Progress in the management of solid tumours

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Gastric cancer

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Summary

We are gaining a clearer insight into the causes and mechanisms of gastric carcinogenesis, and may be able to reduce the incidence in the future by *Helicobacter pylori* eradication, perhaps in conjunction with nutritional supplements. The work required to establish this kind of prevention programme still has a long way to go. Surveillance and early detection are a key area, and current hopes rest with an increasingly low threshold for gastroscopy together with improved awareness in both patients and general practitioners. Identification of a high-risk group for surveillance would be a major advance, and may become possible due to advances in molecular biology. In terms of treatment, surgery remains the mainstay, but for useful analysis of its efficacy, uniform and detailed pathological staging is vital. Pre-operative assessment has improved greatly in recent years, resulting in fewer nontherapeutic laparotomies, thanks to a combination of improved imaging techniques and laparoscopy. Limited endoscopic surgery is now feasible for very early disease. The extent of radical surgery remains controversial: a strong argument can be made for concentrating this kind of surgery in the hands of a limited number of specialist units who will have the numbers and the expertise to answer the outstanding questions. Chemotherapy has yet to prove its value, but there are hopes that the newest regimes may do this. Treatment results in the West remain unsatisfactory, but they have improved in the last two decades, and should be capable of considerable further improvement.

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Gastric cancer has an old and evil reputation, and has retained its aura of incurability in the minds of many doctors. The commonly held belief that it is a disease in rapid decline provides false comfort in Britain, where the decrease has been gentle, and stomach cancer still rates fourth or fifth as a cause of cancer death in this country. The key to improving survival is early detection combined with appropriate surgery. In both areas the rest of the world has much to learn from the Japanese, who have long struggled with the greatest problem in numerical terms, with some notable success. Many of the factors which have contributed to the progress achieved by the Japanese are unique to their population, culture and healthcare system, however, and it would be unwise to adopt their practices without bearing this in mind.

Advances in understanding the disease

EPIDEMIOLOGY

There has been a decline in gastric cancer incidence world-wide since the 1940s. This has been dramatic in some countries such as the US and Australia. The incidence of the disease varies greatly in different parts of the world. Epidemiologists are working towards explanation of these historical and geographic variations. The countries with the highest incidence are Japan and China, with other Far-Eastern countries, those of Eastern Europe and the Andean countries of South America also recording high rates.¹ The countries with the lowest rates are Australia and the US. There is a more than 10-fold difference in incidence between the extremes. Differences in diet appear amongst the most likely explanations for these geographic and historical contrasts. The high incidence areas can be loosely characterised as having a high-starch diet, low in fresh fruit and vegetables. This has suggested hypotheses implicating deficiency of particular vitamins and micronutrients such as vitamins A, C and E, and dietary supplementation projects have begun in several countries. Salt used in the preservation of food has also been implicated.² Historically, the reduction in stomach cancer incidence occurred most quickly and dramatically in areas where refrigeration replaced salting. There are also pathophysiological arguments for implicating salt. High salt concentrations enhance the conversion of nitrates to nitrites and potentially to carcinogenic *n*-nitrosamines in the stomach.³

The newest important environmental factor implicated by population studies is infection with *Helicobacter pylori*. *H. pylori* infection is too common to be considered a direct precursor of cancer, but probably creates the conditions for carcinogenesis by inducing chronic inflammation, atrophy and metaplasia. There is a very strong correlation between the population incidence of *H. pylori* infection and the incidence of gastric cancer. Calculations suggest that a population with a 100% infection rate would have a cancer incidence five times higher than one with a zero incidence.⁴ The fact that infection alone is insufficient and that other environmental factors are likely to be important is illustrated by the existence of communities with a high incidence of *H. pylori* infection and a low incidence of gastric cancer.⁵

The relative incidence of different types of gastric cancer is undergoing important changes. The intestinal type of disease (see below) is much more variable worldwide, and is the common type in countries with a high incidence: diffuse cancer has a rather more constant international incidence. Cancer of the proximal stomach, particularly the cardiac area, has increased in recent years whilst all other types have declined.^{6,7} This type of cancer may have a similar aetiology to adenocarcinoma of the lower oesophagus, which has also increased remarkably in incidence over recent years. The prognosis for these proximal cancers is noticeably poorer than that of distal tumours, perhaps for anatomical reasons.

MOLECULAR BIOLOGY

The molecular biology of gastric cancer is not as well understood as that of colonic cancer, but rapid progress is being made. There are a number of similarities with other tumours of the gastrointestinal tract, but gastric cancer also has its' own distinctive pattern of genetic abnormality. Abnormal activity of growth factors, or their receptors, is commonly found. Enhanced expression or amplification of the growth factor receptors c-erbB2 and c-met (the hepatocyte growth factor receptor) as well as K-sam and others, has been reported.⁸ Like most other solid tumours, gastric carcinomas often express mutated and non-functional forms of the apoptosis-related genes p53 and bcl-2.^{8,9} The two morphological forms of stomach cancer have rather different patterns of associated genetic abnormality. E-Cadherin and the catenins, a group of associated proteins which subserve cell-adhesion functions, are more frequently abnormal in diffuse cancer.¹⁰ Attempts are now being made to use molecular biology to address important clinical questions. Comparisons have been made between cancer in high (Japan) and lower (UK) incidence areas. So far these have failed to show any convincing difference in the molecular biology of the tumour.¹¹ p53 Abnormalities have been reported in a small proportion of cases of intestinal metaplasia or dysplasia¹³; this may prove a useful marker for potentially premalignant tissues, but this has yet to be demonstrated. Tahara⁸ has proposed a mechanism for the pathogenesis of the two Lauren types of gastric cancer based on the differences in their molecular biology noted to date, and this has provided a useful model for further research.

CLASSIFICATION

Accurate systems for staging and grading allow prediction of prognosis, and therefore better comparison of treatments. The work of Japanese pathologists has been very valuable in this respect. The Japanese classification of lymph node metastasis is very detailed and soundly based on exhaustive clinical and pathological studies (figure). A number of anatomical 'stations' are recognised and are assigned to nodal tiers between n1 and n4 depending on their anatomical proximity to the tumour.¹³ The different staging systems used in Europe, America and Japan have hindered mutual understanding, but a recent attempt to unify the Japanese, American and International Union Against Cancer staging groups represents a promising way forward.¹⁴ A major difficulty which has complicated comparisons of Japanese and Western experiences is the 'stage migration' phenomenon. This occurs because of the extensive lymph node dissection practised by Japanese surgeons, which naturally results in many more nodes being studied. This in turn reveals a proportion of cases with unsuspected positive nodes which would otherwise have been assigned to a

Figure Japanese lymph node classification. The numbers indicate the 'stations' or groupings of lymph nodes recognised by the Japanese around the stomach. As the table indicates, the selection of these for removal depends partly on the location of the primary tumour. D1 resection involves resection of all nodes regarded as 'n1' for a particular tumour: D2 involves resection also of all 'n2' nodes. Key: 1, right cardiac nodes; 2, left cardiac 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 around the coeliac 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 in the mesocolon of the transverse colon

Lymph node locations and groupings

Location	CMA	A,AM	MA,M	C,CM MC
Group 1 (n1)	1 2 3 4 5 6	3 4 5 6	3 4 5 6 1	1 2 3 4
Group 2 (n2)	7 8 9 10 11	7 8 9 1	2* 7 8 9 10* 11	5* 6* 7 8 9 10 11
Group 3 (n3)	12 13 14	2* 10* 11	12 13 14	12 13 14
Group 4 (n4)	consists of transverse mesocolon, para-aortal and perirenal nodes			

*Optional

lower stage. Overall, this has the apparent effect of improving the prognosis in all stages, since a proportion of cases in each would have been classified as less advanced but for the migration caused by the extended node dissection.¹⁵

Like other cancers, gastric cancer can be simply described as well, poorly, or moderately differentiated. Some cancers exhibit extensive mucus secretion or a massive fibrous reaction giving them a distinctive morphology, and these tumours are usually classified separately. Lauren described gastric cancers as intestinal and diffuse, and this has proved the most influential histological classification.¹⁶ The system is open to criticism, especially because most tumours exhibit features of both types of cancer somewhere, and up to 25% of cases remain unclassifiable. It is also true that the prognostic significance of the classification is not great.¹⁶ The saving grace of the Lauren system is its correlation with epidemiological and, more recently, molecular genetic findings, which suggest that there is a real biological difference between the two types. The Japanese system has five categories ranging from tubular to poorly differentiated, but correlates closely with the Lauren class. The system of Ming makes special note of the growth pattern and type of margin of the tumour and whether it has a lymphocytic infiltrate, but also fails to predict prognosis very well.¹⁷ A recent system devised by Goseki classifies tumours according to the degree of mucin production and tubule formation.¹⁸ Early reports suggest that it may have advantages over existing systems.¹⁹

Advances in detection and evaluation

The symptoms of gastric cancer are not particularly pressing, and the pain in particular is usually rather mild. Most of the classical signs of gastric cancer taught at medical school such as Virchow’s node, Blumer’s pelvic shelf, ascites and jaundice are those of incurable late disease. Perhaps the most useful feature in the history is the degree to which neoplastic dyspepsia is associated with profound anorexia (though only rarely with vomiting). A high index of suspicion is the best diagnostic aid: in the UK the diagnosis can be virtually ignored in the young, but new symptoms of indigestion, anorexia, vomiting or weight loss in the middle aged or elderly merit an urgent gastroscopy. Barium meal can be extremely sensitive if a prolonged double-contrast examination with a skilled team, high quality equipment and a compliant patient are combined. Outside Japan, gastroscopy has considerably greater sensitivity for early disease. Dye-spray gastroscopy techniques may assist in showing up subtle lesions which would otherwise be missed.

EARLY DETECTION INITIATIVES

The benefits of early detection in gastric cancer are substantial. Cancer confined to the mucosa has a less than 5% chance of involving lymph nodes, but once it reaches the submucosa this rises to 20%.²⁰ The five-year survival rate after radical surgery for early cancer is over 90%.^{21,22} Early gastric cancer may begin either *de novo* or more commonly against a background of obviously diseased mucosa. Lesions may ulcerate at this early stage but often heal over again either spontaneously or in response to antisecretory drugs. Progression to advanced cancer (the distinction is whether the primary tumour breaches the submucosal layer) probably takes an average of five years.²³ As many as 50% of early cancers produce some symptoms.²⁴ Early cancer is being diagnosed more frequently in Western countries, but not yet as commonly as in Japan, where 50% of all cancers are now diagnosed at this stage.²⁵ In Japan there are numerous programmes for ‘screening’ of the population over 40 by endoscopy or barium meal, but many of these leave the initiative to the individual, or are restricted to employees of a particular company and their dependents. The population covered by the screening programmes is only 13% of all Japanese,²⁶ despite which they have experienced a striking improvement in the stage at diagnosis over the last 30 years. In Western countries, and in many poorer countries with a high incidence, the problems of developing a general population screening programme which meets World Health Organisation criteria seem insurmountable. The tests available are sensitive and specific, but expensive, high-tech and relatively invasive. Cheaper tests based on analysis of serum or gastric juice for pepsinogens or other markers have lower specificity.²⁷ The ability of screening to detect the disease at a curable stage in a Western population is unproven. In the West many gastric cancer patients are old people with substantial comorbid pathology which effectively rules out curative radical surgery. In the face of this depressing picture, a number of attempts have been made to identify and investigate a high-risk group which might yield more worthwhile results if followed up. Open-access endoscopy has become widely practised, and this cuts down on delays and errors introduced during the

Case history 1

A 57-year-old ex-miner complains of intermittent mild indigestion for three months with two episodes of vomiting. There is no previous dyspeptic history. His symptoms are relieved by an H2-antagonist which he takes for two months. He returns after a further three months with recurrent indigestion, profound anorexia and an 18 pound weight loss. At gastroscopy he has an advanced cancer of the body and antrum.

Message: Always investigate persistent new dyspepsia in the over 40s. Treatment can mask cancer symptoms whilst disease progresses.

Case history 2

A 71-year-old widow who underwent Billroth I gastrectomy for peptic ulcer 28 years ago complains of tiredness and is found to be anaemic. The blood picture is normocytic but with anisocytosis and hypochromia; the B12 is borderline and the iron is low. Faecal occult blood testing with Haemoccult is positive. Gastroscopy reveals a 2.5-cm ulcerated carcinoma just proximal to the anastomosis, which is successfully resected.

Message: Consider the possibility of gastric cancer in the non specifically unwell older person. Survivors of ulcer surgery over 20 years ago are at increased risk.

process of general practitioner/specialist consultation. The population selected is still that which presents with symptoms to their family doctor, and this may explain why this strategy does not appear to have substantially improved the early detection of gastric cancer.^{28,29} An important study from the Midlands showed that introducing a system of liaison between general practitioners and surgeons had considerable success in identifying early cancers.³⁰ Although the proportion of early cancers increased to 25%, the demands placed on specialist resources make widespread adoption of the approach unlikely. We have recently conducted a study which attempted to encourage earlier presentation by alerting patients over 40 to the importance of dyspeptic symptoms by sending personalized letters. This has increased the endoscopy rate by 18–95%, but the effect on stage at presentation has yet to be analysed (to be published).

Diagnostic pitfalls in gastric cancer

- failure to think of the diagnosis
- masking of symptoms by inappropriate treatment
- failure to inflate the stomach at gastroscopy (linitis plastica)
- failure to identify the lesion at gastroscopy (difficult areas, linitis)
- failure to obtain biopsy confirmation (ulcer slough, linitis)

DIAGNOSTIC PITFALLS

There are a number of well-recognised pitfalls in the diagnosis of gastric cancer. Perhaps the commonest is failure to diagnose the malignant nature of an ulcer at first endoscopy due to inadequate biopsy. Malignant ulcers generate a good deal of necrotic slough, and it is not uncommon for this or reactive inflammatory tissue to be the only finding on biopsy if only one or two samples are taken. All gastric ulcers should therefore be biopsied at least six times, preferably from the edge of the crater just inside the wall, where viable tumour is most likely to be found. Clinical suspicion should lead to early re-biopsy without a prolonged trial of anti-ulcer medication. Failure to obtain either a positive biopsy or a good view of the mucosa is characteristic of linitis plastica. The infiltration of the stomach with fibrous tissue containing cancer cells renders it inelastic and incapable of inflation, whilst the depth at which the majority of cancer cells are found makes the normal small biopsy ineffective. The appearances of linitis at barium meal are characteristic. If there is no suspicion of any technical problem, a typical X-ray and history should merit laparotomy. Alternative measures are laparoscopy (see below) or fine needle aspiration cytology using a variceal injection needle down the gastroscope biopsy channel.

Failure to see or recognise the tumour is surprisingly common. The upper part of the lesser curve and the posterior wall of the body are the areas which are difficult to visualise ‘end-on’ at gastroscopy. Early lesions can be extremely subtle, and the only safe policy is to take repeated biopsies of any mucosal abnormality in patients over 45.

Advances in diagnosis and staging

- increased awareness amongst patients and general practitioners
- endoscopic ultrasound
- staging laparoscopy +/- cytology, endoscopic ultrasound
- modified CT techniques

STAGING

Staging is important to plan treatment tactics as well as for audit of outcome. Advances in imaging and surgical techniques have improved our ability to avoid nontherapeutic laparotomies whilst offering radical resection to all those likely to benefit. Clinical and gastroscopic findings can give a strong indication of potential curability but are not an adequate basis for the decision to operate. Computed tomography (CT) or ultrasound scanning will detect liver metastasis with perhaps 75% overall accuracy.^{31,32} Neither is particularly accurate in the evaluation of the primary tumour. Assessment of posterior fixation is particularly difficult, although this may be improved if the patient is scanned prone with a water-filled stomach.³³ Endoscopic ultrasound, on the other hand, is proving extremely valuable in the assessment of the primary lesion. It has the highest currently available accuracy for the degree of penetration of the wall and/or involvement of adjacent structures.³⁴ It is somewhat less accurate in the assessment of regional nodes, and indeed there are no modalities which can differentiate between larger reactive and involved nodes with any useful accuracy.^{35,36} Laparoscopy is being increasingly used as a regular part of pre-operative assessment.³⁷ Its greatest value is in the detection of peritoneal carcinomatosis, which renders the disease incurable but is extremely difficult to detect by any other means. Local invasion of the liver, diaphragm, colon and other structures can also be assessed, and liver metastasis can be detected on occasion when ultrasound or CT has failed. The value of laparoscopy may be extended by current attempts to perform peritoneal cytology during the procedure, or to examine the organs directly with an ultrasound probe passed via the scope.³⁹

Advances in prevention and treatment

PREVENTION TRIALS

Trials of preventative measures have begun only in recent times. The focus has been on vitamin supplementation and *H pylori* eradication. One large intervention trial in China reported that supplementation of the diet with beta-carotene, selenium and vitamin E reduced the incidence of gastric

cancer.⁴⁰ In the West several trials are currently studying vitamin C supplementation with or without eradication of *H pylori* and supplementation of other vitamins. Secondary prevention by surveillance of patients at high risk has been hampered by the large size and low relative risk of the known risk categories. Patients with dysplasia on biopsy are a small group, but those with intestinal metaplasia are much commoner. Attempts have been made to define the high risk group within this population, but the value of typing of the intestinal metaplasia remains controversial.^{40,41} Doubts have also been expressed about the value of prolonged follow-up of patients after gastrectomy for benign disease.⁴²

SURGERY

Early cancer

Early gastric cancer represents an oncologically ideal situation for curative surgery. A distinction should be made between mucosal cancer, where metastasis is very unlikely, and submucosal cancer, where it is much commoner. The argument in favour of radical surgery with extended lymphadenectomy at least to the D2 level (see below) is strongest in the latter type. In mucosal cancer, and in the very unfit, local treatment of the primary lesion may be considered. The Japanese now have much experience of the so-called ‘strip biopsy’ endoscopic resection technique. After the mucosa and submucosa are separated from the muscle layers by infiltration of saline and adrenaline solution, a large bite of mucosa and submucosa is resected using a diathermy snare.⁴³ The technique appears safe, and recurrence rates are very low providing the indications for surgery are strict, and any suspected failure to achieve complete resection is pursued.⁴⁴ Innovative attempts have been made to use laparoscopic approaches to lesions which are unsuitable for gastroscopic removal.⁴⁵

D2 versus D1

The classical curative treatment for gastric cancer is radical resection but two controversies have arisen over the meaning of this term. Total gastrectomy has been advocated for all gastric cancers because of the high rates of positive resection margins and local recurrence in many Western series of partial gastrectomies.⁴⁶ The Japanese have developed a much more extensive lymphadenectomy than is traditional in the West, and have made exciting claims for its superiority.⁴⁷ Advocates of total gastrectomy ‘de principe’ still exist but are few in number. Locoregional recurrence is usually a clear consequence of residual disease in the lymph nodes or peritoneum, whilst the symptomatic benefits of even a small retained gastric reservoir are considerable.

The controversy over extended lymphadenectomy is likely to continue. Japanese surgeons define *en-bloc* resection of the n1, n2 and n3 tiers of nodes defined by their staging system as D1, D2 or D3. The ideal curative operation removes one ring beyond that in which nodal metastasis can be expected. The standard operation for nonmucosal cancer is therefore D2 resection, which involves clearing the hepatic and splenic arteries of nodes, and may in some cases require splenectomy and distal pancreatectomy.⁴⁸ Western surgeons have usually restricted themselves to removing the nodes associated with the left gastric artery, and the greater omentum. Unfortunately the Japanese have been unwilling to conduct randomised clinical trials of their surgical approach. Two large prospective trials comparing the Japanese and Western operations in a European setting have recently finished accrual. Both have confirmed the finding of a previous (small) prospective trial that morbidity and mortality were doubled by the more extensive operation.^{49–51} Results from Western specialist centres performing a large number of D2+ operations per year, on the other hand, have been very encouraging.^{52–54} The multicentre trials have been criticised for the inadequacy of the training provided in the D2 technique.⁵⁵ Preliminary reports also suggest that strict adherence to either one or the other

Definition of D1 and D2 gastrectomy
D1
● removes omenta and perigastric lymph nodes along gastric and gastro-epiploic vessels (stations 1-6)
● considerably briefer, with less retroperitoneal dissection
D2
● removes omenta, perigastric nodes and nodes along hepatic and splenic arteries and around the coeliac axis
● in case of total gastrectomy, may require splenectomy and distal pancreatectomy

Table Survival after radical surgery in Britain⁷³ and Japan⁴⁸

	Curative resections (%)	Overall survival (%)	Node negative (%)	Node positive (%)
Britain	30	43	60	18
Japan	75	75	85	36

The two series are contemporary (1987/8). The survival figures are percentages of patients alive five years after apparently curative surgery.

Advances in surgery
<ul style="list-style-type: none">● extended lymphadenectomy in suitable cases by specialist surgeons● endoscopic resection for selected early gastric cancers

resection type was very difficult to achieve.⁵⁶ It seems likely that a further trial restricted to centres providing full training in both techniques may be required, but the logistic problems are likely to be formidable. The episode has been a stark example of the enormous difficulty of successfully performing a valid randomised comparison of two major operations, and has led to much thought about the most appropriate ways to conduct research on surgical techniques in the future.

Another current controversy is over the removal of the spleen at total gastrectomy. The argument for splenectomy in cases of advanced cancer affecting the proximal stomach or the greater curve of the body is based on pathological studies suggesting that the nodes at the splenic hilum are involved in about 20% of such tumours.⁵⁷ Several authors in both East and West have noted the association of splenectomy with poor prognosis in the long term and with postoperative morbidity in the short term, and have argued from this that it should be avoided.⁵⁸ Cases in which splenectomy seems appropriate represent a poor prognostic group, and in the absence of prospective trials it is difficult to demonstrate that splenectomy is actually harmful. There is some experimental support for the idea that immunological resistance to cancer may be adversely affected by splenectomy,⁵⁹ and convincing evidence that postoperative sepsis is significantly increased in middle-aged and elderly humans.⁶⁰

Surgical palliation

Vomiting due to mechanical obstruction of the pylorus can be effectively treated by gastrojejunostomy, and dysphagia due to localised obstruction of the cardia can be relieved by intubation or laser ablation. Often, however, widespread involvement of the stomach frustrates these strategies. Palliative partial gastrectomy has long been accepted as the operation of choice where a distal tumour allows it. Palliative total gastrectomy has been more controversial because of the finer balance between risks and benefits. In recent years our ability to operate with a lower predicted postoperative mortality has encouraged acceptance of the operation.⁶¹ In cases deemed unsuitable it is sometimes possible to by-pass the entire stomach by opening the hiatus widely and bringing a loop of jejunum up to the lower oesophagus. The Devine exclusion operation involves transection of the stomach above an irresectable distal cancer, with a gastrojejunostomy to the proximal healthy stomach.⁶² In practice it is often found that cancers advanced enough to need the operation are too advanced to allow safe transection on the lesser curve. No operation is successful in relieving the symptoms of widespread peritoneal disease. A feeding jejunostomy is generally unkind and ineffective, and surgical relief of obstruction in one area is quickly followed by obstruction in another. Ascites and ileus develop readily after surgery in such advanced disease, and often hasten death by exacerbating malnutrition.

Non-surgical interventions

Advances in chemotherapy
<ul style="list-style-type: none">● improved survival in advanced disease with ECF (see text)● improved survival with adjuvant slow-release intraperitoneal mitomycin C instilled at surgery

CHEMOTHERAPY

Previous evidence

Adjuvant chemotherapy for gastric cancer has had very little success in large prospective trials.^{63,64} Only two trials, the GITSG study⁶⁵ and the Estape study from Spain,⁶⁶ have reported a significant survival benefit. Chemotherapy for advanced disease has improved insofar as modern regimes such as EAP (etoposide, adriamycin, cisplatin) and ECF (epirubicin, cisplatin and continuous infusion of 5-fluorouracil) produce greater objective response rates than the earlier generation regimes of 5-fluorouracil alone or FAM (fluorouracil, adriamycin and mitomycin C). There are some reports suggesting improved overall survival with the newer regimes.⁶⁷ Patients with a good response undoubtedly do survive longer, but the average response times remain restricted to a few months. The best responses are seen in those with the best initial performance status, and for these patients chemotherapy is now an option worth considering if surgery is ruled out.

Japanese evidence

The approach to chemotherapy in Japan has different historical roots to that in the West. The Japanese have for many years given adjuvant chemotherapy to patients with high risk disease, using regimes based on mitomycin C and/or 5-fluorouracil. Chemotherapy is usually started within a few days of surgery in Japan, whereas this would be exceptional in the UK. Japanese regimens have also experimented extensively with biological response modifiers intended to enhance the immune response to the tumour. The commonest of these is

OK432, a preparation derived from the cell wall of *Streptococcus pyogenes*. Adequate randomised trials of adjuvant chemotherapy versus surgery alone have not been performed in Japan. A sequential combination of 5-fluorouracil and mitomycin C and a combination of intravenous and intraperitoneal mitomycin have both been reported as more successful than conventional intravenous regimens.⁶⁸ A recent large study showed a highly significant advantage for immunochemotherapy over chemotherapy alone, but the rationale for this approach remains somewhat vague, and Western oncologists seem cautious about it.⁶⁹

The use of H2-antagonists as a palliative treatment for advanced disease has been studied in a number of small trials, some of which suggest an effect on survival. A large British trial has recently closed recruitment. There are current plans for two new multicentre trials of adjuvant chemotherapy in the UK. One will use the ECF regime whilst the other is adopting a Japanese idea and giving single dose per-operative intraperitoneal mitomycin C in a slow-release form to reduce peritoneal recurrence.

RADIOTHERAPY

The place of radiotherapy in gastric cancer treatment is very limited. A rational case for adjuvant therapy to the gastric bed was made by Gunderson and Sosin in a study of recurrence sites⁷⁰ (although the Japanese would suggest that more radical surgery would be more appropriate). The British Stomach Cancer Group trial which studied adjuvant radiotherapy showed no benefit, however, and there have been no convincing reports to the contrary.⁷¹ Some more promising results of pilot studies of intra-operative radiotherapy from Japan have not been developed into large studies.⁷²

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