Long-term survival in pancreatic ductal adenocarcinoma with lung and brain metastases: a case report

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, with a 5-year survival rate of approximately 10% [1]. Unfortunately, surgical resection is indicated in $< 20\%$ of patients [2]. Many of these patients have distant metastases, which decreases the median overall survival time to < 1 year, and most die within 2 years [3]. PDAC most frequently metastasizes to the liver (76%), followed by the lungs (19.9%). The brain (0.6%) is extremely rare site of metastasis[4]. However, in a few cases, long-term survival has been achieved via multidisciplinary treatment including chemotherapy, radiotherapy, and local excision, even after distant metastasis, such as lung and brain metastases, was observed [5,6]. Herein, we report the case of a patient with PDAC who achieved long-term survival after pylorus-preserving pancreaticoduodenectomy (PpPD) despite metachronous lung and brain metastases.

2. Case report

A 70-year-old male patient who was referred to our hospital, for the treatment of obstructive jaundice was diagnosed with pancreatic head cancer. He was 168 cm tall, weighed 71.6 kg, had a body mass index of 25.4 kg/m^2, did not smoke or drink alcohol, and had no history of chronic pancreatitis or diabetes. His blood test results were as follows: total bilirubin, 15.0 mg/dL (0.3–1.2); direct bilirubin, 11.4 mg/dL (<0.4); aspartate aminotransferase, 125 U/L (10–40); alanine aminotransferase, 218 U/L (5–40); carbohydrate antigen 19–9 (CA19-9), 38.2 U/mL (<37.0); carcinoembryonic antigen (CEA), 4.4 ng/mL (5.0); duke pancreatic monoclonal antigen type 2 (DUPAN-2), >1600 U/mL (<150); and s-pancreas-1 antigen (SPan1), 240 U/mL (<30). Computed tomography (CT) revealed a low-density mass (27 mm in diameter) with no major vessel involvement in the pancreatic head (Fig. 1) and no distant metastases. Endoscopic retrograde cholangiopancreatography was performed for biliary drainage, and the pancreatic tumor was pathologically diagnosed as a PDAC. The clinical stage was T3N1M0, stage IIB, according to the eighth edition of the TNM classification of the American Joint Committee on Cancer (AJCC) /Union for International Cancer Control (UICC). The tumor was considered resectable and the patient underwent PpPD. Because tumor invasion was observed in the superior mesenteric vein (SMV), combined resection and reconstruction of the SMV was performed. No postoperative complications were observed and the patient was discharged on the 21st postoperative day.

Macroscopic examination revealed a whitish solid mass, 50×40×30 mm in size, located in the pancreatic head (**Fig. 2A and 2B**). The mass was histologically diagnosed as a well-differentiated adenocarcinoma, T3 N1(7/38) M0, stage IIB, according to the eighth edition of the TNM classification of the AJCC/UICC (**Fig. 2C**). The lymphatic invasion was severe, vascular invasion was moderate, and neural invasion was severe. Biliary, duodenal, anterior tissue, retroperitoneal tissue, superior mesenteric vein, and extrapancreatic nerve plexus invasions were observed.

One month after surgery, the patient received gemcitabine and S-1 (GS: gemcitabine at a dose of 800 mg/m^2 on days 1 and 8 plus S-1 at a dose of 100 mg/body twice daily on days 1–14 of a 21-day cycle) as postoperative adjuvant chemotherapy. At the time, only gemcitabine was recommended for adjuvant chemotherapy after PDAC surgery in Japan, and S1 was not yet recommended[7]. In addition, since there have been some reports that GS therapy is effective as adjuvant chemotherapy[89], GS therapy was not standard clinical treatment at that time, but selected after providing sufficient explanation to the patient and obtaining informed consent. Eleven months post-PpPD, multiple microscopic bilateral pulmonary metastases were suspected on CT. Since the lesions suspected to be multiple lung metastases remained almost unchanged in size and only gemcitabine was the chemotherapy medication recommended for unresectable PDAC in Japan at that time [7], GS therapy was continued with sufficient informed consent for an extended period, even after lung metastasis recurrence.

At 4 years and 6 months post-PpPD, only one lesion in the right lower lung grew rapidly (**Fig. 3A**), and bronchoscopy revealed class V cytopathology (**Fig. 3B**). Whole-body dynamic CT showed no metastasis except in the lung, and since the possibility of primary lung cancer could not be ruled out, the bottom portion of the right lung was thoracoscopically resected 5 years and 5 months post-PpPD. Other pulmonary lesions showed almost no change in size; therefore, we concluded that chemotherapy was effective. In addition, they were not resected because they were numerous and complete resection was impossible.

The lesion was pathologically diagnosed as an adenocarcinoma, similar to the primary lesion (**Fig. 4A**). Immunostaining was positive for CK7 (**Fig. 4B**), and negative for CK20 (**Fig. 4C**) and TTF-1 (**Fig. 4D**). This indicated a low likelihood of primary lung cancer. Based on these findings, metastatic PDAC was diagnosed. In addition, multiple lung lesions were obscured, and after obtaining sufficient informed consent from the patient, he was followed up without chemotherapy. However, 6 months after the second surgery (5 years and 10 months after PpPD), CT revealed a nodule in the upper lobe of the right lung. Although GS was resumed, the number of lung metastases increased. Seven years and five months post-PpPD, the treatment regimen was switched to a combination therapy of gemcitabine plus nab-paclitaxel (GEM + nab-PTX: gemcitabine at a dose of 450 mg/m^2 and nab-PTX at a dose of 115 mg/m^2 on days 1 and 8 of a 21-day cycle). Eleven years and one month post-PpPD, FOLFIRINOX (a combination of folinic acid, fluorouracil, irinotecan hydrochloride, and oxaliplatin) was required to stem the growth of the lung metastases. However, the resulting adverse effects compelled the physicians to discontinue the treatment after only one course, and the patient was subsequently treated with S-1 alone (at a dose of 80 mg/body twice daily on days 1–14 of a 21-day cycle).

11 years and 2 months post-PpPD, the patient was readmitted because of dizziness and left hemiplegia. Contrast-enhanced magnetic resonance imaging (MRI) revealed a 23×22×20-mm neoplasm in the right inferior parietal lobule. A strong contrast effect was evident at the edges and center, and mulberry-like papillary structures were observed within the lesion (**Fig. 5A**). A 5-mm ring-shaped contrast effect was also observed in the right cingulate gyrus. Metastatic brain tumors were suspected in the right inferior parietal lobule and right cingulate gyrus. Only the right inferior parietal lobe lesion was resected to relieve symptoms at 11 years and 4 months post-PpPD.

Histopathological analysis revealed metastatic PDAC in the brain (**Fig. 5B**). Six weeks after the third surgery, S-1 treatment was resumed (at a dose of 100 mg/body twice daily on days 1–14 of a 21-day cycle).

MRI performed at this time demonstrated numerous small lesions in the brain, and a tumor appeared in the meninges at the site of the previous surgery. Subsequently, the patient underwent whole-brain irradiation, and his condition improved to the point where he was able to walk without assistance. However, the patient died of PDAC recurrence 6 months after the craniotomy (11 years and 8 months after the first surgery).

The CA19-9, CEA, SPan1, and DUPAN-2 levels were measured monthly. CA19-9 was slightly elevated only at the first visit but remained low throughout the observation period, and CEA only spiked just before death. SPan1 and DUPAN-2 levels increased as metastasis increased and decreased as the chemotherapy regimen was changed (**Fig. 6**).

3. Discussion

Although PDAC outcomes have been improving owing to progress in multidisciplinary treatments, the 5-year survival rate remains $< 5\%$ [10]. As previously reported, approximately 75% of patients with resectable PDAC who have undergone radical resection experience tumor relapse and have an overall survival time of < 30 months [11].

Surgery is usually not indicated for postoperative recurrence of PDAC, except when it occurs in the remnant pancreas [12]. In such cases, systemic chemotherapy (such as FOLFIRINOX or combination therapy consisting of GEM + nab-PTX) is preferred[13,14]. However, surgical treatment may also be considered if chemotherapy is successful and metastasis can be controlled for a sufficient period. Our previous report described a patient in whom long-term survival was achieved via surgery for gallbladder and stomach metastases following surgery for PDAC[15].

Recurrence of lung metastases after surgery for PDAC is known to have a better prognosis than recurrence at other sites, and previous studies have reported successful resection of lung metastases. Zheng *et al.* reported that primary tumor recurrence in the lungs was associated with longer median disease-free survival (15 months) and longer median overall survival after detection (20 months) than any other type of primary recurrence. Moreover, patients with primary recurrence in the lungs have the longest median survival (36 months) among all patients with tumor recurrence [16]. Kurahara *et al.*reported that the median survival time of seven patients with postoperative lung metastases of PDAC who underwent lung resection was 36.5 months, which exceeded that of patients receiving either chemotherapy or the best supportive care [5].

Many case reports on lung metastases of PDAC have shown that local resection prolongs patient survival. Furthermore, a long interval between the initial resection for PDAC and subsequent lung resection has been associated with long-term survival (13-15). However, currently available evidence on the effectiveness of resection for pulmonary metastases of PDAC is insufficient to establish general recommendations, and indications for surgery should be carefully weighed in each case. Okui *et al.* reported that surgery for lung metastasis should be considered under the following conditions: 1) the patient will be able to tolerate the surgery, 2) the primary lesion is under control, 3) no other metastases are present outside the lungs, and 4) multiple lung metastases can be resected [17].

Brain metastases from PDAC are rare and have poor prognosis. Treatment is usually palliative in these cases; however, a previous study has reported that aggressive surgery can result in long-term survival. Lemke *et al.* reported that patients with PDAC who achieved long-term survival were initially treated with cancer-directed surgery with curative intent and had solitary metachronous brain metastasis for which complete (R0) resection followed by adjuvant therapy could be performed. Therefore, surgery for metachronous metastatic PDAC lesions may be considered a viable option in some cases [18]. Kumar et al. reported a 9-year survival case after craniotomy[6]. Matsumoto *et al.* reported that local resection failed to prolong survival in their patient. However, it improved the patient's neurological symptoms and allowed him to spend the remainder of his life meaningfully, without neurological deficits[19]. Therefore, surgical resection may confer benefits to some patients.

In the present case, brain metastases were observed in the right inferior parietal lobule and right cingulate gyrus. The former was the cause of the left hemiplegia, which prompted craniotomy. As a result, neurological symptoms improved significantly and the patient recovered sufficiently to walk unassisted.

Gamma knife treatment was also considered, but craniotomy was chosen for the following reasons: 1) the lesion occurred 11 years after surgery for PDAC, and pathological diagnosis by resection was necessary; 2) the lesion was located in the inferior parietal lobule of the non-dominant hemisphere, was present on the brain surface, and was safely resected; and 3) severe peri-tumor edema worsens after gamma knife treatment. The patient's days were numbered; therefore, prompt improvement of neurological symptoms was required.

Thirteen of the 31 case reports of pancreatic cancer with brain metastasis retrieved in a PubMed search involved surgical resection. Of the 13 patients who underwent surgery, nine underwent radical resection and four underwent palliative surgery, with some patients in both groups experiencing an improvement in prognosis and quality of life[18 19 2021].

A previous report revealed that the incidence of PDAC in patients with brain metastasis and complicated lung metastases was higher than that of overall pancreatic cancer patients (29–37.5% vs. 19.9%). Sasaki *et al.* reported that lung metastasis may be a risk factor for brain metastasis in patients with PDAC [21].

In the present case, lung resection was performed for lung metastasis 5 years and 5 months post-PpPD, craniotomy was performed for brain metastasis 11 years and 4 months post-PpPD, and GS, GEM + nab-PTX, FOLFIRINOX, and S-1 were administered at various time points during the disease course. Considering the transition in tumor markers in Fig. 6, chemotherapy contributed the most to this patient. However, resection of rapidly growing lung metastases and brain tumors that had caused paralysis had significant effects in prolonging the patient's life prognosis and maintaining his quality of life. Although the prognosis of PDAC remains poor in some patients, it can be improved using multimodal therapy that combines chemotherapy and local excision.

4. Conclusion

Multimodal treatment involving local excision and chemotherapy for postoperative metastases has the potential to extend the survival of PDAC patients.

Authors' contributions

Ohgaki Yutaro: Drafted the manuscript.

Makoto Takahashi: Revised the manuscript.

Yasuhiro Morita: Contributed to the preoperative examinations and diagnosis, and performed the first operation and followed-up on the patient.

Tatsuya Hayashi: Followed-up on the patient.

Takuma Kikkawa : Performed the lung surgery.

Takahiro Ota: Planned the craniotomy for the brain tumor, and

Daisuke Sato: Performed the craniotomy.

Sachiko Izumi: Administered the radiation treatment.

Haruka Okada: Pathologically diagnosed the disease.

All the authors have read and approved the final manuscript.

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CONFLICT OF INTEREST

None declared.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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Figure legends

Figure 1: Computed tomography scan showing a 27-mm mass (arrow) and no major vessel involvement in the pancreatic head.

Figure 2: A, B) A whitish, solid, 50-mm mass (arrow) in the pancreatic head. **C)** Pathological findings showing cells with nuclear atypia including ductal and papillary structures. The lesion was diagnosed as a well-differentiated tubular adenocarcinoma.

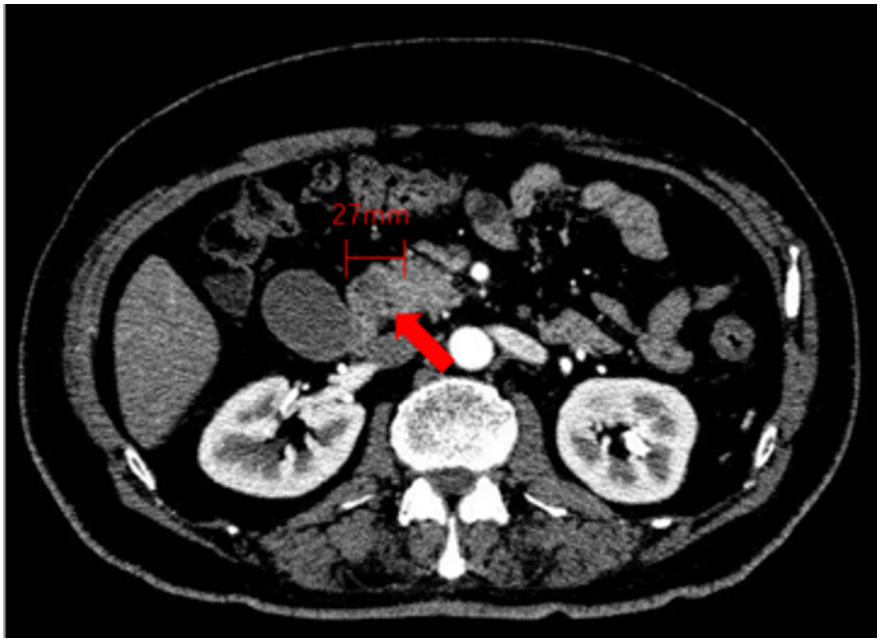
Figure 3: A) Computed tomography scan showing growth of the mass at the bottom of the right lung. **B)** The cytological diagnosis was adenocarcinoma.

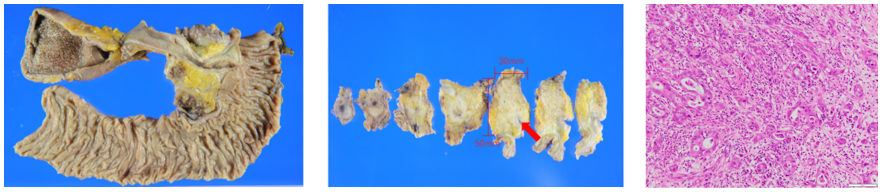
Figure 4: A) Pathological analysis showed an adenocarcinoma similar to the primary lesion, round-shaped enlarged nucleus, and mucin-producing columnar tumor cells proliferating in a tubular or papillary manner. **B)** Immunostaining is positive for CK7. **C)** Immunostaining is negative for CK20. **D)**Immunostaining is negative for TTF-1, indicating a low likelihood of primary lung cancer.

Figure 5: A) Magnetic resonance imaging showing a 23×22×20-mm neoplasm in the right inferior parietal lobule (arrow). **B)**Pathological findings showing a tumor similar to the primary lesion, cells with atypical nuclei, and a high N/C ratio, indicating papillary, fused ductal structures and solid arrangements, which are findings of adenocarcinoma.

Figure. 6) Tumor markers (CA19-9, CEA, DUPAN-2, and SPan1) were measured regularly during the course of the study; DUPAN-2 and SPan1 reflected disease activity.

Both decreased markedly after the PpPD, but not after pulmonary resection or after craniotomy, and decreased when chemotherapy was changed from GS to GEM + nab PTX.





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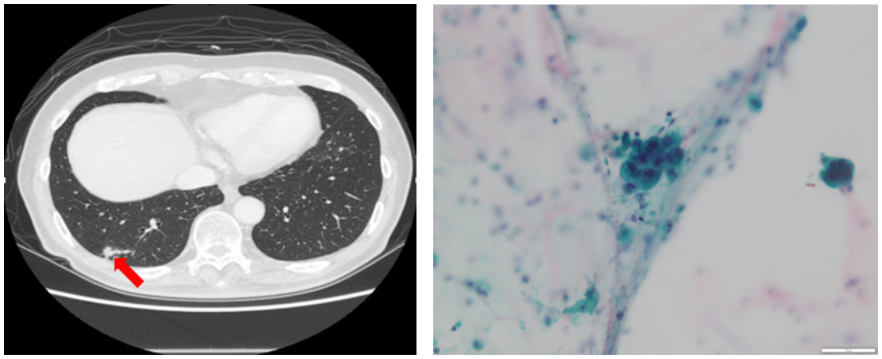

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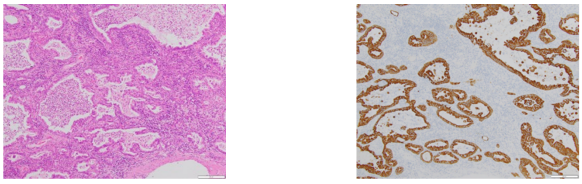

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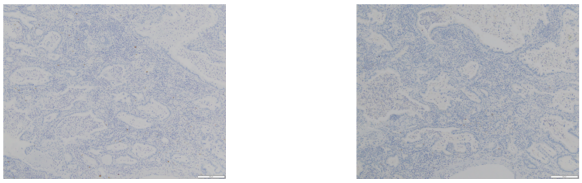

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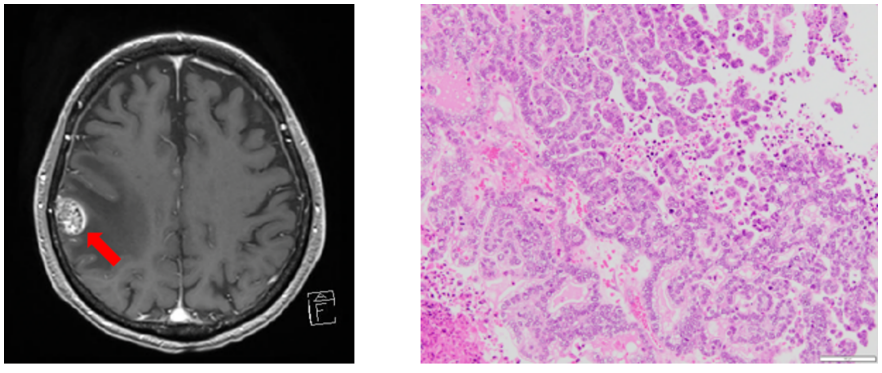

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