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REVIEWS

Chemotherapy for upper gastrointestinal tumours

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Abstract

The aim of this review is to identify current chemotherapy treatment for tumours of the oesophagus, stomach, pancreas, and liver. The role of both neoadjuvant, adjuvant, and palliative chemotherapy regimens will be discussed. This review will be of interest to oncologists in clarifying current issues regarding chemotherapy, and to physicians in other medical specialties, to increase their general understanding of benefits and drawbacks of chemotherapy in this patient group.

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Cancers of the oesophagus, stomach, and pancreas constitute a major cause of cancer death world wide. Despite improvements in both surgical techniques and chemotherapy regimens these tumours remain a great therapeutic challenge and most patients still die of their disease, even after apparent "curative resection". There is a clear need for more effective treatments, particularly for the majority of patients who present with advanced disease. For these patients, quality of life is of great importance and, in the appropriate setting, chemotherapy can provide effective palliation of symptoms. In this article we will examine the role of chemotherapy both as an adjunct to surgery and radiotherapy, and also as a palliative treatment option.

All upper gastrointestinal tumours are staged using the TNM classification.¹ This system describes the extent of a tumour in three components: T = the characteristics of the primary tumour, N = the involvement of regional lymph nodes, and M = the presence of distant metas-

tases. Although surgeons frequently use this method of staging, it is often unhelpful in clinical practice, as it is difficult to apply and does not always correlate with prognosis.

Chemotherapy can be used in three settings: presurgery (neoadjuvant), in the postoperative period (adjuvant), or for advanced disease. The rationale for using preoperative chemotherapy is to downstage the tumour to facilitate surgical resection, improving local control and eradicating micrometastases. The adjuvant use of chemotherapy aims to eradicate any remaining micrometastatic disease after a potentially curative resection. This is based on the observation that disease frequently recurs after surgical resection even when the resection margins are pathologically clear. For metastatic disease, chemotherapy can be useful for symptomatic control and may prolong survival, although side effects should always be considered.

To allow comparisons of the effectiveness of different chemotherapy regimens, fairly strict definitions of response rates have been devised. For an objective response to be achieved there must be 50% reduction in the volume of measurable disease. Although reductions of less than this can produce symptomatic benefit, they are defined as stable disease. One of the best methods of predicting which patients will benefit from chemotherapy is their ability to undertake normal daily activities and several scoring systems (World Health Organisation, Karnofsky, Eastern Cooperative Oncology Group, ECOG) which reflect the performance status are frequently used for this purpose.

Oesophageal cancer

SURGERY AND ADJUVANT RADIOTHERAPY

Oesophageal cancer is one of the 10 most common cancers world wide. Prognosis is dismal with five year survival rates of less than 10%.

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Even though surgical resection offers the chance of cure, the five year survival for patients who have undergone "curative" resections is only 20%. Improvements in surgical techniques and perioperative management have had no real impact on overall survival.

Radiotherapy has traditionally been one of the standard treatment modalities for oesophageal tumours. There have been three randomised studies using adjuvant (postoperative) radiotherapy after surgery. None have shown a significant benefit. Four randomised studies have addressed the role of preoperative radiotherapy. These indicated a trend for improved local recurrence rates with radiotherapy, although the complication rate was high with no overall improvement in survival.²

NEOADJUVANT CHEMOTHERAPY

The survival of patients with clinically localised disease remains poor suggesting that most patients have occult disseminated disease at diagnosis. Chemotherapy in oesophageal cancer therefore has potential value, but its efficacy is limited in that only approximately 50% of tumours are truly chemosensitive. There have been a number of non-randomised studies using preoperative chemotherapy. All the regimens were cisplatin based, most in combination with 5-fluorouracil (5-FU). Response rates of 14%–64% were seen with complete resections performed in 47%–80% of cases. Median survival figures were 8–23 months. There have only been four randomised prospective studies using preoperative chemotherapy and all are open to criticism of size and design. None showed significant benefit in the chemotherapy arms and there was a notable increase in toxicity and perioperative mortality rates. Therefore neoadjuvant chemotherapy can only be recommended in the context of clinical trials. There are several ongoing trials comparing chemotherapy with surgery alone and results should be available in the next 2–3 years.

CHEMORADIOOTHERAPY

Treatment of carcinoma of the oesophagus with combinations of chemotherapy and radiotherapy began about 20 years ago. It was hoped that the radiotherapy would control locoregional disease and chemotherapy the systemic disease. It was also anticipated that chemotherapy could sensitise these relatively resistant tumours to radiotherapy. This combined approach has been useful in treating other solid tumours such as anal cancer. Eight non-randomised and four randomised studies have examined this combination. In the early studies, results were encouraging with median survival rates of 12–20 months and two year survival rates of 35%–40%. When treatment was followed by oesophagectomy, higher complete resection rates were seen compared with the use of radiotherapy alone preoperatively.

In the randomised study by Roussel *et al*,³ patients were treated with radiotherapy or chemoradiotherapy. In the combined arm of this trial single agent methotrexate was the chemotherapy used. No significant difference in the two treatment groups was seen. In a

phase III Radiation Therapy Oncology Group (RTOG) prospective study, 129 patients with squamous carcinoma of the oesophagus were randomised to either 5-FU and cisplatin with radiotherapy or radiotherapy alone.⁴ After two years the study had to be closed prematurely as there was a statistically significant improvement in the combined treatment arm. None of these studies addressed the question whether combined chemoradiotherapy is better than surgery alone. To date only one group has found a significant survival benefit for preoperative chemoradiotherapy over surgery alone in a prospective randomised study.⁵ This study must be interpreted with caution as the three year survival rate in the surgical arm was only 6%, which is lower than expected. Three other randomised studies have not demonstrated any advantage.

Despite some encouraging results in response rates for patients treated with a combined modality approach, most of the failures were due to local relapse. Studies have therefore been established to examine whether neoadjuvant chemoradiotherapy followed by surgical resection would improve survival rates and symptomatic control. There has been only one randomised trial of chemoradiotherapy followed by surgery versus radiotherapy alone preoperatively.⁶ Bleomycin was chosen as the chemotherapy and the outcome in both arms of the study was equally poor. There have been five non-randomised studies and all have shown a definite trend to improved survival with better local control for the chemoradiotherapy arms. In the study of Forastiere *et al*, 36 of 41 patients actually underwent resection and of these only five relapsed locally.⁷ These results are encouraging and have provided the basis for an ongoing randomised prospective study. While this approach remains interesting it should be appreciated that there can be significant perioperative mortality. In the largest of these studies by the South West Oncology Group/RTOG the operative mortality was 11%.⁸

CHEMOTHERAPY IN ADVANCED DISEASE

Unfortunately most patients with carcinoma of the oesophagus present with either locally advanced or metastatic disease. The main aim of treatment in this group is for symptom control. This can be achieved by stenting or endoscopic laser ablation.⁹ Both radiotherapy and chemotherapy can also have a role in the palliation of these patients. Response rates of single agent chemotherapy are 15%–30% and can rise to 30%–40% when a cisplatin based combination is used. Chemotherapy does not appear to confer a survival advantage. There is no evidence that adenocarcinomas respond better than squamous cell tumours. Currently cisplatin and 5-FU should be considered the standard first line agents. Newer cytotoxics such as the taxanes are currently being investigated in phase II studies and paclitaxel appears to have a response rate of 32% which is promising.¹⁰

To improve survival rates from oesophageal cancer it is important to develop multimodality

treatments in clinical trials and examine the role of newer agents. In addition, quality of life data should be collected on all patients in clinical trials as symptom control is a major aim of treatment for the majority of patients (fig 1).

Gastric cancer

Gastric cancer is the second most common cancer in the world and the fourth commonest in Europe. Although the incidence of cancer arising from the distal half of the stomach is declining, the incidence of tumours of the gastro-oesophageal junction, particularly in young patients, is increasing. Although surgical resection is the only "curative" treatment option, the five year survival in those patients who have apparently localised disease is only 10%–15%. In Japan, where there is an intense screening programme, tumours are detected at stage 0 (mucosal disease only), but unfortunately most patients in other countries present with advanced disease (only approximately 20% being operable).

ADJUVANT TREATMENT

After radical surgery, even patients without lymph node metastases have 50% chance of dying within five years and this rises to 90% with lymph node involvement. As a result, systemic adjuvant therapy has frequently been combined with surgery. Numerous studies have reported the use of combination treatments in this setting but most have been relatively small. In one of the largest studies, 315 patients who underwent a "curative" resection were randomised to either combination chemotherapy with FAM (5-FU, Adri-

amycin, and mitomycin) or no chemotherapy.¹¹ No significant difference in survival was seen. Moreover, in a meta-analysis of 14 randomised trials of adjuvant therapy after "curative" resection there was no survival difference.¹² The criticism of this analysis is that some of the treatments would be suboptimal by today's standards. Nevertheless, there is no evidence based role for the use of adjuvant therapy for gastric cancer outside the setting of a clinical trial.

Very few studies have evaluated adjuvant radiotherapy alone after surgery. Most have used radiotherapy in combination with 5-FU. The British Stomach Cancer Group study randomised 436 patients with gastric adenocarcinoma to postoperative radiotherapy, postoperative FAM chemotherapy, or to surgery alone.¹³ There was no significant difference in five year survival rates between the three arms. The local recurrence rate in the radiation arm did appear to be lower. There have been eight subsequent trials, of which three were randomised, using combined chemoradiotherapy after surgery. No clear survival benefit has been seen.

It is well documented that intra-abdominal recurrence is the most common cause of treatment failure. Therefore, in an attempt to reduce this risk, trials have been completed giving intraperitoneal chemotherapy postoperatively. To date this treatment modality appears to produce increased perioperative complication rates with no survival benefit.¹⁴

NEOADJUVANT CHEMOTHERAPY

Since a high proportion of gastric cancers are clearly inoperable at presentation, neoadjuvant chemotherapy has been used in an attempt to downstage the tumour to improve operability. To date there have been eight studies, of which two were randomised, using combination chemotherapy before surgery. The interpretation of these trials is limited since different staging methods were used to initially assess the extent of the tumour.^{15 16} Using this treatment modality there did not appear to be any increase in the morbidity, downstaging of tumours appeared to occur in about 50%, and there was a possible improvement in survival. In view of this trend, further randomised neoadjuvant studies in gastric cancer are now ongoing and an important one will be discussed later in this review.

CHEMOTHERAPY IN ADVANCED DISEASE

Since the 1970s a number of chemotherapy agents including 5-FU, doxorubicin, mitomycin C, cisplatin, and etoposide have been used in gastric cancer.¹⁷ An overall single agent objective response rate of 21% has been reported. Numerous attempts have been made to develop more effective combination regimens. Most of these are based on 5-FU and cisplatin combinations with average response rates of 35%–50% seen in phase II studies. The FAM regimen has been widely used and is associated with a median duration of remission of 5–10 months. In an attempt to modulate the efficacy of 5-FU, methotrexate was substituted in this

Figure 1 Management of oesophageal cancer.

regimen for mitomycin (FAMTX). The European Organization for Research and Treatment of Cancer (EORTC) performed a multicentre randomised prospective study comparing FAM and FAMTX in just over 200 patients.¹⁸ The response rate of 41% for FAMTX was significantly better than the 9% for FAM. Survival in the FAMTX group was also greater. Two further randomised studies have confirmed the superiority of FAMTX and it has therefore been used as the control arm in other studies.

The *in vitro* synergy of 5-FU and cisplatin has led to trials using the two drugs in combination with anthracyclines such as doxorubicin and epirubicin. One such combination is ECF in which epirubicin and cisplatin are given in boluses with infusional 5-FU. This method of 5-FU administration requires the drug to be given as a protracted infusion via a central venous catheter. In a prospective study, 274 patients were randomised to receive this regimen or FAMTX.¹⁹ The overall response rate of ECF was 45% compared with 21% in the FAMTX arm. The median survival duration was 8.9 months in the ECF arm compared with 5.7 months in the control arm which was also statistically significant. The major drawback of this combination is the potential complication associated with the insertion of central venous catheters. It is possible to give this combination using a short rather than continuous infusion of 5-FU.²⁰ While the objective response rate with this schedule was lower (23%), symptomatic response was good and the toxicity manageable. Therefore, in patients not suitable for intensive chemotherapy, non-infusional ECF may produce valuable symptom control.

There are limited data available investigating the role of combination chemotherapy for palliation in advanced gastric cancer. There have been four small studies comparing combination chemotherapy versus best supportive care. The chemotherapy appeared to be well toler-

ated with good symptomatic benefit. The average median response duration was nine months with survival rates for the chemotherapy arms of 40% at one year and 10% at two years. Almost all the supportive care patients had died within one year.¹⁷

Clearly there is a need to develop new treatment strategies to improve the outlook of patients with gastric cancer. This will need to include phase II studies of new agents. The area of neoadjuvant chemotherapy continues to look interesting with novel studies underway. One of these is the MRC Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial. This has been developed in view of the encouraging response rates seen using infusional 5-FU in advanced gastric cancer. Patients with operable gastric cancer are being randomised to a trial of preoperative and postoperative infusional chemotherapy compared with surgery alone. Trials like these will hopefully improve survival rates in this tumour type (fig 2).

Pancreatic cancer

Pancreatic cancer carries a dismal prognosis with overall five year survival rates of 1%–5%. Pancreaticoduodenectomy (Whipple's procedure) is performed in patients who have apparently localised disease but unfortunately even in this group the long term survival rate is only approximately 20% with a median survival of 15–19 months. Unlike gastric and oesophageal tumours where there is a definite role for palliative surgical procedures, this is a more contentious issue in pancreatic cancer. Studies have compared surgical bypass procedures and endoscopic insertion of stents to relieve jaundice and improve quality of life in patients with unresectable tumours. Stenting is associated with lower initial morbidity and mortality, although readmission and stent replacement may be necessary for annular obstruction. Given the short median survival for such patients (4–10 months), it would seem appropriate to offer stenting as the procedure of choice since laparotomy is associated with a median hospital stay of two weeks.

ADJUVANT TREATMENT

Pancreatic tumours are inherently chemoresistant. For patients who have undergone surgical resection, local recurrences occur in up to 85%. Several studies have examined the role of adjuvant chemotherapy with and without radiotherapy in patients undergoing surgical resection. Most of these have been small and non-randomised. An important study from the Johns Hopkins University involved 174 patients treated with surgery alone or with the addition of radiotherapy plus chemotherapy or chemotherapy alone.²¹ While the trial was not randomised, patients were well matched in each group. The use of adjuvant chemoradiotherapy was associated with a significantly longer survival (19.5 months compared with 13.5 months for the surgery alone arm). This approach is now being studied in an EORTC randomised study comparing surgery with or without adjuvant 5-FU based chemoradiotherapy. This pivotal study is

Figure 2 Management of gastric cancer.

recruiting well with over 500 patients randomised.

CHEMOTHERAPY IN ADVANCED DISEASE

In 1969 Moertel *et al.* published the first study using 5-FU in combination with radiotherapy for the treatment of locally advanced pancreatic cancer.²² The Gastrointestinal Tumour Study Group confirmed the findings of Moertel *et al.*, that median survival was improved from six to 10 months with the use of chemoradiation rather than radiation alone.²³ An ECOG study failed to demonstrate this advantage and found that the toxicity of treatment was substantial.²⁴

It has been difficult to compare many of the treatments for metastatic pancreatic tumours as response rates have been very variable, mainly due to difficulty imaging the pancreas and providing bidimensional measurements. Two British randomised studies of chemotherapy versus best supportive care have shown a survival advantage for the chemotherapy arm with no deterioration in quality of life for patients with inoperable pancreatic cancer.^{25 26} 5-FU chemotherapy continues to be the mainstay of treatment 30 years after it was first used with response rates varying from 15%–28%. There has been a suggestion that high dose 5-FU in combination with high dose cisplatin (100 mg/m²) may be more effective.²⁷ However in a randomised trial, although there was a

trend to improvement in overall survival, the toxicity associated with the combination arm was substantial at 48% compared with 20% for 5-FU alone.²⁸

Since it was first reported that pancreatic tumours contain hormone receptors, there has been interest in treating patients with tamoxifen, cyproterone acetate, octreotide, and flutamide. In a placebo controlled randomised study tamoxifen failed to confer any significant survival benefit.²⁹ With flutamide there has been one reported randomised study suggesting potential benefit. Unfortunately the study design was flawed and there is no evidence available to support the use of this drug.³⁰

With the albeit limited activity of 5-FU in pancreatic tumours there has been interest in the potent thymidylate synthase inhibitor raltitrexed. In 42 patients with advanced pancreatic cancer, disappointingly only two partial responses were seen.³¹ Initial work with the taxane, docetaxel, was encouraging with a response rate of 29%. Unfortunately a confirmatory phase II study at the Memorial Sloan Kettering Cancer Centre demonstrated only a 17% response rate.³²

The nucleoside analogue, gemcitabine, has generated the greatest recent interest in the treatment of pancreatic cancer. This has stemmed from a phase II study where, although the objective response rate was 11%, a substantial number of patients had stable disease and/or improvement in quality of life.³³ These observations led to two subsequent studies using gemcitabine in patients with advanced pancreatic cancer. In the first, chemonaïve patients were randomised to either gemcitabine or 5-FU.³⁴ In the second study, patients who had failed 5-FU chemotherapy were treated with gemcitabine second line.³⁵ In these studies the endpoint was “clinical benefit response” (CBR) which took into account reduction in pain intensity, reduction in daily analgesic requirement, and improvement in Karnofsky performance status. This is not a traditional study endpoint and as such has generated criticism. One could however argue that in these patients the emphasis on quality of life should be paramount and therefore this is a valid observation. In the first study there was a statistically significant advantage of gemcitabine over 5-FU in terms of survival and CBR. In the 5-FU refractory patients there also appeared to be improvement, with 27% achieving CBR. These studies have been the basis for the trials currently underway using gemcitabine in combination with other drugs such as the matrix metalloproteinase inhibitor, marimastat.

For patients with metastatic pancreatic cancer who have a good performance status at presentation, treatment with systemic chemotherapy is appropriate. In view of the limited impact of many of the available drugs, continued patient enrollment into clinical trials is essential if we are to develop new treatment options. For those patients who have poor performance status, the emphasis is very much on symptom control and early involvement with a

Figure 3 Management of pancreatic cancer.

palliative care team in combination with the oncologist is advocated (fig 3).

Hepatocellular carcinoma

Although hepatocellular carcinoma is uncommon in Europe, it constitutes an important cause of malignancy world wide. For patients with stage I/II disease (solitary tumour) who undergo resection, the three year survival rate is 75%. This figure is reduced to 10%–20% with stage IVA disease (multiple tumours including lymph node involvement). Even if liver transplantation is performed in patients with advanced disease the results do not seem to be improved with only 15% three year survival rates. The role of adjuvant or neoadjuvant chemotherapy has not yet been defined by randomised studies and should only be considered in the context of a trial.

CHEMOTHERAPY IN ADVANCED DISEASE

In patients who are deemed inoperable, treatment is aimed at symptom control, particularly for pain since these tumours can be large and cause a great deal of hepatic capsular distension. Endoscopically placed stents are used very effectively to decompress the biliary tree and resolve jaundice. There have been many non-randomised and randomised studies using systemic chemotherapy given as single agent and in combination.³⁶ Doxorubicin is the most widely used drug with a 25% response rate. Several other agents appear to have similar activity. Treatment with these drugs has no effect on survival.

Unlike the poor results with systemic chemotherapy, reports of the use of regional chemotherapy are more promising. Most of these studies have originated from Asia where the incidence of hepatocellular carcinoma is high. Many of the studies using regional intra-hepatic arterial chemotherapy also use an embolising agent such as starch or arterial ligation. The response rates for regional treatment with cisplatin are approximately 55% which increase to 68% when embolisation is added. There are considerable associated side effects which include fever, abdominal pain, and anorexia. More than 20% of patients experience increased ascites and cholecystitis. Survival rates are 20%–24% at two years. Careful consideration must therefore be given to which patients are suitable for this toxic treatment. For practical purposes, the emphasis remains palliation of symptoms in this patient group and wherever possible chemotherapy should be restricted to use in a clinical trial.

Conclusion

The aim of this review has been to identify the chemotherapy that is standard treatment for upper gastrointestinal tumours and where future developments are likely to be. In oesophageal tumours both preoperative and postoperative chemoradiotherapy show potential and need to be studied further. Chemotherapy in advanced disease can offer palliation in approximately 30% of patients. For gastric carcinoma, neoadjuvant chemotherapy is promising. 30%–50% of patients with ad-

Multiple choice questions in chemotherapy for upper gastrointestinal tumours (answers at end of paper)

- The aims of neoadjuvant chemotherapy in upper gastrointestinal tumours are to:
 - Facilitate surgical resection
 - Erradicate micrometastases
 - Prevent the use of chemotherapy in the advanced setting
 - Avoid the need for surgery
 - Improve symptoms
- The following are useful predictors of those patients with oesophageal tumours who would benefit from chemotherapy:
 - Age
 - Performance status
 - Histology
 - Ability to perform daily activities
 - Ability to swallow
- The five year survival rate for patients who have had surgical resection of oesophageal tumours is:
 - 10%
 - 20%
 - 30%
 - 40%
 - 50%
- The following prolong survival following surgical resection of gastric tumours:
 - Chemotherapy
 - Radiotherapy
 - Megestrol acetate
 - Omeprazole
 - None of the above
- Useful anticancer agents in pancreas cancer include:
 - Tamoxifen
 - 5-FU
 - Gemcitabine
 - Cisplatin
 - Cyclophosphamide
- Side effects of regional therapy in the treatment of hepatomas include:
 - Anorexia
 - Fever
 - Pain
 - Cholecystitis
 - Lethargy

vanced disease will gain palliation, with cisplatin based combination chemotherapy regimens being the most effective. In early stage pancreatic cancer, chemoradiotherapy with or without surgery offers the most hope. Gemcitabine is currently the most effective drug and appears

to offer benefit in terms of symptom control and survival in advanced disease. In hepatocellular tumours, regional chemotherapy should be considered. Clearly many questions remain and patients therefore need to be referred to specialist centres so that trials can be completed. It is to be hoped that some of the many novel approaches to treatment including signal transduction modifiers, angiogenesis inhibitors, liposome encapsulation, and antibody directed therapy will result in improvements in disease outcome in the near future.

- 1 Hermanek P, Hutter RVP, Sobin LH, *et al.* *TNM atlas: illustrated guide to the TNM/pTNM classification of malignant tumours*. 4th Ed. Berlin: Springer-Verlag, 1997.
- 2 Wobst A, Audisio RA, Colleoni M, *et al.* Oesophageal cancer treatment: strategies and facts. *Ann Oncol* 1998;9: 951–62.
- 3 Roussel A, Bleiberg H, Dalesio O. 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.
- 4 Herskovic A, Martz K, Al-Sarraf M, *et al.* Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the oesophagus. *N Engl J Med* 1992;326:1593–8.
- 5 Walsh TN, Noonan N, Holywood D. A comparison of multimodal therapy and surgery for oesophageal adenocarcinoma. *N Engl J Med* 1996;335:462–7.
- 6 Anderson AP, Berdel P, Edsmyr F, *et al.* Irradiation, chemotherapy and surgery in esophageal cancer: a randomized clinical study. *Radiother Oncol* 1984;2:179–88.
- 7 Forastiere AA, Orringer MB, Perez-Tamayo C, *et al.* Concurrent chemotherapy and radiation therapy followed by transhiatal esophagectomy for local-regional cancer of the esophagus. *J Clin Oncol* 1990;8:119–27.
- 8 Poplin E, Fleming T, Leichman L, *et al.* Combined therapies for squamous-cell carcinoma of the esophagus, a Southwest Oncology Group Study (SWOG-8037). *J Clin Oncol* 1987;5:622–8.
- 9 Boyce HW. Palliation of dysphagia of esophageal cancer by endoscopic lumen restoration techniques. *Cancer Control: Journal of the Moffitt Cancer Center* 1999;6:73–83.
- 10 Ajani JA, Ilson DH, Daugherty K, *et al.* Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. *J Natl Cancer Inst* 1994;86:1086–91.
- 11 Coombes R, Schein P, Chilver C, *et al.* A randomized trial comparing adjuvant fluorouracil, doxorubicin and mitomycin with no treatment in operable gastric cancer. *J Clin Oncol* 1990;8:1362–9.
- 12 Hermans J, Bonenkamp JJ, Boon MC, *et al.* Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. *J Clin Oncol* 1993;11:1441–7.
- 13 Hallissey MT, Dunn JA, Ward LC, *et al.* The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: a five year follow-up. *Lancet* 1994;343:1309–12.
- 14 Rosen HR, Jatzko G, Repse S, *et al.* Adjuvant intraperitoneal chemotherapy with carbon-absorbed mitomycin in patients with gastric cancer: results of a randomized multicenter trial of the Austrian Working Group for Surgical Oncology. *J Clin Oncol* 1998;16:2733–8.
- 15 Kang YK, Choi DW, Im Y-H, *et al.* A phase III randomized comparison of neoadjuvant chemotherapy followed by surgery versus surgery for locally advanced stomach cancer. *Proceedings of the American Society of Clinical Oncology* 1996; 15:215.
- 16 Yonemura Y, Sawa T, Kinoshita K. Neoadjuvant chemotherapy for high-grade advanced gastric cancer. *World J Surg* 1993;17:256–62.
- 17 Alexander HR, Kelsen DG, Tepper JC. Cancer of the stomach. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. 5th Ed. Philadelphia: Lippincott-Raven, 1997: 1021–54.
- 18 Wils O, Klein HO, Wagener DJT. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin: a step ahead in the treatment of gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Co-operative Group. *J Clin Oncol* 1991;9:827–31.
- 19 Webb A, Cunningham D, Scarffe JH, *et al.* Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;15:261–7.
- 20 Lacko APJW, Langley RE, Thomas A, *et al.* CEF chemotherapy for advanced gastro-oesophageal cancer. *Eur J Cancer* 1997;33(S8):1272.
- 21 Yeo CJ, Abrams RA, Grochow LB, *et al.* Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. *Ann Surg* 1997; 225:621–36.
- 22 Moertel CG, Childs DS, Reitermeier RJ. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable cancer. *Lancet* 1969;ii:865–7.
- 23 Gastrointestinal Tumour Study Group. A multi-institutional comparative trial of radiation therapy alone and in combination with 5-FU for locally unresectable pancreatic carcinoma. *Ann Surg* 1979;189:205–8.
- 24 Klaasen DJ, MacIntyre JM, Catton GE, *et al.* Treatment of locally unresectable cancer of the stomach and pancreas: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1985;3:373–8.
- 25 Mallinson CN, Rake MO, Cockling JB, *et al.* Chemotherapy in pancreatic cancer: results of a controlled prospective, randomised, multicentre trial. *BMJ* 1980;281:1589–91.
- 26 Palmer KR, Kerr M, Knowles G, *et al.* Chemotherapy prolongs survival in inoperable pancreatic carcinoma. *Br J Surg* 1994;81:882–5.
- 27 Rougier P, Zarba JJ, Ducreux M. Phase II study of cisplatin and 120 hour continuous infusion of 5-fluorouracil in patients with advanced pancreatic adenocarcinoma. *Ann Oncol* 1993;4:333–6.
- 28 Rougier P, Ducreux M, Douillard JY, *et al.* Efficacy of 5FU+cisplatin (FUP) compared to bolus 5FU (FU) in advanced pancreatic carcinoma (APC): a randomized trial from the French Anticancer Centers Digestive Group (FNLCCDG). *Proceedings of the American Society of Clinical Oncology* 1999;18:1050.
- 29 Taylor OM, Benson EA, McMahon MJ. Clinical trial of tamoxifen in patients with irresectable pancreatic adenocarcinoma. *Br J Surg* 1993;80:384–6.
- 30 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.
- 31 Pazdur R, Meropol NJ, Casper ES, *et al.* Phase II trial of ZD1694 (Tomudex (TM)) in patients with advanced pancreatic cancer. *Investigational New Drugs* 1996;13:355–8.
- 32 Abbruzzese JL, Evans D, Markowitz A. Docetaxel, a potentially active agent for patients with pancreatic adenocarcinoma. *Proceedings of the American Society of Clinical Oncology* 1995;14:221.
- 33 Casper ES, Green MR, Kelsen DP. Phase II study of gemcitabine (2',2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. *Investigational New Drugs* 1994;12:29–34.
- 34 Burris HA, Moore MJ, Andersen J, *et al.* Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403–13.
- 35 Rothenberg ML, Moore MJ, Cripps MC, *et al.* A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. *Ann Oncol* 1996;7:347–53.
- 36 Nerenstone SR, Ihde DC, Friedman MA. Clinical trials in primary hepatocellular carcinoma: current status and future directions. *Cancer Treatment Reviews* 1988;15:1–31.

Answers: true (T)/false (F)

1. (A) T, (B) T, (C) F, (D) F, (E) F; 2. (A) F, (B) T, (C) F, (D) T, (E) F; 3. (A) F, (B) T, (C) F, (D) F, (E) F; 4. (A) F, (B) F, (C) F, (D) F, (E) T; 5. (A) F, (B) T, (C) T, (D) F, (E) F; 6. (A) T, (B) T, (C) T, (D) T, (E) T.