Case Report

Metastatic pancreatic acinar cell carcinoma with *BRCA2* gene alternation resected after modified FORFIRINOX therapy: a case report and literature review

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Background: Pancreatic acinar cell carcinoma (PACC) is a rare subtype of pancreatic cancer, and its clinicopathological behavior is not fully understood because of its rarity. The excision of the tumor is the best treatment, but PACC patients often have distant metastasis at the time of first diagnosis and sometimes have relapse after surgery. Thus, appropriate anti-tumor agents need to be administered; however, there is still no standard chemotherapy regimen for PACC. We report a case of PACC in a patient with breast cancer susceptibility gene (*BRCA*)*2* gene alternation whose hepatic metastasis was shrunk by a treatment with a modified FORFIRINOX (mFFX) regimen. The patient also underwent conversion surgery after the mFFX treatment.

Case Description: A 67-year-old man was treated for breast cancer in 2016. In 2022, he experienced a continuous left back pain, and abdominal computed tomography (CT) revealed a 47-mm hypo-dense mass in the pancreatic tail and a 100-mm slightly enhanced mass in the liver at segment 8. He was diagnosed with PACC with liver metastasis by liver and pancreatic tumor biopsies. He was started on mFFX and, at the same time, we performed an analysis of the *BRCA* gene alternation with blood and genetic screening using a liver biopsy specimen. Later, the germline *BRCA2* gene alternation was identified, and mFFX was continued. He had considerable tumor shrinkage after 13 mFFX cycles and was then sent for surgery. An excised sample showed no tumor in the liver and a 900-μm residual tumor in the pancreatic tail. He had relapse in the liver at segment 6 at 12 months after surgery, which was then excised. He had a lymph node relapse at 3 months after the second surgery, and was receiving olaparib.

Conclusions: mFFX might be prioritized as the first-line chemotherapy for PACC patients, and an analysis of the *BRCA* gene alternation needs to be conducted.

Keywords: Acinar cell carcinoma; pancreatic cancer; FORFIRINOX (FFX); breast cancer susceptibility gene 2 (*BRCA2*); case report

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Introduction

Pancreatic acinar cell carcinoma (PACC) is a rare subtype of pancreatic cancer, accounting for 0.3–4.3% of all exocrine pancreatic neoplasms (1). The prognosis is considered to be better than that of pancreatic ductal adenocarcinoma (PDAC), with a 5-year survival rate of 21.5–42.8% (1), but its clinicopathological behavior is not fully understood because of its rarity. If curative resection is possible, surgical resection is considered to be the best first-line treatment approach for PACC (2). Further, the conversion surgery for unresectable tumors (locally advanced and metastatic cases) after treatment with an anti-tumor agent reportedly is better to achieve a longer prognosis (3). Thus, effective anti-tumor agents for PACC are necessary. However, there is no standard chemotherapy regimen for PACC; instead, the treatment regimens for PDAC are generally used for PACC. We experienced a case of PACC in a patient with breast cancer susceptibility gene (*BRCA*)*2* alternation whose hepatic tumor considerably shrunk after treatment with modified FORFIRINOX (mFFX). After the mFFX treatment, resection was also possible for this case. An appropriate chemotherapy regimen personalized for each patient is necessary. We present this article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-845/rc).

Highlight box

Key findings

- Pancreatic acinar cell carcinoma (PACC) can be sensitive to a fluoropyrimidine or a platinum drug; thus, FORFIRINOX (FFX) [modified FFX (mFFX)], not gemcitabine (GEM), could be the first-choice drug for PACC.

What is known and what is new?

- There is currently no standard chemotherapy regimen for PACC; instead, the treatment regimens for pancreatic ductal adenocarcinoma are generally used for PACC.
- PACC was considerably shrunk by mFFX.
- Our patient had a breast cancer susceptibility gene 2 alternation.

What is the implication, and what should change now?

- When managing PACC patients with anti-tumor agents, the treatment might be better to start with FFX (mFFX), rather than GEM plus ablaxan. Further, we should perform cancer genomic profiling and analyze the gene alternation to select the optimal anti-cancer drugs.

Case presentation

A 67-year-old man who was treated for breast cancer in 2016 experienced continuous left back pain and visited Kure Medical Center in 2022. Abdominal computed tomography (CT) revealed a 47-mm hypo-dense mass in the pancreatic tail, requiring further examination. He underwent a mastectomy for the left breast cancer and a transurethral resection of the bladder tumor in 2016. Abdominal CT was performed annually to monitor for any relapse of breast cancer. He had hypertension and hyperlipidemia. The patient did not smoke or drink alcohol. His father died from cholangiocarcinoma. Physical examination results on admission were as follows: height, 170 cm; weight, 64 kg; and body temperature, 36.4 ℃. His abdomen was soft and flat with no palpable mass. His relevant laboratory results were as follows: amylase, 62 IU/L; lipase, 2,738 IU/L; and elastase-1, 906 ng/dL. The carbohydrate antigen 19-9 and S-pancreas-1 antigen levels were 41 IU/L and 152 U/mL, respectively.

CT revealed a 47-mm hypo- or iso-dense mass with a cystic component in the pancreatic tail (*Figure 1A*) and a 100-mm round mass with slightly enhanced compared to liver and a cystic component in early phase at segment 8 of the liver (*Figure 1B*). We performed fine needle aspiration with endoscopic ultrasonography and percutaneous liver biopsy. Histopathological examination of the specimens obtained from both masses revealed atypical cells with swollen nuclei and eosinophilic granular cytoplasm with scant vascular interstitium and sheet-like proliferation in a scattered rosette-like arrangement (*Figure 1C*). Immunohistochemical examination of the tumor revealed B-cell lymphoma/leukemia 10 (BCL10) positivity (*Figure 1D*), leading a diagnosis of PACC.

We decided to administer anti-tumor agents to the patient and started with a mFFX regimen as the first-line chemotherapy because of the following reasons: that there were more reports that FFX (mFFX) was effective for PACC, as compared to GEM; and the patient was likely to have a *BRCA* gene alternation as he had a history of breast cancer. Concurrently, we performed an analysis of

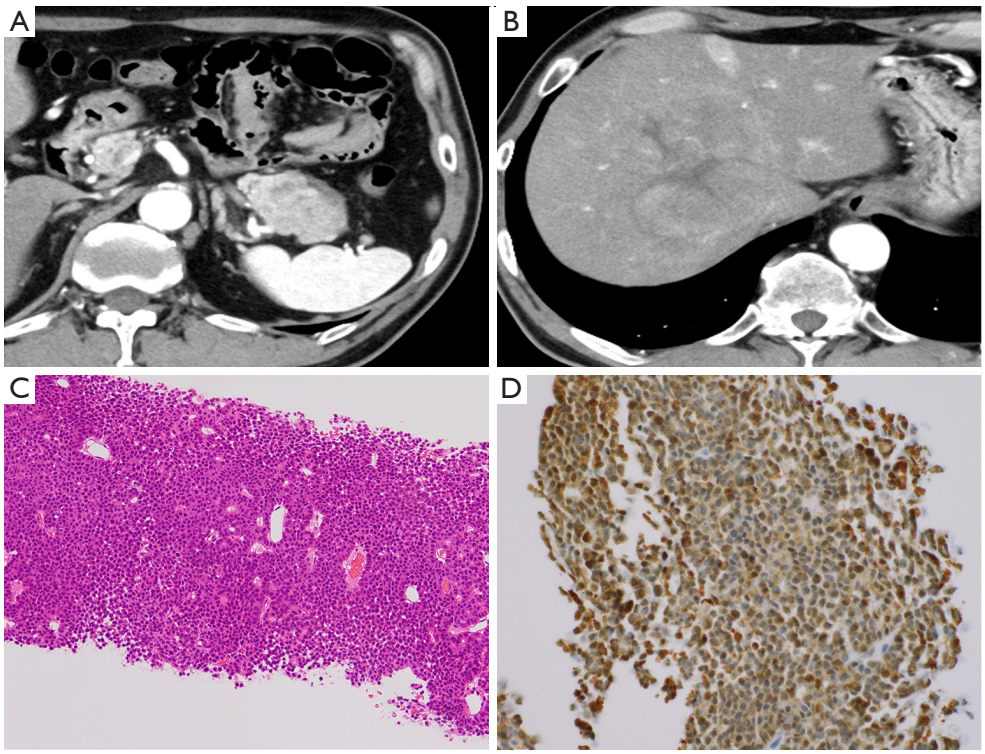

Figure 1 CT imaging and histological findings of the tumor. (A) Abdominal CT of the patient showing a 47-mm hypo-dense mass in the pancreatic tail. (B) A 100-mm hypo-dense mass considered as a hepatic metastasis is also seen. (C) Histological examination of the liver biopsy showing tumor cells that are similar to acinar cells, appearing with round nuclei, eosinophilic vesicles, and a solid growth pattern (hematoxylin-eosin staining at ×200). (D) Immunohistochemistry showed positivity for BCL10 at ×400. BCL10, B-cell lymphoma/leukemia 10; CT, computed tomography.

BRCA gene alternation with blood and genetic screening (FoundationOne CDx, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) using a liver biopsy specimen. Both tests identified the germline *BRCA2* gene alternation; hence, chemotherapy with mFFX was continued. In the liver biopsy sample, *NRAS Q61H* gene mutation was also detected.

After five cycles of mFFX, the size of the pancreatic and hepatic tumors decreased to 24 mm (*Figure 2A*) and 32 mm (*Figure 2B*), respectively. After 13 treatment cycles, the pancreatic and hepatic tumors were 10 mm (*Figure 2C*) and 24 mm (*Figure 2D*), respectively, in size. Consequently, he underwent a distal pancreatectomy and a partial hepatectomy of segment 8. The resected specimen showed a residual tumor with a size of approximately 900 µm in the pancreatic tail (effect 3) (*Figure 3A,3B*), but no residual tumor was noted in the liver (effect 4) (*Figure 3C,3D*).

Afterward, he received tegafur-gimeracil-oteracil potassium (S1) for 6 months as an adjuvant therapy. At 18 months after his first visit to our department (at 12 months after surgery), a 30-mm hepatic metastasis was found in segment 6 (*Figure 4*). He received three cycles of mFFX. As CT revealed a stable disease (SD), he then underwent partial hepatectomy (*Figure 4*). At 3 months after the second surgery, he was started on olaparib due to the presence of a relapse in the lymph nodes (8p, 13a) (*Figure 5*). At 3 months after treatment with olaparib, the metastasis had expanded, and olaparib was considered to be inefficacious.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration and its subsequent amendments. Written informed consent for publication of this case report and accompanying images was obtained from the patient. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

We report the case of a patient with PACC who had a

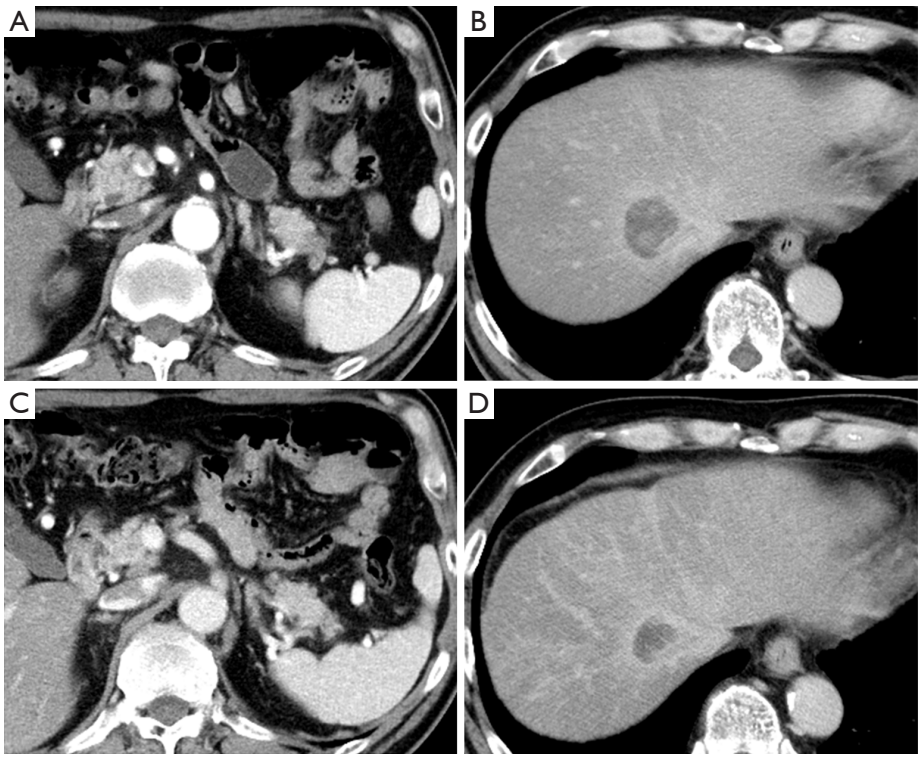

Figure 2 CT imaging after the mFFX therapy. (A,B) After five treatment cycles, the pancreatic (A) and hepatic (B) tumors shrunk to 24 and 32 mm, respectively. (C,D) After 13 treatment cycles, the pancreatic (C) and hepatic (D) tumors shrunk to 10 and 24 mm, respectively. CT, computed tomography; mFFX, modified FORFIRINOX.

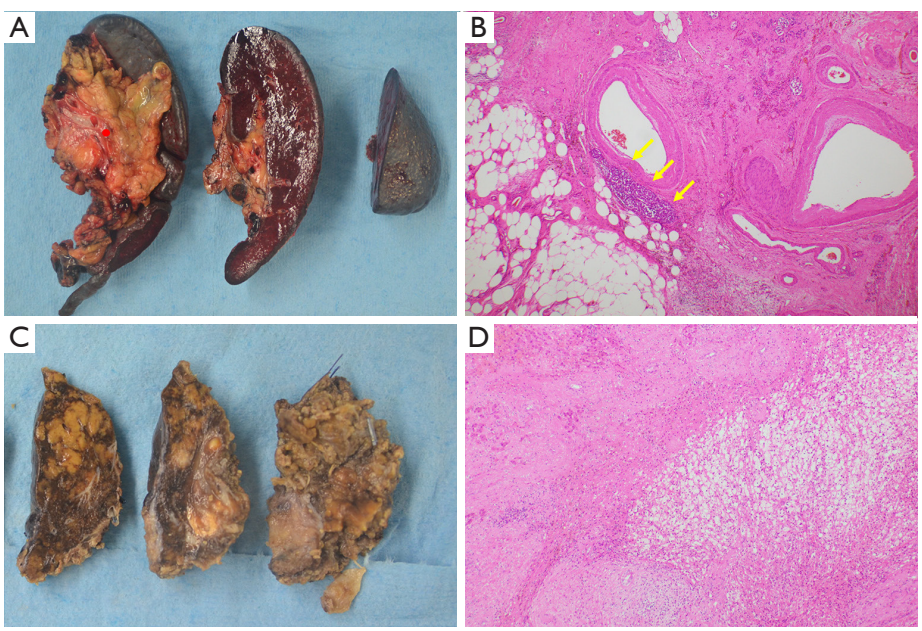

Figure 3 Conversion surgery with distal pancreatectomy and partial hepatectomy of segment 8 of the liver. (A,B) A residual tumor with a size of approximately 900-μm was found in the pancreatic tail (arrows). (B) Hematoxylin-eosin staining at ×40 magnification. (C,D) There were no residual tumors in the liver. (D) Hematoxylin-eosin staining at ×100 magnification.

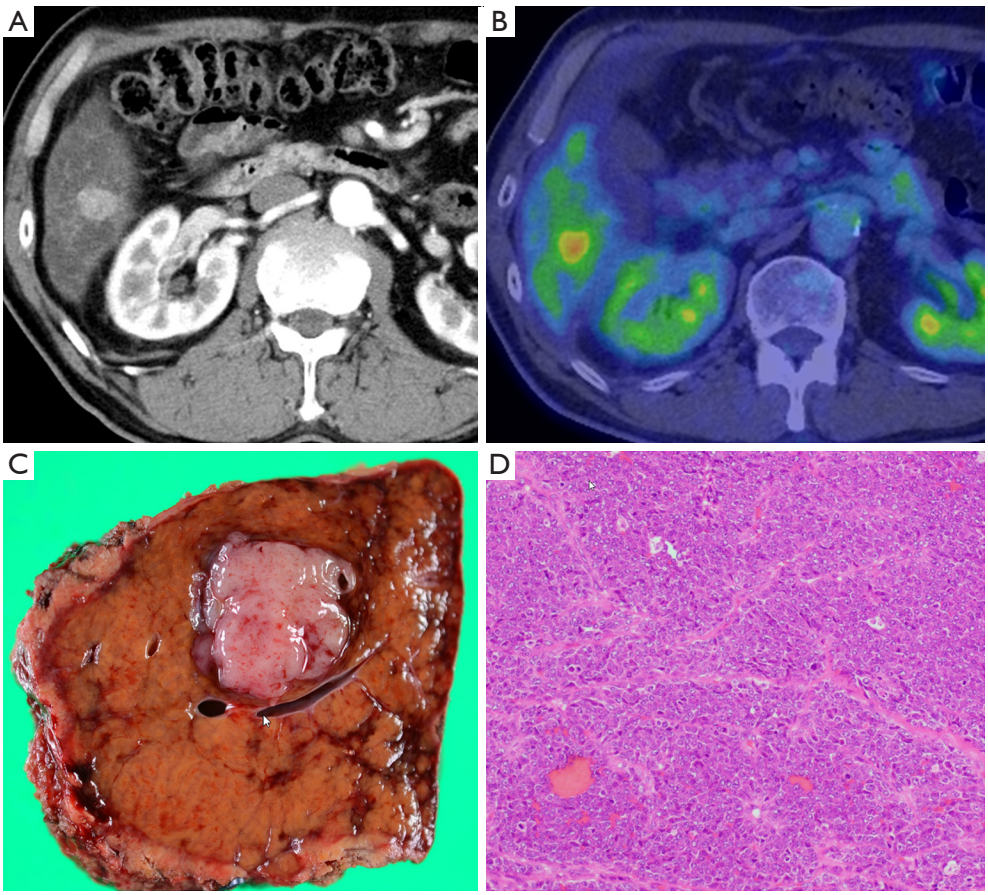

Figure 4 A relapse was seen at liver segment 6 at 12 months after surgery. (A) CT showing a 30-mm new tumor at liver segment 6, which is considered a metastasis. (B) In a PET-CT scan, the tumor had a high accumulation of fluorodeoxyglucose (SUVmax: 4.6). (C,D) An excised specimen obtained after three cycles of mFFX showed a viable acinar cell carcinoma. (D) Hematoxylin-eosin staining at ×400 magnification. CT, computed tomography; mFFX, modified FORFIRINOX; PET, positron emission tomography; SUVmax, maximum standard uptake value.

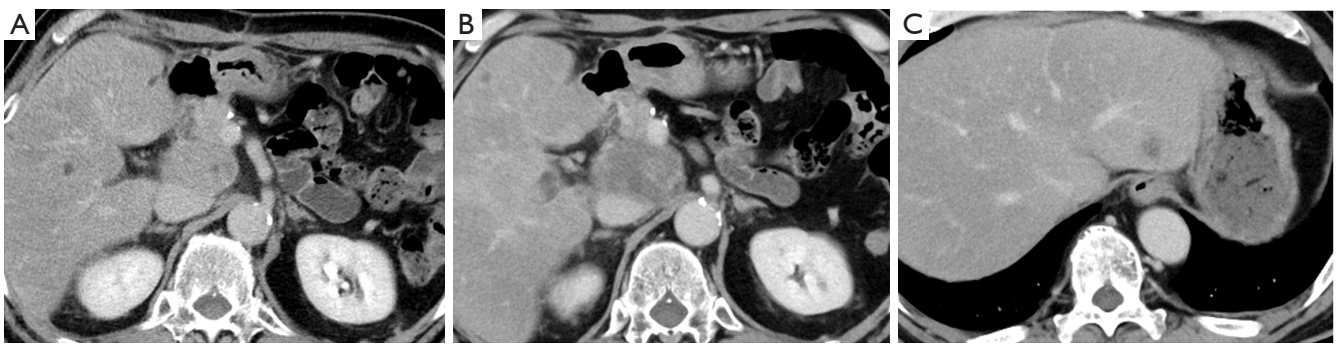

Figure 5 A relapse in the lymph node was noted at 3 months after the second surgery and the effectiveness of olaparib. (A) A relapse with a size of 39 mm was seen in the lymph node at the back of the pancreatic head in CT. (B,C) Disease progression was noted at 3 months after starting olaparib in CT: (B) growth of the lymph node, (C) new metastasis in the liver. CT, computed tomography.

BRCA2 gene alternation, in whom conversion surgery was possible owing to the considerable tumor reduction by mFFX therapy. Our case report is valuable, as it recommends multimodal therapy for PACC.

PACC is a tumor originating from the acinar cells of the pancreas and occupied 0.2–4.3% in pancreatic exocrine tumors. The characteristics of PACC are rather different from those of PDAC, and the prognosis of PACC is considered to be better than that of PDAC. However, the 5-year survival rate of PACC is not very high; thus, it is considered a relatively aggressive tumor. Approximately 50% of patients with PACC have a distant metastasis at the time of diagnosis, and the recurrence rate after radical resection could reach as high as 72% (3). From the abovementioned facts, multimodal therapies, including chemotherapy regimens, are needed for PACC (1,3,4).

Our case was metastatic disease and excision of the hepatic metastasis was difficult because of the small remnant liver volume after excision even if we tried. Thus, chemotherapy was selected for the patient. Currently, the standard therapy for PACC has not been established yet and the chemotherapy regimens for PDAC are recommended for PACC. In Japan, GEM plus nab-paclitaxel (GnP) and FFX (mFFX) are recommended as the first-line therapies (5-7). In these two regimens, more patients, especially elderly, tend to receive GnP than FFX (mFFX), because of the weaker side effects of GnP. There were more reports that FFX (mFFX) was effective for PACC, as compared to GEM (Table S1). Thus, we need to reconsider the first-line chemotherapy for PACC based not only on its side effects but also on its effectiveness.

Fluoropyrimidine-based regimen, especially FFX (mFFX), was reported to be more effective than GEM-based regimens (1,3,8-10). Additionally, our male patient had a breast cancer and was suspected of having a BRCA gene alternation. Thus, we started the chemotherapy treatment with mFFX including fluorouracil and oxaliplatin because a patient with a *BRCA* gene alternation was considered to be sensitive to platinum-based chemotherapy drugs (1,4,11-13). During the treatment course, the presence of *BRCA2* gene alternation was determined by centrifugation with blood and liver biopsy samples, and treatment with mFFX was continued, resulting in a considerable tumor shrinkage. The *BRCA2* gene is used for DNA repair and the tumor with a *BRCA2* gene alternation is sensitive to platinum-based anti-cancer drugs, which inhibit DNA repair. Furthermore, the effectiveness of fluoropyrimidine for PACC is considered to be based on the theory of adenomatous polyposis coli (APC)/β-catenin pathway sensitivity observed in pancreatic acinar cells (8,14,15).

We found 53 PACC cases treated with chemotherapies after a database search in PubMed using the keywords "acinar cell carcinoma" and "case report" from January 2003 to September 2024 (Table S1). We analyzed 54 cases including our case. Altogether, 84 anti-tumor therapies, excluding treatments with molecular-targeted agents, were found and analyzed. Fifty-two treatment regimens that were first initiated for the patients are shown in *Table 1*. The response rate was significantly higher in the FFX-treated (mFFX-treated) (68.8%) and S1-treated (100%) patients than in the GEM-treated (0%) and GnP-treated (0%) patients. These results suggest that FFX (mFFX) and S1 are more effective than GEM-based chemotherapy. Additionally, some cases had complete remission and partial response (PR) with 5-fluorouracil (5-FU) treatment only (16). Although there have been case reports of partial and complete responses with combination therapy including GEM [GEM + oxaliplatin (17), GEM + S1 (18), GEM + mitomycin (19)], these effects might be induced by other drugs, except for GEM. For irinotecan (IRI), treatment regimens utilizing IRI only were not reported; however, four treatment regimens including IRI except for mFFX (FFX) have been described in previous reports (2,20-22). A GEM plus IRI regimen (20) resulted in progressive disease (PD), and a treatment with cisplatin plus IRI (2) resulted in SD. Two cases receiving IRI hydrochloride hydrate plus 5-FU (21,22) and folic acid showed PR and PD. Although Takahashi *et al.* (9) have reported that IRI-based agents were favored for PACC, on the basis of the abovementioned data, we considered that IRI might not be very effective. On conversion surgery after chemotherapy in patients with unresectable PACC, fluoropyrimidine-based regimen, especially FFX (mFFX), had shown favorable result (3,12,16,22-30).

In PACC, the alternation of the *BRCA1/2* gene was reported to be high as compared with that in PDAC. In particular, the rate of *BRCA2* gene alternation reportedly was 13.6–36.7% (PDAC: 2.7–2.9%) (1,31). On the basis of the abovementioned facts, we might need to select treatment regimens that include platinum and fluoropyrimidine for PACC as the first-choice treatment. Under insurance, we should select the FFX (mFFX) as the first regimen.

Patients with a *BRCA* gene alternation are considered to be sensitive to the platinum-based anti-tumor agents and poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors (32). The PARP inhibitor acts through multiple mechanisms, including the trapping of PARP on the DNA at the sites of single-strand breaks. In our literature search

Table 1 Effectiveness of reported chemotherapy agent for PACC

Regimen	First line			Second line			All		
	Number	RR	DCR	Number	RR	DCR	Number	RR	DCR
FFX (mFFX)	16	11/68.8	14/87.5	3	3/100	3/100	19	14/73.7	17/89.4
GEM	12	0/0	5/33.3	1	0/0	0/0	13	0/0	4/30.8
GnP	5	0/0	1/20	5	0/0	0/0	10	0/0	1/10
S1	3	3/100	3/100	5	1/20	1/20	8	4/50	4/50
GEMOX	2	2/100	2/100	2	0/0	1/50	4	2/50	3/75
GEM plus S1	2	2/100	2/100	–	–	–	2	2/100	2/100
Cisplatin plus IRI	1	1/100	1/100	–	–	–	1	1/100	1/100
FOLFOX	1	0/0	1/100	3	2/66.7	2/66.7	4	2/50	3/75
CAPTEM	1	0/0	0/0	–	–	–	1	0/0	0/0
XEROX	1	1/100	1/100	–	–	–	1	1/100	1/100
GEM plus cisplatin	1	1/100	1/100	–	–	–	1	1/100	1/100
Paclitaxel	1	0/0	0/0	1	1/100	1/100	2	1/50	1/50
5-FU	1	1/100	1/100	–	–	–	1	1/100	1/100
GEM plus IRI	1	0/0	1/100	–	–	–	1	0/0	1/100
GEM plus mitomycin	1	1/100	1/100	–	–	–	1	1/100	1/100
5-FU plus cisplatin	1	0/0	1/100	–	–	–	1	0/0	1/100
Nal-IRI	–	–	–	2	1/50	1/50	2	1/50	1/50
SOX	–	–	–	1	0/0	0/0	1	0/0	0/0
FORFIRI	–	–	–	4	2/50	2/50	4	2/50	2/50
Carboplatin	–	–	–	1	0/0	1/100	1	0/0	1/100
GEM plus 5-FU	–	–	–	1	1/100	1/100	1	1/100	1/100
Docetaxel plus capecitabine	–	–	–	1	0/0	0/0	1	0/0	0/0
Capecitabine	–	–	–	1	0/0	0/0	1	0/0	0/0
CAPOXIRI	–	–	–	1	0/0	0/0	1	0/0	0/0
Total	51	–	–	32	–	–	83	–	–

Data in RR and DCR are presented as number/%. 5-FU, 5-fluorouracil; CAPOXIRI, capecitabine, raltitrexed with oxaliplatin, and irinotecan; CAPTEM, capecitabine plus temozolomide; DCR, disease control rate; FFX, FORFIRINOX; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FORFIRI, folinic acid, fluorouracil, and irinotecan; GEM, gemcitabine; GEMOX, gemcitabine plus oxaliplatin; GnP, gemcitabine plus nab-paclitaxel; IRI, irinotecan; mFFX, modified FORFIRINOX; nal-IRI, folinic acid, fluorouracil, and nanoliposomal irinotecan; PACC, pancreatic acinar cell carcinoma; RR, response rate; SOX, S1 and oxaliplatin; XEROX, capecitabine and oxaliplatin.

for cases of PACC with *BRCA* gene alternation (*Table 2*), the PARP inhibitor had shown favorable effect. Thus, we need to analyze the gene alternation of germline and somatic *BRCA1/2* in PACC patients.

PACC and PDAC are known to have a different gene alternation profile (1,31,37). PDAC has a higher frequency of gene alternation in *KRAS*, *TP53*, and *CDKN2A* (PACC *vs.* PDAC: 13.6% *vs.* 85.1%, 15.9% *vs.* 69.1%, and 25.0% *vs.* 35.4%, respectively) and lower frequency of gene alternation in *BRCA1*, *BRCA2*, *BRAF*, mismatch repair-deficient (dMMR)/microsatellite instability, and tumor mutational burden-high (PACC *vs.* PDAC: 2.3% *vs.* 0.9%, 13.6% *vs.* 2.9%, 15.9% *vs.* 1.7%, 2.6% *vs.* 0.3%, and 7.9% *vs.* 1.8%, respectively) (1). Additionally, PACC is more likely to have germline and somatic gene alternations as compared to other solid tumors (33). Recently, several reports have described the effectiveness of molecular-targeted drug for PACC (*Table 3*). Thus, it is essential

Table 2 Reported cases of PACC with *BRCA* gene alternation

Case No.	DOI (ref.)	Author	Reported year	Age (years old)	Gender (M/F)	Altered gene	Reason for chemotherapy	First line chemotherapy	Effect	Clinical course
1	10.1007/s10689-024-00390-3 (11)	Matsubayashi	2024	73	M	*BRCA2*	Liver metastasis in 13 months after surgery	Olaparib	PR	Not available
2	10.1002/cnr2.70007 (13)	Kubo	2024	53	M	*BRCA1*	Liver metastasis after surgery	GnP	PD	PR with mFFX in19 cycles. Switch to olaparib (PD in 4 months). PD with mFFX. PD with GEM
3	10.1007/s12328-024-01981-4 (4)	Urabe	2024	80	M	*BRCA2*	Relapse in remnant pancreas after surgery	GnP	PD	PD with S1 in 8 months. Radiation. PD with S1 in 5 months. PR with mFFX (continued a year and 3 months). Switch to olaparib (maintained PR in a year). Survival in a year after stopping olaparib
4	10.1007/s12328-024-01992-1 (30)	Watanabe	2024	60	M	*BRCA1*	Locally advanced	GnP	PD	PR with FFX in 6 cycles. Sent for conversion surgery. FFX as adjuvant chemotherapy in 6 months. No recurrence in 10 months after stopping FFX
5	10.3748/wjg.v28.i45.6421 (33)	Lee	2022	70	M	*BRCA2*	Liver metastasis	mFFX	PR	PR with mFFX in 15 cycles. Switch to olaparib due to peripheral neurological disorders. Maintained PR in 5 months
6	10.1002/ccr3.6718 (34)	Lelong	2022	38	M	*BRCA2*	Liver metastasis	FFX	PR	PR with FFX in 12 cycles. Switch to olaparib (PR in 24 months)
7	10.1159/000515267 (22)	Dreikhausen	2021	66	M	*BRCA2*	Liver metastasis	FFX	PR	PR with FFX. Exchange to FORFIRI by peripheral neurological disorders by FFX. Sent for conversion surgery. FORFIRI, GnP, and nal-IRI had PD for relapse in the liver. Olaparib was sent but the efficacy was not available
8	10.1080/15384047.2019.1595274 (18)	Kryklyva	2019	52	M	*BRCA2*	Metastasis for liver, lung, peritoneum, and skin in 6 months after surgery	FFX	PR	PR with FFX in 24 months. Stopped FFX due to peripheral neurological disorders. Death in 3 months
9	10.1097/MD.0000000000013113 (35)	Li	2018	59	M	*BRCA2*	Retroperitoneum lymph node metastasis	FFX	PD	Radiation for lymph-node metastasis (not effective). Intra-tumoral brachytherapy by radioiodine-125 (not effective). PR with olaparib. Stopped olaparib due to severe complications. PD and death
10	10.1080/17843286.2016.1168065 (36)	Naeyaert	2016	59	M	*BRCA2*	Liver metastasis	GEM	PD	SD by carboplatin
Our case	–	–	–	67	M	*BRCA2*	Liver metastasis	mFFX	PR	PR with mFFX in 13 cycles. Sent for conversion surgery. Relapse in the liver in 12 months after surgery. SD with FFX in 3 months. Excision liver tumor. Relapse in lymph-node and started olaparib in 3 months after surgery. PD with olaparib

BRCA, breast cancer susceptibility gene; F, female; FFX, FORFIRINOX; FORFIRI, folinic acid, fluorouracil, and irinotecan; GEM, gemcitabine; GnP, gemcitabine plus nab-paclitaxel; M, male; mFFX, modified FORFIRINOX; nal-IRI, folinic acid, fluorouracil, and nanoliposomal irinotecan; PACC, pancreatic acinar cell carcinoma; PD, progressive disease; PR, partial response; ref., reference; SD, stable disease.

Table 3 PACCs with anti-tumor agent in accordance with gene mutation or molecular target anti-tumor agent (excluding *BRCA1/2* gene alternation)

Case No.	DOI (ref.)	Author	Reported year	Age (years old)	Gender (M/F)	Mutated gene	Metastatic lesion or locally advanced	Clinical course before using molecular target drug	Molecular target drug	Anti-tumor effect
1	10.1007/s00432-024-05841-z (12)	Merz	2024	69	M	*MLH1*/MSI-high	Locally advanced	SD with mFFX (6 cycles). Switch to GnP (PD)	Pembrolizumab (anti-PD-1 antibody)	PR. Sent for conversion surgery
2	10.1002/gcc.23222 (38)	Von Fritsch	2024	52	M	*BRAFV600E*	Peritoneum	SD with mFFX (8 cycles). Exchange to 5-FU plus folic acid due to peripheral neurological disorders. Stopped due to fatigue	Dabrafenib/trametinib (*BRAF* inhibitor/MEK inhibitor)	CR in 16 months
3	10.12998/wjcc.v11.i24.5823 (39)	Wang	2023	77	M	*ROS1-CENPW*	Liver	N/A	GnP plus crizotinib (specific tyrosine kinase inhibitor)	PR
4	10.3389/fonc.2024.1357233 (24)	Wu	2024	45	F	High TMB	Locally advanced	N/A	Tripalimab (anti-PD-1 antibody)	PR
5	10.1200/PO.21.00400 (21)	Gaule	2022	62	M	Rearranged *ALK*	Liver metastasis after surgery	PD with GnP (3 cycles), nal-IRI (PR but PD in 6 months). PD with FOLFOX (7 cycles)	Alectinib (ALK tyrosine kinase inhibitor)	PR in 16 months
6	10.6004/jnccn.2020.7641 (40)	Gupta	2021	81	M	*NTRK* fusion gene	Lymph-node relapse after surgery	PD with GEM (5 cycles). PD with GnP (4 cycles)	Larotrectinib (NTRK inhibitor)	CR in 13 months
7	10.1177/0300891620980792 (41)	Xu	2020	68	M	PD-L1 positive plus high TMB	Lung, retroperitoneum lymph-node	SD with GnP (2 cycles) and skin rash. PD with SOX (2 cycles)	SOX plus tripalimab (anti-PD-1 antibody)	PR
8	10.3389/fonc.2021.692480 (42)	Qin	2021	48	F	PD-L1 positive plus high TMB	Liver	None	Sintilimab plus lenvatinib	PR
9	10.4251/wjgo.v10.i4.103 (43)	Richard	2018	54	M	*EGFR*	Liver	PD with FFX (4 cycles). PD with GnP (2 cycles)	Panitumumab (anti-*EGFR*)	PR
10	10.1177/030089161309900230 (44)	Ang	2013	71	M	N/A	Liver	PR with GEM plus cisplatin (6 months). Renal failure. PD with GEM plus oxaliplatin. PR with FORFIRI (1 year). PR with HAI (floxuridine) plus irinotecan. Irinotecan plus cetuximub (1 year). PD with FORFIRI plus cetuximub	FORFIRI plus cetuximub plus bevacizumab	PR
11	N/A (20)	Antonie	2007	44	F	N/A	Liver	SD with GEM plus irinotecan (7 cycles). SD with GEMOX (16 cycles). PD with docetaxel plus capecitabine (6 cycles). PD with FORFIRI	GEM plus erlotinib	PD
12	10.1385/IJGC:34:2-3:067 (45)	Pimenta	2003	43	F	N/A	Peritoneum relapse after surgery	SD with GEM (7 cycles). PD with capecitabine. PD with Raltitrexed plus oxaliplatin. PD with irinotecan. PR with paclitaxel (4 months)	Imatinib mesylate	PD

5-FU, 5-fluorouracil; *BRCA*, breast cancer susceptibility gene; CR, complete response; F, female; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FORFIRI, folinic acid, fluorouracil, and irinotecan; FFX, FORFIRINOX; GEM, gemcitabine; GEMOX, gemcitabine plus oxaliplatin; GnP, gemcitabine plus nab-paclitaxel; HAI, hepatic arterial infusion; M, male; mFFX, modified FORFIRINOX; MSI, microsatellite instability; nal-IRI, folinic acid, fluorouracil, and nanoliposomal irinotecan; N/A, not available; PACC, pancreatic acinar cell carcinoma; PD, progressive disease; PR, partial response; ref., reference; SD, stable disease; SOX, S1 and oxaliplatin; TMB, tumor mutational burden.

that we analyze the gene alternation of the tumor. For improvement of the prognosis of patients with PACC, first, a surgery may need to be performed. Even not at the time of the first diagnosis, conversion surgery should be the aim of treatment. During this time, FFX (mFFX) including the administration of a fluoropyrimidine and a platinum-based anti-tumor agent might be the best regimen. Additionally, multimodal approaches can be used, as analyzed in 54 cases describing 15 cases of surgeries, four cases of arterial injection chemotherapy, three cases of radiofrequency ablation, and one case of radiation. Furthermore, many treatment regimens using anti-tumor drugs have been tried (*Tables 1-3* and Table S1), which sometimes obtained a response. Thus, patients with PACC might need to be treated through a multimodal approach. Unfortunately, our patient showed disease progression, at the time of writing this manuscript, but we were confident that we might prolong his life by conversion surgery and chemotherapy. Regrading of this point, the effectiveness of resecting PACC with distant metastases and recurrent PACC has not been determined. We need further analysis which therapeutic strategy was useful between chemotherapy only and resecting oligometastatic lesions. FFX, even mFFX, could induce some strong side effects and be difficult to continue for some patients, especially elderly people. A literature search revealed some PACC cases that were sensitive to 5-FU, capecitabine, 5-FU + cisplatin, FOLFOX (folinic acid, fluorouracil, and oxaliplatin), XEROX (capecitabine and oxaliplatin), and SOX (S1 and oxaliplatin). We desire to use these agents under the national insurance coverage in Japan.

Conclusions

PACC seem more sensitive to FFX (mFFX) and even milder fluoropyrimidine-based regimens rather than gemcitabine (GEM) of GnP. Genomic sequencing may provide treatable targets. Surgery may be beneficial in selected oligometastatic cases if notable response to neoadjuvant therapy is seen.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration and its subsequent amendments. Written informed consent for publication of this case report and accompanying images was obtained from the patient. A copy of the written consent is available for review by the editorial office of this journal.

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