

Adjuvant therapy in pancreatic cancer: historical and current perspectives

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The results from pancreatic ductal adenocarcinoma appear to be improving with increased resection rates and reduced postoperative mortality reported by specialist pancreatic cancer teams. Developments with medical oncological treatments have been difficult, however, due to the fundamentally aggressive biological nature of pancreatic cancer and its resistance to chemotherapy coupled with a relative dearth of randomised controlled trials. The European Study Group for Pancreatic Cancer (ESPAC)-1 trial recruited nearly 600 patients and is the largest trial in pancreatic cancer. The results demonstrated that the current best adjuvant treatment is chemotherapy using bolus 5-fluorouracil with folinic acid. The median survival of patients randomly assigned to chemoradiotherapy was 15.5 months and is comparable with many other studies, but the median survival in the chemotherapy arm was 19.7 months and is as good or superior to multimodality treatments including intra-operative radiotherapy, adjuvant chemoradiotherapy and neo-adjuvant therapies. The use of adjuvant 5-fluorouracil with folinic acid may be supplanted by gemcitabine but requires confirmation by ongoing clinical trials, notably ESPAC-3, which plans to recruit 990 patients from Europe, Canada and Australasia. Major trials such as ESPAC-1 and ESPAC-3 have set new standards for the development of adjuvant treatment and it is now clear that such treatment in this field has the potential to significantly improve both patient survival and quality of life after curative resection.

Key words: adjuvant therapy, pancreatic cancer, randomised trials

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the top ten causes of death from cancer in industrialised countries, with over 40 000 deaths/year in Europe [1–4] and nearly 30 000 deaths/year in the USA [1, 5]. The incidence has risen dramatically in many countries as they have become more westernised in their way of life [3]. The peak incidence is around 10–12 per 10⁵ population [3]. In Europe the incidence in women has continued to increase and in most but not all countries virtually matches the levels observed in men [1–4]. Data from the Surveillance, Epidemiology and End Results programme in the United States (http://seer.cancer.gov/faststats/html/inc_pancreas.html), however, have shown a fall in the total incidence of pancreatic cancer from 12.3 per 10⁵ population in 1973 to 10.7 per 10⁵ in 1999. During the same period the decline in rates for men was from 16.1 to 12.1 per 10⁵ and for women from 9.6 to 9.5 per 10⁵, respectively. The changes in incidence in the USA and Europe, both in absolute

terms and as trends, are likely to be accounted for by major environmental aetiological factors, notably tobacco smoking and perhaps dietary factors.

The chief cause of pancreatic cancer so far identified is tobacco consumption, conferring about a two-fold increased risk, even so this only accounts for some 30% of cases [3, 6–9]. Chronic pancreatitis is associated with an increased risk of about, five- to 15-fold, but given a prevalence of only 10 per 10⁵ population the contribution to the overall numbers is small [7, 10, 11]. Although the risk of PDAC is increased 50- to 70-fold in hereditary pancreatitis [12] and forms part of a number of familial cancer syndromes [13], in themselves important in understanding the molecular basis of pancreatic cancer and as a potential for secondary screening, altogether they account for no more than 5% of all cases [13]. Current diagnostic techniques lack sufficient sensitivity and specificity to support screening for pancreatic cancer in general [13]. Thus, apart from reducing tobacco consumption there are no special opportunities available by which to reduce the mortality from pancreatic cancer.

The overall median survival from diagnosis is less than 3–5 months with a 12-month survival rate of ~10% and a 5-year survival rate of 0.4–3% [3]. There are three important reasons for these appalling survival figures. First, the disease usually

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advances to a late clinical stage before symptoms are apparent [14]. Secondly, partial or total resection of the pancreas is surgically very demanding with acceptable resection and post-operative mortality rates found only in specialised centres [15–17]. Thirdly, pancreatic cancer has an aggressive biological phenotype that is exceptionally resistant to all forms of therapy [18].

Only 10–15% of patients in most series are suitable for resection due to the presence of locally advanced or metastatic disease, but surgery offers the only hope of cure. The median survival rates are of the order of 13–18 months and 5-year survival rates are at best 15–20% [19–24]. Beyond 5 years there are few long-term survivors, with death from the cancer approaching 100% [19, 24]. Attempts at more radical pancreatic resections and extended lymphadenectomy, although feasible without excessive morbidity and mortality, have failed to produce convincing improved survival results [25–31]. Over the last few years, efforts have been directed towards the development of adjuvant and neo-adjuvant therapies in an attempt to improve outcome [32–47], with the most dramatic and informative data coming from the European Study Group for Pancreatic Cancer (ESPAC) in the form of the ESPAC-1 trial [43–45].

Adjuvant therapy aims to improve survival following curative resection by treating any residual microscopic disease. The toxicity of the agents used is a major consideration since improved survival should not be at the expense of quality of life (QoL). A brief consideration of developments in the treatment of advanced pancreatic cancer is appropriate to place the emerging role of adjuvant treatment into context.

Chemotherapy in advanced pancreatic cancer

Many chemotherapeutic agents have been tried in the treatment of advanced pancreatic cancer, but of the older agents only 5-fluorouracil (5-FU) and mitomycin C (MMC) have been consistently shown to have any beneficial effect [48–50], and more recently gemcitabine (Gemzar) [51–57]. Although earlier 5-FU-based combinations of cytotoxic agents conveyed a survival advantage over supportive care [58–60], such regimens had increased toxicity without any survival benefit compared with single-agent 5-FU [61].

Gemcitabine has become increasingly popular and is one of a number of newer cytotoxic agents that are being actively investigated in pancreatic cancer (Table 1) [62–95]. Gemcitabine is an S phase nucleoside (deoxycytidine) analogue (difluorodeoxycytidine) that competes for incorporation into DNA thus inhibiting its formation [51]. Gemcitabine is phosphorylated stepwise by deoxycytidine kinase to difluorodeoxycytidine triphosphate, which is incorporated into nascent DNA to inhibit DNA synthesis. This incorporation facilitates the insertion of another base pair before DNA polymerase is inhibited making DNA repair more difficult, a process called masked termination. Ribonucleotide reductase is also inhibited by gemcitabine thereby reducing the pool of dNTPs. Over and above these actions, gemcitabine stimulates deoxycytidine kinase, thus promoting its own phosphorylation to the active triphosphate, and inhibits deoxycytidine monophosphate deaminase that is otherwise involved in its degradation. In the single phase III study in which gemcitabine

was compared with another single agent, it was shown to confer a significant survival benefit in advanced pancreatic cancer, increasing median survival from 4.4 months [for intravenous (i.v.) bolus 5-FU] to 5.7 months and increasing 1-year survival from 2% to 18%, respectively [52]. A key end point in this study was ‘clinical benefit response’, based on reducing pain, improving performance status and inducing weight gain, which was attained in 24% of patients receiving gemcitabine compared with 5% for those receiving 5-FU. The range in response rates for gemcitabine from this and two phase II studies was 5–11% with a median survival rate of 5.7–6.3 months [52–54]. In patients with metastatic pancreatic cancer that had progressed with 5-FU and then been treated with gemcitabine, the median survival (in 63 of 74 patients enrolled) was 3.9 months (range 0.3–18.0) [55]. Seventeen patients (27%) attained a clinical benefit response with a median duration of 14 weeks (range 4–69). Gemcitabine was generally well-tolerated with a low incidence of grade 3/4 toxicities [55].

Pharmacokinetic studies showed that the activity of deoxycytidine kinase was saturable, indicating that conversion of gemcitabine to the triphosphorylated active form was dose-rate dependent [56]. The maximal tolerated dose of gemcitabine was found to be 2250 mg/m²/week due to dose-limiting toxicity from myelosuppression [57]. Based on these two facts patients were randomly assigned to receive i.v. gemcitabine at either 2200 mg/m² given over 30 min or 1500 mg/m² at a fixed dose rate of 10 mg/m²/min, both weekly for 3 out of every 4 weeks [57]. The levels of triphosphorylated gemcitabine were higher in patients given the fixed dose rate infusion arm (336 versus 114 μmol, respectively) and also associated with a better objective response rate (17% versus 3%), median survival (6.1 versus 4.7 months) and 1-year survival (23% versus 8%) [57]. A larger randomised phase II trial is now in progress. Studies of doublet or triplet therapy that include gemcitabine have revealed objective response rates of 7–58% and median survival rates of 5.7–11 months [64–83].

There remains continued interest in fluoropyrimidines, as seen in studies that aim to optimise the effectiveness of 5-FU such as protracted venous infusion (PVI) [64, 83, 96, 97] and the development of orally active agents [67, 88, 89]. Auerbach et al. [96] treated 54 patients with PVI 5-FU 300 mg/m²/day for 70 days and carboplatin 100 mg/m² weekly on weeks 1–10 of a 12-week cycle that, after a 2-week rest, was repeated until progression. They found an objective response of 17% with a median survival of 22 weeks and a 1-year survival of 13%. Maisey et al. [97] randomly allocated 208 patients to PVI 5-FU (300 mg/m²/day for up to 24 weeks) or PVI 5-FU plus MMC (7 mg/m² every 6 weeks for four courses). The response rates were 8.4% and 17.6%, respectively ($P = 0.04$) and toxicities in both arms were mild. The difference in response rates did not translate into a significant difference in median survival (5.1 versus 6.5 months, respectively). In a phase II study 26 patients were given PVI 5-FU (200 mg/m²/day) and gemcitabine (700–1000 mg/m²) weekly for 3 out of every 4 consecutive weeks [64]. The response rate was 19% and the median survival was 10.3 months [64]. Quadruplet therapy consisting of 40 mg/m² each of cisplatin and epirubicin

Table 1. Some of the agents currently being investigated in clinical trials in advanced pancreatic cancer

Class of agent	Mode of action
Nucleoside analogues	Gemcitabine (Gemzar) [51–56] is an S phase nucleoside (deoxycytidine) analogue (difluorodeoxycytidine) that is phosphorylated to difluorodeoxycytidine triphosphate by deoxycytidine kinase. Gemcitabine also stimulates deoxycytidine kinase and inhibits both ribonucleotide reductase and deoxycytidine monophosphate deaminase. Gemcitabine triphosphate is incorporated into nascent DNA to inhibit DNA synthesis. The fixed dose rate regimen may be better [57]; being used in numerous trials of doublet and triplet therapies and as a radiosensitiser [64–83]. Troxacitabine (Troxyatl) is a dioxolane nucleoside analogue of cytidine that is incorporated into DNA during replication, inhibiting DNA polymerase and DNA synthesis. Unlike other cytidine analogues, troxacitabine is not degraded by cytidine deaminases [84].
Anti-metabolites	Raltitrexed (Tomudex) is a second-generation thymidylate synthase inhibitor with similar efficacy to 5-FU [85–87]. Pemetrexed (Alimta, LY231514) is a new-generation anti-folate with 'triple' inhibitory activity against multiple enzymes involved in pyrimidine and purine metabolism. Systemic toxicity is reduced by co-administration of folic acid and vitamin B12 and dexamethasone prevents an associated skin rash [68]. Capecitabine (Xeloda) is an oral, tumour-selective fluoropyrimidine carbamate that is sequentially converted to 5-FU by three enzymes located in the liver and in tumours. The final step is the conversion of 5'-deoxy-5-fluorouridine to 5-FU by thymidine phosphorylase in tumours [67]. ZD9331 is a novel oral non-polyglutamated anti-folate thymidylate synthase inhibitor. This enzyme is crucial for DNA synthesis and catalyses the reductive methylation of dUMP to form thymidylate, which is subsequently converted to dTTP [88]. Tegafur is also an active 5-FU prodrug that is active taken orally [89].
Topoisomerase-I inhibitors	Topoisomerase-I inhibitors include irinotecan (CPT-11, Camptosar), camptothecin, topotecan, rubitecan and DX-8951f. Topoisomerase inhibitors impede the DNA helix torsional stress-relieving activity of DNA topoisomerases and also prevent their release from the DNA thus prompting apoptosis. Studies of doublet and triplet therapy are in progress [69–72].
Platinum analogues	These form adducts with DNA inhibiting transcription and replication causing cell death. Oxaliplatin is a third-generation platinum analogue (a diamminocyclohexane platinum derivative) that may have activity in tumours resistant to cisplatin or carboplatin and may have an additive/synergistic activity in doublet or triplet therapy. Trials are ongoing with cisplatin [73–75] and oxaliplatin [76–78]. Oxaliplatin may also have a role as second-line therapy with relapse on gemcitabine [90].
Taxanes	The taxanes include paclitaxel and docetaxel (Taxotere) and are semi-synthetic microtubule inhibitors with a different mechanism of action from the vinca alkaloids. Taxanes bind to β -tubulin, promoting microtubule assembly and preventing depolymerisation thus forming stable non-functional complexes and inhibiting the function of the mitotic spindle. The net result is cell cycle arrest and increased sensitivity to radiation [79–82].
Proteasome inhibitors	PS-341 is a reversible and specific inhibitor of the proteasome with activity against pancreatic cancer [91]. The 26S proteasome is a key part of the system that degrades regulatory proteins that govern cell trafficking, transcription factor activation, cell cycle regulation and apoptosis.
Cyclo-oxygenase-2 inhibitors	Celecoxib has been found to be active against pancreatic cancer [92]. Specific cyclo-oxygenase-2 (COX-2) inhibitors reduce proliferation, inhibit angiogenesis and promote apoptosis. First-generation COX-2 inhibitors include celecoxib and rofecoxib and second-generation agents include parecoxib, valdecoxib and etoricoxib.
5-Lipoxygenase and thromboxane A2 inhibitor	CV6504 is a novel 5-lipoxygenase and thromboxane A2 synthase inhibitor shown in a phase II to produce stable disease in 32% of patients and a 1-year survival of ~25% [93].
Histone deacetylase inhibitor	CI-994 (<i>N</i> -acetyl dinaline, PD 123654) is a novel orally active agent causing inhibition of both histone deacetylation and the G ₁ to S transition phase of the cell cycle [94, 95].

on day 1, gemcitabine 600 mg/m² on days 1 and 8 every 4 weeks, and PVI 5-FU 200 mg/m² was evaluated in 49 patients with stage IV pancreatic cancer [83]. The objective response rate was 58% in 43 assessable patients and the median survival was 11 months [83]. The combination of gemcitabine and bolus 5-FU versus gemcitabine alone has been assessed in a phase III randomised study in 322 patients with advanced pancreatic cancer. There was no significant difference in median survival between the two groups [98]. Gemcitabine has also been combined with the farnesyl transferase inhibitor R115777 (Zarnestra) in a phase III trial of 688 patients with advanced pancreatic cancer. There was no difference in median survival between patients randomly assigned to receive the above combination versus patients randomly

assigned to receive gemcitabine and placebo [99]. Studies such as these have been the basis of the recently launched Gem-Cap Trial by the National Cancer Research Institute in the UK, which will compare gemcitabine with or without capecitabine in a large phase III study.

Although the survival benefit to be derived from gemcitabine alone is small in absolute terms compared with bolus 5-FU it is increasingly accepted as the standard drug for advanced pancreatic cancer. This is important for clinical trials in pancreatic cancer as there is now a benchmark, making cross-study comparisons much easier. Gemcitabine, perhaps in combination, may be expected to have a role in the adjuvant setting, although the evidence for this has yet to be collected.

Chemoradiotherapy in advanced pancreatic cancer

Moertel et al. [100] demonstrated an improved median survival with a combination of external-beam radiotherapy (EBRT) plus 5-FU when compared with EBRT alone (10.4 versus 6.3 months, respectively) in 64 patients with advanced PDAC. This study from 1969 established the importance of radiosensitisation by concomitant cytotoxic therapy, and 5-FU has remained the mainstay of chemoradiotherapy (CRT) since then. A combination of methyl-CCNU (125 mg/m² orally, every 6 weeks) and bolus 5-FU (400 mg/m² weekly) with or without testolactone (200 mg, orally daily) was given to 69 patients during treatment with 60 Gy EBRT [101]. The median survival was 38 weeks (and 30 weeks for those receiving testolactone), but the authors demonstrated that the regimen was exceptionally toxic [101].

Another study treated 16 patients (five with American Joint Committee on Cancer stages I–II and 11 with stage III) with intra-arterial cisplatin (100 mg/m²) by selective coeliac arteriography followed by i.v. infusional 5-FU (1000 mg/m²/day for 4 days) and concomitant split-course EBRT of 20 Gy given in 10 fractions over 12 days [102]. After a 2-week rest the CRT was repeated and after a second 2-week interval a third cycle of CRT was given with a final 10 Gy dose [102]. There were only two (12%) partial responses and the median survival was 9 months [102]. Nguyen et al. [103] treated 23 patients with high-dose EBRT (60 Gy continuously) and daily cisplatin (6 mg/m²/day). The median survival was 10 months but the authors concluded that there was an urgent need for new agents in this disease.

There has been some interest in using PVI 5-FU as a radiosensitiser. The 1-year survival of 54 patients given 54–64 Gy with concurrent PVI 5-FU (200–250 mg/m² beginning on day 1 and continuing until the completion of radiotherapy) or by bolus (500 mg/m² on days 1–3 and days 29–31) was 34% and 18%, respectively ($P = 0.9$) [104]. Boz et al. [105] treated 42 patients with CRT using a four-field technique to a total dose of 59.4 Gy in 33 fractions and PVI 5-FU (300 mg/m²/day, 7 days/week throughout the entire course of EBRT) with a median survival time of 9.1 months.

There have been two studies of CRT using hyperfractionation. Luderhoff et al. [106] treated 13 patients with a combination of accelerated radiotherapy and 5-FU. The radiotherapy was given in 1.1 Gy fractions three times a day over 3 weeks for up to a total dose of 45–50 Gy. 5-FU was administered as a continuous infusion (25 mg/kg/24 h) during the first and the third week of radiotherapy. The median survival was 36 weeks. Prott et al. [107] reported a median survival of 12.7 months in 32 patients with locally advanced pancreatic cancer treated with hyperfractionated, accelerated radiotherapy and simultaneous administration of 5-FU and folinic acid. The total tumour dose of 44.8 Gy was applied in two daily fractions of 1.6 Gy (10 fractions/week). On each of the first 3 days of radiotherapy, 600 mg/m² 5-FU and 300 mg/m² of folinic acid were given i.v. and repeated in 4-week intervals according to the response.

More recently there is increased interest in the use of gemcitabine as a radiosensitiser, and there have been several phase I and phase II studies with some partial tumour responses [108–110].

The combination of gemcitabine with PVI 5-FU and concomitant radiotherapy was found to be unusually toxic [111].

Patients eligible for treatment with CRT (and without maintenance chemotherapy) are those who have locally advanced disease without metastases. A major problem is that the definition of ‘locally advanced disease’ is to a significant extent operational and is to a large extent dependent on the expertise of the local pancreatic cancer surgical team. Frequently patients with ‘locally advanced disease that is not resectable’ in one institution may successfully undergo resection in a specialist pancreatic cancer centre [112]. Thus results from oncology centres that lack integrated team work with a specialist pancreatic cancer team need to be treated with caution.

CRT and maintenance chemotherapy in advanced pancreatic cancer

Of course CRT alone cannot deal with metastases outside the immediate radiation field and this has led to the notion of combination CRT and maintenance chemotherapy. In theory such a combination provides the dual benefit of both local and systemic control. This approach remains popular in the USA but any clear advantage over chemotherapy alone has yet to be demonstrated. In 1981 the Gastrointestinal Tumour Study Group (GITSG) [113] randomly assigned patients to one of three groups: (i) 60 Gy EBRT without radiosensitising 5-FU; (ii) 60 Gy EBRT with radiosensitising 5-FU and follow-on 5-FU; and (iii) 40 Gy EBRT with radiosensitising 5-FU and follow-on 5-FU [109]. The median survival times were 23, 40 and 42 weeks, respectively, suggesting that the higher CRT dose conferred no benefit and that the best effect was associated with either concurrent and/or maintenance chemotherapy. Subsequently, a GITSG study in 1985 [114] randomly assigned 157 patients with locally unresectable pancreatic cancer to 60 Gy EBRT (as a double split course) plus 5-FU or 40 Gy (as a single continuous course) plus doxorubicin. The median survival times were 8.5 and 7.5 months, respectively (not statistically significant). The toxicity in the doxorubicin arm was more substantial ($P < 0.05$) and primarily attributable to doxorubicin chemotherapy after the completion of radiotherapy [114].

Klaassen et al. [115], also in 1985, reported on behalf of the Eastern Cooperative Oncology Group (ECOG) a phase III study of 91 patients with locally unresectable pancreatic cancer. The patients were randomly allocated to: (i) bolus 5-FU (600 mg/m²) once weekly; or (ii) 40 Gy EBRT (plus concurrent bolus 5-FU, 600 mg/m² on the first 3 days of each course) then followed by weekly maintenance 5-FU (600 mg/m²) [115]. The median survival time was 8.2 months for the 5-FU arm and 8.3 months for the EBRT plus concurrent and maintenance 5-FU arm [115]. Substantially more toxicity was experienced by patients treated with the combined modality arm (51%) than by those patients receiving 5-FU alone (27%) [115].

The findings of the ECOG study [115] were subsequently contradicted by a much smaller GITSG study [116]. Forty-three patients were randomly allocated to streptozocin, MMC and 5-FU triplet chemotherapy (SMF) versus EBRT with concomit-

ant 5-FU followed by maintenance with the same SMF regimen [116]. The median survival rate for the SMF-only group was 32 weeks (19% 1-year survival) compared with 42 weeks (41% 1-year survival) for the combined modality arm ($P < 0.02$) [116].

Kamthan et al. [117] treated 35 patients with unresectable stage II and III pancreatic cancer with split-course EBRT and three-drug chemotherapy. The EBRT (54 Gy) was given in three phases of 2 Gy/day (on days 1–5 and 8–12) concurrently with continuous infusion 5-FU (1000 mg/m²/day for 4.5 days), streptozotocin 300 mg/m² (days 1, 2, and 3) and cisplatin 100 mg/m² on (day 3 of each 28-day cycle). Subsequent treatment consisted of leucovorin (200 mg/m²) and 5-FU (600–1000 mg/m² every 14 days). Fifteen patients (43%) had an objective response, including six (17%) with a complete response, and five patients subsequently underwent resection. Three of four others who could not be resected had intra-operative radiotherapy (IORT). The overall median survival time was 15 months and 26% of patients were alive at 24 months.

Ishii et al. [118] treated 20 patients with locally advanced pancreatic cancer with 50.4 Gy (in 28 fractions over 5.5 weeks) and PVI 5-FU (200 mg/m²/day) beginning on the first day of EBRT and continued through the entire radiation course, and thereafter with weekly infusions (500 mg/m²) until disease progression. The median survival was 10.3 months and the 1-year survival rate was 42%. The same group [119] also reported a median survival of 7.7 months and a 1-year survival rate of 36% in 41 patients treated with 50.4 Gy EBRT (in 28 fractions over 5.5 weeks) and daily cisplatin (5 mg/m²/day as a 30-min infusion just before each radiation fraction) and follow-on 5-FU (500 mg/m² once weekly after completion of the EBRT and continued until disease progression or unacceptable toxicity). Andre et al. [120] treated 32 patients with 45 Gy over 5 weeks, combined with 5-FU and cisplatin during the first and fifth weeks, followed 3 weeks later by four cycles of the same chemotherapy plus leucovorin. The median survival was 9 months and the 1- and 2-year survival rates were 31% and 13%, respectively [120].

The Radiation Therapy Oncology Group (RTOG) [121] explored the role of prophylactic hepatic irradiation in 1992 (RTOG 8801). Eighty-one patients received high continuous EBRT to the pancreas (61.2 Gy in 34 fractions over 7 weeks) and simultaneous prophylactic hepatic irradiation (23.4 Gy in 13 fractions for the last 2.5 weeks). Seventy-five per cent of patients completed both treatments according to the protocol, but two patients died of complications, nine had life-threatening reactions and 31 had severe side-effects. The median survival was only 8.4 months [121]. The authors concluded that prophylactic hepatic irradiation might reduce the frequency of hepatic metastasis, but failure to control the primary tumour and intra-abdominal spread were overwhelming.

Seydel et al. [122] treated 18 patients with CRT and maintenance chemotherapy using hyperfractionation. The radiation dose to the pancreas was 40.8 Gy with an additional 9.6 Gy to the pancreatic tumour and a surrounding margin; 1.2 Gy were given twice daily 4–6 h apart. Concurrent 5-FU (350 mg/m²) was given on the first 3 and last 3 days of radiation therapy. On day 53, SMF chemotherapy was given consisting of streptozotocin (1 g/m²),

i.v. MMC (10 mg/m²) and bolus 5-FU (600 mg/m²). The 5-FU and streptozotocin were repeated on days 60, 81 and 88, and the streptozotocin and MMC cycles were repeated every 8 weeks until progression. The median survival was 35 weeks with a 1-year survival rate of 39%; severe toxicity was experienced by 67% of patients. Hyperfractionated radiation for pancreatic cancer remains an experimental approach and cannot be recommended for routine use.

Although the more recent studies suggest a reasonable survival time with CRT and maintenance chemotherapy, the results are not convincingly better than chemotherapy alone. Thus it follows that it is not clear whether CRT confers any survival advantage when compared with chemotherapy alone.

IORT and brachytherapy in advanced pancreatic cancer

IORT has the theoretical advantage that it can deliver a more intense and targeted dose to the pancreatic resection bed, the site of most recurrences [123]. Particular interest has been shown in IORT because of the poor results from EBRT. Like CRT for locally advanced disease, good control can be achieved with IORT, but unfortunately with little impact on long-term survival due to the development of metastases outside the fields of radiation [123]. Shipley et al. [124] in 1984 reported a median survival of 16.5 months in 29 patients given electron beam IORT in combination with EBRT and chemotherapy. However, Gundersen et al. [125] from the Mayo Clinic found little change in the median or long-term survival in 52 patients given 17.5–20 Gy IORT and 45–50 Gy EBRT (with or without 5-FU) from that seen with EBRT alone. Roldan et al. [126] gave 60 Gy EBRT to one group of 122 patients and 45–55 Gy EBRT with an IORT electron boost to a second group of 37 patients; both groups also received 5-FU. The median survival rates were 12.6 versus 13.4 months, respectively. In a subsequent study from the Mayo Clinic, Garton et al. [127] gave preoperative EBRT (50–54 Gy with or without concomitant bolus 5-FU) followed by surgical exploration and IORT (20 Gy). The median survival was 14.9 months and the 2- and 5-year survival rates were 27% and 7%, respectively. These survival data were comparable to 6% and 0% 2- and 5-year survival rates observed in 56 patients who underwent IORT followed by EBRT ($P = 0.001$). Mohiuddin et al. [128] treated 49 patients with initial IORT and perioperative chemotherapy (5-FU/leucovorin) followed by combined EBRT (40–55 Gy) and continued chemotherapy. The median survival time was 16 months, with a 2-year survival rate of 22%.

A prospective multi-institutional study of IORT was carried out in 86 patients by the RTOG [129]. The patients were treated with a combination of 20 Gy of IORT and postoperative 50.4 Gy EBRT and bolus 5-FU (500 mg/m²/day on the first 3 days of the EBRT). The median survival was only 8 months and the 18-month survival rate was only 9%, similar to conventional therapy and indicating that IORT failed to prolong survival [129]. The United States National Cancer Institute randomly assigned 32 patients with stage III (locally advanced, positive nodes) or stage IV (visceral or peritoneal metastases) to receive either

25 Gy IORT with 50 Gy postoperative EBRT, or 60 Gy EBRT only; both groups also received 5-FU [130]. The median survival was only 8 months for both groups [130].

Two studies have been conducted using iodine-125 implants to boost local control in combination with EBRT. Shipley et al. [131] treated 12 patients with 20–39 mCi iodine-125 implantation and 40–45 Gy EBRT with a median survival of 11 months. Mohiuddin et al. [132] treated a total of 86 patients with three different combinations of iodine-125 implantation, EBRT and systemic chemotherapy. Patients in group 1 ($n = 13$) were treated with an iodine-125 implantation followed by 50–60 Gy EBRT delivered in 6 weeks. Patients in group 2 ($n = 19$) were treated as in group 1 followed by adjuvant chemotherapy. Patients in group 3 ($n = 54$) were treated with iodine-125 implantation seeds (12 Gy minimal peripheral dose), perioperative chemotherapy (5-FU and MMC) and 50–55 Gy EBRT followed by further chemotherapy. The median survival rates were 5.5, 11.3 and 12.5 months, respectively, and the 2-year survival rates were 0%, 15% and 22% [132].

Interpretation of these studies is difficult because no large randomised studies have ever been conducted and the definitions of 'locally advanced unresectable disease' vary from one institution to the next.

Adjuvant systemic chemotherapy

Few studies have been published which examine the role of adjuvant chemotherapy alone in pancreatic cancer. Most published series also included radiotherapy (or rather CRT) as part of the adjuvant treatment, and therefore data on the efficacy of chemotherapy in isolation are scarce. The few published trials on adjuvant chemotherapy alone without radiotherapy are summarised in Table 2. Splinter et al. [133], in the early 1980s, treated 16 patients with five courses of 5-FU, doxorubicin and MMC (FAM) and compared them with a historical control group of 36 patients. The FAM regimen was poorly tolerated and half of the treatment group received no more than 60% of the planned chemotherapy dose. There was no benefit from adjuvant chemotherapy, with similar 3-year actuarial survival rates of 24% and

28% for the treatment and control groups, respectively. The first prospective, randomised controlled trial was by Bakkevold et al. from Norway [34]. Forty-seven patients with resected PDAC (plus 14 with ampullary tumours) were randomly assigned to receive either chemotherapy with moderate-dose FAM, or observation alone. No long-term survival benefit with chemotherapy was shown, with similar 5-year survival rates of 4% and 8% in the FAM and control groups, but there was an improvement in median survival (23 months for chemotherapy versus 11 months for controls), with a delay in time to disease recurrence. The multi-agent chemotherapy regimen was rather toxic, with one reported death directly attributed to chemotherapy, four cases of septicaemia and 16 patients hospitalised after the first course of chemotherapy. The inclusion of ampullary carcinomas in the study makes it difficult to draw firm conclusions regarding the benefits of chemotherapy for PDAC, as the two types of cancer were not differentiated in the survival analysis.

Baumel et al. [134] reported on a retrospective survey of the French Association of Surgeons involving 787 patients who had undergone pancreatic resection for PDAC between 1982 and 1988. Of these 787 patients, 43 had received some sort of chemotherapy, although there was no standardisation of the chemotherapeutic regimens used. No differences in median survival were reported between those patients who had received chemotherapy and those who had not. The median survival was 12.4 months for 527 patients who had undergone resection alone and 11.5 months for those who had received adjuvant chemotherapy. (The remaining 127 patients had received radiotherapy with or without chemotherapy.) No information was given with regard to the comparative stage profile of the chemotherapy and no chemotherapy groups, and it may well be that the group chosen to receive chemotherapy did so by virtue of having more advanced disease.

The most recently published study is the ESPAC-1 trial [43–45]. The ESPAC-1 trial was a prospective randomised controlled study involving 61 centres across 11 European countries between 1994 and 2000. The original aim was to recruit 280 patients into a 2 × 2 factorial study in which each patient was randomly assigned to chemotherapy versus no chemotherapy and also radiotherapy

Table 2. Adjuvant systemic chemotherapy for pancreatic ductal adenocarcinoma (PDAC)

Series	Period	Number of cases	Regimen	Median survival (months)	Actuarial survival (%)		
					1 year	3 years	5 years
Splinter et al. [133]	1972–1984	36	–		28		
	1980–1984	16	FAM		24		
Bakkevold et al. [34] ^a	1984–1987	31 (24 PDAC) ^b	–	11	45	30	8
		30 (23 PDAC) ^b	FAM	23	70	27	4
Baumel et al. [134]	1982–1988	527	–	12.4			
		43	Unspecified	11.5			
Neoptolemos et al. [43] ^a	1994–2000	235	–	14			
		238	5-FU/FA	19.7			

^aRandomised controlled trial.

^bThe remainder had other pancreatic cancers. FAM, 5-fluorouracil (5-FU), doxorubicin and mitomycin C; FA, folini acid; –, no treatment; empty cells, data not available.

versus no radiotherapy. A subsequent protocol change also permitted randomisation into one of these options. A total of 541 patients were recruited, of whom 285 were entered into the full 2 × 2 randomisation (Figure 1), and the rest randomly assigned into a single option [43]. Of these 541 patients, 238 were allocated to receive chemotherapy versus 235 allocated to no chemotherapy. The chemotherapeutic regimen chosen was bolus 5-FU with folinic acid given on 5 consecutive days for six cycles at 28-day intervals. The median survival in patients receiving chemotherapy was significantly improved at 19.7 months compared with 14 months in the no chemotherapy group ($P < 0.0005$). The survival benefit in favour of chemotherapy was maintained even after stratification by resection margin involvement, lymph node involvement and tumour grade and size. The overall reduction in the hazard of death for chemotherapy was ~35%. If the analysis was restricted to the 285 patients entered into the full 2 × 2 randomisation only, the difference between the two arms was reduced (17.4 versus 15.9 months) and did not reach statistical significance at the time of analysis with a median follow-up of 10 months. In general, the chemotherapeutic regimen used was better tolerated than that reported by Bakkevold et al. [34], with only one death directly attributed to chemotherapy, although severe toxicity was reported in 24% of the chemotherapy group and a 5-FU dose reduction was necessary in 22%. Fifty-eight per

cent of patients completed the planned 6-month course of chemotherapy.

The survival benefit of chemotherapy also applied to patients with histologically positive resection margins (R1) as well as those with histologically clear resection margins (R0) [44]. Of the 541 patients, 101 (19%) had R1 resections. Resection margin status was confirmed as an influential prognostic factor, with a median survival of 10.9 months for R1 compared with 16.9 months for R0 patients ($P = 0.0006$). For R0 patients, chemotherapy produced an improvement in survival compared with no chemotherapy: 20.7 versus 15.3 months. This difference was less apparent for the smaller subgroup of R1 patients: chemotherapy 11.0 months [95% confidence interval (CI) 8.8–19.5] versus no chemotherapy 10.3 months (95% CI 8.5–16.3), but there was no significant heterogeneity between the R0 and R1 groups. In other words, adjuvant chemotherapy was of real benefit to patients with R1 as well as R0 tumours. Moreover, resection margin-positive pancreatic tumours were shown to represent a biologically more aggressive cancer [44]. A more recent analysis (now on 546 patients) has shown that neither the type of resection nor the development of complications influenced the results of adjuvant treatment [45].

As a secondary end point, this study also assessed QoL using both global and disease-specific QoL questionnaires. Data on

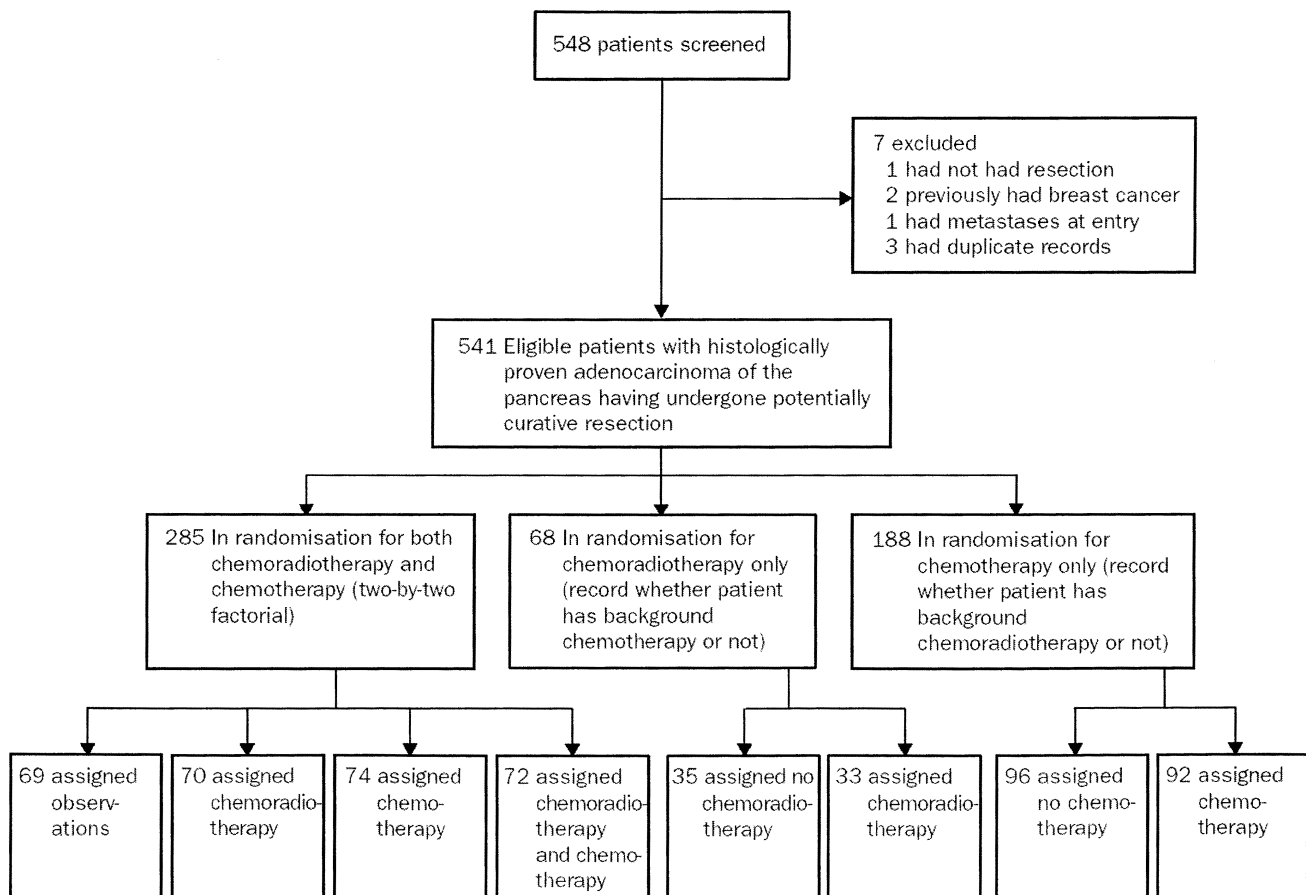


Figure 1. ESPAC-1 trial profile [43]. No chemoradiotherapy versus chemoradiotherapy: 69 + 74 + 35 versus 70 + 72 + 33; 178 versus 175. No chemotherapy versus chemotherapy: 69 + 70 + 96 versus 74 + 72 + 92; 235 versus 238. Reprinted with permission from Elsevier (The Lancet 2001; 358: 1576–1585).

176 patients were available for the QoL analysis (90 chemotherapy and 86 no chemotherapy). There was no significant difference between the two groups in QoL, with both groups showing a similar improvement in scores over the 3 months following surgery (12.2 versus 11.6 for the chemotherapy and no chemotherapy groups, respectively) [43].

The ESPAC-1 study was the first trial to demonstrate a survival advantage for adjuvant chemotherapy alone in resected PDAC, although this difference did not reach statistical significance when analysed according only to the 2 × 2 factorial design. It has therefore been followed by the current ESPAC-3 trial, which aims to randomly assign 990 patients into three arms comprising observation, 5-FU/folinic acid, as used in ESPAC-1, and gemcitabine. ESPAC-3 is recruiting patients from Europe, Canada and Australasia.

Adjuvant regional chemotherapy

Regional therapy aims to maximise the dose of the administered chemotherapy to the principal focus of metastatic disease within the liver and yet minimise systemic toxicity. The coeliac axis, portal vein and hepatic arteries have all been used as points of access by different groups. Thus far these studies have been small but do show promising results, with some studies reporting patients in whom previously unresectable tumours were down-staged sufficiently for resection to take place (Table 3). Ishikawa et al. [135, 136] placed catheters in the hepatic artery and portal vein in 27 patients at the time of pancreatic resection for continuous hepatic perfusion with 5-FU for 28–35 days after surgery. There was a significant improvement in 1- and 3-year actuarial survival compared with 67 historical controls, and only 8% of patients died from hepatic metastases.

The group of Hans Beger [137, 138] treated 20 patients (18 with PDAC and two with cystadenocarcinoma) with six cycles of mitoxantrone, 5-FU, folinic acid and cisplatinum infused via the

coeliac axis and achieved a median survival of 21 months compared with 9.3 months for a historical control group. Only 15% of the treatment group developed liver metastases. An update of this study with 24 patients showed a median survival of 23 months with regional perfusion and a 4-year survival rate of 54% [139]. The addition of radiotherapy to regional perfusion does not appear to add any additional survival benefit when compared with regional perfusion alone [140].

Adjuvant IORT

Not surprisingly, IORT has been used alone and in combination with EBRT as adjuvant therapy [37, 40, 141, 142]. In terms of survival IORT is perhaps inferior to EBRT alone and the combination of EBRT with IORT is also not obviously superior (Table 4) [35–37, 40, 43, 141, 143]. IORT alone has been shown to give a 50% reduction in local recurrence [144], yet this does not translate into a survival benefit [35–37, 40, 43, 141, 143]. The United States National Cancer Institute randomly assigned 32 patients who had undergone resection into two groups [141]. The first group ($n = 16$) received no further treatment if the tumour was R0 with no lymph nodes involved, otherwise they received 50 Gy EBRT. The second group ($n = 16$) received 20 Gy IORT (9–12 MeV electrons). After excluding nine postoperative deaths (27%) the median survival was 12 versus 18 months, but this was not statistically significant [141]. These data do not provide convincing evidence for the use IORT in treatment of resectable pancreatic cancer.

Adjuvant CRT

Adjuvant radiotherapy (EBRT) with chemotherapy (CRT) has been used in a number of non-randomised studies mainly in the USA (Table 4) [36, 40, 143, 145, 146]. Although generally well-tolerated, it has not been clearly shown to offer a survival advantage over either no adjuvant treatment or chemotherapy

Table 3. Adjuvant regional chemotherapy for pancreatic ductal adenocarcinoma (PDAC)

Series	Period	Number of cases	Regimen	Median survival (months)	Actuarial survival (%)			
					1 year	3 years	4 years	5 years
Ishikawa et al. [135, 136]	1987–1995	67	–		62	35		25
		27	HAI + HPVI		92	51		41
Gansauge et al. [137] ^a	1992–1995	18	CAI	17.8				
Link et al. [138] ^a	1992–1997	29	–	9.3				
		20 (18 PDAC) ^b	CAI	21				
Beger et al. [139] ^a	1992–1999	?	–	10.5			9.5	
		24	CAI	23			54	
Ozaki et al. [140]	1983–1993	27 ^c	IORT + HPVI or HAI	31.1				31
		19 ^d	IORT + HPVI or HAI	36	95	50		28

^aReferences [137–139] refer to the same series, but with increasing numbers of cases.

^bThe remainder had other pancreatic cancers.

^cTwenty-seven of 30 patients—excluding three with metastasis to liver, peritoneum or lung.

^dNineteen of 30 patients with regional lymph node metastases.

CAI, coeliac artery infusion; HAI, hepatic arterial infusion; HPVI, hepatic portal vein infusion; IORT, intra-operative radiotherapy; –, no treatment; empty cells, data not available.

Table 4. Adjuvant chemoradiotherapy for pancreatic ductal adenocarcinoma (PDAC)

Series	Year	Number	EBRT (Gy)	IORT (Gy)	Median survival (months)	Actuarial survival (%)			
						1 year	2 years	3 years	5 years
Willett et al. [36]	1993	16 (nm)	40–50	–	21				29
		23 (pm)	40–50	–	11				0
Johnstone et al. [145]	1993	26	45–55	20	18				
Zerbi et al. [144]	1994	43	–	12.5–20	19	71		7	
		47	–	–	12	49		10	
Di Carlo et al. [37]	1997	27	–	–	14				
		27	–	12.5–20	17				
Dobelbower et al. [147]	1997	14	–	–	6.5	15		0	0
		6	–	10–20	9	50		35	33
		14	50–67	–	14.5	64		28	0
		10	27–54	10–25	18	70		10	0
Farrell et al. [148]	1997	14	60	12–15	16	62		22	15
Hishinuma et al. [149]	1998	34	<i>n</i> = 24	<i>n</i> = 13 EBRT + IORT	13	59			19
Klinkenbijn et al. [35] ^a	1999	54 PDAC	–	–	12.6				10
		60 PDAC	40	–	17.1				20
Mehta et al. [40]	2000	52 PDAC	45–54 (PVI 5-FU)	<i>n</i> = 8	32		62	39	
		17 PDAC	Not specified (bolus 5-FU)	–	12				
Lee et al. [143]	2000	22	–	–				47	
		13	49	–				81	
Kokubo et al. [142]	2000	34 PDAC ^b	–	25	15		25		
		18 PDAC ^b	45–55	–	17		24		
Alfieri et al. [146]	2001	20	–	–	10.8				6
		26	<i>n</i> = 26	<i>n</i> = 21	14.3				16
Neoptolemos et al. [43] ^a	2001	175 PDAC	40	–	15.5				
		178 PDAC	–	–	16.1				
Allen et al. [150]	2002	29 PDAC	42 (with gemcitabine)	–	16.2				

^aRandomised controlled trial.

^bAll had negative resection margins and some had regional chemotherapy.

EBRT, external-beam radiotherapy; 5-FU, 5-fluorouracil; IORT, intraoperative radiotherapy; nm, negative resection margin; pm, positive resection margin; PVI, protracted venous infusion; –, no treatment; empty cells, data not available.

alone. A multicentre randomised phase III trial organised by the European Organisation for Research and Treatment of Cancer (EORTC) compared CRT with surgery alone in 218 patients following potentially curative surgery for pancreatic or ampullary cancers [35]. One hundred and ten patients were randomly allocated to receive 40 Gy EBRT with concomitant continuous infusion of 5-FU (but only actually given to 93 patients). There were 114 patients with PDAC, of which 54 were in the observation group and 60 patients were in the treatment group. The apparent improvement in survival in the PDAC treatment group (median survival 17.1 versus 12.6 months for observation) was not statistically significant. The trial was compromised by the fact that it was probably underpowered, and ~20% of patients with PDAC did not receive the assigned treatment. Unlike the

GITSG adjuvant trial [39, 40] there was no maintenance treatment with 5-FU. In addition, there was incomplete knowledge about resection margin status because the posterior resection margin was not assessed. It was concluded that adjuvant CRT was safe and well-tolerated, but that there was no survival benefit. This conclusion was supported by the overall results of the ESPAC-1 trial [43] with a median survival of 15.5 months in the 175 patients who received CRT versus 16.1 months in the 178 patients who did not. Again there was no survival benefit conferred by adjuvant CRT in those patients with histologically positive resection margins (R1) [44]. A new EORTC study (40013-22011) will try to assess the use of gemcitabine followed by gemcitabine plus concomitant radiation (50.4 Gy) versus resection-only in a randomised phase II/III trial (www.eortc.be).

One non-randomised study of particular interest is by Mehta and colleagues [40] from Stanford, who treated 52 patients between 1994 and 1999. The tumour bed and regional nodes were irradiated with a dose of 45 Gy in 1.8 Gy fractions followed by a boost to the tumour bed in the 35% of patients with a positive resection margin (total dose 54 Gy). Concomitant PVI 5-FU (200–250 mg/m²/day, 7 days/week) was given during the entire radiotherapy course. A remarkable median survival of 32 months was achieved. Certainly these results are far superior to other studies that have used concomitant bolus 5-FU or even continuous infusion 5-FU.

The latest study is by Allen et al. [150] from the University of Michigan, who undertook a phase I study to determine the maximum-tolerated dose of EBRT (with a conformal technique) in combination with full-dose gemcitabine (1000 mg/m² weekly × 3), in patients with a positive resection margin (*n* = 9), positive nodes (*n* = 27) or both (*n* = 7). The starting EBRT dose was 24 Gy in 1.6 Gy fractions and escalation was achieved by increasing the fraction size in 0.2 Gy increments, keeping the duration at 3 weeks. Twenty-five patients completed the protocol therapy, and at the final EBRT dose level of 42 Gy both of two patients experienced gastrointestinal dose-limiting toxicity. The median survival was 16.2 months (95% CI 12.3–19.9).

Adjuvant CRT and maintenance chemotherapy

The regimen originally adopted by GITSG for patients with advanced pancreatic cancer [113] was used in the adjuvant setting for a randomised trial in the 1970s [32, 33]. Forty-three patients, all with clear resection margins (R0), were randomly assigned to either surgery alone or surgery combined with 40 Gy radiotherapy (with 5-FU radiosensitisation) and weekly 5-FU for 2 years or until relapse. The median survival in the treated group was 20 months compared with 11 months in the surgery-only group and the 2-year survival rates were 42% and 15%, respectively. To increase numbers in the treatment group a further 30 patients were added to the adjuvant therapy arm and the outcome modified to a median survival of 18 months and a 2-year survival of 46% [33]. Unfortunately, the number of patients was still too small for convincing conclusions to be drawn and it was uncertain whether any benefit was wholly due to the combination, the chemotherapy alone or the radiotherapy alone. Despite these caveats, variations of this combination protocol were widely adopted, especially in the USA (Table 5) [22, 32, 33, 38, 39, 41, 42, 118, 150–153].

Table 5. Combination adjuvant chemoradiotherapy with follow-on chemotherapy for pancreatic ductal adenocarcinoma

Series	Year	Number	Radiotherapy (Gy)	Chemotherapy	Median survival (months)	Actuarial survival (%)			
						1 year	2 years	3 years	5 years
Kaiser and Ellenberg [32] ^a	1985	21	EBRT 40	5-FU	20	67	42	24	18
		22	–	–	11	50	15	7	8
GITSG [33]	1987	30	EBRT 40	5-FU	18		46		
Conlon et al. [151]	1996	56	EBRT 45	5-FU	20		35		
Yeo et al. [22]	1997	53	–	–	13.5		30		
		99	EBRT 40–45	5-FU	21		44		
		21	EBRT 50–57	5-FU + FA	17.5		22		
UKPACA [38]	1998	35	EBRT 40	5-FU	13	56	38	29	15
Abrams et al. [39]	1999	23	EBRT	5-FU + FA	15.9				
Paulino et al. [152]	1999	30	EBRT	5-FU	26				
		8	EBRT	–	5.5				
Andre et al. [120]	2000	10	EBRT	5-FU + FA + Cis	17				
Nukui et al. [41]	2000	16	EBRT 40	5-FU			54		
		17	EBRT 45–54	5-FU + Cis + IFN- α			84		
Sohn et al. [42]	2000	119	–	–	11	48			9
		333	EBRT 40–50 (mostly; see [22, 39, 140])	5-FU (mostly; also FA, mitomycin C, dipyrindamole; see [22, 39, 140])	19	71			20
Chakravarthy et al. [153]	2000	29	EBRT 50	5-FU, FA, mitomycin C, dipyrindamole	16	52			
Kachnic et al. [154]	2001	9	EBRT 40–50.4	Gemcitabine	16	78	39	39	

^aRandomised controlled trial.

Cis, cisplatin; EBRT, external-beam radiotherapy; FA, folinic acid; 5-FU, 5-fluorouracil; IFN- α , interferon alpha; –, no treatment; empty cells, data not available.

Yeo et al. [22] from Johns Hopkins reported a retrospective analysis of three different regimens in selected patients who had undergone pancreatoduodenectomy. Patients had received: (i) 40–45 Gy EBRT plus follow-on bolus 5-FU for 4 months; (ii) 50–57 Gy EBRT plus hepatic radiation plus continuous infusion 5-FU/folinic acid for 4 months; or (iii) no adjuvant treatment. Group (i) had a significantly better median survival (21 months) and 2-year survival (44%) when compared with the control group (13.5 months and 30%, respectively). There was, however, no significant difference between groups (ii) and (iii), questioning the value of adjuvant treatment *per se* because of patient selection. The same group treated 23 patients with continuous infusion of 5-FU and folinic acid during radiation for 5 days/week and then 1 month later, four cycles of the same chemotherapy regimen for 2 weeks out of every 4 [39]. Patients were given either ‘low-dose’ radiotherapy (consisting of 23.4 Gy to the whole liver, 50.4 Gy to regional nodes and 50.4 Gy to the tumour bed) or ‘high-dose’ radiotherapy (comprising 27.0 Gy to the whole liver, 54.0 Gy to regional nodes and 57.6 Gy to the tumour bed) [39]. The overall median survival was 15.9 months, with little difference in median survival between the ‘low’ and ‘high’ dose groups (14.4 versus 16.9 months, respectively) [39]. The Johns Hopkins group also treated 29 patients with split-course loco-regional EBRT and concurrent 5-FU, folinic acid, dipyrindamole and MMC [150]. The EBRT consisted of split-course 50 Gy over 20 fractions with a 2-week planned rest after the first 10 fractions (25 Gy). Every 4 weeks the patients received bolus 5-FU (400 mg/m²) and folinic acid (20 mg/m²) on days 1–3, dipyrindamole (75 mg p.o., four times/day) on days 0–3 and every 8 weeks and MMC (10 mg/m²; maximum of 20 mg) on day 1 during EBRT. This was followed by four cycles of the same chemotherapy as adjuvant therapy 1 month following the completion of EBRT. The median survival was 16 months and the 1-year survival was 58% [150]. Altogether between 1984 and 1999 the Johns Hopkins team treated 333 patients selected from a consecutive series of 616 patients who had had resection for PDAC with adjuvant CRT and maintenance chemotherapy [42]. Even given the biased treatment sample the median survival was 19 months, the 1-year survival was 71% and the 5-year survival was 20% [42].

The UKPACA-1 trial [48] utilised the same adjuvant regimen used in the GITSG trial, in 34 patients with PDAC and six with ampullary carcinoma. The median survival rate for patients with PDAC was 13.2 months and the 5-year survival was 15%. Survival in patients with clear lymph nodes was 60% at 2 years compared with 18% in those with positive lymph nodes at the time of resection. There were no treatment-related deaths and no hospitalisations due to this regimen, even with a prolonged course of postoperative chemotherapy that laid the basis of the ESPAC trials in Europe. In the ESPAC-1 trial the beneficial effect of chemotherapy was reduced when taking into account whether patients also received CRT ($P = 0.0005$ versus $P = 0.001$), demonstrating that CRT may have reduced the overall benefit of chemotherapy. This may be due in part to the delay in administering chemotherapy in those patients undergoing both treatments or other factors to be identified.

The RTOG adjuvant phase III study 97-04 [154] has just been closed with over 500 patients recruited. The trial design is a 3-week course of chemotherapy, then CRT and then a final 3-month course of chemotherapy. Patients were randomly allocated to one of two adjuvant pre-CRT chemotherapy regimens (continuous infusion 5-FU at 250 mg/m²/day for 3 weeks versus gemcitabine 1000 mg/m²/day, once for 3 weeks) and parallel post-CRT chemotherapy (two 4-week cycles of continuous infusion 5-FU at 250 mg/m²/day for 3 weeks each followed by a 2-week rest for 3 months versus three cycles of gemcitabine 1000 mg/m² day, once weekly followed by a 1-week rest for 3 weeks also for 3 months). Both groups received identical CRT starting 1–2 weeks after completion of pre-CRT chemotherapy and then no later than 13 weeks after resection [50.4 Gy/5.5 weeks at 1.8 Gy/fraction (field reduction at 45 Gy) and continuous infusion 5-FU, 250 mg/m²/day during EBRT] [154]. The survival results from this trial will be of enormous importance for comparing survival achieved with other large adjuvant therapy trials.

Neo-adjuvant therapy

Proponents of neo-adjuvant therapy for pancreatic cancer point out that a significant proportion of patients are not considered for adjuvant treatment because of postoperative complications [47, 155]. The incidence of postoperative complications following major pancreatic resections remains in the region of 30–45% despite the dramatic reduction in postoperative mortality [42, 156]. Neo-adjuvant therapy may also be given in the hope of being able to downstage locally advanced tumours and achieve an enhanced resection rate [47, 155].

There have been no large randomised controlled studies on the use of neo-adjuvant therapy in pancreatic cancer (Table 6) [46, 47, 157–164]. The total number of patients who have actually had resection following neo-adjuvant therapy is rather small. The series shown in Table 6 includes patients that have been counted ‘twice’ as the initial series are expanded, such as that from the MD Anderson group [47, 158, 160]. The quoted resection rates vary considerably, from 45% to 100% in patients with tumours initially deemed ‘resectable’ and from 20% to 64% in those with ‘unresectable’ tumours [155]. The median survival rates in general range from 16 to 21 months, which is comparable with both adjuvant systemic chemotherapy and regional chemotherapy.

Specific comment is necessary on two studies with exceptional median survival rates of 31 and 32 months, respectively [46, 162]. Snady et al. [46] reported a median survival of 32 months in 20 patients (29%) who had resection from an original group 68 patients treated firstly with simultaneous split-course EBRT plus 5-FU, streptozotocin and cisplatin (RT-FSP; 0% mortality rate <30 days). The median survival of the whole group was 23.6 months, and 32 months in the 20 patients who also had resection. During the same period another group of 91 patients initially underwent resection (5% mortality rate <30 days), of whom 63 (69%) received adjuvant chemotherapy with or without EBRT. The median survival in this latter group was 14.0 months ($P = 0.006$ compared with the RT-FSP group). The median survival in patients who had resection and adjuvant treatment was 16 months

Table 6. Neo-adjuvant therapy for pancreatic ductal adenocarcinoma

Series	Period	No. of cases	Neo-adjuvant regimen	Pre-treatment assessment of resectability	Number resected (%)	Median survival (months)	Actuarial survival (%)		
							3 years	4 years	5 years
Ishikawa et al. [158]	1994	23	EBRT	Both	17 (74)				22
Coia et al. [159]	1994	27	EBRT + 5-FU/MMC	Both	13 (48)	16	43		
Staley et al. [160]	1996	39	EBRT + IORT + 5-FU	Resectable	39 (100)	19		19	
Spitz et al. [161]	1997	91	EBRT + 5-FU	Resectable	41 (51)	19.2			
Hoffman et al. [162]	1998	53	EBRT + 5-FU/MMC	Resectable	24 (45)	15.7			
White et al. [163]	1999	25	EBRT + 5-FU/MMC/Cis	Unresectable	5 (20)				
Wanebo et al. [164]	2000	14	EBRT + 5-FU/Cis	Unresectable	9 (64)				
Snady et al. [46]	2000	68	EBRT + 5-FU/Cis/Strep	Unresectable	20 (29)	32	32		
					48 not resected	21	13		
					(91) ^a (± adjuvant chemotherapy ± EBRT)	Resectable	(63 with adjuvant treatment) (28 no adjuvant treatment)	16	13
Mehta et al. [165]	2001	15	EBRT + 5-FU	Unresectable	9 (60)	30			
Breslin et al. [47]	2001	(132)	EBRT + 5-FU/Pac/Gem	Resectable	not applicable	21			

^aAll of these patients had resection and none had neo-adjuvant treatment, but some had adjuvant treatment.

Cis, cisplatin; EBRT, external-beam radiotherapy; 5-FU, 5-fluorouracil; Gem, gemcitabine; IORT, intra-operative radiotherapy; MMC, mitomycin C; Pac, paclitaxel; Strep, streptozocin; empty cells, data not available.

compared with 11 months in those who did not have adjuvant therapy after resection ($P = 0.025$). In contrast, The MD Anderson group in their (non-randomised) studies [47, 158, 160] have not shown a significant difference in survival between those patients who have received neo-adjuvant compared with adjuvant treatment. Mehta et al. [162] have recently reported a median survival of 30 months with neo-adjuvant treatment but only in nine selected patients.

All of the aforementioned studies suffer to a lesser or greater extent from a number of confounding factors. A specialist pancreatic cancer surgery team can often resect what is considered by another team to be 'unresectable locally advanced disease'. For example, the Johns Hopkins group was able to carry out resections on 52 of 78 patients (67%) operated upon elsewhere and thought to have had irresectable diseases [112]. Patients with intra-pancreatic bile duct cancers and/or ampullary cancers, which have much better survival figures than PDAC, are not always excluded from neo-adjuvant series. Indeed the distinction between intra-pancreatic bile duct adenocarcinoma and PDAC cannot be made except on the resected specimen. A tumour in the head of the pancreas is almost invariably affected by EBRT to the extent that often the tissue of origin of the adenocarcinoma cannot be determined. Following neo-adjuvant therapy the tumour undergoes re-staging (usually several months after the initial diagnosis) and patients who have developed interval metastases are excluded. Thus the group of patients who eventually go

on to resection are a biased population with a better prognosis than the group as a whole. Finally, subgroup analysis of selected patients from single institutions is subject to significant statistical error, especially with the small numbers quoted. Thus in the absence of randomised studies the role of neo-adjuvant treatment for pancreatic cancer can only be regarded as experimental.

Discussion

The relative lack of high-quality randomised trials in the treatment of pancreatic cancer is alarming, but this is beginning to change. There is little evidence to support the use of IORT either alone or in combination. In the absence of controlled trials the roles of regional chemotherapy and neo-adjuvant treatment are not yet defined, but perhaps they have a place in selected cases. The best evidence so far suggests that adjuvant chemotherapy is probably of benefit after resection of pancreatic cancer. The current standard treatment regimen is 5-FU/folinic acid, but this may be superseded or added to by gemcitabine, pending the results of currently ongoing clinical trials such as ESPAC-3. There is evidence from the ESPAC-1 trial that EBRT given before maintenance chemotherapy may even have a detrimental effect on the response to chemotherapy.

The three largest randomised controlled trials of adjuvant treatment of pancreatic cancer are consistent with each other [34, 35, 43–46] and swamp the previous very small GITSG trial [32, 33].

Despite this there is still a healthy criticism of the ESPAC-1 trial and continued support for adjuvant CRT [166]. The retrospective [22, 42] and small prospective studies [39, 152] from Johns Hopkins (amongst others) are mentioned [166] as support for continuing the use of adjuvant CRT. Despite the selection bias, the median survival of patients with pancreatic cancer treated at the Johns Hopkins [22, 39, 42, 152] with a combination of CRT and maintenance chemotherapy was no better than that of patients randomly assigned to chemotherapy in the ESPAC-1 study [43–46] (19.0 versus 19.7 months, respectively). It is argued [164] that neither of the two European trials of adjuvant CRT [35, 43–46] used sufficient radiation, yet this dose was identical to that given in the GITSG study [32, 33]. Since the ESPAC-1 trial was initiated, conformal beam radiotherapy, which enables more radiation to be delivered to targeted areas in the abdomen, has been introduced [39]. Even so the median survival rates using conformal EBRT with more intensive radiation and chemotherapy regimens have for example produced median survival rates of only 14.4, 16.0 and 16.9 months [39, 152]. The survival rates from these intensive combination regimens are consistent with a median survival of 15.5 months in the 175 patients treated with split-course CRT in the ESPAC-1 trial [43–46] and 17.1 months in the 60 patients treated in the same way in the EORTC trial [35]. Indeed a remarkably good survival rate was achieved in the control arm of the ESPAC-1 trial [43–46], with a median of 16.1 months in the 178 patients not given CRT. The survival results of combination regimens using other approaches including IORT (Table 4) and neo-adjuvant CRT (Table 6) are also comparable to the survival achieved by the chemotherapy arm of ESPAC-1 [43–46]. Adjuvant and neo-adjuvant CRT exposes the patient to an extra burden of treatment and related toxicity and their use can only be justified if survival is shown to be prolonged. This is of great importance given the limited life expectancy of patients with pancreatic cancer undergoing resection.

Many other approaches and agents are at differing stages of development, but some of these are almost certain to find a place in the adjuvant setting in due course [62, 63, 167, 168]. Participation in major trials, however, is a necessary prerequisite for such progress. Whilst the proliferation of phase I and phase II studies is most welcome, clinical practice should be developed around the consolidated results of phase III studies. With this in mind we can conclude that there is now considerable scope for optimism in the treatment of pancreatic cancer.

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