Management of carcinomas of the upper gastrointestinal tract

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This is the third in a series of articles examining developments in cancer and updating what we know about the disease

Patients with oesophageal, gastric, and pancreatic carcinomas present a common and difficult problem for the clinician. Surgery is the best option for curative treatment but overall survival figures remain low. Recent improvements in our understanding of the biology of these tumours and improvements in their clinical staging, along with the development of combined modality approaches to local-regional disease, have led to renewed optimism that survival figures may be improved. This is particularly so for oesophageal and gastric carcinomas. In addition, there have been advances in the palliative management of all three tumours. This article examines some of these developments and looks at future prospects.

Epidemiology and pathology

OE SOPHAGEAL CANCER

Oesophageal cancer accounts for around 2% of cancer deaths in the United Kingdom annually. The diagnosis is associated with a median survival of 10 months, and fewer than 5% of patients are cured. In the past, squamous cell carcinomas have accounted for most oesophageal cancers (around 90%) but the incidence of adenocarcinoma of the lower oesophagus is increasing, and these tumours now account for 20-40% of cases. In the Western World the risk of squamous cell cancer is modestly increased with cigarette smoking or alcohol consumption, whereas Barrett's oesophagus is an important risk factor for adenocarcinoma of the oesophagus. Other medical conditions associated with an increased risk include achalasia and the Plummer-Vinson syndrome.

GASTRIC CANCER

Gastric cancer is the second most common tumour type globally and the fourth commonest in Europe. Though the overall incidence has been decreasing over the past few decades, the incidence of adenocarcinomas of the proximal stomach and oesophagogastric junction is rising. Gastric cancer presenting at an early stage can be cured surgically; however, 80% of cases are too advanced at presentation.

The association of gastric cancer with blood group A and dietary factors (particularly increased nitrites in food preservatives) has been established. Other dietary factors such as vitamin C, vitamin E, and carotene seem to exert a protective effect through their antibacterial or antioxidant activity. Recently there has been interest in the role of *Helicobacter pylori* in the development of this tumour. Several prospective epidemiological studies have shown that seropositivity to *H. pylori* may lead to a significantly (up to sixfold) increased risk of gastric cancer.^{1,2} It is postulated that atrophic gastritis induced by this infection leads to a reduction in intraluminal acid secretion and a bacterial overgrowth which produces increased nitrite formation. This association raises the possibility of preventive strategies, and studies are currently looking at the use of antioxidant ascorbic acid and metronidazole aimed at eradicating *H. pylori* infection.

PANCREATIC CANCER

Pancreatic carcinoma is the fifth commonest cause of cancer deaths in Britain and is responsible for one fifth

of all deaths due to gastrointestinal cancer. The prognosis is very poor, with only 3-5% of patients alive at five years. For reasons that are not clear its incidence has continued to increase since the 1930s. Though its aetiology is unknown, several risk factors have been implicated. The most well established is cigarette smoking, the risk increasing with the amount smoked. Dietary factors also seem to be important, particularly high intakes of fat and red meat.

Ductal adenocarcinomas account for 80% of pancreatic malignancies and are more common in the head (66%) than in the body and tail (33%). At presentation only 10-15% of patients have disease confined to the pancreas, though roughly half are free of distant metastases. Cystadenocarcinomas make up 1% of all pancreatic cancers and may be ductal (mucinous) or acinar (serous). They tend to present with a long duration of symptoms, have a lower biological grade, and have a much improved five year survival compared with pancreatic adenocarcinoma. Other, rarer tumours include lymphoma, neuroendocrine tumours, and anaplastic carcinomas. Detailed discussion of the management of these tumours is beyond the scope of this article. It is of paramount importance, however, that all patients should have a histological diagnosis. There is an increasing trend to treat patients non-surgically with palliative endoluminal procedures in the absence of a clear cut tissue diagnosis. The natural course of neuroendocrine tumours and the specialised treatment of lymphomas mean that assuming that a tumour is adenocarcinoma is entirely inappropriate.

Screening

In Japan, where the incidence of gastric cancer is very high, screening by means of double contrast barium meal examination and endoscopy has increased the proportion of patients presenting with early gastric cancer to 30-40%.³ In the United States and Europe, where there is a much lower incidence of gastric cancer, population screening of asymptomatic patients is not practicable. There has been one British study aimed at identifying patients with early stage disease, where all patients over the age of 40 presenting to their general practitioner with dyspepsia were referred for endoscopy.⁴ Two per cent of patients were found to have gastric cancer, half of them being amenable to curative surgery. These data suggest that an open endoscopy service for all patients developing dyspepsia over the age of 40, coupled to a public health awareness campaign of the possible relevance of dyspepsia, may be the most pragmatic way forward. Nevertheless, it should be borne in mind that dyspepsia is very common in the general population.

Staging

All three tumours (oesophageal, gastric, pancreatic) are staged according to the TNM criteria. Double contrast barium studies and endoscopy with biopsy are the most common means of diagnosis for oesophageal and gastric tumours. Computed tomography (CT) detects spread to regional lymph nodes and distant metastases. Endoluminal ultrasound has been shown to be superior to CT in identifying the depth of tumour

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penetration and presence of local adenopathy (fig 1).⁵ As it becomes generally available, this technique will allow more precise preoperative assessment of primary oesophageal and gastric cancers. In pancreatic cancer CT can identify the size of the primary tumour but is less useful at identifying local invasion. By contrast, colour Doppler ultrasound and angiography are particularly valuable in excluding vessel invasion. Magnetic resonance imaging can also be used to show locally advanced tumours. Laparoscopy permits direct visualisation of liver, peritoneal, and omental metastases. By using these techniques the selection of appropriate patients for successful surgical resection is optimised.

FIG 1—Oesophageal cancer visualised by endoluminal ultrasound showing narrowed luminal diameter and spread to local lymph nodes. (Courtesy of Professor S G Bown)

Surgery

OESOPHAGEAL CANCER

Fewer than 10% of patients with oesophageal cancer present with disease confined to the mucosa or sub-mucosa (stage I). In these patients oesophageal resection alone remains the treatment of choice and can result in a 60/80% five year survival. In stages II and III disease, however, only 15% of patients become long term survivors.

GASTRIC CANCER

Similarly, in gastric cancer the best results are obtained when the disease is caught early (T1 with or without N1 nodes), 70% of such patients treated surgically being alive at five years. Comparatively few patients (<5%), however, present at such an early stage. Moreover, penetration of the serosa by the tumour predicts a risk of recurrence of 80-85%. Tumours of the distal stomach may be adequately treated by partial gastrectomy, mid-stomach tumours often require total gastrectomy, while proximal and oesophagogastric junction tumours may require oesophagogastric resection. Apart from the type of surgery needed, the other issue concerns the extent of removal of regional lymph nodes. Extensive lymphadenectomy is routinely used in Japan, but a survival advantage for this approach is unproved. A randomised trial by the Medical Research Council is currently comparing R₁ (more limited) with R₂ (more extensive) resection. In patients in whom a curative resection is not feasible palliative resection can be performed with minimal morbidity.

PANCREATIC CANCER

Only a small proportion of patients with pancreatic cancer have early stage disease suitable for curative surgical resection. The standard operative procedure

is pancreaticoduodenectomy—Whipple's procedure. The extent of the resection, however, ranging from preservation of the pylorus to radical operations combining Whipple's procedure with extensive lymph node dissection, seems to have little effect on the five year survival figures of around 5-10%.⁶ In carefully selected patients—that is, those with a small primary tumour, no lymphadenopathy, and clear margins postoperatively—five year survival figures of 25% are possible.⁷ Patients with pancreatic cancer should not be denied the surgical option, and proper assessment by an experienced pancreatic surgeon is essential to achieve the best outcome. When definitive surgery is not possible surgical biliary bypass procedures such as choledochojejunostomy or cholecystojejunostomy provide effective palliation of obstructive symptoms or prophylaxis against these symptoms in most patients. Prophylactic gastroenterostomy is often also performed in order to prevent gastric outlet obstruction. In patients for whom operation is not considered, non-surgical biliary decompression can often be accomplished endoscopically or percutaneously.

Chemotherapy and radiotherapy

ADJUVANT TREATMENT

The objectives of treatment given as an adjunct to potentially curative surgery are to reduce the rate of local-regional recurrence and prevent systemic failure.

Oesophageal cancer

For oesophageal cancer, preoperative radiotherapy has not been shown to improve outcome.⁸ Several trials including an MRC trial are currently investigating the role of perioperative chemotherapy with cisplatin based regimens.⁹

Gastric cancer

Postoperative radiotherapy adds nothing to the management of gastric cancer. A meta-analysis of adjuvant chemotherapy in gastric cancer presented at the 1993 meeting of the American Society of Clinical Oncology showed no benefit from chemotherapy.¹⁰ Two, more recent randomised studies—one from Spain using single agent intravenous mitomycin,¹¹ and a small study from Japan using intraperitoneal carbon adsorbed mitomycin¹²—showed a survival advantage for chemotherapy, but the data require confirmation.

Pancreatic cancer

Regional failure is an important feature of relapse in pancreatic cancer. Though radiotherapy is occasionally employed as adjuvant therapy, there are no randomised trials to support the practice. One randomised trial, however, found substantial prolongation of survival (median 21 months) for patients treated with combined modality therapy (fluorouracil plus 40 Gy external beam radiotherapy after resection) when compared with survival (median 11 months) in the surgery alone group.¹³ This trial has been criticised because of the small numbers of patients, the modest benefit, and the difficulty in distinguishing the relative contributions of the radiotherapy and chemotherapy. As a result, this approach has not been adopted as standard in Europe, though many centres in the United States routinely offer adjuvant radiotherapy and chemotherapy. A new European initiative—the ESPAC-1 trial—is shortly to be launched which will examine the role of postoperative adjuvant radiotherapy and chemotherapy in a randomised trial.

LOCALLY ADVANCED AND METASTATIC DISEASE

In the past it has been difficult to quantify the benefits of palliative chemotherapy in upper gastrointestinal

Reference	Regimen	No of evaluable patients	Median survival (months)	p Value
Gastric cancer				
Pyrhönen <i>et al</i> ⁴	Fluorouracil-epirubicin-methotrexate (FEMTX)	17	12.3	< 0.001
	Best supportive care	19	3.1	
Murad <i>et al</i> ⁵	Fluorouracil-doxorubicin-methotrexate (FAMTX; modified)	30	10.0	< 0.001
	Best supportive care	10	3.0	
Pancreatic cancer				
Mallinson <i>et al</i> ²⁰	Fluorouracil-cyclophosphamide-methotrexate-vincristine plus fluorouracil-mitomycin as maintenance	21	9.0	< 0.0001
	Best supportive care	19	2.0	
Leonard <i>et al</i> ²³	Fluorouracil (FAM)	23	8.0	< 0.002
	Best supportive care	20	3.5	

tract cancers. Indeed, in the United Kingdom and Europe many patients do not receive chemotherapy because the clinician considers it to be of no value and likely to have a detrimental effect on quality of life. Nevertheless, several randomised studies have shown a benefit for this form of treatment when compared with best supportive care (table). In the light of these results there needs to be careful re-evaluation of the role of chemotherapy in the palliation of symptoms and prolongation of life expectancy.

Gastric cancer

Two studies have shown a survival benefit for chemotherapy in patients with advanced gastric cancer. One study, in which 36 evaluable patients were randomised to fluorouracil-doxorubicin-methotrexate (FEMTX) or best supportive care, found a nine month median survival advantage for chemotherapy.¹⁴ In another study patients were randomised to a modified version of fluorouracil-doxorubicin-methotrexate (FAMTX) or best supportive care.¹⁵ In the middle of this study the randomisation was interrupted because of strong evidence of benefit in the treatment arm. Further patients were accrued to the treatment arm, and by the end of the study 30 evaluable patients had

received chemotherapy and 10 best supportive care. Ultimately this trial showed a seven month advantage in median survival among the patients given chemotherapy.

As yet there is no one established standard chemotherapy regimen in advanced gastric cancer, and the benefit of combination chemotherapy over fluorouracil given alone remains controversial.¹⁶ Combination chemotherapy with fluorouracil-doxorubicin-methotrexate has been shown in randomised trials to be superior to other combination regimens in terms of survival¹⁷ and toxicity¹⁸ and is currently regarded as one of the best comparators against which new combinations should be examined. With this regimen objective tumour regression is obtained in roughly 40% of patients. Adding cisplatin to a short infusion of fluorouracil increases the response rate (51% versus 25%) without survival benefit.¹⁹ Higher response rates may be particularly relevant in the preoperative setting but less relevant to advanced disease. We have recently completed a phase II trial of epirubicin and cisplatin in conjunction with continuous infusion of fluorouracil (ECF).²⁰ This regimen was well tolerated and was associated with objective tumour regression in 91 (71%) of 128 patients with measurable disease, including complete remission (confirmed histologically in 15 (12%) (fig 2). The study included adenocarcinomas of the oesophagus, oesophagogastric junction, and stomach, which responded similarly to the chemotherapy.

In view of these results there is considerable interest in the use of preoperative chemotherapy in gastric cancer where the aim is to reduce tumour bulk, increase resection rates, treat micrometastases, and thereby improve survival. When considering this approach, however, it is important to exclude early gastric cancer, as these patients have a good prognosis with surgery alone. Experienced endoscopists can diagnose early gastric cancer but transluminal endoscopic ultrasound may increase accuracy. We have used epirubicin-cisplatin-fluorouracil to treat 35 patients with unresectable or clinically locally advanced disease. Twenty eight patients (80%) responded to treatment, of whom 20 went forward to surgery. Of these, 11 had their tumours completely resected. Other studies of chemotherapy in the setting of locally advanced disease have also resulted in the downstaging of tumours, permitting resection.²¹ It is too early to say whether this approach will influence survival in cases of resectable tumours and locally advanced disease, but this clearly looks a promising topic for research. A randomised trial of perioperative epirubicin-cisplatin-fluorouracil in operable gastric cancer is planned by the British Stomach Cancer Group and the MRC.

Pancreatic cancer

There have been two British randomised trials of best supportive care versus chemotherapy in inoperable pancreatic cancer. Both showed a survival advantage for the chemotherapy arm, the most recent showing no deterioration in the quality of life in the chemotherapy treatment group (table).^{22, 23} In contrast, a trial from the United States showed no benefit for chemotherapy in this setting, possibly because the number of courses given was surprisingly low.^{23A} Certainly there is no evidence that combination chemotherapy is superior to fluorouracil alone.²⁴

Locally advanced pancreatic tumours are occasionally treated with chemotherapy and radiotherapy. One randomised trial carried out by the North American Gastrointestinal Tumor Study Group reported a doubling of survival (10.5 months versus 5.5 months) among patients treated with fluorouracil (either 40 Gy or 60 Gy) versus radiotherapy alone.²⁵ Another group compared streptozocin-mitomycin-fluorouracil (SMF)

FIG 2—CT scans in July 1989 and six months later showing complete resolution of liver metastases after six courses of epirubicin and cisplatin in conjunction with continuous infusion of fluorouracil (ECF)

with the same regimen combined with radiotherapy (54 Gy) and found a significantly superior survival difference in favour of chemotherapy plus radiotherapy (one year survival 41% versus 19%).²⁶ These results contrast with a study that found no improvement in survival for patients treated with either fluorouracil plus radiotherapy or fluorouracil alone,²⁷ which implies that chemotherapy was the most important component of the treatment. We therefore believe that the combined modality approach cannot routinely be recommended.

Oesophageal cancer

The standard approach to patients with locally advanced oesophageal cancer (T2-T3, N1) is surgery or radical radiotherapy. Five year survival rates of 0-10% for radiotherapy and 10-20% for surgery are commonly quoted. Surgical patients are usually more selected, with less comorbid disease, which could partially account for this difference. There has never been a randomised trial of surgery versus radiotherapy and one seems unlikely.

Two large randomised trials have compared radiotherapy and chemotherapy versus radiotherapy alone in patients with locally advanced oesophageal cancer. One study randomised patients to treatment with fluorouracil-mitomycin and 60 Gy radiotherapy versus radiotherapy alone.²⁸ It showed an improved median survival of six months (14.9 versus 9.0) for the combined modality arm, with two year survival figures of 30% versus 12%. Another study compared radiotherapy alone (64 Gy) with concurrent radiotherapy and cisplatin-fluorouracil.²⁹ This also showed a benefit for the combined modality arm, with a fourfold improvement in survival at two years (42% versus 10%). These results confirm combined modality treatment as being superior to radiotherapy alone in this disease. The encouraging results of combined modality treatment alone in locally advanced inoperable tumours have led investigators to look at this approach in the preoperative setting. So far there are several single arm uncontrolled trials suggesting that this approach is feasible and may result in improved survival. One trial using cisplatin, vinblastine, and continuous infusion of fluorouracil along with 30 Gy radiotherapy preoperatively had not reached median survival at 26 months.³⁰ This group is now undertaking a large randomised trial comparing this regimen with surgery alone.

Laser therapy

Several approaches have been used to try to palliate malignant dysphagia in patients with advanced oesophageal and oesophagogastric junction tumours. The most common form of palliation has been intubation, and external beam radiotherapy has also been used. The advent of laser technology (most commonly in the form of neodymium; yttrium-aluminium garnet-Nd: YAG lasers) offers a new and potentially powerful tool in the palliation of dysphagia. Laser vaporises or coagulates tumour tissue, and the aim of therapy is to debulk tumours causing intraluminal obstruction and coagulate bleeding tumours (fig 3). This procedure can be done quickly as a day case and produces rapid improvement of symptoms. The disadvantage is that symptomatic relief may be short lived (four to six weeks), requiring repeated treatments. There are several reports of the efficacy of this technique in patients with malignant dysphagia.³¹

Several groups have now examined the value of adding external beam radiotherapy to laser therapy, at least one having conducted a randomised trial.³² The doses of radiotherapy used are lower than with radical treatment and are better tolerated, and initial data

FIG 4—CT Scans showing devascularisation of 4 cm hypervascular metastasis from gastroma in left lobe of liver by use of interstitial laser photocoagulation. (Top: before laser photocoagulation; bottom: after.) (Courtesy of Dr W R Lees)

suggest that this method produces a longer symptomatic response. A study of repeated laser endoscopy in conjunction with epirubicin-cisplatin-fluorouracil has also shown excellent palliation of symptoms.³³ Laser therapy can also be used to treat liver metastases (fig 4).³⁴ It is particularly useful in slow growing tumours such as carcinoid but is also useful in metastatic gastrointestinal tumours when systemic control can be achieved with chemotherapy.

Future approaches

We hope that newer, more effective chemotherapy combinations and exploration of the best way of delivering chemotherapy and radiotherapy, particularly in a perioperative setting, may produce further benefits in survival. There remains, however, an urgent need for novel forms of therapy in these tumour types. A new camptothecin analogue, CPT-11, which has been found to be active in colon cancer, is being tested in gastric cancer and has already been shown to have activity.³⁵ Recent developments in the understanding of molecular abnormalities in these tumours—in particular, recognition of oncogene proteins important in the intracellular signalling in oncogenesis—now provide molecular targets for new anticancer treatments using monoclonal antibody and gene therapy technology.

Conclusion

Perioperative chemotherapy looks particularly promising in gastric and oesophageal cancer and will be the focus of many clinical trials over the next few years. New drugs and novel approaches such as gene therapy and antisense therapy are on the agenda, but with the optimal use of currently available treatment it should be possible sooner rather than later to improve the outcome in terms of both cure and palliation of patients with upper gastrointestinal cancers.

FIG 3—Top: Oesophageal cancer occluding most of lumen, seen on oesophagoscopy. Bottom: Appearance after laser therapy. (Courtesy of Professor S G Bown)

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ANY QUESTIONS

Could the administration of inhaled steroids to children with asthma predispose them to develop osteoporosis in later life?

The maximum bone mass achieved at skeletal maturity (usually by age 18) is termed the peak bone mass. Peak bone mass is important because the risk of osteoporotic fracture in later life is related to both it and the subsequent age related bone loss.

With growth during early childhood, bone mass gradually increases in a linear fashion until puberty, when the most rapid accumulation in skeletal mass occurs. In girls this is most pronounced between the ages of 11 and 14 (or the first few years after the menarche) at the lumbar spine and femoral neck, whereas after age 16 further gains in bone mass are limited.¹ In boys the most rapid accumulation occurs between the ages of 14 and 17.

Peak bone mass is largely determined by genetic factors but may be modified by environmental influences such as calcium intake and physical activity.² Corticosteroids may also modify peak bone mass. Although inhaled steroids are less likely to have systemic effects than oral steroids, in high doses they may result in adrenal suppression and retarded growth. For example, in controlled studies budesonide has been associated with dose related reductions in growth velocity in lower limb long bones at least in short term studies.³ In addition, there have been case reports of impairment with even low doses of inhaled steroids, indicating that there may be considerable variability in individual response. Studies of biochemical

markers of bone turnover such as osteocalcin have also shown effects from inhaled steroids.⁴ These changes may be more pronounced with beclomethasone dipropionate than budesonide.⁵

These findings suggest that inhaled steroids, especially if used in high doses for long term treatment, have the potential to result in reductions in peak bone density. This effect may be most pronounced during puberty, when gains in peak density are greatest. Recovery from steroid osteoporosis with increases in bone density have been reported in adults with Cushing's disease after successful treatment, so it may be possible for the growing skeleton to recover from any effect of inhaled steroids after these agents are stopped. Therefore, when inhaled steroids are used to treat asthma in children they should be given in the lowest dose possible, used in conjunction with a spacer to reduce systemic absorption, and stopped whenever possible. In addition, growth should be regularly monitored in children taking inhaled steroids.—PHILIP SAMBROOK, associate professor, Darlinghurst, New South Wales

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