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ORIGINAL ARTICLE

Chemoradiotherapy with Gemcitabine and Continuous 5-FU in Patients with Primary Inoperable Pancreatic Cancer

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ABSTRACT

Context Gemcitabine and 5-fluorouracil (5-FU) sensitize tumor cells to radiation. Furthermore, 5-FU enhances the cytotoxic effect of gemcitabine.

Objective We report the efficacy and the toxicity of concurrent chemoradiation with gemcitabine and 5-FU in the treatment of patients with locally advanced, unresectable pancreatic cancer.

Patients Thirty-two patients (20 men, 12 women; median age 69.9 years) with histologically proven advanced pancreatic carcinoma were included in the study.

Interventions The patients received chemotherapy with gemcitabine 300 mg/m^2 on days 1, 15, 29 and 5-FU as continuous infusion 350 mg/m^2/day of radiation while concurrent radiation (45-50 Gy) was given to the tumor and regional lymph nodes (1.8-2.0 Gy/fraction on 5 days/week). Subsequent to chemoradiotherapy, the treatment was continued with an additional two cycles of gemcitabine (1,000 mg/m^2) and cisplatin (50 mg/m^2) applied on days 1 and 15 of a four-week cycle.

Main outcome measures Patient survival, time to progression, and toxicity of chemoradiation. Tumor responses (complete resolution; partial response; stable disease, and progressive disease) were also evaluated.

Results After the completion of chemo-radiotherapy, 2 patients (6.3%) achieved complete resolution and 18 patients (56.3%) a partial response, for an overall response rate of 62.5%. Twelve patients (37.5%) were considered resectable and 9 underwent laparotomy, 7 of whom had definitive pancreatic resection. Four patients had negative surgical margins. With a median follow-up of 49.7 months (95% CI: 48.6-60.8 months) after the completion of chemo-radiation, distant metastasis occurred in 25 patients (78.1%) while local recurrence was seen only in 4 of 32 patients (12.5%). Median time to progression was 9.2 months (95% CI: 8.2-10.2 months). Median survival amounted to 13.6 months (95% CI: 12.7-14.6 months) for all patients while it was prolonged to 16.4 months (95% CI: 13.4-19.4 months) for those undergoing secondary resection. In addition, performance status proved to be another prognostic factor for overall survival. The main toxicity of chemoradiation included grade 3-4 leukopenia in 18 patients (56.3%) and thrombocytopenia in 8 patients (25.0%). Episodes of cholangitis were observed in 7 patients (21.9%).

Conclusion Gemcitabine and 5-FU can safely be combined with external beam radiation. This preoperative treatment approach is

highly effective and appears to improve survival in patients with good performance status and in those who are eligible for a secondary resection.

INTRODUCTION

Pancreatic carcinoma has a dismal prognosis with a 5-year overall survival of only 1-4%. Because early disease is not associated with typical symptoms, only 10-20% of the patients are eligible for curative surgery at the time of diagnosis [1] while up to 40% of the patients present with locally advanced disease [2]. The combined application of radiation and chemotherapy is one treatment option for patients with locally advanced disease which is no longer amenable to curative surgery. In particular, the randomized Gastrointestinal Tumor Study Group (GITSG) trials have demonstrated that a combined modality treatment is superior to either radiation therapy or chemotherapy given alone [3, 4]. During the past decades, pancreatic cancer has been considered a disease which is relatively resistant to radiation and chemotherapy. More recently, however, this view has increasingly been recognized to be inappropriate. Many authors have shown that, after primary chemoradiotherapy, at least some of the patients initially considered inoperable are eligible for secondary surgery with curative intention [5, 6, 7].

Over decades, 5-fluorouracil (5-FU) has been considered the agent of choice for cytotoxic chemotherapy, and it is still regarded as the current standard for use with concurrent radiation. Since 1996, the pyrimidine analogue gemcitabine is approved for the treatment of pancreatic cancer. Because of its favorable safety profile and the superior response rates when compared to 5-FU, as demonstrated in several trials [8, 9, 10],

Table 1. Inclusion and exclusion criteria for the Munich Pancreas Trial

Inclusion criteria

- Histologically proven, locally advanced, primarily inoperable pancreatic carcinoma stage III, IVa
- Carcinoma of the Papilla of Vater from ductal type
- No systemic metastases
- Age between 18-75 years
- Karnofsky-Performance Status equal to, or greater than 70 % (ECOG less than 2)
- At least a 2-dimensionally measurable tumor lesion
- Leucocytes, thrombocytes, and hemoglobin equal to or greater than 3,500/µL, 100,000/µL, and 10 g/dL, respectivel
- Written consent statement
- Patients' compliance and geographical proximity
- Life expectancy equal to or greater than 3 months
- Appropriate contraception as long as 3 months after completion at women at childbearing age

Exclusion criteria

- Previous abdominal radiotherapy
- Serious psychological disease
- Pregnancy and inadequate or not secure contraception or breastfeeding women
- Creatinine clearance less than 80 mL/min
- Other previous malignant disease in the past two years (excluding: non-melanoma-type skin cancer, as well a curative treated carcinoma in situ of the cervix and tumor disease, treated only with operative therapy and having 10-year disease-free survival)
- Actual cerebral metastasis. Excluding patients with cerebral metastases removed with stereotaxy or other types c surgery (intervention carried out more than 8 weeks earlier)
- Serious systemic concomitant diseases, excluding participation in a trial (according to the judgment of the inspectin physician)
- Other experimental treatment during or within 6 weeks prior to this trial (including chemotherapeutic medicine c immune-therapies)
- Every other condition or therapy assessed by the physician as an eventual risk for the patient or restricting the aim of the trial
- Distant metastasis

gemcitabine has become the new chemotherapy standard for pancreatic cancer. Moreover, gemcitabine has a well-documented radiosensitizing effect and therefore is a promising agent for concurrent treatment with radiation [11, 12].
This study investigates the clinical application of chemoradiotherapy with gemcitabine and 5-FU applied as continuous infusion in locally advanced inoperable pancreatic cancer with a specific focus on feasibility and local efficacy.

MATERIALS AND METHODS

Patient Characteristics

Since April 1999, a total of 32 patients with histologically verified pancreatic cancer received chemoradiation with gemcitabine plus continuous infusion 5-FU at our institution. All patients had non-metastatic, locally advanced disease considered unresectable by an interdisciplinary team. Surgical unresectability was defined by computerized tomography (CT) scanning showing portal and/or mesenteric and/or celiac axis involvement. An additional exploratory laparotomy was performed in 11 (34%) patients. No patient fulfilled the inclusion criteria (Table 1) for the multicenter Munich Pancreas Trial (Phase-II study where chemoradiation (CRT) with 5-FU is compared with CRT + gemcitabine/cisplatin plus/minus sequential chemotherapy) regarding age (greater than 75 years in 16 patients, 50.0%), performance status (AJCC-ECOG equal to 2 in 15 patients, 46.9%) or second malignancy in case history (1 patient, 3.1%). The patient and tumor characteristics are shown in Table 2. The period of concurrent chemoradio-therapy was administered as inpatient and the sequential chemotherapy was completed as outpatient.

Radiotherapy

All patients had conformal radiotherapy with 6 to 15 MV photon beams using CT-assisted three-dimensional treatment planning (HELAX^{TM}, Version 6, Nucletron, Columbia, MD, USA). The radiation dose to adjacent organs at risk (liver, kidneys, spinal cord) was derived from dose-volume histograms to avoid exceeding the tolerance limits. The dose was limited to 40.0 Gy for the spinal cord, to 30.0 Gy for the right kidney in 50%, to 20.0 Gy for the left kidney in 50 % organ volume and to 12.5 Gy for the liver in 75%, 25.0 Gy in 50% and 37.5 Gy in 25% organ volume.
The clinical target volume (clinical target volume II = CTV II) included the macroscopic pancreatic tumor and the regional peripancreatic lymph nodes with a safety margin of 2-3 cm. In 19 patients, this

Table 2. Patient and tumor characteristics.

Characteristics	Patients (n=32)
Age (years)	
Median (95% CI)	69.9 (52.9-82.7)
Less than or equal to 75 years	16 (50.0%)
Greater than 75 years	16 (50.0%)
Sex	
Female	12 (37.5%)
Male	20 (62.5%)
Symptoms at baseline	
Jaundice	12(37.5%)
Pain	15(46.9%)
Weight loss	15(46.9%)
Performance status	
ECOG 0-1	17 (53.1%)
ECOG 2	15 (46.9%)
Primary tumor site	
Head of the pancreas	23 (71.9%)
Body/tail of the pancreas	6 (18.8%)
Tail of the pancreas	3 (9.4%)
Stage (UICC 1997)	
III	4 (12.5%)
IVa	28 (87.5%)
Nodal involvement	
No	15 (46.9%)
Yes	17 (53.1%)
Grading [a]	
Well differentiated (G1)	1 (3.1%)
Moderately differentiated (G2)	16 (50.0%)
Poorly differentiated (G3)	13 (40.6%)

[a] The histopathological grading was not classified in two patients

volume was irradiated to a total dose of 45.0 Gy at the reference point by the International Commission on Radiation Units and Measurements (ICRU) with conventional fractionation (1.8 Gy per fraction, 5 days a week).
In 13 patients, the macroscopic tumor was irradiated with a safety margin of 1-2 cm (clinical target volume I = CTV I) with single doses of 2.0 Gy at the ICRU reference point to a total dose of 50.0 Gy; in these cases, planning was aimed at the 90% isodose surrounding the CTV II as defined above to ensure that single doses of 1.8 Gy and a total dose of 45.0 Gy were achieved in that volume. Dose increase in CTV I was carried out only in case of patients where we could distinguish between the macroscopic tumor and the desmo-plastic reactions of the pancreas through contrast medium absorption in treatment planning CT.

Administration of Chemotherapy with Gemcitabine and 5-FU

In addition to radiation therapy, patients received concurrent chemotherapy with gemcitabine 300 mg/m^2 on days 1, 15, and 29 given approximately 1 hour before irradiation. 5-FU was applied each radiation day as continuous infusion with 350 mg/m^2/day. Three weeks after the completion of concurrent chemoradiation, in 19 patients, an additional one or two cycles of gemcitabine 1,000 mg/m^2 (30 min) and cisplatin 50 mg/m^2 (60 min) (gemcitabine/cisplatin regimen) were administered on days 1 and 15 of a 4-week regimen. This sequential chemotherapy was administered only in patients having no leuko- and thrombopenia 3 weeks after the completion of CRT and having a completely normal blood count at this time. Doses of gemcitabine and cisplatin were reduced to 50% when hematological grade 2 toxicity was observed on the scheduled day of chemotherapy application. Chemotherapy was withheld at hematological toxicities grade 3-4.

Follow-up and Restaging

Response to treatment was assessed by CT scans after the completion of sequential chemotherapy, i.e., approximately 8 to 10 weeks after the completion of chemo-radiation. Patients who responded were then reassessed for resectability. In addition, all patients were monitored clinically and chemically, with abdominal and chest CT scans, and tumor markers CA19-9 and CEA after the completion of radiation, after the completion of sequential chemotherapy and then every 8 to 12 weeks.

Surgery

After the completion of chemoradiotherapy, staging was performed by CT scans and patients were reevaluated for surgery. Decisions on surgery were based on technical resectability as defined by CT imaging.

Study Definitions

Tumor responses were generally evaluated by CT scanning. Complete response (CR) was defined as complete resolution of all evidence of the tumor without development of new lesions during the time of evaluation. Partial responses (PRs) were diagnosed when tumors showed an at least 50% reduction of the maximum perpendicular tumor measurements without the appearance of new lesions. Stable disease (SD) required a modification of lesion measurement ranging from less than 50% reduction to less than 25% increase. Progressive disease (PD) was defined as an increase of tumor lesions greater than 25% or the occurrence of new lesions.
Time to progression was defined as the interval between the start of treatment until the documentation of local progression or metastasis by imaging procedures (CT or MRT). Median overall survival was measured from time of histological diagnosis until patient death. Chemoradiotherapy was generally started subsequent to diagnosis.

After secondary surgery, resection margins were considered free of tumor (R0-resection) when margins exceeded 5 mm. Otherwise surgical results qualified as R1-resections, unless macroscopically categorized as R2-resections by the surgeons.
Toxicities related to radiochemotherapy and subsequent chemotherapy were assessed according to the common toxicity criteria (CTC) for the grading of acute and subacute side effects.

ETHICS

Written informed consent was obtained from each patient. Treatment was performed conforming to the ethical guidelines of the "World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo 2004.

STATISTICS

Survival and time to progression were measured according to the Kaplan-Meier method, and the median values, together with 95% confidence intervals (CI), were reported. Comparison between prognosis groups was performed by log rank analysis. Backward stepwise multivariate Cox regression was also applied and the hazard ratios (HRs) of the variables which entered the procedure were reported together with their 95% CI. Data were analyzed by means of the SPSS for Windows, version 11.5.1. Two-tailed P values less than 0.05 were considered significant.

RESULTS

Thirty-two patients were included in the study and completed chemoradiotherapy. At the time of data evaluation in March 2005, 4 (12.5%) of the 32 treated patients were still alive with a median follow-up of 10.6 months (95% CI: 8.4-12.8 months) after completion of chemoradiation.

Response

Response to chemoradiation is shown in detail in Table 3. All patients were valuable for response. Partial response as documented by CT imaging was observed in 18 patients (56.3%),ì and complete response was achieved in 2 patients (6.3%) for an overall response rate of 62.6%.The remaining 12 (37.5%) patients had stable disease and no patients had progressive disease. Upon reassessment after chemoradiation, 12 patients (37.5%) were considered resectable. Three patients refused surgery and two patients were found to be ineligible for curative resection intraoperatively because of local unresectability (1 patient) or unexpected metastasis (1 patient). In these patients, the surgery was terminated and served as an explorative laparotomy. A pancreatico-duodenectomy was conducted in 6 patients with a margin-negative histology (R0) in 4 patients and microscopic tumor residues (R1) in 2 patients. One patient had left pancreatic resection (R1 resection) (Figure 1).

Survival

The median overall survival rate for the 32 study patients was 13.6 months (95% CI: 12.7-14.6 months) from diagnosis. The

Table 3. Response to chemoradiotherapy.

	Patients (n=32)
Response (CT and/or MRI)	
Complete response (CR)	2 (6.3%)
Partial response (PR)	18 (56.3%)
Stable disease (SD)	12 (37.5%)
Patients deemed operable	12 (37.5%)
Operation refused	3
Laparotomy	9 (28.1%)
Explorative laparotomy	2 (6.3%)
- Locally inoperable	1
- Peritoneal carcinosis	1
Margin-negative resection (R0)	4 (12.5%)
- Pancreaticoduodenectomy	4
Margin-positive resection (R1)	3 (9.4%)
- Pancreaticoduodenectomy	2
- Left resection	1

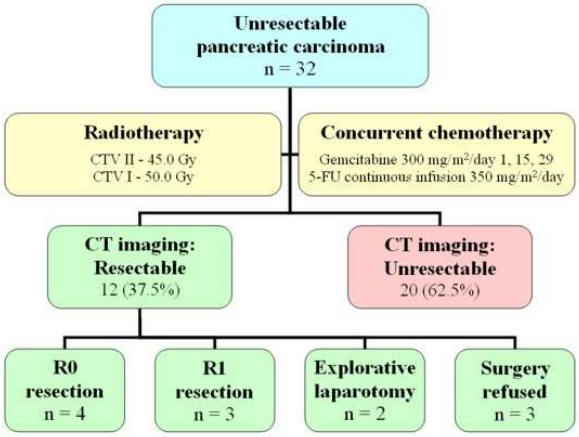

Figure 1. Resectability after chemoradiotherapy of initially unresectable, locally advanced pancreatic cancer. Following resection or registration of unresectability, all patients were monitored without therapy until tumor progression was observed.

actuarial 1-, 2-, 3- and 4-year survival-rate rates were 67.2%, 20.0%, 8.0% and 0%, respectively. In patients completing concurrent and sequential chemotherapy (n=19), the median overall survival rate was 15.2 months (95% CI: 12.0-18.4 months). Median tumor-related survival (considering only cancer-related deaths, n=18) was 13.3 months (95% CI: 12.0-14.7 months) from diagnosis, and median time to progression was 9.2 months (95% CI: 8.2-10.2 months) from the start of chemoradiotherapy.

Distant metastases developed in 25 of the 32 patients (78.1%) at a median of 9.2 months (95% CI: 8.2-10.2 months) following the start of chemoradiotherapy. The most frequently involved sites of metastasis were the liver (n=9, 36.0%), the lung (n=7, 28.0%) and the peritoneum (n=4, 16.0%). Local tumor progression was seen in only 4 patients (12.5%) at a median of 6.7 months (95% CI: 2.7-10.9) after chemoradiation.

A total of 28 (87.5%) patients died during follow-up. Of these, 18 patients died from disease progression, with a median time from diagnosis of 13.3 months (95% CI: 12.0-14.7 months). Ten patients died of causes unrelated to cancer (median time from diagnosis: 12.3 months; 95% CI: 5.3-19.4 months), including 2 deaths due to complications from secondary surgery (2 sepsis/liver abscess). The other 8 patients died from gastrointestinal bleeding by portal occlusion (n=3), infection (n=1), cardiac causes (n=2), cerebral insult (n=1), and pulmonary embolism (n=1).

Table 4. Prognostic factors.

	Survival from diagnosis (months)	
	Median	**95% CI**
Performance status		
ECOG 0-1 (n=17)	15.6	14.4-17.1
ECOG 2 (n=15)	11.5	8.4-14.6
	P=0.003	
Gender		
Female (n=12)	13.7	8.4-19.0
Male (n=20)	13.6	11.7-15.6
	P=0.464	
Age		
Less than or equal to 75 years (n=16)	15.3	10.2-20.3
Greater than 75 years (n=16)	13.6	11.9-15.7
	P=0.305	
Primary tumor stage (UICC 1997)		
III (n=4)	13.6	11.5-15.7
IVa (n=28)	13.3	11.2-15.5
	P=0.476	
Tumor site		
Head (n=23)	13.7	13.0-14.3
Body/tail (n=9)	13.0	8.8-17.2
	P=0.149	
Nodal involvement		
Yes (n=17)	13.7	11.4-16.0
No (n=15)	12.0	8.4-15.6
	P=0.264	
Histopathological grading [a]		
G2 (n=16)	13.7	10.1-17.3
G3 (n=13)	12.0	8.0-16.0
	P=0.799	
Response [b]		
CR/PR (n=20)	13.6	11.6-15.7
SD (n=12)	13.7	11.5-15.8
	P=0.715	
Sequential chemotherapy		
Yes (n=19)	15.2	12.0-18.4
No (n=13) [c]	13.6	5.3-22.0
	P=0.225	
Resectability		
Resection (n=7)	16.4	13.4-19.4
No resection (n=25)	13.0	10.8-15.3
	P=0.056	

[a] One patient with a well-differentiated tumor (G1) was not considered in this analysis and for two patients the histopathological grading was not classified

[b] Progression-free survival (CR/PR *vs*. SD): 8.9 months (95% CI: 6.7-11.1) *vs*. 9.5 months (95% CI: 8.6-10.3) (P=0.991)

[c] Chemotherapy with gemcitabine and 5-FU was applied only concomitant with radiotherapy, no sequential chemotherapy after combined chemo-radiation was given

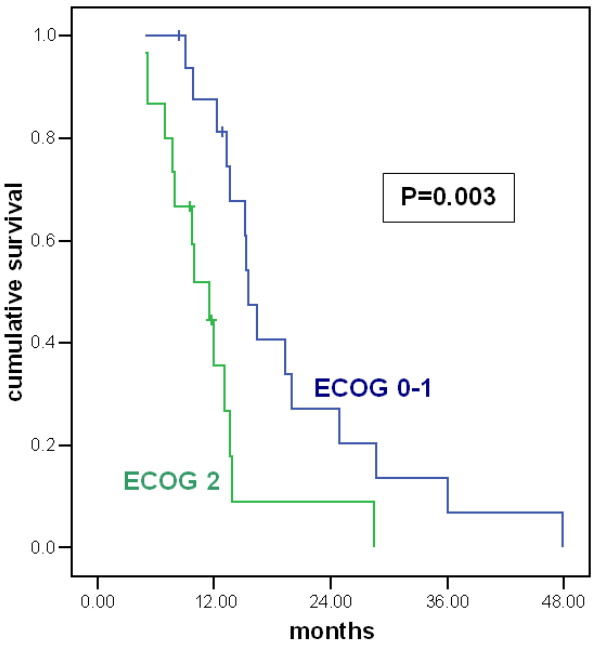

Figure 2. Kaplan-Meier survival curves by performance status.

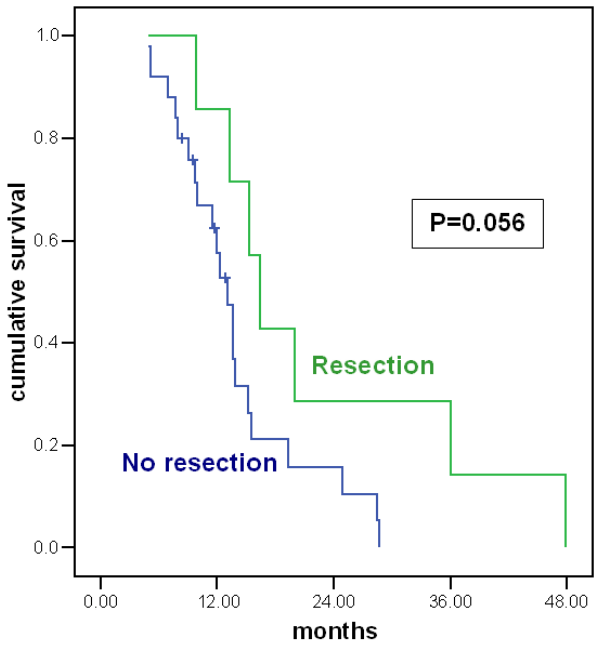

Figure 3. Kaplan-Meier survival curves by secondary operability.

Several factors which influence prognosis are outlined in Table 4. There was a significant association between survival and performance status (ECOG 0-1, median survival 15.6 months, 95% CI: 14.4-17.1 months; ECOG 2, median survival 11.5 months, 95% CI: 8.4 14.6 months; log rank P=0.003, Figure 2) while gender (P=0.464), age (P=0.305), initial tumor stage (P=0.476), tumor site (P=0.149), nodal involvement (P=0.264), histo-pathological grading (P=0.799), and response to chemoradiotherapy (P=0.715) were not significantly related to survival. Patients who could undergo a secondary resection had an improved overall survival rate which was borderline significant (P=0.056) when compared to the non-resected patients (Figure 3). The application of additional sequential chemotherapy did not prove to be a significant prognostic factor, neither for time to progression (0.693) nor for overall survival (P=0.225) (Table 4).

Multivariate Cox regression analysis was performed taking into account objective and reproducible factors. Despite the existing definitions for the performance status, this factor still remains subjective depending on the examiners evaluation; therefore it was not considered in the analysis. Table 5 shows the results of the backward stepwise multivariate Cox regression analysis, including the following factors: gender (female *vs*. male), tumor localization (body/tail *vs*. head), histopathologic grading (G3 *vs*. G2), initial lymph node involvement (yes *vs*. no), radiation dose (50 Gy *vs*. 45 Gy), sequential chemotherapy (yes *vs*. no), local remission (CP+PR *vs*. SD), and secondary resection. Secondary resection was the only factor capable of independently increasing the overall survival rate (P=0.042) while tumors of the head (P=0.045) and initial lymph node involvement (P=0.096) were the independent factors capable of increasing the time to

Table 5. Results of the backward stepwise multivariate Cox analysis [a].

Dependent variable	Independent variables in the analysis	HR	95% CI	P value
Overall survival	Secondary resection (yes *vs*. no)	0.347	0.125-0.963	0.042
Time to progression	Tumor localization (head *vs*. body/tail)	0.353	1.127-0.979	0.045
	Initial lymph node involvement (yes *vs*. no)	0.462	0.186-1.146	0.096

[a] Performed in the 29 patients with histopathological grading G2 or G3.

Table 6. Acute toxicities during treatment.

	All Patients (n=32)	Age		Performance status	
		Less than or equal to 75 years (n=16)	Greater than 75 years (n=16)	ECOG 0-1 (n=17)	ECOG 2 (n=15)
Leukopenia grade (nadir)					
0	1 (3.1%)	-	1 (6.3%)	-	1 (6.7%)
1	2 (6.3%)	1 (6.3%)	1 (6.3%)	1 (5.9%)	1 (6.7%)
2	11 (34.4%)	6 (37.5%)	5 (31.3%)	6 (35.3%)	5 (33.3%)
3	13 (40.6%)	5 (31.3%)	8 (50.0%)	7 (41.2%)	6 (40.0%)
4	5 (15.6%)	4 (25.0%)	1 (6.3%)	3 (17.6%)	2 (13.3%)
Thrombocytopenia grade (nadir)					
0	12 (37.5%)	6 (37.5%)	6 (37.5%)	7 (41.2%)	5 (33.3%)
1	9 (28.1%)	4 (25.0%)	5 (31.3%)	5 (29.4%)	4 (26.7%)
2	3 (9.4%)	3 (18.8%)	-	1 (5.9%)	2 (13.3%)
3	7 (21.9%)	2 (12.5%)	5 (31.3%)	3 (17.6%)	4 (26.7%)
4	1 (3.1%)	1 (6.3%)	-	1 (5.9%)	-

progression.

Toxicities and Complications

With the administration of adequate supportive care including metoclopramide or ondansetron, no grade 3 or 4 gastrointestinal toxicities (nausea/emesis) occurred during concurrent chemoradiation or the sequential administration of chemotherapy. We could see a WHO grade 1 or 2 nausea and emesis both in patients in ECOG 0-1 (12/17, 70.6%) *vs*. patients in ECOG 2 (11/15; 73.3%) and in patients less than or equal to 75 years of age (13/16, 81.3%) *vs*. patients more than 75 years of age (12/16, 75.0%) equally frequent (P=1.000 for both).

Hematotoxicity was noted as a major side effect during chemoradiotherapy (Table 6). At nadir, CTC grade 3 and 4 leukopenia was documented in 13 (40.6%) and 5 (15.6%) patients, respectively, while grade 3 and 4 thrombocytopenia developed in 7 (21.9%) and 1 (3.1%) patients, respectively. No significant (P=1.000) difference of grade 3-4 leukopenia was seen between the groups of patients less than or equal to 75 years of age (9/16, 56.3%) *vs*. those more than 75 years of age (9/16, 56.3%) as well as in ECOG 0-1 (10/17, 58.8%) *vs*. ECOG 2 (8/15; 53.3%) (Table 6). Similar results were observed for thrombocytopenia (less than or equal to 75 years of age: 3/16, 18.8%; more than 75 years of age: 5/16, 31.3%; P=0.685. ECOG 0-1: 4/17, 23.5%; ECOG 2: 4/15; 26.7%; P=1.000). With the appearance of leucopenia and/or thrombocytopenia, CTC grade III or IV, 5-FU infusion was discontinued for 2-3 days. A dose adaptation of gemcitabine on treatment days 15 and 29 was required in only 2 patients. In 7 of 19 patients, the dose of sequential chemotherapy had to be reduced due to hematological toxicity.

Repeated episodes of cholangitis presented a rather serious clinical problem. Patients at the highest risk for this complication were those with a stent placed because of bile duct obstruction. Episodes of cholangitis occurred in 7 patients. This included sepsis in four patients. Radiation-induced liver changes manifested as radiogenic hepatosis occurred in two patients but were completely reversible. Five patients experienced thromboembolic complications with consecutive pulmonary embolism, most likely of paraneoplastic origin. Directly after the completion of radiochemotherapy, a

Table 7. Complications occurring after treatment.

	Patients
Cholangitis [a]	7 (21.9%)
Radiogenic hepatosis	2 (6.3%)
Pulmonary embolism	5 (15.6%)
Radiogenic enteritis (subacute)	2 (6.3%)
Erosive gastritis (subacute)	2 (6.3%)

[a] Cholangitic sepsis: 4 patients

radiogenic duodenitis/enteritis was diagnosed by CT in two patients, clinically presenting as gastric outlet stenosis which improved rapidly under treatment with steroids. (Table 7). Another two patients developed erosive gastritis 3 and 5 months after radiochemotherapy, respectively which was treated conservatively.

Lethal complications did not occur during therapy nor did we observe any serious late adverse events potentially attributable to treatment.

DISCUSSION

The combined use of external-beam radiation and systemic chemotherapy has been widely recognized as the most effective treatment approach for patients with unresectable locally advanced pancreatic cancer. Based on the results of the GITSG trials [3, 4], several studies have evaluated 5-FU-based chemoradiation protocols and demonstrated improved response and survival rates when compared with radiation or chemotherapy alone. Furthermore, some studies have indicated that chemoradiotherapy may result in a downstaging of primarily inoperable pancreatic carcinomas permitting secondary potentially curative surgery [5, 6, 7].

5-FU-based chemoradiation is still regarded as a treatment standard for patients with locally advanced pancreatic cancer given the abundant experience gained with these protocols in the past. More recently, however, gemcitabine has assumed increased importance when chemotherapy is administered alone. This agent is well-tolerated, has a favorable toxicity profile and has shown superior efficacy in terms of response rate and symptom control when compared to 5-FU [8, 13]. Moreover, a radiosensitizing effect has been demonstrated for gemcitabine which lends further support to its concurrent use with radiation therapy.

Meanwhile, an increasing number of studies investigated concurrent chemoradiotherapy using gemcitabine either as a single agent [14, 15, 16, 17, 18, 19, 20, 21, 22] or in combination with other cytotoxic drugs [23, 24, 25, 26]. While the results appear promising with regard to local efficacy (OR=30-75%) [17], treatment-associated toxicity has evolved as a major concern. Crane *et al*. [27] analyzed 51 patients who received radiotherapy (30-33 Gy) with concurrent gemcitabine infusions (250-500 mg/m^2 weekly x 7). Severe acute toxicity was described in 24% of the patients, and 33% of the patients needed to be hospitalized. However, this study used an accelerated radiation regimen with a daily dose of 3.0 Gy. Since hypofractionation with high daily radiation doses may increase bowel toxicity, it cannot be ruled out that the radiation regimen itself contributed to enhanced toxicity. Talamonti *et al*. performed a phase I study [28] using radiotherapy (59.4 Gy in conventional fractionation) with concurrent continuous infusion 5-FU and a weekly application of gemcitabine. In this trial, toxicities associated with the skin, the stomach and the duodenum as well as prolonged thrombocytopenia (5 of 7 patients) already occurred at low weekly gemcitabine doses of 50 and 100 mg/m^2. It should be taken into account that the target dose of radiation was high (59.4 Gy) and that the authors chose a rather large field of radiation involving the pancreatic tumor and all lymph node groups at risk for occult metastasis. Again, it may be argued that the combination of a high dose of radiation with a large radiated volume may have caused the unexpectedly high gastrointestinal toxicity. In view of the radiation regimens used in both trials, the contribution of concurrent chemotherapy can not be defined.

The interaction between a standard dose of gemcitabine (1,000 mg/m^2, applied on days 1, 8, and 15) and radiation was explored in a phase I trial by McGinn *et al*. [29]. An escalation of the radiation dose up to 36.0 Gy (2.4 Gy/fraction) applied within 3 weeks proved to be tolerable when the radiation volume included only the pancreatic tumor (CTV I). This trial demonstrated a direct relationship between the radiation dose and the predominantly gastrointestinal toxicities.

Since the radiation dose of 36 Gy (2.4 Gy/fraction) relates to the biological

equivalence dose of 41.4 Gy (1.8 Gy/fraction), the radiation dose of 45 Gy (1.8 Gy/fraction) used in our trial appears to be comparable. Moreover, the gemcitabine doses used in our trial (300 mg/m^2) were considerably lower than those reported by McGinn *et al*. (1,000 mg/m^2) [29]. Adequate tolerability and a low rate of acute gastrointestinal side-effects has consequently been observed in both studies even though our trial included combination chemotherapy with additional 5-FU and also involved a larger volume of radiation including the regional lymph nodes.

The study presented here demonstrates that gemcitabine and 5-FU can be safely administered together with a lower dose of conventionally fractionated radiation (45-50 Gy, 1.8 Gy/fraction). The toxicity of the combination was acceptable and well-manageable with inpatient treatment. The low progression rate at the site of the radiated primary tumor (4/32) supports the high local efficacy of this protocol. Furthermore, the overall response rate of 63% achieved by this regimen was greatly superior to results reported for locally advanced pancreatic cancer patients treated with chemotherapy alone. Of the 32 initially inoperable patients, 38% were considered surgically resectable after completion of chemoradiotherapy. A complete (R0) resection was eventually achieved in 13% of the population analyzed (4/32).

As shown in Table 4, patients undergoing resection had a prolonged survival approaching significance when compared to unresectable patients, and it is only in these patients that prolonged disease-free survival can reasonably be expected.

The trials published up to now on 5-FU-based chemoradiotherapy which were performed in locally advanced unresectable pancreatic cancer showed response rates of 13% [6], 22% [30], 45% [31], and 67% [32]. Complete tumor resection was subsequently achieved in 13% [6], 13% [32], and 16% (100% R0) [30] of patients undergoing surgery with curative intention and was accompanied by a prolonged survival rate of up to 30 months.

A comparison of these data with our results indicates that gemcitabine-based chemoradiotherapy may improve local efficacy with a higher tumor control rate while prolonged survival has not yet been demonstrated.

On the other hand, Li *et al*. demonstrated in a randomized study [33] a significantly improved survival by chemoradiotherapy with gemcitabine versus 5-FU (14.5 *vs*. 6.7 months). The median time to progression was also significantly better (6.1 *vs*. 2.7 months). Nevertheless, it remains unclear whether these data really prove the superiority of chemoradiotherapy with gemcitabine regarding survival as the 5-FU results in this study appear quite poor and the number of patients is small (18 *vs*. 16 patients).

In conclusion, our data suggest that chemoradiotherapy with gemcitabine and 5-FU is safely applicable with a moderate and well manageable toxicity profile. Therefore, older patients and those with reduced performance status can be treated with this regimen. Primarily unresectable tumors may be rendered operable and prolonged survival can be achieved when complete resection is possible.

To define the relevance of gemcitabine-based chemoradiotherapy in terms of survival as compared to the former standard, i.e. 5-FU-based chemoradiation, controlled randomized trials are needed.

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Abbreviations 5-FU: 5-fluorouracil; CR: complete response; CRT: chemoradiation therapy; CTC: common toxicity criteria; CTV: clinical target volume; GITSG: Gastrointestinal Tumor Study Group; ICRU; International Commission on Radiation Units and Measurements; PD: progressive disease; PR: partial response; SD: stable disease

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