Long-term Survival Following Resection of Brain Metastases from Pancreatic Cancer

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Abstract. *Brain metastases originating from pancreatic cancer are associated with a dismal prognosis and, generally, therapeutic options remain palliative. We present the cases of two patients that developed brain metastases after resection of a pancreatic ductal adenocarcinoma. Brain metastases were resected successfully and neither patients developed any further tumor recurrence. These cases demonstrate that resection of brain metastatic lesions originating from pancreatic ductal adenocarcinoma is a reasonable therapeutic option with a chance for complete cure in some cases.*

Pancreatic ductal adenocarcinoma (PDAC) is a fatal disease, with a mortality rate approaching its incidence rate (1). Nowadays, it is the fourth most common cancer cause of death in the Western world (2). The five-year survival rate among patients diagnosed with PDAC amounts to only 5%. The only chance for cure is complete surgical resection of the tumor. One reason for the poor prognosis is the fact that the majority of patients are diagnosed with the disease at an advanced non-resectable tumor stage. In consequence, fewer than 20% of all patients can be treated with curative intention and undergo surgical resection (1). Treatment of all other patients remains palliative, whereas a surgical approach in most cases is not even considered. In patients presenting with a locally resectable pancreatic tumor but synchronous distant metastases, palliative treatment is standard, omitting resection for asymptomatic patients and preferring palliative surgery for symptomatic patients (3). Resection of metachronous distant metastases from PDAC is discussed controversially (4). In contrast, resection of distant metastases originating from other types of carcinoma of the gastrointestinal tract (*e.g.* colorectal cancer) is strongly recommended (5). In this report, we present the cases of two patients who benefited from resection of metachronous metastases originating from PDAC, converting an initially palliative situation into a chance for cure.

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Key Words: Pancreatic cancer, pancreatic neoplasms, long-term survivors, surgery, brain metastasis.

Case 1

A 48-year-old woman was diagnosed in November 1994 with a tumor of the pancreatic tail which appeared malignant in positron-emission tomography (PET). Serologic carcino-embryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were not elevated. Since preoperative staging examination revealed no evidence of distant metastases, left pancreatectomy including splenectomy was performed. Histologically, the tumor (2.5 cm in diameter) was identified as ductal adenocarcinoma, which was completely resected (R0). All six resected lymph nodes showed no metastatic cells. The International Union Against Cancer (UICC) tumor stage was Ib. After recovery from surgery, the patient underwent adjuvant combined radiochemotherapy (ESPAC-I scheme (6)). The patient was admitted to the follow-up program. Clinically and in the conducted imaging, no pathological findings were detected until July 1997, when computed tomography revealed a solitary liver metastasis (segment VII). Having no evidence of further metastases or local recurrence, the metastasis was successfully resected. Histological examination proved that the metastasis originated from the pancreatic adenocarcinoma. The patient was admitted to the pancreatic cancer follow-up program again and was regularly staged, by both sonography and computed tomography. None of the examinations regularly carried out showed any evidence of local recurrence or metastases. In March 2000, the patient suffered for the first time from

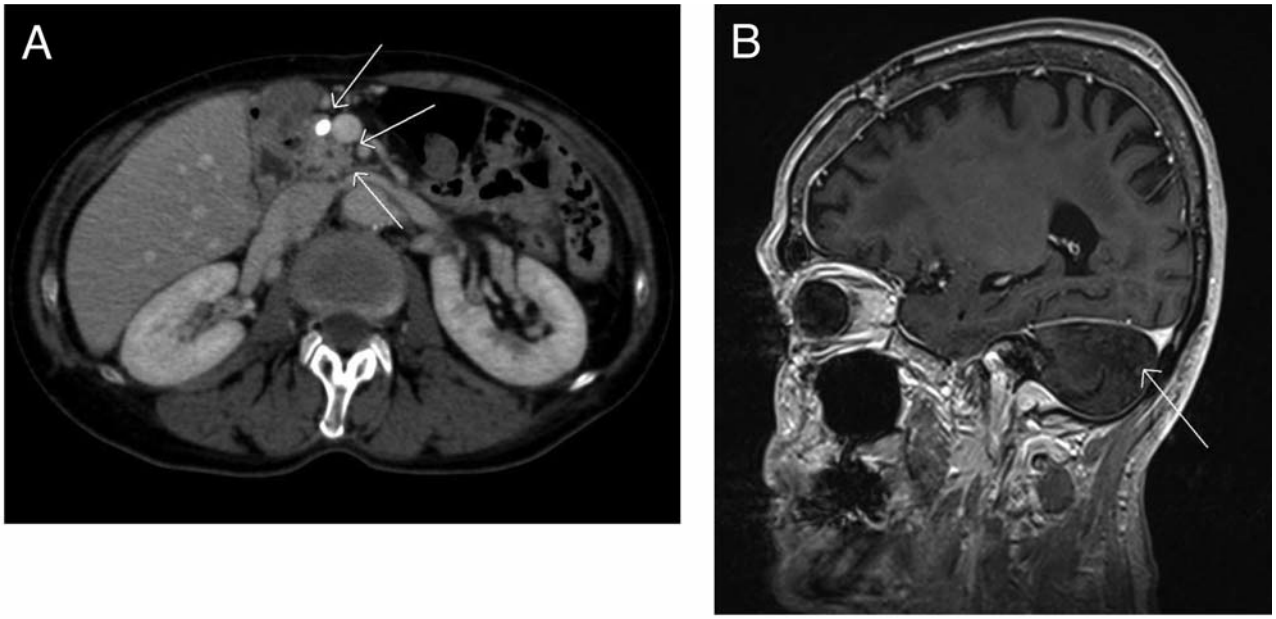

Figure 1. *Recent follow-up imaging of abdomen and brain (Case 1). A: Computed tomography of the abdomen (January 2006) performed as follow-up after resection of the pancreatic ductal adenocarcinoma (PDAC) showed the resection margin of the pancreatic corpus (white arrows) with no evidence of tumor recurrence. B: Magnetic resonance tomography of the brain (March 2009) showed postoperative alterations of the right cerebellum (white arrow) but no evidence of tumor recurrence.*

headache, vertigo, nausea and vomiting. Tomographically, a metastasis of the right cerebellum was identified, which was resected completely using microneurosurgery. Again, histological analysis confirmed a metastasis of the pancreatic adenocarcinoma. Postoperatively, the patient underwent irradiation (46 Gy) of the neurocranium. Since that time, the patient has continued attending the follow-up program (computed tomography and sonography of the abdomen) which was extended to periodic imaging of the brain. Fortunately, to date no local recurrence or further metastasis has been detected (Figure 1) and the patient enjoys a good quality of life without any remaining symptoms.

Case 2

A 66-year-old man was diagnosed in July 2004 with a tumor of the pancreatic tail (Figure 2A). Left pancreatectomy and splenectomy, as well as resection of parts of the ventral renal capsule, were performed. In the histopathological analysis the tumor was classified as ductal adenocarcioma (4.8 cm in diameter, Figure 3A and B). In five out of eleven examined lymph nodes, tumor cells were detected. The UICC tumor stage was IIb. In addition, in September of the same year, a urothelial carcinoma of the bladder was diagnosed and treated curatively by transurethral resection. Chemotherapy with gemcitabine was administered for 6 months. The patient was admitted to the follow-up program. In June of 2005, the patient reported headache, vertigo and nausea, as well as hemiparesis of the right arm. Magnetic resonance tomography of the brain revealed a tumor of the right postcentral cerebrum (Figure 2C), which was subsequently completely resected by microneurosurgery. The histological analysis showed a morpholgy identical to that of the PDAC and the lesion was therefore diagnosed as a metachronous metastasis of the resected PDAC (Figure 3C). Postoperatively, the patient underwent irradiation of the neurocranium (30 Gy). This patient also attended the follow-up program (extended to periodic imaging of the brain), which has shown there to be no pathologies to date (Figure 2B and D). All neurological symptoms vanished after surgical resection.

Discussion

Both patients described above suffered from a PDAC and developed brain metastases after resection of the primary tumor. Brain metastases originating from the pancreas are described as being extremely rare and indicate a very poor prognosis (7-10). Recommended therapy for patients staged with distant metastases of a PDAC is usually palliative using gemcitabine-based chemotherapy (11-13). The prognosis of these patients remains poor with a median survival of approximately six months (11). Surgical approaches to treatment of synchronous and metachronous liver metastases

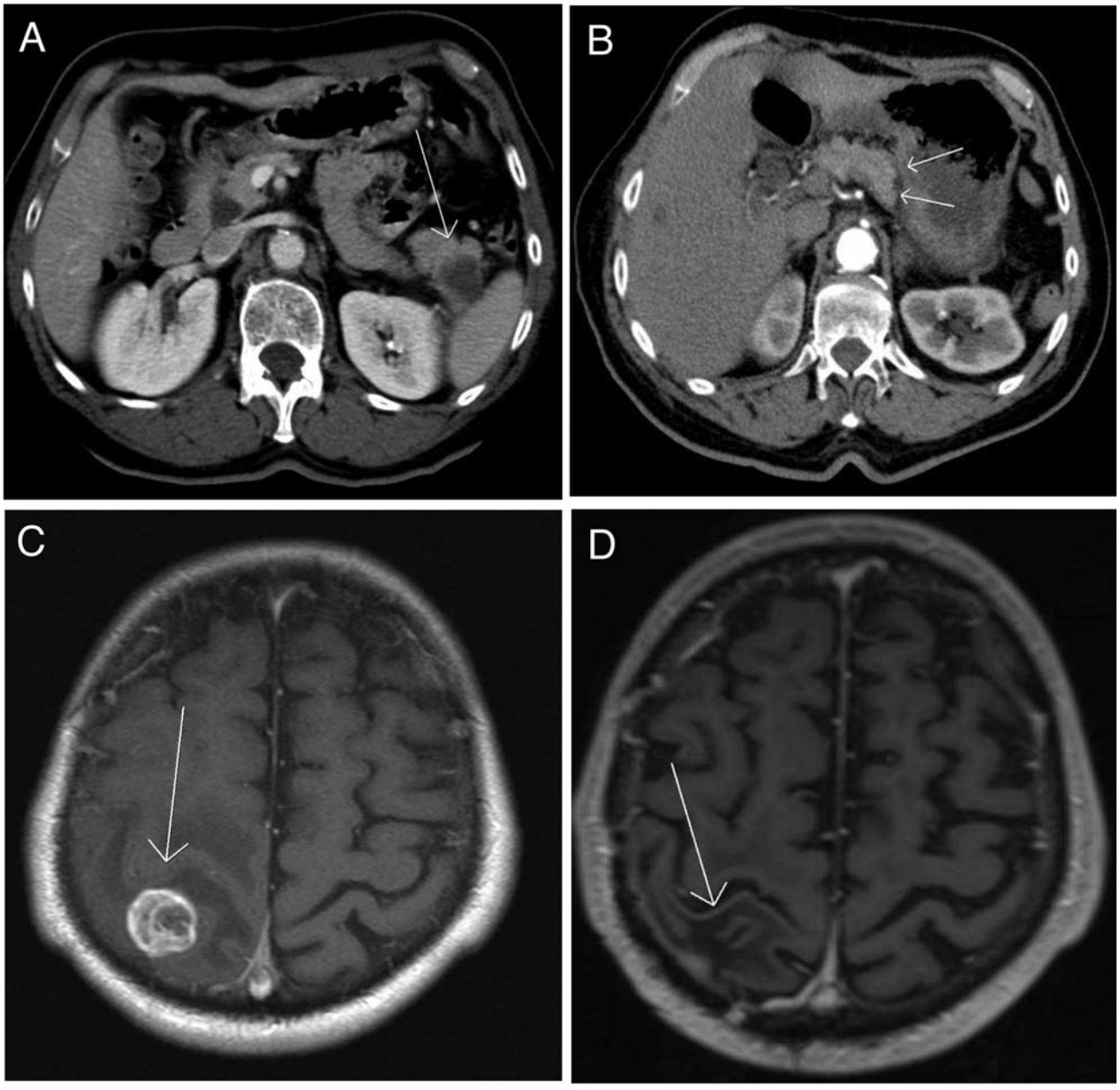

Figure 2. *Imaging identifying the primary tumor and the brain metastasis, as well as recent follow-up imaging of abdomen and brain (Case 2). A: Computed tomography of the abdomen in July 2004 revealed a tumor of the pancreatic tail (white arrow) that was diagnosed as pancreatic ductal adenocarcinoma (PDAC) (UICC Stage IIb; pT3, pN1, M0, G2, R0). B: Computed tomography of the abdomen (April 2011) performed as follow-up after resection of the PDAC showed the resection margin of the pancreatic corpus (white arrows) with no evidence of tumor recurrence. C: Magnetic resonance tomography of the brain (June 2005) revealed a tumor of the right postcentral cerebrum (white arrow) that was identified as a metachronous metastasis of the PDAC. D: Recent magnetic resonance tomography of the brain (March 2011) showed postoperative alterations of the right cerebrum (white arrow) but no evidence of tumor recurrence.*

are reported as a therapeutic option, but their impact on improving survival remains unclear. Therefore, resective approaches for metastasis are still discussed controversly for PDAC (4, 14, 15). Long-term survival following resection of acinar cell carcinoma of the pancreas and resection of metachronous liver metastases has been described, but not of PDAC (16). We present two patients that benefited from a resection of distant metachronous metastases which originated from PDAC. Even more surprisingly both patients have achieved long-term survival with no evidence of tumor

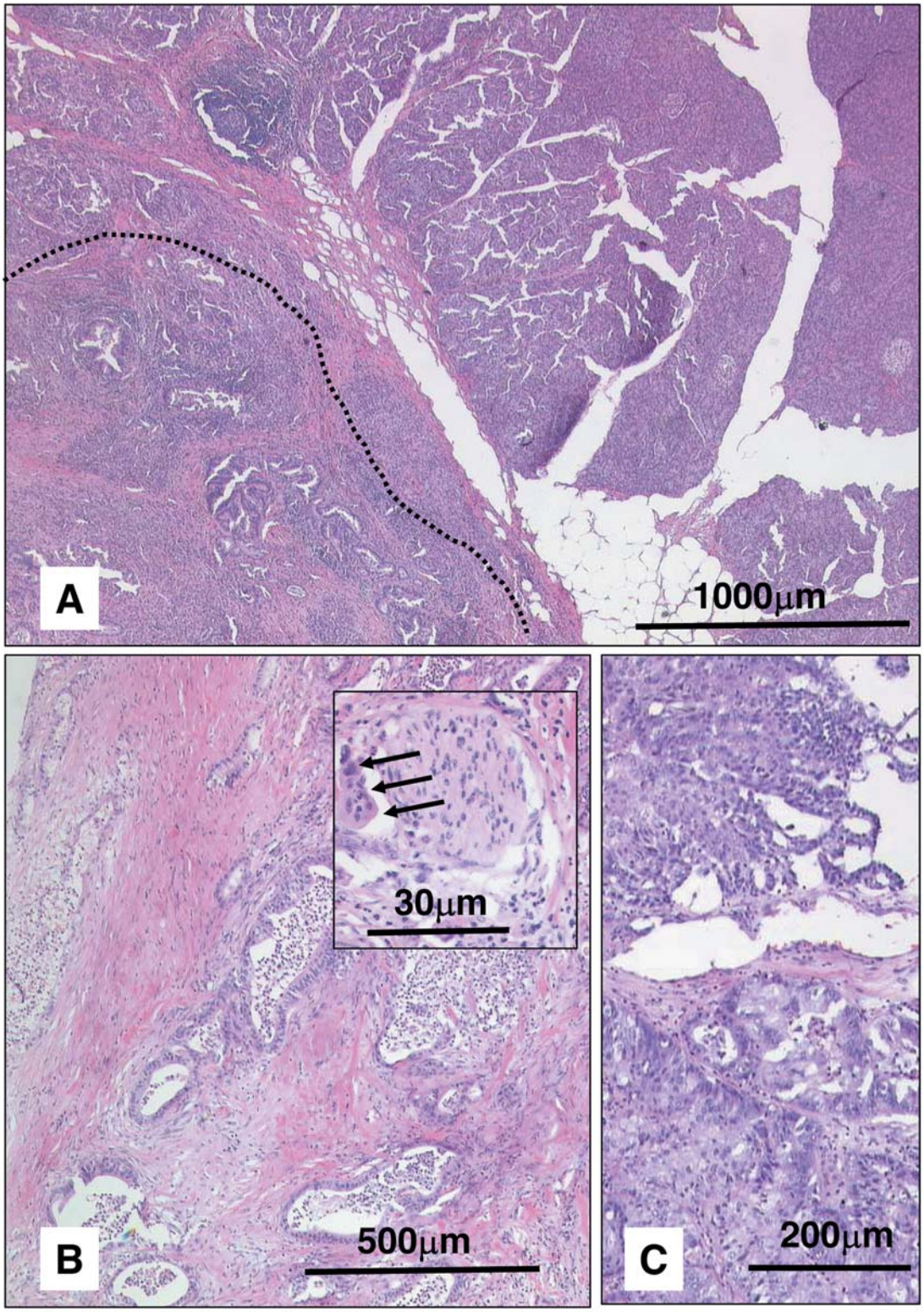

Figure 3. *Histomorphology of pancreatic ductal adenocarcinoma (PDAC) and of the metachronous brain metastasis (hematoxylin-eosin staining) (Case 2). A: Overview of the ductal adenocarcinoma. The dashed line marks the infiltration front of the neoplastic tissue (lower left) from non-neoplastic pancreas tissue (upper right). B: Detail of the ductal adenocarcinoma, with desmoplastic stromal reaction and perineural invasion (insert: carcinoma cells are marked by arrows). C: Morphology of the brain metastasis resected 13 months after primary surgery. Histology is identical to that of the primary tumor with a ductal growth pattern.*

recurrence after 17 years and 7 years since resection of the primary tumor, respectively. As demonstrated by these interesting cases, we want to emphasize that resection of distant metastases originating from PDAC can result in an immense benefit to survival in selected cases. On this context, there is evidence that surgical approaches for recurrent PDAC might also lead to a benefit in subgroups of patients (17). In summary, we conclude that resection of metastatic lesions of PDAC should be considered as a potential treatment strategy, even as an option for cure.

Conflict of Interest Statement

The Authors declare no conflicts of interest.

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Received August 24, 2011
Revised October 24, 2011
Accepted October 26, 2011