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ABOUT COVER

Editorial board member of *World Journal of Gastrointestinal Oncology*, Dr. Cao is an Assistant Research Fellow at the Second Affiliated Hospital of Soochow University in Suzhou, China. Having received his Bachelor's degree from Soochow University in 2006, Dr. Cao undertook his postgraduate training at Soochow University, receiving his Master's degree in 2009 and his PhD in 2015. He works in the Department of Pathology, the Second Affiliated Hospital of Soochow University, Soochow University, where his ongoing research interests involve the molecular pathological mechanisms of malignant tumors, particularly in relation to oncogenesis, radiation resistance and cellular signal transduction involving tumors of the digestive system. To date, he has published 16 SCI papers as corresponding author or first author. (L-Editor: Filipodia)

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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REVIEW

One size does not fit all for pancreatic cancers: A review on rare histologies and therapeutic approaches

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Abstract

Exocrine pancreatic neoplasms represent up to 95% of pancreatic cancers (PCs) and are widely recognized among the most lethal solid cancers, with a very poor 5-year survival rate of 5%-10%. The remaining < 5% of PCs are neuroendocrine tumors that are usually characterized by a better prognosis, with a median overall survival of 3.6 years. The most common type of PC is pancreatic ductal adenocarcinoma (PDAC), which accounts for roughly 85% of all exocrine PCs. However up to 10% of exocrine PCs have rare histotypes, which are still poorly understood. These subtypes can be distinguished from PDAC in terms of pathology, imaging, clinical presentation and prognosis. Additionally, due to their rarity, any knowledge regarding these specific histotypes is mostly based on case reports and a small series of retrospective analyses. Therefore, treatment strategies are generally deduced from those used for PDAC, even if these patients are often excluded or not clearly represented in clinical trials for PDAC. For these reasons, it is essential to collect as much information as possible on the management of PC, as assimilating it with PDAC may lead to the potential mistreatment of these patients. Here, we report the most significant literature

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regarding the epidemiology, typical presentation, possible treatment strategies, and prognosis of the most relevant histotypes among rare PCs.

Key words: Rare pancreatic cancers; Pancreatic acinar cell cancer; Pancreatic adenosquamous cancer; Undifferentiated pancreatic cancer; Pancreatoblastoma; Pseudopapillary pancreatic cancer

Core tip: Due to their rarity and lack of consistent literature, rare subtypes of exocrine pancreatic cancer are often assimilated with the more frequent pancreatic ductal adenocarcinoma, even if they have peculiarities in their presentation and treatment strategy. The aim of this review is to summarize the most relevant literature regarding these rare subtypes of pancreatic cancers.

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INTRODUCTION

Traditionally, when speaking about pancreatic cancer (PC), we refer to exocrine pancreatic neoplasms, which represent up to 95% of all PCs and are widely recognized among the most lethal solid cancers, with a very poor 5-year survival rate of 10%[1]. Exocrine PCs account for 7.8 new cases every 100000 people and is the 11th most common cancer worldwide[2]. The remaining approximately < 5% of PCs are neuroendocrine tumors, which are characterized by a better overall survival (OS), with a median OS (mOS) of 3.6 years (ranging from 15 mo for grade 3 disease to 140 mo for grade 1 disease)[3].

Since roughly 85% of exocrine PCs are pancreatic ductal adenocarcinomas (PDACs), the vast majority of literature and data from clinical trials and basic research are focused on this particular histotype. However, up to 10% of PCs have a rare histotype such as adenosquamous carcinoma, undifferentiated carcinoma (UC), acinar cell carcinoma (ACC), cystic tumors, papillary adenocarcinoma, and other exocrine variants[4]. As reported in Table 1, the World Health Organization (WHO) has identified more than 10 subtypes of PCs according to their anatomopathological characteristics[4] (Figure 1). Due to their very low incidence, the biological and clinical features of these rare types of PC are still poorly understood. Furthermore, since patients with rare histotypes of PC are often excluded or not well represented in clinical trials for PDAC, there are limited data regarding the best treatment strategy and most information is from case reports or small case series. The aim of this review was to discuss the most relevant rare subtypes and their peculiarities in terms of epidemiology, diagnosis, prognosis, and treatment.

ACC

Epidemiology and prognosis

ACC of the pancreas represents < 2% of all PCs. As for most rare cancers, there are no prospective data and nearly all of the information is from small single-center series and the United States National Registry of PC[5-8]. Compared to patients with PDAC, those with ACC appear to be younger, with a median age of 60-67 years, and more frequently male. Additionally, patients with ACC tend to have larger tumors, with a median diameter ranging from 8 to 10 cm. Despite previous evidence stating that these tumors are more frequently located in the tail of the pancreas, the most recent WHO classification states that this specific histotype is more often located in the head of the

Table 1 World Health Organization classification of exocrine malignant epithelial tumors 5th edition

Histotype	Subtype	Frequency, %
Ductal adenocarcinoma	NOS	85%
	Carcinoma undifferentiated	1%-7%
	Adenosquamous carcinoma	1%-4%
	Undifferentiated carcinoma with osteoclast-like giant cell	< 1%
	Colloid carcinoma	1%-3%
	Poorly cohesive carcinoma	Extremely rare
	Signet-ring cell carcinoma	Extremely rare
	Medullary carcinoma NOS	Extremely rare
	Hepatoid carcinoma	Extremely rare
	Large cell with rhabdoid phenotype	Extremely rare
Acinar cell carcinoma	NOS	< 2%
	Acinar cell cystadenocarcinoma	Extremely rare
	Mixed acinar-neuroendocrine carcinoma	Extremely rare
	Mixed acinar-endocrine-ductal carcinoma	Extremely rare
	Mixed acinar -ductal carcinoma	Extremely rare
Pancreatoblastoma		Extremely rare
Solid pseudopapillary neoplasm	NOS	3%
	With high-grade carcinoma	Extremely rare

NOS: Not otherwise specified.

pancreas. However, these cancers do not usually cause jaundice, and patients typically have several non-specific symptoms, such as weight loss and abdominal pain. Despite this, compared to PDAC, ACC is less likely to have distant disease at diagnosis and is more frequently diagnosed at an earlier stage, allowing for surgical resection in about 38% of patients[7,8].

These tumors seem to be less aggressive than the most common PDAC, even if their prognosis is still poor. In particular, in previously reported series, the mOS of ACC patients ranged from 17 to 19 mo, reaching 47 mo in those who underwent surgical resection[5-9]. Based on a more recent analysis of 57804 PC patients who underwent surgical resection, ACC achieved an mOS of 67.5 mo (51% 5-year OS)[10]. In a few case reports, OS reached up to 123 mo. To date, there are no variables that can help select these patients with long OS. These data might encourage a more aggressive approach for evaluating and treating these tumors[11,12].

Pathology and molecular biology

Macroscopically, ACCs are large tumors, which are frequently well circumscribed and partially encapsulated. The cut surface is usually homogeneous, and pink to tan with a fleshy or friable consistency. Necrosis, cystic evolution, and hemorrhage are sometimes observed. Upon histological examination, the most frequent feature is an acinar pattern, with neoplastic cells arranged in small glandular units, followed by a trabecular, glandular, and solid architecture. Nonetheless, some case series have also shown that ACC can rarely show pleomorphic or spindle cells[4,13,14]. Furthermore, neoplastic cells have a moderate amphophilic to eosinophilic granular cytoplasm rich in zymogen granules, which are usually positive with periodic-acid Schiff and are resistant to diastase. When present, this feature is highly supportive of ACC diagnosis. However, the milestone for diagnosis of ACC is the immunohistochemical identification of pancreatic enzyme. Upon analysis with a specific antibody, trypsin and chymotrypsin can be useful for diagnosis, but B-cell lymphoma/leukemia 10 (BCL-10) shows high specificity[4]. Cytokeratin (CK) 19 and CK 7 can also be expressed, as in PDAC.

Recent studies with whole-exome sequencing, even with the limits of small

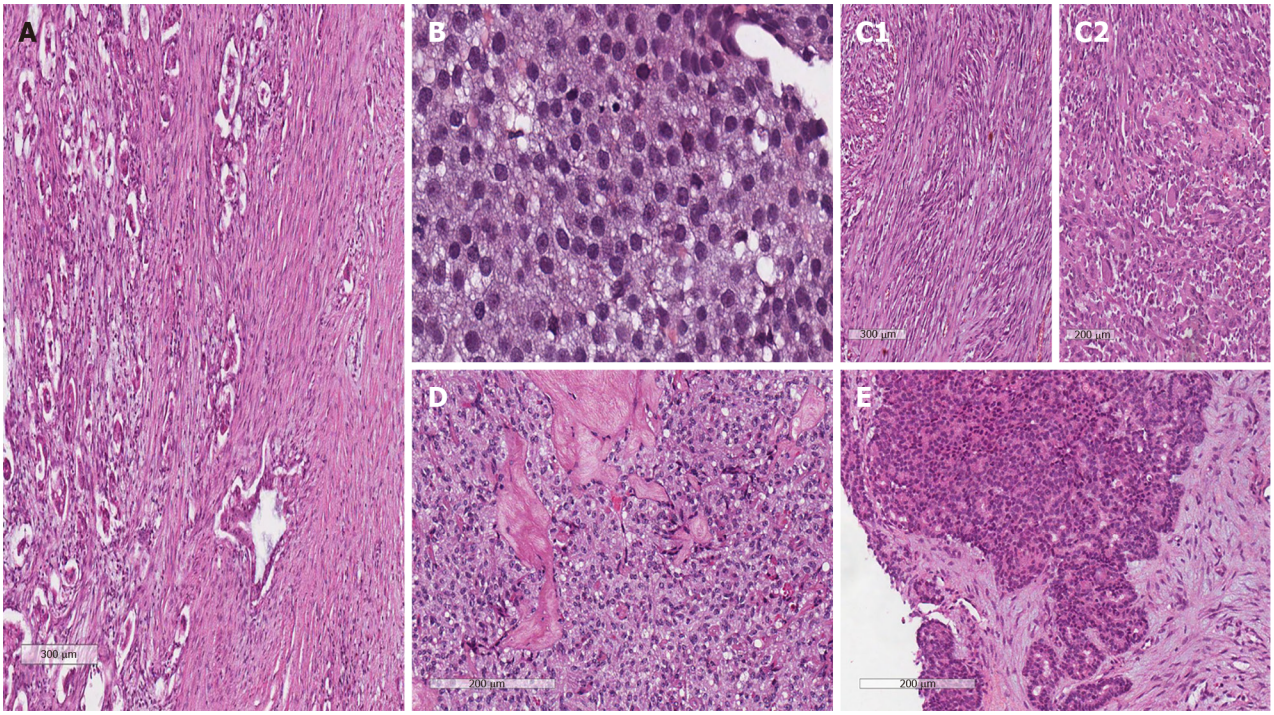

Figure 1 Microscopic anatomopathological characteristics (hematoxylin and eosin stain). A: Ductal adenocarcinoma; B: Acinar cell carcinoma; C1: Undifferentiated carcinoma with spindle cell features; C2: Undifferentiated carcinoma with rhabdoid cells; D: Pseudopapillary; E: Pancreatoblastoma.

numbers, have revealed specific molecular patterns of ACC that apparently differ from those known for PDAC[15-17]. First of all, ACC seems to be characterized by a higher mutational frequency than PDAC, comparable to those of other digestive tract cancer such as colorectal cancer. Additionally, typical PDAC mutations such as *KRAS* are not as frequent in these small series of ACC. In particular, Jiao *et al*[15] analyzed 17 ACCs, identifying somatic mutations in *SMAD4* (23%), *JAK1*, *RB1* or *TP53* (17%) *APC*, *ARID1A*, *GNAS*, *MLL3*, *PTEN*, *FAT4*, and *CTNNB1* (11%) as the most frequent alterations[15]. In addition, Furukawa *et al*[16] described somatic or germline mutations of *BRCA2* (3 of 7 cases) and *FAT* genes (4 of 7 cases)[16]. Finally, Jäkel *et al*[17] showed that ACC is also characterized by chromosomal alterations with a numerous copy number variations, an aberrantly DNA methylation, and downregulation of the tumor suppressor genes *ID3*, *ARIDI1A*, *APC*, and *CDKN2A*, which may be related to the loss of function of DNA repair systems[17]. Chromosomal alterations were well explored in several other studies, which demonstrated *BRAF* (about 20%)[18,19] and *RET* (7.5%) rearrangements[20]. Although these alterations were found in very small series, some of them may be susceptible to targeted therapy, opening the door to possible new treatment developments in ACC.

Imaging

On computed tomography (CT), ACC lesions tend to be large, partially, or completely exophytic and mostly hypodense due to relative hypovascularity in comparison to the surrounding pancreas, on both arterial and venous phase images. A sizeable proportion has an enhancing capsule, cystic, hemorrhage or necrotic component, which may be related to the digestive effect of the pancreatic enzymes released by neoplastic cells[21]. Moreover, lesions located in the pancreas head or uncinate process unfrequently cause severe pancreatic or biliary ductal dilatation[21-24].

On magnetic resonance imaging (MRI), ACC predominantly presents as an oval, large, well-marginated exophytic mass with moderate and heterogeneous enhancement after intravenous administration of contrast. It is frequently characterized by cystic and necrotic areas, and hemorrhage can be observed. Interestingly, ACC is clearly visible in diffuse-weighted MRI, which may be a promising useful tool for ACC diagnosis[23,24].

MRI yields excellent soft tissue contrast and appears to be superior to CT in showing the tumor margin, cystic and necrotic areas, peripancreatic extension, and vascular involvement even without the administration of contrast. Imaging of ACC is so characteristic that it may have a key role in suggesting the diagnosis of this rare

histotype. However, some exceptions have been reported[23].

Treatment

Overall, surgical resection for localized disease remains the only curative treatment. To date, the contribution of adjuvant chemotherapy and radiotherapy has not been well investigated. However, considering the available data, resection and adjuvant chemotherapy are associated with the longest rate of mOS, whereas in some cases, chemoradiation has shown activity in both the neoadjuvant and locally advanced settings[5,8,9,25-28].

In metastatic patients, various first-line treatments have been reported, even if only in small series and case reports. Most of the time, these patients are treated with regimens commonly used for PDAC, such as capecitabine or gemcitabine monotherapy or Gemcitabine- (gemcitabine/nab-paclitaxel, GEMOX) or fluoropyrimidine-based (FOLFOX, FOLFIRI, FOLFIRINOX) regimens. There are very few data available for the second-line setting. In 2002, Holen *et al*[5] published a retrospective monocentric series of 18 patients treated with various regimens: Only 2 patients had a partial response (PR) obtained respectively with FOLFIRI and the combination of cytarabine plus cisplatin and caffeine[5]. In 2011, Lowery *et al*[29] published a new retrospective study, from the same institution, describing the results obtained in 25 patients treated with various regimens in first- and/or second-line. The mOS of patients with metastatic disease was 19.6 mo, with survival up to 57 mo in the 11 patients who had PR or confirmed prolonged stable disease (SD). These patients were treated with GEMOX, gemcitabine-docetaxel-capecitabine, cisplatin plus gemcitabine, gemcitabine plus erlotinib and cisplatin plus irinotecan[29]. The potential activity of regimens containing fluoropyrimidine and/or platin-based compounds was confirmed by Kruger *et al*[30], who reported PR to first- and second-line treatments. In first-line setting, the authors reported PR with FOLFIRINOX in two patients (maintained for up to 14 mo) and with GEMOX and capecitabine in two other patients (maintained for up to about 6 and 13 mo, respectively). In the second-line setting, the objective response was reported in three patients treated with FOLFOX and FOLFIRINOX, with progression-free survival ranging from 9 to 12 mo[30]. This work is not the only report of FOLFIRINOX activity in this setting, as there are at least three case reports in which prolonged SD (time to progression [TTP] of 9 mo) and two PRs were observed[31-33]. Similarly, Yoo *et al*[28] observed a PR in three of four patients treated with FOLFOX in second-line, with 6.5 mo (95%CI, 2.8 to 10.2 mo) of progression-free survival[28]. Finally, in a recent multicenter Italian retrospective study including patients with rare pancreatic histotype tumors, Brunetti *et al*[26] showed that PR was achieved in first-line in 2 of 23 patients treated with GEMOX and gemcitabine-fluorouracil, and in second-line in 1 patient treated with FOLFIRINOX[26].

Regarding the use of single-agent gemcitabine, three small series reported poor activity[28,30,34]. Finally, there have been reports of the potential activity of S-1 in first and second-line settings[34-36].

In conclusion, the published literature shows promising activity of combination treatments, particularly regimens based on fluoropyrimidine and oxaliplatin. In addition, studies have also shown signs of activity for gemcitabine-based regimens, whereas no data support the efficacy of its use as a single agent in the first-line treatment of patients with ACC. As more data regarding molecular classification and alterations involving DNA repair genes arise such as *BRCA2* mutations[16], there is interest in the development of novel therapeutic strategies that can exploit these characteristics.

PSEUDOPAPILLARY

Epidemiology and prognosis

Pseudopapillary tumors (PTs) account for about 3% of all exocrine PCs, with increasing prevalence due to improvements in imaging devices. PTs are more frequent in adolescent girls and young women, with a median age of 28 years at diagnosis, whereas less than 10% of PTs are diagnosed in slightly older men (median age 35). There is no known association with ethnic origin or clinical or genetic syndromes, although very rare cases have been reported in the setting of familial adenomatous polyposis[37]. At diagnosis, PT is characterized by a large round solid or mixed solid cystic lesion frequently located in the pancreatic tail, which may be the reason that patients infrequently experience jaundice. Additionally, there are no specific symptoms of PT and it often presents as a palpable abdominal mass, abdominal

discomfort and pain, nausea, vomiting, asthenia, weight loss, back pain, or pancreatitis.

Despite being counted among malignant pancreatic neoplasms, PTs are considered to be a low-grade, indolent disease. Indeed, only 10% to 15% of cases recur or metastasize and the overall 5-year survival is about 97% even in the presence of metastasis. These survival rates are definitely better and more encouraging than those of PDACs or other aggressive histotypes. Furthermore, the more aggressive cases are often tumors that harbor an undifferentiated component or have peculiar pathological features usually associated with an aggressive behavior such as diffuse growth pattern, high mitotic activity, nuclear atypia, and tumor necrosis[4,38,39].

Pathology and molecular biology

Grossly, PTs appear as large lesions with solid and cystic components, they are usually very soft, but may be firm and sclerotic. They are well-demarcated with a rim of fibrous capsule and adjacent organs invasion is rare[4,40,41]. Cut sections of PT show alternate solid and yellow areas with cystic, necrotic, and hemorrhagic zones which sometimes may be as large as a pseudocyst. Calcifications are also frequently observed[39].

Histologically, the solid component of PT consists of poorly cohesive epithelioid cells with oval nuclei, finely dispersed chromatin low nucleus and either eosinophilic or clear vacuolated cytoplasm and perivascular pseudo papillae. Some of the neoplastic cells contain eosinophilic, diastase-resistant PAS-positive globules of varying size, which may also occur extracellularly, sometimes in large amounts. Glycogen is not prominent and mucin is absent. Mitotic figures might be present, although they are usually rare[4,39,42].

Immunohistochemistry analysis has shown that PT has a low Mib1/Ki67 rate and is positive for beta-catenin (nuclear and cytoplasmic), vimentin, synaptophysin, progesterone receptor (nuclear), CD56, neuron-specific enolase, CD10, and nuclear E-cadherin. Extracellular expression of e-cadherin is lost due to mechanisms that are not clear yet[4,42,43], E-cadherin is a transmembrane protein that has a pivotal role in cell adhesion through interactions with catenins, and its extracellular loss may explain the loss of cell cohesiveness of pseudopapillary pattern[44], making it useful in distinguishing PT from other histotypes[45].

Immunohistochemical beta-catenin overexpression is strongly correlated with mutations of its gene which frequently occur in PT, mostly on exon-3. This mutation leads to hyperactivation of the beta-catenin/Wnt pathway and subsequent activation of the transcription of several oncogenic genes, such as cyclin D1. The consequent deregulation of cell cycle plays an important role in PT development[46-48]. However, several studies have shown that PTs are also characterized by the overexpression of cyclin-dependent kinase inhibitors p21 and p27, which have inhibitory effects on cyclin D1 and its cyclin-dependent kinases complex. Although the mechanism of p21 and p27 upregulation is unknown, it may explain the low growth rate of this rare histotype of PC[48]. By contrast, molecular changes often detected in PDAC, such as alterations of p53 and K-RAS, have not been detected in PT[46].

Imaging

CT features of PT include both solid and cystic lesions without any internal septation, secondary to hemorrhagic degeneration, which are well demarcated by a surrounding capsule. At the margin of the mass, calcification and solid areas can be identified[49,50]. During the CT pancreatic phase, there is weak enhancement compared to the surrounding pancreatic parenchyma, which gradually increases in the hepatic venous phase[51]. Atypical PTs on CT have no surrounding capsule, solid or cystic component, with hyperattenuation during the pancreatic phase and dense internal calcification with no defined margin[51].

Otherwise, on MRI, PT is defined as an encapsulated lesion with both a solid and cystic component as well as hemorrhage without internal septation[52]. Interestingly, Yu *et al*[52] proposed an MRI classification in which PT lesions were separated in three main classes by specific MRI features on T1- and T2-weighted images related to the predominance of solid or hemorrhagic areas. According to their study, MRI may be considered superior to CT in terms of correlation of clinicopathological and radiological findings of PT[52].

Treatment

For localized disease, surgery is the treatment of choice and more than 95% of patients can be cured after radical resection. Due to the favorable behavior of this disease,

surgery with organ preservation is indicated when feasible[53]. Moreover, since evidence of lymph node metastasis is extremely rare[42,54] a formal lymphadenectomy should not be routinely performed[42,53]. Considering the excellent long-term prognosis even for metastatic disease, which is mostly confined to the liver, mesentery, and peritoneum, surgical approaches[53,55] or locoregional treatments[56] are reported to be potentially effective even in this setting, with a high 5-year survival rate with en bloc resection of locally progressed PTs or with synchronous or metachronous resection of distant metastases[57-60]. Furthermore, in highly selected cases, even orthotopic liver transplantation (OLT) may be taken into account for patients with unresectable liver metastases. To date, four cases of patients with liver metastatic PT who underwent OLT have been published. In the first two reports, young 14- and 21-year-old patients with PTs and multiple unresectable hepatic metastases were successfully treated with partial liver transplantation from a living donor without any sign of disease recurrence after 2 years of follow up[61,62]. Longer recurrence-free survival was later reported by Łągiewska *et al*[63], whose patient was free of disease after 5 years from cadaveric OLT. However, in two other patients, disease recurred within 1 and 4 years[64,65].

There are only anecdotal data on the role of systemic treatment in neoadjuvant, adjuvant and metastatic settings. Tumor response to preoperative chemotherapy using cisplatin in combination with 5-fluorouracil (5-FU) or gemcitabine were reported[66-68]. Similar results were observed in a patient treated with a combination of etoposide, cisplatin, cyclophosphamide, doxorubicin, and vincristine[54] and combination of cisplatin, ifosfamide, etoposide, and vincristine followed by intraoperative radiofrequency ablation[69]. By contrast, no response to multiple agents was seen in another case report[58]. Radiotherapy showed activity in a single case of a locally advanced unresectable disease[70].

Regarding the metastatic setting, in a small series, Brunetti *et al*[26] treated two patients with GEMOX, achieving 1 SD and 1 progressive disease (PD) with a TTP of 5 and 2 mo, respectively: One patient received first-line treatment with gemcitabine plus 5-FU with SD, and the last one interestingly achieved a 22-mo SD with single agent gemcitabine[26]. In the same study, those patients who progressed to GEMOX received second line with gemcitabine plus 5-FU with SD reaching a TTP of 9 and 8 mo, respectively. Similar results were also observed with capecitabine used as second line after progression to gemcitabine plus 5-FU with SD and a TTP of 6 mo[26]. Moreover, Morikawa *et al*[71] described a case of a patient treated with paclitaxel as second line after S1 and gemcitabine, who was alive and without progression after 20 mo of follow-up[71]. The low malignant potential of PT was also confirmed by an interesting case of a patient with long survival after several lines of treatment: gemcitabine alone (6 cycles), gemcitabine plus irinotecan (3 cycles), oxaliplatin plus irinotecan and capecitabine (8 cycles), gemcitabine plus capecitabine (6 cycles), weekly 5-FU and lastly, until publication of the data, capecitabine alone[72].

UC

Epidemiology and prognosis

UC is a histological variant of PDAC that accounts for 1% to 7% of all exocrine PCs. Anaplastic, sarcomatoid, and carcinosarcomas are recognized morphological variants of UC composed of pleomorphic mononuclear cells admixed with bizarre giant cells or spindle and rhabdoid cells. UC of the pancreas has been defined as an epithelial neoplasm without a definitive direction of differentiation with a diffuse sheet-like growth pattern without overt glandular differentiation. UC with osteoclast like giant cells (OCGC) is another histologic subtype of PDAC, with different morphologic features and clinical behavior. UC is usually diagnosed at a median age of 61 years and tends to be more frequent in males and Caucasians. At diagnosis, it is observed as a bulky tumor, usually involving the pancreatic head. Its clinical presentation is similar to that of PDAC and is characterized by abdominal pain, jaundice, weight loss, and fatigue[73-76]. In addition, anemia and elevated leukocyte count have been reported, possibly related to hemorrhage and necrosis that follow the rapid and uncontrolled tumor growth[75]. Some authors also reported increased secretion of granulocyte colony-stimulating factor, which may contribute to leukocytosis and is correlated with a worse prognosis[75,77,78]. However, even with some discrepancies in the literature, cancer antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) levels are reportedly lower than those found in PDAC[74].

Considering the rarity and aggressive behavior of this histotype, survival data about UC are mostly represented by single case reports or small case series. To date, there

are no large prospective clinical studies. The overall prognosis of patients affected by UC appears to be worse than those affected by PDAC, with a median OS of about 5.5 mo. There are reports of advanced patients dying within weeks from the onset of symptoms. However, patients who undergo surgical resection have a mOS similar to that of PDAC[74,75,79]. Several reports have shown that among UC patients, those with OCGC tend to have a longer survival. This may be related to the more indolent biological behavior of this specific subtype, which allows a higher rate of curative resections or slower disease progression in the metastatic setting[73,75,79,80].

Pathology and molecular biology

Since the first description in 1954, UC has been described using various terms including anaplastic, spindle cell, giant cell, pleomorphic giant cell, and round cell. In 2019, the WHO classified this heterogeneous neoplasm as a subtype of PDAC under the name of UC[4]. As mentioned above, however, OCGC is described as a separate variant of PDAC due to its different biological and clinical behaviors.

Macroscopic examination of UC has shown that it can be a large solid or cystic lesion, or a mixture of both. Cystic evolution is consequent to the rapid uncontrolled growth of neoplastic cells that are highly prone to degeneration, hemorrhage, and necrosis. This feature may help to distinguish UC from PDAC, in which cystic components are infrequent (< 1%). The histological examination of UC is remarkably heterogeneous and characterized by the presence of pleomorphic and/or spindle cells, whose predominance differentiates the two main subtypes (anaplastic UC/sarcomatoid UC), which grow in poorly cohesive nests supported by scanty fibrous stroma. Pleomorphic cells are usually arranged in solid sheets without gland formation showing markedly pleomorphic nuclei and abundant eosinophilic cytoplasm. On the contrary, spindle cells tend to arrange in a storiform pattern and to be more uniform, ovoid to spindle shaped. Furthermore, areas of infiltrating ductal adenocarcinoma at the periphery of the lesions, squamous differentiation, and areas of phagocytic activity are frequently observed[73,81,82]. Although this bizarre morphology, electron microscopy, and above all, immunohistochemistry analysis have demonstrated the epithelial origin of UC neoplastic cells. In particular, similar to PDAC, these cells express CKs such as CK7, CK8, CK18 and CK19. Vimentin, CA 19.9, CEA, and p53 may also be expressed. In addition, similar to PDAC, KRAS point mutations are frequently observed upon molecular analysis[73,82]. Although further studies are still needed, these specific features support the hypothesis that these cells may be the result of a dedifferentiation process of a preceding ductal adenocarcinoma.

On the other end, UC with OCGC is defined by the abundance of non-neoplastic osteoclast-like multinucleated giant cells admixed with a mononuclear histiocytic component and a neoplastic mononuclear cell component[4]. OCGC is frequently located in the junction between necrotic hemorrhagic areas and viable areas of the tumor. Abundant hemosiderin pigment is scattered throughout the tumor; moreover, osteoid formation and foci of *in situ* or invasive adenocarcinoma may also be found. To date, the real origin of these cells is still not clear. In contrast to pleomorphic and spindle cells, OCGC is immunohistochemically negative for CKs, but positive for histiocytic markers, supporting the hypothesis of a histiocytic origin. Indeed, some authors have hypothesized that OCGC may result from the fusion of histiocyte/macrophages chemoattracted to the tumor site by factors released by neoplastic cells, and this may be the reason why phagocytic areas are commonly described[83]. Neoplastic cells may be spindle-shaped or epithelioid and can be very large and pleomorphic; these cells can show keratin positivity and have a high Ki-67 proliferation index.

Imaging

In reported imaging series, on enhanced CT scan, UC is described as a large mass, usually in the pancreatic head, with relative hypodensity compared to normal parenchyma during the pancreatic and portal vein phases, with a peripheral contrast enhancement. Therefore, it may sometimes be difficult to distinguish UC from cystic lesions. Additionally, pancreatic duct dilatation and rare calcifications was observed[84-86].

At MRI, several authors have described UC as a well-defined lesion with low intensity on T1-, T2-, and diffusion-weighted images. This last feature, in particular, may be related to hemosiderin deposits on mononuclear histiocytic and OCGC and may be helpful for the differential diagnosis between UC and cystic lesions, in which hemorrhage and hemosiderin deposits are unusual. Calcifications are also occasionally described[85,86].

Treatment

To date, there is no a standard treatment for UC. For patients with resectable disease, surgery represents the only curative option, with a survival rate that is comparable with that of patients with PDAC who undergo R0 resection. No significant benefits have been reported for neoadjuvant/adjuvant treatments or palliative surgery[74,87].

For advanced disease, only few case reports with various systemic treatment have been reported[80,87]. For example, Wong *et al*[88] treated a patient with GEMOX in combination with radiofrequency ablation of liver metastases, reaching SD with an OS of 15 mo[88]. Gemcitabine-base regimes was also explored by Brunetti *et al*[26], who reported PR with an OS of 14 mo and SD with OS of 8 mo in two patients treated with gemcitabine plus nab-paclitaxel. Furthermore, there are case reports showing benefits of first-line and second-line therapy with FOLFIRINOX[89] and FOLFIRI[90], respectively. Finally, an interesting approach presented by Wakatsuki *et al*[91]. In their case report, paclitaxel as a single agent was selected to treat the patient, using a chemosensitivity test with the adenosine triphosphate assay achieving a complete response after two cycles and a disease-free survival of 23 mo[91].

PANCREATOBLASTOMA

Epidemiology and prognosis

Pancreatoblastoma (PBL) presents more often in children, where it accounts for 25% of all pancreatic tumors[92], whereas it is an extremely rare histotype in adults, accounting for less than 1% of PC. In the few series available in English literature (accounting for < 100 patients in total), PBL typically appears as a large tumor (up to 20 cm), which is more frequently localized in the pancreatic head. It usually presents with nonspecific signs and symptoms such as abdominal pain, abdominal mass, jaundice, weight loss, chronic diarrhea and upper gastrointestinal bleeding[93-96]. The prognosis is poor, with an mOS of 5 mo in patients who cannot undergo surgery. About 40% of patients are metastatic at diagnosis, with the liver being the most common site of secondary involvement; local infiltration of surrounding tissues is also frequent[97]. Of note, even if PBL is considered to be a sporadic tumor, there have been reports of its association with familial adenomatous polyposis syndrome[93,98] and Beckwith-Weidemann syndrome[99].

Pathology and molecular biology

There are two populations of cells with distinctive characteristics: blast-like tumor cells and squamous morules. In particular, blast-like cells are monotonous, round, and small (1.5-2.0 times the size of a red blood cell), with a high nuclear-to-cytoplasmic ratio, scant cytoplasm, and infrequent anisonucleosis. Focal nuclear molding and crushing resembling small-cell carcinoma are seen in all cases. Abnormal mitotic figures were occasionally described in a case with metastatic disease with a poor prognosis (< 10 d). The immunohistochemical staining was positive for trypsin, chymotrypsin, lipase, BCL10 and alpha-fetoprotein. Squamous morules were seen in 75% of patients. They were composed of whorling or streaming epithelioid cells with abundant, dense, granular cytoplasm; syncytial arrangement; low nuclear to cytoplasmic ratio; and elongated nuclei with blunted ends and vesicular chromatin. Morule overexpress estrogen receptor beta and have aberrant nuclear/cytoplasmatic B catenin staining. Aberrant Wnt pathway activation manifest as somatic *CTNNB1* mutations (in 90% of cases) and loss of heterozygosity (LOH) of *APC* (in 10%). Other abnormalities include upregulation of the R-spondin/LGR5/RNF43 module, a progenitor-like pancreatic cell expression profile, and LOH of chromosome 11p. APC/β-catenin pathway alterations are seen in patients with and without familial adenomatous polyposis. Another syndrome seen in childhood PBL is Beckwith-Wiedemann syndrome, which is also associated with chromosome 11p LOH.

Previous data on nine case of pancreatoblastoma showed in 78% of cases strong nuclear and cytoplasmic accumulation of b-catenin protein, 86% had LOH for TH and D11S1984, microsatellite markers near the WT-2 locus on chromosome 11p15.5. There is frequent involvement of the APC/β-catenin pathway, with no evidence for *KRAS* mutations or *TP53* tumor suppressor gene alterations[98,100].

Imaging

On ultrasound, PBL appears as a solid inseparable pancreatic mass, with mixed echotexture[101]. On CT scan, it is usually a large, well-circumscribed, and

heterogeneous mass, with both solid and cystic components[102]. MRI can be used to delineate intratumoral hemorrhage and necrotic areas.

Treatments

Due to the rarity of this histology there is no guideline regarding treatment for this cancer. The only curative therapy remains surgical resection. The role of postoperative chemoradiotherapies is still unclear and there is no consensus on the best chemo regimen neither in adjuvant nor in palliative setting. There are clinical case reports describing the use of regimens containing platinum and/or doxorubicin and fluorouracil (*e.g.*, cisplatin/vincristine/bleomycin, 5-FU/doxorubicin/mitomycin, doxorubicin/carboplatin, cisplatin/doxorubicin), with mixed results[103,104]. Furthermore, there are reports of long-term disease-free survival for patients with liver metastases undergoing surgical resection of primary and metastatic lesions, suggesting a role for aggressive surgical approach[105,106].

ADENOSQUAMOUS CARCINOMA AND SQUAMOUS CELL PANCREATIC CARCINOMA

Epidemiology and prognosis

Adenosquamous pancreatic cancer (ASPC) accounts for about 1%-4% of all pancreatic cancer and it is defined as a mixture of the adenocarcinoma and the squamous cell carcinoma components[107]. Based on data from the National Cancer Database and Surveillance, Epidemiology and End Results database, ASPC tends to be larger, more frequently in body/tail, undifferentiated and in early stage at diagnosis time[108,109]. When compared to the 205328 PDAC present in the NCBD, overall prognosis of the 1745 ASPC is similarly poor, with a mOS of 5.7 mo. In patients who underwent surgery, ASCP had worse OS (14.8 mo *vs* 20.5 mo, $P < 0.001$) than PDAC, unless there was negative lymph node status, R0 surgical resection, and receipt of chemotherapy[109]. In surgical patients retrieved from the Surveillance, Epidemiology and End Results database between 2004 and 2015, mOS was 12 mo, with a median cancer specific survival of 16 mo.

Pure primary pancreatic squamous cell carcinoma is extremely rare and accounts for 0.5% to 5% of all exocrine PC. It is characterized by a worse prognosis than PDAC, with reported overall mOS of about 4-7 mo. Squamous cell carcinoma is more frequently located in the head of the pancreas, commonly presenting with pain, weight loss and jaundice. More than half of patients are diagnosed in stage IV, with liver being the most frequent site of metastasis, and the median age at diagnosis is 69 years[10,110,111].

Pathology and molecular biology

Squamous differentiation in PC usually occurs in association with conventional PDAC, in which a squamous component of at least 30% of the neoplasm should be detected in order to classify it as an adenosquamous carcinoma[4].

On macroscopy, ASPC made of is yellowish-white to gray, firm masses. Common findings are central necrosis and cystic degeneration.

Histologically, the adenocarcinoma component forms glandular structures, while squamous differentiation is detected by sheets of cells with distinct cellular borders, prominent intercellular junctions, dense eosinophilic cytoplasm and keratinization, expressing p63, p40 and low molecular weight cytokeratins[4].

The immunohistochemistry analysis demonstrate loss of p16 protein expression and strong reactivity for p53, with a profile similar to PDAC[4].

Almost all cases harbor *KRAS* mutation at codon 12 and *TP53* mutations. There are reports showing that the adenous and the squamous part of the adenosquamous cancer had similar molecular alterations, suggesting that the two components may results from the same progenitor cancer cell origin[112].

The angiogenic pattern appears to be more active in ASCP than PDAC[113], while there are data showing high PD-L1 expression mostly in the squamous cell carcinoma component of ASPC[114].

Of note, in the integrated evaluation about histopathological pancreatic cancer and whole-genome and deep-exome sequencing of PC, ASCPs were mostly represented in the squamous subtype, that was also an independent poor prognostic factor[115]. Squamous tumors are characterized by alterations in four core gene programs, including gene networks involved in inflammation, hypoxia response, metabolic

reprogramming, TGF-β signaling, MYC pathway activation, autophagy and upregulated expression of TP63ΔN and its target genes.

Imaging

ASPC is a hyper-vascular tumor. On CT scan with contrast enhancement, it appears as a large well defined predominantly solid and lobulated mass with ring enhancement in the peripheral area and central necrosis. Patients with vessel invasion have a poor prognosis[116].

Usually ASPC presents as a large mass in the pancreatic tail; small adenosquamous lesions appear to be more frequently in the head of pancreas. Venous tumor thrombus was seen only in large masses[117].

At CT scan hypervascularity can be observed. Fajardo *et al*[118] reported the use of dynamic CT scan with a bolus injection of intravenous contrast to examine a patient with pancreatic squamous cell carcinoma: the attenuation of this tumor increased from 35 HU to 61 HU[118].

Treatment

As per the other types of PC, surgical resection is the only curative approach for ASPC and SCC , that can significantly improve survival[107,110,119,120]. Patients affected by ASPC or SCC undergoing surgery and post-operative treatment with chemotherapy, radiotherapy or both appear to have a benefit[108,121-123], even though there is no consensus regarding the best regimen to use, that are commonly fluoropyrimidine-based, gemcitabine based or platinum-based. Data from Johns Hopkins Hospital show, in particular, benefit for ASPC patients treated with platinum-based chemotherapy, with a mOS of 19.1 mo[121].

In the metastatic setting, several chemotherapy regimens are reported to be active, including fluoropyrimidine-, gemcitabine- or platinum-based therapy[124-127]. For instance, Brunetti *et al*[26] and De Souza *et al*[128] reported 1 PR each in patients affected by ASPC treated with gemcitabine and GEMOX, respectively, and SD maintained for 10 mo, 9 mo and 8 mo in patients treated with gemcitabine, FOLFOXIRI and cisplatin + gemcitabine, respectively.

CONCLUSION

Despite the increase of retrospective case series and data regarding rare histological subtypes of PC that can help in their diagnosis, there are still many unanswered questions about the management of these cancers, due to the absence of prospective trials or guidelines. For clinicians facing these patients in their real-life routine, the key question is whether they have to be approached and treated in the same way as the more common PDAC or if they need to have a specific strategy. As described above, if taken singularly, these histotypes may differ significantly from PDAC, especially in terms of prognosis. While ASPC has a similar prognosis to PDAC and SCC appears in some reports to have even worse outcomes, the natural history of a patient with PT or ACC can be radically different, considering the unequivocal survival advantage showed in these subtypes[129]. Based on the analysis of 57804 PC patients who underwent surgical resection, the mOS of PDAC and ACC is 20.2 mo (22% 5-year OS) and 67.5 mo (51% 5-year OS), respectively, while the mOS of resected PT is not even reached (97% 5-year OS)[10]. This consideration alone may justify for a more aggressive surgical approach for these tumors than what we are used to consider for PDAC, with special interest to the possible benefit reported for the surgical resection of metastatic disease. On the contrary, the poor prognosis and aggressive behavior of UC, ASPC and SCC must be taken in consideration for the treatment strategy of these tumors.

Finally, for the majority of these subtypes, there are no clear data regarding chemosensitivity and the role of specific chemotherapy regimens both for locoregional and advanced disease. Nevertheless, we tried to summarize the most relevant data that, to the best of our knowledge, can give some inputs for clinical decision-making.

Even if the very low incidence of these malignancies makes it almost impossible to design and run prospective clinical trials, we believe that multi center collaborations are essential, in order to gather as much homogeneous information as possible leading to a more histotype-guided therapeutic approach to these cancers.

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