Management of upper gastrointestinal cancers

A Melville, E Morris, D Forman, A Eastwood

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*.¹ 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 1997.² 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).³⁻⁶

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.^{8,9}

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 55.²

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.¹¹

Figure 1 Trends in upper gastrointestinal cancer mortality, England and Wales.¹⁰

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%.¹²⁻²⁰

GPs use open access endoscopy services effectively, thus avoiding unnecessary clinic visits.²¹ The proportion of patients with malignancies—generally under 2%—is as high among patients referred by GPs as among those referred by specialists.²¹⁻²⁶ 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.²¹⁻⁴⁰

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 cases.^{41,42} 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.⁴³ Radiology fails to identify some cases; some patients found to have cancer by endoscopy had negative results from diagnostic imaging.³³ Studies of delay report that cancer may be missed when patients are assessed by radiology.^{44,45} No report was

Melville Johnson,
1 Osmond Terrace,
Porthmadog, Gwynedd
LL49 9AN, UK
A Melville, freelance
consultant

NHS Centre for
Reviews and
Dissemination,
University of York,
York YO10 5DD, UK
A Eastwood, senior
research fellow

Cochrane
Collaboration Review
Group in Upper
Gastrointestinal and
Pancreatic Diseases,
Cancer Epidemiology,
School of Medicine,
University of Leeds,
Leeds LS2 9LN, UK
E Morris, research
assistant
D Forman, professor

Correspondence to:
Dr A Melville
Arabella_Melville@
port35.freeserve.co.uk

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Table 1 UGI cancers: incidence rates,⁷ survival rates,^{8,9} and death rates²

Cancer site	Incidence: rate per 100 000, England and Wales		One year survival rate, England	Five year survival rate, England	Deaths, England and Wales, 1997	Death rate per 100 000, England and Wales	
	Men	Women				Men	Women
Oesophagus	14.0	9.2	27%	9%	5855	13.6	8.4
Stomach	24.3	13.8	28%	12%	6613	15.1	9.5
Pancreas	11.7	12.0	12%	3%	5782	10.5	11.2

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.⁴⁶⁻⁵⁰ It is not reliable for determining whether the disease is resectable.^{51 52}

A systematic review of endoscopic ultrasound (EUS) in gastric and oesophageal cancer concluded that it can discriminate between operable and inoperable tumours.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.^{52 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,⁵⁶⁻⁶⁷ and pancreatic cancer.^{51 52 54 55 68-74} 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.^{57 61 73}

ERCP AND MRCP IN PANCREATIC CANCER

Pancreatic cancer can sometimes be diagnosed by endoscopic retrograde cholangiopancreatography (ERCP).^{47 75 76} However, this is a difficult technique for which competence requires experience of up to 200 procedures.^{77 78} Other drawbacks include high failure rates, reaching 18% for attempts to image the pancreatic duct in an audit in northern England.⁷⁹ 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%).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.^{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.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%.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 11.⁸⁵ Another study reported 3% (95% CI 0.09% to 5.1%) perioperative mortality in five hospitals which carried out 265 Medicare funded oesophagectomies in 1994-6.⁸⁶

Oesophageal resection leads to impaired quality of life for some months after surgery.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 swallowing. 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.^{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%.⁹³ Meta-analyses of earlier studies show no significant advantage for neoadjuvant or adjuvant chemotherapy.^{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.⁹⁶ Radiotherapy after surgery impairs quality of life without improving survival.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".⁹⁷ A meta-analysis of seven earlier trials comparing neoadjuvant chemoradiotherapy with surgery alone did not produce clear results.⁹⁴

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.⁹⁸⁻¹⁰⁷

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.⁸⁴ 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.^{108–113}

Tumour in the oesophagus may be reduced by laser, chemotherapy, radiotherapy, and other methods. Small studies suggest that stenting gives longer lasting relief from dysphagia than laser treatment.^{114–118} 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.^{119–120} Intraluminal radiotherapy (brachytherapy) may also increase survival time.^{121–122}

Treatment for gastric cancer

SURGERY

In Yorkshire just under half of all patients with gastric cancer undergo surgery, with 20% alive after 5 years.¹²³ In south west England in 1996–7 perioperative mortality was 14%.⁸⁴ 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.^{124–127} 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).¹²⁴ 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%, $p=0.04$).¹²⁵ Two smaller randomised controlled trials also reported significantly poorer outcomes after D2 surgery.^{126–127}

Splenectomy and pancreatectomy, part of the original protocol for D2 surgery, reduced the probability of survival.^{125–127–128} The suggestion that outcomes could be optimised by D2

surgery without splenectomy or pancreatectomy has not been tested,¹²⁵ 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.¹²⁸

These trials have been criticised on a variety of points, particularly non-compliance with the protocol which could have blurred the distinction between procedures.^{129–130} 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.^{131–139} 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%.¹⁴⁰

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.^{141–143} ECF is beneficial for fitter patients.¹¹⁹

RADIOTHERAPY

There is no reliable evidence to suggest that radiotherapy alone, or in combination with surgery, benefits patients with gastric cancer.^{144–150} However, improved survival has been reported after adjuvant chemoradiotherapy with 3 year survival rates of 52% versus 41% after surgery alone ($p=0.03$).⁹⁷ No randomised controlled trial has shown any benefit for chemoradiotherapy in advanced disease.^{148–151–153}

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.¹⁵⁴ Such poor results are not universal, however; specialist institutions report 5 year survival rates as high as 20%.^{155–158}

Hospitals which deal with larger numbers achieve lower mortality rates.^{159–160} 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.¹⁶¹ 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^{141 162 163} while others reported no significant difference.^{164–168} 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.^{169–175} One small trial of flutamide ($n=49$) reported dramatic improvements in survival, but only 35% of the patients had histologically confirmed pancreatic cancer.¹⁷⁶

Chemoradiotherapy can improve survival by a few weeks compared with single modality treatment, but it causes toxicity problems.^{152 177–182}

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.^{110 183 184} 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.^{185–188} 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.¹⁸⁹ 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.¹⁹⁰ 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*⁸⁴ (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 for each additional patient 1.11; 95% CI 1.07 to 1.14) and less likely to provide no active treatment (adjusted odds ratio 0.94; 95% CI 0.11 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.¹⁹¹ 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.¹⁹² Better outcomes are achieved when multidisciplinary home care team members visit patients at home and when teams hold regular meetings.¹⁹³

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,¹ will lead to substantial improvements.

- 1 National Cancer Guidance Steering Group. *Improving outcomes in upper gastro-intestinal cancers: the manual*. London: NHS Executive, Department of Health, 2000.
- 2 Office for National Statistics. *Mortality statistics: cause*. London: Office of National Statistics, 1999.
- 3 Devesa S, Blot W, Fraumeni J. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;**83**:2049–53.
- 4 Hansen S, Wiig J, Giercksky K, et al. Esophageal and gastric carcinoma in Norway 1958–1992: incidence time trend variability according to morphological subsites and organ subsites. *Int J Cancer* 1997;**71**:340–4.
- 5 Hansson L, Sparen P, Nyren O. Increasing incidence of both major histological types of esophageal carcinomas among men in Sweden. *Int J Cancer* 1993;**54**:402–7.
- 6 Thomas R, Lade S, Giles G, et al. Incidence trends in oesophageal and proximal gastric carcinoma in Victoria. *Aust NZ J Surg* 1996;**66**:271–5.
- 7 Office for National Statistics. Registrations of cancer diagnosed in 1993–1996, England and Wales. *Health Statistics Quarterly* 1999;**4**:59–70.
- 8 Faivre J, Forman D, Esteve J, et al. The Eurocare Working Group. Survival of patients with primary liver cancer, pancreatic cancer and biliary tract cancer in Europe. *Eur J Cancer* 1998;**34**:2184–90.
- 9 Faivre J, Forman D, Esteve J, et al. The Eurocare Working Group. Survival of patients with oesophageal and gastric cancers in Europe. *Eur J Cancer* 1998;**34**:2167–75.
- 10 Office for National Statistics. Information provided on request. 1999.
- 11 Gillen D, McColl KEL. Does concern about missing malignancy justify endoscopy in uncomplicated dyspepsia in patients aged less than 55? *Am J Gastroenterol* 1999;**94**:75–9.
- 12 Graham DY, Schwartz JT, Cain GD, et al. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. *Gastroenterology* 1982;**82**:228–31.
- 13 Kochlar R, Rajwanshi A, Malik AK, et al. Endoscopic fine needle aspiration biopsy of gastroesophageal malignancies. *Gastrointest Endosc* 1988;**34**:321–3.
- 14 O'Donoghue J, Waldron R, Gough D, et al. An analysis of the diagnostic accuracy of endoscopic biopsy and cytology in the detection of oesophageal malignancy. *Eur J Surg Oncol* 1992;**18**:332–4.
- 15 O'Donoghue JM, Horgan PG, O'Donohoe MK, et al. Adjunctive endoscopic brush cytology in the detection of upper gastrointestinal malignancy. *Acta Cytol* 1995;**39**:28–34.
- 16 Dittler HJ, Pesarini AC, Siewert JR. Endoscopic classification of esophageal cancer: correlation with the T stage. *Gastrointest Endosc* 1992;**38**:662–8.
- 17 Tatsuta M, Iishi H, Okuda S, et al. Prospective evaluation of diagnostic accuracy of gastrofiberscopic biopsy in diagnosis of gastric cancer. *Cancer* 1989;**63**:1415–20.
- 18 Gupta RK, Rogers KE. Endoscopic cytology and biopsy in the diagnosis of gastroesophageal malignancy. *Acta Cytol* 1983;**27**:17–22.
- 19 Cardillo MR, Agnello M. Endoscopic brush cytology in the diagnosis of gastric malignancy. *J Exp Clin Cancer Res* 1990;**9**:113–20.
- 20 Keighley MR, Thompson H, Moore J, et al. Comparison of brush cytology before or after biopsy for diagnosis of gastric carcinoma. *Br J Surg* 1979;**66**:246–7.
- 21 O'Neill L, Quirke M, Hogan S, et al. Uncensored open access gastroscopy: limited resources, limited demand. *Irish J Med Sci* 1998;**167**:89–91.
- 22 Adang RP, Vismans JF, Talmon JL, et al. The diagnostic outcome of upper gastrointestinal endoscopy: are referral source and patient age determining factors? *Eur J Gastroenterol Hepatol* 1994;**6**:329–35.
- 23 Goy JA, Herold E, Jenkins PJ, et al. Open access endoscopy for general practitioners. *Med J Aust* 1986;**144**:71–4.
- 24 Holdstock G, Wiseman M, Loehry CA. Open access endoscopy service for general practitioners. *BMJ* 1979;**1**:457–9.
- 25 Kerrigan DD, Brown SR, Hutchinson GH. Open access gastroscopy: too much to swallow? *BMJ* 1990;**300**:374–6.
- 26 Mann J, Holdstock G, Harman M, et al. Scoring system to improve cost effectiveness of open access endoscopy. *BMJ* 1983;**287**:937–40.
- 27 Fraser AG, Ali MR, Yeates NJ, et al. Diagnostic tests for *Helicobacter pylori*: can they help select patients for endoscopy. *NZ Med J* 1996;**109**:95–8.
- 28 Gear MW, Ormiston MC, Barnes RJ, et al. Endoscopic studies of dyspepsia in the community an 'open access' service. *BMJ* 1980;**280**:1135–7.
- 29 Gear M, Wilkinson S. Open access upper alimentary endoscopy. *Br J Hosp Med* 1989;**41**:399–444.
- 30 Graham PW. Upper gastrointestinal endoscopy: findings in an isolated rural general practice. *Australian Family Physician* 1989;**18**:703–7.
- 31 Hungin A, Thomas P, Bramble M, et al. What happens to patients following open access gastroscopy? An outcome study from general practice. *Br J Gen Pract* 1994;**44**:519–21.
- 32 Hungin APS. Use of an open access gastroscopy service by a general practice: findings and subsequent specialist referral. *J R Coll Gen Pract* 1987;**37**:170–1.
- 33 Jones R. Upper gastrointestinal endoscopy: a view from general practice. *J R Coll Gen Pract* 1986;**36**:6–8.
- 34 Kagevi I, Lofstedt S, Persson LG. Endoscopic findings and diagnoses in unselected dyspeptic patients at a primary health care center. *Scand J Gastroenterol* 1989;**24**:145–50.
- 35 MacIntyre IMC. Open-access endoscopy for general practitioners. *Practitioner* 1988;**232**:348–51.
- 36 Martin IG, Young S, Sue-Ling H, et al. Delays in the diagnosis of oesophagogastric cancer: a consecutive case series. *BMJ* 1997;**314**:467–71.
- 37 Patel P, Khulusi S, Lloyd R, et al. Prospective screening of dyspeptic patients by *Helicobacter pylori* serology. *Lancet* 1995;**346**:1315–8.
- 38 Quine MA, Bell GD, McCloy RF, et al. Appropriate use of upper gastrointestinal endoscopy: a prospective audit. Steering Group of the Upper Gastrointestinal Endoscopy Audit Committee. *Gut* 1994;**35**:1209–14.
- 39 Schroeder P. Upper gastrointestinal endoscopy at a student health centre. *Scand J Primary Health Care* 1990;**8**:191–5.
- 40 Williams B, Luckas M, Ellingham JHM, et al. Do young patients with dyspepsia need investigation? *Lancet* 1988;**ii**:1349–51.
- 41 Dekker W, Op den Orth JO. Biphasic radiologic examination and endoscopy of the upper gastrointestinal tract. A comparative study. *J Clin Gastroenterol* 1988;**10**:461–5.
- 42 Halpert RD, Feczko PJ, Spickler EM, et al. Radiological assessment of dysphagia with endoscopic correlation. *Radiology* 1985;**157**:599–602.
- 43 Levine MS, Chu P, Furth EE, et al. Carcinoma of the esophagus and esophagogastric junction: sensitivity of radiographic diagnosis. *AJR* 1997;**168**:1423–6.
- 44 Arvanitakis C, Nikopoulos A, Giannoulis E, et al. The impact of early or late diagnosis on patient survival in gastric cancer in Greece. *Hepato-Gastroenterology* 1992;**39**:355–7.
- 45 Zilling TL, Walther BS, Ahren B. Delay in diagnosis of gastric cancer: a prospective study evaluating doctors' and patients' delay and its influence on five year survival. *Anti-cancer Res* 1990;**10**:411–6.
- 46 Karlson BM, Forsman CA, Wilander E, et al. Efficiency of percutaneous core biopsy in pancreatic tumor diagnosis. *Surgery* 1996;**120**:75–9.
- 47 Pasanen P, Partanen K, Pikkarainen P, et al. Diagnostic accuracy of ultrasound, computed tomography and endoscopic retrograde cholangiopancreatography in the detection of pancreatic cancer in patients with jaundice or cholestasis. *In Vivo* 1992;**6**:297–301.
- 48 Savarino V, Mansi C, Picciotto A, et al. Comparison of ultrasound and computed tomography in the detection of pancreatic diseases. *Ital J Gastroenterol* 1983;**15**:27–9.
- 49 Taylor KJW, Buchin PJ, Visconti GN, et al. Ultrasonographic scanning of the pancreas. Prospective study of clinical results. *Radiology* 1981;**138**:211–3.
- 50 Tomiyama T, Ueno N, Tano S, et al. Assessment of arterial invasion in pancreatic cancer using color Doppler ultrasonography. *Am J Gastroenterol* 1996;**91**:1410–6.
- 51 De Roos WK, Welvaart K, Bloem JL, et al. Assessment of resectability of carcinoma of the pancreatic head by ultrasonography and computed tomography. A retrospective analysis. *Eur J Surg Oncol* 1990;**16**:411–6.
- 52 Palazzo L, Roseau G, Gayet B, et al. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma. *Endoscopy* 1993;**25**:143–50.
- 53 Harris KM, Kelly S, Berry E, et al. *Systematic review of endoscopic ultrasound in gastro-oesophageal cancer*. Volume 2. Rockville, MD: Health Technology Assessment, 1998:iii–129.
- 54 Legmann P, Vignaux O, Dousset B, et al. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. *AJR* 1998;**170**:1315–22.
- 55 Cellier C, Cuillerier E, Palazzo L, et al. Intraductal papillary and mucinous tumors of the pancreas: accuracy of preoperative computed tomography, endoscopic retrograde pancreatography and endoscopic ultrasonography, and long-term outcome in a large surgical series. *Gastrointest Endosc* 1998;**47**:42–9.
- 56 Consigliere D, Chua CL, Hui F, et al. Computed tomography for oesophageal carcinoma: its value to the surgeon. *J R Coll Surg Edinb* 1997;**13**:113–7.
- 57 Lehr L, Rupp N, Siewert JR. Assessment of resectability of esophageal cancer by computed tomography and magnetic resonance imaging. *Surgery* 1988;**103**:344–50.
- 58 Markland CG, Manhire A, Davies P, et al. The role of computed tomography in assessing the operability of oesophageal carcinoma. *Eur J Cardiothorac Surg* 1989;**3**:33–6.
- 59 Schurawitzki H, Kumpan W, Niederle B, et al. Esophageal carcinoma: CT staging of tumor infiltration. *Dysphagia* 1988;**2**:170–4.
- 60 Sharma OP, Chandermohan, Mashankar AS, et al. Role of computed tomography in preoperative evaluation of esophageal carcinoma. *Indian J Cancer* 1994;**31**:12–8.
- 61 Takashima S, Takeuchi N, Shiozaki H, et al. Carcinoma of the esophagus: CT vs MR imaging in determining resectability. *AJR* 1991;**156**:297–302.
- 62 Thompson WM, Halvorsen RA, Foster WL, et al. Computed tomography for staging esophageal and gastro-esophageal cancer: reevaluation. *AJR* 1983;**141**:951–8.

- 63 Dehn TC, Reznick RH, Nockler IB, et al. The pre-operative assessment of advanced gastric cancer by computed tomography. *Br J Surg* 1984;71:413-7.
- 64 Kim JJ, Jung HC, Song IS, et al. Preoperative evaluation of the curative resectability of gastric cancer by abdominal computed tomography and ultrasonography: a prospective comparison study. *Korean J Intern Med* 1997;12:1-6.
- 65 Sussman SK, Halvorsen RA, Illescas FF, et al. Gastric adenocarcinoma: CT versus surgical staging. *Radiology* 1988;167:335-40.
- 66 Sondenaa K, Skaane P, Nygaard K, et al. Value of computed tomography in preoperative evaluation of resectability and staging in oesophageal carcinoma. *Eur J Surg* 1992;158:537-40.
- 67 Andaker L, Morales O, Hojer H, et al. Evaluation of preoperative computed tomography in gastric malignancy. *Surgery* 1991;109:132-5.
- 68 Bluemke DA, Cameron JL, Hruban RH, et al. Potentially resectable pancreatic adenocarcinoma: spiral CT assessment with surgical and pathologic correlation. *Radiology* 1995;197:381-5.
- 69 Coley SC, Strickland NH, Walker JD, et al. Spiral CT and the pre-operative assessment of pancreatic adenocarcinoma. *Clin Radiol* 1997;52:24-30.
- 70 Diehl SJ, Lehmann KJ, Sadick M, et al. Pancreatic cancer: value of dual-phase helical CT in assessing resectability. *Radiology* 1998;206:373-8.
- 71 Freeny PC, Marks WM, Ryan JA, et al. Pancreatic ductal adenocarcinoma: diagnosis and staging with dynamic CT. *Radiology* 1988;166:125-33.
- 72 Freeny PC, Traverso LW, Ryan JA. Diagnosis and staging of pancreatic adenocarcinoma with dynamic computed tomography. *Am J Surg* 1993;165:600-6.
- 73 Megibow AJ, Zhou XH, Rotterdam H, et al. Pancreatic adenocarcinoma: CT versus MR imaging in the evaluation of resectability. Report of the Radiology Diagnostic Oncology Group. *Radiology* 1995;195:327-32.
- 74 Phoa SS, Reeders JW, Rauws EA, et al. Spiral computed tomography for preoperative staging of potentially resectable carcinoma of the pancreatic head. *Br J Surg* 1999;86:789-94.
- 75 Freeny PC, Ball TJ. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) in the evaluation of suspected pancreatic carcinoma: diagnostic limitations and contemporary roles. *Cancer* 1981;47:1666-78.
- 76 Snady H, Cooperman A, Siegel J. Endoscopic ultrasonography compared with computed tomography with ERCP in patients with obstructive jaundice or small peri-pancreatic mass. *Gastrointest Endosc* 1992;38:27-34.
- 77 Jowell PS, Baile J, Branch MS, et al. Quantitative assessment of procedural competence. A prospective study of training in endoscopic retrograde cholangiopancreatography. *Ann Intern Med* 1996;125:983-9.
- 78 Watkins JL, Etzkorn KP, Wiley TE, et al. Assessment of technical competence during ERCP training. *Gastrointest Endosc* 1996;44:411-5.
- 79 Tanner AR. ERCP: present practice in a single region. Suggested standards for monitoring performance. *Eur J Gastroenterol Hepatol* 1996;8:145-8.
- 80 Loperfido S, Angelini G, Benedetti G, et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicentre study. *Gastrointest Endosc* 1998;48:1-10.
- 81 Diehl SJ, Lehmann KJ, Gaa J, et al. Pancreatic cancer: value of MRI including MR cholangiopancreatography (MRCP) compared to endoscopic retrograde cholangiopancreatography (ERCP). *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb* 1999;170:463-9.
- 82 Gaa J, Wendl K, Tesdal IK, et al. Combined use of MRI and MR cholangiopancreatography and contrast enhanced dual phase 3-D MR angiography in diagnosis of pancreatic tumors: initial clinical results. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb* 1999;170:528-33.
- 83 Adamek HE, Albert J, Breer H, et al. Pancreatic cancer detection with magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography: a prospective controlled study. *Lancet* 2000;356:190-3.
- 84 Bachmann M, Alderson D, Peters T, et al. *Survival, clinical practice and costs in patients with pancreatic, oesophageal and gastric cancers: influences of doctor and hospital volumes.* Bristol: Departments of Social Medicine and Surgery, University of Bristol, 1999.
- 85 Begg CB, Cramer LD, Hoskins WJ, et al. Impact of hospital volume in operative mortality for major cancer surgery. *JAMA* 1998;280:1747-51.
- 86 Swisher SG, DeFord L, Merriman KW, et al. Effect of operative volume on morbidity, mortality, and hospital use after esophagectomy for cancer. *J Thorac Cardiovasc Surg* 2000;119:1126-34.
- 87 Blazeby JM, Farndon JR, Donovan J, et al. A prospective longitudinal study examining quality of life in patients with oesophageal cancer. *Br J Surg* 1999;86:419.
- 88 O'Hanlon DM, Harkin M, Karat D, et al. Quality of life assessment in patients undergoing treatment for oesophageal carcinoma. *Br J Surg* 1995;82:1682-5.
- 89 van Knippenberg FCE, Out JJ, Tilanus HW, et al. Quality of life assessment in patients with resected oesophageal cancer. *Soc Sci Med* 1992;35:139-45.
- 90 Zieren HU, Jacobi CA, Zieren J, et al. Quality of life following resection of oesophageal carcinoma. *Br J Surg* 1996;83:1772-5.
- 91 Badwe RA, Sharma V, Bhansali MS, et al. The quality of swallowing for patients with operable oesophageal carcinoma: a randomized trial comparing surgery with radiotherapy. *Cancer* 1999;85:763-8.
- 92 Fok M, McShane J, Law SYK, et al. Prospective randomised study on radiotherapy and surgery in the treatment of oesophageal carcinoma. *Asian J Surg* 1994;17:223-9.
- 93 Clark P, on behalf of the MRC Upper GI Tract Cancer Group. Medical Research Council (MRC) randomised phase III trial of surgery with or without pre-operative chemotherapy in resectable cancer of the oesophagus. *Br J Cancer* 2000;83(Suppl 1):1, abstract CT2.
- 94 Malthaner RA. *Neoadjuvant or adjuvant therapy for resectable esophageal cancer. Practice guideline-in-progress report #2-11.* Ottawa: Cancer Care Ontario, Ontario Ministry of Health, 1999.
- 95 Bhansali MS, Vaidya JS, Bhatt RG, et al. Chemotherapy for carcinoma of the esophagus: a comparison of evidence from meta-analyses of randomized trials and of historical control studies. *Ann Oncol* 1996;7:355-9.
- 96 Arnott SJ, Duncan W, Gignoux M, et al. Preoperative radiotherapy in esophageal carcinoma: a meta-analysis using individual patient data (Oesophageal Cancer Collaborative Group). *Int J Radiat Oncol Biol Phys* 1998;41:579-83.
- 97 Macdonald JS, Smalley S, Benedetti J, et al. Postoperative combined radiation and chemotherapy improves disease free survival (DFS) and overall survival (OS) in resected adenocarcinoma of the stomach and GE junction. Results of intergroup study INT-0116 (SWOG 9008). *Proc Am Soc Clin Oncol* 2000;19:1.
- 98 Alberts AS, Anderson JD, Goedhals L, et al. Palliative radiation schedules with and without chemotherapy in advanced carcinoma of the oesophagus. *S Afr Med J* 1984;66:289-91.
- 99 Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999;281:1623-7.
- 100 Andersen AP, Berald P, Edsmyr F, et al. Irradiation, chemotherapy and surgery in esophageal cancer: a randomized clinical study. The first Scandinavian trial in esophageal cancer. *Radiother Oncol* 1984;2:179-88.
- 101 Hatlevoll R, Hagen S, Hansen HS, et al. Bleomycin/cisplatin as neoadjuvant chemotherapy before radical radiotherapy in localized, inoperable carcinoma of the esophagus. A prospective randomized multicentre study: the second Scandinavian trial in esophageal cancer. *Radiother Oncol* 1992;24:114-6.
- 102 Hukku S, Fernandes P, Vasishta S. Radiation therapy alone and in combination with bleomycin and 5-fluorouracil in advanced carcinoma esophagus. *Indian J Cancer* 1989;26:131-6.
- 103 Kolaric K, Maricic Z, Roth A, et al. Combination of bleomycin and adriamycin with and without radiation in the treatment of inoperable esophageal cancer. A randomized study. *Cancer (Philadelphia)* 1980;45:2265-73.
- 104 Araujo CMM, Souhami L, Gil RA, et al. A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus. *Cancer* 1991;67:2258-61.
- 105 Roussel A, Bleiberg H, Dalesio O, et al. Palliative therapy of inoperable oesophageal carcinoma with radiotherapy and methotrexate: final results of a controlled clinical trial. *Int J Radiat Oncol Biol Phys* 1989;16:67-72.
- 106 Smith TJ, Ryan LM, Douglass HO, et al. Combined chemoradiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group. *Int J Radiat Oncol Biol Phys* 1998;42:269-76.
- 107 Zhefang Z. Radiation combined with bleomycin for esophageal carcinoma: a randomized study of 99 patients. *Chin J Oncol* 1984;6:372-4.
- 108 Alfke H, Wagner HJ, Knyrim K, et al. Palliative therapy of dysphagia due to malignant esophageal stenoses and quality of life. *Medizin Welt* 1996;47:62-9.
- 109 De Palma GD, di Matteo E, Romano G, et al. Plastic prosthesis versus expandable metal stents for palliation of inoperable esophageal thoracic carcinoma: a controlled prospective study. *Gastrointest Endosc* 1996;43:478-82.
- 110 Knyrim K, Wagner HJ, Pausch J, et al. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. *Endoscopy* 1993;25:207-12.
- 111 Roseveare CD, Patel P, Simmonds N, et al. Metal stents improve dysphagia, nutrition and survival in malignant oesophageal stenosis: a randomized controlled trial comparing modified Gianturco Z-stents with plastic Atkinson tubes. *Eur J Gastroenterol Hepatol* 1998;10:653-7.
- 112 Sanyika C, Corr P, Haffjee A. Palliative treatment of oesophageal carcinoma: efficacy of plastic versus self-expandable stents. *S Afr Med J* 1999;89:640-3.
- 113 Siersema PD, Hop WC, Dees J, et al. Coated self-expanding metal stents versus latex prostheses for esophago-gastric cancer with special reference to prior radiation and chemotherapy: a controlled, prospective study. *Gastrointest Endosc* 1998;47:113-20.
- 114 Adam A, Ellul J, Watkinson AF, et al. Palliation of inoperable esophageal carcinoma: a prospective randomized trial of laser therapy and stent placement. *Radiology* 1997;202:344-8.
- 115 Alderson D. Laser recanalization versus endoscopic intubation in the palliation of malignant dysphagia. *Br J Surg* 1990;77:1151-3.
- 116 Carter R, Smith JS. Laser recanalization versus endoscopic intubation in the palliation of malignant dysphagia: a randomized prospective study. *Br J Surg* 1992;79:1167-70.

- 117 Fuchs KH, Freys SM, Schaube H, *et al.* Randomized comparison of endoscopic palliation of malignant esophageal stenoses. *Surg Endosc* 1991;5:63–7.
- 118 Mason R. Palliation of malignant dysphagia: an alternative to surgery. *Ann R Coll Surg Engl* 1996;78:457–62.
- 119 Waters JS, Norman A, Cunningham D, *et al.* Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. *Br J Cancer* 1999;80:269–72.
- 120 Ross P, Cunningham D, Scarffe H, *et al.* Results of a randomised trial comparing ECF with MCF in advanced oesophago-gastric cancer. *Eur J Cancer* 1999;35:S137.
- 121 Dinshaw KA, Sharma V, Pendse AM, *et al.* The role of intraluminal radiotherapy and concurrent 5-fluorouracil infusion in the management of carcinoma esophagus: a pilot study. *J Surg Oncol* 1991;47:155–60.
- 122 Sur RK, Donde B, Levin VC. Fractionated high dose rate intraluminal brachytherapy in palliation of advanced esophageal cancer. *Int J Radiat Oncol Biol Phys* 1998;40:447–53.
- 123 Northern and Yorkshire Cancer Registry and Information Service. *Quick data*. 1999.
- 124 Bonenkamp JJ, Hermans J, Sasako M, *et al.* Extended lymph-node dissection for gastric cancer. Dutch Gastric Cancer Group. *N Engl J Med* 1999;340:908–14.
- 125 Cuschieri A, Weeden S, Fielding J, *et al.* Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. *Br J Cancer* 1999;79:1522–30.
- 126 Dent DM, Madden MV. Randomized comparison of R1 and R2 gastrectomy for gastric carcinoma. *Br J Surg* 1988;75:110–2.
- 127 Robertson CS, Chung SC, Woods SD, *et al.* A prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. *Ann Surg* 1994;220:176–82.
- 128 Sasako M. Risk factors for surgical treatment in the Dutch Gastric Cancer Trial. *Br J Surg* 1997;84:1567–71.
- 129 Bunt AM, Hermans J, Smit VT, *et al.* Surgical/pathologic-stage migration confounds comparisons of gastric cancer survival rates between Japan and Western countries. *J Clin Oncol* 1995;13:19–25.
- 130 Bunt TM, Bonenkamp HJ, Hermans J, *et al.* Factors influencing noncompliance and contamination in a randomized trial of “Western” (r1) versus “Japanese” (r2) type surgery in gastric cancer. *Cancer* 1994;73:1544–51.
- 131 Cheng J, Wang W. Surgical treatment of gastric cardia cancer with fundoplication—a report of 193 cases. *Chung Hua Chung Liu Tsa Chih* 1995;17:444–6.
- 132 Chareton B, Landen S, Manganas D, *et al.* Prospective randomized trial comparing Billroth I and Billroth II procedures for carcinoma of the gastric antrum. *J Am Coll Surg* 1996;183:190–4.
- 133 Kodama M, Koyama K, Chida T, *et al.* Early postoperative evaluation of pylorus-preserving gastrectomy for gastric cancer. *World J Surg* 1995;19:456–60.
- 134 Liedman B, Bosaeus I, Hugosson I, *et al.* Long-term beneficial effects of a gastric reservoir on weight control after total gastrectomy: a study of potential mechanisms. *Br J Surg* 1998;85:542–7.
- 135 Svedlund J, Sullivan M, Liedman B, *et al.* Quality of life after gastrectomy for gastric carcinoma: controlled study of reconstructive procedures. *World J Surg* 1997;21:422–33.
- 136 Anderson ID, MacIntyre IM. Symptomatic outcome following resection of gastric cancer. *Surg Oncol* 1995;4:35–40.
- 137 Furukawa H, Hiratsuka M, Iwanaga T, *et al.* Extended surgery: left upper abdominal exenteration plus Appleby's method for type 4 gastric carcinoma. *Ann Surg Oncol* 1997;4:209–14.
- 138 Gennari L, Boffi L, Cucchiara G, *et al.* A randomized multinational study comparing total and subtotal gastrectomy in cancer of the distal half of the stomach. *Chirurgia (Bucuresti)* 1993;6:428–34.
- 139 Gouzi JL, Huguier M, Fagniez PL, *et al.* Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. *Ann Surg* 1989;209:162–6.
- 140 Mari E, Floriani I, Tinazzi A, *et al.* Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. *Ann Oncol* 2000;11:837–43.
- 141 Glimelius B, Ekstrom K, Hoffman K, *et al.* Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997;8:163–8.
- 142 Murad AM, Santiago FF, Petroianu A, *et al.* Modified therapy with 5-fluorouracil, doxorubicin and methotrexate in advanced gastric cancer. *Cancer* 1993;72:37–41.
- 143 Pyrhonen S, Kuitunen T, Nyandoto P. Randomised comparison of fluorouracil, epirubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995;71:587–91.
- 144 Kramling HJ, Wilkowski R, Duhmke E, *et al.* Adjuvant intraoperative radiotherapy of stomach carcinoma. *Langenbeck's Arch Chir Suppl Kongressbd* 1996:211–3.
- 145 Bleiberg H, Goffin JC, Dalesio O, *et al.* Adjuvant radiotherapy and chemotherapy in resectable gastric cancer. A randomized trial of the gastro-intestinal tract cancer cooperative group of the EORTC. *Eur J Surg Oncol* 1989;15:535–43.
- 146 The Gastrointestinal Tumor Study Group (GITSG). Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. *Cancer* 1982;49:1116–22.
- 147 The Gastrointestinal Tumor Study Group (GITSG). Randomized study of combination chemotherapy in unresectable gastric cancer. *Cancer* 1984;53:13–7.
- 148 Dent D, Werner D, Novis B, *et al.* Prospective randomized trial of combined oncological therapy for gastric carcinoma. *Cancer* 1979;44:385–91.
- 149 Hallissey MT, Dunn JA, Ward LC, *et al.* The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. *Lancet* 1994;343:1309–12.
- 150 Moertel CG, Childs DS, O'Fallon JR, *et al.* Combined 5-fluorouracil and radiation therapy as a surgical adjuvant for poor prognosis gastric carcinoma. *J Clin Oncol* 1984;2:1249–54.
- 151 Childs DJ, Moertel-CG, Holbrook-MA, *et al.* Treatment of unresectable adenocarcinomas of the stomach with a combination of 5-fluorouracil and radiation. *Am J Roentgenol Radium Ther Nucl Med* 1968;102:541–4.
- 152 Klaassen DJ, MacIntyre JM, Catton GE, *et al.* Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1985;3:373–8.
- 153 Livstone EM. A controlled randomized evaluation of combined modality therapy (5000 r + 5-FU + MeCCNU versus combination chemotherapy (5-FU + Me CCNU) in the treatment of locally unresectable gastric carcinoma. *Digestion* 1977;16:256.
- 154 Northern and Yorkshire Cancer Registry and Information Service. *Cancer treatment policies and their effects on survival: Pancreas*. Leeds: NYCRIS/University of Leeds, 1999.
- 155 Crist DW, Sitzman JV, Cameron JL. Improved hospital morbidity, mortality and survival after the Whipple procedure. *Ann Surg* 1987;206:358–65.
- 156 Braasch JW, Deziel DJ, Rossi RL. Pyloric and gastric preserving pancreatic resection. Experience with 87 patients. *Ann Surg* 1986;204:411–8.
- 157 Trede M, Schwall G, Saeger H. Survival after pancreaticoduodenectomy: 118 consecutive resections without an operative mortality. *Ann Surg* 1990;211:447–58.
- 158 Yeo CJ, Cameron JL, Lillemoe KD. Pancreaticoduodenectomy for cancer of the head of the pancreas: 201 patients. *Ann Surg* 1995;221:721–33.
- 159 Hillner BE, Smith TJ, Desch CE. Hospital and physician volume or specialisation and outcomes in cancer treatment: importance in quality of cancer care. *J Clin Oncol* 2000;18:2327–40.
- 160 Harding M, Lord J, Littlejohns P, *et al.* A systematic review of the evidence relating process of care or outcome to treatment in specialist and non-specialist hospital settings. London: Health Care Evaluation Unit, Department of Public Health Services, St George's Hospital Medical School, 2000.
- 161 ESPAC-1, Neoptolemos J, Dunn J, *et al.* ESPAC-1 interim results: a European randomised study to assess the roles of adjuvant chemotherapy (5FU and folinic acid) and adjuvant chemoradiation (40Gy and 5FU) in resectable pancreatic cancer. *Proc Am Soc Clin Oncol* 2000 (in press).
- 162 Mallinson CN, Rake MO, Cocking JB, *et al.* Chemotherapy in pancreatic cancer: results of a controlled, prospective, randomized, multicentre trial. *BMJ* 1980;281:1589–91.
- 163 Palmer K, Kerr M, Knowles G, *et al.* Chemotherapy prolongs survival in inoperable pancreatic carcinoma. *Br J Surg* 1994;81:882–5.
- 164 Andersen JR, Friis MA, Hancke S, *et al.* A controlled trial of combination chemotherapy with 5-FU and BCNU in pancreatic cancer. *Scand J Gastroenterol* 1981;16:973–5.
- 165 Andren-Sandberg A, Holmberg JT, Ihse I. Treatment of unresectable pancreatic carcinoma with 5-fluorouracil, vincristine, and CCNU. *Scand J Gastroenterol* 1983;18:609–12.
- 166 Frey C, Twomey P, Keehn R, *et al.* Randomized study of 5-FU and CCNU in pancreatic cancer: report of the Veterans Administration Surgical Adjuvant Cancer Chemotherapy Study Group. *Cancer* 1981;47:27–31.
- 167 Klapdor R, Lehmann U, Bahl M, *et al.* Palliative chemotherapy of pancreatic carcinoma. A prospective randomized study with 5-FU + BCNU and FAM. *Z Gastroenterol* 1982;20:534.
- 168 Takada T, Kato H, Matsushiro T, *et al.* Prospective randomized trial comparing 1/2 FAM (5-fluorouracil (5-FU) + adriamycin + mitomycin C) versus palliative therapy for the treatment of unresectable pancreatic and biliary tract carcinomas (the 2nd trial in non-resectable patients). Japanese Study Group of Surgical Adjuvant Therapy for Carcinomas of the Pancreas and Biliary Tract. *Gan To Kagaku Ryoho* 1996;23:707–14.
- 169 Bakkevd KE, Pettersen A, Arnesjo B. Tamoxifen therapy in unresectable adenocarcinoma of the pancreas and the papilla of Vater. *Br J Surg* 1990;77:725–30.
- 170 Huguier M, Samama G, Testart J, *et al.* Treatment of adenocarcinoma of the pancreas with somatostatin and gonadoliberein (luteinizing hormone-releasing hormone). *Am J Surg* 1992;164:348–53.
- 171 Keating JJ, Johnson PJ, Cochrane AMG, *et al.* A prospective randomised controlled trial of tamoxifen and cyproterone acetate in pancreatic carcinoma. *Br J Cancer* 1989;60:789–92.

- 172 Pederzoli P, Maurer U, Vollmer K, et al. Phase 3 trial of SMS 201-995 pa LAR (SMS pa LAR) vs. placebo in unresectable stage II, III and IV cancer. *Proc Am Soc Clin Oncol* 1998;988.
- 173 Roy A, Jacobs A, Bukowski R, et al. Phase 3 trial of SMS 201-995 pa LAR (SMS pa LAR) and continuous infusion (CI) 5FU in unresectable stage II, III and IV pancreatic cancer. *Proc Am Soc Clin Oncol* 1998;987.
- 174 Sperti C, Pasquali C, Catalini S, et al. Hormonal treatment of unresectable pancreatic cancer with LHRH analogue (goserelin). *Eur J Surg Oncol* 1992;18:267-71.
- 175 Taylor OM, Benson EA. Clinical trial of tamoxifen in patients with irresectable pancreatic adenocarcinoma. The Yorkshire Gastrointestinal Tumour Group. *Br J Surg* 1993;80:384-6.
- 176 Greenway BA. Effect of flutamide on survival in patients with pancreatic cancer: results of a prospective, randomised, double blind, placebo controlled trial. *BMJ* 1998;316:1935-8.
- 177 The Gastrointestinal Tumor Study Group (GITSG). A multi-institutional comparative trial of radiation therapy alone and in combination with 5-fluorouracil for locally unresectable pancreatic carcinoma. *Ann Surg* 1979;189:205-8.
- 178 The Gastrointestinal Tumor Study Group (GITSG). Radiation therapy combined with adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. *Cancer* 1985;56:2563-8.
- 179 The Gastrointestinal Tumor Study Group (GITSG). Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. *J Natl Cancer Inst* 1988;80:751-5.
- 180 Earle JD, Foley JF, Wieand HS, et al. Evaluation of external-beam radiation therapy plus 5-fluorouracil (5-FU) versus external-beam radiation therapy plus hycanthone (HYC) in confined, unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 1994;28:207-11.
- 181 Hazel JJ, Thirlwell MP, Huggins M, et al. Multi-drug chemotherapy with and without radiation for carcinoma of the stomach and pancreas: a prospective randomized trial. *J Can Assoc Radiol* 1981;32:164-5.
- 182 Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. *Cancer* 1981;48:1705-10.
- 183 Prat F, Chapat O, Ducot B, et al. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. *Gastrointest Endosc* 1998;47:1-7.
- 184 Travis S, Nicholson T. Palliation of unresectable pancreatic malignant biliary obstruction: results of a randomized trial comparing percutaneously placed metal and plastic endoprosthesis. *J Intervent Radiol* 1997:17-21.
- 185 Andersen JR, Sorensen SM, Kruse A, et al. Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. *Gut* 1989;30:1132-5.
- 186 Bornman PC, Harries-Jones EP, Tobias R, et al. Prospective controlled trial of transhepatic biliary endoprosthesis versus bypass surgery for incurable carcinoma of head of pancreas. *Lancet* 1986;i:69-71.
- 187 Shepherd HA, Royle G, Ross AP, et al. Endoscopic biliary endoprosthesis in the palliation of malignant obstruction of the distal common bile duct: a randomized trial. *Br J Surg* 1988;75:1166-8.
- 188 Smith AC, Dowsett JF, Russell RCG, et al. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bile duct obstruction. *Lancet* 1994;344:1655-60.
- 189 Eisenberg E, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. *Anesthes Analges* 1995;80:90-5.
- 190 Haugstvedt T, Viste A, Eide GE, et al. The survival benefit of resection in patients with advanced stomach cancer: the Norwegian multicenter experience. Norwegian Stomach Cancer Trial. *World J Surg* 1989;13:617-21.
- 191 Raftery JP, Addington-Hall JM, MacDonald LD, et al. A randomized controlled trial of the cost-effectiveness of a district co-ordinating service for terminally ill patients. *Palliat Med* 1996;10:151-61.
- 192 Smeenk FWJM, de Witte LP, van Haastregt JCM, et al. Transmural care. A new approach in the care for terminal cancer patients: its effects on re-hospitalization and quality of life. *Patient Educ Counselling* 1998;35:189-99.
- 193 Smeenk FWJM, van Haastregt JCM, Gubbels EMAC, et al. Effectiveness of home care programmes for patients with incurable cancer on their quality of life and time spent in hospital: systematic review. *BMJ* 1998;316:1939-44.