Management of upper gastrointestinal cancers

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This paper is an edited version of *Effective Health Care* volume 6 number 4 (December 2000), which deals with the management of cancers of the oesophagus, stomach and pancreas. It summarises systematic reviews undertaken to inform *Improving Outcomes in Upper Gastro-intestinal Cancers*. These publications form part of a series providing guidance on NHS services for patients with cancer, all of which are available at www.doh.gov.uk/cancer.

**Introduction**
Upper gastrointestinal (UGI) tumours caused 13.5% of all cancer deaths in England and Wales in 1997. Incidence and mortality rates are shown in table 1. Gastric (stomach) cancer is declining but adenocarcinomas of the oesophagus and the junction between the stomach and oesophagus are becoming more common in many countries (fig 1). These cancers are often at an advanced stage at the time of diagnosis and over three quarters of patients in England and Wales die within a year. This mortality rate is worse than in many other developed countries, particularly for gastric cancer.

**Diagnosis and assessment**
Many people with oesophageal or gastric cancer have indigestion, reflux, and pain or discomfort in the area of the chest or upper abdomen—symptoms generically described as dyspepsia. Dyspepsia prompts a substantial proportion of primary care consultations but fewer than 2% of these patients have cancer. The risk rises sharply in middle age, with incidence increasing from 1 per 100 000 people under the age of 40 to 155 per 100 000 over the age of 55.

A large retrospective review suggested that only one person per million population under the age of 55 presenting with uncomplicated dyspepsia and no sinister symptoms (persistent vomiting, dysphagia, or weight loss) is likely to have cancer.

**Endoscopy**
Endoscopy is effective for diagnosis, permitting suspect tissue to be sampled for pathological examination. Prospective studies report accuracy figures for initial diagnosis of oesophageal or gastric cancer of over 90%. GPs use open access endoscopy services effectively, thus avoiding unnecessary clinic visits. The proportion of patients with malignancies—generally under 2%—is as high among patients referred by GPs as among those referred by specialists. Prompt endoscopy tends to yield a higher proportion of early (treatable) cancers, but there has been no long term comparative study to determine whether rapid access to endoscopy improves survival.

Radiology (barium meal or swallow) may also be used in diagnosis. In two studies which compared radiology with endoscopy for diagnosis of oesophageal cancer, both methods identified all early (treatable) cancers, but there has been no long term comparative study to determine whether rapid access to radiology improves survival.

A retrospective review reported a positive predictive value of 42% for barium studies, so the majority of patients whose test results were suspicious did not have cancer. Radiology fails to identify some cases; some patients found to have cancer by endoscopy had negative results from diagnostic imaging. Studies of delay report that cancer may be missed when patients are assessed by radiology. No report was available at www.doh.gov.uk/cancer.

**Table 1** UGI cancers: incidence rates, survival rates, and death rates

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Incidence rate per 100 000, England and Wales</th>
<th>One year survival rate, England</th>
<th>Five year survival rate, England</th>
<th>Deaths, England and Wales, 1997</th>
<th>Death rate per 100 000, England and Wales</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>25%</td>
<td>9%</td>
<td>5855</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>14.0</td>
<td>9.2</td>
<td>27%</td>
<td>9%</td>
<td>5855</td>
</tr>
<tr>
<td>Stomach</td>
<td>24.3</td>
<td>13.8</td>
<td>28%</td>
<td>12%</td>
<td>6613</td>
</tr>
<tr>
<td>Pancreas</td>
<td>11.7</td>
<td>12.0</td>
<td>12%</td>
<td>3%</td>
<td>5782</td>
</tr>
</tbody>
</table>
found of cancer missed by endoscopy and diagnosed by radiology.

Abdominal ultrasound is effective for detecting pancreatic tumours; a correct diagnosis can be made in over 80% of patients with symptoms of cancer.\(^\text{46-50}\) It is not reliable for determining whether the disease is resectable.\(^\text{51, 52}\)

A systematic review of endoscopic ultrasound (EUS) in gastric and oesophageal cancer concluded that it can discriminate between operable and inoperable tumours.\(^\text{53}\) It is less accurate for assessing lymph node status than for tumour staging and is not adequate for assessing metastatic spread. In pancreatic cancer, EUS may be more reliable than other forms of imaging for determining whether a tumour can be resected, but there is wide variability between reports.\(^\text{54-55}\)

The sensitivity of computed tomographic (CT) scanning for staging tumours and assessing spread is very variable and often poor, but its specificity is high in oesophageal and gastric cancers.\(^\text{56-70}\) and pancreatic cancer.\(^\text{51, 52, 54-55}\) CT scanning is therefore appropriate for identifying patients whose cancer is so far advanced that radical surgery is unlikely to be effective. However, perhaps half of those whose CT results suggest localised disease will actually have more widespread tumour. Magnetic resonance imaging (MRI) produces similar results to CT scanning.\(^\text{57, 61-71}\)

**ERCP AND MRCP IN PANCREATIC CANCER**

Pancreatic cancer can sometimes be diagnosed by endoscopic retrograde cholangiopancreatography (ERCP).\(^\text{72-76}\) However, this is a difficult technique for which competence requires experience of up to 200 procedures.\(^\text{77-79}\) Other drawbacks include high failure rates, reaching 18% for attempts to image the pancreatic duct in an audit in northern England.\(^\text{70}\) Major complication rates are also high at 6% overall and 10% with stent insertion. In an Italian study complications were significantly more common in centres where fewer procedures were carried out (7% versus 2%).\(^\text{80}\)

Magnetic resonance cholangiopancreatography (MRCP) is a new imaging technique which is not invasive and does not require contrast media. Small studies suggest that it may be more accurate than other non-invasive diagnostic methods.\(^\text{81-82}\) A study in 124 patients suggested that MRCP might be more sensitive than ERCP but the difference did not reach statistical significance (p=0.06); however, this calculation did not allow for ERCP failure in 16 patients. MRCP caused no complications and was successful in all but one patient, whereas 7% of patients suffered adverse effects from ERCP.\(^\text{83}\)

**Treatment for oesophageal and junctional tumours**

**SURGERY**

In England one third of patients with oesophageal cancer undergo surgery, of whom about 14% survive for 5 years. In a study by Bachmann et al of 781 patients treated by 23 hospital trusts in south west England in 1996–7, the overall perioperative mortality rate was 11%.\(^\text{84}\) Mortality rates were inversely associated with the number of operations carried out by individual surgeons.

Studies in the USA have shown that hospitals which deal with larger numbers of patients achieve lower perioperative mortality. Mortality among patients over the age of 65 was 17.3% (95% CI 13.3% to 22.0%) in hospitals which carried out fewer than five oesophagectomies per year and 3.4% (95% CI 0.7% to 9.6%) in hospitals where the corresponding figure was over 11.\(^\text{85}\) Another study reported 3% (95% CI 0.09% to 5.1%) perioperative mortality in five hospitals which carried out 265 Medicare funded oesophagectomies in 1994-6.\(^\text{86}\)

Oesophageal resection leads to impaired quality of life for some months after surgery.\(^\text{87-90}\) In long term survivors, quality of life returns to baseline levels about 6 months after surgery and may continue to improve. However, in those who survive less than 2 years, quality of life deteriorates without returning to preoperative levels despite improved swelling. Thus, surgery appears to be beneficial only when the operation is curative.

Two randomised controlled trials found that surgery was significantly more likely than radiotherapy to improve both swallowing and survival (p=0.002) in patients with operable tumours.\(^\text{91, 92}\)

**MULTI-MODALITY TREATMENT**

Early results from a large randomised controlled trial (n=802) suggest that cisplatin/5-FU before surgery for resectable oesophageal cancer improves survival rates by 10% (95% CI 3% to 16%) at 2 years from 35% to 45%.\(^\text{93}\) Meta-analyses of earlier studies show no significant advantage for neoadjuvant or adjuvant chemotherapy.\(^\text{94-95}\)

Analysis of data from 1147 patients in trials comparing preoperative radiotherapy with surgery alone revealed that radiotherapy improved 2 year survival rates from 30% to 34% despite greater surgical mortality, but this fell short of statistical significance (p=0.06) and is offset by increased morbidity and longer duration of treatment.\(^\text{96}\) Radiotherapy after surgery impairs quality of life without improving survival.\(^\text{94}\)

A recent large trial (n=556) reported higher 3 year survival rates after adjuvant chemoradiotherapy (52% versus 41% after surgery only; p=0.03). Toxicity was described as “tolerable”.\(^\text{97}\) A meta-analysis of seven earlier trials comparing neoadjuvant chemoradiotherapy with surgery alone did not produce clear results.\(^\text{98}\)

No trials have compared surgery after chemoradiotherapy with chemoradiotherapy alone for patients who show a complete response, so it is not clear whether surgery confers any additional benefit. In advanced disease survival time is longer after chemoradiotherapy than radiotherapy alone, but no study has measured quality of life.\(^\text{99-107}\)
PALLIATIVE INTERVENTIONS

Most patients require interventions to relieve dysphagia. Stents can permit swallowing by keeping the oesophagus open and sealing fistulae; they can be used on their own or in combination with other types of palliative treatment. Currently, about 40% of patients receive them. Expanding metal stents (Wallstents) cause fewer complications than other types, giving better quality of life, less need for re-intervention, and less time spent in hospital. Intraluminal radiotherapy (brachytherapy) could have obscured evidence of putative benefits without affecting hazards.

Tumour in the oesophagus may be reduced by laser, chemotheraphy, radiotherapy, and other methods. Small studies suggest that stenting gives longer lasting relief from dysphagia than laser treatment. In practice, however, these methods may be used in combination.

Chemotherapy can palliate symptoms of advancing cancer and may extend survival time in previously untreated patients; comparative trials suggest that epirubicin, cisplatin, and 5-FU (ECF) is particularly effective. Intraluminal radiotherapy (brachytherapy) may also increase survival time.

Treatment for gastric cancer

SURGERY

In Yorkshire just under half of all patients with gastric cancer undergo surgery, with 20% alive after 5 years. In south west England in 1996–7 perioperative mortality was 14%. As with oesophageal cancer, surgeons who treated more patients achieved significantly lower mortality rates.

In Japan long term survival rates after surgery are around 50%. This high rate has been attributed by some to the use of a more radical operation (D2 resection) in which 30 or more lymph nodes are removed, along with the spleen and part of the pancreas in some cases. There have been no randomised controlled trials in Japan comparing this procedure with less extensive operations. Results similar to those achieved in Japan have been reported from uncontrolled studies in the west, leading to a widespread belief that D2 resections are more effective than D1 (conventional western) surgery.

Four randomised controlled trials have shown that, contrary to this belief, more radical surgery leads to worse outcomes. The largest (n=998) found no difference in 5 year survival rates (47% and 45% after D2 and D1 resections, respectively), but perioperative mortality and complication rates were much higher after D2 surgery (10% versus 4%, p=0.004, and 43% versus 25%, p=0.001, respectively). An MRC trial (n=400) also found no difference in 5 year survival rates (33% and 35%), but again, D2 perioperative mortality was higher (13% versus 6.5%, p=0.04). Two smaller randomised controlled trials also reported significantly poorer outcomes after D2 surgery. Spalnectomy and pancreactectomy, part of the original protocol for D2 surgery, reduced the probability of survival. The suggestion that outcomes could be optimised by D2 surgery without splenectomy or pancreactectomy has not been tested, but multivariate analysis of results from the largest randomised controlled trial shows that the defining feature of D2 surgery—removal of more lymph nodes—increases mortality.

These trials have been criticised on a variety of points, particularly non-compliance with the protocol which could have blurred the distinction between procedures. Despite this, there were significant differences in outcomes and the D2 procedure caused more adverse effects. This criticism therefore seems to be based on the supposition that non-compliance could have obscured evidence of putative benefits without affecting hazards.

Different types of gastrectomy (stomach resection) have been compared in 10 trials. These show that palliative resection can relieve symptoms when potentially curative surgery is impossible. Less extended surgery is associated with better quality of life; no trial has reported any advantage for total gastrectomy when a subtotal operation is possible.

CHEMOTHERAPY

A recent meta-analysis of 20 randomised controlled trials (n=3658) shows that adjuvant chemotherapy improves survival after curative resection for gastric cancer, with a hazard ratio for combination chemotherapy of 0.86 (95% CI 0.78 to 0.94). In stage II/III disease the absolute increase in 5 year survival rate was 4%.

Palliative chemotherapy can improve quality of life and may extend survival time in patients with advanced gastric cancer by about 6 months compared with best supportive care. ECF is beneficial for fitter patients.

RADIOThERAPy

There is no reliable evidence to suggest that radiotherapy alone, or in combination with surgery, benefits patients with gastric cancer. However, improved survival has been reported after adjuvant chemoradiotherapy with 3 year survival rates of 52% versus 41% after surgery alone (p=0.03). No randomised controlled trial has shown any benefit for chemoradiotherapy in advanced disease.

Treatment for pancreatic cancer

SURGERY

Surgery for pancreatic cancer is difficult and hazardous. In Yorkshire between 1986 and 1994 17.7% of patients died within 30 days of surgery and fewer than 3% survived 5 years. Such poor results are not universal, however; specialist institutions report 5 year survival rates as high as 20%. Hospitals which deal with larger numbers achieve lower mortality rates. Risk adjusted perioperative mortality rates are around 14% in hospitals which treat one or fewer such patients per year, but 2.2–4.2% for those treating more than 10. The relative risk of death within 3 years was 0.69 (95% CI 0.62 to 0.76) after treatment in higher volume centres (>5 cases per year). In every study the best
outcomes were achieved by the highest volume hospitals.

ADJUVANT THERAPY
A major study (ESPAC-1) is assessing the effectiveness of postoperative treatment for patients with pancreatic cancer. Preliminary results for 530 patients suggest that adjuvant 5-FU chemotherapy is beneficial (median survival 19.5 months versus 13.5 months; p=0.003) but radiotherapy is not.

PALLIATIVE CHEMOTHERAPY
Three randomised controlled trials found that chemotherapy extended median survival by a few weeks or months compared with best supportive care while others reported no significant difference. Quality of life may improve but this has not been unequivocally demonstrated and it is often not clear whether reported benefits outweigh toxicity. Hormone therapy offers no clear benefits. One small trial of flutamide (n=49) reported dramatic improvements in survival, but only 35% of the patients had histologically confirmed pancreatic cancer.

Chemoradiotherapy can improve survival by a few weeks compared with single modality treatment, but it causes toxicity problems.

RELIEF OF BILE DUCT OBSTRUCTION
Trials comparing interventions to relieve jaundice due to bile duct obstruction show that metal stents (Wallstents) are superior to polythene. Patients with metal stents have fewer complications, less pain, and better quality of life. Stents and surgery are equally effective for relief of jaundice but the balance of risks and costs differs. Stenting requires shorter initial hospitalisation and costs significantly less, but stents can become blocked. Although surgery can have a high perioperative mortality rate (see above), longer term survival rates do not appear to differ between patient groups.

PAIN CONTROL
Pancreatic cancer can cause particularly severe pain. 90% of patients report good to excellent pain relief after coeliac plexus block, and some benefit persists for 3 months or until death. This method is more likely to be effective when it is used within 2 months of onset of pain than if it is delayed. Overall, the adverse effects of coeliac plexus block appear to be less severe than those of high doses of analgesics.

Nutrition in UGI cancer
Despite the importance of adequate nutrition to patient comfort and, indeed, to survival, little research evidence has been identified. One study reported particularly poor outcomes for patients with gastric cancer after stoma creation and tube feeding. However, these results could be biased by patient selection. Diet after surgery is discussed in pamphlets produced by the Oesophageal Patients’ Association (0121 704 9860).

Structure of services
CONCENTRATION OF SERVICES
There is considerable evidence that treatment in hospitals which manage larger numbers of patients with UGI cancers and/or by clinicians who see larger numbers leads to better outcomes. The most important study for the NHS is that by Bachmann et al (see above) who followed 2294 patients treated in 29 hospitals in south west England and Wales for 16–34 months from the time of first presentation to hospital.

The study revealed a fragmented service where few patients received specialist care. About one third of patients with each type of cancer were managed by clinicians who treated four or fewer new cases of that cancer per year. These patients were less likely to receive active treatment and they survived for significantly shorter periods than those whose doctors treated larger numbers.

In oesophageal cancer, consultants who dealt with one new case per week achieved mortality rates 31% lower than those who managed one case a month (after adjustment for case mix, numbers treated at the hospital, and types of treatment provided). In gastric cancer, doctors who managed larger numbers were more likely to offer resection (adjusted odds ratio 1.11; 95% CI 1.07 to 1.14) and less likely to provide no active treatment (adjusted odds ratio 0.94; 95% CI 0.91 to 0.97). The risk of death was 23% lower for patients treated in hospitals which admitted one case per week compared with those which admitted one per month, even after adjustment for prognostic factors and treatment provided. In pancreatic cancer the risk of death among patients managed by hospitals that dealt with one new case each week was 36% lower than in those dealing with one new case a month. These results suggest that aspects of care which were not measured in the study—for example, nursing and nutrition—may have contributed to better outcomes in more specialised hospitals.

COORDINATION BETWEEN HOSPITAL AND HOME CARE
Effective coordination and communication between hospital based care providers and home care teams is crucial to patient welfare. It may reduce the need for readmission to hospital after discharge from an oncology ward and reduce costs by reducing duplication of effort. Excellent results have been obtained by combining the following elements: a specialist nurse coordinator, a 24 hour telephone service based in the hospital ward where the patient had stayed, a home care team linked with the hospital, a collaborative case file, and the use of protocols developed by a multidisciplinary team. Better outcomes are achieved when multidisciplinary home care team members visit patients at home and when teams hold regular meetings.

Conclusions
Outcomes for most patients with UGI cancers in the UK are currently poor. While this is
largely due to the nature of these tumours, it is also likely to be a consequence of fragmentation of services and lack of specialist management in the NHS. It is hoped that recommendations for the reorganisation of services, developed by the National Cancer Guidance Group, will lead to substantial improvements.


10 Office for National Statistics. Information provided on request. 1999.


67 Freeny PC, Traverso LW, Ryan JA. Diagnosis and staging of pancreatic adenocarcinoma: diagnosis and staging with dynamic CT. Radiology 1988;166:125–33.


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