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

Monica Niger, Michele Prisciandaro, Maria Antista, Melissa Anna Teresa Monica, Laura Cattaneo, Natalie Prinzi, Sara Manglaviti, Federico Nichetti, Marta Brambilla, Martina Torchio, Francesca Corti, Sara Pusceddu, Jorgelina Coppa, Vincenzo Mazzaferro, Filippo de Braud, Maria Di Bartolomeo

ORCID number: Monica Niger 0000-0002-9055-5338; Michele Prisciandaro 0000-0001-5596-469X; Maria Antista 0000-0002-6153-1863; Melissa Anna Teresa Monica 0000-0003-1773-9058; Laura Cattaneo 0000-0001-8890-719X; Natalie Prinzi 0000-0002-6261-7239; Sara Manglaviti 0000-0003-2693-0743; Federico Nichetti 0000-0001-8044-4207; Marta Brambilla 0000-0003-1148-7056; Martina Torchio 0000-0001-7529-6668; Francesca Corti 0000-0001-5245-0860; Sara Pusceddu 0000-0002-5096-660X; Jorgelina Coppa 0000-0003-2466-0524; Vincenzo Mazzaferro 0000-0002-4013-8085; Filippo de Braud 0000-0003-0103-730X; Maria Di Bartolomeo 0000-0002-7954-6609.

Author contributions: Niger M designed and wrote the final version of the manuscript; Antista M, Prisciandaro M, Niger M, Monica MAT, and Cattaneo L were critical for the acquisition of data and drafting the manuscript; Prinzi N, Manglaviti S, Coppa J, Brambilla M, Torchio M, Corti F, Nichetti F, and Pusceddu S contributed to the analysis and interpretation of the literature; Mazzaferro V, de Braud F, and Di Bartolomeo M made critical revisions to the design and gave final approval for the article to be submitted.

Monica Niger, Michele Prisciandaro, Maria Antista, Natalie Prinzi, Sara Manglaviti, Federico Nichetti, Marta Brambilla, Martina Torchio, Francesca Corti, Sara Pusceddu, Filippo de Braud, Maria Di Bartolomeo, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan 20133, Italy

Melissa Anna Teresa Monica, Laura Cattaneo, First Pathology Division, Department of Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan 20133, Italy

Jorgelina Coppa, Vincenzo Mazzaferro, Hepato-biliary-pancreatic Surgery and Liver Transplantation Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan 20133, Italy

Vincenzo Mazzaferro, Filippo de Braud, Università degli studi di Milano, Milan 20133, Italy

Corresponding author: Maria Di Bartolomeo, MD, Doctor, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giacomo Venezian 1, Milan 20133, Italy. maria.dibartolomeo@istitutotumori.mi.it

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...
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

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Citation: Niger M, Prisciandaro M, Antista M, Monica MAT, Cattaneo L, Prinzi N, Manglaviti S, Nichetti F, Brambilla M, Torchio M, Corti F, Pusceddu S, Coppa J, Mazzaferro V, de Braud F, Di Bartolomeo M. One size does not fit all for pancreatic cancers: A review on rare histologies and therapeutic approaches. World J Gastrointest Oncol 2020; 12(8): 833-849

URL: https://www.wjgnet.com/1948-5204/full/v12/i8/833.htm

DOI: https://dx.doi.org/10.4251/wjgo.v12.i8.833

**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 anatomicopathological characteristics[5] (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]. 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
One size does not fit all for pancreatic cancers

## 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[6-9]. 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 homogenous, 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[8,13,14]. Furthermore, neoplastic cells have a moderate amphiphilic 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[10]. 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
numbers, have revealed specific molecular patterns of ACC that apparently differ from those known for PDAC\(^\text{[15-17]}\). 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\(^\text{[15]}\). In addition, Furukawa et al\(^{[16]}\) described somatic or germline mutations of BRCA2 (3 of 7 cases) and FAT genes (4 of 7 cases)\(^\text{[16]}\). 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, ARID1A, APC, and CDKN2A, which may be related to the loss of function of DNA repair systems\(^\text{[17]}\). Chromosomal alterations were well explored in several other studies, which demonstrated BRAF (about 20%)\(^{[18,19]}\) and RET (7.5%) rearrangements\(^\text{[20]}\). 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\(^\text{[21]}\). 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
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.

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 capcitabine 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. 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 capecitabine. In 2011, Lowery et al. 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. The potential activity of regimens containing fluoropyrimidine and/or platin-based compounds was confirmed by Kruger et al., 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 capcitabine 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. 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. Similarly, Yoo et al. 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. Finally, in a recent multicenter Italian retrospective study including patients with rare pancreatic histotype tumors, Brunetti et al. 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.

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

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, there is interest in the development of novel therapeutic strategies that can exploit these characteristics.

Pseudopapillary tumors (PTs) account for about 3% of all exocrine PC, 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. 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.

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. 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.

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.

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. 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, making it useful in distinguishing PT from other histotypes.

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. 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. By contrast, molecular changes often detected in PDAC, such as alterations of p53 and K-RAS, have not been detected in PT.

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. During the CT pancreatic phase, there is weak enhancement compared to the surrounding pancreatic parenchyma, which gradually increases in the hepatic venous phase. 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.

Otherwise, on MRI, PT is defined as an encapsulated lesion with both a solid and cystic component as well as hemorrhage without internal septation. Interestingly, Yu et al. 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.

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\cite{57}. Moreover, since evidence of lymph node metastasis is extremely rare\cite{62} a formal lymphadenectomy should not be routinely performed\cite{63}. Considering the excellent long-term prognosis even for metastatic disease, which is mostly confined to the liver, mesentry, and peritoneum, surgical approaches\cite{64,65} or locoregional treatments\cite{66,67} 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 and with synchronous or metachronous resection of distant metastases\cite{58,59}. 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\cite{68,69}. Longer recurrence-free survival was later reported by Łągiewska et al\cite{70}, whose patient was free of disease after 5 years from cadaveric OLT. However, in two other patients, disease recurred within 1 and 4 years\cite{68,69}.

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\cite{71,72}. Similar results were observed in a patient treated with a combination of etoposide, cisplatin, cyclophosphamide, doxorubicin, and vincristine\cite{73} and combination of cisplatin, ifosfamide, etoposide, and vincristine followed by intraoperative radiofrequency ablation\cite{74}. By contrast, no response to multiple agents was seen in another case report\cite{75}. Radiotherapy showed activity in a single case of a locally advanced unresectable disease\cite{76}.

Regarding the metastatic setting, in a small series, Brunetti et al\cite{77} 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\cite{78}. 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\cite{79}. Moreover, Morikawa et al\cite{80} 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\cite{81}. 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\cite{82}.

**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 (OCCG) 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\cite{83,84}. In addition, anemia and elevated leukocyte count have been reported, possibly related to hemorrhage and necrosis that follow the rapid and uncontrolled tumor growth\cite{85}. Some authors also reported increased secretion of granulocyte colony-stimulating factor, which may contribute to leukocytosis and is correlated with a worse prognosis\cite{86-88}. 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\cite{89}.

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. 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.

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. 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. 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. 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. 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 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. 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.

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 observed.
**PANCREATOBLASTOMA**

**Epidemiology and prognosis**
Pancreatoblastoma (PBL) presents more often in children, where it accounts for 25% of all pancreatic tumors\[^{91}\], 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\[^{87}\]. 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\[^{92}\]. Of note, even if PBL is considered to be a sporadic tumor, there have been reports of its association with familial adenomatous polyposis syndrome\[^{93}\] and Beckwith-Weidemann syndrome\[^{94}\].

**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/cytoplasmic 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\[^{88,90}\].

**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. 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. 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.

**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. 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. 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, ASPC 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. 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.

**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.

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.

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

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.

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

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.

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 TP63∆N 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. 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.

At CT scan hypervascularity can be observed. Fajardo et al. 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.

**Treatment**

As per the other types of PC, surgical resection is the only curative approach for ASPC and SCC, that can significantly improve survival. Patients affected by ASPC or SCC undergoing surgery and post-operative treatment with chemotherapy, radiotherapy or both appear to have a benefit, 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.

In the metastatic setting, several chemotherapy regimens are reported to be active, including fluoropyrimidine-, gemcitabine- or platinum-based therapy. For instance, Brunetti et al. and De Souza et al. 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. 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). 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.
REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]
2 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424 [PMID: 30207393 DOI: 10.3322/caac.21492]
3 Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients with Neuroendocrine Tumors in the United States. JAMA Oncol 2017; 3: 1335-1342 [PMID: 28448665 DOI: 10.1001/jamaoncol.2017.0589]
4 International Agency for Research on Cancer. WHO classification of tumours of the digestive system: International Agency for Research on Cancer, 2019. 5th ed. In: Tumours of the pancreas. World Health Organization, 2019; 295-370
5 Holen KD, Klimstra DS, Hummer A, Gonen M, Conlon K, Brennan M, Saltz LB. Clinical characteristics and outcomes from an institutional series of acinar cell carcinoma of the pancreas and related tumors. J Clin Oncol 2002; 20: 4673-4678 [PMID: 12488412 DOI: 10.1200/jco.2002.02.007]
6 Kitagami H, Kondo S, Hirano S, Kawakami H, Egawa S, Tanaka M. Acinar cell carcinoma of the pancreas: clinical analysis of 115 patients from Pancreatic Cancer Registry of Japan Pancreas Society. Pancreas 2007; 35: 42-46 [PMID: 17575544 DOI: 10.1097/00000478-199208000-00001]
7 Wisnoski NC, Townsend CM Jr, Nealon WH, Freeman JL, Riall TS. 672 patients with acinar cell carcinoma of the pancreas: a population-based comparison to pancreatic adenoscarcinoma. Surgery 2008; 144: 141-148 [PMID: 1865619] DOI: 10.1016/j.surg.2008.03.006]
8 Schmidt CM, Matos JM, Bentrem DJ, Talamonti MS, Lillemoe KD, Bilimoria KY. Acinar cell carcinoma of the pancreas in the United States: prognostic factors and comparison to ductal adenocarcinoma. J Gastrointest Surg 2008; 12: 2078-2086 [PMID: 18387684 DOI: 10.1016/j.jsg.2007.08.006]
9 Glazer ES, Neill KG, Frakes JM, Coppola D, Hodul PJ, Hofie SE, Pimiento JM, Springett GM, Malafa MP. Systematic Review and Case Series Report of Acinar Cell Carcinoma of the Pancreas. Cancer Control 2016; 23: 446-454 [PMID: 27842335 DOI: 10.1177/1073274916650041]
10 Pokrzywa CJ, Abbott DE, Maatkovskij KA, Romnekiev-Kelly SM, Winslow ER, Weber SM, Fisher AV. Natural History and Treatment Trends in Pancreatic Acinar Subtypes. J Gastrointest Surg 2019; 23: 768-778 [PMID: 3070676 DOI: 10.1007/s11605-019-04113-2]
11 Armstrong MD, Von Hoff D, Barber B, Marlow LA, von Roemeling C, Cooper SJ, Travis P, Campbell E, Paz-Fumagalli R, CoplandJA, Colon-Otero G. An effective personalized approach to a rare tumor: prolonged survival in metastatic pancreatic acinar cell carcinoma based on genetic analysis and cell line development. J Cancer 2011; 2: 142-152 [PMID: 21475719 DOI: 10.7150/jca.2.142]
12 Suzuki A, Sakaguchi T, Moriita Y, Oishi K, Fukumoto K, Inaba K, Takehara Y, Baba S, Suzuki S, Kenno H. Long-term survival after a repetitive surgical approach in a patient with acinar cell carcinoma of the pancreas and recurrent liver metastases: report of a case. Surg Today 2010; 40: 679-683 [PMID: 20582524 DOI: 10.1007/s00595-009-1426-0]
13 Klimstra DS, Heffess CS, Oertel JE, Rosai J. Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. Am J Surg Pathol 1992; 16: 815-837 [PMID: 1384374 DOI: 10.1097/00000478-199209000-00001]
14 La Rosa S, Fessa F, Capella C. Acinar Cell Carcinoma of the Pancreas: Overview of Clinicopathologic Features and Insights into the Molecular Pathology. Front Med (Lausanne) 2015; 2: 41 [PMID: 26137463 DOI: 10.3389/fmed.2015.00041]
15 Jiao Y, Yonescu R, Offerhaus GJ, Klimstra DS, Maitra A, Eshleman JR, Herman JG, Poh W, Pelosi L, Wolfgang CL, Vogelstein B, Kinzler KW, Hruban RH, Papadopoulos N, Wood LD. Whole-exome sequencing of pancreatic neoplasms with acinar differentiation. J Pathol 2014; 232: 428-435 [PMID: 24293923 DOI: 10.1002/path.4310]
16 Furukawa T, Sakamoto H, Takeuchi S, Ameri M, Kuboki Y, Yamamoto T, Hatori T, Yamamoto M, Sugiyama M, Ohike N, Yamaguchi H, Shimizu M, Shibata N, Shimizu K, Shiratori K. Whole exome sequencing reveals recurrent mutations in BRCA2 and FAT genes in acinar cell carcinomas of the pancreas. Sci Rep 2015; 5: 8829 [PMID: 25743105 DOI: 10.1038/srep08829]
17 Jäkel C, Bergmann F, Toth R, Assenov Y, van der Duijn D, Strelow O, Hank T, Klöppel G, Dorrell C, Grompe M, Moss J, Dor Y, Schirmacher P, Plass C, Popand O, Schneese P. Genome-wide genetic and epigenetic analyses of pancreatic acinar cell carcinomas reveal aberrations in genome stability. Nat Commun 2017; 8: 1323 [PMID: 29109526 DOI: 10.1038/s41467-017-01118-x]
18 Chmieliecki J, Hutchinson KE, Frampton GM, Chalmers ZR, Johnson A, Shi C, Elvin J, Ali SM, Ross JS, Basturk O, Balasubramanian S, Lipson D, Yelensky R, Pao W, Miller VA, Klimstra DS, Stephens P. Comprehensive genomic profiling of pancreatic acinar cell carcinomas identifies recurrent RAF fusions and frequent inactivation of DNA repair genes. Cancer Discov 2014; 4: 1398-1405 [PMID: 25266736 DOI: 10.1158/2159-8290.CD-14-0617]
19 Wang L, Basturk O, Wang J, Benayed R, Middha S, Zehir A, Linkov I, Rao M, Aryeequaye R, Cao L, Chmieliecki J, Ross J, Stephens PJ, Adsay V, Askam G, Balci S, Klimstra DS. A FISH assay efficiently screens for BRAF gene rearrangements in pancreatic acinar-type neoplasms. Mod Pathol 2018; 31: 132-140 [PMID: 28884748 DOI: 10.1038/modpathol.2017.106]
20 Chou A, Brown IS, Kumarasinghe MP, Perren A, Riley D, Kim Y, Pajic M, Steinmann A, Rathiv, Jamieson NB, Verheij J, van Roesss S, Nahm CB, Mittal A, Samra J, Gill AJ. RET gene rearrangements occur in a subset of pancreatic acinar cell carcinomas. Mod Pathol 2020; 33: 657-664 [PMID: 31558734 DOI: 10.1038/s41379-019-0115-v]
21 Liu K, Peng W, Zhou Z. The CT findings of pancreatic acinar cell carcinoma in five cases. Clin Imaging 2013; 37: 302-307 [PMID: 23465983 DOI: 10.1016/j.clinimag.2012.06.003]
22 Raman SP, Hruban RH, Cameron JL, Wolfgang CL, Kawamoto S, Fishman EK. Acinar cell carcinoma of the pancreas: computed tomography features—a study of 15 patients. Abdom Imaging 2013; 38: 137-143
Pancreatic neuroendocrine tumor and solid-pseudopapillary neoplasm: Key immunohistochemical profiles of pure acinar cell carcinoma of the pancreas. AJR Am J Roentgenol 2005; 184: 511-519 [PMID: 15671372 DOI: 10.2214/ajr.184.2.0184051]

Matos JM, Schmidt CM, Turrmn O, Agaram NP, Niedergermann M, Saeger HD, Merchant N, Johnson CS, Lillermo KD, Grützmahn R. Pancreatic acinar cell carcinoma: a multi-institutional study. J Gastrointest Surg 2009; 13: 1495-1502 [PMID: 19495891 DOI: 10.1007/s11605-009-0936-z]

Brunetti O, Arpiro G, Marchetti P, Valsile E, Casadei Gardini A, Mazzini M, Darni S, Delfanti S, De Vita F, Di Costanzo F, Millella M, Cella CA, Berardi R, Cataldo I, Scarpa A, Basile D, Mazzana F, Graziano G. Argentiero A, Santini D, Reni M, Cuscini S, Silvestris N. Systemic Chemotherapy for Advanced Rare Pancreatic Histotype Tumors: A Retrospective Multicenter Analysis. Pancreases 2018; 47: 759-771 [PMID: 29771769 DOI: 10.1097/MPA.0000000000001063]

Serra S, Morteke JK, Levy AD, Glickman JN, Ros PR, Banks PA, Silverman SG. CT and MRI features of acinar cell carcinoma of the pancreas in adults. AJR Am J Roentgenol 2005; 184: 511-519 [PMID: 15671372 DOI: 10.2214/ajr.184.2.0184051]

Niger M et al. One size does not fit all for pancreatic cancers [PMID: 22349806 DOI: 10.1007/s00261-012-9688-4]

Hsu MY, Pan KT, Chu SY, Hung CF, Wu RC, Tseng JH. CT and MRI features of acinar cell carcinoma of the pancreas with pathological correlations. Clin Radiol 2010; 65: 223-229 [PMID: 20152279 DOI: 10.1016/j.crad.2009.11.010]

Tatli S, Morteke JK, Levy AD, Glickman JN, Ros PR, Banks PA, Silverman SG. CT and MRI features of pure acinar cell carcinoma of the pancreas in adults. AJR Am J Roentgenol 2005; 184: 511-519 [PMID: 15671372 DOI: 10.2214/ajr.184.2.0184051]

Yoo C, Kim BJ, Kim KP, Lee JH, Kim TW, Ryoo BY, Chang HM. Efficacy of Chemotherapy in Patients with Unresectable or Metastatic Pancreatic Acinar Cell Carcinoma: Potentially Improved Efficacy with Oxaliplatin-Containing Regimen. Cancer Treat Review 2017; 49: 759-765 [PMID: 27857025 DOI: 10.1016/j.ctrt.2016.07.371]

Lowery MA, Klimstra DS, Shia J, Yu KH, Allen PJ, Brennan MF, O'Reilly EM. Acinar cell carcinoma of the pancreas: new genetic and treatment insights into a rare malignancy. Oncologist 2011; 16: 1714-1720 [PMID: 22042765 DOI: 10.1634/theoncologist.2011-0231]

Kruger S, Haas M, Burger PJ, Oettesch S, Modest DP, Westphalen CB, Kleespie A, Angele MK, Hartwig W, Bruins CJ, Kirchner T, Werner I, Heinemann V, Boeck S. Acinar cell carcinoma of the pancreas: a rare disease with different diagnostic and therapeutic implications than ductal adenocarcinoma. J Cancer Res Clin Oncol 2016; 142: 2585-2591 [PMID: 27629876 DOI: 10.1007/s00432-016-2264-7]

Callata-Carhuapoma HR, Pato Cour E, Garcia-Paredes B, Fernandez RM, Mendoza Fernandez ML, Fernandez AM, De La Rosa CA, Sotelo Lezama MJ, Cabezas-Camarero S, Sastre Varela J. Pancreatic acinar cell carcinoma with bilateral ovarian metastases, panniculitis and polyarthritis treated with FOLFIRINOX chemotherapy regimen. A case report and review of the literature. J Gastrointest Surg 2018; 22: 145-155 [PMID: 29592424 DOI: 10.1016/j.jgs.2015.04.004]

Schemp U, Sigas B, Künig C, Malek NP, Bitzer M, Plentz RR. FOLFIRINOX as first-line treatment for unresectable acinar cell carcinoma of the pancreas: a case report. J Gastroenterol 2014; 52: 200-203 [PMID: 24526405 DOI: 10.1007/s00333-1356439]

Pfrommer S, Weber A, Dukowski P, Schäfer NG, Müllhaup B, Bourquin JP, Breitenstein S, Pestalozzi BC, Stenner F, Renner C, DAddario G, Graf HJ, Knuth A, Clavien PA, Samaras P. Successful Salvage Chemotherapy with FOLFIRINOX for Recurrent Mixed Acinar Cell Carcinoma and Ductal Adenocarcinoma of the Pancreas in an Adolescent Patient. Case Rep Oncol 2013; 6: 497-503 [PMID: 24163668 DOI: 10.1159/000355320]

Seki Y, Okasaka T, Ikeda M, Morizane C, Ueno H. Four cases of pancreatic acinar cell carcinoma treated with gemcitabine or S-1 as a single agent. Jpn J Clin Oncol 2009; 39: 751-755 [PMID: 19666905 DOI: 10.1093/jjco/hyp085]

Yamamoto T, Ohzato H, Fukunaga M, Imamura H, Furukawa H. Acinar cell carcinoma of the pancreas: a possible role of S-1 as chemotherapy for acinar cell carcinoma. A case report. JOP 2012; 13: 87-90 [PMID: 22233953]

Sumiyoshi T, Shima Y, Okabayashi T, Kozuki A, Iwata J, Saisaka Y, Tokumura T, Nakamura T, Morita S. Long-term survival following pancreatectomy and s-1 chemotherapy for pancreatic acinar cell carcinoma with peritoneal dissemination: a case report and literature review. Medicine (Baltimore) 2015; 94: e378 [PMID: 25569665 DOI: 10.1097/MD.0000000000003378]

Ruo L, Coit DG, Brennan MF, Guillem JG. Long-term follow-up of patients with familial adenomatous polyposis undergoing pancreaticoduodenal resection. J Gastrointest Surg Endosc 2018; 10: 145-155 [PMID: 30283357 DOI: 10.4235/wjes.10.9.145]

Tang LH, Aydin H, Brennan MF, Klimstra DS. Clinically aggressive solid pseudopapillary tumors of the pancreas: a report of two cases with components of undifferentiated carcinoma and a comparative clinicopathologic analysis of 34 conventional cases. Am J Surg Pathol 2005; 29: 512-519 [PMID: 15767807 DOI: 10.1097/01.mp.0000151519.28530.88]

Santini D, Poli F, Lega S. Solid-papillary tumors of the pancreas: histopathology. JOP 2006; 7: 131-136 [PMID: 16407635]

Cai H, Zhou M, Hu Y, He H, Chen J, Tian W, Deng Y. Solid-pseudopapillary neoplasms of the pancreas: clinical and pathological features of 33 cases. Surg Today 2013; 43: 148-154 [PMID: 22825652 DOI: 10.1007/s00595-012-0260-1]

Katz MH, Mortenson MM, Wang H, Hwang R, Tamn EP, Staerkel G, Lee JH, Evans DB, Fleming JB. Diagnosis and management of cystic neoplasms of the pancreas: an evidence-based approach. J Am Coll Surg 2008; 207: 106-120 [PMID: 18589369 DOI: 10.1016/j.jamcollsurg.2007.12.048]

Serra S, Chetty R. Revision 2: an immunohistochemical approach and evaluation of solid pseudopapillary tumour of the pancreas. J Clin Pathol 2008; 61: 1153-1159 [PMID: 18708424 DOI: 10.1136/jcp.2008.057828]

Ohara Y, Oda T, Hashimoto S, Akashi Y, Miyamoto R, Enomoto T, Satomi K, Morishita Y, Okohchi N. Pancreatic neuroendocrine tumor and solid-pseudopapillary neoplasm: Key immunohistochemical profiles for differential diagnosis. World J Gastroenterol 2016; 22: 8596-8604 [PMID: 27784972 DOI: 10.3748/wjg.v22.i33.8596]
Niger M et al. One size does not fit all for pancreatic cancers

10.3748/wjg.v22.i38.8596

Kim MJ, Jang SJ, Yu E. Loss of E-cadherin and cytoplasmic-nuclear expression of beta-catenin are the most useful immunoprofiles in the diagnosis of solid-pseudopapillary neoplasm of the pancreas. Hum Pathol 2008; 39: 251-258 [PMID: 17992228 DOI: 10.1016/j.humpath.2007.06.014]

Tanaka Y, Kato K, Notohara K, Hojo H, Ijiri R, Miyake T, Nagahara N, Sasaki F, Kitagawa N, Nakatani Y, Kobayashi Y. Frequent beta-catenin mutation and cytoplasmic/nuclear accumulation in pancreatic solid-pseudopapillary neoplasm. Cancer Res 2001; 61: 8401-8404 [PMID: 11731417]

Müller-Höcker J, Zietz CH, Sendelhofert A. Deregulated expression of cell cycle-associated proteins in solid pseudopapillary tumor of the pancreas. Mod Pathol 2001; 14: 47-53 [PMID: 11235905 DOI: 10.1038/modpathol.3880255]

Tiemann K, Heitling U, Kosmahl M, Klüppel G. Solid pseudopapillary neoplasms of the pancreas show an interruption of the Wnt-signaling pathway and express gene products of 11q. Mod Pathol 2007; 20: 955-960 [PMID: 17632456 DOI: 10.1038/modpathol.3809002]

Choi JY, Kim MJ, Kim JH, Kim SH, Lim JS, Oh YT, Chung JJ, Yoo HS, Lee JT, Kim KW. Solid pseudopapillary tumor of the pancreas: typical and atypical manifestations. AJR Am Roentgenol 2006; 187: W178-W186 [PMID: 16861508 DOI: 10.2214/AJR.05.0569]

Buetow PC, Buck JL, Pantongrag-Brown L, Beck KG, Ros PR, Adair CF. Solid and papillary epithelial neoplasm of the pancreas: imaging-pathologic correlation on 56 cases. RadioLOGY 1996; 199: 707-711 [PMID: 8637992 DOI: 10.1148/radiology.199.3.8637992]

Back JH, Lee JM, Kim SH, Kim SJ, Kim SH, Lee JY, Han JK, Choi BI. Small (≤ 3 cm) solid pseudopapillary tumors of the pancreas at multiphasic multidetector CT. Radiology 2010; 257: 97-106 [PMID: 20663966 DOI: 10.1148/radiol.10092089]

Yu CC, Tseng JH, Yeh CN, Hwang TL, Jan YY. Clinicopathological study of solid and pseudopapillary tumor of pancreas: emphasis on magnetic resonance imaging findings. World J Gastroenterol 2007; 13: 1811-1815 [PMID: 17465471 DOI: 10.3748/wjg.v13.i12.1811]

Romics Jr L, Ölah A, Belágyi T, Hajdú N, Gyurás P, Ruszinkó V. Solid pseudopapillary neoplasm of the pancreas--proposed algorithms for diagnosis and surgical treatment. Langenbecks Arch Surg 2010; 395: 747-755 [PMID: 20155425 DOI: 10.1007/s00423-010-0599-0]

Tipton SG, Smyrk TC, Sarr MG, Thompson GB. Malignant potential of solid pseudopapillary neoplasm of the pancreas. Br J Surg 2006; 93: 733-737 [PMID: 16609955 DOI: 10.1002/bjs.5334]

de Castro SM, Singhal D, Aronson DC, Busch OR, van Gulik TM, Oberth H, Gouma DJ. Management of solid-pseudopapillary neoplasms of the pancreas: a comparison with standard pancreatic neoplasms. World J Surg 2005; 31: 1150-1153 [PMID: 17429567 DOI: 10.1007/s00268-006-0214-2]

Prasad TV, Madhusudhan KS, Srivastava DN, Dash NR, Gupta AK. Transarterial chemoembolization for liver metastases from solid pseudopapillary tumour of pancreas: a case report. World J Radiol 2015; 7: 61-65 [PMID: 25825635 DOI: 10.4329/wjr.v7.i3.61]

Klimstra DS, Wenig BM, Heffess CS. Solid-pseudopapillary tumour of the pancreas: a typically cystic carcinoma of low malignant potential. Semin Diagn Pathol 2000; 17: 66-80 [PMID: 10721808]

Martin RC, Klimstra DS, Brennan MF, Conlon KC. Solid-pseudopapillary tumor of the pancreas: a surgical enigma? Ann Surg Oncol 2002; 9: 35-40 [PMID: 11833495 DOI: 10.1245/aso.2002.9.135]

Papavramidis T, Papavramidis S. Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. J Am Coll Surg 2005, 200: 965-972 [PMID: 15922121 DOI: 10.1016/j.jamcollsurg.2005.02.011]

Panieri E, Krige JE, Bormann PC, Graham SM, Terblanche J, Cruse JP. Operative management of papillary cystic neoplasms of the pancreas. J Am Coll Surg 1998; 186: 319-324 [PMID: 9516263 DOI: 10.1016/S1072-7515(98)00015-5]

Sumida W, Kaneko K, Tainaka T, Ono Y, Kiuchi T, Ando H. Solid pseudopapillary tumor of pancreas--proposed algorithms for diagnosis and surgical treatment. J Hepatobiliary Pancreat Surg 2004; 11: 65-70 [PMID: 15304017 DOI: 10.1002/jhbs.48]

Kocman B, Jadrjević S, Skopljanc A, Mikušič D, Gustin D, Buhin M, Matošić H, Gasparov S, Suknaić S, Ivanović D. Living donor liver transplantation for unresectable liver metastases from solid pseudopapillary tumor of the pancreas: a case report. Transplant Proc 2008; 40: 3787-3790 [PMID: 19100491 DOI: 10.1016/j.transproceed.2008.03.160]

Łągiewska B, Pacholeczyk M, Lisiew S, Cichocki A, Nawrocki G, Trzebiicki J, Chmura A. Liver transplantation for nonresectable metastatic solid pseudopapillary pancreatic cancer. Ann Transplant 2013; 18: 651-653 [PMID: 24280737 DOI: 10.12659/ATOT.899979]

Dovigo AG, Díaz MB, Güterrez MG, Selles CF, Grobas JP, Valladares M, Suárez F, Mariní M. Liver transplantation as treatment in a massive metastasis from Gruber-Frantz pancreatic tumor: a case report. Transplant Proc 2011; 43: 2272-2273 [PMID: 21839254 DOI: 10.1016/j.transproceed.2011.05.029]

Wójcik M, Gozdowska J, Pacholeczyk M, Lisiew S, Kosieradzki M, Cichocki A, Trzebiicki J, Chmura A. Liver Transplantation for a Metastatic Pancreatic Solid-Pseudopapillary Tumor (Frantz Tumor): A Case Report. Ann Transplant 2018; 23: 520-523 [PMID: 30061554 DOI: 10.12659/AOT.908764]

Strauss JF, Hirsch VJ, Rubey CN, Pollock M. Resection of a solid and papillary epithelial neoplasm of the pancreas following treatment with cis-platinum and 5-fluorouracil: a case report. Med Pediatr Oncol 1993; 21: 365-367 [PMID: 8492753 DOI: 10.1002/mpo.2950210511]

Maffuz A, Bustamante Fde T, Silva JA, Torres-Vargas S. Preoperative gemcitabine for unresectable, solid pseudopapillary tumour of the pancreas. Lancet Oncol 2005; 6: 185-186 [PMID: 15737835 DOI: 10.1016/S1470-2045(05)01770-5]

Machado MC, Machado MA, Bacchella T, Jukemura J, Almeida JL, Cunha JE. Solid pseudopapillary neoplasm of the pancreas: distinct patterns of onset, diagnosis, and prognosis for male versus female patients. Surgery 2008; 143: 29-34 [PMID: 18154930 DOI: 10.1016/j.surg.2007.07.030]

Hah JO, Park WK, Lee NH, Choi JH. Preoperative chemotherapy and intraoperative radiofrequency ablation for unresectable solid pseudopapillary tumor of the pancreas. J Pediatr Hematol Oncol 2007; 29: 851-853 [PMID: 18090937 DOI: 10.1097/MPH.0b013e318158159c]

Fried P, Cooper J, Balthazar E, Fazzini E, Newall J. A role for radiotherapy in the treatment of solid and...
papillary neoplasms of the pancreas. *Cancer* 1985; 56: 2783-2785 [PMID: 2045292 DOI: 10.1002/1097-0142(19851215)56:12<2783::aid-cncr28205612111>3.0.co;2-q]

71 Morikawa T, Omogawa T, Manda S, Takadate T, Shirasaki K, Yoshida H, Ishida K, Motti F, Naitoh T, Rikiyama T, Katayose Y, Egawa S, Unno M. Solid pseudopapillary neoplasms of the pancreas: an 18-year experience at a single Japanese Institution. *Surg Today* 2013; 43: 26-32 [PMID: 23114787 DOI: 10.1007/s00595-012-0345-z]

72 Sperri C, Berselli M, Pasquali C, Pastorelli D, Pedrazzoli S. Aggressive behaviour of solid-pseudopapillary tumor of the pancreas in adults: a case report and review of the literature. *World J Gastroenterol* 2008; 14: 960-965 [PMID: 18240360 DOI: 10.3748/wjg.v14.i6.960]

73 Paal E, Thompson LD, Frommelt RA, Przygocki RM, Heffess CS. A clinicopathologic and immunohistochemical study of 35 anaplastic carcinomas of the pancreas with a review of the literature. *Ann Diagn Pathol* 2001; 5: 129-140 [PMID: 11436166 DOI: 10.1016/s10/2001.25404]

74 Strobel O, Hartwig W, Bergmann F, Hinz U, Hackert T, Grenacher L, Schneider L, Fritz S, Gaida MM, Büchler MW, Werner J. Anaplastic pancreatic cancer: Presentation, surgical management, and outcome. *Surgery* 2011; 149: 200-208 [PMID: 20542529 DOI: 10.1016/j.surg.2010.04.026]

75 Hoshimoto S, Matsui J, Miyata R, Takigawa Y, Miyauchi J. Anaplastic carcinoma of the pancreas: Case report and literature review of reported cases in Japan. *World J Gastroenterol* 2016; 22: 8631-8637 [PMID: 27749756 DOI: 10.3748/wjg.v22.i38.8631]

76 Molberg KH, Heffess C, Delgado R, Alberos-Saavedra J. Undifferentiated carcinoma with osteoclast-like giant cells of the pancreas and periampullary region. *Cancer* 1998; 82: 1279-1287 [PMID: 9592019 DOI: 10.1002/scti.199801282.7-1279:a7-129d:aid-cncr10-3.0.co;2-3]

77 Kitade H, Yangaida H, Yamada M, Satoi S, Yoshioka K, SHikata N, Kon M. Granulocyte-colony stimulating factor producing anaplastic carcinoma of the pancreas treated by distal pancreatectomy and chemotherapy: report of a case. *Surg Case Rep* 2015; 1: 46 [PMID: 2636342 DOI: 10.1186/s40792-015-0044-w]

78 Murata T, Terasaki M, Sakaguchi K, Okubo M, Fukami Y, Nishimae K, Kitayama Y, Hoshi S. A case of anaplastic carcinoma of the pancreas producing granulocyte-colony stimulating factor. *Clin J Gastroenterol* 2009; 2: 109-114 [PMID: 26192175 DOI: 10.1016/s1232-008-0058-4]

79 Clark CJ, Graham RP, Arun JS, Harnsens WS, Reid-Lombardo KM. Clinical outcomes for anaplastic pancreatic cancer: a population-based study. *J Am Coll Surg* 2012; 215: 627-634 [PMID: 23084492 DOI: 10.1016/j.jamcollsurg.2012.06.418]

80 Hartwig W, Derenzberg M, Bergmann F, Hackert T, Hinz U, Strobel O, Büchler MW, Werner J. Acinar cell carcinoma of the pancreas: is resection justified even in limited metastatic disease? *Am J Surg* 2011; 202: 23-27 [PMID: 21440887 DOI: 10.1016/j.amjsurg.2010.06.004]

81 El Hussein S, Khader SN. Cytopathology of anaplastic carcinoma of the pancreas: Review of a rare entity and description of a variant with ring sign cell features. *Diagn Cytopathol* 2019; 47: 956-960 [PMID: 31254330 DOI: 10.1002/dc.24263]

82 Hoorens A, Prezel K, Lernoine NR, Klöppel G. Undifferentiated carcinoma of the pancreas: analysis of intermediate filament profile and Ki-ras mutations provides evidence of a ductal origin. *J Pathol* 1998; 185: 53-60 [PMID: 9713360 DOI: 10.1002/(sici)1097-0274(199801)185:1<53::aid-jpath2-3.0.co;2-1]

83 Newbold MJ, Benbow EW, Sene A, Young M, Taylor TV. Adenocarcinoma of the pancreas with osteoclast-like giant cells: a case report with immunocytochemistry. *Pancreas* 1992; 7: 611-615 [PMID: 1513808 DOI: 10.1097/00006667-19920900-00015]

84 Ichikawa T, Federle MP, Ohsb S, Ohtomo K, Sugiyama A, Fujimoto H, Haradome H, Araki T. Atypical exocrine and endocrine pancreatic tumors (anaplastic, small cell, and giant cell types): CT and pathologic features in 14 patients. *Abdom Imaging* 2000; 25: 409-419 [PMID: 10926196 DOI: 10.1007/s00261000035]

85 Ishigami K, Nishie A, Yamamoto T, Asayama Y, Ushijima Y, Kakihara D, Fujita N, Morita K, Ohtsuka T, Kawa K, Mochidome N, Honda H. Imaging features of undifferentiated carcinoma of the pancreas. *J Med Imaging Radiat Oncol* 2019; 63: 580-588 [PMID: 31268241 DOI: 10.1111/jmri.12925]

86 Fukukura Y, Kumagae Y, Hirahara M, Hakamada H, Nagano H, Nakajo M, Kamimura K, Nakajo M, Hidagi M, Yoshiura T. CT and MRI features of undifferentiated carcinomas with osteoclast-like giant cells of the pancreas: a case series. *Abdom Radiol (NY)* 2019; 44: 1246-1255 [PMID: 30815714 DOI: 10.1007/s00261-019-1955-9]

87 Khashab MA, Emerson RE, DeWitt JM. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of anaplastic pancreatic carcinoma: a single-center experience. *Pancreas* 2010; 39: 88-91 [PMID: 20055229 DOI: 10.1097/MPA.0b013e3181bb2a68]

88 Wong M, See JY, Sufyan W, Diddapur RK. Splenic infarction. A rare presentation of anaplastic pancreatic carcinoma of the pancreas. *JOP* 2008; 9: 493-498 [PMID: 18648141]

89 Shinagare AB, Ramaiya NH, Bellizzi AM, Mayer RJ. Locally advanced anaplastic pancreatic adenocarcinoma with initial response to FOLFIRINOX and rapid progression after five months. *Pancreatology* 2012; 12: 35-38 [PMID: 22487471 DOI: 10.1016/j.pan.2012.01.001]

90 Uzgaro A, Orsi F, Casadio C, Galdy S, Spada F, Cella CA, Tomo CD, Bonomo G, Vigna PD, Mugioni S, Freeza AM, Fazio N. Successful palliative approach with high-intensity focused ultrasound in a patient with metastatic anaplastic pancreatic carcinoma: a case report. *Ecancermedicalscience* 2016; 10: 635 [PMID: 27170835 DOI: 10.3332/ecancer.2016.635]

91 Wakatsuki T, Irisawa A, Inamura H, Terashima M, Shibukawa G, Takagi T, Takahashi Y, Sato A, Sato M, Ikeda T, Suzuki R, Hikichi T, Obara K, Ohira H. Complete response of anaplastic pancreatic carcinoma to paclitaxel treatment selected by chemosensitivity testing. *Int J Clin Oncol* 2010; 15: 310-313 [PMID: 20195681 DOI: 10.1007/s10147-010-0038-9]

92 Shorter NA, Glick RD, Klimstra DS, Brennan MF, Laquaglia MP, Luagguaglia MP. Malignant pancreatic tumors in childhood and adolescence: The Memorial Sloan-Kettering experience, 1967 to present. *J Pediatr Surg* 2002; 37: 887-892 [PMID: 12037756 DOI: 10.1016/j.pds.2002.32897]

93 Reid MD, Bhattarai S, Graham RP, Pehlivanoglu B, Sigel CS, Shi J, Saqi A, Shirazi M, Xue Y, Basturk O, Adsay V. Pancreatoblastoma: Cytologic and histologic analysis of 12 adult cases reveals helpful criteria in
One size does not fit all for pancreatic cancers

Petersen GM; Australian Pancreatic Cancer Genome Initiative, Munzy DM, Fisher WE, Karim SA, NB, Graham JS, Duthie F, Oien K, Hair J, Grützmann R, Maitra A, Iacobuzio-Donahue CA, Wolfgang CL, JG, Lovell JA, Merrett ND, Toon CW, Epari K, Nguyen NQ, Barbour A, Zeps N, Moran-Jones K, Jamieson L, Wu J, Pinese M, Cowley MJ, Jones MD, Colvin EK, Nagrial AM, Humphrey ES, Chantrill LA, Mawson Holmes O, Chin V, Anderson MJ, Kazakoff S, Leonard C, Newell F, Waddell N, Wood S, Xu Q, Wilson 10.1016/j.prp.2018.10.006

Akagi Y, Yano H. PD-L1 expression in pancreatic adenosquamous carcinoma: PD-L1 expression is limited to the squamous component.

Ribatti D, Tommasi S. Angiogenesis in adenosquamous cancer of pancreas.

Tella SH, Ntanasis-Stathopoulos I. Pancreatic adenocarcinoma metastatic to the liver: A review of the literature. 28722109

Fang Y, Pu N, Zhang L, Wu W, Lou W. Chemoradiotherapy is associated with improved survival for resected pancreatic adenocarcinoma in the absence of liver metastases. 10.1002/cncy.22187

Hester CA, Augustine MM, Choti MA, Mansour JC, Minter RM, Polanco PM, Porembka MR, Wang SC, Yopp AC. Comparative outcomes of adenocarcinomas of the pancreas: A retrospective cohort study from the SEER database. 10.1080/028418500127345604

Yamaguchi S, Fujii T, Irami Y, Fukumura Y, Han M, Yamaguchi H, Akita T, Yamashita C, Kato S, Sekiya T. Identification and characterization of a novel adenomatous polyposis coli mutation in adult pancreatoblastoma. Oncotarget 2018; 9: 10818-10827 [PMID: 29535845 DOI: 10.18632/oncotarget.24017]

Lee JY, Kim IO, Kim WS, Kim CW, Yeon KM. CT and US findings of pancreatoblastoma. J Comput Assist Tomogr 1996; 20: 370-374 [PMID: 8626892 DOI: 10.1097/00002278-199605000-00007]

Montemarano H, Lonergan GJ, Bulas DI, Selby DM. Pancreatoblastoma: imaging findings in 10 patients and review of the literature. Radiology 2000; 214: 476-482 [DOI: 10.1148/radiology.214.2.88063470]

Zhang D, Tang N, Liu Y, Wang EH. Pancreatoblastoma in an adult. Indian J Pathol Microbiol 2015; 58: 93-95 [PMID: 25673604 DOI: 10.4103/0377-4929.151199]

Salmon B, Brat G, Yoon YS, Hruban RH, Singhid EK, Herman JM, Wolfgang CL. The diagnosis and surgical treatment of pancreatic cancers in adults: a case series and review of the literature. J Gastrointest Surg 2013; 17: 2153-2161 [PMID: 24081396 DOI: 10.1007/s11605-013-2294-2]

Benoist S, Penna C, Julic C, Malafosse R, Rougier P, Nordlinger B. Prolonged survival after resection of pancreatoblastoma and synchronous liver metastases in an adult. Hepatogastroenterology 2001; 48: 1340-1342 [PMID: 11677959]

Charlton-Ouw KM, Kaiser CL, Tong GX, Allendorf JD, Chabot JA. Revisiting metastatic adult pancreatoblastoma. A case and review of the literature. JOP 2008; 9: 733-738 [PMID: 18981556]

Boyd CA, Benaroch-Gampel J, Sheffield KM, Cooksley CD, Riall TS. 415 patients with adenosquamous carcinoma of the pancreas: a population-based analysis of prognosis and survival. J Surg Res 2012; 174: 12-19 [PMID: 21816433 DOI: 10.1016/j.jss.2011.06.015]

Fang Y, Su Z, Xie J, Xue R, Ma Q, Li Y, Zhao Y, Song Z, Lu X, Li H, Peng C, Bai F, Shen B. Genomic signatures of pancreatic adenocarcinoma carcinoma: A retrospective cohort study from the SEER database. Ann Transl Med 2019; 7: 522 [PMID: 31075798 DOI: 10.21037/atm.2019.10.12]

Hester CA, Augustine MM, Choti MA, Mansour JC, Minter RM, Polanco PM, Porembka MR, Wang SC, Yopp AC. Comparative outcomes of adenocarcinomas of the pancreas: An analysis of the National Cancer Database. J Surg Oncol 2018; 118: 21-30 [PMID: 29878370 DOI: 10.1002/jso.25112]

Ntanasis-Stathopoulos I, Tsilimigras DI, Georgiadou D, Kanavidis P, Ricciioni O, Salla C, Psaltoulpoulou T, Sergentanis TN. Squamous cell carcinoma of the pancreas: A systematic review and pooled survival analysis. Eur J Cancer 2017; 79: 193-204 [PMID: 28511147 DOI: 10.1016/j.ejca.2017.04.006]

Tella SH, Kommalapati A, Yadav S, Bergquist JR, Trayt MJ, Durgin L, Ma WW, Cleary SF, McWilliams RR, Malapal A. Survival and prognostic factors in patients with pancreatic squamous cell carcinoma. Eur J Surg Oncol 2019; 45: 1700-1705 [PMID: 31181133 DOI: 10.1016/j.ejso.2019.05.011]

Fang Y, Su Z, Xie J, Xue R, Ma Q, Li Y, Zhao Y, Song Z, Lu X, Li H, Peng C, Bai F, Shen B. Genomic signatures of pancreatic adenocarcinoma carcinoma (PASC). J Pathol 2017; 243: 155-159 [PMID: 28722109 DOI: 10.1002/path.4943]

Silvestris N, Danzka K, Longo V, Brunetti O, Fucci L, Argentiere A, Calabrese A, Cataldo I, Tamma R, Ribatti D, Tommasi S. Angiogenesis in adenocarcinoma of the pancreas. Oncotarget 2017; 8: 95773-95777 [PMID: 29221165 DOI: 10.18632/oncotarget.23131]

Tanagawa M, Naito Y, Akiba I, Kawahara A, Okabe Y, Ishida Y, Ishikawa H, Hisaka T, Fujita F, Yasunaga M, Shiigiaki T, Udo T, Mihara Y, Nakayama M, Kondo R, Kusano H, Shimamatsu K, Okuda K, Akagi Y, Yano H. PD-L1 expression in pancreatic adenocarcinoma carcinoma: PD-L1 expression is limited to the squamous component. Pathol Res Prat 2018; 214: 2069-2074 [PMID: 30477643 DOI: 10.1016/j.prp.2018.10.006]

Bailey P, Chang DK, Nokes J, Johns AL, Patch AM, Gingras MC, Miller DK, Christ AN, Bruxner TJ, Quinn MC, Nourse C, Murtaugh LC, Harlison I, Idrisoglu S, Manning S, Nourbakhsh E, Wani S, Fink L, Holmes O, Chin V, Anderson MJ, Kazakoff S, Leonard C, Newell F, Wood S, Xu Q, Wilson PJ, Cloonan N, Kassahn KS, Taylor D, Quek K, Robertson A, Pantano L, Mincarelle L, Sanchez LN, Evers L, Wu J, Pinse M, Cowley MJ, Jones MD, Colvin EK, Nagrial AG, Humphrey ES, Chantritt LA, Mawson A, Humphria J, Chou A, Pajic M, Scarlett CJ, Pinho AV, Giry-Laterriere M, Rooman I, Samra JS, Kench JG, Lovell JA, Morriitt ND, Toon CW, Epari K, Nguyen QN, Barbour A, Zepa N, Morin-Jones K, Jamieson NB, Graham JS, Duthe F, Oien K, Hair J, Grützmmer R, Maitra A, Iacobuzio-Donahue CA, Wolfgang CL, Morgan RA, Lawlor WT, Corbo V, Bassi C, Ruseb B, Capelli P, Salvia R, Tortora G, Mukhopadhyay D, Petersen GM, Australasian Pancreatic Cancer Genome Initiative, Munzy DM, Fisher WE, Karim SA, Eshleman JR, Hruban RH, Pilsarski C, Morton JP, Sansom OJ, Scarpa A, Musgrove EA, Bailey UM,
One size does not fit all for pancreatic cancers

Hofmann O, Sutherland RL, Wheeler DA, Gill AJ, Gibbs RA, Pearson JV, Waddell N, Biankin AV, Grimmond SM. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* 2016; 531: 47-52 [PMID: 26909576 DOI: 10.1038/nature15965]

Zhao R, Jia Z, Chen X, Ren S, Cui W, Zhao DL, Wang S, Wang J, Li T, Zhu Y, Tang X, Wang Z. CT and MR imaging features of pancreatic adenosquamous carcinoma and their correlation with prognosis. *Abdom Radiol (NY)* 2019; 44: 2822-2834 [PMID: 31187197 DOI: 10.1007/s00261-019-02060-w]

Feng YF, Chen JY, Chen HY, Wang TG, Shi D, Lu YF, Pan Y, Shao CW, Yu RS. 110 Patients with adenosquamous carcinomas of the pancreas (PASC): imaging differentiation of small (<3 cm) versus large (>3 cm) tumors. *Abdom Radiol (NY)* 2019; 44: 2466-2473 [PMID: 30977505 DOI: 10.1007/s00261-019-01989-2]

Fajardo LL, Yoshino MT, Cherrin MM. Computed tomography findings in squamous cell carcinoma of the pancreas. *J Comput Tomogr* 1988; 12: 138-139 [PMID: 3168524 DOI: 10.1016/0149-936X(88)90068-9]

Nikfam S, Sotoudehmanesh R, Pourshams A, Sadeghipour A, Sotoudeh M, Mohamadnejad M. Squamous cell carcinoma of the pancreas. *Arch Iran Med* 2013; 16: 369-370 [PMID: 23725072]

Taibi A, Jacques J, Durand Fontanier S, Charissoux A, Bardet SM, Christou N, Fredon F, Vallex D, Mathonnet M. Long-term survival after surgery of pancreatic primary squamous cell carcinoma: A case report and literature review. *Clin Case Rep* 2019; 7: 2092-2101 [PMID: 31788258 DOI: 10.1002/ccr3.2429]

Wild AT, Dholakia AS, Fan KY, Kumar R, Moningi S, Rosati LM, Laheru DA, Zheng L, De Jesus-Acosta A, Ellsworth SG, Hacker-Prietz A, Voong KR, Tran PT, Hruban RH, Pawlik TM, Wolfgang CL, Herman JM. Efficacy of platinum chemotherapy agents in the adjuvant setting for adenosquamous carcinoma of the pancreas. *J Gastrointest Oncol* 2015; 6: 115-125 [PMID: 25830031 DOI: 10.3978/j.issn.2078-6891.2014.091]

Voong KR, Davison J, Pawlik TM, Uy MO, Hsu CC, Winter J, Hruban RH, Laheru D, Rudra S, Swartz MJ, Nathan H, Edil BH, Schulick R, Cameron JL, Wolfgang CL, Herman JM. Resected pancreatic adenosquamous carcinoma: clinicopathologic review and evaluation of adjuvant chemotherapy and radiation in 38 patients. *Hum Pathol* 2010; 41: 113-122 [PMID: 19801164 DOI: 10.1016/j.humpath.2009.07.012]

Gruhl JD, Garrido-Laguna I, Francis SR, Affolter K, Tao R, Lloyd S. The impact of squamous cell carcinoma histology on outcomes in nonmetastatic pancreatic cancer. *Cancer Med* 2020; 9: 1703-1711 [PMID: 31945808 DOI: 10.1002/cam4.2851]

De Arco H, Chakib-Brugère C, Salabert L, Béchade D. Adenosquamous Carcinoma of the Pancreas. *Clin Med Insights Oncol* 2019; 13: 1179554919868587 [PMID: 31723321 DOI: 10.1177/1179554919868587]

De Souza AL, Saif MW. Squamous cell carcinoma of the pancreas. *JOP* 2014; 15: 630-631 [PMID: 25435587 DOI: 10.6092/1590-8577/2718]

Al-Shбри A, Silverman S, King KM. Squamous cell carcinoma of the pancreas. *Curr Oncol* 2008; 15: 293-297 [PMID: 19079631 DOI: 10.3747/cov.1516.265]

Kodavatiganti R, Campbell F, Hashmi A, Gollins SW. Primary squamous cell carcinoma of the pancreas: a case report and review of the literature. *J Med Case Rep* 2012; 6: 295 [PMID: 22973995 DOI: 10.1186/1752-1947-6-295]

De Souza AL, Saif MW. Platinum-based therapy in adenosquamous pancreatic cancer: experience at two institutions. *JOP* 2014; 15: 144-146 [PMID: 24618440 DOI: 10.6092/1590-8577/2358]

Luo G, Fan Z, Gong Y, Jin K, Yang C, Cheng H, Huang D, Ni Q, Liu C, Yu X. Characteristics and Outcomes of Pancreatic Cancer by Histological Subtypes. *Pancreas* 2019; 48: 817-822 [PMID: 31210663 DOI: 10.1097/MPA.0000000000001338]
