAME plus an antifolate) [38]. The 6.1 month median overall survival seen with 5-FU alone was not statistically inferior to that of any of the multidrug arms, which were associated with greater hematological and gastrointestinal toxicities.

The current generation of studies have several advantages over this NCCTG trial. Following advances in imaging, disease can be better staged, and responses more accurately assessed. Furthermore, the side-effects of combination regimens are more fully understood and more readily managed. The stage is therefore set for new attempts to combat advanced disease, using more active regimens, newer cytotoxic drugs and novel molecularly targeted agents, which may prove valuable in maintaining responses. A phase II/III randomized trial (REAL-2) is currently underway to compare ECF with three new and potentially promising chemotherapy regimens. These regimens include (i) epirubicin, oxaliplatin and prolonged venous infusion 5-FU, (ii) epirubicin, cisplatin and capecitabine, and (iii) epirubicin, oxaliplatin and capecitabine. The primary end point of REAL-2 is to compare overall and disease-free survival in patients with locally advanced or metastatic gastroesophageal cancer.

Radiotherapy, chemotherapy and combined modality treatment in the adjuvant setting

Until recently, randomized trials assessing the use of adjuvant therapy following a potentially curative resection for gastric cancer had failed to show benefit. Since 1990 there have been at least six published meta-analyses that have attempted to better assess any potential benefit of adjuvant therapy that may have been missed in the individual trials [39–44]. The two most recent meta-analyses both showed a significant survival advantage to the use of chemotherapy following surgical resection of gastric cancer. However, the magnitude of this improved survival is of questionable clinical benefit [39, 40]. The same was true for use of adjuvant radiotherapy alone.

Nevertheless, there is a clear rationale for adjuvant radiation in a disease in which there is a 40% rate of local recurrence following resection, and a local component to failure in 80% to 85% of cases. Improved surgical techniques that offer a higher chance of survival may also provide adjuvant chemotherapy with a new opportunity to show benefit.

Based partly on experience with rectal cancer, the combination of radiotherapy with chemotherapy has been advocated, and its use in gastric cancer is supported by the results of the recently completed Intergroup 0116 trial [34]. In this study, 603 patients with gastric or gastroesophageal adenocarcinoma were randomized following potentially curative resection to either chemotherapy plus radiation or an observation control group.

Patients randomized to adjuvant treatment received one cycle of 5-FU and leucovorin followed by a combination of bolus 5-FU and radiation. At the completion of radiotherapy, two additional cycles of 5-FU and leucovorin were administered.

Compared to observation alone, patients treated with adjuvant chemoradiotherapy had a significantly improved chance of 3-year disease-free survival (48% versus 31%, \( P = 0.001 \)). The median survival in the adjuvant group was 42 months, compared with 27 months among controls (\( P = 0.03 \)). These figures represent a 44% improvement in relapse-free survival and a 28% improvement in overall survival; however, the survival gains are comparable to survival figures reported with D1 resection in the literature.

Future directions

The question of optimal surgery remains: should procedures be more radical than those routinely undertaken, at least in the USA? There is also clearly a need for more active chemotherapy regimens. The benefit of adjuvant chemoradiotherapy in the Intergroup 0116 study was achieved primarily through a reduction in locoregional rather than distant failure.

The use of infusional 5-FU may enhance activity, as may the incorporation of ECF into the pre- and post-radiation schedules. In a pilot trial of this approach (00-165), ECF will be given for one cycle prior to radiation (which is accompanied by infusional 5-FU), followed by two further cycles of ECF. If well tolerated in an initial 25 patients, the new approach will be subjected to phase III trial.

There is also considerable interest in the potential in gastric cancer for newer cytotoxics such as irinotecan and docetaxel (considered in this volume), as well as oxaliplatin. There is also interest in exploiting the convenience and improved tolerability of oral fluoropyrimidines. In addition, agents with novel mechanisms of action (notably the antiangiogenic epidermal growth factor receptor and vascular endothelial growth factor inhibitors, the COX-2 inhibitors and the matrix metalloproeinase inhibitors) are likely to be investigated in patients with gastric cancer.
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References


