The Aetiology and Management of Gastric Carcinoma in Japan

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Abstract

With the rapid development of modern technologies, Japan has increased its population's average lifespan to become the longest in the world. Since 1981, its industrial lifestyle has seen cancer as the leading cause of death in Japan, accounting for 31.1% of the total number of deaths in 2004. Gastric cancer ranked first in morbidity until replaced by lung cancer in 1992.[1] However, it still remains an important malignancy with significant geographical, ethnic, cultural, and socioeconomic differences in distribution. Although genetic factors can predispose individuals to contracting the disease, the environment, particularly diet, contributes to between one-third and one-half of all gastric cancers.[2]

There are three distinct approaches to gastric cancer treatment in Japan: endoscopic, surgical and oncological. This article describes the techniques employed in the treatment of gastric cancer in Japanese hospitals in the context of its aetiology.

Introduction

Gastric cancer is the second leading cause of cancer deaths, with Japan having the highest global mortality rate.[3] While the Japanese possess the longest average life span (81 years) in the world, more than 100,000 Japanese are diagnosed with gastric carcinoma each year.[1,4] A definitive carcinogen remains to be identified, but multiple factors have been recognized to contribute towards its pathogenesis. These include a high salt intake, high prevalence of *Helicobacter pylori* infection and atrophic gastritis, low consumption of vitamins A and C, and smoking.

Nearly 500 gastrectomies are carried out at National Cancer Centre Hospital (NCCH) in Tokyo per year.[4] This hospital has a well-reputed gastrointestinal (GI) team subdivided into endoscopic, surgery and medical oncology divisions. This method allows each division to focus their efforts on a specialized task and may offer more treatment modalities than a non-divided GI team.

Pathogenesis

Dietary Considerations

It is well recognized that malignant mutation in gastric cancer occurs over a long period of time. Therefore, it is difficult to separate familial and environmental factors in its pathogenesis. Despite a large number of studies on aetiologic factors, the definitive carcinogens are not yet established. Certain environmental and genetic are associated with increased risk of gastric carcinoma formation. Dietary considerations include high salt and nitrate consumption from food preparation and preservation techniques, low supply of vitamins A and C due to poor consumption of fruit and vegetables, lack of refrigeration and water sanitation, cigarette smoking, and *Helicobacter pylori* infection.[3]

Regional distribution of gastric cancer matches the salt consumption rate within Japan. The Tohoku district, which has the highest salt consumption, also sees the highest incidence of gastric cancer. The colder locale increases the frequency of smoking and salt-curing food preservation methods, exposing its population to saltier foods.[4] Contact with N-nitroso compounds in fertilizers and pickled foods common to the Japanese diet also correlates with an increased risk of gastric cancer.[14] In contrast, green vegetable consumption among Japanese people is low.[4] Diets low in vegetables, fruits, milk and vitamin A have been associated with increased risk for gastric carcinoma,[10] as these foods have a protective effect.[3]

In particular, the antioxidant properties of vitamin C may have a preventative role against damaged caused by *H. pylori*.[10] Although the mechanism of *H. pylori* influence on the progression to gastric carcinoma is unclear, infection increases the incidence of atrophic gastritis, metaplasia and dysplasia. Gastric adenocarcinomas of the stomach body and antrum are profoundly associated with *H. pylori* infection. The bacteria is present in approximately eighty percent of Japan's population.[3]

The influence of the Japanese diet in relation to gastric cancer incidence is supported by a number of migration studies. Emigration to geographically lower-risk areas decreased the risk of gastric cancer to a level halfway between that of Western and Japanese values.[3] The incidence rates of Japanese living in Hawaii are 24.3 and 11.1 in males and females, respectively.[7]   While these rates are one-third of those found in the Japanese population, they are nonetheless three times the risk of the American Caucasian population.[2] The incidence of gastric cancer is also high in second-generation offspring who continue to consume a Japanese-style diet, whereas low in those who adopted a Westernized diet.[3] The mortality rate of subsequent generations born in the US continues to decline towards the lower rate of US Caucasians.[8]

Genetic Polymorphisms

Although a genetic predisposition to gastric carcinoma has been frequently confirmed,[15] the mechanisms by which genes exert their influence are not well-understood. Certain factors include Type A blood, pernicious anaemia and family history.[3] A familial risk for chronic atrophic gastritis, which is a precursor for gastric carcinoma, has been associated with a number of cases.[16] Gastric carcinoma has been associated with certain hereditary syndromes: hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), and Peutz-Jeghers syndrome.[10]

DO A REFERENCE CHECK! ENGLISH TOO GOOD?

The interleukin 1 beta (IL-1beta) gene has been postulated as a candidate gene which may affect the clinical consequences of *H. pylori* infection. It is upregulated by infection, is strongly pro-inflammatory, and is the most potent acid inhibitor known.[19] Certain polymorphisms of the IL-1beta gene (carriers of IL-1B-551 *T) and the IL-1 receptor antagonist gene (IL-1RN*2/*2) have been associated with a high risk of gastric carcinoma. Host genetic factors that influence IL-1beta may determine why some individuals infected with *H pylori* develop gastric carcinoma while others do not.[17]

Treatment Methods

Endoscopic Mucosal Resection (EMR)

Endoscopic Mucosal Resection (EMR) is an endoscopic alternative to invasive surgery for early gastric cancer (EGC). EGC is defined as a cancerous lesion confined to the mucosa or submucosa regardless of the presence of perigastriac lymph node metastases (LNM).[19]

Japanese people are now aware of the high incidence of gastric tumours. Most cases are discovered incidentally through routine screenings using oesophagogastroduodenoscopy during annual checkups. While mass-screening programmes using barium meal ingestion may be performed, Gotoda mentions that only 10% of gastric carcinomas are detected by this method. More than 50% of all gastric cancers identified in Japan are EGC, versus 5% or less in the West.[19] For EGC, it is more sensible to offer a local treatment rather than radical surgery in terms of high risk of complications and poor quality of life following the operation.[19] EMR, therefore, has become more widely used

in recent decades.

The original criteria for tumours amenable to EMR include elevated lesions less than 2 cm in size, depressed lesions less than 1 cm in size with no ulceration, and well-differentiated lesions. It must be emphasised that EMR can be performed only when the possibility of LNM has been excluded.[19]. The presence of LNM plays an important role in patient prognosis, and accurate histological assessment is required prior to the procedure.[5] However, it can be difficult to define the degree of mucosal invasion. In fact, 20 percent of pre-treatment diagnoses are incorrect. Overall, 5-year survival for EMR is similar to the outcome with more invasive gastrectomy.[19] With EMR, the recurrence rate is 4.2%, requiring repeat mucosectomy; however, the cumulative cure rate is between 90 and 100%.[5]

Fig. 1 Schematic drawing of the strip biopsy of EMR. **(a,b)** The lesion is identified and saline is injected into the submucosal flat to elevate the tumour. **(c)** The snare is placed around the lesion, which is elevated by use of the grasping forceps. **(d)** The snare is tightened around the base producing a polyp, which is removed with diathermy.[22]

FIG 2 (Credit: Gotoda)

Endoscopic Submucosal Dissection (ESD)
Another endoscopic procedure has been introduced into the NCCH called 'endoscopic submucosal dissection (ESD),' which utilizes an insulation-tipped (IT) needle knife. ESD enables larger en-bloc resection than EMR, and is associated with fewer local recurrences. It also offers precise and complete histological assessment.[23] It is especially beneficial for performing one-piece resection and lowering recurrence rate. ESD operations use an IT knife, hook knife and flex knife, followed by marking, injection, pre-incision, mucosal cutting, submucosal dissection and endoscopic management for complications.[19,23]

Fig 3: Mucosal cutting and Submucosal dissection using IT knife
ICC 200;   Endocut 80W effect 3, VIO 300D; Dry cut 50W effect 4 (Credit: Gotoda)

Surgery
At NCCH nearly 500 patients undergo gastrectomies each year. Gastrectomy with

extended lymph node dissection (D2 gastrectomy) has been the gold standard of surgery in Japan. More than two-thirds of the stomach is usually dissected, with over 25% of operable gastric cancers accompanied by seven to fifteen LNM.[24] Japanese doctors number the lymph nodes surrounding the GI tract into 16 groups in order to identify the LNM more efficiently.

Fig 4

CUT THIS OUT? DO WE REALLY NEED AN EXPLANATION OF TNM INCLUDED?

A modified TNM classification is commonly used for gastric carcinoma in Japan. T categories demonstrate the areas into which tumours invade, N categories indicate the numbers of lymph nodes involved, M1 shows metastasis to other organs, H1 demonstrates hepatic metastasis, P1 is peritoneal dissemination and CY1 indicates the presence of cancerous cells. T1 denotes invasion to the lamina propria and submucosa, T2 to the muscularis propria and submucosa, T3 involves penetration into the serosa, and T4 indicates invasion into adjacent structures. Nodal involvement is broken into subgroups N0 for no lymph node involvement, N1 for 1-6 nodes involved, N2 for 7-15 involved, and N3 for greater than 15 affected. [26]

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Table 1 Stage Grouping for Gastric Cancer

	N0	N1	N2	N3
T1	Ia	Ib	II	IV
T2	Ib	II	IIIa	IV
T3	II	IIIa	IIIb	IV
T4	IIIa	IIIb	IV	IV
H1,M1 P1, CY1	IV	IV	IV	IV

Source: Japanese Classification of Gastric Carcinoma (1999)

CUT GRAPH OUT?

Although there are no significant long-term survival differences between limited LN dissection (D1) and extended LN dissection (D2) in Europe, it should be considered that the skills and experience of doctors may vary. Comparison studies reveal that the

hospital mortality rate of patients under 70 years old is 5.9% in the Netherlands, versus 0.8% in Japan.

Table 2 Survival rates (%) of Stomach cancer at the National Cancer Center

Hospital (1990～1994)

Stage	No. of cases	1-year	2-year	3-year	4-year	5-year
I	757	97.9	96.8	94.3	92.6	91.2
II	122	95.7	90.4	86.1	82.7	80.9
III	187	84.5	66.3	61.3	56.0	54.7
IV	224	55.2	26.8	15.7	9.4	9.4
Total	1,290	88.3	79.7	75.5	72.6	71.4

Source: Gastric Cancer Research Group, National Cancer Centre Hospital (new cases admitted during 1990-4)[26]

From the latest statistics at the NCCH provided in Table 2, D2 gastrectomy has provided good therapeutic outcome for patients with EGC, especially in those contracting Stage I or II stomach cancers.[26] The overall 5-year survival rate is 96%, and the surgery mortality rate less than 2%.[24] This suggests that good prognosis using this method has been achieved.

Chemotherapy

Approximately 49,500 patients with gastric carcinoma die yearly in Japan.[1] Some may have suffered a relapse gastric carcinoma after successful surgery, with or without metastases into adjacent organs. Others may have had an aggressive gastric carcinoma which invaded other organs (Stage IV). For these advanced gastric cancers (AGC), the surgical approach is of little or no benefit, and curative treatment becomes impossible. Only chemotherapy can improve patients' quality of life and prolong survival.

Chemotherapy is a systemic treatment which targets not only cancer cells but normal cells as well.[28] Adverse effects include nausea, vomiting, diarrhoea, fatigue, alopecia, numbness and pigmentation in the extremities, anaemia, leukopenia and increased fragility of the nails. Randomly controlled trials comparing the benefits of chemotherapy and supportive palliative care have shown a significant difference in the

median survival time (MST) to be 6-9 months versus 3-4 months respectively.[28]

The development of new agents and different drug combination regimens has brought about major improvements to the treatment of AGC in the last decade. However, no universal "gold standard" currently exists. Single use of chemotherapeutic agents (e.g. 5-FU (fluorouracil), mitomycine C, CDDP (cisplatin), irrinotecan (CPT-11), docetaxel, paclitaxel, tegafur/ uracil, 5'-doxifluridine, and S-1) and combinations of these agents (i.e. 5-FU + CDDP, methotrexate (MTX) and 5-FU + leucovorin, 5-FU + l-leucovorin (l-LV), and irrinotecan + CDDP) are widely used throughout the world. FAMTX (5-FU+ ADM + MTX) are most commonly used in Western countries.[28] S-1 has become one of the standard agents for AGC in Japan, where it was initially developed. S-1 is a novel oral fluoropyrimidine derivative, in which the oral 5-FU prodrug, tegafur, is combined with two 5-FU modulating substances - gimeracil (5-chloro-2,4-dihydropyridine) and oteracil (potassium oxonate) at a molar ratio of 1: 0.4: 1. It was designed to improve antineoplastic activity while reducing side effects, particularly GI disturbance.[31] As it is the very first oral alternative to the conventional intravenous administration of 5-FU, a large number of studies have been performed. The MST of S-1 is 7-8 months, which is comparable to that of 5-FU, and its response rate (RR) reaches 50%.[24]

Combination therapies improve the chances of survival in comparison to use of the single-agent 5-FU.[29] A combination of 5-FU + anthracyclines + CDDP achieves the best survival rates. In particular, the ECF combination (epirubicin + CDDP + continuous infusion of 5-FU) is tolerated best by patients.[29] Thus, ECF therapy has been recommended as a new standard regimen in Europe.[28] In the USA, there is also a shift towards using DCF (docetaxel + CDDP + 5-FU) as a new standard of chemotherapy.[30] In contrast, a randomized phase III trial of combination 5-FU + CDDP (FP) therapy versus 5-FU alone was carried out by the Japan Clinical Oncology Group (JCOG), and found in favour of treatment with 5-FU alone.[30] The JCOG study concludes that 5-FU alone should remain as a standard treatment for advanced gastric carcinoma .[32] However, the results of emerging studies may suggest new gold standard chemotherapy regimens for AGC treatment in Japan.

Conclusion

With the improvement of conventional therapy and the development of new therapies, the mortality rate of gastric cancer has gradually decreased over the last decade. This is

mainly due to a decrease in incidence, not a favourable change in curability rates.[31] The high incidence in Japan may be related to several environmental factors, including high consumption of salt, *H. Pylori* infection, cigarette smoking, family history, and low intake of ascorbic acid, carotene and vitamin E. Therefore, it has been postulated that ascorbic acid supplementation or eradication of *H Pylori* infection may reduce the risk of developing gastric carcinoma.[10] Migration studies also indicate that environmental factors play an important role in the aetiology of gastric carcinoma.[2,3]

There are three distinct approaches to gastric cancer in Japan: endoscopic mucosal resection and endoscopic submucosal dissection, D2 gastrectomy and chemotherapy. The surgical procedures for early gastric carcinoma result in good survival rates. However, mean survival time for advanced gastric carcinoma treated with chemotherapy is low, at 6-9 months on average and 9-11 months at longest.[24] Chemotherapy agent used in Japan, S-1, has the advantage of being safely administered orally, with a moderate response similar to that of 5-FU.[28,30] It should be considered that the efficacy of the drug may vary depending on ethnic origin. The toxicity profile of Caucasian patients with gastric cancer differs from Japanese patients, and Caucasians present with more diarrhoea and hand-foot syndromes, but less myelotoxicity.[31] These highlight the need for further global studies regarding treatment approaches towards gastric cancer.

Acknowledgements

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