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Long-Term Relapse-Free Survival by Interdisciplinary Collaboration in a Patient with Metastatic Pancreatic Cancer (UICC IV)

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Key Words
Pancreatic cancer · Chemotherapy with palliative intent · Gemcitabine · Weekly high-dose 5-FU as a 24-hour infusion

Abstract
Introduction: The prognostic outlook for patients suffering from pancreatic cancer is generally poor. Particularly in cases of advanced and metastatic disease, long-term relapse-free survival may be achieved only in a few cases.
Case Report: A 45-year-old patient presented with metastatic pancreatic cancer. Liver metastases had been intra-operatively confirmed by histology. Prior to initiating treatment, a portacath was surgically implanted. Subsequently, the patient received a weekly dose of 1,000 mg/m^2 gemcitabine combined with 2,000 mg/m^2 high-dose 5-fluorouracil as a 24-hour infusion for palliative treatment. As the patient was suffering from a stenosis of the ductus hepaticus communis, an endoprosthesis was primarily implanted. After 18 applications of chemotherapy during which only low toxic side effects such as nausea, vomiting and alopecia (NCI-CTC grade 1) presented, a partial remission of the primary tumor was observed. In the course of chemotherapy treatment, the carbohydrate antigen 19-9 tumor marker value normalized. Thus, the interdisciplinary tumor board of the University of Erlangen decided to perform a laparoscopy to evaluate the status of liver metastases after palliative chemotherapy

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treatment. Subsequently, the primary tumor could be completely resected (pT2, pN0, pM0, L0, V0, G2, R0); liver metastases were not observed. Eight years after the initial diagnosis, the patient is relapse-free, professionally fully integrated and presents with an excellent performance status.
Conclusion: Patients suffering from metastatic pancreatic cancer may benefit from treatment combinations with palliative intent. In singular cases, patients may even have a curative treatment option, provided a close interdisciplinary collaboration exists.

Introduction

Pancreatic cancer is responsible for 227,000 deaths per year worldwide, and is the eighth most common cause of death from cancer in the world in both sexes combined [1]. In the USA, approximately 34,000 patients per year develop pancreatic cancer [2]. The prognosis for those patients is generally unfavorable, as the relative 5-year survival rate is less than 5%. Due to uncharacteristic early presenting symptoms at diagnosis, disseminated disease is observable in 40–50% of all cases; other patients tend to develop local recurrence or metastatic disease after surgical intervention with curative intent [3].

Single-agent gemcitabine has been considered the established standard palliative treatment since 1997. Compared with 5-fluorouracil (5-FU) given as bolus, single-agent gemcitabine has turned out to be the superior therapeutic option both in terms of clinical benefit ($p = 0.0022$) as the primary endpoint and in terms of median survival ($p = 0.0025$) [4, 5].

In 2007, the tyrosine-kinase inhibitor erlotinib (Tarceva®) combined with gemcitabine was licensed and admitted for the treatment of metastatic pancreatic cancer. For the first time, a phase III study achieved a significant prolongation of survival time by applying combined erlotinib and gemcitabine versus single-agent gemcitabine in unresectable locally advanced or metastatic pancreatic cancer [6].

Here, we report on a patient with metastatic pancreatic cancer treated with an initially palliative chemotherapy regimen of gemcitabine plus weekly high-dose 5-FU as a 24-hour infusion followed by a surgical intervention with curative intent.

Case Report

In August 2002, a 45-year-old male presented to our department with epigastric pain and weight loss. He consumed alcohol only socially and had a 25-year history of smoking approximately 6 cigarettes a day. Clinical examination revealed a reduced nutritional and performance status (weight = 70 kg, height = 185 cm, BMI = 21 and Eastern Cooperative Oncology Group (ECOG) index = 1). Carbohydrate antigen 19-9 (CA 19-9) was elevated to 1,851 U/ml (normal value <37 U/ml), and the carcinoembryonic antigen value was within the normal range (<5 ng/ml).

An abdominal CT scan revealed a tumor of 2.5 × 1.7 cm, located in the head of the pancreas and, additionally, several pathologically enlarged lymph nodes (>1 cm) in the truncus coeliacus area; no liver metastases were detectable by abdominal CT scan. Thus, the tumor was defined as a UICC stage IIB (cT3, cN1, cM0) entity. Because the patient suffered from a stenosis of the ductus hepaticus communis, a trouble-free bile flow was assured by endoprosthetic treatment (endoscopic retrograde cholangiopancreatography). Subsequently, the case was presented to the interdisciplinary tumor board of the University of Erlangen and an explorative laparotomy was performed. During this surgical

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intervention, 2 nodal structures of approximately 1 cm each were detected in the right liver lobe. After having extracted several specimens during the surgical intervention, a histological examination of the liver tissue revealed infiltrations of moderately differentiated adenocarcinoma consistent with the carcinoma located in the head of the pancreas of the primary tumor (**fig. 1**). As the patient had an intra-operatively confirmed metastatic disease (cT3, cN1, pM1 [HEP], UICC stage IV), it was decided to start chemotherapy treatment with palliative intent.

Prior to chemotherapy, an abdominal CT scan was repeated. This staging presented a primary tumor with an expansion of 3.5 × 2.0 cm (**fig. 2**) located in the head of the pancreas. Even at this point, neither CT scan nor MRI of the liver, with contrast medium or contrast-enhanced ultrasound, showed any signs of the intra-operatively proven liver metastases.

According to our experience, based on a phase II study and a subsequent analysis of a validation group (n = 60 patients), and according to the results of a phase I–II study [7], the application of gemcitabine plus weekly high-dose 5-FU as a 24-hour infusion offers a good tumor control rate accompanied by tolerable toxicity in patients with metastatic pancreatic cancer (UICC IV). Therefore, we started chemotherapy treatment based on this regimen [8, 9].

After the placement of a portacath, the patient received a weekly dose of 1,000 mg/m^2 gemcitabine as a 0.5-hour infusion combined with 2,000 mg/m^2 high-dose 5-FU as a 24-hour infusion via a miniature pump on days 1, 8 and 15, followed by one week of rest. Altogether, 18 chemotherapy administrations comprising 6 cycles (duration: 24 weeks) were applied. The chemotherapy treatment was well tolerated. Except for low-grade nausea, vomiting and alopecia (NCI-CTC grade 1), no higher grade toxicity was observed during all cycles. The patient even gained about 20 kg within 5 months. After 2 cycles of chemotherapy, CA 19-9 decreased from 1,851 U/ml to 49 U/ml (normal value <37 U/ml), and after 4 cycles it was within the normal range.

After 6 cycles of chemotherapy, an MRI was conducted for staging. No signs of liver metastases were detectable, either in the previous MRI of the liver and abdominal CT scan, or in the current MRI. The pathologically enlarged lymph nodes (>1 cm) in the truncus coeliacus area appeared unchanged. The primary tumor located in the head of the pancreas had a diameter of 2.4 × 1.6 cm. According to RECIST criteria, this is regarded as partial remission with an initial tumor expansion of 3.5 × 2.0 cm.

Subsequently, the case was again presented to the interdisciplinary tumor board of the University of Erlangen, and a laparoscopy was performed with the objective of excluding distant metastases. This surgical intervention (in March 2003) was followed by a Whipple operation and dissection of the lymph node compartments 2 and 3. In contrast to a previous explorative laparotomy (in August 2002), no liver metastases could be intra-operatively detected. The primary tumor was completely resected (R0). Histological examination of the specimen revealed a moderately differentiated adenocarcinoma located in the head of the pancreas [pT2, pN0 (0/31), pM0, L0, V0, G2, R0] (**fig. 3**). Subsequent to the surgical intervention, the patient was followed up for several years at the outpatients' section of the Department of Internal Medicine 1, University of Erlangen, without manifesting any signs of relapse or distant metastases. In November 2007, while performing an MRI, an undefined liver lesion (segment 2) with an expansion of 1.8 cm was observed. A specimen of this lesion was extracted by computerized puncture. The subsequent histopathological examination only showed traces of scar tissue and a suppurative abscess-forming inflammation. Signs of malignity were not observed. Furthermore, the CA 19-9 tumor marker was within the normal range. During the follow-up, the described lesion turned out to be completely regredient, in accordance with subsequent sonographic checkups. To date, i.e. 8 years after initially presenting for diagnosis, the patient is relapse- and symptom-free. He is able to maintain a stable weight and continue his working life without any restrictions.

Discussion

As most patients suffering from pancreatic cancer present for diagnosis with metastatic disease, the prognostic outlook is generally poor and curative options are extremely rare [3].

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During the last few years, several meta-analyses demonstrated that the prognostic outlook in terms of survival and response rate for locally advanced or metastatic pancreatic cancer could be improved by administering combined chemotherapy regimens instead of single-agent gemcitabine [10, 11]. Complete remission or long-term relapse-free survival, however, could be achieved only in a very limited number of cases. In the registration trial for the approval of gemcitabine, none of the 126 patients treated with either gemcitabine or 5-FU had complete remission [5].

In several phase III studies, patients with locally advanced or metastatic pancreatic cancer were treated with different combined regimens [6, 12–15]. Median survival ranged from 5.4 to 8.4 months. Despite the high case numbers of clinical trials, the number of patients with complete remission is extremely low. In a randomized phase III study conducted by Cunningham et al. [12], complete remission was observed only in 9 out of 533 patients. In the study by Herrmann et al. [13], 1 out of 319 patients had complete remission; in Bramhall et al. [14], complete remission was equally observed in only 1 out of 293 patients, and in the study conducted by Heinemann et al. [15], not a single one of the 195 enrolled patients achieved complete remission.

In the case report literature, Chadha et al. [16] describe a patient with locally advanced unresectable pancreatic cancer treated with TNFerade™, a novel multimodal gene therapy, and concurrent chemoradiation. This treatment was followed by a successful surgical resection and 12 weeks of adjuvant chemotherapy with gemcitabine. The patient remained in good health until 18 months after completion of adjuvant gemcitabine. Okamoto et al. [17] describe the case of a patient with advanced pancreatic cancer which was initially diagnosed during laparotomy as unresectable. After a hepaticojejunostomy had been performed, the patient received palliative gemcitabine chemotherapy. Complete remission was achieved after 3 courses of chemotherapy, lasting for over 4 years to the date of the case report.

Here, we report on a patient with metastatic pancreatic cancer who achieved long-term survival after downsizing with 6 cycles of palliative gemcitabine combined with weekly high-dose 5-FU as a 24-hour infusion with partial remission followed by surgical resection. The good tolerability and response to systemic treatment was remarkable. After only 4 cycles of chemotherapy treatment, the initially elevated tumor marker CA 19-9 (1,851 U/ml) was again within the normal range (<37 U/ml). In October 2010, the patient presented relapse-free and with an excellent performance (ECOG 0) status at our outpatients' section of the Department of Internal Medicine 1, University of Erlangen.

Our case report demonstrates that even in cases of metastatic pancreatic cancer, it is, albeit in rare cases, possible to achieve long-term relapse-free survival by administration of chemotherapy with palliative intent in the context of close interdisciplinary cooperation.

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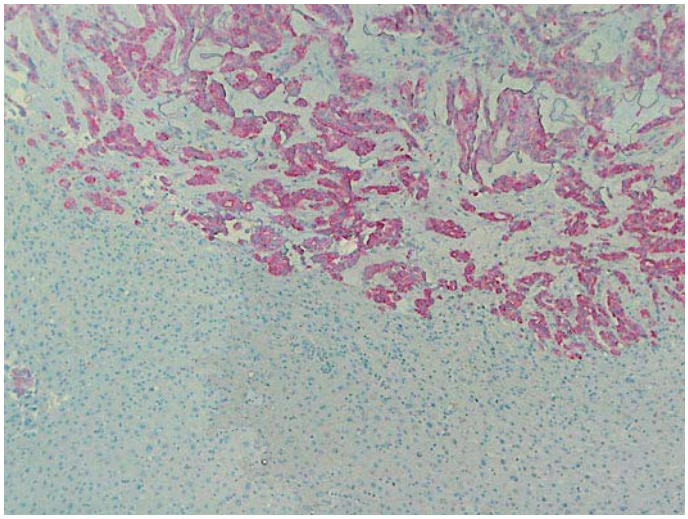

Fig. 1. Liver metastasis confirmed by histological examination: liver infiltration by a poorly differentiated adenocarcinoma with cytokeratin 7-positive tumor cells. Immunohistochemistry using an antibody against cytokeratin 7, magnification: × 20.

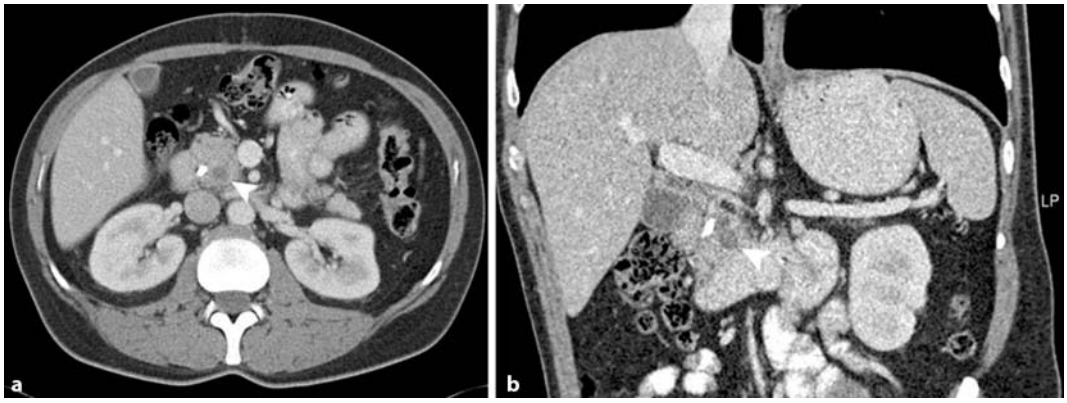

Fig. 2. Spiral CT (arterial phase, 35 s after contrast media injection) of the 45-year-old patient with pancreatic carcinoma, before starting palliative chemotherapy. In the axial source image (**a**) and the oblique coronal reconstruction (**b**), good delineation of an oval-shaped hypointense mass with a maximum diameter of 3.5 cm (white arrowhead) can be seen within the pancreatic head. Stent prosthesis is located beside the tumor in the common bile duct.

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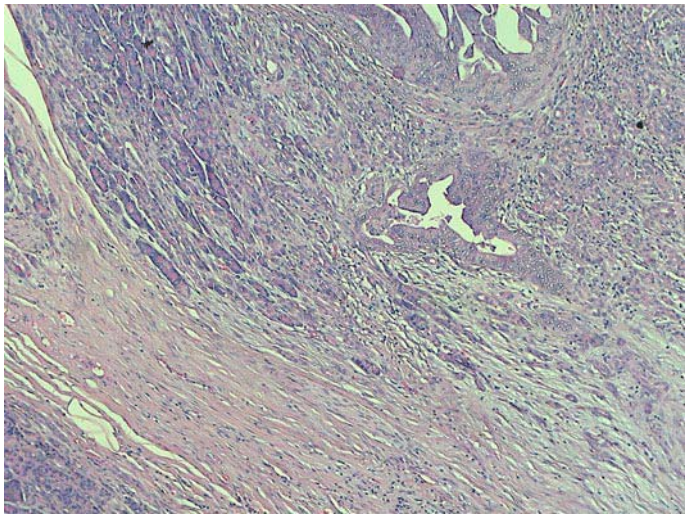

Fig. 3. Excised pancreatic tumor after palliative chemotherapy and duodenopancreatectomy (pT2, pN0, pM0, R0): poorly differentiated adenocarcinoma of the pancreas with desmoplastic reaction. PAS stain, magnification: × 40.

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