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Gastric Cancer – An Overview

K M Chu,* FRCS(Ed), FACS, FHKAM(Surgery), FCSHK
Department of Surgery
Queen Mary Hospital

Summary

Gastric cancer remains the second leading cause of cancer-related deaths worldwide. Apart from dietary factors, Helicobacter pylori is currently considered as one of the most important risk factors. The incidence of gastric cancer in Hong Kong is not high enough to justify population screening with upper endoscopy. Clinical features, however, can be quite non-specific. Patients may be asymptomatic, especially during early stage of the disease. Upper endoscopy should be considered in patients presenting with recent onset of ulcer-like symptoms, weight loss, symptoms of obstruction, bleeding or anaemia, especially if they are elderly. By the time clinical features of metastases are apparent, the disease would be beyond cure. In recent years, endoscopic ultrasonography and staging laparoscopy have greatly enhanced the pre-operative staging accuracy. Such information will be important if neoadjuvant chemotherapy is contemplated for advanced disease. At present, surgery remains the mainstay of potentially curative treatment. Post-operative adjuvant chemotherapy is not recommended unless on a proper trial basis. Early results of pre-operative neoadjuvant chemotherapy are encouraging but further studies are required to confirm its efficacy. For unresectable gastric cancer, various treatment options are available and selection has to be individualised. (*HK Pract* 1999;21:357-364)

摘要

胃癌在世界上佔癌相關死因的第二位。目前幽門螺旋菌被認為是飲食因素外最重要的危險因素之一。香港胃癌的發病率尚未算太高無須使用胃鏡做人群的篩選。但是因為胃癌的臨床表現不具有特異性，特別在疾病的早期，病人可以毫無症狀。如果病人近期有潰瘍樣症狀、體重減輕、梗阻、出血、貧血等症狀，尤其是老年人，就應考慮使用胃鏡檢查。到出現明確的轉移症狀時，便不可能治愈了。近年來，內窺鏡超聲檢查和分級腹腔鏡檢查大大地提高了手術前分級的精確度，這些資料對晚期病人使用新型輔助化療很重要。現在手術仍是胃癌主要的治療方法。除非作為研究，否則不建議使用術後輔助化療。術前新型輔助化療的結果令人鼓舞，但還有待進一步研究。對無法手術的胃癌，可考慮按病人個人情況選擇其他治療方法。

Introduction

Despite a steady decline in incidence in many developed countries, gastric cancer continues to be the second leading cause of cancer-related deaths worldwide.[1] In Hong Kong, it is the fourth leading cause of cancer-related deaths.[2] Complete surgical extirpation of the tumour remains the mainstay of potentially curative treatment. If discovered early, prior to dissemination of disease, gastric cancer is curable after surgical resection. Nevertheless, despite advances in medical knowledge and technology, gastric cancer is rarely diagnosed at an early stage. In Japan, where the incidence of gastric cancer is high and screening is practised, early

* ***Address for correspondence:*** *Dr. K M Chu, Associate Professor, Division of Upper Gastrointestinal Surgery, Department of Surgery, University of Hong Kong Medical Centre, Queen Mary Hospital, Pokfulam Road, Hong Kong.*

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gastric cancer confined to the mucosa or submucosa constitutes about 50% of all new cases.[3] In Western countries as well as in Hong Kong, however, approximately two thirds of patients with gastric cancer present with stage III or IV disease.[4] Curative surgical resection is therefore impossible in the majority of patients. The prognosis of the disease remains dismal because of the delay in presentation as well as a high recurrence rate despite an apparent curative resection for advanced disease.

Epidemiology

Gastric cancer has a predilection for males in virtually every population studied. Geographically, there is wide variation in incidence of gastric cancer in different parts of the world. Japan has one of the highest incidence in the world; the incidence rate in Japan is about 8.5 times that observed in North America. Other areas with high incidence include, for example, China, Costa Rica, Korea, Chile, Poland, and the former Soviet Union. Various epidemiological studies have examined a number of potential risk factors which might help explain the global variation in incidence. In general, gastric cancer appears to have a multifactorial aetiology, and the etiological factors may have different relative importance in different parts of the world. Traditionally, dietary factors have been given the greatest emphasis, although there is no single dietary item that could account for all the differences in cancer incidence. Gastric cancer has previously been reported to be associated with an increased dietary intake of N-nitroso compounds, nitrites and salts, and a decreased intake of ascorbate, fresh fruits and vegetables.[1] Allium vegetables, like onion and garlic, may play a protective role by detoxifying carcinogens.[5] Other risk factors for gastric cancer include smoking, a past history of partial gastrectomy, family history of the disease, pernicious anaemia, atrophic gastritis, Menetrier's disease, and adenomatous polyps of the stomach.

Nowadays, *Helicobacter pylori* has been considered as one of the most important risk factors for gastric cancer. The International Agency for Research on Cancer (IARC) of the World Health Organisation has recently classified *H. pylori* as a Group I carcinogen, a definite cause of gastric adenocarcinoma in humans.[6] More evidence has been accumulated to support its role in gastric carcinogenesis.[7] It is not yet certain whether global eradication of the bacteria will help in bringing down the incidence of the disease. A vaccine for the prevention of chronic *H. pylori* infection is not yet available for clinical use. Screening for and eradication of *H. pylori* in asymptomatic individuals is currently not recommended.

Pathology

Macroscopically, gastric cancer could be divided into four types according to the Borrmann's classification (1926): polypoid, fungating, ulcerative, and infiltrative. Linitis plastica represents a special type of gastric cancer which infiltrates diffusely below the gastric mucosa. Endoscopically, the stomach with linitis plastica appears rigid but there is no macroscopic mucosal lesion.

Histologically, the Lauren's classification (1965) separates gastric cancer into intestinal and diffuse types. These two types of carcinoma differ from each other with respect to their epidemiology, pathogenesis, and behaviour. In general, the intestinal type of carcinoma is more distally located and is associated with a better prognosis in comparison with the diffuse type.

Gastric cancer disseminates by four main routes. Locally, gastric cancer may infiltrate directly into surrounding structures like pancreas, transverse colon, mesocolon or liver. Lymphatic spread to the regional lymph nodes is common and supraclavicular lymph node metastasis signifies systemic spread. Liver is one of the common organs involved by haematogenous spread. When a gastric cancer penetrates the serosa, cancer cells may exfoliate into the peritoneal cavity resulting in peritoneal dissemination, or transcoelomic spread. Apart from peritoneal seedlings and ascites, the ovary may be involved by transcoelomic spread (also called Krukenberg tumour).

The staging of gastric cancer is according to the TNM evaluation. T stands for the penetration of the gastric wall by the primary tumour. N stands for the nodal involvement while M represents systemic metastasis. There are three staging

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systems in use. The International Union Against Cancer (UICC) classification is the same as the American Joint Committee on Cancer (AJCC) classification.[8] The Japanese Research Society for gastric cancer (JRSGC) classification differs from the other two classifications mainly in the N staging criteria. While the most recent edition of UICC/AJCC classification categorises N according to the absolute number of lymph nodes being positive for metastases,[8] the JRSGC classifies lymph nodes into different stations according to their location in relation to the primary tumour.[9] The interested reader may refer to the relevant literatures for further details.

Clinical features

Clinical features can be quite non-specific. Patients may be asymptomatic, especially during early stage of the disease. On the other hand, patients with advanced disease may present with non-specific symptoms like anorexia, weight loss, and malaise. Symptoms such as epigastric pain and distending discomfort may mimic benign ulcer disease. In fact, treatment with ulcer healing drugs either by the patients themselves or by the unwary medical practitioner accounts for a significant proportion of delay in diagnosis. Otherwise, the presentation of gastric cancer depends on its location, whether it has produced any complication, and whether it has metastasised. Obstructing tumours in the gastric outlet may produce symptoms like distending discomfort or vomiting. Tumours in the gastric inlet (or cardioesophageal junction) may give rise to dysphagia. Bleeding from gastric cancer could be overt or occult. Occult bleeding may lead to symptoms of anaemia ultimately. Acute presentation with symptoms and signs of upper gastrointestinal bleeding like coffee ground vomiting and melaena is not infrequent. Acute free perforation of gastric cancer, however, is uncommon and the presentation is not different from perforation of benign peptic ulcer. Patient with advanced disease may present with an abdominal mass which could be due to a bulky primary tumour, omental secondary, or ovarian secondary (Krukenberg tumour). Clinical features of patients with systemic metastases are dependent on the location of metastases (**Table 1**). Acanthosis nigricans is an uncommon phenomenon associated with adenocarcinoma of the gastrointestinal tract, especially gastric cancer. It appears as hyperpigmented, velvety plaque that often affects the neck, axilla, flexor areas, and anogenital region. The cause of this hyperpigmentation is currently unknown.

Investigations

Laboratory investigations are usually unhelpful for diagnosis. Anaemia may be present as a result of bleeding. Flexible upper endoscopic examination is the most useful and specific investigation. In the presence of a gastric ulcer or any suspicious gastric lesion, multiple biopsies should be taken for histologic examination even if it appears benign endoscopically. Barium meal examination is seldom required unless endoscopic facility is not readily available. Serum tumour markers such as carcinoembryonic antigen (CEA) and CA 19-9 are non-specific and cannot be utilised for diagnostic purposes. On the other hand, tumour markers may be helpful

Table 1: Clinical features in the presence of metastatic disease

Metastases	Clinical features
Supraclavicular lymph node	Enlarged supraclavicular lymph node
Pleura, lung	Dyspnoea, pleural effusion, haemoptysis
Peritoneum	Abdominal distension, ascites, mass, bowel obstruction
Portal lymph node	Obstructive jaundice
Liver	Hepatomegaly, jaundice (late stage)
Umbilicus	Sister Joseph's nodule
Ovary	Ovarian mass (Krukenberg tumour)
Pelvis	Pelvic nodule, rectal (Blumer's) shelf
Bone	Bone pain, pathological fracture
Brain	Neurologic deficit, change in conscious state

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in patients known to have the disease with raised titres for monitoring response to therapy and detection of recurrence.

After histological confirmation of gastric carcinoma, the clinician's task is to determine whether the patient is suitable for surgery. This will mainly involve the assessment of the patient's fitness for general anaesthesia as well as screening for metastatic disease. Clinically obvious metastatic disease should have been identified during the physical examination. A plain chest x-ray is recommended for screening metastatic disease as well as for pre-operative assessment. Ultrasonography or computed tomography (CT) are of value in the identification of ascites, liver metastases, or para-aortic lymphadenopathy. Ultrasonography, however, is operator dependent. Specific investigations may be applied for clinically suspicious metastatic disease. Fine needle aspiration for cytology, for example, would be arranged for enlarged supraclavicular lymph node.

In recent years, endoscopic ultrasonography (EUS) has been found to be one of the most accurate methods for assessment of T and N stages of gastric cancer. Its accuracy is dependent on the experience of the endoscopist. At present, usage of EUS is best limited to specialist centres where an accurate pre-operative staging is important as guidance for inclusion in neoadjuvant chemotherapy trials.[10] Its use is probably not warranted in centres where knowledge of T and N staging will not affect the surgical decision.

Advanced gastric cancer frequently spreads through the peritoneal route. Such peritoneal seedlings are usually small in size initially and not visible even on CT scanning. Laparoscopy permits direct visualisation of the peritoneal cavity and is the most sensitive and specific modality for the detection of peritoneal metastases. The detection of peritoneal dissemination may obviate the need for laparotomy in patients who do not require any palliative surgery for bleeding or obstruction.

Management

Infrequently, gastric cancer may perforate acutely with clinical signs of peritonitis. An emergency gastric resection may be performed if the patient's condition is stable enough to withstand the procedure. A significant proportion of such patients can be saved and offered good palliation by emergency gastrectomy.[11] In the elective situation, the management of gastric cancer depends on the fitness of the patient and the clinical stage of disease on presentation. At present, surgery remains the mainstay of potentially curative treatment. If the patient is medically unfit for surgery, only non-surgical options could be offered.

In Hong Kong, gastric cancer is rarely diagnosed at an early stage. In Japan, where screening is practised, early gastric cancer confined to the mucosa or submucosa constitutes about 50% of all new cases. Radical gastric resection for such patients carries a five-year survival rate of about 90% in most series. The distinctly lower incidence of lymph node metastasis in early mucosal cancer, coupled with the morbidity associated with standard radical gastric resection, has led to the introduction of other forms of treatment. Such treatment options can be broadly classified into endoscopic, laparoscopic and open surgical techniques. Of the various endoscopic techniques, endoscopic mucosal resection (EMR) is probably the best known. The success of EMR requires that the lesion is limited to the mucosa and that there is no lymph node metastasis. Endoscopic ultrasonography is very helpful is this respect. The general selection criteria for EMR include mucosal lesion, well-differentiated adenocarcinoma, lesion of not more than 2 cm in diameter and absence of ulceration. For larger lesion or lesion that invades the submucosa, laparoscopic wedge resection or partial gastrectomy have been performed in various centres. Modifications to the open surgical technique include wedge resection, pylorus-preserving gastrectomy, vagus-preserving gastrectomy, and D1 radical gastric resection. D1 indicates lymph node dissection of the first tier of lymph node stations (N1) under the Japanese (JRSGC) classification.

The majority of gastric cancer diagnosed in Hong Kong, as in other Western countries, is advanced. The standard treatment of such patients involves radical gastric resection whenever the disease is deemed resectable. The extent of resection

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depends on the location of tumour. Distal subtotal gastrectomy is indicated for a distal lesion while total gastrectomy is indicated for a lesion in the body or proximal stomach. Splenectomy or distal pancreatectomy is avoided unless there is direct tumour involvement. Splenectomy is associated with a marked increase in septic complications. The issue of extended lymph node dissection has not been settled. The value of D2 lymph node dissection, removing the second tier of lymph node stations (N2) under the JRSGC classification, has not been proven with two recent prospective randomised trials comparing D1 with D2 dissection.[12-13] These studies were, however, criticised for being multi-centre trials as well as for their high morbidity associated with distal pancreatectomy. At present, extended lymph node dissection is best limited to surgeons with experience in the procedure. Extended lymph node dissection by inexperienced hands, albeit out of good will, may do more harm than good to patients.

The results of surgical resection vary between different centres.[14] In general, the prognosis worsens with increasing pathological stages. As a rough guideline, the five-year survival rates after resection for stages I, II, III, and IV diseases are about 85%, 50%, 25%, and 10%, respectively.

The value of postoperative adjuvant chemotherapy has been questioned. In the hope of reducing recurrence after surgical resection, various studies on adjuvant chemotherapy have been performed with contradicting results. A meta-analysis of published randomised trials on adjuvant chemotherapy after curative resection for gastric cancer did not reveal any significant survival benefit.[15] This study was subsequently criticised for omitting one Japanese randomised trial. At present, adjuvant chemotherapy is not recommended after surgical resection. Its use should be restricted to a proper trial setting.

In view of the disappointing results associated with the use of post-operative adjuvant chemotherapy and the high recurrence rate after an apparent curative resection, pre-operative neoadjuvant chemotherapy has been introduced. Neoadjuvant chemotherapy may help reduce locoregional tumour volume and downstage the disease and thus increase the chance of complete tumour resection. Accurate pre-operative staging, including the use of endoscopic ultrasonography and staging laparoscopy, is necessary for patient selection and proper analysis. Early results were encouraging but genuine survival benefit has yet to be confirmed by proper randomised trials.

In the presence of systemic metastases, gastric resection is generally not indicated. For patients with synchronous liver metastases, palliative gastrectomy did not confer any prolongation of survival nor improvement in quality of life.[16] Palliative surgery may, however, be indicated in patients with obstruction or profound bleeding. A palliative bypass in the form of gastrojejunostomy may be performed for outlet obstruction. Alternatively, for patients who are unfit for general anaesthesia, a self-expanding metallic stent could be deployed endoscopically across the site of obstruction. Pain control is an important facet of palliative management and should not be overlooked. In the presence of a partially obstructed gastrointestinal tract, transdermal narcotics would be an useful alternative to oral medication. Neurolytic blockade of the coeliac ganglion by the anaesthetist could provide lasting relief for selected patients having tumour infiltration of the retroperitoneum.

Systemic chemotherapy has been considered to be a possible treatment option for unresectable gastric carcinoma. Several randomised trials have confirmed survival benefit for unresectable disease treated with systemic chemotherapy in comparison to best supportive care alone.[17-19] FAMTX (a methotrexate-based regimen consisting of 5-Fluorouracil, doxorubicin, and methotrexate) has been a gold standard in the early 90s. More recently, ECF (an infusional 5-Fluorouracil-based regimen consisting of epirubicin, cisplatin, and 5-Fluorouracil) was found to be a more active regimen than FAMTX.[20] Although the results of the various new systemic chemotherapy regimens have been encouraging, the gain of prolonged survival is, not infrequently, offset by systemic toxicity which may lengthen hospital stay, prolong suffering, and deprecate the quality of survival.

In the hope of reducing the systemic toxicity, we have recently

Figure 1a: Contrast CT scan abdomen of a patient with carcinoma of stomach and multiple bilobar liver metastases (arrows) before chemotherapy

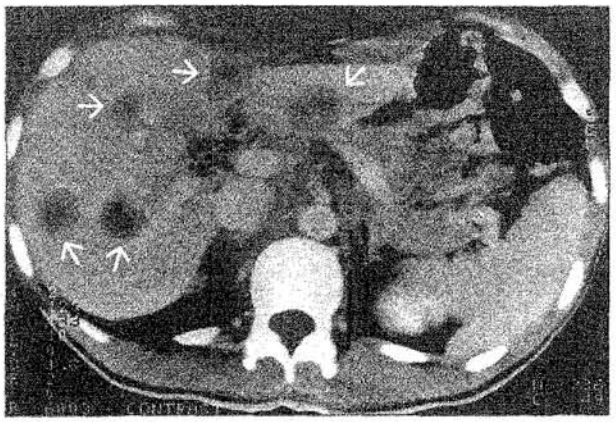
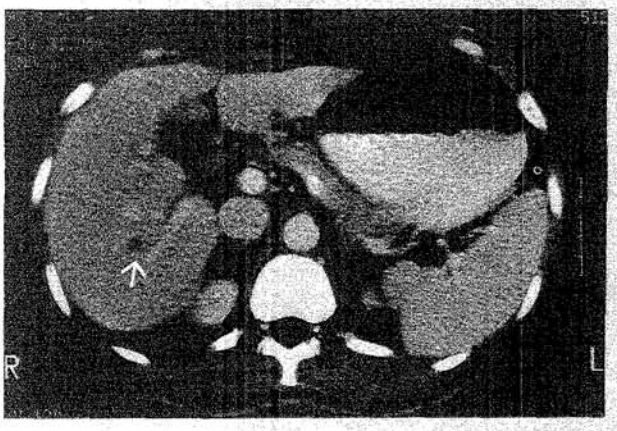


Figure 1b: Reassessment CT scan of the same patient revealing significant response of the liver metastases to regional intra-arterial chemotherapy. His primary tumour (arrow) also disappeared completely after chemotherapy



introduced the use of regional intra-arterial chemotherapy for unresectable gastric carcinoma (**Figures 1a & 1b**). Regional intra-arterial chemotherapy maximises the local concentration of chemotherapeutic agents and minimises levels in the systemic circulation. The local effects may thus be enhanced while systemic side effects are obviated as far as possible. Our results so far are encouraging with a clinical response rate comparable to the best systemic regimens while the systemic toxicity is minimal.

Conclusion

The management of gastric cancer has evolved over the years. With better understanding of its epidemiology and etiological factors, preventive measures may hopefully further reduce its incidence in the future. The issue of *Helicobacter pylori* eradication or vaccination as a preventive measure is currently unsettled. Surgery still remains the most important treatment for resectable gastric cancer. It is very important for the family physician to be aware of the non-specific presentations of gastric cancer. For patients with suspicious symptoms, immediate investigation, preferably with upper endoscopy, should be arranged. The only hope for cure is to diagnose the disease at its early stages. The role of pre-operative neoadjuvant chemotherapy will be further clarified with ongoing studies. For unresectable disease, various treatment options are available nowadays. The quality of life of these patients should not be ignored when palliative treatment is being offered. ■

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Key messages

1. *Helicobacter pylori* is considered as one of the most important risk factors for gastric cancer. However, screening for and eradication of *H. pylori* in asymptomatic individual is currently not recommended.
2. Patients with suspicious symptoms should be investigated promptly, preferably with upper endoscopy. Do not wait until the patient develops obvious signs of metastases.
3. Surgery remains the mainstay of potentially curative treatment.
4. Various treatment options are available for unresectable gastric cancer and selection has to be individualised.

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