# Adjuvant treatment of pancreatic cancer

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There have been a few large randomised controlled trials of adjuvant treatment following resection in pancreatic cancer that have now enabled the establishment of the standard of care.

Pancreatic cancer is one of the major causes of cancer death with a five-year survival rate of less than 5%. Patients who can undergo surgical resection have a better outlook and in specialised centres resection rates of above 15% can be achieved. The five-year survival improves to around 10% following resection, although cure cannot be achieved in the vast majority of cases. There is an obvious need to improve long-term survival in these patients.

The first adjuvant study ever undertaken was by the North American Gastrointestinal Tumor Study Group (GITSG) who randomised 43 patients between chemoradiation (40 Gy with weekly 5-Fluorouracil (5FU) for two years) vs. surgery alone [1]. Median survival was significantly increased in the treated group (20 vs. 11 months, $P = 0.035$) with 2-year survival estimates of 42% vs. 15%. This was considered enough evidence to make chemoradiation standard treatment in America.

The European Study Group for Pancreatic Cancer (ESPAC) 1 trial was the first adequately powered, randomised study to assess chemoradiotherapy concurrent with 5-fluorouracil and maintenance 5-fluorouracil and folinic acid chemotherapy in resected pancreatic cancer [2]. Initial analysis of all 541 patients indicated no survival benefit for adjuvant chemoradiotherapy but the results for chemotherapy were considered to be inconclusive with only ten months' median follow-up. The final results of this trial after a median follow-up of 47 months in the 289 patients restricted to the original 2x2 factorial design definitively demonstrated a survival benefit for chemotherapy, but not for chemoradiotherapy [3]. In the $2 \times 2$ factorial design 73 patients were randomised to chemoradiation, 75 to chemotherapy, 72 for both and 69 to observation. Analysis was based on 237 (82%) deaths and a median (inter-quartile range) follow-up of 47 (33, 62) months. Five-year survival for patients receiving chemoradiation was 10.0% and 19.6% without ($P = 0.05$) and 21.1% for patients receiving chemotherapy and 8.4% without ($P = 0.009$). Five-year survival estimates were 10.7% for patients randomised to observation, 7.3% for patients randomised to chemoradiation only, 29.0% for the patients randomised to chemotherapy only and 13.2% for patients randomised to chemoradiation followed by chemotherapy. The chemotherapy benefit remained when adjusting for influential prognostic factors.

Quality of life improved after adjuvant therapy irrespective of the modality or combination of modalities [4]. A survival advantage was also demonstrated for adjuvant combination chemotherapy using 5-FU, doxorubicin and mitomycin C in another randomised controlled trial [5]. A meta-analysis using individual patient data showed that the survival benefit of adjuvant chemotherapy extended to patients with R1 resection margins although the treatment effect was much less [6].

The failure of adjuvant chemoradiotherapy to enhance survival was also reflected in the results of the European Organisation for Research and Treatment of Cancer multicentre prospective randomised trial [7,8]. 218 patients (104 with ampullary tumours) were randomised between adjuvant chemoradiation (as in the GITSG regimen, but with no follow-on chemotherapy) vs. surgery alone. Median survival was not significantly increased with treatment (17 vs. 13 months) with two-year and five-year survival estimates of 37% vs. 23% and 20% vs. 10% in 114 patients with tumours in the pancreatic head.

The Radiation Therapy Oncology Group (RTOG) 9704 trial randomised 538 patients to either pre- and post-chemoradiation gemcitabine or to pre- and post-chemoradiation 5-fluorouracil [9]. The median survival in the 451 'eligible' patients was 16.7 and 18.8 months respectively ($P = 0.34$) and in the 388 patients with pancreas head cancer 20.5 months versus 16.9 months respectively ($P = 0.09$). This trial of course does not support the principle adjuvant

chemoradiation per se, but provides survival data that in no way demonstrate superior survival to chemotherapy and in fact have survival data similar to those shown for chemoradiation in ESPAC-1.

The primary end-point in the CONKO-001 trial was disease-free survival [10]. This was 13.4 months for gemcitabine and 6.9 months for surgery alone ($P < 0.001$) whilst the median overall survival was 22.1 months and 20.5 months respectively ($P < 0.06$). With further follow-up the overall survival difference also appeared to become significant. A smaller multicentre phase III trial undertaken in Japan which enrolled 119 patients showed significantly longer disease-free survival in the gemcitabine group than those in the surgery-only group (median 11.4 versus 5.0 months; $P = 0.01$) [11]. The overall survival did not differ significantly between the gemcitabine and surgery-only groups (median survival, 22.3 versus 18.4 months respectively; $P = 0.19$).

The ESPAC-3 trial was designed to compare the survival benefit of adjuvant 5-fluorouracil and folinic acid versus gemcitabine, which, during the conduction of the ESPAC-1 trial, had become established as the standard care for advanced pancreatic cancer [12]. Initially this was a three-arm study that included an observation arm based on the survival uncertainty of adjuvant chemotherapy, but the latter arm was dropped following the definitive results of ESPAC-1. The ESPAC-3 trial represents the largest ever randomised adjuvant trial conducted in pancreatic cancer and included pancreas cancer centres in Europe, Australasia, Japan and Canada. 1088 patients were randomised (2000–2007), 551 to 5-fluorouracil and folinic acid and 537 to gemcitabine. Final analysis was carried out on an intention-to-treat basis after a median of 34.2 months' (inter-quartile range: 27.1–43.4) follow-up after 753 (69%) deaths. Median (95%CI) survival of patients treated with 5-fluorouracil and folinic acid was 23.0 (21.1, 25.0) months and for patients treated with gemcitabine this was 23.6 (21.4, 26.4) months ($P = 0.39$; 0.81, 1.08). 77 (14%) patients receiving 5-fluorouracil and folinic acid had 97 treatment-related serious adverse events compared with 40 (7.5%) patients receiving gemcitabine with 52 events ($P < 0.001$). There were no significant differences in either progression-free survival or global quality of life scores between the treatment groups. Thus, there were no significant differences between the two treatments although adjuvant gemcitabine had an improved safety profile.

Using individual patient data from both ESPAC-1 and ESPAC-3 a composite data analysis confirmed that adjuvant 5FU/FA had a significant survival benefit compared to observation for patients with pancreatic cancer. [13]

Two major Editorials have supported the conclusions of the ESPAC trials and raise very serious questions about the continued use of adjuvant chemoradiation [14,15].

As a logical progression from these trials the (ESPAC/GERCOR) ESPAC-4 trial is now comparing combination chemotherapy with gemcitabine plus capecitabine, an orally active fluoropyrimidine, with gemcitabine alone [16]. There is already rapid recruitment with sites throughout the United Kingdom, Sweden, France and Germany.

## Conflict of interest statement

The author has no conflicts of interest associated with this abstract.

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