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Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

This bulletin reviews the evidence for the effectiveness of interventions for the management of upper gastro-intestinal cancers

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Management of upper gastro-intestinal cancers

- Most people with cancer of the upper gastro-intestinal system survive for only a few months after diagnosis. Long-term (five-year) survival rates for England and Wales for oesophageal, stomach and pancreatic cancer are 9%, 12%, and 3% respectively.
- These survival rates are generally worse than those reported by other developed countries. This is particularly apparent in stomach cancer, for which the European average five-year survival rate is 21%.
- Surgery is difficult and hazardous. One English region has reported that 15% of patients with oesophageal cancer and 18% with pancreatic cancer die within a month of surgery. Equivalent figures from specialist centres are below 5%.
- Clinicians and hospitals treating larger numbers of patients with these cancers achieve better outcomes.
- Chemotherapy can have some impact on survival and may help with symptom control. Radiotherapy is only appropriate for a small minority of patients with oesophageal cancer.
- Most patients require palliative interventions, in particular stent insertion to permit swallowing or treat jaundice.
- Pain control is crucial, especially in pancreatic cancer. Surgical interventions such as destruction of the local nerve plexus are often effective.

THE UNIVERSITY of York

NHS CENTRE FOR REVIEWS AND DISSEMINATION

A. Background

This bulletin summarises systematic reviews of research evidence published as *Improving Outcomes in Upper Gastro-Intestinal Cancers: The Research Evidence.*[1] Methods used for the reviews are summarised in the Appendix.

The review of research evidence was carried out to inform guidance for commissioners, produced by the National Cancer Guidance Group and published as *Improving Outcomes in Upper Gastro-Intestinal Cancers: The Manual.*[2] The key recommendations from this Manual are given in Section K of this bulletin.

These publications form part of a series on improving services for the management of the major cancers, all of which may be obtained by calling the NHS Response Line on 0541 555 455. A summary is available for GPs and primary care teams.[3]

B. Incidence and death rates

Cancers of the oesophagus, stomach, and pancreas, referred to collectively as upper gastro-intestinal (UGI) cancers, led to 18,250 deaths in England and Wales in 1997, or 13.5% of all cancer deaths.[4] Figures for incidence, survival rates and deaths are shown in Table 1.

Mortality rates for gastric (stomach) and oesophageal cancers have been changing over recent years (Figure 1).[8] Incidence and mortality rates for gastric cancer have been declining for more than half a century but one type of oesophageal cancer (adenocarcinoma) is becoming more common. Adenocarcinomas of the junction between the stomach and the oesophagus (junctional tumours) are increasing particularly rapidly.[9-12]

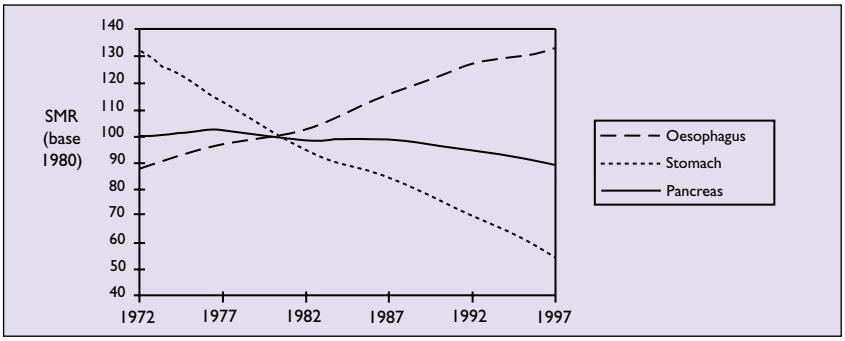

Figure 1 Trends in UGI cancer mortality, England and Wales.[8]

Whilst the poor survival figures can be attributed mainly to the late stage at which the disease usually becomes apparent, it may also be due to poor management in some NHS hospitals. Reported survival rates among patients in England are generally worse than in other developed countries.[6,7] This is particularly apparent for patients with gastric cancer, among whom the European average five-year survival rate is 21%, compared with 12% in England.

C. Risk factors

C.1 Age

The majority of patients with UGI cancer are over 70 years old. These cancers are diagnosed in 1 per 100,000 people under the age of 40, 20 per 100,000 in those aged 45-54, and 155 per 100,000 in the over 55 age-group.[4]

C.2 Smoking and alcohol consumption

Alcohol and tobacco consumption can both increase risk independently and act synergistically to increase risk of cancer of the oesophagus. A French case-control study found a relative risk (RR) of oesophageal cancer among non-smokers in the highest category of alcohol use (>57 units per week) of 5.1, compared with non-smokers who drank least; for those in the highest category of tobacco use (20 cigarettes per day) the RR was 18.0; but among those in the highest categories for both alcohol and tobacco use, the RR was 44.4.[13] Cigarette smoking is the most important known risk factor for pancreatic cancer.[14]

C.3 Diet

As with most cancers, the risk of developing UGI cancers is lower among people who eat more fruit and vegetables.[14,15]

C.4 Reflux

A Swedish case-control study found that people who had suffered from recurrent reflux five years earlier were nearly eight times as likely to develop adenocarcinoma of the oesophagus, and twice as likely to

Table 1 UGI cancers: incidence rates[5] survival rates,[6,7] and death rates.[4]

Cancer site	Incidence: rate per 100,000 England & Wales		One-year survival rate, England	Five-year survival rate, England	Deaths, England & Wales, 1997	Death rate per 100,000, England & Wales	
	Men	Women				Men	Women
Oesophagus	14.0	9.2	27%	9%	5,855	13.6	8.4
Stomach	24.3	13.8	28%	12%	6,613	15.1	9.5
Pancreas	11.7	12.0	12%	3%	5,782	10.5	11.2

develop adenocarcinoma of the gastric cardia (upper stomach), as those who did not have these symptoms (odds ratios 7.7, 95% CI: 5.3, 11.4 and 2.0, 95% CI: 1.4, 2.9 respectively).[16] More severe symptoms were associated with greater risk. Treatment of reflux does not appear to reduce risk; those who had used medication had higher rates of cancer.

Chronic reflux can cause Barrett's oesophagus, an abnormality of the lining of the lower oesophagus. This is associated with increased risk of cancer but there is no reliable evidence that surveillance or treatment of patients with Barrett's oesophagus reduces morbidity or mortality.[17]

D. Diagnosis and assessment

D.1 Symptoms

People with oesophageal or gastric cancer may present with common symptoms such as indigestion, heartburn, reflux, and pain or discomfort in the area of the stomach, chest or upper abdomen, generically described as dyspepsia. Oesophageal and junctional tumours are likely to cause dysphagia (food sticking when swallowed). Pancreatic cancer can lead to jaundice. Any UGI cancer can cause persistent nausea, vomiting and pain.

D.2 Identification of potential patients

The most common symptom of early disease, dyspepsia, prompts a substantial proportion of primary care consultations, but fewer than 2% of these patients will have cancer. 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 (in particular, persistent vomiting, dysphagia or weight loss) is likely to have oesophageal or gastric cancer.[18]

The following criteria were selected by the Department of Health (Referral Guidelines for Suspected Cancer, available from http://www.doh.gov.uk/cancer) to identify patients who should have fast-track (two-week) access to investigation:

- Dysphagia – food sticking on swallowing (any age).
- Dyspepsia combined with one or more of the following 'alarm' symptoms:
  - weight loss;
  - proven anaemia;
  - vomiting.
- Dyspepsia in a patient aged 55 years* or more with at least one of the following 'high-risk' features:
  - onset of dyspepsia less than one year ago;
  - continuous symptoms since onset.
- Dyspepsia combined with at least one of the following known risk factors:
  - family history of UGI cancer in more than two first-degree relatives;
  - Barrett's oesophagus;
  - pernicious anaemia;
  - peptic ulcer surgery over 20 years ago;
  - known dysplasia, atrophic gastritis, intestinal metaplasia.
- Jaundice.
- Upper abdominal mass.

D.3 Endoscopy

Diagnostic endoscopy allows samples of suspect lesions to be collected for pathological examination. A series of prospective studies report that the accuracy of such sampling (by brushing and biopsy or fine needle aspiration) for initial diagnosis of oesophageal cancer can be between 90% and 100%.[19-21] In most cases, it is also possible to assess the extent of tumour spread within the oesophagus by endoscopy.[22] Endoscopic diagnosis of gastric cancer appears to offer similar levels of accuracy.[23-27]

Achieving competence in endoscopy requires considerable practice. A study of gastroenterology fellows and fourth year surgical residents concluded that experience of over 100 procedures was necessary before success was achieved in 90% of attempts to pass an endoscope through the oesophagus.[28] Although diagnostic endoscopy is not risk-free, most adverse effects are mild and transient. The perforation rate is around 1 in 2,000, and the overall death-rate around 1 in 10,000.[29,30]

D.4 Access to endoscopy

GPs appear to use open-access endoscopy services effectively and this can avoid a large number of unnecessary outpatient clinic visits.[31] A Danish trial which compared prompt endoscopy for patients with dyspepsia (average age 44 years) with attempted symptom control with an H2 blocking drug found that prompt endoscopy was associated with reduced treatment costs and increased patient satisfaction.[32] The proportion of patients with malignancies is generally as high among patients referred by GPs as among patients referred by specialists. Overall 1–2% of patients referred for endoscopy were likely to have cancer.[31,33-37]

Although several studies suggest that rapid access to endoscopy could be associated with improved survival, there is as yet no evidence that demonstrates this unequivocally. Prompt access to endoscopy tends to yield a higher proportion of early (treatable) cancers, but there has been no comparative study demonstrating that this affects long-term survival rates.[31,33-51]

Imaging

D.5 Barium meal/swallow

Radiology (barium meal or swallow) may be used as the initial diagnostic procedure for patients with possible oesophageal or gastric cancer. It has been compared with endoscopy in two

*Age 55 years is considered to be the maximum age threshold. Local Cancer Networks may elect to set a lower age threshold (e.g. 50 years or 45 years).

studies; all cases of oesophageal cancer were identified by both methods.[52,53] However, a retrospective review reported a positive predictive value of 42% for barium studies; in other words, more than half of those who had a positive or suspicious test result did not, in fact, have cancer.[54]

Other evidence suggests that radiology may fail to identify some cases. In studies of endoscopy, some patients found to have cancer had already undergone diagnostic imaging but no abnormality had been apparent.[44] Also, studies of delay in diagnosis report that cancer may be missed when patients are assessed by radiology rather than endoscopy.[55,56] No report was found which described cases where radiology had revealed cancer missed by endoscopy.

D.6 Abdominal ultrasound

Abdominal ultrasound can detect pancreatic abnormalities and allows a correct diagnosis to be made in over 80% of patients with symptoms of cancer.[57-61] It is not reliable for determining whether the disease is resectable.[62,63]

D.7 Endoscopic ultrasound

A systematic review of endoscopic ultrasound (EUS) in gastric and oesophageal cancer concluded that it can discriminate between oesophageal or stomach tumours that are likely to be operable and those that are not.[64] 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.[63,65,66]

D.8 CT and MRI

The sensitivity of computed tomography (CT) for staging tumours and assessing the extent of spread is very variable and often poor, but its specificity is high in oesophageal and gastric cancers,[67-78] and pancreatic cancer.[62,63,65,66,79-85] This means that CT is a fairly reliable means of identifying patients whose cancer is so far advanced that radical surgery is unlikely to be effective. However, perhaps half of those who appear from CT results to have localised disease will actually have more widespread tumour. Magnetic resonance imaging (MRI) produces similar results to CT scanning.[68,72,84] The combination of CT and EUS offers considerably higher levels of accuracy for staging gastric tumours than CT alone.[64]

D.9 ERCP and MRCP in pancreatic cancer

In patients with jaundice, endoscopic retrograde cholangio-pancreatography (ERCP) may permit a diagnosis of pancreatic cancer when other imaging shows no abnormality or is inconclusive.[86] ERCP with bile cytology and brushing can provide tumour cells for tissue diagnosis.[58,87,88]

ERCP has serious drawbacks. Failure rates of 18% and 11% for attempts to image the pancreatic and biliary ducts, respectively, were found in an audit in northern England.[89] Major complication rates were 6% overall and 10% with stent insertion. An Italian study found that complications were significantly more common in centres where fewer procedures were carried out (7% versus 2%).[90] This is a difficult procedure which has to be practised on up to 200 patients before the endoscopist achieves technical competence.[91]

Magnetic resonance cholangio-pancreatography (MRCP) is a new technique. Small studies suggest that it may offer a higher level of accuracy than other non-invasive methods used to diagnose pancreatic cancer, with the additional advantage that contrast media are not required.[92,93] A comparison between MRCP and ERCP in 124 patients reported that the difference in sensitivity was not quite statistically significant (p=0.06), but this calculation did not allow for the fact that ERCP failed in 16 of the original group of 141 patients. MRCP was impossible in one patient, who had claustrophobia. There were no complications after MRCP, whereas ERCP caused adverse effects in 7% of patients.[94]

E. Oesophageal cancer and junctional tumours

Radical treatment

E.1 Surgery

About a third of patients with oesophageal cancer undergo surgery. Success rates are poor and operative mortality and morbidity can be high. In Yorkshire, the five-year survival rate after surgery in 1991–3 was 13.9% (95% CI: 10.3, 17.6); peri-operative mortality was 15%.[95] In a study by Bachmann et al of 781 patients treated by 23 hospital trusts in south west England, the peri-operative mortality rate in 1996–7 was 11%.[96] These rates were significantly lower for surgeons who carried out these operations more frequently; an increase of 10 in the number of patients treated over the period of the study was associated with 32% fewer deaths (odds ratio, adjusted for case-mix: 0.68, 95% CI: 0.52, 0.96).

There is additional evidence from the US that hospitals which deal with larger numbers of patients achieve lower peri-operative mortality. Mortality among patients over the age of 65 was 17.3% (95% CI: 13.3%, 22.0%) in hospitals which carried out fewer than five oesophagectomies per year and 3.4% (95% CI: 0.7%, 9.6%) in hospitals where the corresponding figure was over 11.[97] Another study reported 3% (95% CI: 0.09%, 5.1%) peri-operative mortality in five hospitals which carried out 265 Medicare-funded oesophagectomies between them in 1994–6.[98]

Oesophageal resection leads to impaired quality of life for some months after surgery.[99-102] In patients who survive for more than two years, quality of life returns to baseline levels after about six months and may continue to improve. However, among those who do not become long-term survivors, quality of life continues to deteriorate despite improved ability to swallow. Thus the overall effect of surgery appears to be beneficial only when the operation is curative.

Two randomised controlled trials (RCTs) found that surgery was significantly more likely than radiotherapy to improve both swallowing and survival (p=0.002) in patients with operable tumours.[103,104]

E.2 Neo-adjuvant and adjuvant chemotherapy

Analysis of early results from a Medical Research Council (MRC) RCT (OEO2) involving 802 patients with resectable oesophageal cancer found that two cycles of cisplatin/5-FU before surgery (neo-adjuvant chemotherapy) was associated with a 10% (95% CI: 3%, 16%) improvement in survival at two years, from 35% to 45%; median survival increased from 13.4 to 17.4 months.[105] Physical activity, dysphagia, and general well-being after treatment were not significantly affected.

Meta-analyses of earlier studies show no significant advantage for either neo-adjuvant or adjuvant chemotherapy.[106,107]

E.3 Neo-adjuvant and adjuvant radiotherapy

A meta-analysis of data from 1,147 patients in trials comparing pre-operative radiotherapy with surgery alone found that radiotherapy improved survival rates from 30% to 34% at two years despite increased surgical mortality, but this difference fell short of statistical significance (p=0.06).[108] This possible survival benefit is offset by increased morbidity and duration of treatment. Radiotherapy after surgery impairs quality of life without improving survival.[106]

E.4 Chemo-radiotherapy

Recent results from a large trial (n=556) show improved 3-year survival rates after adjuvant chemo-radiotherapy (52% in the multimodality therapy arm, versus 41% after surgery only; p=0.03). Median survival increased from 27 to 42 months. Serious adverse effects of treatment seem to have been relatively common, with 1% toxic deaths; nevertheless, toxicity was described as 'tolerable'.[109]

Neo-adjuvant chemo-radiotherapy has been compared with surgery alone in a meta-analysis of seven earlier trials,[106] but differences between the trials mean that the results could be misleading.

No trials compare chemo-radiotherapy alone with chemo-radiotherapy followed by surgery, so it is not clear whether surgery confers any additional benefit for patients who show a complete response to chemo-radiotherapy. In advanced disease, chemo-radiotherapy appears to extend survival time more than radiotherapy alone, despite local failure rates of 40-50%.[110-119] No study measured quality of life.

Palliative interventions

Most patients require palliative interventions to relieve dysphagia. A range of techniques is used, including removal of tumour in the oesophagus by laser and other methods, and chemotherapy and/or radiotherapy to shrink the tumour. There is no evidence that any one of these techniques should be used routinely in preference to others.

E.5 Stents

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.[96] Compared with other types, expanding metal stents (Wallstents) are associated with fewer complications, better quality of life for patients, less need for re-intervention, and less time spent in hospital.[120-125]

E.6 Chemotherapy

Two studies comparing epirubicin, cisplatin and 5-FU (ECF) with adriamycin, 5-FU and methotrexate (FAMTX) (n=256) or mitomycin, cisplatin and 5-FU (MCF) (n=580) report that chemotherapy reduces symptoms in patients with previously untreated advanced oesophageal cancer.[126,127] In the former trial, ECF was associated with a significantly higher one year survival rate than FAMTX: 37% versus 12.5% (p=0.032).[126] The latter trial suggests that quality of life is better with ECF than MCF.[127]

A French trial comparing palliative chemotherapy (cisplatin and 5-FU) with no treatment found no evidence of improved outcomes with chemotherapy, but many of these patients had undergone sugery.[128]

E.7 Intra-luminal interventions

Intra-luminal radiotherapy (brachytherapy) may increase survival time and can relieve dysphagia.[129,130] In one study, 10%, 22% and 35% of patients who received 12Gy, 16Gy (two fractions) or 18Gy (three fractions), respectively, were alive one year later.[130]

Small studies suggest that stenting gives longer-lasting relief from dysphagia than laser treatment.[131-135] In practice, however, these methods may be used in combination.

F. Treatment for gastric cancer

F1. Surgery: patient numbers

In the UK (Yorkshire), just under half of all patients with gastric cancer undergo surgery.[136] The Bachmann et al study, which included 731 patients with gastric cancer, found an overall peri-operative mortality rate in south

west England of 14%.[96] An increase of 10 in the number of patients treated by individual surgeons over the period of the study was associated with a reduction in mortality of about a third (odds ratio for peri-operative death, adjusted for case-mix: 0.60, 95% CI: 0.39, 1.00).

F.2 Surgery: type of operation

Long-term survival rates reported from Japan are around 50% – considerably higher than those in the UK. This has been attributed by some to the use of a more extended operation known as a 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 RCTs in Japan comparing this procedure with less radical operations.

Results similar to those achieved in Japan have been reported from uncontrolled trials in the West, leading to a widespread belief that D2 resections would lead to higher long-term survival rates than D1 (conventional western) surgery. However this belief has now been tested in four RCTs, all of which found that more radical surgery was associated with worse outcomes.[137-140] (Table 2)

In the largest study (998 patients), no difference was found in five-year survival rates (47% and 45% after D2 and D1 resections, respectively). However, D2 surgery led to significantly higher peri-operative mortality (10% versus 4%, p=0.004) and more complications (43% versus 25%, p=0.001).[137] An MRC trial (n=400) also found no difference in five-year survival rates (33% and 35%), but peri-operative mortality of D2 surgery was twice that of D1 (13% versus 6.5%, p=0.04).[138]

The other two RCTs, although small, produced similar results: D2 surgery led to significantly poorer short-term outcomes (greater blood transfusion requirements, longer hospital stay), and no longer-term benefits.[139,140] Median survival time in one study was significantly shorter in patients who underwent D2 resections (30 versus 50 months, p=0.04).[140]

Splenectomy and pancreatectomy, part of the original protocol for some patients undergoing D2 surgery, significantly reduced the probability of survival.[138,140,141] The suggestion that outcomes could be optimised by a modified D2 procedure, without routine splenectomy or pancreatectomy,[138] has not been tested in an RCT. Multivariate analysis of results from the largest RCT show that the defining feature of D2 surgery, removal of larger numbers of lymph nodes, doubles the risk of death.[141]

These trials have been criticised on a variety of points, including non-compliance with the protocol, which could have reduced the distinction between the procedures.[142,143] Despite this, the results did show significant differences in outcomes between the trial arms: specifically, that the D2 procedure led to 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 nine trials.[144-152] These show that resection can relieve the symptoms of gastric cancer when potentially curative surgery is impossible. Less extended surgery is associated with fewer symptoms and better quality of life after surgery; no trial reports any advantage for total gastrectomy when a sub-total operation is possible. No differences were demonstrated between types of gastrectomy in survival rates or post-operative mortality.

F.3 Chemotherapy

A recent meta-analysis of 20 RCTs (n=3,658) shows that adjuvant chemotherapy improves survival after curative resection for gastric cancer, but the effect is not large.[153] This included 21 comparisons from 20 studies and produced a combined hazard ratio of 0.82 (95% CI: 0.75, 0.89) in favour of chemotherapy but there was significant heterogeneity between trials. Studies of combination chemotherapy were homogeneous and of better quality than those of single agents. The hazard ratio for combination chemotherapy was 0.86 (95% CI: 0.78, 0.94). After adjuvant chemotherapy, five-year survival rates increase from 20% to 24% (95% CI: 21%, 28%) in patients with Stage III disease (or 50% to 54%, 95% CI: 51%, 57% in Stage II).[153]

Western trials of intra-peritoneal chemotherapy report increased complication rates with no improvements in survival rates.[154-157] Japanese trials, by contrast, report that intra-peritoneal chemotherapy improves survival.[158-162] The reasons for this discrepancy are not apparent.

Palliative chemotherapy can improve quality of life and may extend survival time in patients with advanced gastric cancer by about six months, compared with best supportive care.[163-165] Epirubicin, cisplatin and 5-FU (ECF) is beneficial for fitter patients.[126]

F.4 Radiotherapy

There is no reliable evidence to suggest that radiotherapy is beneficial for patients with gastric cancer.[166-172]

F.5 Chemo-radiotherapy

Improved survival has been reported after adjuvant chemo-radiotherapy, with three-year survival rates of 52% versus 41% after surgery alone (p=0.03).[109] This study has yet to be published in full and few details are available.

No RCT shows any benefit for chemo-radiotherapy in advanced disease.[170,173-175] Patients who undergo multi-modality treatment are likely to suffer from severe toxic effects.

G. Treatment for pancreatic cancer

G.1 Surgery

Radical surgery for pancreatic cancer can lead to long-term survival but curative resection is rarely possible. Mortality rates are high. In Yorkshire between 1986 and 1994, 17.7% of patients died within 30 days of surgery (palliative or curative); fewer than 3% survived for five years.[95] Such poor results are not universal, however; case-series from institutions with a specialist interest in pancreatic surgery report five-year survival rates as high as 20%.[176-179]

Two systematic reviews found clear evidence that higher hospital volume was associated with lower mortality rates.[180,181] Risk-adjusted peri-operative mortality rates are around 14% in hospitals treating, on average, one such patient per year, but 2.2% to 4.2% for >10 patients. Relative risk of death within three years was 0.69 (95% CI: 0.62, 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.

Chemotherapy

G.2 First-line chemotherapy

A variety of chemotherapy regimens have been used in attempts to improve survival rates and palliate symptoms of advanced disease. These trials have, in general, been small and for that reason, are often inconclusive. Three RCTs found that chemotherapy extended median survival by a few weeks or months, compared with best supportive care;[163,182,183] others reported no significant difference.[184-188] Quality of life may improve, but this has not been unequivocally demonstrated and it is often not clear whether reported benefits outweigh toxicity. There is no reliable evidence that any particular drug regimen is more effective than others.[189-197]

Hormone therapy offers no clear benefits.[198-204] One small trial of flutamide (n=49) reported dramatic improvements in survival, but only 35% of the patients had histologically confirmed pancreatic cancer.[205] This result requires replication before it can be considered reliable.

G.3 Chemo-radiotherapy

Concurrent chemo-radiotherapy can improve survival by a few weeks compared with single-modality treatment, but it is also likely to cause toxicity problems.[174,206-211]

G.4 Adjuvant therapy

A major study (ESPAC-1) is assessing the effectiveness of post-operative treatment for patients with pancreatic cancer.[212] Adjuvant 5-FU plus folinic acid (5-FU/FA) or chemo-radiotherapy (40Gy plus 5-FU) were compared with surgery alone. Preliminary results for 530 patients suggest that chemotherapy is beneficial (median survival 19.5 months versus 13.5 months; p=0.003) but radiotherapy is not (median survival 14 months with chemo-radiotherapy, versus 15.7 months without). No information is yet available on adverse effects.

In July 1999, the Independent Data Monitoring Committee recommended that patients should no longer receive radiotherapy. The trial will roll into ESPAC-3, comparing surgery alone with surgery followed by 5-FU/FA or gemcitabine.

G.5 Relief of bile duct obstruction

Pancreatic cancer frequently causes obstruction of the bile ducts and jaundice. Trials comparing interventions to relieve obstruction show that self-expanding metal stents (Wallstents) are superior to polythene stents.[122,213,214] Patients who receive metal stents are less likely to suffer from pain and inflammation of the gall bladder; they are less likely to have complications and require less time in hospital, and their quality of life is better.

Studies comparing stents with surgery show that both types of procedure are effective for relief of jaundice but the balance of associated risks and costs differs.[215-218] Stenting requires shorter initial hospitalisation and costs significantly less than surgery, but stents can become blocked, leading to recurrent jaundice. Although surgery can have a high peri-operative mortality rate (see above), longer-term survival rates do not appear to differ between patient groups.

H. Patient focus and palliative care

There is no evidence of substantive differences between the psychosocial, information, practical, or other general needs of patients with UGI cancers and those with other tumours. Research evidence on these issues has been discussed in bulletins dealing with cancers of the breast and lung.[219,220] In addition, patients with UGI cancers have specific problems with nutrition.

H.1 Nutrition

Despite the importance of adequate nutrition to patient comfort and, indeed, to survival, little research evidence was found on problems with eating and digestion. Specialists in the field acknowledge that those who have undergone surgery for cancer of the oesophagus or stomach suffer from a variety of post-gastrectomy syndromes, and suggest that the impact of these problems can often be reduced by appropriate dietary adjustments. Dietary issues are discussed in pamphlets based on patients' experience, available from the Oesophageal Patients Association (0121 704 9860).

Table 2 Randomised controlled trials comparing standard with radical resection for gastric cancer.

Author, year, country, grade	Patients and interventions	Results	Conclusions	Comments
Bonenkamp (1999, 1995, 1992)[137,226,227] The Netherlands IA	998 patients with histologically confirmed adenocarcinoma of the stomach randomised; 711 underwent curative resection. D1 (standard Western) resection: n=380. D2 (radical/Japanese) resection: n=331. D2 surgery included removal of specified lymph nodes, plus the distal pancreas and spleen in patients with proximal tumours. The mean yield of lymph nodes was 15 in D1 resections and 30 in D2. In 632 patients, there was no evidence of residual tumour after surgery. 80 hospitals participated; each treated about 2 patients per year, supervised by an experienced Japanese surgeon.	D2 resection associated with significantly greater complication rate (D1: 25%, D2: 43%, p<0.001), more peri-operative deaths (D1: 4%, D2: 10%, p=0.004) and longer median hospital stay (D1: 14 days, D2: 16 days, p<0.001). No significant difference in five year survival rates (D1: 45%, D2: 47%). 29% of patients who underwent D2 resection without pancreatico-splenectomy had recurrence, compared with 41% of D1 patients (p=0.02). Risk factor analysis revealed that men aged over 65 years were most likely to die. Relative risk (RR) for age greater than 65: 4.35 (95% CI: 2.07, 9.15); RR for male sex: 2.51 (95% CI: 1.24, 5.08). The extent of nodal dissection was also a significant risk factor for death (RR 2.13, 95% CI: 1.05, 4.32). For complications, splenectomy was the most important risk factor (RR 2.13, 95% CI: 1.44, 3.16) whilst pancreatectomy (RR 3.03, 95% CI: 1.98, 4.65) and type of gastrectomy (RR 2.00, 95% CI: 1.43, 2.78) influenced the occurrence of major surgical complications.[141]	Results do not support routine use of D2 lymph-node dissection in patients with gastric cancer. Pancreatico-splenectomy associated with particularly poor outcomes, but greater nodal dissection also independently hazardous. Risk factors should be considered carefully when planning surgery for individual patients.	Criticisms of study hinge on blurring of differences between D1 and D2 procedures: for example, 6% of patients who underwent D1 resections had lymph nodes excised from stations that were not designated, whilst 36% of patients who underwent D1 had fewer lymph nodes excised than was designated. 51% of patients who underwent D2 resection had no lymph nodes removed from at least 2 of the designated stations.[143,228] It has been suggested that the therapeutic benefit of D2 resection may have remained undetected due to diminished distinction between the two procedures.[228] This argument ignores clear differences between groups in outcomes. If the two procedures had indeed been indistinguishable, these should not be significantly different. Post-hoc sub-group analyses seem to aim to support authors bias in favour of D2 resection; the results of the RCT by contrast, favour less radical surgery.
Cuschieri (1999 and 1996)[138,229] UK IA	400 patients with histologically proven and potentially curable gastric carcinoma, randomised after staging laparotomy to 2 equal groups. D1 (standard Western) resection: n=200. D2 (radical) resection: n=200. D2 surgery involved removal of additional specified lymph nodes and hemipancreatico-splenectomy for middle and upper third lesions. Median follow-up 6.5 years.	No difference in 5 year survival (D1: 35%, D2: 33%, p=0.43, hazard ratio HR=1.10, 95% CI: 0.87, 1.39). Higher post-operative mortality after D2 resection: 13% (95% CI: 9, 18%) versus 6.5% (95% CI: 4, 11%) for D1. If post-operative deaths removed from analysis still no significant difference in 5 year survival: HR=1.05 (95% CI: 0.79, 1.39). No difference in recurrence-free survival: HR=1.03, 95% CI: 0.82, 1.29). Resection included pancreatico-splenectomy for 57% in D2 group and 4% of D1 group. Significantly worse survival among patients who had pancreatico-splenectomy (p=0.01).	Routine D2 resection offers no long-term survival advantage over D1. Authors suggest that D2 resection without pancreatico-splenectomy might be better than standard D1 resection but there is no reliable evidence on this.	Problems with contamination and non-compliance as in the Bonenkamp study.
Robertson (1994)[140] Hong Kong IB	55 patients with histologically proven adenocarcinoma of the gastric antrum. R1 resection (equivalent to D1): n=25. R3 total gastrectomy (omentectomy, splenectomy, distal pancreatectomy, lymphatic clearance of the celiac axis and skeletonization of vessels in the porta hepatis: n=30.	Radical surgery associated with poorer median survival: R1=1,511 days, R3=911 days, log rank test p=0.04, Mantel Cox log-rank test p=0.07. Only one post-operative death, but R3 resection associated with high morbidity reflected in increased hospital stay, greater blood transfusion requirement and greater need for re-operation.	Poorer outcomes after R3 surgery. No evidence for routine use of R3 resection for antral gastric cancer.	Differences consistent with other studies.
Dent (1988)[139] South Africa IB	42 patients with histologically confirmed gastric carcinoma, Japanese stage S_{0-2}, P_0, H_0, N_{0-1}. (i.e. in UICC system T_{1-3}, N_{0-1}, M_0). R1 gastrectomy: n=21. R2 gastrectomy (including radical lymphadenectomy) n=21.	Radical (R2) surgery took longer (p<0.05), required more blood transfusion (p<0.005) and a longer post-operative hospital stay (p<0.05). After a median follow up period of 3.1 years, 18% of R1 group and 23% of R2 group had died.	Poorer outcomes after R2 surgery. No evidence that R2 gastrectomy offers survival advantage.	Differences consistent with other studies, significant despite small groups. Final histology showed that seven patients had disease stages in excess of the protocol requirement: stage underestimated at surgery.

A variety of techniques may be used to enable patients to ingest food and drink when their tumours block the oesophagus or digestive tract. These include stenting (see E5, above), bypass surgery, and insertion of a feeding tube directly into the digestive tract via a stoma (PEG feeding). One study found that outcomes for patients with gastric cancer were particularly poor after stoma creation for tube feeding, which was associated with higher mortality than resection.[221] However, these results could be biased by patient selection.

H.2 Symptom control

Pain, nausea, vomiting, fatigue and weight loss are symptoms common to these and other abdominal cancers. Whilst most of these symptoms may be managed medically, some patients will require specialist interventions, some of which have been discussed above.

Pain control can be particularly difficult in advanced pancreatic cancer. 90% of patients report good to excellent pain relief after coeliac plexus block, and some benefit persists for three months or until death.[222] This method is more likely to be effective when it is used within two 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.

I. Structure of services

I.1 Concentration of services

There is a considerable amount of research evidence for each type of upper GI cancer that shows that treatment in hospitals which manage larger numbers of these patients, and/or by clinicians who see larger numbers, leads to better outcomes. Evidence on surgical outcomes has been discussed above (sections E1, F1 and G1).

The most important study for the NHS is that by Bachmann et al[96] which followed a total of 2,294 patients treated in 23 hospitals in south west England and six in south Wales (pancreatic cancer only), for 16 to 34 months from the time of first presentation to hospital. This is a well adjusted study which considered specialisation, patient numbers, interventions used, survival rates, and costs.

The study revealed a fragmented service in which many patients were managed by clinicians who dealt with small numbers. In general, these patients were less likely to receive active treatment and their survival time was significantly shorter than those whose doctors managed larger numbers.

31% of patients with oesophageal cancer were treated by doctors who managed six or fewer such patients during the period of the study. The mortality rate for patients managed by consultants who dealt with one new case per week was 31% lower than that for patients whose consultants managed one new case a month (after adjustment for case-mix, numbers treated at the hospital, and types of treatment provided).

35% of patients with gastric cancer were managed by doctors who dealt with four or fewer new cases per year. Patients whose doctors managed larger numbers were more likely to undergo surgery, particularly resection (adjusted odds ratio for an increase in volume of one patient: 1.11; 95% CI: 1.07, 1.14), and less likely to have no active treatment (adjusted odds ratio, 0.94; 95% CI: 0.11, 0.97). Better outcomes were achieved in hospitals which treated larger numbers of these patients. The risk of death was 23% lower for patients treated in hospitals which admitted one case per week, compared with hospitals which dealt with one per month, even after adjustment for prognostic factors and types of treatment provided. This suggests 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.

77% of patients with pancreatic cancer died within a year of first presentation to hospital, but survival rates throughout the period of the study were significantly higher for patients cared for by hospitals which dealt with larger numbers. 31% of patients were the responsibility of doctors who managed fewer than three new cases per year. The risk of death among patients managed by hospitals that dealt with one new case each week was 36% lower than for those treated in hospitals that managed one new case a month. This risk was independent of both case-mix and the nature of the treatment provided, which again suggests that it could be due to variables which were not measured.

I.2 Co-ordination and communication

A Dutch study demonstrates the importance for patients' quality of life of effective co-ordination and communication between hospital-based care providers and home care teams. Excellent results were obtained by combining the following elements: a specialist nurse co-ordinator, a 24-hour telephone service based in the hospital ward where the patient had undergone assessment or treatment, a home care team linked with the hospital, a collaborative case file designed to improve communication, and the use of protocols for specific interventions developed by a multidisciplinary team.[223]

A systematic review of studies which compared standard home care with interventions based in hospitals, hospices or the community, found that better results were reported in studies in which multidisciplinary palliative home care team members visited patients at home, and when teams held regular meetings.[224] Improved

co-ordination and co-operation among providers can lead to improvements in patients' physical functioning, and may reduce the need for re-hospitalisation after discharge from an oncology ward. It can also reduce costs by reducing duplication of effort.[225]

J. Costs

Hospital costs were recorded by Bachmann et al as part of the study of acute hospital trusts in the South and West Region of England, discussed above.[96] These figures reveal that the largest component is bed days, accounting for 56%, 72% and 65% of costs for oesophageal, gastric and pancreatic cancers respectively.

Figures 2, 3 and 4 show costs between July 1996 and June 1997 for each type of cancer.

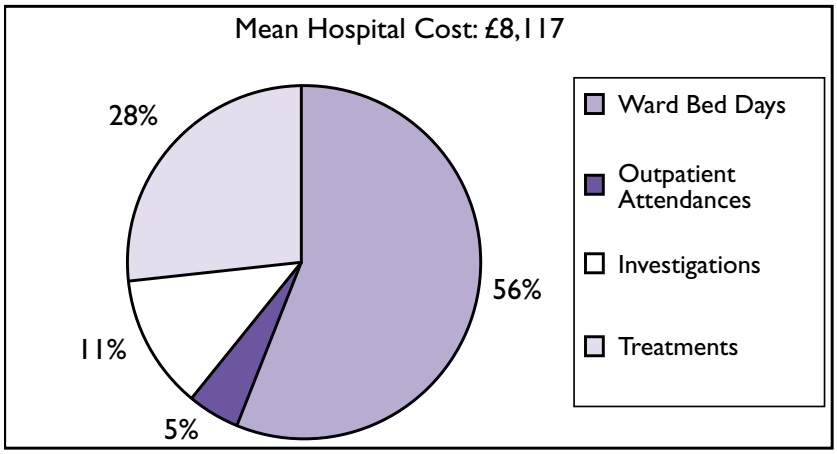

Figure 2 Breakdown of costs per oesophageal cancer patient

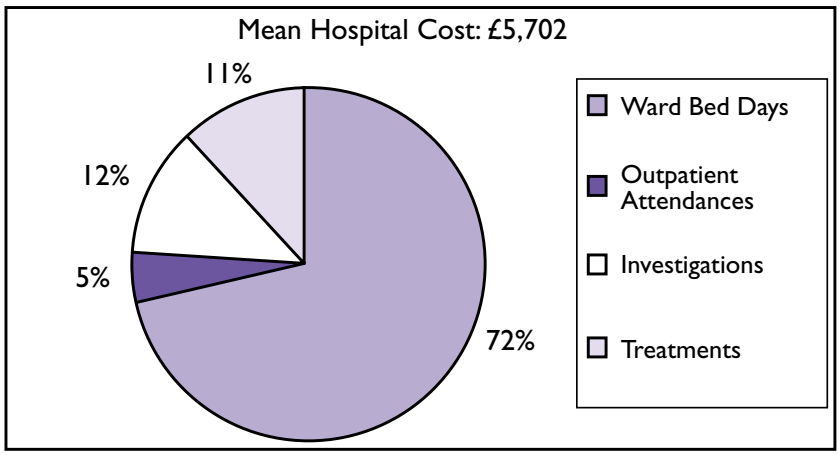

Figure 3 Breakdown of costs per gastric cancer patient

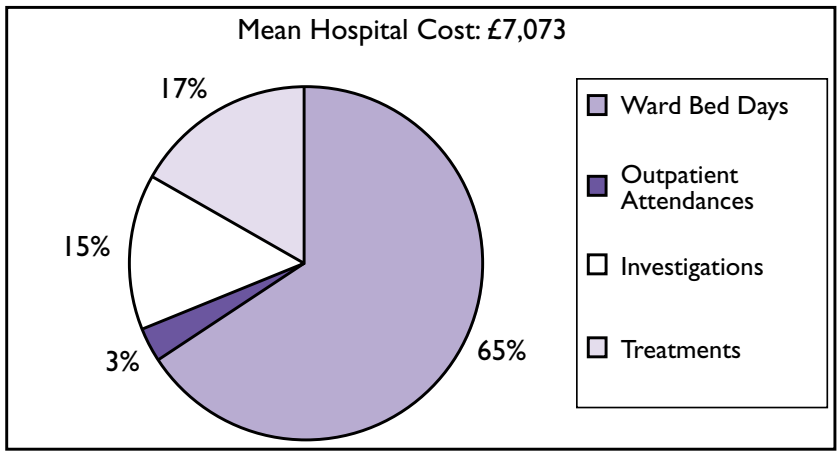

Figure 4 Breakdown of costs per pancreatic cancer patient

K. Key recommend-ations

The following key recommendations were identified as priorities for the NHS in *Improving Outcomes in Upper Gastro-intestinal Cancers: the Manual*.[2]

- All hospitals which intend to provide services for patients with upper gastro-intestinal cancer should be fully involved in appropriate Cancer Networks which include inter-linked Cancer Centres and Cancer Units. Each region should review proposals for these services, to ensure that proposed local arrangements reflect the recommendations in this guidance manual accurately.
- There should be documented local referral policies for diagnostic services for suspected upper gastro-intestinal cancer. These should be jointly agreed between GPs in Primary Care Groups and Trusts, and appropriate specialists in local hospitals and Cancer Units and Centres in each Network.
- Specialist treatment teams should be established at appropriate Cancer Centres or Units. Oesophago-gastric Cancer Teams should aim to draw patients from populations of more than one million; Pancreatic Cancer Teams should aim to draw patients from populations of two to four million.

- There should be clear documented policies for referral of patients between hospitals, and for processes by which clinicians in local hospitals seek advice from specialist treatment teams about the management of individual patients for whom referral may not be appropriate.
- Palliative support and specialist care should be available to all who need it. This will require effective co-ordination and communication between primary care, social and voluntary services, local palliative care teams, hospital services and those who provide specialist advice and interventions.
- Monitoring systems using common data-sets should be established throughout each Cancer Network to audit patient management, key communications, referral processes, and key outcomes of treatment.

Appendix – Research methods

A number of computerised databases were searched and relevant journals were hand-searched. Reference lists of papers identified were used to retrieve other potentially relevant studies and additional material was provided by referees and experts in the various fields. Studies were graded and included in the reviews according to predefined criteria. Further details are available in *Improving Outcomes in Upper Gastro-intestinal Cancers: The Research Evidence.*[1]

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