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ORIGINAL REPORT

Prospective Phase II Trial of Neoadjuvant Chemotherapy With Gemcitabine and Cisplatin for Resectable Adenocarcinoma of the Pancreatic Head

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ABSTRACT

Purpose
To test the safety of neoadjuvant chemotherapy for resectable pancreatic cancer.

Patients and Methods
Patients with cytologically proven resectable adenocarcinoma of the pancreatic head were eligible for this prospective phase II trial. After confirmation of resectability by contrast-enhanced computed tomography (ceCT), positron emission tomography/CT, laparoscopy, and endoscopic ultrasound, patients received four biweekly cycles of gemcitabine 1,000 mg/m^2 and cisplatin 50 mg/m^2. Thereafter, staging was repeated and patients underwent surgery. Quality of life (QoL) and prealbumin serum levels were determined pre- and postchemotherapy. Follow-up included 3-month CA 19-9 measurements and ceCT after 6, 12, 18, and 24 months. Histologic tumor response was assessed by two scoring systems.

Results
Twenty-eight patients entered this study. Adverse effects were mainly gastrointestinal and hematologic, most often mild, and never of grade 4. Twenty-six patients (93%) had resectable cancer on restaging examinations, and the R0 resection rate was 80%. Histologic tumor response and cytopathic effects were documented in 54% and 83% of patients, respectively. On intention-to-treat analysis, disease-free and overall survival were 9.2 months (95% CI, 5.6 to 12.9 months) and 26.5 months (95% CI, 11.4 to 41.5 months) and 9 months (95% CI, 6.99 to 10.1 months) and 19.1 months (95% CI, 15 to 23.1 months) for ductal adenocarcinoma, respectively. QoL improved in two items and was unchanged in all other items. Moreover, prealbumin serum levels significantly improved during chemotherapy ($P = .008$).

Conclusion
Neoadjuvant chemotherapy with gemcitabine and cisplatin is well tolerated and does not impair resectability of pancreatic cancer. Furthermore, it improves the QoL and the nutritional status of affected patients with favorable overall and disease-free survival.

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INTRODUCTION

Surgery offers the only potentially curative treatment for patients with pancreatic cancer. Refinements of the surgical technique and improved perioperative management have decreased mortality after pancreatico-duodenectomy (PD) to less than 5% during recent years.[1] Nevertheless, the long-term prognosis of patients with resectable cancer of the pancreatic head remains dismal, with a median overall survival of approximately 12 months after surgery alone.[2,3] This poor outcome is generally attributed to an aggressive tumor biology with early metastatic spread, although metastases are often undetected at the time of surgery.[4]

A better patient selection and multimodality treatment concepts are pivotal to improve survival. Although the addition of radiotherapy to adjuvant chemotherapy remains controversial,[5,6] adjuvant chemotherapy alone has demonstrated a benefit in recurrence-free and overall survival.[7,8] However, at least 25% of the patients at risk do not receive adjuvant treatment after PD for various reasons.[9] This major shortcoming can be avoided by the use of a neoadjuvant regimen. Preoperative regimens for patients with resectable pancreatic cancer have only been investigated in a few studies and were based on chemoradiotherapy (CRT),[10] in which the final resectability rates ranged between 45% and 65%.[11,12] The aim of the current study was to assess the safety

and efficacy of neoadjuvant chemotherapy in patients with resectable pancreatic cancer in a prospective phase II trial.

PATIENTS AND METHODS

Eligibility Criteria

Patients with resectable adenocarcinoma of the pancreatic head without contraindications for surgery, such as uncontrolled bleeding disorders or severe cardiovascular or pulmonary diseases, were eligible for this study. Patients with distant metastases or vascular infiltration of the superior mesenteric or the celiac arteries (T4) were excluded. Patients with infiltration of the portal vein (PV), the duodenum, or the stomach (T3) were not considered to have unresectable cancer. Other eligibility criteria were more than 18 years of age, WHO performance status of 0 to 2, absence of peripheral neuropathy, and adequate laboratory parameters (neutrophil count $>$ 1,000/μL, platelet count $>$ 100,000/μL, and creatinine clearance $>$ 60 mL/min). If the bilirubin level was greater than 100μmol/L, biliary decompression was mandatory. Female patients of childbearing age had to use adequate contraceptive measures.

Each case was reviewed in the weekly interdisciplinary tumor board before study inclusion, and all patients gave written informed consent. The study protocol was approved by the local ethics committee.

Staging Procedures

Staging included a contrast-enhanced computed tomography (ceCT) of the abdomen, endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) cytology, positron emission tomography (PET)/CT, and diagnostic laparoscopy. In the absence of a ceCT, PET/CT was performed with intravenous contrast (cePET/CT). In addition, CA 19-9 and prealbumin serum levels were measured, and the quality of life (QoL) was assessed with the Quality of Life Questionnaire Q-30 (QLQ-30) of the European Organisation for Research and Treatment of Cancer. Restaging was performed during the week before surgery (EUS and cePET/CT), and laparoscopy was always performed at the start of PD. Also, CA 19-9 and prealbumin serum levels as well as the QoL were reassessed.

Treatment Plan

Neoadjuvant chemotherapy consisted of four bi-weekly cycles of gemcitabine (1,000 mg/m^2) and cisplatin (50 mg/m^2). Before the administration of cisplatin, patients were adequately hydrated, and prophylactic antiemetic treatment with tropisetron, dexamethasone, and, in later years, aprepitant was applied. Adverse effects were ranked according to the common toxicity criteria of the National Cancer Institute (NCI).[13]

Dose Adjustment

Gemcitabine and cisplatin dosages were reduced by 50% in the event of neutrophil count of 500 to 1,000/μL or platelet count of 50,000 to 100,000/μL and paused if the neutrophil and platelet counts were less than 500/μL and 50,000/μL, respectively. The cisplatin dosage was also reduced by 50% if the creatinine clearance was less than 60 mL/min and paused if the clearance was less than 40 mL/min.

Furthermore, chemotherapy was postponed in the event of any NCI grade 3 to 4 toxicity until recovery to NCI grade 1, except nausea, emesis, and alopecia. In case of prolonged toxicity of more than 1 week, chemotherapy was terminated, and surgery was performed after restaging had excluded distant metastases.

Surgery

Surgery was scheduled 2 weeks after the last gemcitabine/cisplatin treatment. Sandostatin (3 $\times$ 0.1 mg) was started the evening before surgery and continued until postoperative day 5 to decrease the risk for pancreatic fistula.[14] A standard PD was performed, and all patients received a feeding jejunostomy. Low-dose enteral nutrition was started on postoperative day 1 using 10 mL/h and was adjusted during the postoperative period.

Follow-Up Schedule

Clinical follow-up with CA 19-9 measurement and QoL assessment was scheduled at 3-month intervals. CeCT was performed at months 6, 12, 18, and 24 and thereafter every 12 months. It was performed earlier in case of clinical evidence suggestive of recurrence.

Disease Recurrence

Disease recurrence was defined as any new or progressing lesion with histologic proof of adenocarcinoma or if a concomitant increase in CA 19-9 was followed by further progression on follow-up scans.

Radiologic Tumor Response

Radiologic tumor response was determined using Response Evaluation Criteria in Solid Tumors criteria for staging and restaging ceCT (magnetic resonance imaging).[17]

Pathologic Reassessment and Tumor Response

All resected specimens were independently reassessed by a staff pathologist (A.W.) after study completion according to the sixth edition of the TNM staging system.[15] Histologic tumor response to chemotherapy was assessed and graded according to an established score[16]: tumor destruction up to 10%, grade 1; 10% to 50%, grade 2a; 50% to 90%, grade 2b, greater than 90%, grade 3; and complete response, grade 4.

We also assessed cytopathic effects of cancer cells to chemotherapy from grade 0 to 2 based on cell swelling, cytoplasmic vacuolation/clearing, and nuclear condensation/irregularities. Tumors without any or only one of these criteria were grade 0, those with two were grade 1, and those revealing all criteria were grade 2.

Statistics

The primary study end point was the resectability rate ($\geq$ 70%) based on the restaging procedures. If a tumor was found to be nonresectable only on surgical exploration, nonresectability was not attributed to neoadjuvant chemotherapy, because resectability was presumably also misdiagnosed by the initial staging. On the basis of this assumption, a total of 28 patients were required according to Simon's two-stage phase II design to achieve a power of 80% ($P <$ .05).[18] The risk of rejecting an effective treatment or of accepting an ineffective treatment is 10% each.

Secondary study end points were a local recurrence rate less than 50% within the first year after resection and a median survival of more than 18 months. Overall and disease-free survivals were estimated according to the Kaplan-Meier method using the log-rank test from study inclusion until the event. Continuous variables were compared using the (paired) student t test and are expressed as mean ($\pm$ standard deviation [SD]). Dichotomous data were compared using the χ^2 test (McNemar, where appropriate). P values less than .05 were considered significant. The SPSS 12.0.1 program (SPSS Inc, Chicago, IL) was used for statistical analyses.

RESULTS

This prospective phase II trial was performed at the University Hospital of Zurich between August 2001 and April 2007. Twenty-eight consecutive patients were entered onto the study (Table 1). One patient had simultaneous rectal cancer (T3N0) and received neoadjuvant chemotherapy after reconvalescence from rectal resection. One patient was diagnosed with pancreatic cancer 10 months after renal transplantation. Furthermore, one patient had hepatic echinococcus alveolaris infection and was treated by simultaneous hemihepatectomy and PD.

Treatment Outcome/Resectability

After chemotherapy, all patients were considered to have resectable cancer by cePET/CT and EUS, including two patients with false-positive lesions in the liver on PET/CT. Two patients had peritoneal

Table 1. Baseline Patient Characteristics

Characteristic	No.	%
Age, years		
Median	59	
Range	39-77	
Sex		
Male	16	57
Female	12	43
Internal biliary drainage	22	79
Duodenal stent	1	3
Time from study inclusion to treatment, days		
Median	13.5	
Range	4-56	
Follow-up, months		
Median	16.6	
Range	3.1-58.5	

metastases at restaging laparoscopy (see Protocol Violations). Therefore, 26 (93%) of 28 patients were considered to have resectable disease based on restaging examinations.

However, another tumor was locally nonresectable at surgical exploration because of infiltration of the mesenteric axis. Finally, 25 (89%) of 28 patients underwent PD. Of these, 20 patients (80%) underwent an R0 resection. Portal vein resections were performed in three patients (12%) because of the macroscopic suspicion of cancer invasion, which was histologically confirmed in only one patient. Another patient required a reconstruction of the superior mesenteric artery because of iatrogenic vascular laceration.

We observed one pancreatic fistula and no delayed gastric emptying postoperatively. One patient died 39 days after surgery from massive bleeding from a pseudoaneurysm of the hepatic artery owing to an abscess. Autopsy revealed lymph node metastases in one portal lymph node.

Toxicity and Adverse Events

Eighteen patients (64%) received full-dose chemotherapy. Adverse effects are displayed in Table 2. One patient developed severe persistent emesis during the first treatment cycle (NCI grade 3). For this reason, neoadjuvant chemotherapy was terminated and the patient underwent successful surgery. Postoperatively, this patient received the second cycle of chemotherapy, which was well tolerated. Additional dose reductions were necessary in eight patients for cisplatin and in three patients for gemcitabine. The patient who underwent renal transplantation was given weekly gemcitabine monotherapy from week 3 to 8 because of renal toxicity after the first dose of gemcitabine and cisplatin.

Four patients (18%) required re–endoscopic retrograde cholangigraphy for stent exchange during neoadjuvant chemotherapy owing to cholangitis (n = 3) or recurrent cholestasis (n = 1). None of the patients required more than one intervention during chemotherapy.

Radiologic Tumor Response

Of those patients with cancer who had completed chemotherapy (n = 26), baseline ceCT was not available from three patients. The tumor size was not measurable on pre- and/or postchemotherapy imaging in seven patients. Tumor progression was documented in three patients (13%), stable disease was documented in 14 patients (61%), and partial remission was documented in one patient (4%).

Pathologic Reassessment and Tumor Response

Pathologic review confirmed that one patient had high-grade dysplasia without invasive cancer and revealed that three patients had cancer of the Ampulla Vateri rather than ductal adenocarcinoma. Tumor stages based on this reassessment are listed in Table 3.

Eleven patients had a minimal tumor response (less than 10%), whereas 13 patients (54%) had a grade 2 tumor response. Of these, five responses were considered grade 2a and eight responses were considered grade 2b. We did not observe grade 3 or 4 responses. Furthermore, 20 (83%) of 24 patients demonstrated significant cytopathic effects, of which 15 were grade 1 and five were grade 2 responses.

Protocol Violations

One patient with a suggestive history, positive PET scan, and FNA revealing high-grade dysplasia was included based on the interdisciplinary tumor board decision, but the final histology revealed no invasive cancer. The protocol staging laparoscopy was not performed

Table 2. Adverse Effects of Neoadjuvant Gemcitabine and Cisplatin

	Grade, Day 1				Grade, Day 15				Grade, Day 29				Grade, Day 43			
Toxicity	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Hematologic																
Leukopenia	—	2	—	—	2	1	—	—	1	1	—	—	—	4	—	—
Thrombopenia	1	—	—	—	6	—	—	—	8	6	—	—	8	—	—	—
Anemia	18	6	—	—	18	6	1	—	19	6	—	—	14	9	1	—
Gastrointestinal																
Diarrhea	—	—	—	—	1	—	—	—	2	—	—	—	1	—	—	—
Nausea	12	3	2	—	10	3	1	—	9	1	—	—	10	1	—	—
Vomiting	1	2	1	—	1	—	1	—	1	—	1	—	2	—	—	—
Renal																
Creatinine	3	—	—	—	5	—	—	—	4	1	—	—	6	—	—	—
Total	35	13	3	—	43	10	3	—	44	15	1	—	41	14	1	—

NOTE. Adverse effects were graded according to the National Cancer Institute Common Toxicity Criteria, and the nadir of toxicity after 14 days of chemotherapy was graded. Episodes are displayed per treatment application.

Table 3. Outcome Parameters After Neoadjuvant Chemotherapy

Outcome	No.	%
R0 resection	20 of 25	80
Cancer of the Ampulla Vateri		
T3N1	2	6
T4N1	1	3
Ductal adenocarcinoma		
unresectable	3	11
T0N0	1	3
T3N0	5	18
T3N1	16	57

in one patient, because he had had a laparoscopic cholecystectomy a few days before the diagnosis of pancreatic cancer. In another patient, restaging laparoscopy had to be postponed for 4 weeks as a result of severe coronary artery disease requiring coronary bypass surgery before PD. However, restaging laparoscopy revealed peritoneal metastases in both patients.

Disease Recurrence

Twenty patients developed disease recurrence, resulting in an actuarial recurrence-free survival of 9.2 months (95% CI, 5.6 to 12.9 months) on an intention-to-treat analysis, which did not change after excluding the patient without proof of invasive cancer (Fig 1A). Patients with resected ductal adenocarcinoma had a median recurrence-free survival of 9 months (95% CI, 6.99 to 10.1 months; Fig 1B).

Recurrences occurred in the bed of the pancreatic head in nine patients (45%) and in the regional lymph nodes in four patients (20%). Six of these patients simultaneously developed liver (n = 3) and lung (n = 3) metastases. Furthermore, seven patients (35%) developed distant metastases in lungs (n = 2), liver (n = 3), or lymph nodes (n = 2) without local recurrence.

Sixteen of the 20 patients received palliative chemotherapy after disease recurrence: 14 patients received gemcitabine, one patient received capecitabine, and one patient received gemcitabine and capecitabine therapy. Palliative chemotherapy was started a median of 1.2 months (range, 1 day to 8 months) after disease recurrence. Two patients underwent a surgical block of the splanchnic nerves for pain control from local recurrence, of whom one also had undergone previous radiation therapy.

Overall Survival

The actuarial overall survival was 26.5 months (95% CI, 11.4 to 41.5 months) on an intention-to-treat basis (Fig 1A), which did not change after exclusion of the patient without invasive cancer (n = 27). Those with resected ductal adenocarcinoma had a median overall survival of 19.1 months (95% CI, 15 to 23.1 months; Fig 1B).

Nutritional Status

Baseline prealbumin serum levels were available from 26 of 28 patients, and postchemotherapy values were available from all patients. At baseline, 11 patients (42%) had abnormal prealbumin serum levels (<180 mg/dL), with a mean of 153 mg/L. After chemotherapy, mean prealbumin levels were 213 mg/L ($P < .001$), and only three remained abnormal ($P = .008$).

Baseline prealbumin levels were available from five of six patients who did not require stent implantation before neoadjuvant chemotherapy. Two patients presented with low serum levels, and all six patients had normal prealbumin serum levels before surgery.

QoL

Complete pre- and post-chemotherapy QLQ-30 results were available from 22 patients. Results of the QoL evaluation are shown in Fig 2.

DISCUSSION

Cancer of the pancreatic head is considered resectable when distant metastases or infiltration of surrounding organs and arteries are absent.[4] Although an infiltration of the PV may lead to worse outcome, a PV resection can be safely performed without adding morbidity in experienced hands[14] and is therefore no longer considered a contraindication for PD.[19] Proven negative prognostic factors include a positive resection margin (R+), large tumors (> 3 cm = T3), poor histologic differentiation, lymph node involvement (N1), and a perioperative blood loss of more than 750 mL.[19]

Adjuvant chemotherapy improves survival,[7,8,20] but at least 25% of patients cannot receive this treatment because of complications

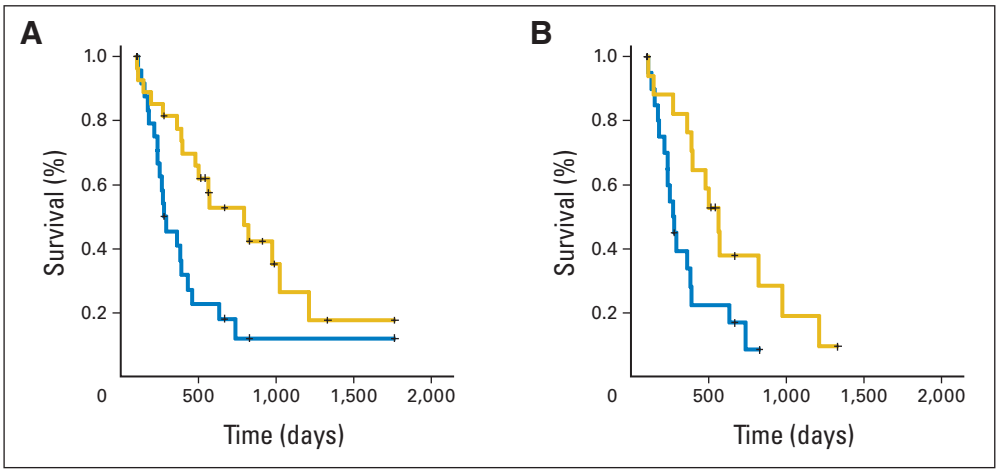

Fig 1. (A) Overall-survival (gold line) and disease-free survival (blue line) on intention-to-treat analysis (n = 28) and (B) of patients after successful resection of ductal adenocarcinoma (n = 21).

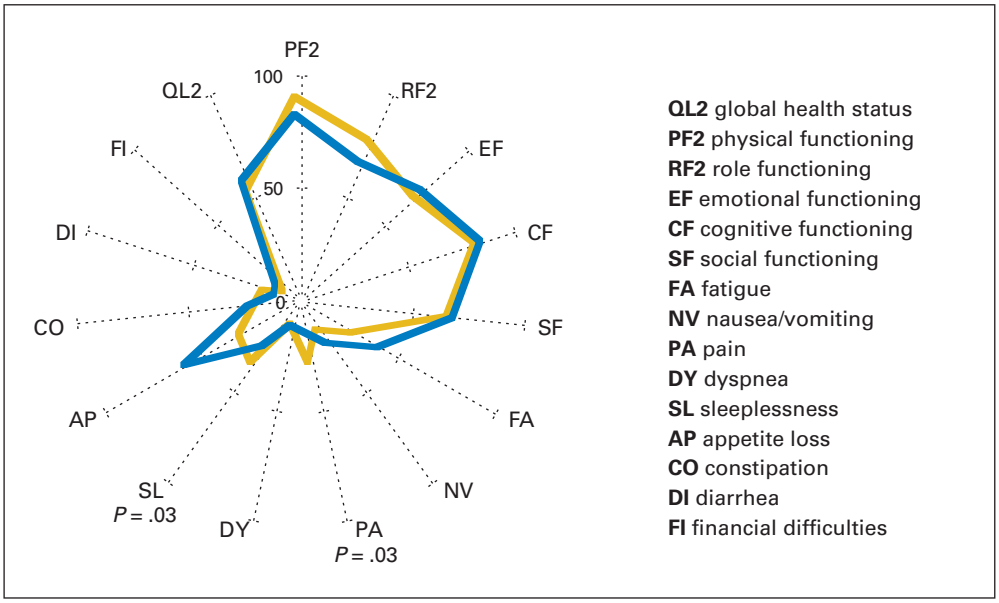

Fig 2. Quality of life assessed by the European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire—30 before (gold line) and after (blue line) chemotherapy. Pain (P = .03) and sleeplessness (P = .03) significantly improved during chemotherapy. The increased loss of appetite during chemotherapy was not significant (P = .49). The other 13 items were unchanged after chemotherapy compared with study entry. The maximal value of 100% indicates best social and physical functioning and best overall quality of life, as well as most intense symptoms for each item.

related to surgery.[9] A preoperative (neoadjuvant) treatment offers several theoretical advantages over an adjuvant treatment, including a multimodal treatment concept for all patients, a potentially higher R0 resection rate, and a treatment of micrometastases before surgery.[4] On the other hand, this concept harbors the risk of disease progression during therapy because of the aggressiveness of the tumor or an ineffective treatment.[4]

Therefore, we selected the resectability rate as the primary end point for this trial. Two patients had peritoneal metastases at restaging laparoscopy. Although protocol violations regarding staging and restaging occurred in these cases, retrospective exclusion of these patients would have caused major bias. We therefore included these patients in our intention-to-treat analysis and attributed the unresectability to the neoadjuvant treatment. Consequently, the resectability rate on restaging examinations was 93%. The secondary end points of this study were also attained, with a local recurrence rate of 45% and a median survival of 26.5 months.

When we initiated this phase II trial, neoadjuvant protocols were based on CRT and were mainly applied to locally advanced cancer with the aim of a tumor downsizing. Gemcitabine and cisplatin yielded promising results in a phase III trial at that time and seemed attractive for its acceptable toxicity profile.[21] As expected, gemcitabine and cisplatin was well tolerated and did not impair QoL during neoadjuvant chemotherapy. Two symptom scales even showed improvement during chemotherapy, an effect probably attributable to gemcitabine.[22]

We observed a higher local recurrence rate than reported from neoadjuvant CRT, which might be related to a higher local efficacy of CRT or more advanced tumor stages in our study population.[11,23] On the other hand, we achieved higher resectability rate and survival than neoadjuvant CRT with similar study designs,[11,16] which is presumably due to the higher systemic efficacy of gemcitabine and cisplatin.

The main reason for the prolonged accrual time is the complexity of the study design. In contrast to a recent randomized phase II trial of neoadjuvant gemcitabine alone versus gemcitabine and cisplatin,[24] cytologic proof of adenocarcinoma was required for study inclusion in our protocol. Consequently, 96% of the patients had adenocarcinoma in the final histology in our study, whereas the diagnosis was incorrect in the latter study in 26% of patients based on clinical information only.[24] Conversely, a fair number of patients were ineligible in our study because of false negative FNA results, distant metastases detected by the extensive staging protocol,[25] or refusal of the patient. However, patient inclusion was unselective, as the study population indicates with disadvantageous comorbidities as well as advanced tumor stages. We had more node-positive and locally advanced tumors (T3) in our series compared, for example, with the study of Oettle et al (70% and 86%, respectively).[7] Despite this, the R0 resection rate of 80% is comparable with both recent randomized studies on adjuvant chemotherapy, and the overall survival in our study is even higher.[7,8] The limited effect on disease-free survival is presumably due to the extensive follow-up protocol with frequent CT scans, which detected asymptomatic disease recurrence in the majority of the patients.

As reported by Schima et al,[26] the exact delineation of the tumor was not possible in several cases, and most ceCTs were performed before referral and were usually not focused on the pancreas. Also, the radiologic response to four cycles of gemcitabine and cisplatin was limited. Therefore, we assessed the histologic tumor response to neoadjuvant chemotherapy by an established scoring system specifically developed for patients after neoadjuvant CRT. The lower histologic response rate compared with neoadjuvant CRT may be related to a higher local toxicity of CRT.[16] However, more important are probably the different timings of neoadjuvant therapy and resection: whereas surgery was performed within 2 weeks after the last chemotherapy cycle in our study, resections were performed at least 5 weeks after CRT,[16] a period after which the histologic effects of neoadjuvant chemotherapy could also be expected to be more pronounced. Therefore, we additionally assessed cytopathic effects to this treatment, because these early histologic changes are not reflected by the score of Evans et al.[16] By these criteria, 83% of the patients had an objective response to the neoadjuvant treatment.

Malnutrition is a frequent finding (> 50%) in patients with bile duct obstruction. It is caused by both a lower caloric intake and malabsorption owing to the absence of intestinal bile.[27] Cholestasis resolves quickly after internal biliary drainage, and both the spontaneous food intake as well as the nutritional markers with a short half-life time improve significantly within 10 days.[27] However, a decreased complication rate after PD by the reduction of malnourishment has only been confirmed if complications related to the stent placement were excluded.[28] Similarly, 42% of the patients presented with low prealbumin serum levels and improved significantly during chemotherapy in our study. Interestingly, the nutritional status of two patients without biliary obstruction also improved under chemotherapy, indicating that the disease itself also has an impact on the food intake.

In summary, short-term neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable pancreatic cancer is safe and well tolerated. It achieves a significant tumor response and seems to improve the nutritional status. Therefore, we are planning a randomized trial comparing neoadjuvant plus adjuvant (gemcitabine) therapy with adjuvant chemotherapy (gemcitabine) alone.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Final approval of manuscript: Stefan Heinrich, Bernhard C. Pestalozzi, Markus Schäfer, Achim Weber, Peter Bauerfeind, Alexander Knuth, Pierre-Alain Clavien

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