ANTICANCER RESEARCH *25*: 1523-1530 (2005)

Results and Follow-up of Locally Advanced Cancer of the Exocrine Pancreas Treated with Radiochemotherapy

OLIVER MICKE[1], STEFAN HESSELMANN[1], FRANK BRUNS[1], ECKEHARD HORST[1], ALEXANDER DEVRIES[2], PATRICK SCHÜLLER[1], NORMANN WILLICH[1] and ULRICH SCHÄFER[1]

[1]*Department of Radiotherapy, Münster University Hospital, Münster, Germany;*
[2]*Department of Radiotherapy, University of Innsbruck, Innsbruck, Austria*

Abstract. *In locally advanced carcinoma of the exocrine pancreas combined radiochemotherapy has been established as a standard treatment. Materials and Methods: Two different treatment schemes have been consecutively used. Between 1/1994 and 12/2001, a total of 110 patients with locally advanced adenocarcinoma of the pancreas were treated with hyperfractionated accelerated radiotherapy to a total dose of 44.8 Gy combined with 5-fluorouracil (5-FU) (600 mg/m^2) and folinic acid (FA) (300 mg/m^2) injection. Chemotherapy was repeated monthly in non-progressive disease. From 1/2002 to 11/2003, in another 15 consecutive patients, chemotherapy was changed to gemcitabine (Gem) (300 mg/m^2) and cisplatinum (Cis) (30 mg/m^2), followed by gemcitabine (1000 mg/m^2) every 2 weeks in non-progressive patients. Results: Median survival in the 5-FU/FA group was 10.3 months with a 1-year survival of 46.6% and a 2-year survival of 20.1%. Median time to progression was 8.6 months. Treatment was well tolerated with nausea/vomiting grade I/II in 58.2%, grade III/IV in 14.5%, diarrhea grade I/II in 27.3%, leucopenia/thrombopenia grade I/II in 21.8%, grade III/IV in 7.2%, and mucositis grade III/IV in 7.2%. In the Gem/Cis group, median survival was 13.8 months with a 1-year survival of 54.9% and a 2-year survival of 24.4%. The toxicity data also revealed comparable feasibility: nausea/vomiting grade I/II in 46.7%, grade III/IV in 20%, diarrhea grade I/II in 20%, leucopenia/thrombopenia grade I/II in 26.7%, and grade III/IV in 13.3%. Conclusion: Radiochemotherapy in locally advanced pancreatic cancer is an effective and well-tolerated treatment. The long-term efficacy concerning survival is limited. The integration of predictive factors and new chemotherapeutic agents like gemcitabine in the multimodality treatment may give a more promising perspective. Because of the narrow therapeutic index of gemcitabine-based radiochemotherapy schemes, a feasible combination of radiotherapy treatment volume and gemcitabine dose must be found.*

Correspondence to: Dr. Oliver Micke, Klinik und Poliklinik für Strahlentherapie - Radioonkologie, Universitätsklinikum Münster, Albert-Schweitzer-Str. 33, 48129 Münster, Germany. Tel: +49 251 8347839, Fax: +49 251 8347355, e-mail: omicke@uni-muenster.de

Key Words: Pancreatic cancer, radiochemotherapy, CA 19-9, gemcitabine, toxicity.

Ductal adenocarcinoma is the most frequently occurring malignant tumor of the pancreas, located in the pancreatic head in 2/3 and in the corpus or tail in 1/3 of patients. The incidence of pancreatic carcinoma in Western countries is about 1:10,000 with a correlation with the patient's age. Pancreatic cancer is a morbid disease with dismal prognosis. In Germany, this disease was listed rank 6 in the statistics of deaths caused by malignant diseases in 1997 (1-3).

Survival rates are low because, by the time pancreatic cancer is detected, it usually has advanced, so that a complete surgical resection, the best chance of cure at present, is no longer possible (1, 4-6). Without surgical intervention, the mean length of survival is approximately 6 months. Thus, in the majority of patients, optimal palliation of symptoms is of primary importance, to maximize the quality of remaining life (7-11). Excluding surgical bypass, endoscopic biliary drainage to reduce obstructive jaundice and other alleviating measures (*e.g.*, celiac plexus block), the treatment of patients with locally advanced, unresectable pancreatic cancer consists of radiotherapy, chemotherapy, or a combination of both (7, 12-17).

In particular, the use of chemotherapy with concurrent radiation therapy remains standard treatment for patients with unresectable or resected adenocarcinoma of the pancreas, since previous randomized trials by the Gastrointestinal Tumor Study Group (GTSG) showed that concurrent external-beam radiation therapy (EBRT) and bolus 5-fluorouracil (5-FU) therapy resulted in significantly better survival compared with EBRT alone or chemotherapy alone (18, 19). With 5-FU-based radiochemotherapy treatment schemes, it is possible to improve the patient quality of life and prolong survival in locally advanced and unresectable cancer of the exocrine pancreas (7, 12, 14-16, 18, 20-28). Unfortunately, the majority of patients continue to succumb to the disease process.

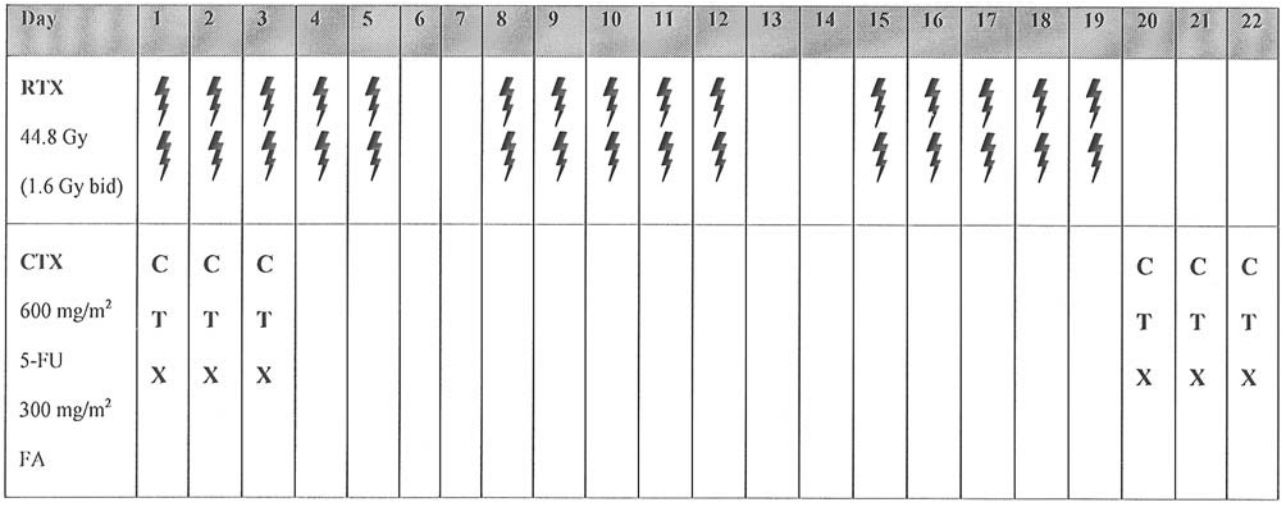

Figure 1. *Treatment scheme of combined radiochemotherapy (5-FU/FA group). Repetition of chemotherapy every 28 days in non-progressive patients.*

Recently, there has been a resurgence in clinical trials utilizing gemcitabine as a single agent, in combination chemotherapy regimens, and with concurrent radiation therapy (29).

Materials and Methods

Study patients. Between 1/1994 and 11/2003, a total of 125 patients with locally advanced irresectable adenocarcinoma of the exocrine pancreas, histologically biopsy proven, were included in the study. Local inoperability was determined by an experienced surgical team during explorative laparotomy. Further inclusion criteria were no distant metastasis, Karnofsky performance status ≥70%, age ≥18 and ≤75 years, normal pretherapeutic blood counts, renal and liver function. Histologically, 13 (10.4%) tumors were graded G1, 67 (53.6%) G2 and 45 (36%) G3.

The median age was 62 years (range: 26-75 years); 71 patients were male and 44 were female. According to the UICC-classification (30), 4% of patients had a stage I, 54.4% a stage II, 28% a stage III and 13.6% a stage IVa. Tumors were predominantly (84%) located in the head of pancreas.

Treatment schemes. Two different treatment schemes have been consecutively used: between 1/1994 and 12/2001 all patients (n=110) received a combined radiochemotherapy, consisting of hyperfractionated accelerated conformal radiotherapy and simultaneous application of 5-fluorouracil and folinic acid, as previously described by Prott *et al.* (15). Determination of the target volume for radiotherapy and 3D-treatment planning was based on computerized axial tomography. Conformal radiotherapy was carried out under megavoltage condition by linear accelerators from 10 MeV to 15 MeV. A total tumor dose of 44.8 Gy was applied relative to the 90% isodose in two daily fractions of 1.6 Gy, resulting in ten fractions per week (Figure 1). On the first three days of radiotherapy, 600 mg/m^2 of 5-fluorouracil (5-FU) and 300 mg/m^2 of folinic acid (FA) were given intravenously. Chemotherapy was repeated monthly in all cases of no progressive disease after evaluation of the radiological tumor response.

From 1/2002 to 8/2003, in another 15 consecutive patients, chemotherapy regimen was changed to a gemcitabine (Gem) (300 mg/m^2) and cisplatinum (Cis) (30 mg/m^2), followed by gemcitabine (1000 mg/m^2) every 2 weeks in all non-progressive patients. There were 9 male and 6 female patients with a median age of 57 years (range: 41-69 years).

Follow-up. Follow-up was performed parallel to the cycles of maintenance chemotherapy. Follow-up visits included medical history, physical examination, total blood counts, serum electrolytes, liver and renal function tests. The length of follow-up ranged between one months and 90 months. Response evaluation and follow-up was regularly carried out by abdominal ultrasound (every month) and CT-scans (every two to three months). In case of suspicion for recurrent disease the intervals were shortened. Serum levels of CA 19-9 were measured before treatment, each week under therapy, and every four weeks during the regular follow-up intervals, using a commercially available assay [Electrochemilumnescenceimmunoassay (ECLIA) by ELECSYS 1010 (Roche Diagnostics GmbH, Mannheim, Germany)]. The upper cut-off level for this system was defined at 37 U/ml, according to the specification in the literature (31, 32).

Statistical methods. Survival was calculated from the first day of radiation therapy. All patients expiring in the follow-up period died from tumor disease or tumor complications. Survival curves were estimated by the method of Kaplan and Meier (33). The differences in the survival estimates between groups of patients were evaluated using the log-rank test (34). A forward, stepwise Cox regression model was used to examine the prognostic significance of covariates on survival (35). Values of $p<0.05$ were considered statistically significant. All statistical analyses were performed using the commercially available program package SPSS 10.0.7 (SPSS, Chicago, IL, USA).

Results

The median overall survival of the 5-FU/FA group was 10.3 months, measured from the beginning of treatment and analyzed by Kaplan & Meier method (33). The actuarial

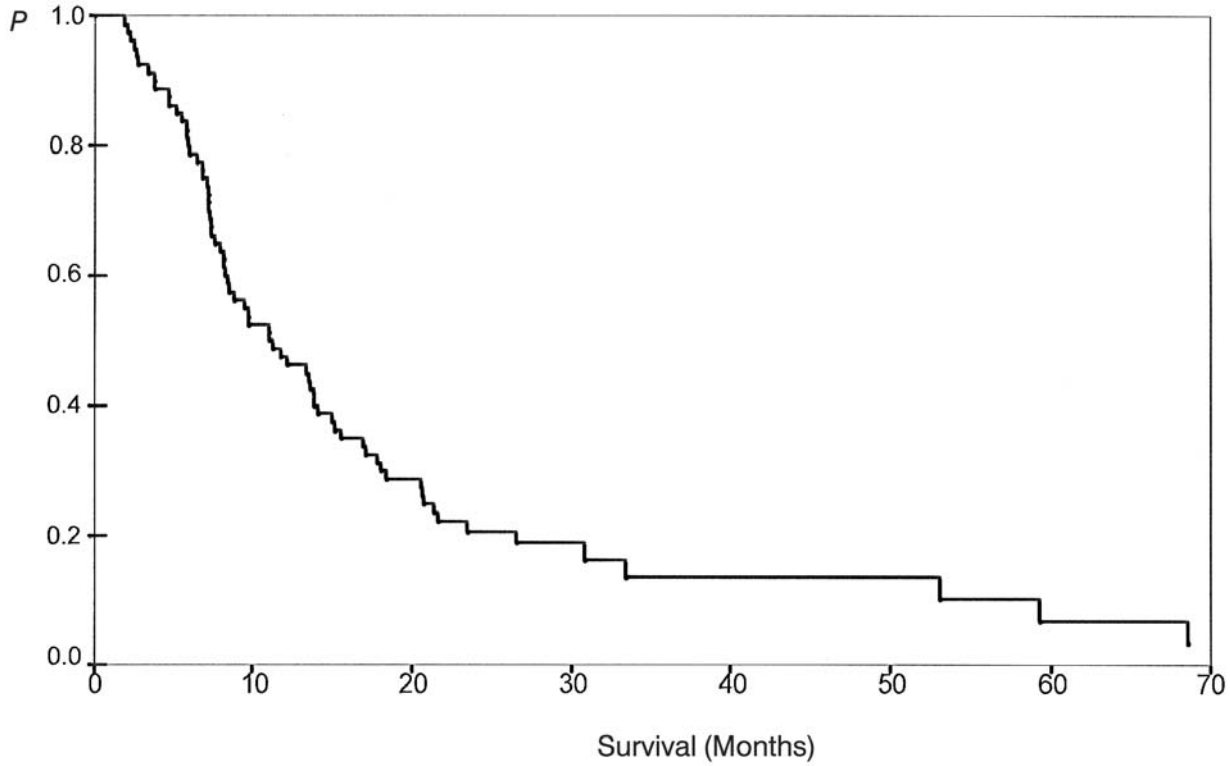

Figure 2. *Kaplan-Meier analysis of overall survival of patients in the 5-FU/FA group.*

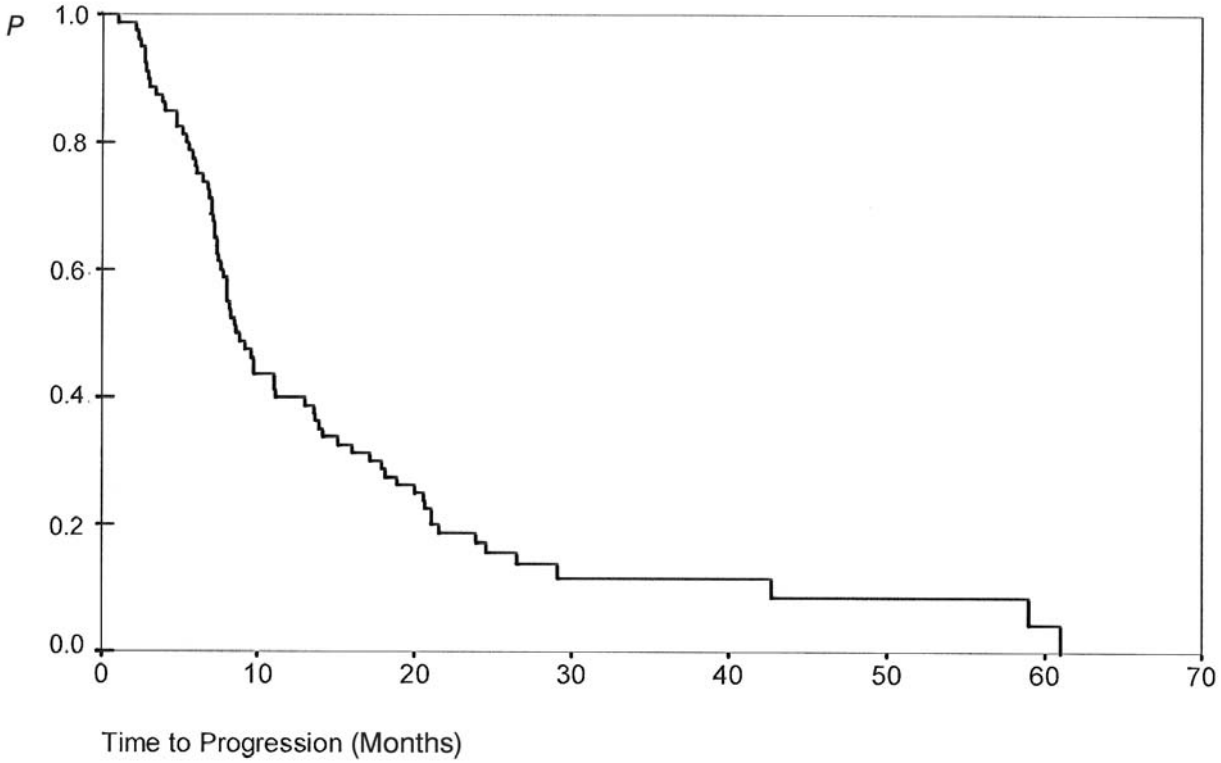

Figure 3. *Kaplan-Meier analysis of progression-free survival of patients in the 5-FU/FA group.*

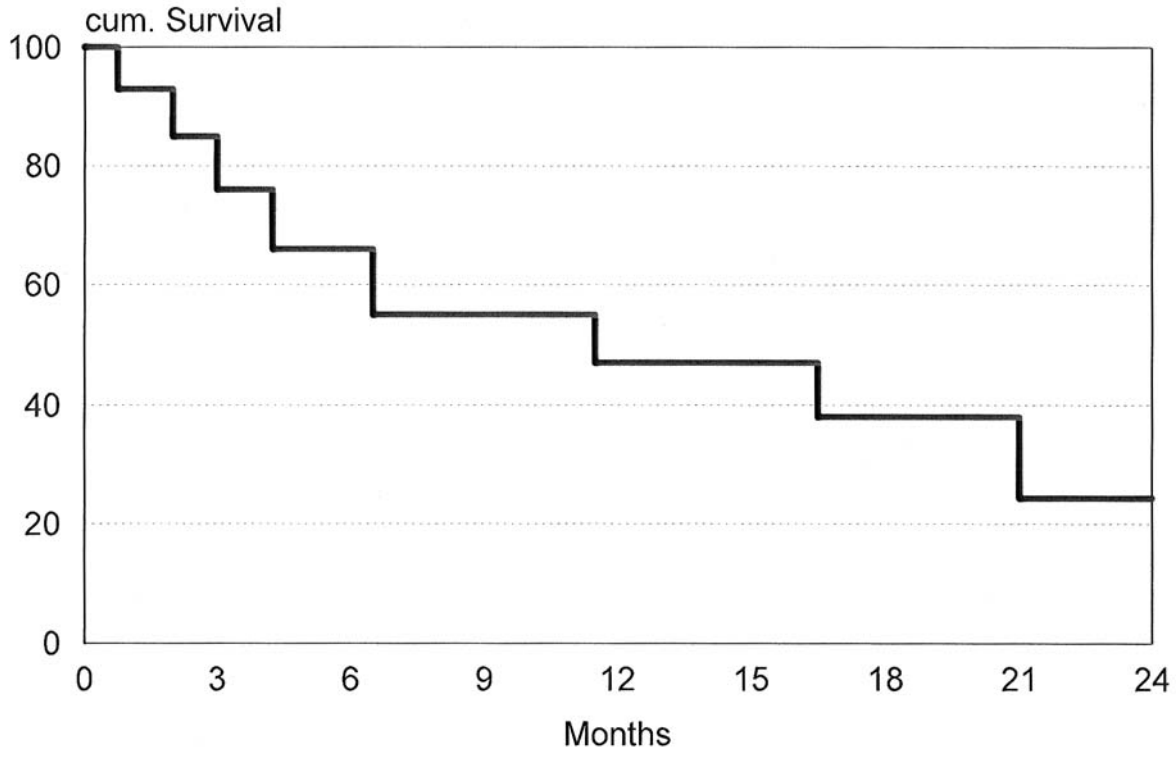

Figure 4. *Kaplan-Meier analysis of overall survival of patients in Gem/Cis group.*

1-year survival was 46.6%, the 2-year survival 20.1% and the 3-year survival 15.5% (Figure 2). Median time to progression was 8.6 months. The actuarial progression-free survival rate was 40.0% after one year, 18.8% after two years and 11.5% after three years (Figure 3).

In the Gem/Cis group, median survival was 13.8 months with a 1-year survival of 54.9% and a 2-year survival of 24.4%. Median time to progression was 11.1 months. The actuarial progression-free survival rate was 40.0% after one year and 18.8% after two years (Figure 4).

The overall survival and the progression-free survival was significantly superior in the Gem/Cis group [Log-rank test: $p=0.01$, resp. 0.046].

The median CA 19-9 serum level of all patients before treatment was 420 U/ml, ranging from 2.0 to 39,700 U/ml.

Concerning tumor response, evaluated 3 months after the end of radiotherapy by imaging procedures, 7 patients (6.4%) of the 5-FU/FA group achieved a complete response (CR), 26 patients (23.6%) a partial response (PR), 32 patients (29.1%) had no significant change (NC) of their disease, and 45 patients (40.9%) a progression of their disease (PD). All patients dying during the first 3 moths before the first restaging were counted as having progressive disease. In the Gem/Cis group, one patient (6.7%) achieved a complete response (CR), 4 patients (33.3%) a partial response, 6 patients (40%) had no significant change (NC) of their disease, and 4 patients (33.3%) a progression of their disease (PD).

Patients with a pretreatment CA 19-9 serum level below the median value of 420 U/ml had a better tumor response than those above the median (χ^2-test: $p=0.003$). These patients also had a significantly better survival prognosis in univariate Kaplan and Meier analysis [Log-rank test: $p=0.0056$] (Figure 5). In addition, patients with no decline of CA 19-9 levels had a significantly worse outcome concerning overall survival [Log-rank test: $p=0.0002$]. These results were confirmed by multivariate Cox regression, showing pretreatment CA 19-9 serum levels above and below the median value of 420 U/ml ($p=0.003$), post-treatment CA 19-9 values ($p=0.001$) and a tumor marker decrease under therapy ($p=0.001$) to be significantly independent prognostic markers for overall survival. Only achievement of a tumor response showed a similar high prognostic significance ($p=0.001$). It is worth noting that there was a significant relationship between survival and tumor extent, grading and lymph node involvement.

Overall, the treatment in the 5-FU/FA group was well-tolerated with nausea/vomiting grade I/II in 58.2%, grade III/IV in 14.5%, diarrhea grade I/II in 27.3%, leucopenia/thrombopenia grade I/II in 21.8%, grade III/IV in 7.2%, and mucositis grade III/IV in 7.2%. In the Gem/Cis

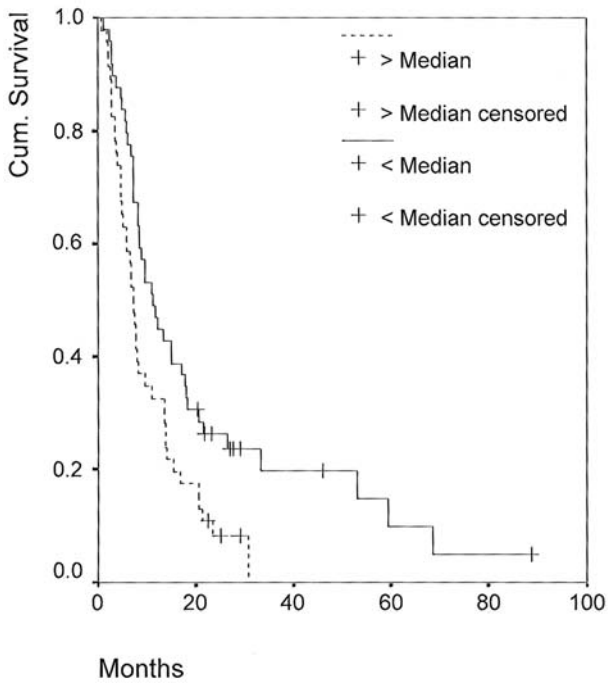

Figure 5. *Kaplan-Meier analysis of disease-specific survival of patients in correlation with the median pretreatment CA 19-9 level of 420 U/ml shows a median disease-specific survival of 11.3 months (CA 19-9 level < 420 U/ml) and 7.4 months (CA 19-9 level > 420 U/ml), respectively.*

group, the toxicity data revealed the comparable feasibility of the two treatment schemes with a slight tendency towards more severe side-effects: nausea/vomiting grade I/II in 46.7%, grade III/IV in 20%, diarrhea grade I/II in 20%, leucopenia/thrombopenia grade I/II in 26.7%, and grade III/IV in 13.3%.

Discussion

Adenocarcinoma of the exocrine pancreas belongs to the neoplasms with the highest rates of mortality in western industrial countries (1-3). Surgical resection is able to cure only a minority of patients with locally confined pancreatic cancer (1, 4-6). In all other non-metastasized patients, an oncologically radical surgical approach is not possible (36) and the value of adjuvant radio- or radiochemotherapy still remains unclear (37).

The use of chemotherapy with concurrent radiation therapy remains standard treatment for patients with unresectable or resected adenocarcinoma of the pancreas, since the previous randomized trials by the Gastrointestinal Tumor Study Group (GTSG) showed that concurrent external-beam radiation therapy (EBRT) with 40 or 60 Gy and bolus 5-fluorouracil (5-FU) therapy resulted in significantly better survival compared with EBRT alone or chemotherapy alone. Radiation doses of 60 Gy were not superior to 40 Gy, but less well tolerated, when combined with 5-FU (18, 19). A problem of the standard radiotherapy technique used in these and other older protocols was that large volumes of small bowel were irradiated inducing dose-limiting acute toxicity (26, 27, 38, 39).

Newer studies, using more advanced radiotherapy techniques, have shown that 5-FU-based radiochemotherapy schemes can improve patient quality of life and prolong survival in advanced disease with survival times of around 11 months (7, 14-16, 20-25, 29, 40). However, the published results of the following larger phase III trials were rather disappointing with a median survival of about 6 months and only 15% of the patients surviving one year. Complete and partial responses have been reported only in approximately 11% of the cases (29, 40). Our study showed, in one of the largest patient collectives (n=110) treated with 5-FU-based radiochemotherapy, a more acceptable median survival of 10.3 months and a satisfying overall response rate of 30%, which directly linked to pain palliation as shown in a pilot study (15). One major advantage of our scheme is the altered fractionation. The hyperfractionated accelerated therapy leads to a reduced length of treatment of only 3 weeks with an acceptable toxicity. These factors are very important in a primarily palliative intention of radiochemotherapy (41). There is only one study in the literature which also uses hyperfractionated accelerated radiochemotherapy with three daily fractions of 1.1 Gy for 3 weeks up to a total dose of 45-50 Gy. 5-Fluorouracil was administered as continuous infusion in a dose of 25 mg/kg/24 h the first and the third week concomitantly to radiotherapy (42). Overall, thirteen patients with localized unresectable pancreas carcinoma were treated and a mild and easily manageable toxicity was observed. However, they only had an overall response rate of 23% and median survival time of 9 months.

Clearly, the long-term efficacy concerning local tumor control and survival of all 5-FU-based radiochemotherapy protocols is limited (12, 14, 15, 43). This justifies the search for new approaches to improve prognosis and local and systemic tumor control. The introduction of predictive factors to identify patients, who may profit from a more aggressive treatment, even in the long course, is one step in this direction.

As shown in this study and our previous studies (32, 40, 44), as well as in other reports from the literature (45-47), the tumor marker CA 19-9 is of predictive value for prognosis and for tumor response. Therefore, it may serve as an additional parameter for radiooncologic treatment decisions and should be integrated in designing future prospective clinical trials (32, 40, 48, 49).

The deoxycytidine analog, gemcitabine (Gemzar®, Lilly Pharma), has recently been shown to be a potent

radiosensitizer in preclinical studies using human tumor cell lines, including pancreatic cancer cell lines (50). In a multicenter trial of patients with metastatic pancreatic cancer published by Burris *et al.* in 1997 (51), single-agent gemcitabine conferred a small but statistically significant survival benefit compared with 5-fluorouracil and what was defined as a "clinical benefit response." These differences led to U.S. Food and Drug Administration approval of gemcitabine in that setting. Thus, its integration with radiation in a combined modality regimen warranted further clinical investigation (37). One of the earliest clinical trials utilizing gemcitabine with concurrent radiation therapy discredited this treatment regimen due to unacceptably high toxicity: (Scalliet *et al.* (52), patients with Stage III non-small cell lung cancer with a combined modality treatment). In this trial, a conventional course of radiation therapy (60 Gy in six weeks) was delivered with a weekly intravenous infusion of gemcitabine at 1000 mg/m^2. The trial was closed after eight patients were accrued, secondary to unacceptable pulmonary toxicity (four out of eight patients with Grade 4/5 pulmonary toxicity). The toxicity was attributed, in part, to large radiation treatment volumes, but also provided evidence of substantial normal tissue radiosensitization. The need for phase I trials to investigate gemcitabine dose escalation with concurrent radiation therapy is thus highlighted (53). A variety of phase I and II studies suggested that, in combination with radiotherapy, gemcitabine doses should generally be reduced to 300–500 mg/m^2 when applied once weekly or to 40 mg/m^2 when given twice weekly (25, 37, 41, 53-59). Recent reports have clearly indicated that control of toxicity is closely dependent on the tight definitions of dose, fractionation and volume of radiation (37, 53, 58-61). Some phase II trials, as well as the results of our study with a non-randomized comparison, suggested gemcitabine-based radiochemotherapy schemes to be more effective concerning local control, time to progression and overall survival compared to the previous 5-FU-based radiochemotherapy studies (24, 29, 37, 41, 54, 58, 62, 63). In fact, this topic is still controversial, particularly with the background of increased toxicity in the gemcitabine-based radiochemotherapy schemes (37, 53, 55, 59-61, 64-66).

In our study we showed significantly superior treatment results in the Gem/Cis group compared to the 5-FU/FA group in this consecutive non-randomized comparison. The toxicity was slightly higher in the Gem/Cis group, but still acceptable and easily manageable, considering the low volume of the three-dimensional conformal radiotherapy used in the study (67). Our results give a hint that even hyperfractionated accelerated radiochemotherapy with a shortened treatment time is possible in combination with gemcitabine. Clearly, the therapeutic index is still narrow and the irradiation volume is one of the most critical variables (29, 54, 61).

Conclusion

Radiochemotherapy in locally advanced pancreatic cancer is an effective and well-tolerated treatment. The long-term efficacy concerning survival is limited. The integration of predictive factors and new chemotherapeutic agents, like gemcitabine, in the multimodality treatment may give a more promising perspective. Because of the narrow therapeutic index of gemcitabine-based radiochemotherapy schemes, a feasible combination of radiotherapy treatment volume and gemcitabine dose must be found.

References

1 Cooperman AM: Pancreatic cancer: the bigger picture. Surg Clin North Am *81*: 557-574, 2001.

2 Niederhuber JE, Brennan MF and Menck HR: The National Cancer Data Base report on pancreatic cancer. Cancer *76*: 1671-1677, 1995.

3 Henne-Bruns D and Vogel I: Does the extent of lymphadenectomy have impact on the prognosis of patients with pancreatic cancer? Onkologie *25*: 69-71, 2002.

4 Beger HG, Gansauge F and Leder G: Pancreatic cancer: Who benefits from curative resection? Can J Gastroenterol *16*: 117-120, 2002.

5 Marotta F, Tajiri H, Yoshimori M, Nakamura K and Ozaki H: A nine year retrospective analysis of resectable pancreatic cancer at the National Cancer Center Hospital in Tokyo: clues to diagnosis and diagnostic assessment. Ital J Gastroenterol *23*: 197-201, 1991.

6 Conlon KC, Klimstra DS and Brennan MF: Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors. Ann Surg *223*: 273-279, 1996.

7 Ishii H, Okada S, Tokuuye K, Nose H, Okusaka T, Yoshimori M, Nagahama H, Sumi M, Kagami Y and Ikeda H: Protracted 5-fluorouracil infusion with concurrent radiotherapy as a treatment for locally advanced pancreatic carcinoma. Cancer *79*: 1516-1520, 1997.

8 Barkin JS and Goldstein JA: Diagnostic and therapeutic approach to pancreatic cancer. Biomed Pharmacother *54*: 400-409, 2000.

9 Ginsberg GG: New developments in pancreatic cancer. Semin Gastrointest Dis *11*: 162-167, 2000.

10 Postier RG: Past, present, and future of pancreatic surgery. Am J Surg *182*: 547-551, 2001.

11 Paulino AC and Latona C: Unresectable adenocarcinoma of the pancreas: patterns of failure and treatment results. Cancer Invest *18*: 309-313, 2000.

12 Pasetto LM, Jirillo A, Stefani M and Monfardini S: Is there a role for chemoradiotherapy in the treatment of pancreatic carcinoma? Anticancer Res *23*: 2805-2813, 2003.

13 Cappelli G, Paladini S and D'Agata A: Tumor markers in the diagnosis of pancreatic cancer. Tumori *85*: S19-21, 1999.

14 McGinn CJ and Zalupski MM: Combined-modality therapy in pancreatic cancer: current status and future directions. Cancer J *7*: 338-348, 2001.

15 Prott FJ, Schonekaes K, Preusser P, Ostkamp K, Wagner W, Micke O, Potter R, Sulkowski U, Rube C, Berns T and Willich N: Combined modality treatment with accelerated radiotherapy and chemotherapy in patients with locally advanced inoperable carcinoma of the pancreas: results of a feasibility study. Br J Cancer *75*: 597-601, 1997.

16 Fisher BJ, Perera FE, Kocha W, Tomiak A, Taylor M, Vincent M and Bauman GS: Analysis of the clinical benefit of 5-fluorouracil and radiation treatment in locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys *45*: 291-295, 1999.
17 Shinchi H, Takao S, Noma H, Matsuo Y, Mataki Y, Mori S and Aikou T: Length and quality of survival after external-beam radiotherapy with concurrent continuous 5-fluorouracil infusion for locally unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys *53*: 146-150, 2002.
18 GTSG: Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. J Natl Cancer Inst *80*: 751-755, 1988.
19 Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, Schutt AJ, Weiland LH, Childs DS, Holbrook MA, Lavin PT, Livstone E, Spiro H, Knowlton A, Kalser M, Barkin J, Lessner H, Mann-Kaplan R, Ramming K, Douglas HO Jr, Thomas P, Nave H, Bateman J, Lokich J, Brooks J, Chaffey J, Corson JM, Zamcheck N and Novak JW: Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5- fluorouracil: The Gastrointestinal Tumor Study Group. Cancer *48*: 1705-1710, 1981.
20 Andre T, Balosso J, Louvet C, Hannoun L, Houry S, Huguier M, Colonna M, Lotz JP, De Gramont A, Bellaiche A, Parc R, Touboul E and Izrael V: Combined radiotherapy and chemotherapy (cisplatin and 5-fluorouracil) as palliative treatment for localized unresectable or adjuvant treatment for resected pancreatic adenocarcinoma: results of a feasibility study. Int J Radiat Oncol Biol Phys *46*: 903-911, 2000.
21 Boz G, De Paoli A, Innocente R, Rossi C, Tosolini G, Pederzoli P, Talamini R and Trovo MG: Radiotherapy and continuous infusion 5-fluorouracil in patients with nonresectable pancreatic carcinoma. Int J Radiat Oncol Biol Phys *51*: 736-740, 2001.
22 Ardalan B, Ucar A, Reddy R, Livingstone AS, Markoe A, Schwade J, Richman SP and Donofrio K: Phase I trial of low dose N-phosphonacetyl-L-aspartic acid and high dose 5-fluorouracil administered concomitantly with radiation therapy for unresectable localized adenocarcinoma of the pancreas. Cancer *74*: 1869-1873, 1994.
23 Cellini N, Costamagna G, Morganti AG, Valentini V, Macchia G, Mutignani M, Pandolfi M and Trodella L: Concomitant radiochemotherapy in unresectable carcinoma of the exocrine pancreas: cost-effectiveness analysis. Rays *24*: 447-452, 1999.
24 Ikeda M, Okada S, Tokuuye K, Ueno H and Okusaka T: Prognostic factors in patients with locally advanced pancreatic carcinoma receiving chemoradiotherapy. Cancer *91*: 490-495, 2001.
25 Wiegel T, Runkel N, Frommhold H, Rube C and Hinkelbein W: Radiotherapeutic strategies in the multimodal therapy of resectable and nonresectable pancreatic carcinoma. Strahlenther Onkol *176*: 299-306, 2000.
26 Seydel HG, Stablein DM, Leichman LP, Kinzie JJ and Thomas PR: Hyperfractionated radiation and chemotherapy for unresectable localized adenocarcinoma of the pancreas. The Gastrointestinal Tumor Study Group experience. Cancer *65*: 1478-1482, 1990.
27 Whittington R, Neuberg D, Tester WJ, Benson AB 3rd and Haller DG: Protracted intravenous fluorouracil infusion with radiation therapy in the management of localized pancreaticobiliary carcinoma: a phase I Eastern Cooperative Oncology Group Trial. J Clin Oncol *13*: 227-232, 1995.
28 Jeekel J and Treurniet-Donker AD: Treatment perspectives in locally advanced unresectable pancreatic cancer. Br J Surg *78*: 1332-1334, 1991.
29 Wenz F, Tiefenbacher U, Fuss M and Lohr F: Should patients with locally advanced, non-metastatic carcinoma of the pancreas be irradiated? Pancreatology *3*: 359-365, 2003.
30 UICC: TNM-Classification of Malignant Tumors. 4th ed. Springer, Berlin Heidelberg New York, 1997.
31 EGTM: Tumour markers in gastrointestinal cancers - EGTM recommendations. European Group on Tumour Markers. Anticancer Res *19*: 2811-2815, 1999.
32 Micke O, Bruns F, Schafer U, Kurowski R, Horst E and Willich N: CA 19-9 in the therapy monitoring and follow-up of locally advanced cancer of the exocrine pancreas treated with radiochemotherapy. Anticancer Res *23*: 835-840, 2003.
33 Kaplan EL and Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc *53*: 457-481, 1958.
34 Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep *50*: 163-170, 1966.
35 Cox DR: Regression models and life-tables. J R Stat Soc [B] *34*: 187-220, 1972.
36 Kuhlmann KF, De Castro SM, Wesseling JG, Ten Kate FJ, Offerhaus GJ, Busch OR, Van Gulik TM, Obertop H and Gouma DJ: Surgical treatment of pancreatic adenocarcinoma; actual survival and prognostic factors in 343 patients. Eur J Cancer *40*: 549-558, 2004.
37 Abrams RA: Primary malignancies of the pancreas, periampulary region and hepatobilary tract - Considerations for the radiation oncologist. 44th Annual Meeting of the American Society for Therapeutic Radiology and Oncology 2002;49.
38 Mohiuddin M, Cantor RJ, Biermann W, Weiss SM, Barbot D and Rosato FE: Combined modality treatment of localized unresectable adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys *14*: 79-84, 1988.
39 Komaki R, Wadler S, Peters T, Byhardt RW, Order S, Gallagher MJ, Herskovic A and Pederson J: High-dose local irradiation plus prophylactic hepatic irradiation and chemotherapy for inoperable adenocarcinoma of the pancreas. A preliminary report of a multi-institutional trial (Radiation Therapy Oncology Group Protocol 8801). Cancer *69*: 2807-2812, 1992.
40 Micke O, Bruns F, Kurowski R, Horst E, deVries AF, Hausler JW, Willich N and Schafer U: Predictive value of carbohydrate antigen 19-9 in pancreatic cancer treated with radiochemotherapy. Int J Radiat Oncol Biol Phys *57*: 90-97, 2003.
41 Micke O, Hesselmann S, Horst E, Bruns F, Horst E, Willich N and Schafer U: Results and follow-up of locally advanced cancer of the exocrine pancreas treated with radiochemotherapy. Anticancer Res *23*: 4486-4487, 2003.
42 Luderhoff EC, Gonzalez Gonzalez D and Bakker P: Pilot study in locally advanced unresectable pancreas carcinoma using a combination of accelerated radiotherapy and continuous infusion of 5-fluorouracil. Radiother Oncol *40*: 241-243, 1996.
43 Ridwelski K, Meyer F, Ebert M, Malfertheiner P and Lippert H: Prognostic parameters determining survival in pancreatic carcinoma and, in particular, after palliative treatment. Dig Dis *19*: 85-92, 2001.
44 Micke O, Hesselmann S, Schafer U, Bruns E, Horst E and Willich N: Results of combined radiochemotherapy in locally advanced cancer of the exocrine pancreas. Strahlenther Onkol *180*: 16-16, 2004.
45 Stemmler J, Stieber P, Szymala AM, Schalhorn A, Schermuly MM, Wilkowski R, Helmberger T, Lamerz R, Stoffregen C, Niebler K, Garbrecht M and Heinemann V: Are serial CA 19-9 kinetics helpful in predicting survival in patients with advanced or metastatic pancreatic cancer treated with gemcitabine and cisplatin? Onkologie *26*: 462-467, 2003.

46 Willett CG, Daly WJ and Warshaw AL: CA 19-9 is an index of response to neoadjunctive chemoradiation therapy in pancreatic cancer. Am J Surg *172*: 350-352, 1996.
47 Ohara K, Tatsuzaki H, Molotkova NG, Oda T, Yuzawa K, Saida Y, Matsuzaki Y, Shimizu W, Todoroki T, Fukao K, Tanaka N and Itai Y: Utility of serum CA 19-9 monitoring in preoperative radiotherapy for pancreatic cancer. Hepatogastroenterology *48*: 859-863, 2001.
48 Klapdor R, Bahlo M, Babinski A, Broemel T, Muller C and Seutter R: Sequential polychemotherapy in exocrine pancreatic cancer. Anticancer Res *23*: 841-844, 2003.
49 Büntzel J, Mücke R, Kisters K and Micke O: Report of the Fifth Workshop on Trace Elements and Electrolytes - AKTE 2/2003, Hannover, Germany, November 15, 2003. Trace Elem Electrolytes *21*: 278-280, 2004.
50 Lawrence TS, Eisbruch A, McGinn CJ, Fields MT and Shewach DS: Radiosensitization by gemcitabine. Oncology (Huntingt) *13*: 55-60, 1999.
51 Burris HA, 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD and Von Hoff DD: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol *15*: 2403-2413, 1997.
52 Scalliet P, Goor C, Galdermans D, Meerbeek J, Groen HJ, Van de Leest AHD, Westerink H, Jungnelius U and Turrisi A: Gemcitabine (Gemzar®) with thoracic radiotherapy: a Phase II pilot study in chemonaive patients with advanced non-small cell lung cancer (NSCLC) [abstract]. Proc Am Soc Clin Oncol *17*: 499a, 1998.
53 McGinn CJ and Zalupski MM: Radiation therapy with once-weekly gemcitabine in pancreatic cancer: current status of clinical trials. Int J Radiat Oncol Biol Phys *56*: 10-15, 2003.
54 Wilkowski R, Thoma M, Heinemann V, Rau HG, Wagner A, Stoffregen C and Duhmke E: Radiochemotherapy with gemcitabine and cisplatin in pancreatic cancer - feasible and effective. Strahlenther Onkol *179*: 78-86, 2003.
55 Talamonti MS, Catalano PJ, Vaughn DJ, Whittington R, Beauchamp RD, Berlin J and Benson AB 3rd: Eastern Cooperative Oncology Group Phase I trial of protracted venous infusion fluorouracil plus weekly gemcitabine with concurrent radiation therapy in patients with locally advanced pancreas cancer: a regimen with unexpected early toxicity. J Clin Oncol *18*: 3384-3389, 2000.
56 Wolff RA, Evans DB, Gravel DM, Lenzi R, Pisters PW, Lee JE, Janjan NA, Charnsangavej C and Abbruzzese JL: Phase I trial of gemcitabine combined with radiation for the treatment of locally advanced pancreatic adenocarcinoma. Clin Cancer Res *7*: 2246-2253, 2001.
57 McGinn CJ, Lawrence TS and Zalupski MM: On the development of gemcitabine-based chemoradiotherapy regimens in pancreatic cancer. Cancer *95*: 933-940, 2002.
58 McGinn CJ, Zalupski MM, Shureiqi I, Robertson JM, Eckhauser FE, Smith DC, Brown D, Hejna G, Strawderman M, Normolle D and Lawrence TS: Phase I trial of radiation dose escalation with concurrent weekly full-dose gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol *19*: 4202-4208, 2001.
59 Crane CH, Janjan NA, Evans DB, Wolff RA, Ballo MT, Milas L, Mason K, Charnsangavej C, Pisters PW, Lee JE, Lenzi R, Vauthey JN, Wong A, Phan T, Nguyen Q and Abbruzzese JL: Toxicity and efficacy of concurrent gemcitabine and radiotherapy for locally advanced pancreatic cancer. Int J Pancreatol *29*: 9-18, 2001.
60 Crane CH, Abbruzzese JL, Evans DB, Wolff RA, Ballo MT, Delclos M, Milas L, Mason K, Charnsangavej C, Pisters PW, Lee JE, Lenzi R, Vauthey JN, Wong AB, Phan T, Nguyen Q and Janjan NA: Is the therapeutic index better with gemcitabine-based chemoradiation than with 5-fluorouracil-based chemoradiation in locally advanced pancreatic cancer? Int J Radiat Oncol Biol Phys *52*: 1293-1302, 2002.
61 Crane CH, Wolff RA, Abbruzzese JL, Evans DB, Milas L, Mason K, Charnsangavej C, Pisters PW, Lee JE, Lenzi R, Lahoti S, Vauthey JN and Janjan NA: Combining gemcitabine with radiation in pancreatic cancer: understanding important variables influencing the therapeutic index. Semin Oncol *28*: 25-33, 2001.
62 Li CP, Chao Y, Chi KH, Chan WK, Teng HC, Lee RC, Chang FY, Lee SD and Yen SH: Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine *versus* 5-fluorouracil, a randomized controlled study. Int J Radiat Oncol Biol Phys *57*: 98-104, 2003.
63 Wilkowski R, Heinemann V and Rau H: Locally advanced pancreatic carcinoma. Radiochemotherapy prolongs survival. MMW Fortschr Med *142*: 31-32, 2000.
64 Crane CH: In response to Li *et al*: Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine *versus* 5-fluorouracil, a randomized controlled study. IJROBP *57*: 98-104, 2003. Int J Radiat Oncol Biol Phys *58*: 1009; author reply 1009-1010, 2004.
65 Li CP, Chao Y and Yen SH: In response to Dr. Crane: role of concurrent gemcitabine-based chemoradiation and regional nodal irradiation in the treatment of locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys *58*: 1009-1010, 2004.
66 Morganti AG, Trodella L, Valentini V, Macchia G, Alfieri S, Smaniotto D, Luzi S, Costamagna G, Doglietto GB and Cellini N: Concomitant gemcitabine (Gemzar) and extended nodes irradiation in the treatment of pancreatic and biliary carcinoma: a phase I study. Onkologie *26*: 325-329, 2003.
67 Horst E, Micke O, Moustakis C, Schuck A, Schafer U and Willich NA: Conformal therapy for pancreatic cancer: variation of organ position due to gastrointestinal distention--implications for treatment planning. Radiology *222*: 681-686, 2002.

Received August 2, 2004
Revised December 27, 2004
Accepted January 12, 2005