Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy

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There is no consensus on the management of locally advanced pancreatic cancer, with either chemotherapy or combined modality approaches being employed (Maheshwari and Moser, 2005). No published meta-analysis (Fung et al, 2003; Banu et al, 2005; Liang, 2005; Bria et al, 2006; Milella et al, 2006) has included randomised controlled trials employing radiation therapy. The aim of this systematic review was to compare the following: (i) chemoradiation followed by chemotherapy (combined modality therapy) vs best supportive care (ii) radiotherapy vs chemoradiation (iii) radiotherapy vs combined modality therapy (iv) chemoradiation vs combined modality therapy (v) 5FU-based combined modality treatment vs another-agent-based combined modality therapy. Relevant randomised controlled trials were identified by searching databases, trial registers and conference proceedings. The primary endpoint was overall survival and secondary end points were progression-free survival/time-to-progression, response rate and adverse events. Survival data were summarised using hazard ratio (HR) and response-rate/adverse-event data with relative risk. Eleven trials involving 794 patients met the inclusion criteria. Length of survival with chemoradiation was increased compared with radiotherapy alone (two trials, 168 patients, HR 0.69; 95% confidence interval (CI) 0.51–0.94), but chemoradiation followed by chemotherapy did not lead to a survival advantage over chemotherapy alone (two trials, 134 patients, HR 0.79; CI 0.32–1.95). Meta-analyses could not be performed for the other comparisons. A survival benefit was demonstrated for chemoradiation over radiotherapy alone. Chemoradiation followed by chemotherapy did not demonstrate any survival advantage over chemotherapy alone, but important clinical differences cannot be ruled out due to the wide CI.

Keywords: pancreas cancer; radiotherapy; chemoradiation; chemotherapy; combined modality

Pancreatic cancer is a difficult condition to treat, evidenced by the fact that the annual mortality figures are close to the incidence rate (Jemal et al, 2006). Ninety per cent of patients have unresectable disease at diagnosis, of whom 40–50% have locally advanced disease (White et al, 1999), and reported to have better median survival of 6–10 months compared to the 3–6 months noted in metastatic disease (American Cancer Society, 2003). Radiotherapy approaches, with or without chemotherapy, have been frequently used in this subset (Maheshwari and Moser, 2005). Previous meta-analyses in this area have looked at chemotherapy and novel agents (Fung et al, 2003; Banu et al, 2005; Liang, 2005; Bria et al, 2006; Milella et al, 2006), and the Cochrane Collaboration (Yip et al, 2006) have done a recent systematic review on advanced pancreatic cancer that included a qualitative overview of trials involving radiotherapy, but there has been no meta-analyses performed to date addressing this treatment option. Evaluating this approach is important, as currently there is no uniformly agreed standard of care in the management of patients with locally advanced disease.

We have attempted an up-to-date analysis of the different radiotherapeutic options employed in locally advanced pancreatic cancer, thereby including an area not covered by previous meta-analyses. Furthermore, we have adopted the most appropriate statistical methods for meta-analysis of time to event data extracted from published reports (Parmar et al, 1998).

METHODS

Aims

To review systematically the published and unpublished literature, comparing the following therapies:

1. Chemoradiotherapy, followed by chemotherapy vs best supportive care
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2. Radiotherapy vs chemoradiotherapy
3. Radiotherapy vs chemoradiotherapy, followed by chemotherapy
4. Chemotherapy vs chemoradiotherapy, followed by chemotherapy (combined modality therapy)
5. 5FU-based chemoradiotherapy followed by chemotherapy vs another agent-based chemoradiotherapy, followed by chemotherapy

Search strategy

Trials were identified by searching MEDLINE, OLDMEDLINE (1950–1965), EMBASE (1974 to date), ISI Web of Science (incorporating Science Citation Index 1945 to date; ISI Science and Technology Proceedings 1990 to date; CancerLit (1960 to date) and Current contents databases (from 1996 to date) as far back as they go. In addition, trial registries (Registries of the National Cancer Institute Physician Data Query, the UK Co-ordinating Committee on Cancer Research, National Clinical Trials Registry, and the Cochrane Controlled Trials Register) and conference proceedings (American Society of Clinical Oncology, American Association of Cancer Research and the European Cancer Conference, European Society of Medical Oncology, American Gastroenterological Association, European Pancreatic Club, American Association of Pancreatology, British Society of Gastroenterology, and the United European Gastroenterology Week) were searched. References of selected papers and previous systematic reviews were scanned for any other relevant trials, and original trialists were contacted for possible unpublished trials.

Selection criteria

Randomised controlled trials were selected based on their abstract, or if that was unclear, the paper. Inclusion criteria were randomised controlled trials involving patients with advanced pancreatic cancer of the exocrine pancreas, comparing the therapies listed above. The exclusion criteria were trials which were nonrandomised, or included surgical resection of tumours and cancers other than pancreas cancers, wherein data was not available for the pancreas cancer subset. The study selection was done by two independent assessors, with any difference of opinion sorted by discussion.

End points

Overall survival (OS) defined as time from randomisation to death, was the primary outcome measure. Alternative definitions such as time from initiation of therapy to death were also included and noted as a potential source of heterogeneity.

Progression free survival (PFS) or time to progression (TTP), overall response rate (ORR) and adverse events (AE) were the secondary outcome measures. PFS was defined as time from randomisation to progression or death. Time to progression (TTP) was defined as the time from randomisation to disease progression. PFS was analysed separately from TTP as the former accounts for all deaths as well as progression events, whereas the latter only accounts for progression events. Overall response rate (ORR) was defined as the number of partial and complete responses and adverse events defined as side effects occurring from the date of randomisation till either end of study or death.

Quality assessment

Methodological quality was assessed based on the method of allocation generation (method of randomisation), allocation concealment (where the randomisation was carried out), blinding and losses to follow up. These were classified as adequate, inadequate or unknown, and the results of the different components discussed qualitatively.

Data extraction

Data extraction was performed independently by two reviewers using a standardised data extraction sheet. Disagreements were resolved by discussion and any data uncertainties forwarded to the original trialist for clarification.

Statistical analysis

Individual trial level time to event data (OS and PFS/TTP) were summarised by the log hazard ratio (HR) and its variance. As many trials do not report this information directly (Altman et al., 1995), appropriate data such as log rank test results were extracted to allow estimation of the log HR and its variance using previously reported methods (Parmar et al., 1998; Williamson et al., 2002). One of these approaches relies on extracting data from published survival curves (Parmar et al., 1998). The software we used (version 3.9; 28 September, 2004) to estimate the trial level log HR and variance-based on summary data extracted from published survival curves was developed by Matthew Sydes and Jayne Teirney of the MRC Clinical Trials Unit, London. Trial-level log HRs and their variances were entered into RevMan version 4.2 (a Windows-based software package used by the Cochrane Collaboration for writing systematic reviews and undertaking meta-analysis Sterne et al., 2001) and pooled using an inverse variance weighted average with results presented as a HR and 95% confidence interval (CI).

Dichotomous data (response rate/adverse events) were summarised using relative risks and 95% CIs with the Mantel–Haensel method used for pooling results across trials (Deeks et al., 2001). Heterogeneity was assessed by visual inspection of the forest plot, the Cochran’s $\chi^2$ test (using a 10% significance level) and interpretation of the $I^2$ statistic (percentage of variation due to heterogeneity with higher values indicating a greater degree of heterogeneity) (Deeks et al., 2004). The factors set out a priori to investigate heterogeneity were age, gender, performance status, previous treatment, site of the cancer (head, body or tail), and the chemotherapy/radiation used with the dose, combinations, and frequency. A fixed effect (FE) approach was adopted unless there was evidence of significant heterogeneity that could not be adequately explained, in which case a random effects (RE) approach was used.

Publication bias was assessed by visual inspection of funnel plots (Light and Pillemer, 1984).

RESULTS

Eleven trials involving 794 patients met the reviews’ inclusion criteria and six of these trials involving 451 patients were included in the meta-analyses. The quality of included studies is described in Table 1.

As there was only one study identified in two comparisons viz., chemoradiation, followed by chemotherapy vs best supportive care (BSC) comparison (Table 2) (Shinchi et al., 2002), and radiotherapy vs chemoradiation, followed by chemotherapy comparison (Table 3) (Moertel et al., 1981), a meta-analysis could not be undertaken for these comparisons.

In the single randomised controlled trial examined (Shinchi et al., 2002), there was survival advantage for chemoradiation followed by chemotherapy, over BSC (1 trial, 31 patients, HR 0.28; 95% CI 0.13–0.60). The median time-to-progression was 6.1 months, with overall response rate of 31% (5 out of 16) in the treated group but corresponding data were not provided for the BSC group. A quarter of treated patients (4 out of 16) developed

British Journal of Cancer (2007) 96(8), 1183–1190 © 2007 Cancer Research UK
complications secondary to the chemoradiation, with nausea occurring in three patients and one experiencing grade 2 leucopenia.

There was survival advantage with chemoradiotherapy followed by chemotherapy over radiation alone (1 trial, 56 patients, HR 0.50; 95% CI 0.29–0.84) in the trial conducted by Moertel et al. (1981). Time to progression was also better in the chemoradiotherapy arm over radiotherapy alone arm (HR 0.51; 95% CI 0.32–0.81).

There was survival advantage with chemoradiotherapy followed by chemotherapy (62.9 years; 36% women, 64% men) vs comparison to a control arm of 5FU-based chemoradiation (6000 rad, given as 2000 rad over 2 weeks and separated by a 2 weeks’ rest period. A total of 5FU – 6000 rad, given as 2000 rad over 2 weeks and separated by a 2 weeks’ rest period. A total of 5FU – 500 mg m⁻² day⁻¹ on days 1–3 of each 2000 rad radiotherapy course)

A randomised controlled trial of 34 patients found significantly improved overall survival (14.5 vs 6.7 months), time to progression (7.1 vs 2.7 months) and response rate (30 vs 13%) in patients treated with gemcitabine-based chemoradiation (600 mg m⁻² week⁻¹ for 6 weeks), followed by gemcitabine, in comparison to a control arm of 5FU-based chemoradiation (500 mg m⁻² day⁻¹ for 3 days repeated every 2 weeks for 6 weeks), followed by gemcitabine (Li et al., 2003). Toxicity between the two arms was similar and radiation had been given using three-dimensional conformal radiotherapy. These results were not borne out in a recent randomised controlled trial of 65 patients (preliminary results), which did not find improvement in 9 month survival for a group treated with gemcitabine and cisplatin chemoradiation, vs another treated with protracted venous 5-FU infusion chemoradiation (Wilkowski et al., 2006).

Comparison of radiotherapy vs chemoradiotherapy

Two randomised controlled trials with 168 patients were included in this analysis (Table 5) (Moertel et al., 1969; Cohen et al., 2003).

Table 1  Quality of included studies

| Comparison | Trial | Allocation sequence generation | Allocation concealment | Blinding | Follow-up |
|------------|-------|--------------------------------|------------------------|----------|-----------|
| Chemoradiotherapy followed by chemotherapy vs BSC | Shinchi et al (2002) | Unclear | Unclear | Not performed | Adequate |
| Radiotherapy vs chemoradiotherapy, followed by chemotherapy | Moertel et al (1981) | Adequate | Adequate | Not performed | Adequate |
| 5FU-based chemoradiotherapy followed by chemotherapy vs other agent-based chemoradiotherapy, followed by chemotherapy | GITSG (1985) | Unclear | Adequate | Not performed | Adequate |
| Radiosurgery vs chemoradiotherapy | Cohen et al (2005) | Adequate | Adequate | Not performed | Adequate |
| Chemoradiotherapy vs chemoradiotherapy, followed by chemotherapy | GITSG (1988) | Adequate | Adequate | Not performed | Adequate |
| | Klassen et al (1985) | Adequate | Unclear | Not performed | Adequate |
| | Hazel et al (1981) | Unclear | Unclear | Not performed | Adequate |
| | Chauffert et al (2006) | Unclear | Unclear | Not performed | Unclear |

BSC = best supportive care; FU = fluorouracil.

Table 2  Study included in comparison of chemoradiation, followed by chemotherapy vs BSC

| Trial | Group | Mean age and gender | Chemotherapy/radio-therapy used and dose |
|-------|-------|---------------------|-----------------------------------------|
| Shinchi et al (2002) | Chemoradiation, followed by chemotherapy (n = 16) | 62.9 years; 36% women, 64% men | 50.4 Gy per 28 fractions and continuous-infusion 5FU 200 mg m⁻² day⁻¹ |
| BSC (n = 15) | | 64.6 years; 67% women, 33% men | — |

Table 3  Study included in comparison of chemoradiation, followed by chemotherapy vs radiation

| Trial | Group | Mean age and gender | Chemotherapy/radio-therapy used and dose |
|-------|-------|---------------------|-----------------------------------------|
| Moertel et al (1981) | Chemoradiation, followed by chemotherapy (n = 31) | 62.9 years; 36% women, 64% men | 6000 rad, given as 2000 rad over 2 weeks and separated by a 2 weeks’ rest period. A total of 5FU – 500 mg m⁻² day⁻¹ on days 1–3 of each 2000 rad radiotherapy course |
| Radiation alone (n = 25) | | 64.6 years; 67% women, 33% men | 6000 rad |

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One study described adequate methods of allocation generation, one described adequate methods of concealment, and both described adequate losses to follow-up. One trial was blinded (Table 1).

The HR summarises survival for chemoradiotherapy compared to radiotherapy with HR < 1 indicating a survival advantage for chemoradiotherapy. Overall survival (Figure 1) was significantly better, with a 31% reduction in risk of death following chemoradiotherapy, compared to radiation alone (two trials 168 patients HR 0.69; CI 0.51–0.94 (FE)).

AE data could only be assessed for two parameters, vomiting and haematological toxicity, and the latter was lower in the radiotherapy arm compared to the chemoradiotherapy arm (Figure 2). Cohen et al (2005) did not find any difference in disease-free survival (HR 0.77; 95% CI 0.52–1.14) or response rate between the two treatments (RR 1.48; 95% CI 0.37–5.89).

Comparison of chemotherapy to chemoradiotherapy, followed by chemotherapy

Four randomised controlled trials (Table 6) with 283 patients were included (Hazel et al, 1981; Klassen et al, 1985; Gastrointestinal Tumour Study Group, 1988; Chauffert et al, 2006), but overall survival data for time-to-event analysis was only available in two studies (134 patients) (Hazel et al, 1981; Klassen et al, 1985). Adequate methods of allocation generation were described in two studies, adequate methods of concealment in one study and adequate losses to follow-up in 3. No study was blinded (Table 1).

The HR summarises survival for chemoradiotherapy, followed by chemotherapy compared to chemotherapy with HR < 1 indicating a survival advantage for chemoradiotherapy, followed by chemotherapy. Overall survival (Figure 3) was not significantly better in the chemoradiation, followed by chemotherapy arm compared to the chemotherapy only arm (two trials 134 patients HR 0.79; 95% CI 0.52–1.95 (RE)) but the wide CI includes clinically significant differences in both directions. There was significant heterogeneity between the two trials analysed (I² = 83.4%).

The Klassen study found no significant difference in time to progression between the two arms (HR 1.03; 95% CI 0.73–1.47). No other end points could be analysed for this comparison, owing to inadequate published data.

Publication bias Despite our exhaustive searches, examination of the funnel plots revealed evidence of bias, possibly publication bias, for all comparisons assessed. However, due to the small number of trials included within most comparisons, interpretation of funnel plots is difficult.

DISCUSSION

This systematic review includes 11 studies that randomised 794 patients with locally advanced pancreatic cancer and represents the only meta-analyses to date that examine the use of radiotherapeutic approaches in locally advanced pancreas cancer. Compared with the Cochrane Collaboration review (Yip et al, 2006), our review excluded two of their studies (Childs et al, 1965; Earle et al, 1994) but included three additional recent randomised controlled trials (Cohen et al, 2005; Chauffert et al, 2006; Wilkowski et al, 2008). The study conducted by Childs et al (1965) was reported in final form by Moertel et al (1969), and...
here the exclusion of the duplicate former study, whereas the study by Earle et al. (1994) did not fit into the comparisons that were being assessed. The most appropriate statistical methods for meta-analysis of time to event data extracted from published reports have been used in our report (Parmar et al., 1998).

We did not find any randomised controlled trials that compared radiation alone or chemoradiation alone to BSC. The basis for incorporating radiation therapy in pancreatic cancer was based on a Mayo clinic randomised controlled trial that randomised patients to receive radiotherapy or 5FU-based radiotherapy (Moertel et al., 1969) and an uncontrolled study of 23 patients who received chemotherapy (Haslam et al., 1981). Median survival in the study by Haslam et al. (1981) was 7.5 months.

One small randomised controlled trial (Shinchi et al., 2002) of 31 patients compared chemoradiation, followed by chemotherapy, to BSC. 5FU (200 mg m⁻² day⁻¹) was administered for the duration of the radiation therapy, followed by 500 mg m⁻² per week thereafter, until progressive disease or unacceptable toxicity occurred. The regimen of daily 5FU concomitant with radiotherapy differs from all the other randomised controlled trials using chemoradiation (Moertel et al., 1969; Hazel et al., 1981; Klassen et al., 1985; Gastrointestinal Tumour Study Group, 1988; Cohen et al., 2005; Chauffert et al., 2006), wherein weekly 5FU (500–1000 mg m⁻² given either weekly or on first and last 3 days of radiotherapy) was used for radio sensitisation. A nonsignificant reduction in liver and peritoneal metastases was seen in the treatment arm. This finding, along with significant improvement in overall survival, may well be an effect of the chemotherapy rather than the radiation. The fact that the majority of patients died of local disease progression (62%) in the treatment arm supports this possibility.

Overall survival was better with chemoradiation compared to radiotherapy alone. Although there was no statistical heterogeneity between these two trials, both the inclusion criteria and radiation techniques differed. Moertel et al. (1969) staged patients using clinical and surgical techniques, whereas Cohen used extensive imaging, in the form of CT scan of abdomen, chest X-ray and bone and brain scan, followed by surgical staging. Thus, selection criteria were more stringent in the latter study. Radiation techniques have also improved between the 1960s, when Moertel published his findings, to the 1980s, when the Cohen study was open to accrual. The latter study questions the merit of combining these two modalities, in the light of low response rate, poor survival and increased toxicity. Moreover, neither radiotherapy nor chemoradiation address the micro metastases present in patients labelled as locally advanced cancer (Liu and Traverso, 2004; Shoup et al., 2004).

The 1981 GITSG study was instrumental in popularising multimodality therapy in the treatment of locally advanced pancreas cancer, as it showed a doubling of survival duration over radiation alone (Moertel et al., 1981). This was at the price of

### Table 6

| Authors                     | Group (number randomised) | Median age and gender | Chemotherapy/radiotherapy used and dose |
|-----------------------------|--------------------------|----------------------|----------------------------------------|
| Hazel et al (1981)          | Chemo (n = 15)           | NA                   | 5FU 500 mg m⁻² weekly, methyl CCNU 100 mg m⁻² every 6 weeks |
|                            | Combin rx (n = 15)       | NA                   | 5FU 500 mg m⁻² weekly, radiotherapy 4600 rad in 4.5 weeks, After completion of chemoradiation, methyl CCNU added |
| Klassen et al (1985)        | chemo (n = 44)           | NA; 31 men, 13 women| 5FU 600 mg m⁻² weekly                 |
|                            | Combin rx (n = 47)       | NA; 22 men, 25 women | 5FU 600 mg m⁻² on first days of radiotherapy 4000 rad radiotherapy over 4 weeks, After completion of chemoradiation, 5FU 600 mg m⁻² weekly |
| GITSG (1988)                | Chemo (n = 21)           | 60 years; 13 men, 8 women | 5FU 600 mg m⁻² on days 1, 8, 29, 36, streptozocin 1 g m⁻² every 8 weeks, mitomycin 10 mg m⁻² on day 1 every 8 weeks |
|                            | Combin rx (n = 22)       | 61 years; 14 men, 8 women | Radiotherapy 5400 rad over 6 weeks with 5FU 350 mg m⁻² on first 3 days and last 3 days of radiotherapy. After completion of chemoradiation, chemo-SMF regimen: 5FU 600 mg m⁻², streptozocin 1 g m⁻² on days 1, 8, 29, 36 every 8 weeks, mitomycin 5 mg m⁻² at first dose, then 10mg m⁻² every 8 weeks |
| Chauffert et al (2006)      | Chemotherapy (n = 60)    | Mean age = 60.1 years | Gemcitabine 1000 mg m⁻² 7q8 weeks initially, then 3q4 weeks |
|                            | Combination rx (n = 59)  | Mean age = 62.7 years | 60 Gy in 6 weeks, with 5FU 300 mg m⁻² 24h⁻¹ on days 1–5 every week and cisplatin 20 mg m⁻² day⁻¹ on days 1–5 at week 1 and 5. After completion of chemoradiation, gemcitabine 1000 mg m⁻² 3q4 weeks |

C, CCNU = lomustine; chemo = chemotherapy; Combin rx = combination therapy (chemoradiotherapy, followed by chemotherapy); MMC = mitomycin; NA = data not available.
greater toxicity, as myelosuppression was more frequent and severe, and two cases of gastrointestinal bleeding and one instance of moderate azotemia were reported in the combined modality arm.

Meta-analysis of chemotherapy vs chemoradiation, followed by chemotherapy in the two evaluable trials, found no significant difference between the two approaches, in the presence of inter-study heterogeneity. This could be owing to the following factors:

(i) Difference in radiation. The GITSG study (Gastrointestinal Tumour Study Group, 1988) utilised 54 Gy, given via three or four fields whereas the Klassen study (Klassen et al, 1985) used 4000 rad given by parallel-opposed anterior and posterior portals.

(ii) The chemotherapy agents also differed, with the GITSG study using a combination of 5FU, streptozotocin and mitomycin C (SMF), whereas the Klassen study used single agent 5FU.

The difference in effects between the two studies could be due to the difference in the radiotherapy used, as the GITSG study concluded that the SMF regimen did not prove to be superior to single agent 5FU. The CIs here are very wide, with reduction in risk of death with chemoradiation followed by chemotherapy being, on one end of the spectrum, as much as 68%, whereas at the other end, the increase in risk of death being 95% greater compared to chemotherapy alone. Another point to be borne in mind was that the GITSG study had closed prematurely, owing to lack of funding, with the total number of patients accrued only a third of the planned sample size. Early stoppage of a trial could lead to an erroneous estimation of treatment effects, with a propensity for exaggeration, that is, a random high (Schulz and Grimes, 2005).

For the two studies (Hazel et al, 1981; Chauffert et al, 2006) in this comparison wherein we were unable to calculate HR from the published data, the overall results did not support the use of chemoradiotherapy followed by chemotherapy, over chemotherapy alone. In the trials conducted by Hazel et al (1981) of 30 patients, there was no significant difference in median survival between the two arms (7.3 months in multimodality treatment arm vs 7.8 months in the chemoradiotherapy arm). A recent randomised controlled trial, done nearly two decades after the GITSG study, found significant survival advantage (log rank $P=0.014$) with gemcitabine single agent chemotherapy (median survival 14.3 months) over multimodality therapy in locally advanced disease (median survival = 8.4 months), necessitating early stoppage of the trial (Chauffert et al, 2006). All studies found greater haematological toxicity in the multimodality treatment arm, and the Chauffert study found a higher incidence of nonhaematological toxicity as well.

To conclude, survival benefit was demonstrated for the comparison of chemoradiotherapy over radiation alone, with evidence from a single randomised controlled trial demonstrating survival benefit for chemoradiotherapy followed by chemotherapy over radiation alone and chemoradiotherapy followed by chemotherapy over BSC. There is insufficient evidence to support the use of chemoradiation with follow on chemotherapy over chemotherapy alone in the absence of a survival advantage, coupled with greater toxicity. However, the wide CIs make it difficult to rule out important clinical differences. The results of the Intergroup study E4201, which aimed to compare gemcitabine alone to gemcitabine and radiation therapy would have helped settle the issue of whether there is a role, if at all, for multimodality therapy in locally advanced pancreatic cancer (Lockhart et al, 2005). Unfortunately, this trial was closed owing to poor accrual and hence the question remains unanswered (Cardenes et al, 2006).

There are missing links in the chain of evidence using radiation therapy in advanced pancreas cancer, in particular, the fact that at inception, radiation alone was not compared against BSC in a randomised setting, unlike with chemotherapy approaches. In
addition, there are several small inadequately powered randomised controlled trials testing different hypothesis, with a missing golden thread in the evolution of these studies. Staging has improved over time, with significant advances in imaging in the last 5 years following the advent of multidetector row helical CT with or without positron emission tomography (Michl et al, 2005). The frontline approaches to staging today are contrast-enhanced multi-detector row helical CT, with its high sensitivity for identifying vascular invasion, and endoscopic ultrasound, which can pick up tumours as small as 2 – 3 mm. In the event of these modalities being equivocal, there are additional tools available in the form of MRI with MR-angiography, MRCP, PET/CT and staging laparoscopy. Radiotherapy has also evolved, from the two-dimensional split course radiation encompassing larger treatment volumes with resultant toxicity, to the newer, more targeted three-dimensional conformal radiation and the intensity modulated radiation therapy (IMRT) approaches (Garofalo et al, 2006). Image-guided radiation therapy (IGRT) takes into account the interfraction and intrafraction dose variation, as a consequence of organ motion. Better technology and the use of conformal treatment have led to higher tolerable radiation doses (Yang et al, 2005). With improvements in staging and radiation techniques future studies may re-evaluate the application of upfront chemoradiation or the use of early systemic therapy for the treatment of micro metastases followed by consolidation therapy within adequately powered studies.

To conclude, we advocate the use of chemotherapy in patients with locally advanced cancer, as currently there is insufficient evidence to endorse the use of chemoradiation, followed by chemotherapy, over chemotherapy alone. This recommendation is also supported by a recent meta-analysis, which demonstrated a significant survival benefit for chemotherapy over BSC and gemcitabine-based combinations over single agent gemcitabine in patients with advanced pancreatic cancer (Sultana et al, 2007). It is important to bear in mind that no randomised controlled trial has compared radiotherapy to chemotherapy and the single randomised controlled trials that compared chemoradiation, followed by chemotherapy to either BSC or radiation, are small. With improvements in staging and radiation techniques future trials may influence these recommendations.

ACKNOWLEDGEMENTS

The following trialists facilitated these meta-analyses by generously providing clarifications and/or extra data:

1. Dr Steven J Cohen, Department of Medical Oncology, Fox Chase Cancer Centre, Philadelphia, USA and Dr Paul Catalano, Statistician, ECOG (clarifications and extra data: Cohen et al, 2005)
2. Dr Andrew Maksymiuk, Department of Haematology/Oncology, University of Manitoba, Canada (clarifications (Hazel et al, 1981))
3. Prof Harold O Douglass, Former Chair, Gastrointestinal Tumour Study Group (clarifications:Gastrointestinal Tumour Study Group, 1988; Deeks et al, 2004)
4. Dr Hiroyuki Shinchii, Department of Surgical Oncology and HPB Surgery, Kagoshima University, Japan (clarifications: Shinchi et al, 2002)
5. Dr Joel Novak, Statistician for GITSG trials (clarifications: Moertel et al, 1981)

Research support: Cancer Research UK.

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