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Review Article

Comprehensive review of pancreatic acinar cell carcinoma: epidemiology, diagnosis, molecular features and treatment

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Abstract

Pancreatic acinar cell carcinoma is a rare form (0.2–4.3%) of pancreatic neoplasm with unique clinical and molecular characteristics, which largely differ from pancreatic ductal adenocarcinoma. Pancreatic acinar cell carcinoma occurs more frequently in males and can occur in children. Serum lipase is elevated in 24–58% of patients with pancreatic acinar cell carcinoma. Pancreatic acinar cell carcinomas tend to be large at diagnosis (median tumour size: ∼5 cm) and are frequently located in the pancreas head. Radiologically, pancreatic acinar cell carcinoma generally exhibits a solid appearance; however, necrosis, cystic changes and intratumoral haemorrhage can occur in larger lesions. Immunostaining is essential for the definitive diagnosis of pancreatic acinar cell carcinoma. Compared with pancreatic ductal adenocarcinoma, pancreatic acinar cell carcinoma has a more favourable prognosis. Although radical surgery is recommended for patients with pancreatic acinar cell carcinoma who do not have distant metastases, the recurrence rate is high. The effectiveness of adjuvant therapy for pancreatic acinar cell carcinoma is unclear. The response to FOLFIRINOX is generally favourable, and some patients achieve a complete response. Pancreatic acinar cell carcinoma has a different genomic profile compared with pancreatic ductal adenocarcinoma. Although genomic analyses have shown that pancreatic acinar cell carcinoma rarely has *KRAS*, *TP53* and *CDKN2A* mutations, it has a higher prevalence of homologous recombination-related genes, including *BRCA1/2* and *ATM*, than pancreatic ductal adenocarcinoma, suggesting high sensitivity to platinum-containing regimens and PARP inhibitors. Targeted therapies for genomic alternations are beneficial. Therefore, genetic testing is important for patients with pancreatic acinar cell carcinoma to choose the optimal therapeutic strategy.

Key words: genomic analysis, homologous recombination deficiency, immune checkpoint inhibitor, immunostaining

Introduction

Most cases of pancreatic cancer are pancreatic ductal adenocarcinoma (PDAC). Although acinar cells are present in more than 80% of the pancreas, pancreatic acinar cell carcinoma (PACC) is a rare form of pancreatic cancer with unique clinical and molecular characteristics distinct from those of PDAC. The molecular characteristics influence the response to chemotherapeutic agents. This review provides a review of the current state of knowledge regarding PACC, including the epidemiology, pathological diagnosis, role of surgery and (neo)adjuvant treatment, molecular features and treatment options for patients with unresectable PACC.

Epidemiology, clinical features, diagnosis, molecular features and treatment

Epidemiology

PACC is a rare pancreatic epithelial malignancy arising mainly from pancreatic acinar cells, accounting for 0.2–4.3% of all pancreatic carcinomas (Table 1) (1–8). PACC occurs more frequently in males, with a male-to-female ratio of 1.9–3.1:1 (9–14). The peak age at diagnosis of PACC is 60 years (10–12). In a multicenter retrospective analysis of chemotherapy in 58 patients with advanced PACC, 69% were male, and the median age was 60.5 years (11). In the United States, a national cancer database analysis (593 patients with PACC) showed that 72.8% of the patients were male, and the mean age was 64.4 years (13). In a retrospective analysis of German cancer registry group (233 patients with PACC), the median age was significantly lower, and the percentage of males was significantly higher in patients with PACC than in those with PDAC (14). PACC can occur in children and comprises 15% of paediatric pancreatic tumours (15,16).

Symptoms, laboratory data and tumour markers

Similar to other pancreatic neoplasms, PACC presents with many nonspecific symptoms, including abdominal pain, back pain, weight loss, gastrointestinal bleeding, nausea and diarrhoea (11,17). Owing to their growth pattern, jaundice is less common in PACC than in PDAC (2). The serum lipase level is elevated in 24–58% of patients with PACC (11,18–20). Owing to its specificity, an elevated serum lipase level is useful for differentiating PACC from other pancreatic malignancies. Excessive lipase expression can cause lipase hypersecretion syndrome. A minority of patients with PACC (0–15%) display signs of lipase hypersecretion syndrome, including fever, polyarthritis, subcutaneous fat nodular necrosis and eosinophilia, which is associated with poor prognosis (2,8,11,20–23). Although α-fetoprotein (AFP) has been proposed as a serum marker to differentiate PACC from PDAC, the prevalence of elevated AFP varies widely from 7.5 to 47% (10–12,24). The frequency of elevation of other tumour markers, including serum carcinoembryonic antigen (CEA) and CA19–9 levels, was previously thought to be low; however, recent studies have found a relatively high prevalence of CEA (15–24%) and CA19–9 (33–45%) elevation (10,11).

Radiological features

In PACC, the tumour is most frequently located in the pancreas head (24–28). The tumour is frequently large at the time of diagnosis (12,29–31), with a median tumour size of 45–54 mm in cases of resected PACC (25,26,32). PACC frequently presents as a large mass

Table 1. Overview of PACC

Epidemiology
- Incidence: 0.2–4.3% of all pancreatic carcinomas
- Incidence is higher in males (male-to-female ratio: 1.9–3.1:1)
- Peak age: 60 years, but can occur in children

Symptoms, laboratory data and tumour markers
- PACC presents with a range of nonspecific symptoms
- Elevation of lipase 24–58%; CEA 15–24%; CA19–9 33–45%

Radiological features and pathologic examination
- Most frequently located in the head of the pancreas
- Large mass with an ovoid shape and well-circumscribed margin
- Necrosis, cystic changes and intratumoral haemorrhage can occur in larger lesions
- Immunostaining is essential for confirmation of cell differentiation
- EUS-TA is required, not only for pathological diagnosis but also for genetic analysis

Prognosis and surgical treatment
- Prognosis of PACC: more favourable than that of PDAC, with a 5-year survival rate of 21.5–42.8%
- Radical surgery is recommended for PACC without metastasis
- The efficacy of adjuvant treatment remains unclear

Molecular features and treatment for patients with unresectable PACC
- Favourable treatment responses to fluoropyrimidine, platinum and irinotecan
- FOLFIRINOX showed more favourable treatment outcomes than GnP
- Rare *KRAS*, *TP53*, *CDKN2A* and *SMAD4* mutations
- Higher prevalence of homologous recombination-related genes, including *BRCA1/2*
- Targetable alterations in more than 30% of patients with PACC
- Gene-matched therapy can improve the prognosis of PACC, but data are limited

EUS-TA, endoscopic ultrasound-guided tissue acquisition; FFX, FOLFIRINOX, GnP, gemcitabine plus nab-paclitaxel combination therapy; PACC, pancreatic acinar cell carcinoma; PDAC, pancreatic ductal adenocarcinoma.

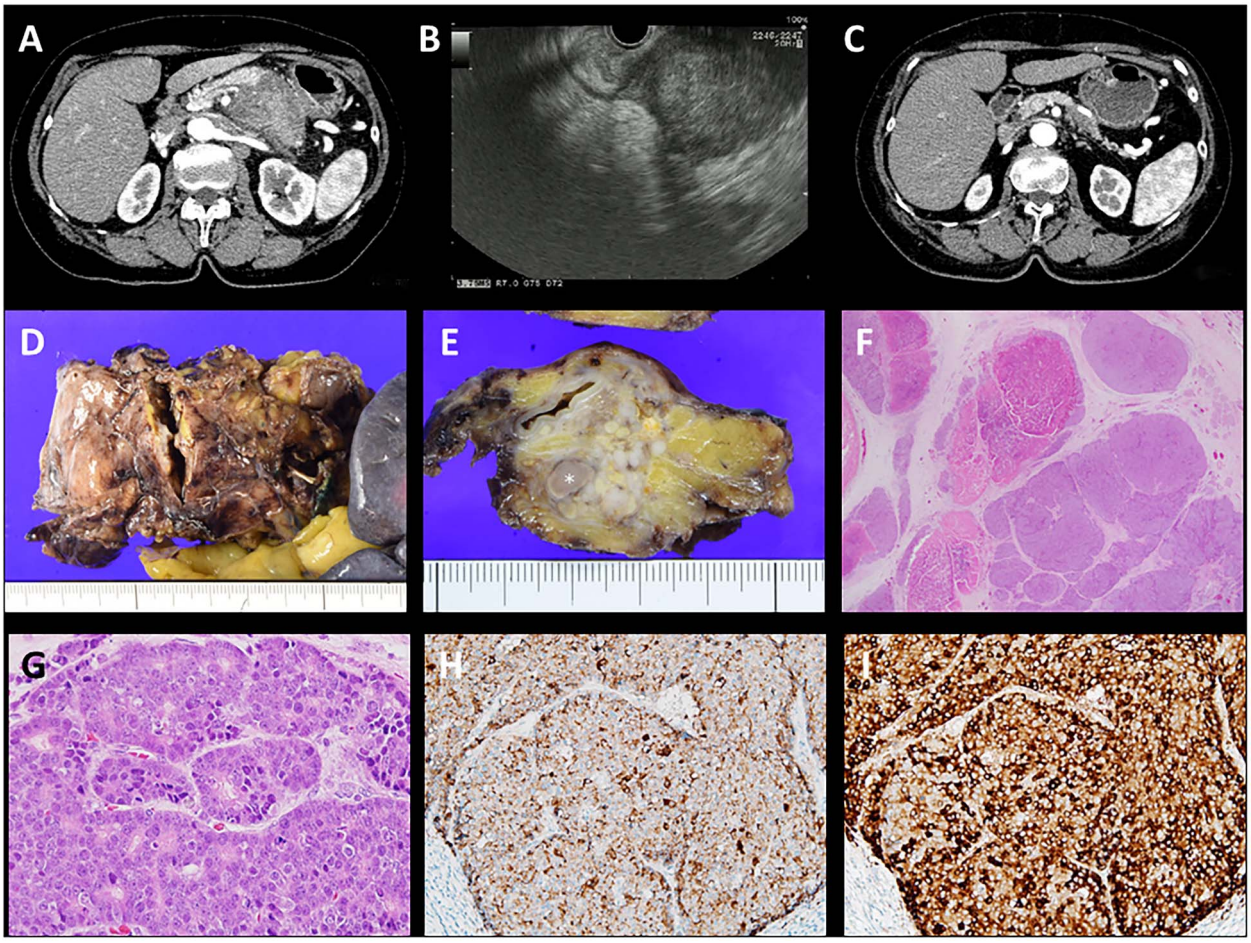

Figure 1. Case presentation of pancreatic acinar cell carcinoma (PACC). (A) Contrast-enhanced computed tomographic (CECT) image showing 6-cm heterogenous mass located in the pancreatic tail. (B) Endoscopic ultrasound image showing a hypoechoic mass with irregular contours, invading the gastric wall. (C) CECT image showing pancreatic tail tumour shrinkage 7 months after initiating modified FOLFIRINOX. (D–I) Pathologic findings of surgically resected PACC (distal pancreatectomy). (D) A surgically resected tumour localized in the body of the pancreas, formalin fixed, showing an expansive and partially encapsulated growth. (E) A lobular or confluent nodular cut-surface of tumour with an adjacent lymph-node metastasis (∗). (F) A low-power microphotograph demonstrating hypercellular tumour in nests with scant fibrous stroma and necrosis (haematoxylin and eosin stain, ×20). (G) The acinar pattern characterized by small lumina and non-mucinous cells with stratified nuclei, occasionally with conspicuous nucleoli (haematoxylin and eosin stain, ×400). (H, I) Immunohistochemical positivity for trypsin (H) and Bcl-10 (I) (immunostaining, ×200).

with an ovoid shape and well-circumscribed margin (Fig. 1) (30,33). Local invasion of the surrounding organs, including the duodenum, stomach, kidney, peritoneum and spleen, is observed in ∼45% of PACC cases (23). Moreover, ∼10% of patients with PACC have pancreatic ductal ingrowth, which can be observed in intraductal papillary mucinous neoplasm and pancreatic neuroendocrine neoplasm (pNEN) (34–38). Calcifications are detected in 0–50% of PACC cases (24,30,33,39). PACC usually has a solid appearance; however, necrosis, cystic changes and intratumoral haemorrhage can occur in larger lesions (24,30,40). Computed tomography (CT) is more sensitive for detecting calcifications, whereas magnetic resonance imaging is more effective for detecting intratumoral haemorrhage, tissue invasion and pancreatic duct dilation (24,40). Approximately 30–50% of patients with PACC have metastatic disease at the time of presentation (4,13,14). Takahashi et al. (11) reported that the most common metastatic sites are the liver (68%), peritoneum (19%) and distant lymph nodes (14%).

Important differential diagnoses of PACC include solid pseudopapillary neoplasm (SPN), pNEN, PDAC and (in children), pancreatoblastoma. The clinical presentation of SPN is quite different from that of PACC. SPN is more common in young and middle-aged women and is frequently located in the tail of the pancreas (41–44). Calcification is also a prominent characteristic of SPN (45). Recently, it was reported that PACC and SPN can be differentiated based on imaging findings (tumour location, maximum diameter, boundary, intratumoral vessels and distant metastasis) (42). Furthermore, PACC is often misdiagnosed as pNEN. PACC is usually hypercellular with scant fibrous stroma, characterized by a lobular pattern of growth and frequent necrosis. Some cases of pNEN show a similar histologic architecture, although necrosis is uncommon (46). The appearance of pNEN on CT is very variable and includes heterogeneous density with haemorrhage, cystic changes, necrosis and calcification (45,47). In children, PACC needs to be distinguished from pancreatoblastoma, a rare type of malignant pancreatic tumour that arises from the exocrine cells of the pancreas and is rare in adults (15,16,48–50). Pancreatoblastoma is also immunoreactive to trypsin and Bcl-10 but can be differentiated from PACC by the presence of squamoid nests on histopathology (48,49).

Pathologic examination with immunohistochemistry

Macroscopically, PACC tumours are typically large and generally well-circumscribed with at least a partial fibrous capsule and a homogenous tan to reddish cut surface, commonly accompanied by haemorrhage and central necrosis (51). Cytohistologic differentiation between PACC and pNEN is occasionally difficult because these neoplasms share similar monomorphic, round, medium-sized cells and some architectural variations such as solid and glandular patterns (41). Ancillary immunostaining on tissue specimens is essential for confirmation of cell differentiation, especially when examining fragmented or crushed cell samples. The sensitivity of immunostaining for lipase and amylase was 30 and 8%, respectively (23). For the definitive diagnosis of PACC, immunostaining with antibodies to identify acinar cell differentiation (trypsin and Bcl-10) (Fig. 1), in addition to the use of general neuroendocrine markers (synaptophysin and Chromogranin A) to exclude pNEN, is important (16,44,52,53). Scattered neuroendocrine cells positive for synaptophysin and/or Chromogranin A can be observed in PACC, and a small subset of pNEN shows focal acinar differentiation (2,54). A recent study showed high sensitivity and specificity of carboxypeptidase A1 immunostaining for acinar differentiation in the pancreas (55–57). Immunostaining with chymotrypsin-like elastase family member 3B, a pancreatic enzyme with digestive function in the intestine, also shows high sensitivity (75%) and specificity (99.9%) (58).

Pancreatic mixed acinar carcinomas include mixed acinar-neuroendocrine carcinoma (MANEC), mixed acinar-ductal carcinoma and mixed acinar-neuroendocrine-ductal carcinoma, which are rare subtypes of pancreatic tumour (59–63). They contain a significant proportion (>30%) of each cellular component (64). MANEC immunohistochemically expresses both neuroendocrine and exocrine markers (23,65,66). The clinicopathological behaviour of MANEC is similar to that of PACC (23,64,67).

Tissue acquisition for pathological diagnosis and creation of patient-derived organoids

Endoscopic ultrasound-guided fine-needle tissue acquisition (EUS-TA) is recommended for the pathological diagnosis of mass lesions in the pancreas and used for the pathological diagnosis of PACC (68–70). EUS-TA is generally successful in obtaining tissue for diagnosis, and the incidence of adverse events is low in patients with pancreatic tumours (71,72). Because genetic analysis using histological specimens is needed in patients with unresectable pancreatic cancer, including PACC, large-gauge biopsy needles should be used, and multiple biopsy specimens should be obtained (73–77). Patient-derived organoids (PDOs) can be created from surgically resected specimens, EUS-TA specimens and residual samples from saline flushes during EUS-TA (78–80). PDOs are useful for determining the sensitivity to chemotherapy and the preclinical evaluation of novel therapies in patients with pancreatic cancer (81–84). Recently, a PACC cell line was established using PDOs (85). The development of PDOs from patients with PACC could help provide new insights into the biological characteristics of PACC and useful data for personalized medicine and drug discovery.

Surgical resection and (neo)adjuvant treatment

PACC differs from PDAC in its clinical and molecular features; PACC also has a more favourable prognosis, with a 5-year survival rate of 21.5–42.8% (7,14,86,89). Tumour size was not associated with overall survival (OS) (25,26,87), whereas surgical resection was identified as an independent prognostic factor (14). Although radical surgery is recommended for patients with PACC who do not have distant metastases, the recurrence rate is high (12,19,88–90). The 5-year survival rate of Stage IV patients was not significantly different between patients who underwent surgery and those who did not (13). Evidence is accumulating regarding the effectiveness of surgical resection for oligometastasis in patients with PDAC (91–95). In patients with PACC, surgical resection for limited metastatic disease may provide a survival benefit (96).

The results of two multicenter studies on radical resection of PACC were recently reported (Table 2) (25,26). In a multicenter European study of 59 patients who underwent radical resection of PACC, the 5-year OS was 60.9%, and the median disease-free survival (DFS) was 30 months (25). The R0 resection rate was 84.7%. Compared with patients with N1 or N0 PACC, patients with N2 PACC had significantly shorter OS and DFS. N2 status was identified as the only significant negative prognostic factor. Eight patients (six with locally advanced disease and two with synchronous distant metastases) underwent neoadjuvant treatment, primarily with FOLFOX and FOLFIRINOX (FFX). Of the 59 patients, 37 (62.7%) underwent adjuvant treatment, primarily with gemcitabine (GEM)-based regimens. The recurrence rate after radical surgery was 52.5% (31/59) (local recurrence 7; local and systemic 6; systemic 18). The OS and DFS did not differ significantly based on whether the patients received adjuvant therapy (P = 0.542 and P = 0.159, respectively).

In a multicenter Korean study of 59 patients who underwent radical resection, the 5-year OS was 57.4%, and the median OS was 78.8 months (26). The 5-year DFS was 38.5%, and the median DFS was 30.9 months. The R0 resection rate was 93.2%. Patients with N2 nodal status had a significantly poorer prognosis than those with N0 status (P = 0.011). Of the 59 patients, 31 (52.5%) underwent adjuvant therapy (chemotherapy n = 22, chemoradiation n = 9). No significant differences were observed in survival based on the type of adjuvant therapy. Multivariable analysis identified CA19–9 level, nodal status (N2), 5-fluorouracil-containing chemotherapy and intraductal and papillary variants as independent prognostic factors.

Although the benefit of adjuvant treatment has been demonstrated in patients with PDAC (97–99), the benefit of adjuvant treatment in patients with PACC is unclear (1,13,14,27,32,100–102). Two recent multicenter studies demonstrated that 52.5–62.7% of patients who underwent adjuvant treatment did not show any survival benefit of adjuvant treatment, and more than 50% of the patients experienced recurrence after surgery (25,26). Thus, effective treatment strategies for preventing recurrence are urgently required.

A neoadjuvant treatment strategy has been developed for resectable and borderline-resectable PDAC (103–105). Treatment primarily with combination chemotherapy for unresectable PDAC enables conversion surgery (106–108). In a multicenter European study on patients with PACC who underwent radical resection, 15% (9/59) of patients underwent conversion surgery (25). Moreover, several recent case reports on conversion surgery after chemotherapy (primarily FFX) in patients with unresectable PACC have shown favourable treatment outcomes (Table 3) (69,109–116). Further research is needed to determine the effectiveness of treatment prior to radical resection and the chemotherapeutic regimens that are most appropriate.

Table 2. Multicenter studies on radically resected patients with PACC

Patient characteristics	European study (25) (59 patients)	Korean study (26) (59 patients)
Age	Median: 64 years	Mean: 59.2 years
Male	74.6%	83.1%
Tumour size	Median: 45.0 mm	Mean: 46.0 mm
Tumour location (%)		
Head	44.1	55.9
Body	30.5	5.1
Tail	20.3	37.3
Overlapping	5.1	1.7
Surgery (%)		
PD or PPPD	44.0	50.8
DP	40.7	35.6
TP	13.6	5.1
Others	1.7	8.5
Staging (%) (AJCC 8th edition)		
0	1.7	0
IA	8.5	13.6
IB	6.8	27.1
IIA	42.3	33.9
IIB	18.6	18.6
III	11.9	6.8
IV	10.2	0
R0 resection rate (%)	84.7	93.2
5-year OS (%)	60.9	57.4
Median OS (months)	NA	78.8
5-year DFS (%)	38.3	38.5
Median DFS (months)	30	30.9
Independent prognostic factors affecting OS	Nodal status (N2)	Nodal status (N2); CA19–9 level; chemotherapy; intraductal and papillary variant
Proportion of patients who underwent neoadjuvant treatment (%)	15.3	0
Proportion of patients who underwent adjuvant treatment (%)	62.7	52.5
Effectiveness of adjuvant therapy	No significant differences in OS and DFS in relation to adjuvant therapy	No significant differences in OS between patients who received no adjuvant therapy, chemotherapy or concurrent chemoradiotherapy
Recurrence rate (%)	52.5	NA

AJCC, American Joint Committee on Cancer; DFS, disease-free survival; DP, distal pancreatectomy; NA, not available; OS, overall survival; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; TP, total pancreatectomy.

Molecular features and optimal treatment for patients with unresectable PACC

Owing to the rarity of PACC, data regarding PACC-specific treatment outcomes is limited. Because the standard treatment of unresectable PACC has not been established, systemic chemotherapy for PACC is derived from the treatment of PDAC, including FFX and GEM plus nab-paclitaxel combination therapy (GnP) (11,12,100,117–119). In previous studies on patients with advanced PACC, GEM-containing regimens have shown poorer treatment outcomes than fluoropyrimidine-containing regimens (11,12,118). OS tended to be better in patients who received a platinum-containing or irinotecan-containing regimen than in patients who did not (11). PACC generally responds favourably to FFX, and some patients achieve a complete response (57,116,119–122). Currently, limited data are available regarding the effectiveness of concurrent chemoradiotherapy for PACC; therefore, further studies are warranted (17,101,118,123–125).

Genomic analysis of pancreatobiliary malignancies has become easier in recent years (126–130). Targeted gene-matched therapies can provide survival benefits for patients with pancreatic cancer who harbour mutations sensitive to chemotherapeutic agents (131). Accumulating evidence indicates that PACC has a different genomic profile compared with PDAC (29,121,125,132–135). Genomic analyses have demonstrated that PACC rarely has *KRAS*, *TP53* or *CDKN2A* mutations, which are frequently observed in PDAC. The results of two recent large studies that compared the genomic profiles of patients with PACC and PDAC are summarized in Table 4 (121,125).

A comprehensive genomic profiling study conducted in the United States (including 51 patients with PACC and 4205 patients with PDAC) revealed that 90.7% of patients with PDAC, but only 3.8% of patients with PACC, harboured *KRAS* mutations (125). *TP53*, *CDKN2A* and *SMAD4* mutations were present in 13.7, 11.6 and 15.1% of patients with PACC, respectively. Approximately 20% (10/51) of patients with PACC, but only 3.6% of patients with PDAC, had *BRCA1/2* mutations. In patients with PACC, the frequency of *PALB2*, *BRAF* (V600E) and *IDH1* mutations and loss-of-function mutations in *FBXW7*

Table 3. Cases of patients with unresectable PACC who underwent conversion surgery following chemotherapy

Authors, year [ref. no.]	Age	Sex	Tumour location	Tumour size (mm)	Reason for unresectable status	Chemotherapy	Treatment period	Effect	Procedure of conversion surgery	Adjuvant chemotherapy	Treatment outcomes after surgery
Distler, et al. 2009 [109]	65	Male	Head	40	Locally advanced disease	5-FU	12 months	PR	PD with combined resection of PV	None	Alive for 18 months without recurrence
Yamamoto et al. 2012 [110]	71	Male	Body	35	Peritoneal dissemination	S1	6 months	PR	DP	S1	Alive for 24 months without recurrence
Jimbo et al. 2016 [111]	56	Male	Body	60	Locally advanced disease	FFX →FOLFOX	6 months	PR	DP	NA	NA
Kida et al. 2017 [112]	59	Male	Body	45	Locally advanced disease	GEM and S-1	8 months	PR	DP	S1	Alive for 60 months without recurrence
Villano et al. 2020 [113]	71	Male	Tail	36	Liver metastasis	FFX	6 cycles	PR	DP and partial right hepatectomy	None	Alive for 6 months without recurrence
Izumo et al. 2022 [69]	65	Male	Head	40	PV tumour thrombosis	FFX	14 cycles	PR	PD with combined resection of PV	None	Alive for 33 months without recurrence
Sunami et al. 2022 [114]	37	Male	Tail	150	Liver metastasis	FFX	12 cycles	PR	DP	S1	Alive for 36 months without recurrence
Uemura et al. 2022 [115]	67	Male	Body and tail	67	Peritoneal dissemination	FFX	12 months	PR	TP	S1	Alive for 32 months without recurrence
Yamada et al. 2023 [116]	60	Male	Tail	70	Liver metastasis	FFX	3 cycles	PR	DP and extended right hemi-hepatectomy	S1	Alive for 36 months without recurrence

GEM, gemcitabine; PR, partial response; PV, portal vein.

was 3.8, 3.8, 3.8 and 3.8%, respectively. Genomic characterization revealed targetable alterations in more than 30% of patients with PACC.

A retrospective study from Japan using Center for Cancer Genomics and Advanced Therapeutics data (including 44 patients with PACC and 2568 patients with PDAC) revealed that the frequency of homologous recombination-related genes, including *BRCA1/2* and *ATM*, was significantly higher in patients with PACC (11.4/15.9%) than in patients with PDAC (2.5/3.7%) (121). Importantly, patients with PACC showed a higher objective response rate with FFX than with GnP (61.5 vs. 23.5%, P = 0.06) and significantly longer time to treatment failure (median: 42.3 vs. 21.0 weeks, P = 0.004).

Platinum-containing regimens and PARP inhibitors show favourable treatment outcomes in patients with germline PDAC with *BRCA* mutations and have become the standard of care for these patients (136–143). Germline PACC with *BRCA* mutations has been reported to respond to PARP inhibitors such as olaparib (144). Homologous recombination deficiency (HRD) in advanced pancreatic cancer is a putative biomarker of therapeutic response to platinum-containing regimens (145–147). In a large pan-cancer cohort, patients with PACC showed a high prevalence of germline *BRCA2* mutations (pure PACC, 35.5%; PDAC, 3.1%), suggesting that PACC should be considered as a part of the *BRCA*-related cancers spectrum (135). Genomic features of HRD were observed in 7 of 12 patients with PACC undergoing whole-genome sequencing. More than half (54.8%) of the pure PACC cases were observed to have germline pathogenic variants in homologous recombination or DNA damage-response genes.

Immune checkpoint inhibitor therapy is effective for microsatellite instability (MSI)/mismatch repair-deficient and high tumour mutational burden (TMB) PDAC (148–150). In 236 patients with PACC, the prevalence of high TMB and high MSI was 6.8 and 1.3%, respectively (150); thus, immune checkpoint inhibitors are a promising option for this population (151). *BRAF/MEK* inhibition achieved a complete response in patients with PACC harbouring the *BRAF* V600E mutation (125,152,153). In patients with PACC, tumours with *ALK-KANK4* gene fusion respond favourably to treatment with alectinib, and tumours with *NTRK* gene fusion respond favourably to treatment with larotrectinib (154,155). Because targeted therapies have been demonstrated to be beneficial, genetic testing should be performed on patients with PACC to guide the choice of therapy. PACC-specific prospective treatment studies are limited (NCT05286827 and jRCTs031220099); therefore, further studies are required to determine the optimal treatment for PACC.

Conclusion

Although PACC is a rare subtype of pancreatic cancer, recent studies have clarified its genomic profile and potential treatment strategies. A combination of chemotherapy and gene-matched therapies improves treatment outcomes, with an increase in the number of patients who undergo conversion surgery. The high frequency of postoperative recurrence is one of the major unresolved problems, and the effectiveness of adjuvant therapy for PACC has not been established. Further studies, including studies of targeted gene-matched therapies, are needed to determine the optimal treatment strategy.

Table 4. Studies on genomic analysis, including PACC and PDAC

Characteristics	Study from the United States (125) (PACC: 51 patients; PDAC: 4205 patients)	Study from Japan (121) (PACC: 44 patients; PDAC: 2568 patients)
Age	Median: PACC 60 years; PDAC 68 years	Mean: PACC 60.6 years; PDAC 63.9 years
Male	PACC 74.5%; PDAC 53.4%	PACC 70.5%; PDAC 56.7%
Genomic alteration		
KRAS	PACC 3.8%; PDAC 90.7%	PACC 13.6%; PDAC 85.1%
TP53	PACC 13.7%; PDAC 77.7%	PACC 15.9%; PDAC 69.1%
CDKN2A	PACC 11.6%; PDAC 23.8%	PACC 25.0%; PDAC 35.4%
SMAD4	PACC 15.1%; PDAC 19.9%	PACC 29.6%; PDAC 19.4%
BRCA1	PACC 2.0%; PDAC 0.9%	PACC 2.3%; PDAC 0.9%
BRCA2	PACC 17.3%; PDAC 2.7%	PACC 13.6%; PDAC 2.9%
PALB2	PACC 3.8%; PDAC 0.6%	PACC 0%; PDAC 0.9%
ARID1A	PACC 11.1%; PDAC 9.6%	PACC 9.1%; PDAC 7.1%
BRAF	PACC 3.8% (V600E); PDAC 1.2%	PACC 15.9%; PDAC 1.7%
IDH1	PACC 3.8%; PDAC 0.2%	PACC 0%; PDAC 0.1%
dMMR/MSI-High	PACC 2.1%; PDAC 0.9%	PACC 2.6%; PDAC 0.3%
TMB-high	PACC 2.0%; PDAC 0.9%	PACC 7.9%; PDAC 1.8%
Time to treatment failure (FFX vs. GnP)	—	PACC 42.3 vs. 21.0 weeks (P = 0.004) PDAC 28.1 vs. 28.0 weeks (P = 0.47)
Overall response rate	—	PACC 61.5 vs. 23.5% (P = 0.06) PDAC 24.1 vs. 25.2% (P = 0.61)

dMMR, mismatch repair-deficient; MSI, microsatellite instability; TMB, tumour mutational burden.

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References

1. Glazer ES, Neill KG, Frakes JM, et al. Systematic review and case series report of acinar cell carcinoma of the pancreas. *Cancer Control* 2016;23:446–54.
2. Klimstra DS, Heffess CS, Oertel JE, Rosai J. Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. *Am J Surg Pathol* 1992;16:815–37.
3. Hoorens A, Lemoine NR, McLellan E, et al. Pancreatic acinar cell carcinoma. An analysis of cell lineage markers, p53 expression, and Ki-ras mutation. *Am J Pathol* 1993;143:685–98.
4. Kitagami H, Kondo S, Hirano S, Kawakami H, Egawa S, Tanaka M. Acinar cell carcinoma of the pancreas: clinical analysis of 115 patients from pancreatic cancer registry of Japan pancreas society. *Pancreas* 2007;35:42–6.
5. Satake T, Morizane C, Rikitake R, Higashi T, Okusaka T, Kawai A. The epidemiology of rare types of hepatobiliary and pancreatic cancer from national cancer registry. *J Gastroenterol* 2022;57:890–901.
6. Matsuno S, Egawa S, Fukuyama S, et al. Pancreatic cancer registry in Japan: 20 years of experience. *Pancreas* 2004;28:219–30.
7. Schmidt CM, Matos JM, Bentrem DJ, Talamonti MS, Lillemoe KD, Bilimoria KY. Acinar cell carcinoma of the pancreas in the United States: prognostic factors and comparison to ductal adenocarcinoma. *J Gastrointest Surg* 2008;12:2078–86.
8. Holen KD, Klimstra DS, Hummer A, et al. Clinical characteristics and outcomes from an institutional series of acinar cell carcinoma of the pancreas and related tumors. *J Clin Oncol* 2002;20:4673–8.
9. Kryklyva V, Haj Mohammad N, Morsink FHM, et al. Pancreatic acinar cell carcinoma is associated with BRCA2 germline mutations: a case report and literature review. *Cancer Biol Ther* 2019;20:949–55.
10. Zhou W, Han X, Fang Y, et al. Clinical analysis of acinar cell carcinoma of the pancreas: a single-center experience of 45 consecutive cases. *Cancer Control* 2020;27:1073274820969447.
11. Takahashi H, Ikeda M, Shiba S, et al. Multicenter retrospective analysis of chemotherapy for advanced pancreatic acinar cell carcinoma: potential efficacy of platinum- and irinotecan-containing regimens. *Pancreas* 2021;50:77–82.
12. Xu JY, Guan WL, Lu SX, et al. Optimizing chemotherapy of pancreatic acinar cell carcinoma: our experiences and pooled analysis of literature. *Clin Med Insights Oncol* 2022;16:11795549221090186.
13. Shaib WL, Zakka K, Huang W, et al. Survival outcomes of acinar cell pancreatic cancer: a national cancer database analysis. *Pancreas* 2021;50:529–36.
14. Petrova E, Wellner J, Nording AK, et al. Survival outcome and prognostic factors for pancreatic acinar cell carcinoma: retrospective analysis from the German cancer registry group. *Cancers* 2021;13:6121.
15. Perez EA, Gutierrez JC, Koniaris LG, Neville HL, Thompson WR, Sola JE. Malignant pancreatic tumors: incidence and outcome in 58 pediatric patients. *J Pediatr Surg* 2009;44:197–203.

16. La Rosa S, Sessa F, Capella C. Acinar cell carcinoma of the pancreas: overview of clinicopathologic features and insights into the molecular pathology. *Front Med* 2015;2:41.
17. Calimano-Ramirez LF, Daoud T, Gopireddy DR, et al. Pancreatic acinar cell carcinoma: a comprehensive review. *World J Gastroenterol* 2022;28:5827–44.
18. Kruger S, Haas M, Burger PJ, et al. Acinar cell carcinoma of the pancreas: a rare disease with different diagnostic and therapeutic implications than ductal adenocarcinoma. *J Cancer Res Clin Oncol* 2016;142:2585–91.
19. Matos JM, Schmidt CM, Turrini O, et al. Pancreatic acinar cell carcinoma: a multi-institutional study. *J Gastrointest Surg* 2009;13:1495–502.
20. Lowery MA, Klimstra DS, Shia J, et al. Acinar cell carcinoma of the pancreas: new genetic and treatment insights into a rare malignancy. *Oncologist* 2011;16:1714–20.
21. Robertson JC, Eeles GH. Syndrome associated with pancreatic acinar cell carcinoma. *Br Med J* 1970;2:708–9.
22. MacMahon HE, Brown PA, Shen EM. Acinar cell carcinoma of the pancreas with subcutaneous fat necrosis. *Gastroenterology* 1965;49:555–9.
23. La Rosa S, Adsay V, Albarello L, et al. Clinicopathologic study of 62 acinar cell carcinomas of the pancreas: insights into the morphology and immunophenotype and search for prognostic markers. *Am J Surg Pathol* 2012;36:1782–95.
24. Qu Q, Xin Y, Xu Y, Yuan Y, Deng K. Imaging and clinicopathological features of acinar cell carcinoma. *Front Oncol* 2022;12:888679.
25. Bellotti, Paiella S, Primavesi F, et al. Treatment characteristics and outcomes of pure acinar cell carcinoma of the pancreas – a multicentric European study on radically resected patients. *HPB* 2023;25:1411–9.
26. Shin SH, Hwang HK, Jang JY, et al. Clinical characteristics of resected acinar cell carcinoma of the pancreas: a Korean multi-institutional study. *Cancers* 2021;13:5095.
27. Burchard PR, Chacon AC, Melucci A, et al. Defining the role of systemic therapy in resectable pancreatic acinar cell carcinoma. *J Surg Oncol* 2022;125:856–64.
28. Duorui N, Shi B, Zhang T, et al. The contemporary trend in worsening prognosis of pancreatic acinar cell carcinoma: a population-based study. *PloS One* 2020;15:e0243164.
29. Thompson ED, Wood LD. Pancreatic neoplasms with acinar differentiation: a review of pathologic and molecular features. *Arch Pathol Lab Med* 2020;144:808–15.
30. Raman SP, Hruban RH, Cameron JL, Wolfgang CL, Kawamoto S, Fishman EK. Acinar cell carcinoma of the pancreas: computed tomography features – a study of 15 patients. *Abdom Imaging* 2013;38:137–43.
31. Tian L, Lv XF, Dong J, et al. Clinical features and CT/MRI findings of pancreatic acinar cell carcinoma. *Int J Clin Exp Med* 2015;8:14846–54.
32. Wang Y, Wang S, Zhou X, et al. Acinar cell carcinoma: a report of 19 cases with a brief review of the literature. *World J Surg Oncol* 2016;14:172.
33. Tatli S, Mortele KJ, Levy AD, et al. CT and MRI features of pure acinar cell carcinoma of the pancreas in adults. *AJR Am J Roentgenol* 2005;184:511–9.
34. Bhosale P, Balachandran A, Wang H, et al. CT imaging features of acinar cell carcinoma and its hepatic metastases. *Abdom Imaging* 2013;38:1383–90.
35. Basturk O, Zamboni G, Klimstra DS, et al. Intraductal and papillary variants of acinar cell carcinomas: a new addition to the challenging differential diagnosis of intraductal neoplasms. *Am J Surg Pathol* 2007;31:363–70.
36. Ciaravino V, De Robertis R, Tinazzi Martini P, et al. Imaging presentation of pancreatic neuroendocrine neoplasms. *Insights Imaging* 2018;9:943–53.
37. Ikeda M, Miura S, Hamada S, et al. Acinar cell carcinoma with morphological change in one month. *Intern Med* 2021;60:2799–806.
38. Sakai A, Takada S, Katano K, et al. Pancreatic acinar cell carcinoma projected from the ampulla of Vater with extensive intraductal tumor growth. *Am J Gastroenterol* 2023;118:198.
39. Chiou YY, Chiang JH, Hwang JI, Yen CH, Tsay SH, Chang CY. Acinar cell carcinoma of the pancreas: clinical and computed tomography manifestations. *J Comput Assist Tomogr* 2004;28:180–6.
40. Hsu MY, Pan KT, Chu SY, Hung CF, Wu RC, Tseng JH. CT and MRI features of acinar cell carcinoma of the pancreas with pathological correlations. *Clin Radiol* 2010;65:223–9.
41. Mustafa S, Hruban RH, Ali SZ. Acinar cell carcinoma of the pancreas: a clinicopathologic and cytomorphologic review. *J Am Soc Cytopathol* 2020;9:586–95.
42. Cai J, Liu Y, Wang C, Yin X. Differentiation between solid pseudopapillary tumor and acinar cell carcinoma of the pancreas based on computed-tomography features. *Asian J Surg* 2023;46:1587–9.
43. Mazzarella G, Muttillo EM, Coletta D, et al. Solid pseudopapillary tumor of the pancreas: a systematic review of clinical, surgical and oncological characteristics of 1384 patients underwent pancreatic surgery. *Hepatobiliary Pancreat Dis Int* 2023. https://doi.org/10.1016/j.hbpd.2023.05.004.
44. Mormul A, Wloszek E, Nowoszewska J, et al. Rare non-neuroendocrine pancreatic tumours. *Cancers* 2023;15:2216.
45. Veron Sanchez A, Santamaria Guinea N, Cayon Somacarrera S, Bennouna I, Pezzullo M, Bali MA. Rare solid pancreatic lesions on cross-sectional imaging. *Diagnostics* 2023;13:2719.
46. Klimstra DS. Nonductal neoplasms of the pancreas. *Mod Pathol* 2007;20:S94–112.
47. Lee NJ, Hruban RH, Fishman EK. Pancreatic neuroendocrine tumor: review of heterogeneous spectrum of CT appearance. *Abdom Radiol* 2018;43:3025–34.
48. Rojas A, Wodskow J, Hogg ME. Adult pancreatoblastoma: a rare pancreatic tumor. *J Gastrointest Surg* 2023. https://doi.org/10.1007/s11605-023-05816-4.
49. Omiyale AO. Adult pancreatoblastoma: current concepts in pathology. *World J Gastroenterol* 2021;27:4172–81.
50. Bien E, Roganovic J, Krawczyk MA, et al. Pancreatoblastoma in children: EXPeRT/PARTNER diagnostic and therapeutic recommendations. *Pediatr Blood Cancer* 2021;68:e29112.
51. Toll AD, Hruban RH, Ali SZ. Acinar cell carcinoma of the pancreas: clinical and cytomorphologic characteristics. *Korean J Pathol* 2013;47:93–9.
52. Hosoda W, Sasaki E, Murakami Y, Yamao K, Shimizu Y, Yatabe Y. BCL10 as a useful marker for pancreatic acinar cell carcinoma, especially using endoscopic ultrasound cytology specimens. *Pathol Int* 2013;63:176–82.
53. Sun T, Gilani S, Jain D, Cai G. Cytomorphologic, immunophenotypical and molecular features of pancreatic acinar cell carcinoma. *Diagn Cytopathol* 2023;51:674–83.
54. Yantiss RK, Chang HK, Farraye FA, Compton CC, Odze RD. Prevalence and prognostic significance of acinar cell differentiation in pancreatic endocrine tumors. *Am J Surg Pathol* 2002;26:893–901.
55. Uhlig R, Contreras H, Weidemann S, et al. Carboxypeptidase A1 (CPA1) immunohistochemistry is highly sensitive and specific for acinar cell carcinoma (ACC) of the pancreas. *Am J Surg Pathol* 2022;46:97–104.
56. Said S, Kurtin PJ, Nasr SH, et al. Carboxypeptidase A1 and regenerating islet-derived 1α as new markers for pancreatic acinar cell carcinoma. *Hum Pathol* 2020;103:120–6.
57. Ishimoto-Namiki U, Ino Y, Esaki M, Shimada K, Saruta M, Hiraoka N. Novel insights into immunohistochemical analysis for acinar cell neoplasm of the pancreas: carboxypeptidase A2, carboxypeptidase A1, and glycoprotein 2. *Am J Surg Pathol* 2023;47:525–34.
58. Uhlig R, Broker N, Weidemann S, et al. CELA3B immunostaining is a highly specific marker for acinar cell carcinoma of the pancreas. *PloS One* 2023;18:e0287528.
59. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr Pathol* 2022;33:115–54.
60. Sakaguchi R, Yamada R, Nose K, et al. Pancreatic mixed acinar-neuroendocrine-ductal carcinoma: a case report and literature review. *Intern Med* 2023;62:3347–53.

61. Abdelrahman AM, Yin J, Alva-Ruiz R, et al. Mixed acinar neuroendocrine carcinoma of the pancreas: comparative population-based epidemiology of a rare and fatal malignancy in the United States. *Cancers* 2023;15:840.
62. Ikeda M, Miura S, Kume K, et al. Pancreatic mixed acinar-neuroendocrine carcinoma in a patient with a germline BRCA2 mutation: a case report. *Clin J Gastroenterol* 2022;15:999–1005.
63. Takano A, Hirotsu Y, Amemiya K, et al. Genetic basis of a common tumor origin in the development of pancreatic mixed acinar-neuroendocrine-ductal carcinoma: a case report. *Oncol Lett* 2017;14:4428–32.
64. Kim JY, Brosnan-Cashman JA, Kim J, et al. Pancreatic acinar cell carcinomas and mixed acinar-neuroendocrine carcinomas are more clinically aggressive than grade 1 pancreatic neuroendocrine tumours. *Pathology* 2020;52:336–47.
65. Whitehair R, Stelow EB. The cytologic and immunohistochemical findings of pancreatic mixed acinar-endocrine carcinoma. *Diagn Cytopathol* 2021;49:287–94.
66. Yoshino K, Kasai Y, Kurosawa M, Itami A, Takaori K. Mixed acinar-neuroendocrine carcinoma of the pancreas with positive for microsatellite instability: a case report and review of the literature. *Surg Case Rep* 2023;9:122.
67. Niiya F, Takano Y, Azami T, et al. A case of pancreatic mixed acinar-neuroendocrine carcinoma successfully diagnosed with endoscopic ultrasound-guided fine needle aspiration. *Clin J Gastroenterol* 2020;13:951–8.
68. Okusaka T, Nakamura M, Yoshida M, et al. Clinical practice guidelines for pancreatic cancer 2022 from the Japan pancreas society: a synopsis. *Int J Clin Oncol* 2023;28:493–511.
69. Izumo W, Higuchi R, Furukawa T, et al. A case of pathologically complete response after preoperative chemotherapy in a pancreatic acinar cell carcinoma patient with portal vein tumor thrombosis. *Clin J Gastroenterol* 2022;15:642–8.
70. Ikeda Y, Yoshida M, Ishikawa K, et al. Rare case of acinar cell carcinoma with multiple lesions in the pancreas. *JGH Open* 2020;4:1242–3.
71. Masuda S, Koizumi K, Shionoya K, et al. Comprehensive review on endoscopic ultrasound-guided tissue acquisition techniques for solid pancreatic tumor. *World J Gastroenterol* 2023;29:1863–74.
72. Itonaga M, Yasukawa S, Fukutake N, et al. Comparison of 22-gauge standard and Franseen needles in EUS-guided tissue acquisition for diagnosing solid pancreatic lesions: a multicenter randomized controlled trial. *Gastrointest Endosc* 2022;96:57–66.
73. Hijioka S, Nagashio Y, Maruki Y, et al. Endoscopic ultrasound-guided tissue acquisition of pancreaticobiliary cancer aiming for a comprehensive genome profile. *Diagnostics* 2023;13:1275.
74. Ashida R, Kitano M. Endoscopic ultrasound-guided tissue acquisition for pancreatic ductal adenocarcinoma in the era of precision medicine. *Dig Endosc* 2022;34:1329–39.
75. Hassan GM, Laporte L, Paquin SC, et al. Endoscopic ultrasound guided fine needle aspiration versus endoscopic ultrasound guided fine needle biopsy for pancreatic cancer diagnosis: a systematic review and meta-analysis. *Diagnostics* 2022;12:2951.
76. Ozono Y, Kawakami H, Uchiyama N, Hatada H, Ogawa S. Current status and issues in genomic analysis using EUS-FNA/FNB specimens in hepatobiliary-pancreatic cancers. *J Gastroenterol* 2023;58:1081–93.
77. Imaoka H, Sasaki M, Hashimoto Y, et al. Impact of endoscopic ultrasound-guided tissue acquisition on decision-making in precision medicine for pancreatic cancer: beyond diagnosis. *Diagnostics* 2021;11:1195.
78. Tiriac H, Bucobo JC, Tzimas D, et al. Successful creation of pancreatic cancer organoids by means of EUS-guided fine-needle biopsy sampling for personalized cancer treatment. *Gastrointest Endosc* 2018;87:1474–80.
79. Ikezawa K, Ekawa T, Hasegawa S, et al. Establishment of organoids using residual samples from saline flushes during endoscopic ultrasound-guided fine-needle aspiration in patients with pancreatic cancer. *Endosc Int Open* 2022;10:E82–7.
80. Kim S, Woo KJ, Yang CM, et al. Simultaneous establishment of pancreatic cancer organoid and cancer-associated fibroblast using a single-pass endoscopic ultrasound-guided fine-needle biopsy specimen. *Dig Endosc* 2023;35:918–26.
81. Huang L, Holtzinger A, Jagan I, et al. Ductal pancreatic cancer modeling and drug screening using human pluripotent stem cell- and patient-derived tumor organoids. *Nat Med* 2015;21:1364–71.
82. Boj SF, Hwang CI, Baker LA, et al. Organoid models of human and mouse ductal pancreatic cancer. *Cell* 2015;160:324–38.
83. Driehuis E, van Hoeck A, Moore K, et al. Pancreatic cancer organoids recapitulate disease and allow personalized drug screening. *Proc Natl Acad Sci U S A* 2019;116:26580–90.
84. Tiriac H, Belleau P, Engle DD, et al. Organoid profiling identifies common responders to chemotherapy in pancreatic cancer. *Cancer Discov* 2018;8:1112–29.
85. Hoshi D, Kita E, Maru Y, et al. Derivation of pancreatic acinar cell carcinoma cell line HS-1 as a patient-derived tumor organoid. *Cancer Sci* 2023;114:1165–79.
86. Wisnoski NC, Townsend CM Jr, Nealon WH, Freeman JL, Riall TS. 672 patients with acinar cell carcinoma of the pancreas: a population-based comparison to pancreatic adenocarcinoma. *Surgery* 2008;144:141–8.
87. He C, Zhang Y, Cai Z, Duan F, Lin X, Li S. Nomogram to predict cancer-specific survival in patients with pancreatic acinar cell carcinoma: a competing risk analysis. *J Cancer* 2018;9:4117–27.
88. Landa K, Freischlag K, Nussbaum DP, Youngwirth LM, Blazer DG 3rd. Underutilization of surgical resection in patients with pancreatic acinar cell carcinoma. *HPB* 2019;21:687–94.
89. Huang X, Li M, Zhang L, Xiong J, Lu H, Tian B. Clinical characteristics and treatment analysis of pancreatic acinar cell carcinoma: a single institutional comparison to pancreatic ductal adenocarcinoma. *Surg Oncol* 2021;37:101528.
90. Patel RK, Parappilly M, Sutton TL, et al. Referral and treatment patterns in pancreatic acinar cell carcinoma: a regional population-level analysis. *Am J Surg* 2023. https://doi.org/10.1016/j.amjsurg.2023.04.010.
91. Miyashita Y, Ose N, Okami J, et al. Outcomes of surgical resection for pulmonary metastasis from pancreatic cancer. *Surg Today* 2023;53:1236–46.
92. Stuart CM, Kirsch MJ, Zhuang Y, et al. Pulmonary metastasectomy is associated with survival after lung-only recurrence in pancreatic cancer. *Surgery* 2023;174:654–9.
93. Takeda T, Sasaki T, Ichinose J, et al. Outcomes of lung oligometastasis in pancreatic cancer. *Jpn J Clin Oncol* 2023. https://doi.org/10.1093/jjco/hyad111.
94. Homma Y, Endo I, Matsuyama R, et al. Outcomes of lung metastasis from pancreatic cancer: a nationwide multicenter analysis. *J Hepatobiliary Pancreat Sci* 2022;29:552–61.
95. Mashiko T, Nakano A, Masuoka Y, Yamamoto S, Ozawa S, Nakagohri T. Significance of pulmonary resection in patients with metachronous pulmonary metastasis from pancreatic ductal adenocarcinoma: a retrospective cohort study. *BMC Surg* 2021;21:237.
96. Hartwig W, Denneberg M, Bergmann F, et al. Acinar cell carcinoma of the pancreas: is resection justified even in limited metastatic disease? *Am J Surg* 2011;202:23–7.
97. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet* 2016;388:248–57.
98. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med* 2018;379:2395–406.
99. Motoi F, Unno M. Adjuvant and neoadjuvant treatment for pancreatic adenocarcinoma. *Jpn J Clin Oncol* 2020;50:483–9.
100. Sridharan V, Mino-Kenudson M, Cleary JM, et al. Pancreatic acinar cell carcinoma: a multi-center series on clinical characteristics and treatment outcomes. *Pancreatology* 2021;21:1119–26.

101. Zong Y, Qi C, Peng Z, Shen L, Zhou J. Patients with acinar cell carcinoma of the pancreas after 2005: a large population study. *Pancreas* 2020;49:781–7.
102. Patel DJ, Lutfi W, Sweigert P, et al. Clinically resectable acinar cell carcinoma of the pancreas: is there a benefit to adjuvant systemic therapy? *Am J Surg* 2020;219:522–6.
103. Yamaguchi J, Yokoyama Y, Fujii T, et al. Results of a phase II study on the use of neoadjuvant chemotherapy (FOLFIRINOX or GEM/nab-PTX) for borderline-resectable pancreatic cancer (NUPAT-01). *Ann Surg* 2022;275:1043–9.
104. Ghaneh P, Palmer D, Cicconi S, et al. Immediate surgery compared with short-course neoadjuvant gemcitabine plus capecitabine, FOLFIRINOX, or chemoradiotherapy in patients with borderline resectable pancreatic cancer (ESPAC5): a four-arm, multicentre, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol* 2023;8:157–68.
105. Springfeld C, Ferrone CR, Katz MHG, et al. Neoadjuvant therapy for pancreatic cancer. *Nat Rev Clin Oncol* 2023;20:318–37.
106. Kunzmann V, Siveke JT, Algül H, et al. Nab-paclitaxel plus gemcitabine versus nab-paclitaxel plus gemcitabine followed by FOLFIRINOX induction chemotherapy in locally advanced pancreatic cancer (NEOLAP-AIO-PAK-0113): a multicentre, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol* 2021;6:128–38.
107. Ushida Y, Inoue Y, Oba A, et al. Optimizing indications for conversion surgery based on analysis of 454 consecutive Japanese cases with unresectable pancreatic cancer who received modified FOLFIRINOX or gemcitabine plus nab-paclitaxel: a single-center retrospective study. *Ann Surg Oncol* 2022;29:5038–50.
108. Takada R, Ikezawa K, Daiku K, et al. The survival benefit of chemoradiotherapy following induction chemotherapy with gemcitabine plus nab-paclitaxel for unresectable locally advanced pancreatic cancer. *Cancers* 2021;13:4733.
109. Distler M, Ruckert F, Dittert DD, et al. Curative resection of a primarily unresectable acinar cell carcinoma of the pancreas after chemotherapy. *World J Surg Oncol* 2009;7:22.
110. Yamamoto T, Ohzato H, Fukunaga M, Imamura H, Furukawa H. Acinar cell carcinoma of the pancreas: a possible role of S-1 as chemotherapy for acinar cell carcinoma. A case report. *JOP* 2012;13:87–90.
111. Jimbo M, Batista PM, Baliff JP, Yeo CJ. Neoadjuvant chemotherapy and Appleby procedure for pancreatic acinar cell carcinoma: a case report. *Case Rep Pancreat Cancer* 2016;2:46–9.
112. Kida A, Matsuda K, Takegoshi K, Matsuda M, Sakai A, Noda Y. Pancreatic acinar cell carcinoma with extensive tumor embolism at the trunk of portal vein and pancreatic intraductal infiltration. *Clin J Gastroenterol* 2017;10:546–50.
113. Villano AM, Barrak D, Jain A, et al. Robot-assisted combined pancreatectomy/hepatectomy for metastatic pancreatic acinar cell carcinoma: case report and review of the literature. *Clin J Gastroenterol* 2020;13:973–80.
114. Sunami T, Yamada A, Kondo T, et al. Exceptional response of pancreatic acinar cell carcinoma and bile duct cancer to platinum-based chemotherapy in a family with a germline BRCA2 variant. *Pancreas* 2022;51:1258–62.
115. Uemura S, Maeda H, Tanioka N, et al. Successful conversion surgery after FOLFIRINOX therapy in a patient with advanced pancreatic acinar cell carcinoma with a solitary peritoneal dissemination: a case report. *Cancer Rep* 2022;5:e1648.
116. Yamada S, Motegi H, Kurihara Y, et al. A resected case of acinar cell carcinoma of the pancreas with liver metastasis following chemotherapy using modified FOLFIRINOX. *Surg Case Rep* 2023;9:147.
117. Busch E, Werft W, Bougatf N, et al. Metastatic acinar cell carcinoma of the pancreas: a retrospective cohort study on systemic chemotherapy and review of the literature. *Pancreas* 2021;50:300–5.
118. Yoo C, Kim BJ, Kim KP, et al. Efficacy of chemotherapy in patients with unresectable or metastatic pancreatic acinar cell carcinoma: potentially improved efficacy with oxaliplatin-containing regimen. *Cancer Res Treat* 2017;49:759–65.
119. Skorupan N, Ghabra S, Maldonado JA, Zhang Y, Alewine C. Two rare cancers of the exocrine pancreas: to treat or not to treat like ductal adenocarcinoma? *J Cancer Metastasis Treat* 2023;9:5.
120. Nakayama S, Fukuda A, Kou T, Muto M, Seno H. A case of unresectable ectopic acinar cell carcinoma developed in the portal vein in complete response to FOLFIRINOX therapy. *Clin J Gastroenterol* 2023;16:610–4.
121. Sakakida T, Ishikawa T, Doi T, et al. Genomic landscape and clinical features of rare subtypes of pancreatic cancer: analysis with the national database of Japan. *J Gastroenterol* 2023;58:575–85.
122. Hashimoto M, Hikichi T, Suzuki T, et al. Successful chemotherapy with modified FOLFIRINOX for pancreatic acinar cell carcinoma. *Clin J Gastroenterol* 2017;10:564–9.
123. Lee JL, Kim TW, Chang HM, et al. Locally advanced acinar cell carcinoma of the pancreas successfully treated by capecitabine and concurrent radiotherapy: report of two cases. *Pancreas* 2003;27:e18–22.
124. Chen CP, Chao Y, Li CP, et al. Concurrent chemoradiation is effective in the treatment of alpha-fetoprotein-producing acinar cell carcinoma of the pancreas: report of a case. *Pancreas* 2001;22:326–9.
125. Florou V, Elliott A, Bailey MH, et al. Comparative genomic analysis of pancreatic acinar cell carcinoma (PACC) and pancreatic ductal adenocarcinoma (PDAC) unveils new actionable genomic aberrations in PACC. *Clin Cancer Res* 2023;29:3408–17.
126. Hagio K, Kikuchi J, Takada K, et al. Assessment for the timing of comprehensive genomic profiling tests in patients with advanced solid cancers. *Cancer Sci* 2023;114:3385–95.
127. Yamai T, Ikezawa K, Sugimoto N, et al. Utility of comprehensive genomic profiling tests for patients with incurable pancreatic cancer in clinical practice. *Cancers* 2023;15:970.
128. Umemoto K, Yamamoto H, Oikawa R, et al. The molecular landscape of pancreatobiliary cancers for novel targeted therapies from real-world genomic profiling. *J Natl Cancer Inst* 2022;114:1279–86.
129. Terashima T, Morizane C, Ushiama M, et al. Germline variants in cancer-predisposing genes in pancreatic cancer patients with a family history of cancer. *Jpn J Clin Oncol* 2022;52:1105–14.
130. Kai Y, Ikezawa K, Takada R, et al. Success rate of microsatellite instability examination and complete response with pembrolizumab in biliary tract cancer. *JGH Open* 2021;5:712–6.
131. Pishvaian MJ, Blais EM, Brody JR, et al. Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial. *Lancet Oncol* 2020;21:508–18.
132. Jiao Y, Yonescu R, Offerhaus GJ, et al. Whole-exome sequencing of pancreatic neoplasms with acinar differentiation. *J Pathol* 2014;232:428–35.
133. Furukawa T, Sakamoto H, Takeuchi S, et al. Whole exome sequencing reveals recurrent mutations in BRCA2 and FAT genes in acinar cell carcinomas of the pancreas. *Sci Rep* 2015;5:8829.
134. Al-Hader A, Al-Rohil RN, Han H, Von Hoff D. Pancreatic acinar cell carcinoma: a review on molecular profiling of patient tumors. *World J Gastroenterol* 2017;23:7945–51.
135. Mandelker D, Marra A, Zheng-Lin B, et al. Genomic profiling reveals germline predisposition and homologous recombination deficiency in pancreatic acinar cell carcinoma. *J Clin Oncol* 2023;33:5151–62.
136. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer. *N Engl J Med* 2019;381:317–27.
137. Kindler HL, Hammel P, Reni M, et al. Overall survival results from the POLO trial: a phase III study of active maintenance olaparib versus placebo for germline *BRCA*-mutated metastatic pancreatic cancer. *J Clin Oncol* 2022;40:3929–39.
138. Stossel C, Raitses-Gurevich M, Atias D, et al. Spectrum of response to platinum and PARP inhibitors in germline *BRCA*-associated pancreatic cancer in the clinical and preclinical setting. *Cancer Discov* 2023;13:1826–43.
139. Golan T, Barenboim A, Lahat G, et al. Increased rate of complete pathologic response after neoadjuvant FOLFIRINOX for *BRCA* mutation

carriers with borderline resectable pancreatic cancer. *Ann Surg Oncol* 2020;27:3963–70.
140. Golan T, Kanji ZS, Epelbaum R, et al. Overall survival and clinical characteristics of pancreatic cancer in *BRCA* mutation carriers. *Br J Cancer* 2014;111:1132–8.
141. O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline *BRCA*/*PALB2* mutation. *J Clin Oncol* 2020;38:1378–88.
142. Reiss KA, Mick R, O'Hara MH, et al. Phase II study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic variant in *BRCA1*, *BRCA2*, or *PALB2*. *J Clin Oncol* 2021;39:2497–505.
143. Shimmura H, Kuramochi H, Jibiki N, Katagiri S, Nishino T, Araida T. Dramatic response of FOLFIRINOX regimen in a collision pancreatic adenocarcinoma patient with a germline BRCA2 mutation: a case report. *Jpn J Clin Oncol* 2019;49:1049–54.
144. Li M, Mou Y, Hou S, Cao D, Li A. Response of germline *BRCA2*-mutated advanced pancreatic acinar cell carcinoma to olaparib: a case report. *Medicine* 2018;97:e13113.
145. Golan T, O'Kane GM, Denroche RE, et al. Genomic features and classification of homologous recombination deficient pancreatic ductal adenocarcinoma. *Gastroenterology* 2021;160:2119–32.
146. Park W, Chen J, Chou JF, et al. Genomic methods identify homologous recombination deficiency in pancreas adenocarcinoma and optimize treatment selection. *Clin Cancer Res* 2020;26:3239–47.
147. Casolino R, Paiella S, Azzolina D, et al. Homologous recombination deficiency in pancreatic cancer: a systematic review and prevalence meta-analysis. *J Clin Oncol* 2021;39:2617–31.
148. Zhen DB, Safyan RA, Konick EQ, Nguyen R, Prichard CC, Chiorean EG. The role of molecular testing in pancreatic cancer. *Therap Adv Gastroenterol* 2023;16:17562848231171456.
149. Taieb J, Sayah L, Heinrich K, et al. Efficacy of immune checkpoint inhibitors in microsatellite unstable/mismatch repair-deficient advanced pancreatic adenocarcinoma: an AGEO European cohort. *Eur J Cancer* 2023;188:90–7.
150. Quintanilha JCF, Storandt MH, Graf RP, et al. Tumor mutational burden in real-world patients with pancreatic cancer: genomic alterations and predictive value for immune checkpoint inhibitor effectiveness. *JCO Precis Oncol* 2023;7:e2300092.
151. Xu H, Wang X, Zhou S, Hu Q, Cao D. Efficacy of chemotherapy combined with toripalimab in PD-L1-positive and high tumor mutation burden pancreatic acinar cell carcinoma: case report. *Tumori* 2021;107:NP24–7.
152. Busch E, Kreutzfeldt S, Agaimy A, et al. Successful BRAF/MEK inhibition in a patient with $BRAF^{V600E}$-mutated extrapancreatic acinar cell carcinoma. *Cold Spring Harb Mol Case Stud* 2020;6:a005553.
153. Cramer S, Marcus MA, Ramkissoon S, Szabo S, Pressey JG. Pediatric *BRAF* (V600E)-mutated pancreatic acinar cell carcinoma with complete and durable response to dabrafenib and trametinib. *JCO Precis Oncol* 2020;4:801–5.
154. Gaule M, Pesoni C, Quinzii A, et al. Exceptional clinical response to alectinib in pancreatic acinar cell carcinoma with a novel *ALK-KANK4* gene fusion. *JCO Precis Oncol* 2022;6:e2100400.
155. Gupta M, Sherrow C, Krone ME, et al. Targeting the *NTRK* fusion gene in pancreatic acinar cell carcinoma: a case report and review of the literature. *J Natl Compr Canc Netw* 2021;19:10–5.