Focus on gastric cancer

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Epidemiology and incidence statistics
Gastric cancer is the second most common cancer in the world (Ferlay et al., 2001). It is unique in that its time trend and geographical distribution are very informative in estimating its risk factors. In the US, the crude mortality rate in Caucasian males was 33/100,000 in the early 20th century, and this declined to 5/100,000 in the late 20th century. The declining trend is worldwide, and the decline began earlier in developed countries. However, even among them, mortality is still high in Korea (43/100,000), Russia (35/100,000), Japan (31/100,000), and Portugal (22/100,000). The age-adjusted incidence reaches as high as 70/100,000 in Korean and Japanese males. The male to female ratio is consistently two to one in many geographical regions.

The decline took place following the popularization of refrigerators, which resulted in a decreased intake of salt and an increased intake of fruit and vegetables (Palli, 2000; Potter et al., 1997). The preventive effects of fruit and vegetables are consistently confirmed by many epidemiological studies. Most epidemiological studies have shown the promoting effect of salt and the preventive effect of vitamin C. The effects of salt were also shown by animal experiments. Some epidemiological studies suggest that consumption of grilled meat/fish increases the risk, and that the consumption of carotenoids and green tea reduce the risk. Epidemiological data linking N-nitrosamines to gastric cancers have so far been inconclusive, although their carcinogenicity at high doses is proven.

Infection by Helicobacter pylori is prevalent in areas with high incidences of gastric cancers, and increases the risk of gastric cancer. However, in some Asian countries, such as India and Thailand, incidences of gastric cancers are not high in spite of the high H. pylori infection rates, a phenomenon known as the “Asian Enigma” (Miwa et al., 2002). Possible explanations for this include host genetic factors, different virulence among strains of H. pylori, and dietary factors. Polymorphisms of proinflammatory cytokine genes have been shown to associate with risk of H. pylori-related gastric cancers (El-Omar et al., 2000).

Animal models
A rat model for gastric cancers induced by a chemical carcinogen, N-methyl-N-nitro-N-nitrosoguanidine, has been widely used for a variety of purposes, such as evaluation of various promoting and preventing factors and clarification of genes involved in genetic susceptibility (Yamashita et al., 2002). A model in which H. pylori could infect an animal was established using Mongolian gerbils, which contributed to clarification of the strong promoting effect of H. pylori (Shimizu et al., 1999).

In addition, there have been more than 10 lines of genetically modified mice that show hyperplasia of the gastric epithelium and/or intestinal metaplasia (Gut et al., 2002). These mouse models were created by targeting genes involved in ion transport, signal transduction, transcriptional regulation, and cell adhesion. Development of gastric cancers was observed in mice lacking the pS2 trefoil protein, those lacking Smad4/Dpc4, those lacking the SHP2 binding site on the Il-6 family corepressor gp130, and those lacking RUNX3 (Judd et al., 2004; Lefebvre et al., 1996; Xu et al., 2000; Li et al., 2002).

Disease mechanism and molecular targets
Histological classification and gastric/intestinal phenotypes
Histological classification of gastric cancers is different between Japan and Western countries. Generally, “differentiated” and “undifferentiated” types in Japanese classification correspond to “intestinal” and “diffuse” types, respectively, in the Western classification established by Lauren. It has been considered that intestinal-type gastric cancers are associated with intestinal metaplasia, whereas diffuse-type gastric cancers are originated from gastric mucosa proper. Recent analysis of gastric and intestinal phenotypes in early gastric cancers has shown that cancer cells with gastric phenotypes were present in both intestinal and diffuse types of gastric cancer. Furthermore, phenotypic expression in gastric cancer cells was shown to be independent of phenotypic changes in the surrounding gastric mucosa (Tatematsu et al., 2003).

Gastric cancer predisposition
Germline mutations of E-cadherin were first found in a large family from New Zealand in which diffuse-type gastric cancers took place at an early age (Guilford et al., 1998). Although E-cadherin germline mutations are very rare, the finding provided to be useful information for clinicians to manage high-risk patients. Gastric cancers, mainly of the intestinal type, can be associated with hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, most cases of which are caused by germline mutations of mismatch repair genes hMLH1 or hMSH2, and are more prominently manifested in older generations of HNPCC patients. Patients with familial adenomatous polyposis, which is caused by germline mutations of APC, and Peutz-Jeghers syndrome also have increased risk for gastric cancer (Oberhuber and Stolte, 2000).

Molecular alterations in gastric cancer
Many genes have been analyzed in attempts to understand the molecular bases for human gastric cancers, but only a few with frequent alterations have been identified (Table 1). Oncogenic activations of β-catenin (17%–27% in intestinal type) and K-ras (0%–18% in both histological types) have been found in human gastric cancers (Lee et al., 2002; Park et al., 1999). In addition, amplifications of the c-erbB2 and the c-met genes have each been found in approximately 10% of both histological types.

As for tumor-suppressor genes, p53 mutations are repeatedly reported in gastric cancers of the diffuse type (0%–21%) and intestinal type (36%–43%) (Maesawa et al., 1995).
Inactivation of tumor suppressor genes

- Oncogene activation
  - \(\beta\)-catenin: 0–21
  - K-ras: 0–6
  - c-erbB2: 12–13

- Inactivation of tumor suppressor genes
  - p53: 0–21
  - APC: 0–5
  - E-cadherin
    - Mutation: 33–50
    - Methylation: 79
  - p16
    - Mutation: 0
    - Methylation: 11*
  - Microsatellite instability: 5–32

*Incidence rates are overestimated due to analysis of CpG islands in exons.

Factors that induce molecular alterations

- Mutations of the APC tumor suppressor gene are found frequently in gastric adenomas, but only rarely in gastric cancers; this is clearly different from the similar frequencies of APC mutations in colorectal adenomas and carcinomas (Lee et al., 2002; Maesawa et al., 1995). Somatic mutations of E-cadherin are observed specifically in sporadic diffuse-type gastric cancers (33%–50%) (Becker et al., 1994). RUNX3 was recently shown to be a tumor-suppressor gene of gastric cancers, although its mutations were rare (Li et al., 2002).

- Microsatellite instability (MSI) is observed in 5%–10% of diffuse-type gastric cancers and in 15%–40% of intestinal-type gastric cancers. The major mechanism for the MSI in gastric cancer is inactivation of the mismatch repair gene hMLH1 resulting from hypermethylation of its promoter (Fang et al., 2002). Similarly, mutation of the p16 gene is infrequent, but hypermethylation of p16 is common (25%–42% overall) in gastric cancer, with the intestinal type having higher incidence (Ding et al., 2003; Oue et al., 2002).

Diagnosis of gastric cancers

Most patients with gastric cancer are diagnosed when they undergo endoscopy and biopsy after exhibiting symptoms. In Japan, about 25% of patients are diagnosed by mass screening or a personal health check (Japanese National Gastric Cancer Registry). In high-risk areas of this disease, the most important issue is the education of general practitioners and the public to make them aware of the risk of this cancer. Early diagnosis used to be made by a barium meal study, especially in mass screening in Japan (Oshima, 1997). Endoscopy is being used more and more for secondary prevention in combination with a serum test of pepsinogen subtypes. However, there is a consensus that the efficacy of mass screening itself should be reevaluated (Tsubono and Hisamichi, 2000).

At an early phase of development, a well-differentiated carcinoma (WDC) replaces the mucosa of atrophic gastritis or IM without showing any invasion. As tumors progress, they start to invade the lamina propria mucosae or the muscularis mucosae, then the submucosal layer. As these invasive parts are often missed by biopsy, the lesions are often diagnosed as dysplasia. Thus, many lesions initially diagnosed as severe dysplasia turned out to be an invasive cancer, sometimes invading even the muscularis propria, after histological evaluation of resected materials (Fertitta et al., 1993).

Diagnostic criteria for early gastric cancers and endoscopic mucosal resection

Diagnostic criteria of WDC differs to some extent between the West and the East (Schlemper et al., 1997). In Western countries, the diagnosis of adenocarcinoma is made only when pathologists can recognize the evidence of invasion, while the term cancer is used in the East when cellular or structural atypia is evident, even without evidence of invasion. WHO classification now clearly states that the lesions called severe dysplasia/adenoma in the West are the same as noninvasive mucosal carcinoma in the East, and this is a result of pathologists’ mutual communication and cooperation (Fenoglio-Preiser et al., 1997). The Western policy runs the risk of overlooking true cancers, but the Eastern policy may induce overtreatment. However, as the result of the development of the technique of endoscopic mucosal resection (EMR), the majority of such lesions are now treated endoscopically in Japan (Ono et al., 2001). Thus, paradoxically, “severe dysplasia” is often treated by surgery in the West, and “noninvasive mucosal carcinoma” is treated by EMR. This treatment can be applied exclusively to mucosal cancer, for which endoscopic ultrasound (EUS) is sometimes helpful. Because the histology of the entire specimen resected using EMR can be examined in detail, additional surgery can be applied without much delay if a patient’s tumor is found to have submucosal invasion. Because of these potential advantages, distribution of the EMR technique to the West is urgently needed.

Metastases and their diagnosis

Gastric cancer remains a localized disease for a long time and metastasizes slowly. Table 2 shows the incidence of metastasis to lymph nodes, the liver, and the peritoneum according to tumor depth. Metastasis to sites other than these three sites is rare. Systemic metastasis seldom occurs until the late phase of
local invasion (T3/4). By deeper invasion, nodal metastasis occurs more massively and to more distant areas. Nearly 20% of T2 tumors have metastasis at the second tier nodes. Systemic and local recurrences of T1/T2 lesions are rare when treated by proper lymph node dissection, while local recurrence is frequent after limited surgery (Sasako, 2003).

Conventional CT scanning is useful in detecting enlarged nodes, which are often irresectable. However, 25% of metastatic nodes are 5 mm or less and undetectable by any imaging diagnostic tool, including MRI, PET scan, or EUS (Noda et al., 1998).

### Treatment of gastric cancers and its recent advances

Tumors without distant metastasis are potentially curable, and treatment comprises resection of the primary tumor and control of lymph node metastasis. For differentiated-type T1 mucosal cancers, EMR is often successful, as metastasis does not generally occur (Gotoh et al., 2000). The Japanese Gastric Cancer Treatment Guideline indicates the criteria for EMR as follows: mucosal cancer of intestinal type, no ulcer nor ulcer scar in the lesion, and size smaller than 21 mm (Nakajima, 2002). For more advanced lesions, gastrectomy of over 2/3 of the stomach with proper lymph node dissection is regarded as standard treatment even in the West (Sasako, 2003; Allum et al., 2002; NCCN Guideline [http://www.nccn.com/physician_gls/f_guidelines.html]), in spite of the negative results of two large randomized trials (Bonenkamp et al., 1999; Cuschieri et al., 1999).

Tumors with distant metastasis are mostly incurable at present, with the rare exceptions of those with solitary liver metastasis or peritoneal nodules. For these advanced or recurrent tumors, chemotherapy shows a modest effect, and cure by medical treatment is rare, even in combination with radiotherapy. Combination chemotherapy using 5-fluorouracil with other agents remains the most popular regimen.

### Chemoradiotherapy and D2 surgery

Recently, chemoradiotherapy (CRT) after a potentially curative operation was shown to improve the results of surgery without lymph node dissection (MacDonald et al., 2001). As adjuvant chemotherapy has not proven its efficacy over surgery alone, these results strongly suggest the efficacy of radiotherapy to achieve good local control. However, the results achieved by limited surgery followed by CRT are still worse than those of extended surgery, so-called D2 nodal dissection. Currently, questions regarding whether CRT in combination with limited surgery can replace D2 surgery and whether CRT can improve the results of D2 surgery alone remain to be answered. The former should be evaluated in the Western specialized centers, where D2 surgery can be carried out safely with sufficient quality. If this proves the efficacy of CRT, both questions should be investigated in Japan. Meta-analysis evaluating the effect of adjuvant chemotherapy without irradiation after curative surgery for gastric cancer suggested strongly the effect of the treatment. As none of the large sized trials has proven the effect of adjuvant chemotherapy, it is urgent to establish standard adjuvant treatment. At the moment, a large randomized trial is going on using TS-1, which showed the highest response rate as a single agent in the past. In Western countries, neoadjuvant chemotherapy for advanced gastric cancer is now being tested in a few large phase III trials. Neoadjuvant CRT is just now under investigation as a phase II trial in some American institutions.

### New chemotherapeutic agent

Some new chemotherapeutic agents, such as Irinotecan, TS-1, and Docetaxel, show promise as being more effective than conventional drugs. A combination chemotherapy including TS-1 has shown a response rate of over 70% (Koizumi et al., 2003). Further studies may change the chemotherapy for gastric cancer.

### Future challenges

Severe dysplasia/noninvasive mucosal carcinoma could contain different entities that have different abilities to invade the lamina propria mucosae. However, key molecular alterations that determine this progression are unknown. The presence of lymph node or distant metastasis is a very important factor in deciding a treatment strategy, but accurate diagnosis is still difficult. Clarification of molecular alterations that are closely linked with these characteristics will be beneficial to decide on a treatment strategy for individual cases. Popular use of EMR raises a new question, whether or not a secondary cancer will arise from the remnant stomach, and prediction of risk for developing gastric cancer is becoming more important. Recent genomic approaches demonstrate great potential for addressing these issues (Hasegawa et al., 2002). The more important and appropriate questions we ask, the more useful these new approaches will be.

### References


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