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Optimizing Chemotherapy of Pancreatic Acinar Cell Carcinoma: Our Experiences and Pooled Analysis of Literatures

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Abstract

Background: Pancreatic acinar cell carcinoma (PACC) is rare and its appropriate treatment remains unknown dued to limited and selection-biased data

Methods: The data on clinicopathologic characteristics, molecular alteration, treatment and survival of patients diagnosed as PACC in Sun Yat-sen university cancer center from 2005 to 2020 were collected. We explored the optimal treatment by co-analyzing our results and published literatures.

Results: 22 PACC patients were enrolled. 8/17 non-metastatic patients received adjuvant chemotherapy. The patients receiving fluoropyrimidine-based regimen (n=3) had better mDFS than those with gemcitabine-based regimen (n=5) (unreached *vs.* 27 months). 8 metastatic patients received 1st-line chemotherapy. 4/5 patients with FOLFIRINOX regimen achieved partial response (PR) and 3 patients with AG (albumin paclitaxel+gemcitabine) regimen got progressive disease (PD). 4 patients received 2nd-line chemotherapy. 2 patients with FOLFIRINOX regimen achieved PR while 2 patients with AG regimen got PD. One patient who had responded to 1st-line FOLFIRINOX regimen received Olaparib as maintenance treatment for 5 months with good tolerance. 31 published literatures and a total of 86 cases were included in the co-analysis. Objective response rate of 1st-line fluoropyrimidine-based regimen (n=47) was higher than that of gemcitabine-based regimen (n=39) (59.6% *vs.*15.3%, P<0.001). 8/11 patients treated with FOLFIRINOX regimen achieved PR.

Conclusions: The benefit of adjuvant chemotherapy remained unclear; however, fluoropyrimidine-based chemotherapy deserves attention. For metastatic patients, fluorouracil-based regimen such as FOLFIRINOX is preferred, and maintenance treatment of PARP inhibitors after effective platinum-containing treatment for BRAC mutation patients is worthy of exploration.

Introduction

Although acinar cells represent over 80% of the pancreas, pancreatic acinar cell carcinoma (PACC) is rare, accounting for approximately 1% of primary pancreatic neoplasms[1]. Recent studies demonstrated that PACC was quite different from pancreatic ductal cell carcinoma (PDCC) in clinical, pathologic and molecular features and had a significantly better survival[2–4]. Therapeutic strategy of PACC should be distinguished[1, 5, 6].

Radical surgery is recommended for non-metastatic PACC with 5-year survival rate of 36.6%-43.9%[7, 8]. PACC was considered to be aggressive with high recurrence rate and frequent metastasis after operation[1, 9, 10]. Systemic chemotherapy may play an important role in improving prognosis. However, there has been to date no prospective studies or meta-analysis. The retrospective studies of small case series or case reports resulted in the lack of high-quality evidence. Limited and selection-biased data make treatment decisions difficult. We collected the data of 22 PACC patients in Sun Yat-sen University cancer center on clinicopathologic characteristic, molecular alteration, treatment and survival. The role of chemotherapy and targeted therapy was explored. We further compared fluoropyrimidine-based regimen with gemcitabine-based regimen by co-analyzing our results and published literatures. We aim to better understand the rare disease and optimize its treatment.

Materials And Methods

We acquired the informed consent in written format. Our study was approved by the institutional ethics committees of Sun Yat-sen University Cancer Center and in accordance with the Declaration of Helsinki. After searching the medical database in our center from Jan 2005 to Apr 2020, we included patients diagnosed as PACC with treatment and follow-up records. All the tumor specimens were reviewed by at least two pathologists. Immunohistochemical staining was used to confirm acinar differentiation and distinguish between acinar cell carcinomas and ductal adenocarcinomas. Data on clinicopathologic characteristics, molecular alteration, treatment and survival were collected. We also searched the literatures or case reports or meeting abstracts describing therapeutic approaches for PACC in Pubmed, Embase and Cochrane library until Aug 25th 2020 and included the literatures which involved systemic therapy containing gemcitabine or fluorouracil. The process of literature selection was performed by Jian-Ying Xu and Wen-Long Guan, independently. The analysis based on our data and published data was conducted to improve the understanding of this rare disease and seek effective treatment.

Computed tomographic scans or magnetic resonance imaging were used for tumor assessment. Revised RECIST guideline (version 1.1) was adopted for tumor response evaluation.

Tumor specimens and matched blood samples were used for next generation sequences (NGS). High depth sequencing and four types of tumor variation (including point mutation, insertion loss of small fragments, copy number variation, and currently known fusion genes) were detected through 1021 gene panel platform (including somatic mutation, germline mutation and tumor mutation burden) .

All quantitative data were analyzed with R version 3.6.2. Survival was estimated by Kaplan-Meier methods. Log-rank tests were performed for differences of survival. Objective response rate (ORR) was calculated by chi-square test. A two tailed P value < 0.05 was considered statistically

significant.

Results

Clinicopathological characteristics

A total of 27 PACC patients were identified from 4508 patients diagnosed as pancreatic neoplasms in Sun Yat-sen University cancer center. We excluded 5 patients without treatment and enrolled 22 patients in our study. There were 17 non-metastatic patients and 5 metastatic patients at initial diagnosis. Table 1 shows the patients' baseline characteristics. Most patients had bulky primary disease with median size of 9.2cm (range from 3 cm to 17 cm). Primary lesions were evenly distributed throughout the pancreas (9 cases in the head, 13 cases in the body or tail). Main metastatic sites were liver (n = 10), distant lymph node (n = 6) and peritoneum (n = 5). Evaluated CA199 level (43.46-123.32 U/ml) was found in 7 patients. Elevated alpha fetoprotein (AFP) level (50.43-23778.56 ng/ml) was detected in 3 patients who developed liver metastasis. Three patients with elevated serum lipase level suffered from subcutaneous fat necrosis and developed distant metastasis. Four patients had family history of cancer including rectal cancer, breast cancer, nasopharyngeal carcinoma or pancreatic cancer.

Table 1
Patient demographics and clinicopathological characteristics (n = 22)

Characteristics	No. of Patients
Sex	
Male	15 (68.2%)
Female	7 (31.8%)
Age, years	
Median, (range)	51 (7–79)
ECOG performance status	
0	4 (18.2%)
1	18 (81.8%)
Size of primary disease, cm	
Median, (range)	9.2 (3.0–17.0)
Location of primary lesions	
Head	9 (40.9%)
Body/Tail	13 (59.1%)
Histology	
PACC	19 (86.4%)
Mixed PACC	3 (13.6%)
Common symptom	
Abdominal pain	11 (50.0%)
Weight loss	5 (28.6%)
Abdominal mass	5 (28.6%)
Subcutaneous fat necrosis	3 (13.6%)
Metastases at initial diagnosis	
Yes	5 (22.7%)
No	17 (77.3%)
Main metastatic site	
Liver	10 (45.5%)
Distant lymph node	6 (27.3%)
Peritoneum	5 (22.7%)
Serum CA-199	
Elevated	7 (31.8%)
Normal	15 (68.2%)
Serum AFP	
Elevated	3 (13.6%)
Normal	14 (63.6%)
Not available	5 (22.7%)
Tumor family history	4 (18.2%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PACC, acinar cell carcinoma; CA-199, Carbohydrate antigen 199; AFP, alpha fetoprotein.

Characteristics	No. of Patients
Non-metastases cases	n = 17
Radical surgery	17 (100%)
Adjuvant chemotherapy	8 (47.1%)
Regional lymph node metastasis	3 (17.6%)
High Ki 67 index (≥ 30%)	4 (23.5%)
Lymph-vascular invasion	6 (35.3%)
Treatment for metastases cases	n = 14
1st palliative chemotherapy	8 (57.1%)
2nd palliative chemotherapy	4 (28.6%)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; PACC, acinar cell carcinoma; CA-199, Carbohydrate antigen 199; AFP, alpha fetoprotein.	

Gene alteration

Next generation sequences (NGS) on tumor sample was performed in 4 PACC patients. All of them showed microsatellite stability (MSS) and wild-type RAS /BRAF and low tumor mutational burden (TMB) (range from 6.72–8.16 mutations/mb). Two patients with BRCA2 germline mutation were identified, including one male patient with somatic mutation of IGF1R, FAT3, SMAD4, APC, SPENA and MLH1 whose mother and sister were diagnosed as breast cancer and one female patient with somatic mutation of TP53, CRTC1, SMAD4, ROS1, NTRK1, ATM and KIF5B, whose grandmother was suspected with pancreatic tumor. One male patient showed mutation of TP53, PML, ATM, ENDRA, ZNF703, whose father and grandfather were diagnosed as rectal cancer. No gene mutation was showed in the last patient.

Treatment for non-metastatic PACC

17 non-metastatic patients performed radical surgery with mDFS of 57 months. 8/17 (47.1%) patients received adjuvant chemotherapy. 9 /17 (52.9%) patients after radical surgery developed metastasis. 6 /6 patients with pathological lymph-vascular invasion developed metastasis and 3/11 patients without lymph-vascular invasion developed metastasis. Ki 67 expression on tumor was positive in 9 patients. By a cut-off of 30%, 4 patients with high index of Ki 67 (≥ 30%) developed metastasis while 5 patients with low index of Ki 67 (< 30%) remained disease free. 5/8 (62.5%) patients in adjuvant therapy group had lymph-vascular invasion or Ki 67 high index, while 2/9 (22.2%) patients in non-adjuvant therapy group had these risk factors.

The chemotherapy regimens include gemcitabine (n = 4), S-1 (n = 2), Gemcitabine + Oxaliplatin (GEMOX) (n = 1) and S-1 + Oxalipaltin (SOX) (n = 1). Most of patients received adjuvant therapy of 2–4 cycles and only 2 patients received more than 6 cycles with DFS over 4 years. Table 2 listed the specific information of adjuvant chemotherapy. There were 5/8 patients with adjuvant therapy and 4 / 9 patients without adjuvant therapy who developed metastasis. mDFS of 9 patients without adjuvant chemotherapy seemed numerically better than that of 8 patients with adjuvant chemotherapy (69 months *vs.* 42 months). mDFS of 5 patients receiving gemcitabine-based adjuvant chemotherapy was 27 months, while mDFS of 3 patients receiving fluoropyrimidine-based adjuvant chemotherapy has not reached.

Table 2
Adjuvant chemotherapy for non-metastatic patients and outcome

Patient sex, age	Regimes	Cycles	DFS (mos)	LV invasion	Ki 67 index	Metastasis
Male 68 yrs	GEM	4	5	Yes	70%	Yes
Male 54 yrs	GEM	4	5	Yes	Unknown	Yes
Male 50 yrs	S1	2	26	Yes	Unknown	Yes
Female 53 yrs	GEMOX	2	27	Yes	30%	Yes
Male 54 yrs	GEM	10	57	No	30%	Yes
Female 48 yrs	S1	12	51	No	15%	No
Male 53 yrs	SOX	5	62	No	20%	No
Male 15 yrs	GEM	4	141	No	10%	No

Abbreviation: LV invasion, lymph-vascular invasion; GEM, Gemcitabine; GEMOX, Gemcitabine + Oxaliplatin; S1, Tegafur/Gemeracil/ Potassium; SOX, S1 + Oxaliplatin.

Treatment for metastatic PACC patients

There were 8 metastatic PACC patients received 1st -line chemotherapy, including 5 patients at initial diagnosis and 3 patients after radical surgery. The chemotherapy regimens include Oxaliplatin + Irinotecan + 5-Fluoropyrimidine (FOLFIRINOX) (n = 3), GEMOX (n = 1), Gemicitabine + Cisplatin (GP) (n = 1), Capecitabine + Oxaliplatin (CAPOX) (n = 1), Albumin-bound paclitaxel + Gemcitabine (AG) (n = 1) and S-1 (n = 1). The chemotherapy regimens and results were shown in Table 3. The ORR of fluoropyrimidine-based regimen was 80% (4/5), which was much better than gemcitabine-based regimen (0/3, all 3 patients got progressive disease).

Table 3
The systemic chemotherapy and response for metastasis patients in our center

1st line	Response	PFS[1] (mos)	2nd line	Response	PFS[2] (mos)	3rd line	Response	PFS[3] (mos)	PFS[4] (mos)	OS (mos)
CAPOX	PR	16	—	—	—	—	—	—	—	24
GEMOX	PD	2	—	—	—	—	—	—	—	57
FOLFIRINOX	PD	2	GP/Nimotuzumab	SD	2	—	—	—	—	61
S1	PR	23	—	—	—	—	—	—	—	66
AG	PD	3	FOLFIRINOX	PR	6	S1/PD-1	PD	2	2	16
#GP	PD	2	FOLFIRINOX	PR	9	Lenvatinib/PD-1	SD	4	—	17
FOLFIRINOX	PR	9	—	—	—	—	—	—	—	32
#FOLFIRINOX	PR	18	GP	PD	1.5	Olaparib	PD	2	1	39

Abbreviation: PR, partial response; SD, stable disease; PD, progressive disease; GEMOX, Gemcitabine + Oxaliplatin; AG, Albumin-bound paclitaxel + Gemcitabine; S1, Tegafur/Gemeracil/Potassium; CAPOX, Oxaliplatin + Capecitabine; GP: Gemcitabine + Cisplatin; FOLFIRINOX, 5-FU + Oxaliplatin + Leucovorin + Irinotecan. F, female; M, male; PFS[1] means the PFS for first-line chemotherapy; PFS[2] means the PFS for second-line chemotherapy. Note: #Patients was detected with BRCA2 mutation.

Four patients received 2nd -line chemotherapy after failing to 1st -line chemotherapy. 2 patients who received 2nd -line FOLFIRINOX regimen achieved partial response (PR) after failing to 1st -line AG regimen. One patient got PD with 2nd -line AG regimen, and one patient with RAS wide-type achieved stable disease (SD) to 2nd -line AG plus nimotuzumab with disease controlled for 2 months.

Two patients with BRCA2 germline mutation had good response to FOLFIRINOX regimen and received Olaparib treatment. One patient achieved PR to 2nd -line FOLFIRINOX regimen and then received the maintenance Olaparib treatment for 5 months with good tolerance. Another patient achieved PR to 1st -line FOLFIRINOX regimen with PFS of 18 months and appeared PD to 2nd -line AG regimen and 3rd -line Olaparib.

Review of published literatures on chemotherapy of metastatic PACC

31 literatures and a total of 86 cases were included. The selection procedure was shown in Fig. 1 and treatment details were shown in Table 4. 86 cases received 1st -line treatment and 33/86 cases failing to 1st -line treatment received 2nd line. All enrolled cases were divided into two groups: fluoropyrimidine-based regimen group and gemcitabine-based regimen group. We classified the cases receiving gemcitabine plus fluorouracil into fluoropyrimidine-based regimen group.

Table 4
Palliative chemotherapy for metastatic patients: Data from literature

Regimen	Response	Author	Publication(year)
1st Line regimen			
Gemcitabine-based			
AG	1SD/2PD	Brunetti O [23]	2018
GEM	1PR/10SD/11PD	Fujii M [24]/ Yokode M [25]/ Seki Y [26]/ Brunetti O [23] / Lowery MA[27]/ Simon M [28]/ Yoo C [15]/ Kuji M[29]/ Kruger S [30]/ Toda, H [31]	2009–2012 2016–2018
GEMOX/GEM + CDDP	4PR/2SD/2PD	Brunetti O [23]/ Kruger S [30] Lowery MA[27]	2011/2016/2018
GEM + Irinotecan	2SD	Lowery MA[27]	2011
GEM + Erlotinib	1PR/3PD	Lowery MA[27]/ Kruger S [30]	2016
Fluoropyrimidine-based			
5-FU/S1/CAP	7 PR	Yamamoto T[32]/ Morishima K[33]/ Kanemasa Y [34]/ Sumiyoshi T [35] Yoo C [15]/ Kruger S [30]/	2010/2012 2013/2015
GEM + 5FU/GEM + S1	2CR/4PR/1SD	Nishimizu T [36]/ Fukui H[37]/ Hatata T [38] Miyagawa K[39]/Toda H[31]/ Brunetti O [23]	2010/2011 2016/2018
FOLFOX/CAPEOX	4PR/3SD/1PD	Yoo C [15]/ Fontenot J[40]/ Morales M[41] Brunetti O [23]/Kruger S [30]/Jordan E [42]	2013/2016–2018 2020
5FU + CDDP	3PR/2SD	Brunetti O [23]/ Butturini, G [5]	1999/2011
		Ukei, T [43]/ Jauch S [44]	2016/2018
GEM + CAP	1PR/2SD/1PD	Yoo C [15]/ Lowery MA[27] Sorscher SM[45]	2011/2017
PEXG	5SD	Brunetti O [23]	2011
GTX	1PR/1SD	Lowery MA[27]	2011
CAPE/ Temozolomide	1PD	Callata-Carhuapoma, H. R [46]	2015
FOLFIRINOX	6PR/2SD	Li M [47]/ Yoshihiro T [48] Kryklyva V[49]/Schempf U[50] Kruger S [30]/Pfrommer S [51]	2013/2014 2016–2019
2nd Line regimen			
Gemcitabine-based			

Abbreviations: GEM, Gemcitabine; 5-FU, 5- Fluorouracil ; S1, Tegafur/Gemeracil/Potassium; CDDP, Cisplatin; AG, Albumin paclitaxel + Gemcitabine; GEMOX, Gemcitabine Oxaliplatin; GEM + S1, Gemcitabine + Tegafur/Gemeracil/Potassium; FOLFOX, 5-FU + Oxaliplatin + Leucovorin; CAPOX, Oxaliplatin + Capecitabine; GEM + CAP, Gemcitabine + Capecitabine; PEXG, Cisplatinum + Epribicin + Gemcitabine + Gemcitabine; FOLFIRINOX, 5-Fluorouracil + Oxaliplatin + Leucovorin + Irinotecan.

Regimen	Response	Author	Publication(year)
AG/GEMOX	1PR/1SD/2PD	Brunetti O [23]/ Lowery MA[27]	2011/2016
			2018
		Kruger S [30]	
GEM	2SD/4PD	Brunetti O [23]/ Yoo C [15]/ Kanemasa Y [34]	2013/2017/2018
Fluoropyrimidine-based			
S1	2PR/3PD	Fujii M [24]/ Yokode M [25]/ Seki Y [26]	2009/2010/2017
GEM + CAP/GEM + S1	1PR/1SD/1PD	Brunetti O [23]/ Lowery MA[27]/ Kuji M[29]	2011/2018
FOLFIRI	1PR/2PD	Lowery MA[27]/ Morales M[41]	2011/2013
FOLFOX	4PR/1SD	Yoo C [15]/ Brunetti O [23]	2016–2018
		Kruger S [30]/ Simon M [28]	
FOLFIRINOX	2PR/1SD	Brunetti O [23]/ Kruger S [30]	2015/2016/2018
		Callata-Carhuapoma HR[46]	

Abbreviations: GEM, Gemcitabine; 5-FU, 5- Fluorouracil ; S1, Tegafur/Gemeracil/Potassium; CDDP, Cisplatin; AG, Albumin paclitaxel + Gemcitabine; GEMOX, Gemcitabine Oxaliplatin; GEM + S1, Gemcitabine + Tegafur/Gemeracil/Potassium; FOLFOX, 5-FU + Oxaliplatin + Leucovorin; CAPOX, Oxaliplatin + Capecitabine; GEM + CAP, Gemcitabine + Capecitabine; PEXG, Cisplatinum + Epribicin + Gemcitabine + Gemcitabine; FOLFIRINOX, 5-Fluorouracil + Oxaliplatin + Leucovorin + Irinotecan.

For first-line chemotherapy, ORR of 86 patients was 39.5%. There were 39 cases in gemcitabine-based regimen group and 47 cases in fluoropyrimidine-based regimen group. ORR of fluoropyrimidine-based group (59.6%, 28/47) was higher than gemcitabine-based group (15.4%, 6/39) ($P < 0.001$). 8 patients received FOLFIRINOX as 1st -line chemotherapy and 6 of them achieved PR. The survival data was available for 74 cases including 42 patients in fluoropyrimidine-based group and 32 patients in gemcitabine-based group. The mPFS and mOS of 74 cases was 8 months and 25.4 months, respectively. mPFS in fluoropyrimidine-based group were significantly better than gemcitabine-based group (mPFS: 12 months *vs.* 6 months, $P < 0.001$, Fig. 2) .

For second-line chemotherapy, ORR of 29 patients were 37.9%. There were 10 cases in gemcitabine-based regimen group and 19 cases in fluoropyrimidine-based regimen group. ORR of fluoropyrimidine-based group (52.6%, 10/19) was much higher than gemcitabine-based group (10%, 1/10) ($P < 0.05$). The comparison of response between fluoropyrimidine-based regimen and gemcitabine-based regimen for metastatic PACC were shown in Table 5.

Table 5
Comparison of response between fluoropyrimidine-based regimen and gemcitabine-based regimen for metastatic PACC

		Gemcitabine-based		Fluoropyrimidine-based		*P*
		Cases	ORR(%)	Cases	ORR(%)	value
Our study	1st -line (n = 8)	3	0 (0)	5	4 (80)	> 0.05
	2nd -line (n = 4)	2	0 (0)	2	2 (100)	> 0.05
Literatures	1st -line (n = 86)	39	6 (15.3)	47	28 (59.6)	< 0.001
	2nd -line (n = 29)	10	1 (10.0)	19	10 (52.6)	< 0.05

Abbreviations: ORR, objective response rate

Discussion

Due to the rarity and limited disease information on PACC, there is to date no consensus on PACC treatment strategy. More clinical data are needed to improve our understanding of this disease and seek reasonable treatments. We collected the data of 22 PACC patients in our cancer center and combined our study results with the published literatures to explore the role of adjuvant chemotherapy for non-metastatic disease and optimized selection of palliative chemotherapy or targeted therapy for metastatic disease. Compared with gemcitabine-based regimens, fluorouracil-based regimens may be the preferred choice for PACC. Further, we preliminarily explored the value of Olaparib for BRCA germline mutation patient and the role of EGFR monoclonal antibody combined with chemotherapy for RAS wild-type patient.

PACC maybe need more aggressive surgical resection because it was considered to have a more favorable prognosis compared to PDCA[9]. In our study, 17 nonmetastatic patients receiving radical surgery achieved a mDFS of 57 months, similar to other clinical reports[1, 11]. 8/9 patients with lymph-vascular invasion or high Ki 67 index (≥ 30%) developed metastasis which was consistent with other studies[12]. Ki 67 and invasion of lymph-vascular invasion may be prognostic indictors for PACC.

The role of adjuvant chemotherapy or chemoradiotherapy for PACC remains controversy or considered to be underpowered. C. Max Schmidt et al[7] included 865 resected PACC patients from 1985 to 2005 in National Cancer Database (NCDB) to identify prognostic factors. The results showed that adjuvant therapy was not associated with better outcomes on multivariable analysis and that T classification, tumor size, and nodal status remained nonsignificant predictors of survival. Dhruv J. Pate, et al[13] included a more contemporary cohort of 298 patients with resectable PACC between 2004 and 2015 from NCDB. The results showed that adjuvant systemic therapy was associated with a significant improvement in OS (HR 0.54, 95% CI: 0.33–0.89) compared to surgery alone and supported that adjuvant systemic therapy should be given due consideration in patients undergoing resection particularly when there is evidence of lymph node involvement. Wang et al[14] reported that 14 patients received radical resection followed by adjuvant chemoradiotherapy had a better outcome than surgery alone. In our study, no DFS benefit of adjuvant chemotherapy was shown. we speculated that the negative result may be related with the higher proportion of patients with poor prognostic factors such as lymphovascular invasion or high Ki67 index in the adjuvant chemotherapy group (62.5% *vs.* 22.2%), inadequate cycles of adjuvant chemotherapy (median cycles of 4) and selection of chemotherapeutic regimen. So far, there is no study to explore the efficacy of different adjuvant chemotherapy regimens. In this study, it is observed that the patients receiving fluoropyrimidine-based adjuvant chemotherapy achieved better mDFS than those receiving gemcitabine-based adjuvant chemotherapy (unreached *vs.* 27 months). The value of fluoropyrimidine-based adjuvant chemotherapy may be worthy of attention.

Palliative chemotherapy is the main treatment for metastatic PACC. However, the appreciate chemotherapy regimen remains unclear because those published retrospective and small sample studies or various case reports had significant heterogeneity and lack of high-quality evidence. Referring to the treatment of PDCC, many physicians were inclined to choose gemcitabine-based regimes with unsatisfied outcomes. Yoo, C et al. reported that oxaliplatin-containing chemotherapy against PACC have improved activity compared with gemcitabine[15]. Research showed that PACC has none of the gene abnormalities commonly found in PDCC and has gene mutations in the APC gene/β-catenin pathway and genetic progression similar to colon cancer[16]. It was referred that chemotherapeutic agents used in the treatment of colorectal cancer may be effective in ACC of the pancreas. In our study, 6/7 patients with FOLFIRINOX regimen achieved PR while 5 patients with AG regimen had no response. To further understand the preferred chemotherapy regimen for metastatic PACC, we compared the efficacy between fluoropyrimidine-based regimen and gemcitabine-based regimen after reviewing previously published literatures. The results based on the analysis of 44 Patients further supported that fluorouracil-based chemotherapy with higher ORR and improved survival was superior to gemcitabine-based chemotherapy. FOLFIRINOX regimen may be the preferred one for PACC.

The molecular feature of PACC is different from other pancreatic cancers[17]. Typical genetic alterations observed in PDAC are normally not detected or occur rarely in ACC, i.e, mutations in KRAS, TP53, CDKN2A, SMAD4. In our study, 4 patients performed NGS and showed MSS, wild-type KAS /BRAF and low TMB. Due to their pivotal role in maintenance of genome integrity, BRCA1/2-deficient tumors are particularly sensitive to therapies introducing cross-linking and DNA damage, namely platinum-based chemotherapies and PARP inhibitors[15, 18, 19]. Olaparib, an oral PAPR inhibitor, has been approved for the treatment for the maintenance treatment of adult patients with germline or BRCA-mutated advanced ovarian cancer[20], breast cancer[21] and pancreatic cancer[22]. In our study, molecular analysis revealed germline BRCA2 in two patients who had family history of breast and pancreatic cancer and achieved PR to 1st -line FOLFIRINOX regimen. We preliminarily explored the value of Olaparib maintenance treatment for one patient who had responded to 1st -line FOLFIRINOX regimen and then received Olaparib for 5 months with good tolerance. It may be crucial to establish the link between ACC and BRCA1/2 mutations in view of the importance to recognize potentially hereditary tumors and identify patients that may benefit from platinum-based chemotherapy and targeted therapy.

There existed some limitations. Firstly, it is a retrospective study from single institution which resulted an inherent selective bias. Secondly, a relatively small sample size and the imbalance in subgroups which results the deviation of analyses.

Conclusion

We further confirmed that PACC is different from PDCC in clinicopathological and molecular characteristic and should have different management strategy and chemotherapy choice. Ki 67 and invasion of lymph-vascular invasion may be prognostic indictors for PACC.

Although the benefit of adjuvant chemotherapy remained unclear, the value of fluoropyrimidine-based chemotherapy deserves attention. For metastatic patients, fluorouracil-based chemotherapy such as FOLFIRINOX is preferred, and the maintenance treatment of PARP inhibitors after effective platinum-containing treatment for BRAC mutation patients is worthy of further exploration.

Declarations

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Disclosure of Potential Conflicts of Interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study protocol was approved by the Independent Ethics Committee of the hospital, and was carried out in full compliance with the principles of the 'Declaration of Helsinki' (current revision) and 'Good Clinical Practice' guideline. Written informed consent was obtained from all participants before the start of treatment or any study-related procedures.

Research involving human participants and/or animals

This is a research involving human participants.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Authors contributions

WFH designed the study; XJY, GWL performed data analysis and wrote the manuscript. WXL, SWJ, RC, LSX, LSP and LYH collected and interpreted data; WFH and QMZ reviewed and revised manuscript. All authors approved final manuscript.

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Figures

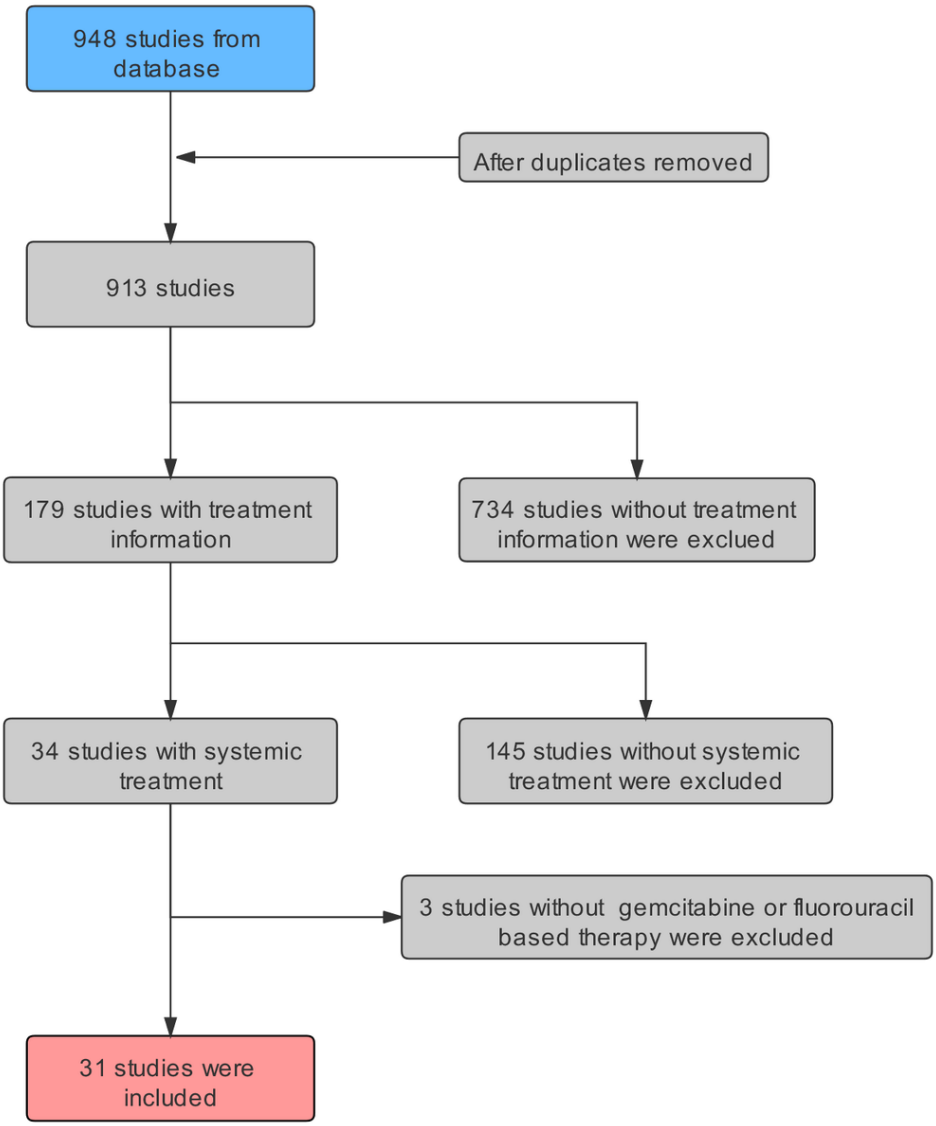

Figure 1

Schematic of literature selection.

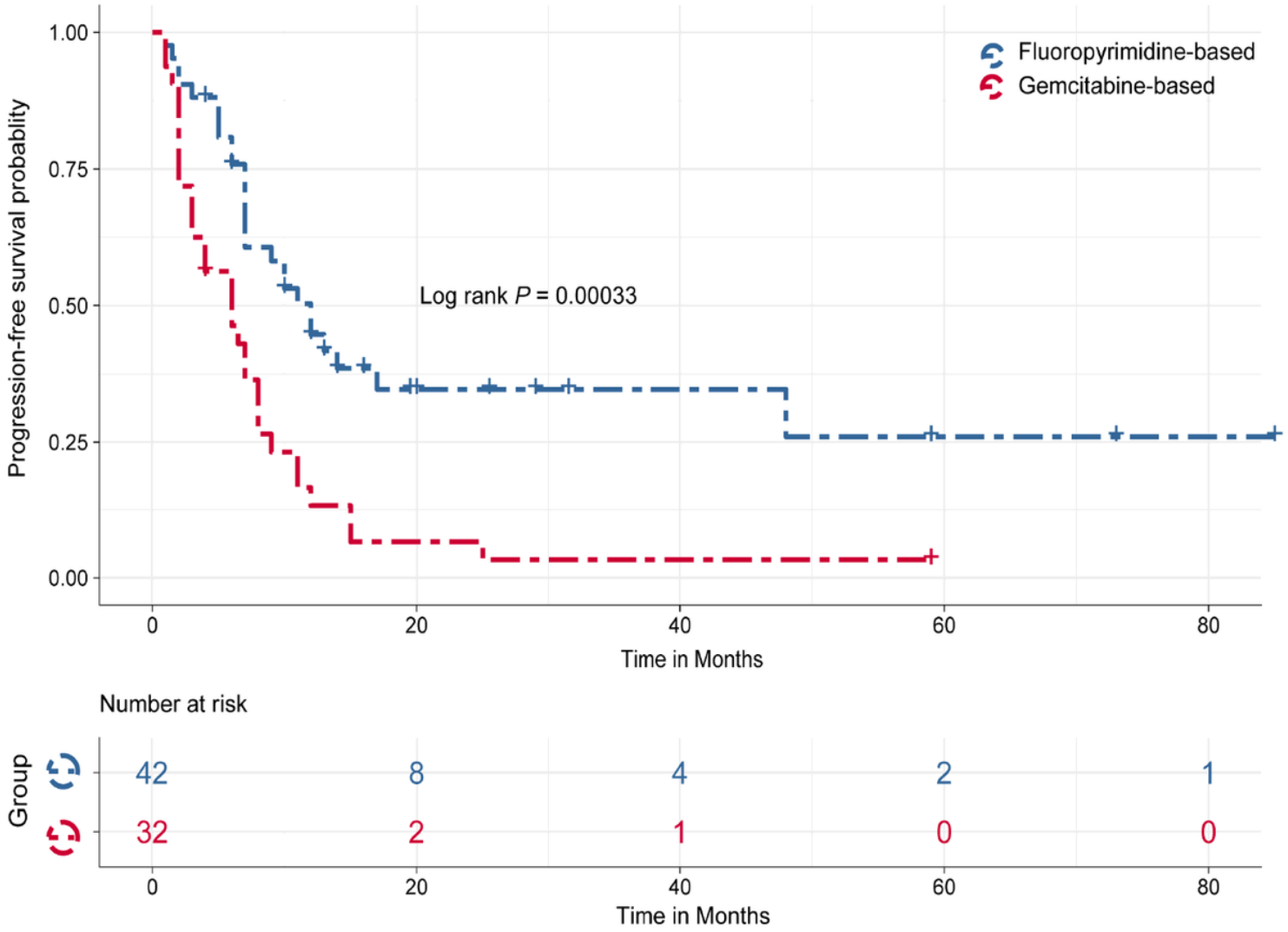

Figure 2

Kaplan-Meier plots of progression free survival stratified by fluorouracil-based therapy and gemcitabine-based therapy for advanced PACC.