

# World Journal of *Gastroenterology*

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### MINIREVIEWS

- 7945** Pancreatic acinar cell carcinoma: A review on molecular profiling of patient tumors  
*Al-Hader A, Al-Rohil RN, Han H, Von Hoff D*
- 7952** Probiotics for gastrointestinal disorders: Proposed recommendations for children of the Asia-Pacific region  
*Cameron D, Hock QS, Kadim M, Mohan N, Ryoo E, Sandhu B, Yamashiro Y, Jie C, Hoekstra H, Guarino A*

### ORIGINAL ARTICLE

#### Basic Study

- 7965** Down-regulation of miR-30a-3p/5p promotes esophageal squamous cell carcinoma cell proliferation by activating the Wnt signaling pathway  
*Qi B, Wang Y, Chen ZJ, Li XN, Qi Y, Yang Y, Cui GH, Guo HZ, Li WH, Zhao S*
- 7978** Mesenchymal stem cells rescue acute hepatic failure by polarizing M2 macrophages  
*Li YW, Zhang C, Sheng QJ, Bai H, Ding Y, Dou XG*
- 7989** Improved experimental model of hepatic cystic hydatid disease resembling natural infection route with stable growing dynamics and immune reaction  
*Zhang RQ, Chen XH, Wen H*

#### Case Control Study

- 8000** Recurrence in node-negative advanced gastric cancer: Novel findings from an in-depth pathological analysis of prognostic factors from a multicentric series  
*Baiocchi GL, Molino S, Baronchelli C, Giacomuzzi S, Marrelli D, Morgagni P, Bencivenga M, Saragoni L, Vindigni C, Portolani N, Botticini M, De Manzoni G*

#### Retrospective Cohort Study

- 8008** Albumin as a prognostic marker for ulcerative colitis  
*Khan N, Patel D, Shah Y, Trivedi C, Yang YX*
- 8017** Pretransplantation fetal-maternal microchimerism in pediatric liver transplantation from mother  
*Yi NJ, Park MS, Song EY, Ahn HY, Byun J, Kim H, Hong SK, Yoon K, Kim HS, Ahn SW, Lee HW, Choi Y, Lee KW, Suh KS, Park MH*

#### Retrospective Study

- 8027** Impact of homogeneous pathologic response to preoperative chemotherapy in patients with multiple colorectal liver metastases  
*Sabbagh C, Chatelain D, Attencourt C, Joly JP, Chauffert B, Cosse C, Regimbeau JM*

- 8035** Two-step method for creating a gastric tube during laparoscopic-thoracoscopic Ivor-Lewis esophagectomy  
*Liu Y, Li JJ, Zu P, Liu HX, Yu ZW, Ren Y*

**Observational Study**

- 8044** Clinical value of liver and spleen shear wave velocity in predicting the prognosis of patients with portal hypertension  
*Zhang Y, Mao DF, Zhang MW, Fan XX*

**Prospective Study**

- 8053** Gender differences in ghrelin, nociception genes, psychological factors and quality of life in functional dyspepsia  
*Choi YJ, Park YS, Kim N, Kim YS, Lee SM, Lee DH, Jung HC*

**Randomized Clinical Trial**

- 8062** Efficacy of combination therapy with natriuretic and aquaretic drugs in cirrhotic ascites patients: A randomized study  
*Uojima H, Hidaka H, Nakayama T, Sung JH, Ichita C, Tokoro S, Masuda S, Sasaki A, Koizumi K, Egashira H, Kako M*

**SYSTEMATIC REVIEW**

- 8073** Double-balloon enteroscopy-assisted dilatation avoids surgery for small bowel strictures: A systematic review  
*Baars JE, Theyventhiran R, Aepli P, Saxena P, Kaffes AJ*

**META-ANALYSIS**

- 8082** Impact of inflammatory bowel disease activity and thiopurine therapy on birth weight: A meta-analysis  
*Gonzalez-Suarez B, Sengupta S, Moss AC*

**CASE REPORT**

- 8090** Midgut neuroendocrine tumor presenting with acute intestinal ischemia  
*Mantzoros I, Savvala NA, Ioannidis O, Parpoudi S, Loutzidou L, Kyriakidou D, Cheva A, Intzos V, Tsalis K*
- 8097** Endoscopic submucosal dissection in a patient with esophageal adenoid cystic carcinoma  
*Yoshikawa K, Kinoshita A, Hirose Y, Shibata K, Akasu T, Hagiwara N, Yokota T, Imai N, Iwaku A, Kobayashi G, Kobayashi H, Fushiya N, Kijima H, Koike K, Kanayama H, Ikeda K, Saruta M*
- 8104** Simultaneous liver, pancreas-duodenum and kidney transplantation in a patient with hepatitis B cirrhosis, uremia and insulin dependent diabetes mellitus  
*Li J, Guo QJ, Cai JZ, Pan C, Shen ZY, Jiang WT*

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## Pancreatic acinar cell carcinoma: A review on molecular profiling of patient tumors

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### Abstract

Pancreatic carcinomas with acinar differentiation are rare, accounting for 1%-2% of adult pancreatic tumors; they include pancreatic acinar cell carcinoma (PACC), pancreatoblastoma, and carcinomas of mixed differentiation. Patients with PACC have a prognosis better than pancreatic ductal adenocarcinomas but worse than pancreatic neuroendocrine tumors. Reports of overall survival range from 18 to 47 mo. A literature review on PACCs included comprehensive genomic profiling and whole exome sequencing on a series of more than 70 patients as well as other diagnostic studies including immunohistochemistry. Surgical resection of PACC is the preferred treatment for localized and resectable tumors. The efficacy of adjuvant treatment is unclear. Metastatic PACCs are generally not curable and treated with systemic chemotherapy. They are moderately responsive to chemotherapy with different regimens showing various degrees of response in case reports/series. Most of these regimens were developed to treat patients with pancreatic ductal adenocarcinomas or colorectal adenocarcinomas. Review of PACC's molecular profiling showed a number of gene alterations such as: *SMAD4*, *BRAF*, *BRCA2*, *TP53*, *RB1*, *MEN1*, *JAK-1*, *BRCA-1*, *BRCA-2*, and DNA mismatch repair abnormalities. PACCs had multiple somatic mutations with some targetable with available drugs. Therefore, molecular profiling of PACC should be an option for patients with refractory PACC.

**Key words:** Pancreatic acinar cell carcinoma; Molecular profiling; Targeted therapy

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**Core tip:** This is a review article on pancreatic acinar cell carcinoma, which is a rare type of pancreatic cancer, with a series of molecularly profiled cases and an insight on how to potentially target specific mutations and genetic abnormalities with different systemic treatments including tyrosine kinase inhibitors, immunotherapy and cytotoxic chemotherapy agents.

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## INTRODUCTION

Pancreatic carcinomas with acinar differentiation are a very rare pancreatic neoplasm, comprising about 1%-2% of all pancreatic tumors in adults<sup>[1-3]</sup>. These tumors also occur in children, accounting for 6% of all childhood tumors and more importantly, 15%, of all pediatric pancreatic tumors<sup>[1,2,4-6]</sup>. These pancreatic neoplasms include pancreatic acinar cell carcinoma (PACC), pancreatoblastoma, and carcinomas of mixed differentiation. They typically occur in late adulthood, with a mean age of 62 at diagnosis. They are more common in males with a male to female incidence ratio of 2:1<sup>[1,7]</sup>. Prognosis of patients with PACC is worse than that of pancreatic neuroendocrine tumors but better than that for patients with pancreatic ductal carcinomas, which has the worst prognosis of the three tumors<sup>[8-11]</sup>. Overall survival for PACC ranges from 18-47 mo<sup>[8,9,11,12]</sup>. Although acinar cells are the most common cell types found in the pancreas, malignant transformation of these cells is very rare, as they involve only 1% of exocrine tumors of the pancreas<sup>[13]</sup>. In contrast, pancreatic ductal adenocarcinomas (PDACs), which arise from the epithelial lining of the pancreatic ducts, comprise the majority of pancreatic malignancies<sup>[1,9]</sup>.

Morphologically, PACCs have different histological patterns, as they can appear to be normal pancreatic acini or they can be solid tumors with sheets of neoplastic cells that are poorly differentiated (Figure 1). This wide variation in histology can make it difficult to distinguish PACCs from other types of pancreatic tumors. One method to distinguish PACCs from other pancreatic tumors is the use of immunohistochemistry to show the proteins that the tumor produces. In the case of PACC, they tend to make acinar-specific enzymes including proteases, lipases, and amylases.

## LITERATURE RESEARCH

The main search tool for identifying articles from MEDLINE was the PubMed system. The keywords

used were "pancreatic cancer," "acinar cell carcinoma," "molecular biology," and "sequencing." Relevant articles that were quoted in publications from the original search were also used. Google Scholar was another search strategy and the search phrase was "pancreatic acinar cell carcinoma".

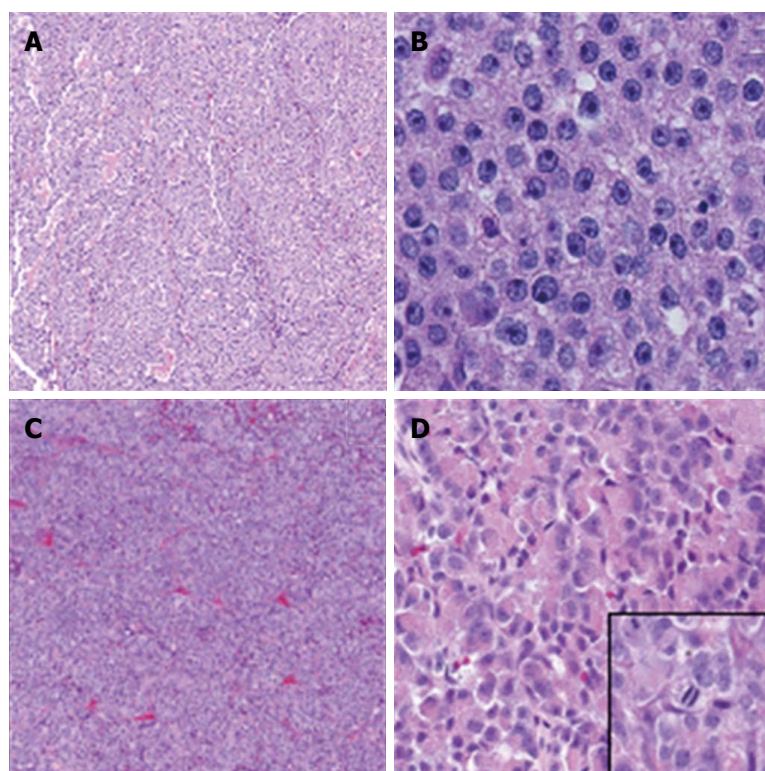
## CLINICAL PRESENTATION

Patients who present with PACCs usually have non-specific symptoms. Their complaints consist of abdominal pain or discomfort, nausea, vomiting, weight loss, and diarrhea. Jaundice is less frequently seen at presentation. In about 50% of patients serum lipase is elevated, and up to 10% of these patients with lipase hypersecretion develop subcutaneous nodules erythematous and edematous subcutaneous nodules that occur in conjunction with eosinophilia, and polyarthralgia<sup>[6,12,14]</sup>. This condition, known as Schmid's triad, is associated with a poor prognosis<sup>[15,16]</sup>.

## DIAGNOSIS

Diagnosing PACCs, like other pancreatic tumors, includes use of various imaging modalities including CT and/or MRI scans. PACCs are well-circumscribed tumors and can be large in diameter, although findings vary<sup>[7,17]</sup>. Imaging is followed by fine-needle aspiration guided by endoscopic ultrasound (EUS) or other techniques dependent upon tumor location to obtain a tissue diagnosis. Resectability is the most important prognostic factor for this disease, and the staging system used in PACCs is the same as the TNM staging used for PDACs.

As mentioned above, PACCs have distinctive features, but there are some variations in appearance that make it difficult to distinguish PACCs from other pancreatic tumors. PACCs are usually highly cellular without a prominent stroma normally observed in PDACs<sup>[6]</sup>. The individual cells are uniform in size and shape with large nucleoli located in the center of the nucleus<sup>[6]</sup>. Other variants of PACC include acinar cell cystadenoma, which are grossly cystic neoplasms lined with simple cuboidal or columnar acinar cells. When a PACC has 25% to 30% of neoplastic endocrine cells, it is called a mixed acinar-endocrine carcinoma. In mixed acinar-endocrine carcinoma, there is evidence of ductal and endocrine differentiation, but only immunohistochemical staining with markers for acinar cells (trypsin, chymotrypsin, lipase, etc.) and endocrine cells (synaptophysin or chromogranin A) can identify the different lines of differentiation. Even though this is a very rare entity, two forms of mixed acinar-endocrine carcinoma have been observed. In one form this cancer has expression of acinar and endocrine markers in histologically distinct cell types, while in the other form both markers are co-expressed in the same cells that show both acinar and endocrine histologies<sup>[18,19]</sup>. However, the majority of mixed acinar-endocrine



**Figure 1** Different histological forms of pancreatic acinar cell carcinomas. A: A case of PACC displaying nested to glandular growth patterns (HE 40 ×); B: Higher magnification of the same tumor in Panel A showing monotonous cells with eosinophilic/granular cytoplasm with well-defined cell borders and uniform nuclei with minimal atypia and prominent nucleoli (HE 200 ×); C: Tumor from a different patient showing a predominantly sheet-like growth with no distinct pattern (HE 40 ×). D: Higher magnification of the same tumor in C showing uniform cells with eosinophilic granular cytoplasm (prominent zymogen granules) with minimal pleomorphism (HE 200 ×). Inset: mitotic figures were identified throughout the tumor (HE 400 ×).

carcinomas have a predominance of acinar cells<sup>[20]</sup>.

## MOLECULAR BIOLOGY

Understanding the role of signal transduction pathways responsible for cell growth and survival is important for development of cancer therapies. Secretion of pancreatic enzymes is a central role for acinar cells and this is evidenced by the fact they have the highest levels of protein synthesis of any adult cell<sup>[21]</sup>. Secretions from the acinar cells are correlated with the stage of digestion, hence pancreas secretion is regulated by hormones secreted by the digestive tract, principally cholecystokinin (CCK) and acetylcholine *via* the vagal nerve, as well as secretin. Increases in intracellular calcium levels play a key role in the control of digestive enzyme secretion, but extracellular stores are required too<sup>[22]</sup>. Protein synthesis, primarily digestive enzymes, are regulated by a number of pathways in the acinar cell including the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/A kinase binding (AKT)/mammalian target of rapamycin (mTOR) pathway<sup>[23]</sup>. In terms of PACC, up to 25% of the PACCs were reported to have inactivating mutations in genes of the adenomatous polyposis coli (*APC*)- $\beta$ -catenin pathway<sup>[5]</sup>. Additionally, these authors reported finding activating mutations in the *CTNNB1* gene in PACC samples.

Table 1 summarizes the molecular abnormalities noted in PACC. Recently, one study reported finding DNA mismatch repair (MMR) abnormalities present in some acinar cell carcinomas. They examined the expression of DNA MMR genes by immunohistochemistry (IHC) in 36 PACC cases and detected the loss of MMR proteins in 5 of the 36 cases (14%) examined. At least two of these five patients with a loss of MMR protein expression had a known history of Lynch syndrome<sup>[24]</sup>. In another case series, microsatellite instability (MSI) was present in 2 out of 42 specimens (5%) examined<sup>[25]</sup>.

Comprehensive genomic profiling has been performed on a number of tumor samples taken directly from patients with PACCs, including those with a mixed acinar carcinoma phenotype and pancreatoblastomas. Genomic profiling using next-generation sequencing (NGS) - based platforms including whole exome sequencing was performed on these tumor samples. Unlike PDACs, where > 90% of cases contain various types of *KRAS* gene mutations, mutation in *KRAS* was observed only in one (a mixed acinar/neuroendocrine tumor) out of the total 78 PACC cases sequenced in the three studies<sup>[12,26,27]</sup>. In addition, genomic alterations in *SMAD4*, *CDKN2A*, and *TP53* genes were observed in PACCs but less frequently than in PDACs. Other mutations noted in PACCs were in the *BRCA1*, *BRCA2*, *RB1* genes, along with mutations in the WNT- $\beta$ -catenin

**Table 1** Somatic genetic alterations observed in pancreatic acinar cell carcinoma specimens *n* (%)

Gene	Ref.	Number of patients	Number of patients with mutation (frequency )
<i>TP53</i>	Jiao <i>et al</i> <sup>[12]</sup>	23	3 (13)
<i>BRAF/RAF1</i> <sup>1</sup>	Chmielecki <i>et al</i> <sup>[26]</sup>	44	10 (23)
	Jiao <i>et al</i> <sup>[12]</sup>	23	3 (13)
	Chmielecki <i>et al</i> <sup>[26]</sup>	44	11 (25)
	Bergmann <i>et al</i> <sup>[25]</sup>	42	0 (0)
<i>SMAD4</i>	Jiao <i>et al</i> <sup>[12]</sup>	23	6 (26)
	Chmielecki <i>et al</i> <sup>[26]</sup>	44	6 (26)
<i>BRCA2</i>	Jiao <i>et al</i> <sup>[12]</sup>	23	1 (4)
	Chmielecki <i>et al</i> <sup>[26]</sup>	44	9 (20)
	Furukawa <i>et al</i> <sup>[27]</sup>	7	3 (43)
<i>CDK2NA</i>	Jiao <i>et al</i> <sup>[12]</sup>	23	4 (17)
	Chmielecki <i>et al</i> <sup>[26]</sup>	44	6 (14)
<i>MMR/MSI</i>	Liu <i>et al</i> <sup>[24]</sup>	36	5 (14)
	Bergmann <i>et al</i> <sup>[25]</sup>	42	2 (5)
<i>RB1</i>	Jiao <i>et al</i> <sup>[12]</sup>	23	3 (13)
	Chmielecki <i>et al</i> <sup>[26]</sup>	44	5 (11)
<i>APC and CTNNB1</i>	Jiao <i>et al</i> <sup>[12]</sup>	23	2 (9)
	Abraham <i>et al</i> <sup>[5]</sup>	17	4 (24)
	Chmielecki <i>et al</i> <sup>[26]</sup>	44	4 (9)
<i>BRCA1</i>	Jiao <i>et al</i> <sup>[12]</sup>	23	0 (0%)
	Chmielecki <i>et al</i> <sup>[26]</sup>	44	4 (9)
<i>JAK1</i>	Jiao <i>et al</i> <sup>[12]</sup>	23	4 (17)
<i>MEN1</i>	Jiao <i>et al</i> <sup>[12]</sup>	23	1 (4)
	Chmielecki <i>et al</i> <sup>[26]</sup>	44	3 (7)
<i>GNAS</i>	Jiao <i>et al</i> <sup>[12]</sup>	23	2 (9)
	Chmielecki <i>et al</i> <sup>[26]</sup>	44	2 (5%)
<i>FAT</i>	Furukawa <i>et al</i> <sup>[27]</sup>	7	4 (57)
<i>Allelic Loss on Chromosome 11p</i>	Abraham <i>et al</i> <sup>[5]</sup>	12	6 (50)

<sup>1</sup>Including *BRAF* gene fusion and point mutations.

pathway (*APC* and *CTNN1* genes). Interestingly, only one patient was found to have mutations in both the *BRCA2* and *CTNNB1* genes<sup>[26]</sup>. Additionally, changes were found in the *BRAF/RAF1*, *ATM* and *GNAS* genes<sup>[5,12,26,27]</sup>. Refer to Table 1 for more details.

## TREATMENT

The treatment of choice for PACC is surgical resection if the tumor is localized and resectable. Surgical resection significantly improved survival; the 5-year survival was 72% in patients with resected PACC compared to 16% in their counterparts with PDAC<sup>[8]</sup>. The efficacy of adjuvant chemotherapy and/or radiotherapy is not clear for patients with PACC; 50% of cases present with metastatic disease, most commonly to regional lymph nodes and the liver. In addition, 25% of patients develop metastatic disease after resection of the primary tumor<sup>[11]</sup>.

PACCs are moderately responsive to chemotherapy. Due to the few cases that present each year, there are no prospective data to guide treatment decisions and most therapeutic regimens used are the same as those utilized for PDACs or colorectal carcinomas. Responses have been seen in PACC patients treated with gemcitabine- or 5-fluorouracil-based combination therapies with irinotecan, a platinum analog, docetaxel, or erlotinib<sup>[1,6,28-30]</sup>. About 50%-60% of patients with metastatic PACC achieve stable disease or a better

response with first-line combination chemotherapy regimens<sup>[6]</sup>. Table 2 describes systemic regimens that have shown activity in patients with PACCs.

For patients with limited metastatic disease, resection of the sites of metastasis may result in greater long-term survival than patients without resection. One case series included six patients with metastatic PACC who underwent resection of metastatic disease (liver metastases or omental metastases); they had a two-year overall survival rate of 67% (OS: 6-47+ mo). Four of these patients received adjuvant gemcitabine treatment in addition to resection of metastases<sup>[31]</sup>.

## CONCLUSION

Various genetic alterations were detected in PACCs; some of these mutations are potentially targetable by Food and Drug Administration (FDA)-approved medications or agents being studied for use in treating other malignancies. For example, *BRAF* inhibitors like vemurafenib are approved for treatment of melanoma with the *BRAF* V600E mutation<sup>[32]</sup>, but these inhibitors have clinical activity against melanomas with the less common *BRAF* V600R mutation as well<sup>[33]</sup>. Tumors with DNA repair abnormalities, including *BRCA* gene mutations, show increased sensitivity to platinum agents. Poly ADP ribose polymerase inhibitors are efficacious in some *BRCA* mutated tumors as well<sup>[34,35]</sup>. One PACC patient with a loss of function mutation



**Table 2** Chemotherapeutic regimens that showed activity in patients with pancreatic acinar cell carcinomas (9, 16, 18, 19, 22)

Regimen	Ref.	Total number of patients	Best responses
Gemcitabine	Lowery <i>et al</i> <sup>[6]</sup>	3	SD at 1 yr
Gemcitabine + erlotinib	Lowery <i>et al</i> <sup>[6]</sup>	4	PR at 5 mo, SD at 10 mo
Gemcitabine + irinotecan	Lowery <i>et al</i> <sup>[6]</sup>	2	SD at 25 mo
Cisplatin + irinotecan	Lowery <i>et al</i> <sup>[6]</sup>	1	PR at 12 mo, POD at 25 mo
Gemcitabine + cisplatin	Lowery <i>et al</i> <sup>[6]</sup>	2	PR at 4 mo
FOLFIRI	Lowery <i>et al</i> <sup>[6]</sup>	4	PR at 1.5 mo, POD at 11 mo
Gemcitabine + capecitabine	Lowery <i>et al</i> <sup>[6]</sup>	1	SD then POD at 9 mo
Gemcitabine + docetaxel + capecitabine	Lowery <i>et al</i> <sup>[6]</sup>	2	SD at 11 mo
Gemcitabine + oxaliplatin	Lowery <i>et al</i> <sup>[6]</sup>	5	PR at 6 mo, POD at 15 mo
Capecitabine + erlotinib	Lowery <i>et al</i> <sup>[6]</sup>	1	SD at 15 mo, stopped because of toxicity
Folfinirinox	Schempf <i>et al</i> <sup>[30]</sup>	1	PR with regression of primary disease and liver mets
Cisplatin + S1 <sup>1</sup>	Furukawa <i>et al</i> <sup>[27]</sup>	1	CR with resolution of Liver mets. NED after 5 yr
Panitumumab <sup>2</sup>	Morales <i>et al</i> <sup>[40]</sup>	2	Clinically stable at 4 mo
Liposomal doxorubicin <sup>3</sup>	Armstrong <i>et al</i> <sup>[29]</sup>	1	PR for ≥ 1 yr. Treatment discontinued due to cardiac toxicity risk
Docetaxel + irinotecan + cetuximab	Cananzi <i>et al</i> <sup>[41]</sup>	1	PR for 7 mo

<sup>1</sup>BRCA-2 mutated; <sup>2</sup>KRAS wild-type gene; <sup>3</sup>The patient was treated with liposomal doxorubicin. DNA microarray and IHC analyses of a biopsy of liver metastases showed elevated topoisomerase II expression and growth inhibition by doxorubicin (a topoisomerase II inhibitor) *in vitro* in a cell line derived from the patient's tumor. FOLFIRI: 5-FU/Leucovorin/Irinotecan; FOLFIRINOX: 5-FU/Leucovorin/Oxaliplatin/Irinotecan; PR: Partial Response; POD: Progression of disease; SD: Stable disease; CR: Complete Response; NED: No evidence of disease.

in the *BRCA2* gene developed liver metastasis after receiving gemcitabine and S-1 as first line treatment; subsequently, the patient achieved a complete remission using cisplatin and S-1 therapy and the patient is alive with no evidence of disease after 5 years<sup>[27]</sup>. This was the only patient out of 11 in this study cohort treated with cisplatin. The results of this therapeutic intervention suggest that PACCs with *BRCA2* mutations might respond well to cisplatin-containing chemotherapy regimens.

As mentioned earlier, 14% of PACCs tested were revealed to have a MMR deficiency status<sup>[24]</sup>. Mismatch repair status in different malignancies (including colorectal, endometrial, gastric, pancreas, and small bowel carcinomas) predicted clinical benefit for use of immune checkpoint blockade by treatment with the PD-1 receptor blocker, pembrolizumab. Patients with MMR-deficient tumors showed a significantly higher objective response rate and progression-free survival compared to MMR proficient patients<sup>[36]</sup>. These findings suggest PD-1 and PD-L1 inhibitors might have antitumor activity in patients with MMR-deficient PACCs. Pembrolizumab has been recently approved by the FDA for the treatment unresectable or metastatic mismatch repair deficient solid tumors that have progressed on prior treatment and those who have no satisfactory alternative treatment options.

Comprehensive genomic analysis revealed that 23% of PACCs had fusions in *BRAF* and *RAF1* genes. One in particular, the staphylococcal nuclease and tudor domain containing 1 (*SND1*) -*BRAF* fusion which results from an amplified, chromosomal rearrangement between chromosome 7q32 and 7q34. This rearrangement results in an overexpression of the *SND1* -*BRAF* fusion protein which is constitutively active, and confers resistance to c-Met receptor tyrosine kinase inhibition<sup>[37]</sup>. Several drugs were studied *in vitro* for use against the

*SND1*-*BRAF* fusion mutation, including trametenib (a MEK inhibitor), sorafenib (a multikinase inhibitor), and TAK-632 (a pan-Raf inhibitor). Trametenib was shown to be superior to the other agents<sup>[26]</sup>. JAK-1 somatic mutations were seen in some cases of PACC, so JAK inhibitors such as ruxolitinib (a JAK-1 and 2 inhibitors), which is FDA approved for myelofibrosis<sup>[38]</sup>, would be an option to consider for PACCs containing mutations in *JAK1/JAK2*. Additionally, there are investigational drugs that target the Wnt pathway and could be potentially studied in patients with PACC tumors with *APC* or *CTNNB1* gene mutations<sup>[39]</sup>.

Unlike PDACs, the vast majority of PACCs are *KRAS* wild-type<sup>[12,26]</sup>. Two patients with PACC with liver metastases (they received two and three lines of prior chemotherapy, respectively) were treated with single agent panitumumab (an EGFR inhibitor). The *KRAS* gene was wild type in both patients. One patient was clinically stable for 4 mo with panitumumab therapy, while the other patient deteriorated clinically after 3 doses of the drug and then succumbed to the disease<sup>[40]</sup>. Panitumumab could be considered for refractory PACC patients with *KRAS* wild type tumors for which no other actionable targets are identified.

In summary, with this review of the literature, some potentially interesting targets were identified for treatment of patients with PACCs. Whether targeting tumors with mutations in the *BRAF* or *BRCA2* genes or a lack of MMR expression will be helpful to patients remains an issue to be settled in future clinical trials.

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