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Review Article

Acinar Cell Carcinoma of the Pancreas, What We Know and Where to Go Next

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Abstract

Acinar cell carcinoma (ACC) of the pancreas is a rare, malignant cancer which arises from the exocrine pancreas. ACC is less studied compared with Pancreatic ductal adenocarcinoma (PDAC) as it accounts for 0.2%-4.3%.

To date, there are no standart treatment guidelines for patients in which a total surgical resection is not possible, and the role of neoadjuvant or adjuvant chemotherapy has not been established. This review article aims to present recent achievement in epidemiology, pathogenesis, diagnosis and treatment of ACC.

Materials and Methods: we have studied more than 40 sources, selected from the databases of PubMed, Scopus, eLibrary, Lancet from 2018 to 2024.

Goals and Objectives: Systematize and structure the accumulated data of diagnosis, treatment of acinar-cell pancreatic cancer on the basis of literary data from 2018 to 2024.

Introduction

The pancreas is an important organ in the regulation of digestion. It consists of an exocrine portion, which constitutes the bulk of the pancreas, and an endocrine portion, predominantly located at the tail of the pancreas. Acinar cells are the major component of exocrine tissue and are epithelial cells responsible for the production of digestive enzymes, including amylase, protease, lipase, and trypsin. The digestive enzymes are transported through a duct system that carries pancreatic juice into the duodenum [1].

Although acinar tissue account for most of the pancreatic organ, pancreatic neoplasms that mainly exhibit acinar differentiation are rare [2].

ACC of the pancreas is a rare malignant tumor composed of cells with morphological resemblance to acinar cells and accounts for 0,2-4,3% of pancreatic neoplasms. ACC has unique morphological

features, and a clinical course that distinguish it from other malignant tumors of the pancreas. ACC usually has large size at diagnosis (average tumor size: ~ 5 cm) and is often localized in the head of the pancreas. Patients also have elevated serum lipase in 24% to 58% of patients. ACC of the pancreas is more common among men and has also been reported in children. Compared with ductal adenocarcinoma, ACC has a better prognosis, but after radical treatment, there is high risk of recurrence [3].

Analysis of Literary Sources

Epidemiology:

Per the latest GLOBOCAN research 18 094 716 cases of cancer are registered in the world in 2020. Of these, pancreatic cancer accounts for 495 773 cases, representing 2,6% of malignant neoplasms. The mortality rate of pancreatic cancer is almost equal to the incidence 4,7% (466 003 cases). Due to its poor prognosis, pancreatic cancer is ranked as the seventh leading cause of cancer death in both genders. Incidence rates are significantly higher in countries with high HDI, approximately 4-5 times. Europe, North America, and Australia/New Zealand have the highest rates [4].

Pancreatic cancer has the poorest (around 10%) five-year survival rate in the US.

The reason behind is because 80 to 85% of patients have unresectable or metastatic cancer at diagnosis. Patients with localized resectable tumors have a prognosis of only 20% survival 5 years after surgery, which is also a poor prognosis [5].

In Russia, 14 004 cases of pancreatic cancer have been detected in 2022. The incidence of pancreatic cancer is 14,1 per 100 000 population. The screening can be presented as follow: 24,5% were identified in stages I-II, 15,9% in stage III and 58,1% in stage IV. One-year mortality rate is 63,9% [6].

The incidence of ACC of the pancreas is 0,2-4,3% of all pancreatic carcinomas. ACC is more common in men than women. For localized disease, median survival is about 47 months. For patients with metastatic ACC, treated with chemotherapy the median overall survival is 12 to 19.6 months. Five-year survival ranges between 36.2% to 72.8% for resectable tumors [7]. Although ACC has a better prognosis than ductal adenocarcinoma, but a poor outcome. Medium age at diagnosis, is 60 years old, but ACC can occur in children and accounts for 15% of childhood pancreatic cancer tumors [3, 8].

Risk factors and predisposition gene:

The incidence of pancreatic cancer is gradually increasing, which may be linked to population aging, unhealthy diets and malnutrition leading to obesity and pancreatitis.

Obesity affects pancreatic cell function both endocrine and paracrine. The increased of sex hormones and insulin productions are noted among endocrine effects that are attributable to both visceral fat and intra-organ fat deposition.

Paracrine effects include adipocyte secretion of proinflammatory cytokines and adipokines, most commonly associated with local ectopic intracellular fat cell accumulation and intracellular lipid molecules. That can create an unfavorable metabolic environment that contributes to the development of pancreatic cancer [9].

Obesity and intravascular fat provoke fatty infiltration of the pancreas which play a role in the direct activation of proinflammatory pathways. The proinflammatory environment plays a role in initiating precancerous pancreatic lesions [10].

Acute pancreatitis is acinar damage and inflammation of the pancreas. Pancreatic necrosis and inflammation are caused by mechanical obstruction of the pancreas or bile ducts that block the flow of digestive enzymes. Systemic factors responsible for acinar cell damage also may be involved. Acute pancreatitis is often followed by an inflammation of the pancreas, characterized by secretion of proinflammatory factors (TNFa, interleukins IL-1, -6, and -8). Damaged epithelium of the pancreas and surrounding tissues, as well as infiltration of macrophages and neutrophils, release additional proinflammatory factors into the circulatory system, which may additionally promote localized tissue damage [9].

Inheritance is also a risk factor. People with Peutz-Jeghers syndrome who have mutations that inactivate the tumor suppressor gene STK11 (the tumor suppressor gene encoding serine/threonine kinase 11 is located in the 19p13.3) are at high risk of developing pancreatic cancer. STK11 encodes LKB1 (multitasking kinase - tumor suppressor), which signals negative regulation of lipid, cholesterol, and glucose metabolism via AMPK (5'-adenosine monophosphate-activated protein kinase); obesity-related metabolic changes inhibit the LKB1-AMPK signaling axis, increasing cancer risk [9].

Type 2 diabetes mellitus is also a risk factor for pancreatic cancer. Epidemiologic studies have shown that new-onset type 2 diabetes mellitus is associated with a 1.5 to 2.0% increase in risk of pancreatic cancer in patients over 50 years old. Insulin resistance, hyperglycemia, hyperinsulinemia, and inflammation are the major mechanisms contributing to pancreatic cancer [11].

While risk factors for pancreatic cancer are predetermined, no specific development factors for ACC have been established at this time. Statistically, the number of observations is so small, that it is not possible to identify specificity, although this issue is interesting and requires further research.

Molecular genetic features:

Molecular genetic features of ACC are markedly different from pancreatic ductal adenocarcinoma (PDAC). Due to its rareness, sufficient treatment guidelines of ACC are limited. Data suggest that ACC has a different genomic profile than pancreatic ductal adenocarcinoma.

Genome tests have concluded that, unlike ductal adenocarcinoma, ACC rarely expresses KRAS, somatic changes in TP53, CDKN2A, and SMAD4; in the other hand, activation of fusion genes affecting BRAF, RAF1, RET, and NTRK1/2/3 has been found in 30% of ACC patients. Higher prevalence of germline pathogenic changes in HR- and DDR- related genes including BRCA1, BRCA2, PALB2, ATM, and CHEK2. Tumors with high microsatellite instability (MSI-H) or DNA mismatch repair (dMMR) deficiency hold promise for development of ACC therapy. In patients with ACC, ALK-KANK4 gene fusion tumors respond favorably to alectinib therapy, whereas fusion tumors NTRK genes respond favorably to treatment with larotrectinib. Although ACC is a rare subtype of pancreatic cancer, further research, breakthrough of the genome profile, will help identify potential treatment strategies, and improve therapy outcomes [3, 19, 20].

Clinical Presentation

ACC patients often present with nonspecific symptoms such as abdominal pain (60%), back pain (50%), weight loss (45%), nausea and vomiting (20%), black stools (12%), fatigue, anorexia, and diarrhea (8%). Early clinical manifestation of ACC is usually abdominal pain and abdominal distention without other pathologic functional abnormalities, a key reason why ACC is initially ignored [21].

Unlike ductal adenocarcinoma, ACC rarely obstructs the bile ducts. Some patients experience paraneoplastic syndrome, known as lipase hypersecretion, levels reaching over 10,000 U/dL. Elevated lipase may be the first sign of ACC. Some patients may present with multiple nodular foci of subcutaneous fat necrosis, in the cancellous bone, and may have peripheral blood eosinophilia and peripheral blood eosinophilia is also possible in complete blood count analysis. Paraneoplastic syndrome may occur following tumor recurrence. Serum lipase levels may normalize after surgical resection of the tumor, and patients may have symptomatic symptoms. In such patients, lipase may be used as a tumor marker [2].

Metastasis

Statistically, pancreatic cancer has an extremely poor prognosis, which is due to the fact that metastases are notified during diagnosis. For ACC, about 30 to 50% of patients have metastasis during diagnosis and for ductal adenocarcinoma, these numbers exceed 50% [12].

Takahashi et al report, the metastasis sites are presented as follow: liver 68% of cases, peritoneum in 19% of cases, and distant lymph nodes in 14% of cases. The phenomenon of "Premetastatic niche" may be considered among the causes of early metastasis and recurrence after surgery [8].

One of the first theories of metastasis appeared about a century ago. Stephen Paget's "seeds and soil" theory suggests that metastasis, as well as its outcome, is not a coincidence, but has a predisposition. One of the postulates of this theory is that metastasis occurs as a result of interaction between tumor cells and microenvironment of the host organ [13].

The "seeds and soil" hypothesis is now widely accepted, and is a common topic of inquiry. The seed can now be identified as a progenitor cell, a tumor stem cell, and the soil discussed as a stroma, niche, or microenvironment of an organ.

Some cancerous cells may have specific phenotypic characteristics and metastatic potential, and secondary organs may have specific characteristics in their microenvironment that facilitate settlement with disseminated tumor cells [12].

The stroma plays a critical role in the development of metastasis. Although previously seen as a mere mass of connective tissue supporting organ sttructure, this perception has recently changed to encompass a structure with a wide range of properties ranging from involvement in matrix cell adhesion to intercellular signaling and controlling cell behavior by altering the mechanical and biochemical properties of stroma [14, 15].

The microenvironment in pancreatic cancer consists of cell-free stroma associated with fibroblast cancer (CAF), also known as pancreatic stellate cells (PSC), immune cells, and factors such as cytokines, chemokines, growth factors, and proangiogenic factors.

Metastasis is one of the most important stages of cancer development and uses intercellular communication for mediated changes in the microenvironment. Small extracellular vesicles (SEVS) carry proteins, nucleic acids, and other biologically active substances and are important means of communication between cells [12].

Pancreatic stellate cells, which account for about 50% of tumor stroma, are most important in remodeling the microenvironment around tumor cells [16].

Six potential traits for premetastatic niche have been proposed: reprogramming, inflammation, immunosuppression, organotropism, lymphangiogenesis, and vascular angiogenesis/permeability.

Cancer cells often use a "Warburg effect" that involves a preferential shift in the glycolytic pathway toward the anaerobic

pathway, leading to lactate production even under normoxic conditions. This "elective aerobic glycolysis" promotes rapid and aggressive proliferation cancer cells [12].

Aggressiveness of tumor growth and metastasis depend largely on degree of neoangiogenesis. Various angiogenic factors such as VEGF, IL-8, PD-ECGF, and HGF have been implicated in the growth of liver metastasis. Various myeloid cells, including neutrophils, dendritic cells, monocytes, and macrophages, may also contribute to tumor angiogenesis by producing proangiogenic factors or inhibiting antiangiogenic factors. Increased vascular permeability helps spread the tumor, enabling tumor extravasation and intravasation [12, 14].

Some tumors are characterized by the formation of a so-called "carotid niche", in which the tumor cells will be at rest, leading to a significant delay in the development of metastase [18].

Diagnosis

Levels of serum tumor markers such as carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) are not consistently elevated in patients with ACC. However, the level of alpha-fetoprotein (AFP) in the blood may be elevated in younger patients.

Immunohistochemistry testing of enzymes (chymotrypsin, trypsin, lipase, and amylase) produced by the pancreas cells helps to confirm the diagnosis of ACC. These enzymes exhibit varying degrees of specificity and sensitivity. Reactivity to trypsin and chymotrypsin can be demonstrated in about 95% of cases, and the combination is reported to be the most sensitive for diagnosing ACC. Detection of chromogranin and synaptophisin occurs in a significant proportion. ACC, indicating the need for further evaluation with clear acinar markers, especially in small specimens, to avoid ACC being misidentified as a neuroendocrine tumor or mixed acinar-neuroendocrine differentiation.

The growths are usually detected by computed tomography (CT) and magnetic resonance imaging (MRI) and then confirmed by fine-needle aspiration biopsy. However, MRI is superior to CT in tumor margins detection, intratumor hemorrhage, tissue infiltration, and ductal dilation [7].

For ACC, the tumor most often is located in the head of the pancreas. The tumor is fairly large during diagnosis, with an average tumor size of 45 to 54 mm. ACC is often an ovoid-shaped formation with well-defined edges. Localized invasion of adjacent organs, including the duodenum, stomach, kidneys, peritoneum, and spleen, occurs in about 45% of ACC [3, 21, 22].

People with ACC rarely have dilated bile ducts. This can be explained by the origin of ACC and has been demonstrated by several studies. Among imaging studies done on ACC, bile duct dilation was found in only about 1/10 of pancreatic ACC patients, confirming the rareness of this in ACC, unlike to common ductal adenocarcinoma [23].

Treatment

Considering the rarity of the ACC, there is no specific therapy at the moment. And first-line treatment is similar to ductal adenocarcinoma.

Surgical tactics aim to achieve radicalization. However, the percentage is small, accounting for no more than 20% of all new cancers detected. Surgery is similar to that for ductal carcinoma. Median survival after surgery is 18 to 24%. Due to the anatomical position of the tumor, directly next to the main vessels - the technical execution of radical resection is difficult. The disease recurrence rate is extremely high among patients who have had surgical resection. Surgical resection is considered the first choice for the treatment of ACC, but there is no standard for the treatment of unresectable tumors [34].

To understand treatment in more detail, the resectability criteria of pancreatic tumors must be clearly understood. This will lead to a further treatment strategy. Consider the resectable criteria for ductal adenocarcinoma, and there are no specific criteria for ACC at this time.

Resectability	Arterial involvement	Venous involvement
Resectable	No tumor contact with major arterial structures (CA, SMA, and/or CHA)	No tumor contact with SMV or PV ≤ 180° contact WITHOUT vein contour irregularity
Bordeline Resectable	Pancreatic head/ uncinated process: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation • Solid tumor contact with SMA of ≤ 180°; •Solid tumor contact with variant arterial anatomy (example: accessory right hepatic artery, replaced right CHA, etc) Pancreatic body/tail: • Solid tumor contact with the CA of ≤ 180°	Solid tumor contact with the SMV or PV of> 180° ≤ 180° solid tumor contactwith contour irregularity of the vein or thrombosis of the vein BUT with suitable vessel proximal and distal to the site of involvement, allowing for adequate vein resection and reconstruction Solid tumor contact with the inferior vena cava
Locally advanced	Pancreatic head/ uncinated process: • Solid tumor contact>180° with the SMA or CA •Pancreatic body/tail: • Solid tumor contact of>180° with the SMA or CA • Solid contact with the CA and aortic involvement	Unreconstructible SMV or PV due to extensive tumor involvement or venous occlusion

Table 1: Non-metastatic pancreatic cancer resectability score (NCCN criteria) [35].

Patients with pancreatic cancer resectable initially undergo surgical repair. Currently, only when risk factors for metastatic disease are high can neoadjuvant treatment be considered. Considered factors include a steady rise in CA19-9 above 500 U/mL, large primary cancer sites, metastatic involvement of regional lymph nodes, and high weight loss and severe pain are also risk factors [35].

Some studies suggest benefit of neoadjuvant therapy for resectable pancreatic cancer. A retrospective analysis of 15 237 patients with pancreatic cancer-resected patients found that patients receiving neoadjuvant treatment for pancreatic cancer were better than those undergoing first-stage resection. Median survival was 26 months versus 21 months [36]. Research is ongoing. A randomized phase II trial, SWOG 1505, establishes a comparative analysis of data for the drugs fluorouracil, irinotecan and oxaliplatin, gemcitabine, and albumin-associated paclitaxel as neoadjuvant therapy for patients who have resectable tumors.

It is also possible to use a combination of chemo-radiation therapy followed by surgery as a pre-operative therapy. The study, which included 132 patients treated with consecutive preoperative chemoradiation therapy and pancreaticoduodenectomy for RV head adenocarcinoma, yielded an overall median survival of 21 months, and 31% of patients were alive without clinical or radiologic evidence of disease [37]. Neoadjuvant therapy is now feasible for patients with resectable tumors at high risk or in clinical trials.

Patients with borderline resectable tumors have a higher risk of R1 resection and should therefore be managed with appropriate neoadjuvant therapy. Preoperative therapy increases the likelihood of R0 resection by shrinking the tumor and eliminates micrometastases early in their development. The preoperative therapy can similarly be drug treatment and radiation therapy, as well as a combination thereof, called chemoradiation therapy.

Regimens of FOLFIRINOX, gemcitabine with nab-paclitaxel and also the combination of gemcitabine and cisplatin (with identified mutation of BRCA1/2 or PALB2) can be used as drug therapy.

Preoperative therapy for patients with borderline resectable pancreatic adenocarcinoma tumors remains a topic of discussion. For chemotherapy, the role in treatment of borderline resectable tumors has been defined, but for radiation therapy, it remains controversial. ALIANCE (A021501) evaluated the effectiveness

of mFOLFIRINOX pre-operative chemotherapy against mFOLFIRINOX chemotherapy with stereotactic or hypopractional radiation therapy. Preliminary evidence suggests that neoadjuvant treatment with mFOLFIRINOX alone has shown beneficial OS, compared with chemoradiation therapy. The 18-month survival rate for the mFOLFIRINOX alone was 66,7% versus 47,3%, respectively [38].

A multicenter, open, randomized, controlled trial, ESPAC5 (formerly known as ESPAC-5f) evaluated a different approach for treatment of borderline resectable pancreatic cancer head tumors. Participants were randomized into 4 groups: immediate surgery group; neoadjuvant chemotherapy group with gemcitabine plus capecitabine; neoadjuvant chemotherapy group with FOLFIRINOX mode and neoadjuvant chemotherapy with capecitabine based chemotherapy. The study showed a one-year OS of 39% for immediate surgery, 78% for neoadjuvant therapy with gemcitabine plus capecitabine, 84% for FOLFIRINOX and 60% for chemotherapy with capecitabine. This study showed a significant advantage in pancreatic cancer for patients undergoing a short course of neoadjuvant chemotherapy compared to immediate surgery for borderline resectable pancreatic tumors [39].

Adjuvant Therapy

There is currently no specific treatment for ACC. And first-line treatment is similar to ductal adenocarcinoma. Patients with ACC survive significantly better than those with ductal adenocarcinoma. Typically, GEMCITABINE or fluoropyrimidine-based combination chemotherapy regimens are used to treat ACC. No standard chemotherapy regimen has been established for patients with non-resectable or recurring ACC because of the rarity of this type of tumor, and there have been no large-scale randomized controlled trials for this disease. Radiation therapy is used primarily to convert tumors from borderline resectable to resectable and is done by both normal fractionation and hypo-fractionation of stereotactic CT (SBRT). Radiation therapy may also be used for palliative purposes, to relieve pain, or to relieve local obstructive symptoms [7].

According to the CONKO-001 study, 354 patients were selected in groups receiving Gemcitabine and not receiving specific anti-tumor treatment. The endpoints were: disease-free survival (DFS), and overall survival (OS). Tests confirm a significant improvement for the group of Gemcitabine-treated patients (DFS after 3 and 5 years was 23,5% and 16,0%), compared to the control group (8,5% and 6,5%, respectively). Overall survival at 3 and 5 years was 36,5% and 21,0% for patients with gemcitabine compared to 19,5% and 9,0% for control groups without cancer treatment.

A ESPAC-3 trial showed that Gemcitabine may be considered a better adjuvant regimen for pancreatic cancer than fluorouracil.

Further study of this topic is reflected in the study ESPAC-4, where the monotherapy with Gemcitabine has been compared to the combination of Gemcitabine + Capecitabine. Median overall survival for patients in the gemcitabine + capecitabine group was 28,0 months, compared with 25,5 months for the gemcitabine monotherapy group.

In a recent phase III MPACT trial, the combination of gemcitabine and nab-paclitaxel (Gem/ NabP) showed an increase in overall survival compared to gemcitabine alone for advanced ductal pancreatic adenocarcinoma. In the general population, median progression-free survival (PFS) and overall survival (OS) were 5,2 and 10,9 months, respectively. In patients with metastatic disease, median OS was 9,4 months and median PFS was 4,5 months, whereas the same rates in the subgroup of topical-extent cancer were 17,1 and 6,8 months, respectively. Grade 3 to 4 hematologic toxicity was reported; neutropenia, leukopenia, thrombocytopenia, and anemia were present in 23, 20, 5, and 4% of patients, respectively. Dose reduction was performed in 80% of patients.

The Phase III trial, involving 493 patients, examined the relative efficacy of a modified FOLFIRINOX regimen with gemcitabine monotherapy in patients with resected ductal carcinoma. After a median of 33.6 months, the modified FOLFIRINOX resulted in a median recurrence-free survival of 21.6 months compared to 12.8 months with gemcitabine. However, the frequency of adverse effects was high with modified FOLFIRINOX: 75.9% of patients in the modified FOLFIRINOX group experienced grade 3-4 toxicity, compared to 52.9% in the gemcitabine group [40].

Tumor drug therapy is the only way to achieve long-term survival for people with ACC. A study of a cohort of 298 patients with ACC resectable from 2004 to 2015 from the National Cancer Database (NCDB) found that systemic adjuvant therapy was associated with a significant improvement in OS compared to a single surgery [24].

A study by Sun-sen University Cancer Center (the Sun Yat-Yat-sen University) conducted from 2005 to 2020 included twenty-two patients with ACC. Eight of the 17 nonmetastatic patients received adjuvant chemotherapy. Patients treated with a fluoropyrimidine (n = 3) regimen had a better median of disease-free survival than patients treated with a gemcitabine (n = 5) regimen (unachieved compared to 27 months). Eight patients with metastatic ACC were receiving first-line chemotherapy. Four patients received second-line chemotherapy. The objective response rate (ORR) for the fluoropyrimidine-based regimen was 85,7% (6/7), far better than that for the gemcitabine-based regimen (0/5). One patient who responded to the first-line FOLFIRINOX regimen received olaparib as maintenance therapy for 5 months with good tolerance [26].

One of the mechanisms underlying the Fluoropyrimidine-based

regimen of ACC is that ACC has none of the gene abnormalities commonly found in ductal adenocarcinoma and has mutations in the ACC gene/ß-catenin pathway and a genetic progression similar to colon cancer [27].

In a multicenter European study of 59 patients who had radical ACC resection, the 5-year overall survival (OS) was 60,9%, and the median recurrence-free survival (RFS) was 30 months. The R0 resection rate was 84,7%. Compared with patients with N1 or N0 of ACC, patients with N2 of ACC had significantly shorter OS and RFS. Stage N2 was considered the only negative predictive factor. Eight patients (six with locally advanced and two with distant metastases) received neoadjuvant treatment, mostly with FOLFOX and FOLFIRINOX. Of the 59 patients, 37 (62,7%) received adjuvant treatment, mostly with gemcitabine-based (GEM) regimens. The recurrence rate after radical surgery was 52,5% (31/59) (local recurrence 7; local and systemic recurrence 6; systemic recurrence 18). Adjuvant protocols (done in 62,7%) have not improved either OS (p = 0,542) or RFS (p = 0,159) [28].

For advanced tumors of the ACC, a retrospective analysis of Asan Medical Center (Korea) from 1997 to 2015 reported that chemotherapy regimens containing oxaliplatin were more effective than Gemcitabine. Chemotherapy drugs used in the treatment of colorectal cancer have been shown to be effective in pancreatic ACC. Patients treated with FOLFOX had DFS significantly better than patients treated with gemcitabine alone (median 6,5 months; 95% MDI 2,8 to 10,2 versus 1,4 months; 95% MDI 0,5 to 2,3; p = 0,007). This observation confirms specific genetic abnormalities of the ACC, including the high detection rate of BRCA mutations [25].

Overall, up to 22% of pancreatic ACPF exhibit variable BRCA1/2 changes. This requires genetic screening for BRCA1/2 deficiency in all patients diagnosed with pancreatic ACC. Notably, genetic testing for the BRCA1/2 gene is widely used in breast and ovarian cancer patients, while the prevalence of these mutations in this cohort of patients is reported to be only 3% and 10%, respectively [29].

The clinical report by Li et al. described the first case of a patient with inoperable pancreatic ACC progression and a germline mutation BRCA2, which demonstrated a partial response to treatment with the oral PARP inhibitor Olaparib [30].

Features of Metastatic Cancer Treatment

In the metastatic form, the precise regimen is based mainly on results of ECOG and profile of comorbidities.

For patients with ECOG 0-1 status, consider either FOLFIRINOX or gemcitabine plus Nab-Paclitaxel for first-line treatment.

For patients with ECOG 2 status or an associated disorder that does not warrant a more aggressive regimen, gemcitabine is recommended as monotherapy, although drugs such as capecitabine may be offered in combination.

Patients with more severe somatic status, ECOG 3 to 4, or patients with severe comorbidities are offered therapy only in certain cases [41].

Notable is the case described in 2011 of a patient with metastatic ACC who achieved long-term survival through personalized treatment, developed in part on the basis of molecular and in vitro data collected by analysis of tumor and cell line derived from liver metastasis. Due to these studies, doxorubicin was selected, which showed an impressive and lasting effect. As far as we know, this is the first reported use of doxorubicin in the ACC [31].

In 2021, a clinical case was published with the support of grant the Roswell Park Comprehensive Cancer Center. A patient who received combined chemotherapy with Gemcitabine and Nab-paclitaxel stopped treatment after 4 courses due to further disease progression with new liver metastases. Molecular testing has shown the presence of the SEL1L-NTRK1 merger. Targeted therapy began with the oral tropomyosin-receptor kinase (TRK) inhibitor larotrectinib 100 mg twice a day. At the time of writing, the patient was receiving therapy for 13 months, and there were no 3rd degree side effects [32]. This clinical case shows opportunities for further research and development of ACC therapy.

In 2023, a clinical case of metastatic ACC with liver manifestations was reported in Japan from a liver biopsy. The patient was treated with a modified FOLFIRINOX regimen, which resulted in partial remission; liver tumor decreased from 110 mm to 47 mm (43% of original area); and pancreatic tumor decreased from 70 mm to 40 mm (57%). The patient is then resected with distal pancreatosplenectomy. Histological studies have revealed a pathological response in the form of replacement of tumor tissue of connective tissue [33].

Conclusion

ACC of the pancreas are a molecularly and morphologically heterogeneous group of diseases that require a multidisciplinary approach to the diagnosis and treatment of the disease. The study of ways and mechanisms of metastasis, interruption of the formation of the tumor niche - a possible way to suppress the spread of tumors and increase the number of radical operations and, as a result, increase the overall survival of the population. The research for new targets through molecular genetic analysis will help find additional treatment options. Given the rarity of the disease and the limited knowledge available, the topic deserves further study.

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List of Abbreviations

PC - Pancreatic Cancer

ACC - acinar cell carcinoma of pancreas

STK11 (Serine/threonine kinase 11) - serine/threonine kinase 11

LKB1 (liver kinase B1) is hepatic kinase B1

AMPK (5 - adenosine monophosphate-activated protein kinase) - 5'-activated adenosine monophosphate protein kinase

BRCA 1.2 (Breast Cancer gene 1.2) - Breast cancer genes 1.2

Microsatellite instability (MSI) - Microsatellite instability

Extracellular matrix (ECM)

CAF (cancer-associated fibroblasts) - tumor-associated fibroblasts

PSC - (pancreatic stellate cells)

VEGF - (vascular endothelial growth factor) - endothelial growth factor

CA 19-9 - (Carbohydrate antigen 19-9)

CEA - Carcinoembryonic antigen

AFP - alpha-fetoprotein

CT - celiac trunk

SMA - Superior Mesenteric artery

CHA - Common Hepatic Artery

SMV - superior mesenteric vein

VP - portal vein

IVC - inferior vena cava

OS - overall survival

SBRT - (Stereotactic body radiotherapy)

RFS - recurrence-free survival

PFS - Progression-free survival

PDAC (pancreatic ductal adenocarcinoma)

Objective response rate (ORR) - objective response rate

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