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Adjuvant Therapy in Pancreatic Cancer

A Critical Appraisal

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Abstract

Adenocarcinoma of the pancreas carries a grim prognosis. Surgery is currently the only curative option, but even the few patients undergoing complete resection of early localised disease run a high risk for relapse and death. Although numerous clinical trials have been conducted during the past 20 years to find an effective adjuvant treatment, thus far no general consensus on the most appropriate regimen has been reached. In a small randomised study performed in the 1980s by the GITSG (Gastrointestinal Tumor Study Group), encouraging results were obtained with fluorouracil (5-FU)-based split-course chemoradiotherapy, but these findings were not confirmed in a randomised study initiated some years later by the EORTC (European Organisation for Research and Treatment of Cancer). More recently, the ESPAC (European Study Group for Pancreatic Cancer)-1 trial even indicated a detrimental effect of chemoradiotherapy, while chemotherapy with 5-FU was shown to have a significant positive impact on long-term survival. However, this latter finding is in contrast to earlier studies of adjuvant chemotherapy with 5-FU combinations from Norway and Japan that did not suggest a prolonged beneficial effect of 5-FU on survival. Thus, the results for adjuvant regimens based on systemic 5-FU with or without external radiotherapy are conflicting. Clinical experience with intraoperative radiotherapy or regionally targeted chemotherapy to prevent local relapse, though encouraging, is still preliminary. More recently, gemcitabine, which is the most effective single agent in advanced pancreatic cancer, has also been evaluated in the adjuvant setting. The RTOG (Radiation Therapy Oncology Group)-9704 trial demonstrated that gemcitabine is superior to 5-FU as an addition to chemoradiotherapy, but the results did not allow conclusions about the value of radiation in the combined modality approach. The Charité Onkologie CONKO-001 is a randomised trial from Germany and Austria that compared adjuvant gemcitabine with observation alone. Gemcitabine was very well tolerated and almost doubled median disease-free survival and overall survival rate at 5 years, although the advantage in overall survival failed to reach statistical significance. In summary, the available data from randomised clinical trials of adjuvant therapy suggest that (i) chemoradiotherapy has no obvious advantage compared with chemotherapy alone; and (ii)

chemotherapy with gemcitabine is effective and probably offers the best benefit-risk ratio of all currently available adjuvant treatment options.

Adenocarcinoma of the pancreas is an extremely aggressive tumour with a high potential for early dissemination, and a relatively poor sensitivity to radiation therapy and cytotoxic agents. Prognosis remains dismal for patients with locally advanced or metastatic disease, although modern gemcitabine-based chemotherapy has been shown to provide significant palliative benefit and to prolong survival by several months. Complete resection of the tumour is currently the only curative option, but only a minority of patients present with localised, potentially resectable disease at the time of diagnosis. Moreover, even after pathologically complete (R0) resection, most patients eventually relapse and die of their disease.[1,2] Therefore, it is widely acknowledged that effective adjuvant therapy is needed for patients with resected pancreatic cancer. Unfortunately, despite several randomised and numerous nonrandomised adjuvant trials and two recent meta-analyses, no broad consensus on the optimal adjuvant regimen has yet been reached.

Thus, chemoradiation with fluorouracil (5-FU) is still widely used and a recommended adjuvant treatment option in the US,[3] based on the results of a small randomised study of the GITSG (Gastrointestinal Tumor Study Group)[4] and a subsequent non-randomised confirmatory study.[5] In contrast, administering radiation in addition to chemotherapy is often considered unnecessary in European centres. The apparent lack of consensus is due to the inconsistency of the available data. This appears to result partly from small sample sizes and partly from significant methodological deficiencies of the trials, making interpretation open to debate. In particular, the recently published ESPAC (European Study Group for Pancreatic Cancer)-1 trial, which has profoundly influenced the results of the meta-analyses as a result of its relatively large patient number, has been a subject of heavy criticism. In this review, we critically discuss the results of the most important clinical trials of adjuvant treatment in patients with resected pancreatic cancer, with particular emphasis on the most recent large-scale randomised trials ESPAC-1, RTOG (Radiation Therapy Oncology Group)-9704 and the German Charité Onkologie CONKO-001. Neoadjuvant (preoperative) treatment is not discussed in this review.

1. Early Randomised Trials of Adjuvant Chemo(Radio)Therapy

1.1 Gastrointestinal Tumor Study Group Trials

External beam radiotherapy (EBRT) alone or in combination with systemic chemotherapy was first used in the late 1960s and early 1970s to treat patients with locally advanced, inoperable pancreatic cancer.[6,7] The anti-tumour effect observed in these studies prompted the GITSG to initiate a prospective randomised trial of adjuvant chemoradiotherapy in patients with resected localised pancreatic cancer.[4] Over a period of 8 years, 43 evaluable patients were recruited and randomised to no adjuvant treatment (22 patients) or adjuvant 5-FU-based chemoradiotherapy (21 patients). All patients were required to have histologically tumour-free resection margins, and six patients in each group (28%) had nodal involvement. Radiation was given in five daily fractions per week in two 2-week courses separated by 2 weeks, to a total dose of 40Gy. Intravenous bolus doses of 5-FU 500 mg/m^2 were added on the first 3 days of each radiotherapy course and on a once-weekly basis thereafter for 2 years or until disease recurrence.

Initial performance status and extent of tumour were found to be independently and significantly related to survival. A survival analysis adjusted for these variables showed that median survival was significantly longer in the adjuvant treatment group compared with the control group (20 vs 11 months; $p = 0.03$ by a one-sided log-rank test). Although the authors specified a minimum goal of 100 patients (50 patients per arm) to provide 90% power to detect

a doubling of survival time,[4] the study was stopped prematurely as a result of the extremely slow recruitment and an increasing difference in survival between the arms. Methodological limitations of this study, in addition to the small patient number that does not allow any reliable conclusions to be drawn, included inadequate quality assurance of radiation therapy, which is a problem that might have been aggravated by the long period of accrual, and poor compliance with protocol-specified maintenance chemotherapy. Moreover, patients with positive resection margins (R1), a group with a less favourable prognosis, were excluded from the trial.

In an effort to replicate the findings of the first small trial, the GITSG treated 30 additional patients with the same chemoradiotherapy protocol in a prospective nonrandomised extension study.[5] More patients in this extension study had an ECOG performance status of 0 or 1 as compared with either arm of the randomised study, suggesting limited comparability of the study populations. Median overall survival was 18 months and 2-year actuarial survival was 43% (a different figure of 46% was reported in the abstract). This publication and a later contribution in a book[8] also delivered updated survival data for the randomised GITSG study, with median survival times of 21 versus 10.9 months, 2-year survival rates of 43% versus 18%, and 5-year survival rates of 19% versus 5%, respectively, for patients in the chemoradiotherapy versus control arm (table I).

1.2 European Organisation for Research and Treatment of Cancer Trial

The phase III EORTC (European Organisation for Research and Treatment of Cancer) trial failed to demonstrate a significant beneficial effect of adjuvant 5-FU-based chemoradiation.[9] Of 207 eligible patients with resected pancreatic head or periampullary cancer, 103 were randomised to observation and 104 to a split-course chemoradiotherapy regimen similar to that used in the GITSG study. The patients received 40Gy in 20 daily fractions of 2Gy (5 days a week for 2 weeks, followed by another 2-week course 14 days later). In contrast to the GITSG regimen, however, 5-FU was delivered concomitantly with radiation by continuous infusion at a constant rate of 25 mg/kg per 24 hours and a maximum daily dose of 1500mg. Moreover, quality assurance measures for radiotherapy were employed. No maintenance chemotherapy was given. Baseline characteristics of eligible patients in the two study arms were comparable. For patients with pancreatic head cancer (n = 54 in the observation arm and n = 60 in the treatment arm), survival was not significantly different between the groups ($p = 0.099$, using a two-sided log-rank test). Median survival was 12.6 months with observation versus 17.1 months with adjuvant chemoradiotherapy, and survival estimates at 2 and 5 years were 23% versus 37%, and 10% versus 20%, respectively (table I).

The authors concluded from these results that the chemoradiation regimen used in the study could not be recommended as adjuvant standard treatment in resected pancreatic cancer. However, based on its calculated sample size, the EORTC trial was clearly underpowered to show a difference in 2-year survival of <15%. The statistical analysis performed in the EORTC trial was recently criticised by the authors of the RTOG study.[15] They argued that a one-sided rather than a two-sided log-rank test should have been used in the EORTC trial to compare survival because the previous GITSG findings had clearly favoured chemoradiotherapy. Reanalysis of the EORTC data by the RTOG authors using the one-sided test resulted in a p-value of 0.049, which they concluded would support the role of adjuvant chemoradiotherapy. In his reply to this letter, a co-author of the EORTC trial rejected the statistical critique.[16] Interestingly, he announced the publication of updated results of the trial after 10 years of follow-up, again demonstrating no benefit of chemoradiation. Nevertheless, it should be remembered that the shortcoming of inadequate statistical power remains valid even after prolonged follow-up. A potential benefit of chemoradiation therefore cannot be definitely excluded on the basis of the EORTC trial results.

Table I. Randomised trials of adjuvant chemotherapy and/or chemoradiotherapy in resected pancreatic cancer

Study	Treatment	No. of eligible patients	R0 (%)	Median DFS (mo)	Overall survival median (mo)	2y (%)	3y (%)	5y (%)	p-value	Comments
GITSG,[5] Kalser and	CRT: split-course RT (2 × 20Gy) + bolus 5-FU→maintenance 5-FU	21	100	11 (p = 0.04)	21	43	–	19[a]	0.03[b]	Regional involvement and poor performance status
Ellenberg,[4] Douglass and Stablein[8]	Observation	22		9	10.9	18	–	5[a]		(ECOG 2/3) predicted poor survival
GITSG,[5] Douglass and Stablein[8]	CRT: split-course RT (2 × 20Gy) + bolus 5-FU→maintenance 5-FU	30	100	–	18	43/46[c]	–	17[b]	–	Non-randomised extension study
EORTC, Klinkenbijl et al.[9]	CRT: split-course RT (2 × 20Gy) + CI 5-FU	104	81	All: 17.4 (37[d])	All: 24.5 PH: 17.1	All: 5 PH: 37	–	All: 28 PH: 20	All: 0.208 PH: 0.099	The group included 60 patients with PH and 44 patients with periampullary cancer
	Observation	103	75	All: 16 (38[d])	19.0 PH: 12.6	41 PH: 23	–	22 PH: 10		The group included 54 patients with PH and 49 patients with periampullary cancer
Bakkevold et al.,[10] Norway	CT: doxorubicin + mitomycin + 5-FU (AMF) q3w × 6 cycles	30	100	–	23 (p = 0.02[e])	43 (p = 0.04[f])	27	4 (p = 0.10[g])		Each group included seven patients with cancer of the
	Observation	31	100	–	11	32	30	8		papilla of Vater
Takada et al.,[11] Japan	CT: mitomycin day 0 + 5-FU weeks 1+3→maintenance 5-FU	81	56	–	≈12[h]	–	–	11.5	NS	48% of MF patients and 40% of controls had stage
	Observation	77	61	–	≈12[h]	–	–	18		IV disease
ESPAC-1, Neoptolemos et al.[12]	*Four groups randomised according to a 2 × 2 factorial design*									Statistical power was insufficient to compare these
	CRT: split-course RT (2 × 20Gy) + bolus 5-FU (Mayo Clinic schedule)	73	82[i]	–	13.9	–	–	7		four groupsdirectly
	CT: 5-FU (Mayo Clinic schedule)	75		–	21.6	–	–	29		
	CRT→CT (CRT as above followed by 5-FU (Mayo Clinic schedule)	72		–	19.9	–	–	13		
	Observation	69		–	16.9	–	–	11		
	Combined groups to compare CRT vs no CRT and CT vs no CT									
	CRT (CRT or CRT→CT)	145	81	10.7 (p = 0.04)	15.9	29	–	10	0.05	1-year relapse-free survival was 46% with CRT vs 55%

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Table I. Contd

Study	Treatment	No. of eligible patients	R0 (%)	Median DFS (mo)	Overall survival median (mo)	2y (%)	3y (%)	5y (%)	p-value	Comments
	No CRT (CT or observation)	144	84	15.2	17.9	41	–	20		with no CRT
	CT (CT or CRT→CT)	147	81	15.3 (p = 0.02)	20.1	40	–	21	0.009	1-year relapse-free survival was 58% with CT vs 43%
	No CT (CRT or observation)	142	84	9.4	15.5	30	–	8		with no CT
RTOG 9704, Regine et al.[13]	CRT + 5-FU (CI 5-FU for 3 weeks→continuous 5-FU-based CRT over 5½ weeks [50.4Gy]→CI 5-FU for 3 months	194[j]	44[k]	10.1 (p = 0.10)	16.9	–	21	–	0.033	Patient numbers and survival data refer to the subgroup of patients with PH tumours. The difference
	CRT + Gem (Gem for 3 weeks →continuous 5-FU-based CRT as above→Gem for 3 months)	187[j]	39[k]	11.4	20.6	–	32	–		in overall survival between groups was not significant (p = 0.15) if 61 patients with pancreatic tumours of body or tail were included
CONKO-001, Oettle et al.[14]	CT: Gem for 24 weeks	179	81	13.4 (p < 0.001)	22.1	47.5	34	22.5	0.061	The difference in overall survival also approached
	Observation	175	85	6.9	20.2	42	20.5	11.5		significance in the subgroup of patients with R1 resection (p = 0.068)

a 10-year survival in the randomised GITSG study was 19% in the treatment group and 0% in the control group.

b One-sided log-rank test, adjusted for disease extent and performance status.

c Different survival figures were reported in the abstract (46%) and the body (43%) of the publication.

d Percentage progression-free at 2 years.

e Median test.

f Generalised Wilcoxon test for survival during the initial 2 years.

g Generalised Wilcoxon test for survival beyond 2 years.

h Estimated from the survival curves.

i For all subgroups combined.

j Refers to the subgroup of patients with tumours of the head of the pancreas only; the total number of patients including those with tumours of the pancreatic body and tail was 221 in each group.

k Refers to the total population of 221 patients in each arm; surgical margins were unknown for a further 23% (5-FU group) and 26% (Gem group) of patients.

5-FU = fluorouracil; **AMF =** doxorubicin, mitomycin, 5-FU; **CI =** continuous infusion; **CRT** = chemoradiotherapy; **CT** = adjuvant chemotherapy; **DFS** = disease-free survival, **EORTC** = European Organisation for Research and Treatment of Cancer**; ESPAC** = European Study Group for Pancreatic Cancer; **Gem** = gemcitabine; **GITSG** = Gastrointestinal Tumor Study Group; **MF** = mitomycin, 5-FU; **NS** = not significant; **PH** = pancreatic head; **RT** = radiotherapy; **R0** = histologically complete surgical resection; **R1** = positive resection margin after surgery; → indicates sequential therapy; **–** indicates data not available.

1.3 Norwegian Trial

Another randomised controlled trial was performed in the early 1990s by a group from Norway.[10] This study compared adjuvant combination chemotherapy with observation in 61 resected patients with either adenocarcinoma of the pancreas (47 patients) or the papilla of Vater (14 patients). The accrual goal of 86 patients was not achieved, thus reducing the statistical power of the study from 90% to 83%. All patients had histologically confirmed radical resection (R0). Adjuvant chemotherapy consisted of six cycles of a moderate-dose FAM regimen (AMF) consisting of doxorubicin 40 mg/m^2, mitomycin (mitomycin C) 6 mg/m^2 and 5-FU 500 mg/m^2 given every 3 weeks. Unfortunately, the results were not specified by diagnosis. In the entire patient population, median survival was significantly improved (23 vs 11 months; p = 0.02 using the median test), as was survival at 2 years (43% vs 32%; p = 0.04). However, long-term survival at 5 years was not significantly different (4% in the AMF groups vs 8% in the control group) [table I]. Toxicity of the AMF regimen was substantial and compliance with therapy poor. Only 24 of the 30 patients randomised to AMF actually received that chemotherapy, and only 13 patients completed all six cycles.

1.4 Japanese Trial

The results of a Japanese randomised controlled trial also could not substantiate the long-term efficacy of postoperative 5-FU-based chemotherapy.[11] This study randomised a total of 508 patients with resected carcinoma of the pancreas, bile duct, gall bladder or papilla of Vater to either adjuvant chemotherapy with mitomycin and 5-FU (MF) or no postoperative treatment. In the adjuvant group, mitomycin 6 mg/m^2 was given by intravenous bolus on the day of surgery and 5-FU was administered at 310 mg/m^2/day by slow intravenous infusion for 5 days in postoperative weeks 1 and 3, followed by maintenance therapy with daily oral 5-FU doses of 100 mg/m^2 until relapse. The pancreatic cancer subgroup included 158 eligible patients, of whom 70 (48% of MF recipients and 40% of controls) had advanced disease (stage IV). Thus, potentially curative resection was possible in only 92 patients (56% of MF recipients and 61% of controls). Five-year survival was not significantly different between the groups for all patients with resected pancreatic cancer (11.5% and 18.0% in the MF and control groups, respectively), nor for those with curative resection (17.8% vs 26.6%) [table I]. Although it could be argued that oral administration of 5-FU does not provide reliable therapeutic plasma concentrations and thus chemotherapy was suboptimal, this cannot explain why patients with gall bladder cancer treated in the same study derived a significant survival benefit from adjuvant MF.

2. Nonrandomised Trials of Adjuvant Chemo(Radio)Therapy

Nonrandomised studies have added little important information to the scientific dispute regarding the optimal adjuvant regimen. The largest nonrandomised prospective study was conducted between 1991 and 1995 at the Johns Hopkins Hospital in Baltimore, Maryland, USA, and included 173 consecutive patients with resected adenocarcinoma of the pancreas.[17] The patients were offered one of three therapeutic options: 99 patients chose a chemoradiotherapy protocol similar to that used in the GITSG trials, 21 patients received intensified chemoradiotherapy with a higher radiation dose (≥50Gy) and concomitant and subsequent infusional 5-FU plus folinic acid (leucovorin), and 53 patients refused any adjuvant therapy. Whereas the intensified regimen did not result in a survival advantage compared with the 'standard' regimen, both adjuvant groups combined had a significantly longer median survival compared with the no-adjuvant therapy group (19 vs 13.5 months; p = 0.003). Chemoradiation was particularly beneficial to patients with positive resection margins (18.0 vs 5.0 months; p = 0.060).

The results of this study were generally interpreted as supporting the GITSG findings. However, as might be anticipated from an allocation system based on the personal decision of the patients, the three groups were not comparable: the patients de-

clining adjuvant therapy were significantly older, had a significantly longer postoperative hospital stay and a significantly higher incidence of postoperative complications. These factors were found to be not predictive of poor survival in a univariate analysis performed both in this study and in another review of 650 consecutive patients undergoing pancreaticoduodenectomy at Johns Hopkins Hospital.[18] Remarkably, this finding is in contrast to clinical experience.

Several other nonrandomised trials of adjuvant therapy have been reported.[2,19-25] However, most of them included <50 patients, and there was a wide variation in study design, inclusion criteria, extent of resection and treatment protocols. This inconsistency makes it virtually impossible to compare the outcome data obtained in these studies with those of patient series of pancreaticoduodenectomy without adjuvant therapy or the treatment arms of randomised trials. The results of the prospective patient series reported by Picozzi et al.[25] are particularly interesting because of the exceptional survival achieved with interferon-based adjuvant chemoradiotherapy. Over a long recruitment period of 7 years, 43 patients with adenocarcinoma of the pancreatic head were entered on the study. Thirty-one (72%) were stage III and six (14%) were stage IVa. All patients underwent pancreaticoduodenectomy, with gross or microscopically positive surgical margins in eight patients (19%). Adjuvant treatment consisted of radiotherapy (25 fractions over 5 weeks) with concomitant continuous infusion 5-FU, weekly bolus cisplatin and daily subcutaneous interferon-α, followed by maintenance continuous infusion 5-FU on weeks 9–14 and 17–22. Toxicity of this regimen was substantial (mainly anorexia, nausea/vomiting, mucositis, diarrhoea and dehydration), and hospitalisation was required in as many as 18 of 43 patients. The estimated 5-year disease-free survival (DFS) and overall survival rates of 52% and 55%, respectively, appear remarkable, even though the 5-year overall survival was corrected to 45% in an updated analysis.[26]

Mehta et al.[21] reported a study of adjuvant fractionated radiotherapy (45–54Gy) with concomitant 5-FU by protracted venous infusion (200–250 mg/m^2/day) that was administered to 52 patients, of whom 35% had positive surgical margins and 59% had involved lymph nodes. Median actuarial survival was 32 months, and survival at 2 and 3 years was 62% and 39%, respectively. Reni et al.[22] enrolled 51 patients with resected pancreatic adenocarcinoma, including 25% with stage IVa and 51% with R1 or R2, to a feasibility study of adjuvant combination chemotherapy followed by radiotherapy with or without concomitant chemotherapy. Initial chemotherapy consisted of cisplatin and epirubicin at doses of 40 mg/m^2 on day 1, gemcitabine 600 mg/m^2 on days 1 and 8, and 5-FU at daily doses of 200 mg/m^2 by continuous infusion for the duration of chemotherapy. This regimen was repeated every 4 weeks for a maximum of four cycles. Toxicity was acceptable. Median DFS and overall survival were 14 and 27 months, and actuarial 2-year and 5-year overall survival were 53% and 22%, respectively.

3. Intraoperative Radiotherapy

The rationale behind intraoperative radiotherapy (IORT) is to promote local control by delivering high-radiation doses to the sites where locoregional recurrence is likely to occur, with simultaneous minimisation of radiation exposure to radiosensitive normal tissues that may be displaced or shielded during the procedure. The technical and clinical feasibility of IORT in combination with pancreatic resection was first demonstrated at the US National Cancer Institute in 1983[27] and, since then, the safety of this procedure has been confirmed in numerous reports. However, the potential benefit of IORT with regard to overall survival in patients undergoing potentially curative resection still remains elusive given the heterogeneity of the reported patient series and the limited number of comparative, mostly retrospective studies. Moreover, eligibility criteria, radiation doses and additional adjuvant therapies used in the comparative studies varied greatly and only a few of these studies included ≥20 patients in the IORT group.[28-36]

A prospective randomised study conducted at the National Cancer Institute included 24 patients with

resected locally advanced adenocarcinoma of the pancreas.[37] The patients were randomised to receive IORT (20Gy to the resection bed) or standard treatment, defined as resection alone in patients with localised disease and additional EBRT (45–55Gy) in those with extrapancreatic extension or nodal disease. Local recurrence occurred in all 12 control patients but only in 4 of 12 patients receiving IORT. Median survival was 18 months in the IORT group compared with 12 months in the control group.

The retrospective studies reported from Milan, Italy,[29-31,36] were obviously updated assessments of the same database of patients treated at San Raffaele Hospital since 1985. The most recent of the Milan studies by Reni et al.[36] compared the outcome of 127 patients with adenocarcinoma of the pancreas undergoing curative-intent resection plus IORT with 76 patients treated in the same period of time with surgery alone. Forty-nine patients (30 with and 19 without IORT) had locally limited disease (stage I or II) and 154 patients (97 with and 57 without IORT) had stage III or IV disease. Nearly one-third of the patients received additional EBRT and 40% also received postoperative chemotherapy with various, mostly 5-FU-based, regimens. IORT (total dose 10–25Gy, median 17.5Gy) was delivered with a linear accelerator to the tumour bed including the celiac axis, the superior mesenteric artery and the edge of the pancreatic stump. IORT did not increase perioperative mortality and morbidity or the incidence of late complications. Among patients with stage I or II disease, IORT significantly reduced the rate of local failure from 60% to 27% and the rate of distant failure from 60% to 42%. Moreover, IORT resulted in significantly prolonged median time to treatment failure (TTF) [≥17.5 vs 12 months] and overall survival (median, ≥18.5 vs 13 months, 5-year survival 22% vs 6%). In a multivariate analysis, the beneficial effect of IORT was independent of age, tumour grade, tumour size, resection margins, adjuvant chemotherapy and use of EBRT. In contrast, IORT did not provide significant advantages in TTF (median, 9 vs 8.5 months) and overall survival (median, 14.5 vs 12 months, 5-year survival 3% vs 5%) among patients with stage III or IV disease.

A retrospective study from Rome, Italy,[35] identified 46 patients with localised pancreatic cancer who underwent resection between 1985 and 1995 in a university hospital setting. Twenty-six of these patients received IORT using a linear accelerator (10Gy with a 6-MeV beam delivered to the tumour bed and the adjacent areas at risk of harbouring tumour cells) and additional postoperative EBRT in daily fractions of 1.8Gy on 5 days per week for a total dose of 50.4Gy. Again, IORT was not associated with increased morbidity or mortality. Although intra- and postoperative radiotherapy decreased the rate of local recurrence from 30% with surgery alone to 11.5%, this translated only in a moderate survival advantage (median, 14.3 vs 10.8 months, 5-year survival 15.7% vs 5.5%; $p = 0.06$).

Three retrospective comparative surveys were reported from groups in Japan. Hosotani et al.[32] compared 86 resected patients who received EBRT (n = 37), IORT (n = 14) or both (n = 31) with 64 patients undergoing potentially curative resection alone at Kyoto University. Median survival in the combined radiotherapy group was significantly better than in the surgery-alone group (12.8 vs 7.9 months). In a more recent report from Kyoto University, Kokubo et al.[34] presented results for a total of 138 patients; 34 (25%) of these patients had also received regional chemotherapy. The median radiation dose was 25Gy for IORT and 50.4Gy for EBRT. Among patients with R0 resection, median and 2-year disease-specific survival was 11 months and 16%, respectively, for the 39 patients treated with surgery alone compared with 15 months and 25%, respectively, for the 34 patients treated with surgery plus IORT, and 17 months for the 18 patients treated with surgery and both IORT and EBRT. The survival differences were not significant. Sunamura et al.[33] also found no survival benefit of IORT among 20 patients with resected adenocarcinoma of the pancreatic head compared with 24 patients who underwent pancreatectomy without IORT (median survival, 14.8 vs 16.4 months, 3-year survival 18.2% vs 21.2%). Median survival was 10.5 months among 13 patients with

resected carcinoma of the pancreatic body and tail who received IORT.

Taken together, it would appear that IORT enhances local tumour control compared with surgery alone with or without adjuvant EBRT, and may result in a moderate survival benefit. It is conceivable that the survival advantage conferred by IORT may become more apparent with effective systemic adjuvant chemotherapy, but to date IORT must still be considered an experimental treatment that is limited to specialised centres.

4. Regionally Targeted Adjuvant Therapy

Postoperative regional chemotherapy in resected pancreatic cancer aims at maximising drug exposure to the tissues that are the main sites of recurrent disease, i.e. liver and pancreatic bed. Moreover, regional chemotherapy has the advantage of minimal systemic toxicity. In the prospective randomised trial reported by Lygidakis et al.,[38] therapy was administered via an arterial catheter inserted in the superior mesenteric artery. This trial was also interesting because one of two adjuvant regimens evaluated in the trial included immunotherapy with interleukin (IL)-2. Of 128 consecutive eligible patients with resected stage III pancreatic duct carcinoma, 40 were randomised to receive no adjuvant therapy, 45 patients were allocated to a 5-day course of regional combination chemotherapy with carboplatin, mitoxantrone, mitomycin and 5-FU plus folinic acid, and 43 patients were treated with the same chemotherapy regimens and an additional 10-day course of regional immunotherapy with IL-2. Chemo(immuno)therapy was repeated every 2 months in the first year, every 4 months in the second and third year, and every 6 months in the fourth and fifth year. Of note, toxicity of regional chemotherapy was minimal, and the adverse effects of IL-2 were restricted to fever and chills. Mean survival duration was 18.8 months and survival rates at 2 and 4 years were 29% and 0% in the control group without adjuvant therapy. Corresponding outcome figures were 25.0 months, 53% and 16% in the chemotherapy group, and 31.0 months, 65% and 28% in the chemoimmunotherapy group. Survival was significantly better in both adjuvant groups compared with the control group, and also significantly better with chemoimmunotherapy compared with chemotherapy alone.

Recently, Cantore et al.[39] reported preliminary results of a nonrandomised comparative trial of adjuvant regional chemotherapy with 5-FU, folinic acid, epirubicin and carboplatin (FLEC) with or without subsequent systemic chemotherapy with gemcitabine. The constituents of FLEC were given sequentially as bolus doses via a transfemoral arterial catheter introduced into the celiac trunk. Chemotherapy was repeated every 3 weeks for a total of three cycles. The first 24 patients enrolled in the trial were treated with FLEC alone, whereas the following 23 patients received three additional cycles of systemic gemcitabine (1000 mg/m^2 weekly for 3 weeks, repeated every 4 weeks). Given the good comparability of the two patient groups with respect to most demographic and tumour characteristics, the results suggest that the addition of gemcitabine may prolong median DFS (22 vs 14 months) as well as overall survival at 1 year (88% vs 67%) and 2 years (70% vs 58%). Unfortunately, the small number of patients and a shorter follow-up in the gemcitabine group did not allow a meaningful analysis of treatment failure patterns in the two groups.

Two other small studies including 26 and 27 patients, respectively, evaluated adjuvant regional chemotherapy in patients with resected pancreatic cancer. Beger et al.[40] infused mitoxantrone, 5-FU plus folinic acid and cisplatin in the celiac trunk (six cycles every 4 weeks), and Ishikawa et al.[41] continuously infused 5-FU via the hepatic artery and portal vein simultaneously for 28–35 days. In both trials, significant survival advantages were observed compared with controls.

It appears from these data that regional chemotherapy with or without immunotherapy is a well tolerated adjuvant treatment option with promising efficacy. It should be expected that the addition of systemic chemotherapy using an active cytotoxic agent, such as gemcitabine, to regional chemotherapy may further prolong DFS and overall survival.

5. Recent Randomised Controlled Trials

5.1 ESPAC (European Study Group for Pancreatic Cancer)-1

The multicentre phase III trial of the ESPAC (ESPAC-1) was first published in 2001,[42,43] and updated results were reported in 2004.[12] The results from this study were awaited with great interest. Given the fairly large number of >500 randomised patients, it was hoped that the results of ESPAC-1 could clarify the respective roles of adjuvant chemoradiotherapy and chemotherapy in resected pancreatic cancer. However, the trial design was inconsistent and highly complex, and the ongoing discussion among clinical oncologists underlines the difficulties in interpreting the study findings.

The patients eligible for ESPAC-1 had histologically verified adenocarcinoma of the pancreas and underwent potentially curative resection. Randomisation was stratified by randomisation centre (UK, Switzerland, Germany, France) and resection margin (R0, R1). Initially, patients underwent double randomisation according to a 2 × 2 factorial design (chemotherapy vs chemoradiotherapy and yes vs no) to result in four groups: (i) postoperative observation only; (ii) adjuvant concomitant chemoradiotherapy (CRT); (iii) adjuvant chemotherapy alone (CT); and (iv) adjuvant chemoradiotherapy followed by chemotherapy (CRT→CT). Thus, the study was designed to compare no chemotherapy (i.e. CRT or observation) versus chemotherapy (i.e. CT or CRT→CT), and no chemoradiotherapy (i.e. CT or observation) versus chemoradiotherapy (i.e. CRT or CRT→CT) rather than comparing the relative efficacy of well defined chemoradiotherapy and chemotherapy regimens with observation alone. The chemoradiotherapy protocol was apparently identical or similar to that used in the GITSG studies in the early 1980s, i.e. it consisted of split-course fractionated radiation (ten daily 2Gy fractions over 2 weeks, followed by another course after a 2-week break) and 5-FU 500 mg/m^2 intravenous bolus doses given on days 1–3 of each course. Chemotherapy, both in the CT group and as follow-on treatment after chemoradiation in the CRT→CT arm, was administered using the Mayo Clinic regimen (a 5-day schedule of 5-FU 425 mg/m^2/day and folinic acid 20 mg/m^2/day repeated every 4 weeks) for a total of six cycles.

Since stratified randomisation into four groups proved to be difficult in practice and resulted in slow recruitment, the protocol was amended to also include two further single randomisation options: CRT versus no CRT and CT versus no CT. The investigators could decide on their own which one of the three randomisation options should be used to allocate their patients. Quite disturbingly, the investigators were also free to administer chemotherapy or chemoradiotherapy (so-called 'background therapy', i.e. the treatment offered in the alternative single randomisation option) before entering the patient into the trial. In the end, the study population included 541 eligible patients, of whom 285 were randomised through the 2 × 2 factorial design and 276 patients through one of the single randomisation schemes (68 patients in randomisation for CRT vs no CRT, each with or without 'background' chemotherapy, and 188 patients in randomisation for CT vs no CT, each with or without 'background' chemoradiotherapy). Nearly 20% of the patients included in the trial had R1 resection.

Preliminary results of ESPAC-1 were reported after a relatively short median follow-up of 10 months (range 0–62) for surviving patients.[42] In this report, separate analyses of the primary endpoint (survival) were made for the 285 patients randomised according to the 2 × 2 factorial design and the total population of 541 eligible, randomised patients. There were no significant differences in median survival between the CRT and no-CRT groups in either analysis, while median survival was significantly longer in the CT group compared with the no-CT group in the analysis that included patients randomised through a 2 × 2 factorial design (19.7 vs 14.0 months; p = 0.0005), but not in the analysis including all randomised patients (17.4 vs 15.9 months; p = 0.19).

In the total patient population, resection margin was identified as a significant independent prognostic factor, with a median and 2-year survival of

10.9 months and 26% for patients with R1 resection compared with 16.9 months and 32% for those with R0 resection, respectively.[43] Again, this analysis failed to demonstrate a beneficial impact of chemoradiotherapy on survival in either resection margin category. On the other hand, the survival advantage conferred by chemotherapy compared with no chemotherapy was largely confined to patients with R0 resection (median, 20.7 vs 15.3 months), whereas chemotherapy was disappointingly ineffective in R1 patients (median survival, 11.0 months with chemotherapy vs 10.3 months with no chemotherapy). Thus, regrettably, patients with incomplete resection, carrying the worse prognosis anyway, were those who benefitted least from adjuvant 5-FU-based chemotherapy.

Another analysis of the ESPAC-1 results was performed after a median follow-up of 47 months for surviving patients and was confined to the subgroup of 289 patients randomised according to the 2×2 factorial design.[12] (There was a slight discrepancy in patient numbers compared with the first publication where 285 patients were included in the 2×2 factorial groups). The authors gave no comment or explanation as to why they did not re-evaluate the total trial population, but it is reasonable to assume that they acknowledged that the introduction of additional randomisation options during the course of the study also added further limitations to the study. Firstly, leaving it to the clinicians' decision into which 'trial inside the trial' they wished to enter their patients was likely to result in a significant selection bias. Secondly, 'background' chemoradiotherapy or chemotherapy prior to randomly allocated treatment was a potential confounder. Moreover, pooling of the data across all three randomisation schemes resulted in bizarre treatment groups, e.g. the 'CT' group as defined in the initial report included a significant proportion of patients who received CRT either as part of sequential CRT→CT or as 'background' therapy prior to randomisation to CT.

By the time of the final survival analysis, 237 (82%) of the 289 patients included in the analysis had died. Unexpectedly, patients randomised to CRT (i.e. CRT alone or sequential CRT→CT) had a worse outcome compared with those randomised to no CRT (i.e. CT or observation): median survival and survival rates at 2 and 5 years were 15.9 months, 29% and 10% for CRT and 17.9 months, 41% and 20%, respectively, for no CRT. The overall survival difference just reached statistical significance (hazard ratio [HR] for death, 1.28; $p = 0.05$). On the other hand, patients randomised to CT (i.e. CT or CRT→CT) faired significantly better than those randomised to no CT (i.e. CRT or observation). Median survival and survival rates at 2 and 5 years were 20.1 months, 40% and 21%, respectively, for CT and 15.5 months, 30% and 8% for no CT (HR for death, 0.71; $p = 0.009$). The deleterious effect of chemoradiotherapy and the favourable effect of chemotherapy on survival were mirrored in the results of the four individual randomisation groups. Median survival was 13.9 months and 5-year survival 7% in patients randomised to CRT, 21.6 months and 29% for those randomised to CT, 19.9 months and 13% for those randomised to sequential CRT→CT, and 16.9 months and 11% for those randomised to observation (table I).

ESPAC-1 was inadequately powered to compare the four groups directly. Thus, the possibility remains that the significant differences found in the study were the result of chance. In addition to the problematic study design, it was criticised that 40Gy of split-course radiotherapy as delivered in ESPAC-1 was underdosed and outdated, and radiotherapy dose was heterogeneous.[44-46] This may explain why survival with chemoradiotherapy (13.9 months) was worse than in other comparable studies (e.g. 17.1 months in the EORTC trial, using a dosage regimen very similar to that in ESPAC-1). In addition, radiotherapy quality assurance was apparently not required in ESPAC-1, and the time interval between surgery and the start of adjuvant therapy was shorter in patients receiving chemotherapy compared with those receiving chemoradiation (46 vs 61 days), which might reflect poorer performance status in the latter group. It was also argued[47] that the median survival of 16.9 months reported for patients who received surgery alone was surprising-

ly good compared with the control groups of previous randomised studies[4,9,10] and the non-randomised Johns Hopkins experience[18] where median survival ranged from 11 to 13 months. However, in the German CONKO-001 trial described in detail in section 5.3, median survival with surgery alone was even longer (20.2 months) than in ESPAC-1. Thus, the improved prognosis in newer trials may reflect a general trend towards improved clinical management of patients with advanced or recurrent pancreatic cancer. Nevertheless, the findings of ESPAC-1 are difficult to explain. The authors of the study suggest that the negative impact of chemoradiotherapy on survival might be due to the fact that this (ineffective) treatment delayed administration of (effective) adjuvant chemotherapy. However, this cannot explain why survival among patients treated with chemoradiotherapy alone was poorer than among those receiving no adjuvant therapy at all. Since excess mortality appeared in the second year, Bydder et al.[37] speculated that this might have been the result of late toxic effects of radiation secondary to the delivery of excessive doses to normal tissues.

In summary, ESPAC-1 was an ambitious European trial that, unfortunately, suffered from striking deficiencies such as a too complex design and a relative lack of sufficient participants. Thus, the study had inadequate power to determine the statistical and clinical significance of its findings. As to the choice of treatments to be compared in the trial, it would be unfair to criticise the authors' decision in retrospect, many years after the trial's initiation, based on today's knowledge. However, it is the tragedy of ESPAC-1 that both treatment regimens, split-course chemoradiotherapy as well as chemotherapy with 5-FU, were outdated by the time mature results of the trial became available. Oncologists would therefore be well advised not to overinterpret the findings of the study. In particular, given the limited activity of 5-FU in advanced pancreatic cancer, it is reasonable to assume that this agent is also not the best choice for adjuvant chemotherapy. For example, in the phase III study by Burris et al.,[48] palliative first-line chemotherapy with 5-FU resulted in significantly inferior survival compared with gemcitabine. Moreover, in the large randomised trial of 5-FU with or without cisplatin reported by Ducreux et al.,[49] the survival rates at 6 months were unacceptably low in both arms (28% with 5-FU alone vs 38% with 5-FU plus cisplatin). With gemcitabine, 6-month survival rates in patients with advanced pancreatic cancer were ≥50% in most randomised trials.[48,50]

5.2 RTOG (Radiation Therapy Oncology Group) 9704

The superior activity of gemcitabine in the palliative setting prompted the US Gastrointestinal Intergroup to initiate a large randomised phase III study (RTOG 9704) to evaluate the impact on survival of adding gemcitabine to adjuvant 5-FU-based chemoradiotherapy.[13] The patients were stratified by nodal status, tumour size and surgical margins, and randomised to one of two treatment arms. Therapy was started 3–8 weeks after surgery, consisting of a three-step sequential CT→CRT→CT protocol separated by treatment-free periods of 1–2 weeks pre-CRT and 3–5 weeks post-CRT. The central CRT part was 5-FU-based and identical for both arms, whereas the pre- and post-CRT 'sandwich' chemotherapies differed between the arms. In arm 1, continuous infusion 5-FU at 250 mg/m^2/day was given for 3 weeks pre-CRT and for 3 months post-CRT (4 weeks on and 2 weeks off, repeated twice). In arm 2, chemotherapy consisted of gemcitabine at weekly doses of 1000 mg/m^2 for 3 weeks pre-CRT, and for 3 months post-CRT (3 weeks on and 1 week off, repeated three times). Unlike the GITSG and ESPAC-1 trials, the chemoradiotherapy protocol consisted of continuous-course radiation in daily fractions of 1.8Gy to a total dose of 50.4Gy, with concomitant continuous infusion of 5-FU at 250 mg/m^2/day for 5½ weeks. To ensure the quality of radiotherapy, a prospective quality assurance programme for radiation fields was employed.

Between 1998 and 2002, a total of 538 patients with resected pancreatic adenocarcinoma were entered into the trial, 442 of whom were eligible and had analyzable results. About one-third of the eligi-

ble patients in either group had definitely positive resection margins (but a high percentage of patients had unknown surgical margins), and 70% of the patients in the 5-FU arm compared with 81% in the gemcitabine arm had stage T3 or T4 disease. Preliminary results of RTOG 9704 were presented at the 2006 Annual Meeting of the American Society of Clinical Oncology.[13] It was shown that in the subgroup of 381 patients with pancreatic head tumours, but not in the total study population that included patients with body or tail tumours, gemcitabine significantly improved overall survival (median, 20.6 vs 16.9 months; 3-year survival, 32% vs 21%; p = 0.033). Median DFS was not significantly improved (11.4 vs 10.1 months; p = 0.10). Treatment, nodal involvement (no vs yes) and tumour diameter (<3 cm vs ≥3 cm) were identified as significant independent predictors of overall survival in a multivariate analysis. Toxicity of adjuvant treatment was substantial, although manageable in both arms. Grade 3/4 non-haematological toxicity occurred in 58% of the patients in either arm, whereas the incidence of grade 3/4 haematological toxicity and any grade 3/4 toxicity was significantly greater in the gemcitabine arm (58% and 79.5% of the patients) compared with the 5-FU arm (10% and 62%, respectively). However, even in the gemcitabine arm, 90% of the patients could complete chemoradiotherapy as scheduled.

What can we conclude from the findings of the RTOG trial? It appears evident that the addition of chemotherapy with gemcitabine to chemoradiotherapy improves survival compared with a chemotherapy plus chemoradiation protocol solely based on 5-FU. Unfortunately, the RTOG investigators took the benefit of 5-FU-based chemoradiotherapy for granted and thus decided to do without a control group such as chemotherapy alone or no adjuvant therapy at all. Therefore, from a European perspective, the trial leaves open several important questions. What contribution did chemoradiotherapy make to the overall effect of adjuvant treatment in the gemcitabine group? Could chemoradiotherapy possibly have been omitted in either treatment arm? Did the 5-FU-based treatment protocol in arm 2 have any impact on survival, and if yes, did the addition of chemotherapy with 5-FU improve the efficacy of chemoradiotherapy? Clearly, additional comparative trials are needed to better define the role of adjuvant chemoradiation with or without gemcitabine, and the efficacy and toxicity of chemoradiotherapy relative to gemcitabine alone.

5.3 Charité Onkologie CONKO-001

CONKO-001 was a large, randomised, multicentre, phase III trial of adjuvant gemcitabine versus surgery alone.[14] Selection of the study treatment was profoundly influenced by the results of the landmark phase III study of Burris et al.,[48] who observed significant improvements both in survival and clinical benefit with single-agent gemcitabine compared with 5-FU as first-line chemotherapy in patients with advanced pancreatic cancer. This finding suggested that gemcitabine was most promising for adjuvant therapy as well. In keeping with the European paradigm of chemotherapy alone as recommended adjuvant therapy in resectable pancreatic cancer, the patients in CONKO-001 did not receive pre- or postoperative radiotherapy. Similar to ESPAC-1, CONKO-001 was a 'pragmatic' trial in that no surgical and histological standards were used, nor were strict quality assurance methods applied. Unlike ESPAC-1, however, the design of the trial was simple and straightforward, comparing a clearly defined chemotherapy protocol with a no-adjuvant-therapy control group.

From 1998 to 2004, a total of 368 patients with gross complete (R0 or R1) resection of pancreatic cancer and no prior chemotherapy or radiotherapy were entered in the study by 88 academic and community-based oncology centres in Germany and Austria. The patients were randomised, with stratification for resection, primary tumour and nodal status, to six cycles of gemcitabine on day 1, 8 and 15 every 4 weeks or no adjuvant therapy (observation). The primary endpoint of the trial was DFS, and it was hypothesised that gemcitabine would prolong median DFS by at least 6 months. Secondary endpoints included overall survival, toxicity and quality

of life. Survival analysis was based on all 354 eligible patients (intention to treat).

The two patient groups (179 in the gemcitabine arm and 175 in the observation arm) were well matched for all demographic, clinical and tumour characteristics. More than 80% of patients had R0 resection and >70% were node-positive. Treatment with gemcitabine was well tolerated, with hardly any grade 3/4 toxicities. Quality of life as measured by the Spitzer index was similar between the groups. During a median follow-up of 53 months, 74% and 92% of patients in the gemcitabine and observation arm, respectively, developed recurrent disease. Median DFS was >6 months longer in the gemcitabine arm (13.4 vs 6.9 months; $p < 0.001$). Estimated DFS at 3 and 5 years was 23.5% and 16.5% in the gemcitabine arm compared with 7.5% and 5.5% in the observation arm, respectively. Exploratory subgroup analyses showed that the effect of gemcitabine on DFS was significant in both R0- and R1-resected patients. Median overall survival was similar in both groups (22.1 months in the gemcitabine arm and 20.2 months in the observation arm), and the difference in actuarial survival between the arms just failed to reach statistical significance, using a log-rank comparison ($p = 0.061$) [table I]. However, as can be seen in figure 1, the survival curves of the two arms began to separate only at ≈16 months. This may be the result of effective palliative chemotherapy with gemcitabine that was administered to most patients in the observation arm upon relapse; many patients also received second- or even third-line chemotherapy. The survival curves diverged more and more over time, and the estimated survival rates at 3 and 5 years clearly favoured the gemcitabine arm (34% and 22.5% with gemcitabine compared with 20.5% and 11.5% with observation). Since many patients were still alive at the time of the survival analysis (survival times were censored for 32% and 22% of patients in the gemcitabine and observation arm, respectively), it is highly likely that the difference in survival between the groups will become significant with longer follow-up. Interestingly, the 3-year survival rate of 21% found in the 5-FU group of the

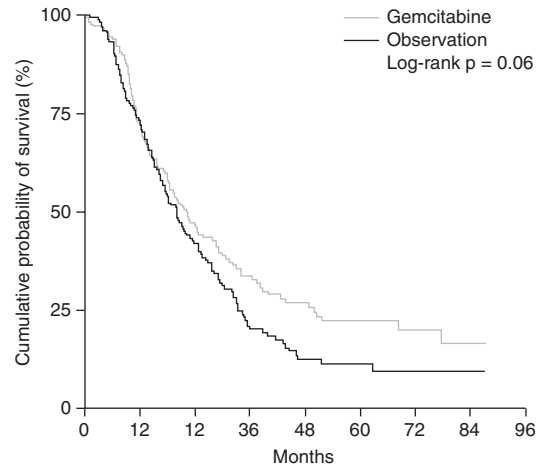

Fig. 1. Overall survival in the randomised phase III trial CONKO-001 that compared adjuvant gemcitabine with observation in patients with curative-intent resection of pancreatic cancer (reproduced from Oettle et al.,[14] with permission. *Copyright © 2007, American Medical Association.* All rights reserved).

RTOG trial is identical to that seen in the observation arm of our study. Although comparing survival data across studies is problematic and the patients treated in CONKO-001 and the RTOG trial differed in some baseline characteristics, this finding appears to add further evidence to the assumption that the beneficial effect of adjuvant 5-FU is small at best.

In summary, postoperative chemotherapy with gemcitabine significantly delayed disease recurrence after gross complete resection of pancreatic cancer compared with surgery alone, and the available data suggest that this beneficial effect of gemcitabine is likely to translate into increased long-term survival. These findings make gemcitabine the prime candidate for adjuvant chemotherapy in resectable carcinoma of the pancreas. The observed survival difference in favour of gemcitabine appears all the more remarkable because of the excellent outcome of patients treated with surgery alone. The median survival of 20.2 months observed in the control group of CONKO-001 (including 15% R1 patients) compares favourably with 11 months reported both in the GITSG[4] and Norwegian trial,[10] each of which included only

R0-resected patients, 12.6 months for patients with pancreatic head cancer in the EORTC study (24% positive resection margin for all patients, including those with periampullary cancer),[6] and 16.9 months in ESPAC-1[12] (19% positive margins in the total patient population)[12] [table I]. This finding may reflect the high quality of care in the participating centres and the widespread acceptance of gemcitabine as a palliative standard.

6. Meta-Analyses of Adjuvant Chemo(Radio)Therapy

Two meta-analyses of adjuvant treatment trials, which differed in their methodology and trial selection criteria, were recently performed in an attempt to clarify the role of adjuvant chemotherapy and chemoradiotherapy.[51,52] Neither of these analyses included the results of CONKO-001 or the preliminary results of the RTOG 9704 trial.

6.1 Stocken et al. Meta-Analysis

The meta-analysis by Stocken et al.[51] sought to pool individual data from patients with pancreatic cancer (excluding those with periampullary cancer) from five randomised controlled trials: the GITSG study,[4] the Norwegian study,[10] the EORTC study,[9] the Japanese study[11] and ESPAC-1, the latter including published data from 289 patients randomised by 2×2 factorial design[12,42] as well as previously unpublished, updated results after a median follow-up of 39.2 months from 261 patients selected for single randomisation ('ESPAC-1 plus'). Individual data could not be obtained from GITSG because of how old the trial was. The pooled data were used to recalculate Kaplan-Meier survival curves and HRs, the latter being estimates of the effect of treatment on the risk of death.

A total number of 875 individual patient data were included in the meta-analysis, of which 550 (63%) were from ESPAC-1. Thus, the overall results were clearly dominated by the ESPAC-1 data. Moreover, in analogy to the ESPAC-1 trial, comparisons were made between chemotherapy and no chemotherapy, and between chemoradiotherapy and no chemoradiotherapy, even though all of the trials included a surgery-alone group. It is hardly surprising, therefore, that the results of this meta-analysis were strikingly similar to those of ESPAC-1. The authors found an HR of 0.75 (95% CI 0.64, 0.90) for adjuvant chemotherapy, indicating a significant reduction by 25% in the risk of death compared with no chemotherapy. The estimates of median survival and survival rates at 2 and 5 years were 19.0 months, 38% and 19%, respectively, for patients receiving adjuvant chemotherapy, and 13.5 months, 28% and 12% for those with no chemotherapy. The HR for chemoradiotherapy was 1.07, which was not significantly different from 1, indicating no survival advantage for adjuvant chemoradiotherapy. The pooled estimates of median survival and survival rates at 2 and 5 years were 15.8 months, 30% and 12%, respectively, for patients receiving adjuvant chemoradiotherapy, and 15.2 months, 34% and 17% for those who did not. Exploratory subgroup analyses by prognostic factors indicated that chemoradiotherapy was significantly more effective and chemotherapy significantly less effective in patients with positive resection margins.

6.2 Khanna et al. Meta-Analysis

The meta-analysis by Khanna et al.[52] also addressed the question as to whether patients with resected pancreatic adenocarcinoma would benefit from 5-FU-based chemotherapy or chemoradiotherapy. The survival estimates were not based on collated individual patient data, which may have affected accuracy. Yet, this meta-analysis was particularly useful in that the treatment effect was measured in terms of the difference in 2-year survival between treated and untreated (surgery-alone) patients and thus provided evidence for the absolute size of the survival benefit of adjuvant treatment. Five prospective, randomised or nonrandomised studies with untreated control groups and a minimum of 20 patients allocated to each arm were included in the analysis: the GITSG,[4] Norwegian[10] and EORTC trial,[9] the 2×2 factorial part of ESPAC-1,[12] and the nonrandomised Johns Hopkins experience reported by Yeo et al.[18] The randomised study by Takada et al.[11] was not considered for this meta-analysis be-

cause it included patients with stage IV disease. The five studies involved a total of 607 patients with pancreatic cancer (including 14 patients with carcinoma of the papilla of Vater in the study from Norway, but excluding patients with periampullary cancer in the EORTC trial). While the difference in 2-year survival did not achieve statistical significance in any of the individual studies, the combined estimate indicated that adjuvant chemotherapy with or without chemoradiotherapy improved 2-year survival significantly by 12% ($p = 0.011$).

7. Conclusions

Several randomised trials have demonstrated that patients with resected adenocarcinoma of the pancreas benefit from adjuvant treatment in terms of improved DFS and overall survival. Given the poor prognosis even after apparently complete resection of localised disease, adjuvant treatment should therefore be offered to all curatively resected patients. However, the data available to date do not permit definite conclusions to be drawn as to the most effective adjuvant regimen or whether specific patient subgroups will benefit to a greater extent from adjuvant treatment. Patients should therefore be included in clinical trials whenever possible.

The results of ESPAC-1 suggest that adjuvant chemotherapy with bolus 5-FU plus folinic acid may provide some benefit. Hopefully, the efficacy of this regimen relative to gemcitabine will be clarified by the ESPAC-3 trial that is currently randomising patients with ductal adenocarcinoma of the pancreas to either of these regimens and will soon be closed to accrual. Current evidence on the role of adjuvant 5-FU-based chemoradiotherapy is hampered by the fact that all randomised studies except RTOG 9704 used suboptimal (split-course) radiation schedules. While some older studies suggested a beneficial effect of chemoradiotherapy on survival, the results of ESPAC-1 imply a detrimental effect. Although ESPAC-1 may be criticised because of methodological deficiencies that cast some doubt on the reliability of the study findings (and hence the conclusions from the meta-analysis by Stocken et al.[51] alike), the results should not be fully ignored. Unfortunately, because of the lack of an appropriate control group, no conclusion as to the value of 5-FU-based chemoradiotherapy alone can be drawn from RTOG 9704. The findings of this trial just indicate that in pancreatic head cancer, gemcitabine is more effective than 5-FU if added to optimised 5-FU-based (continuous) chemoradiation in patients with cancer of the pancreatic head.

The results of CONKO-001 suggest that gemcitabine, which is currently the most active single agent in advanced pancreatic cancer, is well tolerated and effective as adjuvant therapy, thus offering patients with resected cancer a particularly favourable benefit/risk ratio. Gemcitabine alone may therefore be considered a reference standard for adjuvant treatment after R0 and R1 resection of pancreatic adenocarcinoma. The phase II results achieved with IORT or regional (intra-arterial) chemotherapy are also promising with regard to both activity and safety, and future research will have to disclose if these local treatment approaches or additional systemic agents, such as 5-FU, oxaliplatin or targeted therapies, can further improve the efficacy of adjuvant chemotherapy with gemcitabine. At the current state of knowledge, it seems sensible to preferably administer adjuvant chemoradiotherapy in a clinical trial setting to acquire more reliable information about the benefit of this approach. An important ongoing phase III study of the EORTC compares adjuvant gemcitabine-based chemoradiotherapy (two cycles of gemcitabine followed by concomitant gemcitabine and radiotherapy) with four cycles of gemcitabine alone in patients with resected pancreatic cancer. This trial will provide information as to whether the addition of radiotherapy to chemotherapy with gemcitabine will improve survival compared with gemcitabine alone.[53]

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