

REVIEW ARTICLE

Undifferentiated Pancreatic Carcinoma: Presentation, Classification and Prognosis

Marco Chiarelli¹, Morena Burati¹, Fulvio Tagliabue¹, Sabina Terragni¹, Angelo Guttadauro², Gerardo Cioffi³, Matilde De Simone⁴, Ugo Cioffi⁴

¹Department of Surgery, Ospedale Alessandro Manzoni, ASST Lecco, Lecco 23900, Italy

²Department of Surgery, University of Milan-Bicocca, Monza 20900, Italy

³Department of Sciences and Technologies Unisannio, Benevento 82100 Italy

⁴Department of Surgery, University of Milan, Milano 20122, Italy

ABSTRACT

Undifferentiated pancreatic carcinoma, also called anaplastic pancreatic carcinoma or giant cells pancreatic carcinoma, is an uncommon and aggressive variety of ductal adenocarcinoma. Three types of undifferentiated carcinoma of the pancreas are known: Osteoclast-like giant cells tumor, pleomorphic giant cells tumor, and mixed giant cells tumor. Osteoclast-like giant cells tumor is characterized by the presence of large histiocytic elements with many small nuclei showing no atypia. Pleomorphic giant cells tumor is characterized by the presence of bizarre mono- or multinucleated giant cells with atypical mitoses. The mixed giant cells tumor shows the simultaneous presence of both histological histotypes. The histogenesis of giant cells is controversial. Currently osteoclast-like giant cells are considered reactive elements deriving from a histiocytic lineage. Pleomorphic giant cells tumor originates from ductal epithelium with subsequent sarcomatous transformation. The various histotypes show different behavior in terms of survival. Pleomorphic giant cells tumor is characterized by a worse prognosis than ductal adenocarcinoma while osteoclast-like giant cells tumor can be associated with longer survival time. The mixed giant cells tumor presents an intermediate prognosis. In conclusion, in case of undifferentiated pancreatic carcinoma, an accurate histopathological diagnosis can predict different behavioral pathways in terms of tumor progression and prognostic profile.

INTRODUCTION

Pancreatic cancer is the seventh leading cause of cancer death worldwide [1]. The incidence of this aggressive tumor is four times higher in Europe, North America and Australia- New Zealand than in the other region of the world [1]. In the last decades, pancreatic ductal adenocarcinoma (PDAC), the most common histotype of pancreatic cancer, has been well characterized with regard to morphology, immunohistochemistry, and genetics [2, 3, 4].

More recently, series of less frequent variants of pancreatic tumors have been reported: the clinical and

pathological features of these rare neoplasms have been progressively focused [5, 6, 7]. Consequently, in addition to conventional PDAC, a significant number of distinct pancreatic carcinoma variants with peculiar histopathologic characteristic have been described [4]. However these variants still present unclarified clinical and prognostic aspects. Undifferentiated pancreatic carcinoma (UPC) is an uncommon and aggressive histological variant of PDAC [4, 8]. UPC, also known as giant cell carcinoma, was firstly described by Sommers and Meissner in 1954 [9]. To date, according to the WHO classification, UPC is categorized in two different types: undifferentiated carcinoma (with three variants: anaplastic undifferentiated carcinoma, sarcomatoid undifferentiated carcinoma, carcinosarcoma) and undifferentiated carcinoma with osteoclast-like giant cells [8].

The purpose of this manuscript is to focus on the clinical presentation, macroscopic and microscopic features, and prognostic profiles of different UPC histotypes.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

UPC accounts for up to 5% of all pancreatic carcinomas [10]. In a single-center retrospective series, the anaplastic carcinoma accounted 0.3% of all primary and secondary pancreatic tumors [11]. In a large cohort, the osteoclast-like giant cell type represented 1.4% of all invasive pancreatic

Received August 27th, 2019 - Accepted December 11th, 2019

Keywords undifferentiated carcinoma; Pancreatic Carcinoma; Anaplastic Carcinoma

Abbreviations PDAC pancreatic ductal adenocarcinoma; UPC undifferentiated pancreatic cancer; CA 19-9 carbohydrate antigen 19-9; CEA carcino-embryonic antigen; CT computed tomography; MRI magnetic resonance imaging; EUS endoscopic ultrasound; MRCP magnetic resonance cholangio-pancreatography; FNA fine-needle aspiration; OGCT osteoclast-like giant cells tumor; PGCT pleomorphic giant cells tumor; MGCT mixed giant cells tumor; GCT giant cell tumor; OGCs osteoclast-like giant cells; PGCs pleomorphic giant cells; A1ACT α -1-antichymotrypsin; EMA epithelial membrane antigen

Correspondence Ugo Cioffi

Department of Surgery, University of Milan,
Via F Sforza 35, Milano 20122, Italy

Tel +39-341-489665

Fax +39-341-489291

E-mail ugocioffi5@gmail.com

carcinomas [10]. UPC is more frequent in the sixth and seventh decade of life and the highest incidence is found about 7-8 years earlier than PDAC [10,12]. In some series a clear prevalence has been reported in the male population (male:female ratio=2:1) [11,13], but in a recent review this gender difference seems to disappear [14].

UPC usually presents with epigastric or back pain and jaundice due to biliary obstruction; other clinical presentations include nausea, vomiting, weight loss and itching [8, 11, 15]. Rarely patients affected by this variety of pancreatic neoplasm present hypercalcemia or migratory thrombosis [8]. In medical literature, relapsing episodes of acute pancreatitis, due to the intra-ductal growth of the tumor, are described [8, 12]. Advanced symptoms are related to the invasion of colon, stomach (bleeding or stenosis), or peritoneal cavity (ascites) [8]. Physical examination can reveal the presence of a palpable mass in the upper abdominal quadrants [16]. In advanced stages, the occurrence of liver metastases may be the first symptom of presentation [8]. In three cohorts of patients, upper abdominal or back pain, nausea, and significant weight loss, were the most frequent symptoms [11, 12, 13]. High serum levels of carbohydrate antigen 19-9 (CA 19-9) and carcino-embryonic antigen (CEA) could support the clinical diagnosis, but are usually less elevated than in PDAC [13].

RADIOLOGY AND MACROSCOPIC FEATURES

According to international literature, the average tumor size of UPC varies from 2 to 25 cm, depending on the series. UPC involves more frequently the head of the gland [12, 13]. This predominant spatial involvement seems to become less evident in series with larger mean tumor sizes [16, 17]: voluminous masses can infiltrate the entire gland in extreme cases [11]. The tumor dimension is usually larger than PDAC (mean 5.3 cm vs. 3.2 cm in a large series) [12]. The cross-sectional imaging used for diagnosis and staging of UPC are computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS).

A dual phasic multidetector CT scan is needed for studying the pancreatic lesions [18]. In the majority of cases, conventional PDAC appear as a hypodense mass in the arterial phase on CT scan: tumoral desmoplastic reaction determines a decreased perfusion of the lesion compared with the surrounding pancreatic tissue [18]. Differently, UPC presents as hypointense pancreatic mass with a peripheral contrast enhancement most evident in the portal phase [13]. The presence of pancreatic margins erosion or infiltration of the surrounding adipose tissue suggests a malignant lesion [18]. Furthermore, abdomen CT shows lymphatic and hepatic dissemination or mesenteric vessels infiltration, as in the case of PDAC [18].

These large tumors often appears as heterogeneous masses with distinct hyper- and hypodense areas: in many cases a differential diagnosis with benign and

malignant cystic pancreatic lesions is mandatory [13, 16]. In some reports UPC is described as a large, fluid-filled cystic neoplasm with mural nodule on CT scan [19, 20]. In rare cases the tumor reveals itself as a large polypoid mass in the periampullary area protruding from the main pancreatic duct into the duodenal lumen [12, 21].

To date, T1- T2-weighted contrast enhanced MRI with intravenous Gadolinium administration with magnetic resonance cholangio-pancreatography (MRCP) is considered the referral exam for pancreatic cystic lesions [22, 23]. MRI is a second-level imaging exam in pancreatic tumors but it is essential in defining complex masses and allows a detailed assessment of the pancreatic ductal system [23]. MRI can characterize with high accuracy the morphology and nature of cystic areas and solid tissue located between cyst walls [23]. MRCP could confirm a dilatation of main pancreatic and common bile duct and show a communication between the pancreatic ducts and the cystic mass [22, 23].

EUS provides high-resolution images and fine-needle aspiration (FNA) of the gland lesions; it is currently crucial in the diagnostic work-up of pancreatic tumors [24]. The echotexture of UPC tends to be heterogeneous with the simultaneous presence of demarcated hypo- and hyperechoic areas within the same lesion; this typical UPC ultrasound imaging differs from conventional PDAC which is often more uniformly hypoechoic [25]. To date EUS FNA have gained high level of diagnostic accuracy in these lesions: in a cytologic analysis of 15 cases, the preoperative FNA diagnosed a pancreatic malignancy in 90% of the cases and UPC diagnosis (with or without osteoclast-like giant cells) was made in 8 patients [17].

In recent decades the widespread use of abdominal imaging has led to the discovery of a growing number of asymptomatic pancreatic tumors [5, 6, 7]. Consequently case reports of incidentally discovered UPCs have been recently described [21, 26].

Macroscopically these tumors show a wide range of presentations. Small UPCs are usually well-circumscribed smooth-surfaced nodule with focal areas of hemorrhage. At cut, the consistency of these neoplasms can range from firm to soft [11]. However, in most cases, at presentation UPCs are usually large pancreatic complex masses with cystic and solid components [11, 12, 16]. They show hemorrhagic areas and cystic degeneration of variable extent [16]. The cystic cavities are filled by opaque hemorrhagic material [11]. Larger neoplasms tend to exhibit areas of necrosis and the surrounding pancreatic tissue is generally atrophic [11, 13]. In a minority of cases, UPC may protrude into the main pancreatic duct or duodenal lumen [12].

Often the UPC contains foci of conventional ductal adenocarcinoma [16, 27, 28]. Although more rarely, it may also be associated with mucinous cystic neoplasms or intraductal papillary mucinous neoplasms [13, 16, 17, 20, 29].

CLASSIFICATION AND HISTOLOGY

Currently the majority of the Authors defines two types of giant cell tumors (GCT): Osteoclast-like giant cell tumor (OGCT) and pleomorphic giant cells tumor (PGCT) [25, 28, 30, 31, 32]. More recently a third variant containing both cellular types, the mixed giant cell tumor (MGCT), also called mixed osteoclastic-pleomorphic GCT, has been described in the literature, showing the simultaneous presence of both histological histotypes [25, 27, 28, 31, 32, 33].

OGCT is often a large cystic neoplasm and its histological appearance resembles GCT of the bone. Rosai firstly described a type of undifferentiated pancreatic carcinoma containing osteoclast like giant cells [34]. Spindle-shaped cells and giant cells with multiple nuclei are common findings. OGCT is a rare neoplasm: in a study based on Surveillance, Epidemiology, and End Result database it showed a frequency of about 10% of all UPCs [10]. Microscopically this tumor is characterized by the presence of two different cellular elements: spindle or ovoid mononuclear cells and giant cells and osteoclast-like giant cells (OGCs) [16]. Spindle-shaped cells are uniform with mesenchymal differentiation and high mitotic index, while osteoclast-like giants cells are large elements characterized by the presence of many (frequently more than 20) small nuclei without features of atypia [8, 25]. The nuclei of the giant cells are tiny and uniform, without mitoses. Often ovoid mononuclear cells are detected [35]. Some mononuclear cells (histiocytic mononuclear cells) appear regular shaped, without atypical features, and containing a single nucleus; others ovoid mononuclear elements (atypical mononuclear cells) present a neoplastic morphology with bizarre nuclei [35]. The giant cells are diffusely distributed throughout the neoplasm but they are constantly found near to hemorrhagic areas; in many cases these cells contain phagocytized mononuclear cells [8]. Occasionally osteoid tissue is present [16].

PGCT is also known as sarcomatoid carcinoma [8, 31]. This neoplasm derives from ductal carcinoma but the histological features and aggressive behavior make it a distinct variant of pancreatic cancer. PGCT is characterized by the presence of atypical mono- and multinucleated pleomorphic giant cells (PGCs) and a sarcoma-like growth pattern [31]. High mitotic activity invariably determines lymphatic, venous, and perineural invasion [8]. In PGCT three different cellular lines are simultaneously present in various combinations: large eosinophilic pleomorphic cells, spindle-shaped cells, and small regular round cells [36]. All these cell types are aggregated in poorly cohesive clusters surrounded by a fibrillar stroma [8]. PGCs are the hallmark of this type of neoplasms: they consist of bizarre mono- or multi-nucleated giant cells with irregular nuclei with atypical mitoses [25]. The spindle cells give the tissue a sarcomatoid appearance [8, 36].

The mixed type shows an overlap of pleomorphic and osteoclastic-like histologic features (**Figure 1**) [33]. Some Investigators suggest defining pancreatic MGCT as

an independent pathological entity characterized by the presence of a significant of PGCs into OGCT (about 30%-40%) [30, 32, 37].

It is necessary to underline that in the recent past some Authors classified only the PGCT as undifferentiated or anaplastic pancreatic tumor, categorizing the OGCT as a separate variety of pancreatic carcinoma [11, 38]. Also the WHO classification of ductal adenocarcinoma of pancreas foresees only two variants of UPC: undifferentiated carcinoma (previously undifferentiated anaplastic carcinoma) and undifferentiated carcinoma with osteoclast-like giant cells [8].

The histogenesis of GCT has been widely discussed and remains controversial due to the rarity of the neoplasm. The origin of OGCT was debated in the past decades: based on microscopic and immune-histochemical evidence, some Authors favored a possible epithelial origin, while others hypothesized an origin from mesenchymal cells [16, 27, 34, 39]. In the first description of OGCT, the giant cells were supposed to have an epithelial origin, particularly from acinar cells of the pancreas [34]. In 1987, Fischer first demonstrated the mesenchymal differentiation of OGTP, which is also able to form epithelial structures [40]. Mononuclear cells and OGCs, in fact, reacted with antibody against vimentin, but were stained by antibodies against α -1-antichymotrypsin (A1ACT) and α -1-antitrypsin. Recent immune-histochemical studies definitely highlighted that OGCs show no reactivity to epithelial markers and present positive reactivity to histiocytic markers like CD68 and vimentin [16, 28, 31, 35, 41] (**Figure 2**). Conversely the spindle cells express epithelial markers like low-weight cytokeratins and are frequently positive for vimentin [16, 35]. Moreover, the immunoreactivity for Ki-67 shows a low proliferative profile of OGCs and a high proliferative activity for spindle cells and atypical mononuclear cells. Currently it is widely accepted that spindle-shaped cells are tumoral elements, while OGCs are not neoplastic, but reactive cells deriving from a histiocytic lineage [15, 16, 27, 35]. Furthermore some Authors have hypothesized that

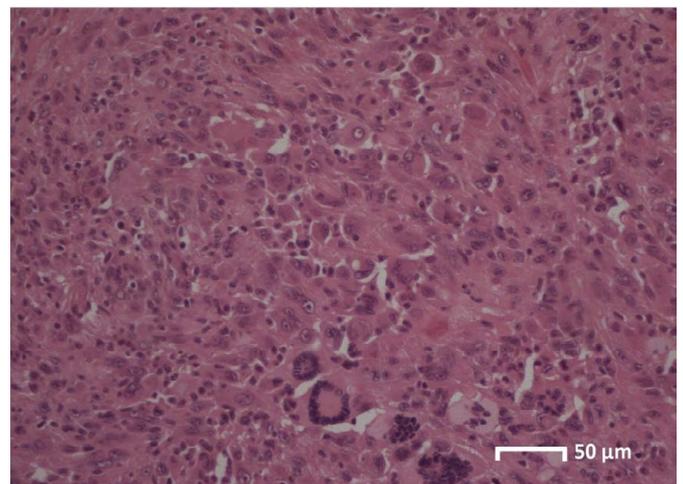


Figure 1. A mixed giant cell tumor composed by mononuclear spindle cells, associated with pleomorphic giant cells and scattered osteoclast-like giant cells (ematoxylin/eosin staining, 20x).

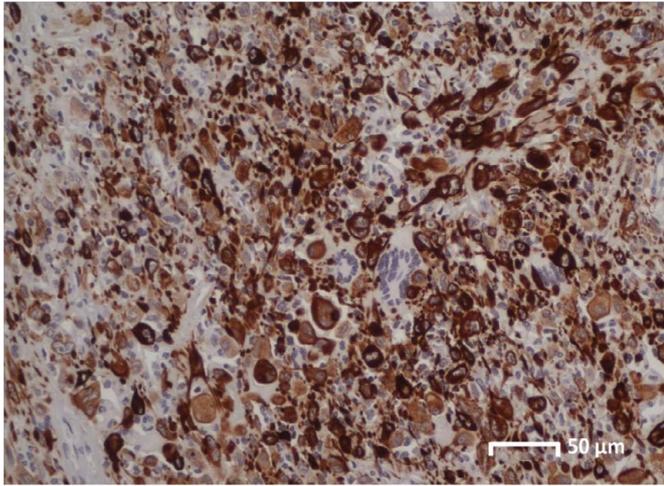


Figure 2. Pleomorphic giant cells are immunoreactive for epithelial markers (cytokeratins 8/18), while multinucleated osteoclast-like giant cells are negative (20x).

OGCs result from the fusion of histiocytic mononuclear cells [35,39]. In summary, OGCT originates from epithelial elements (acinar or ductal is still debated), spindle and atypical mononuclear cells are the neoplastic component of neoplasm, while OGCs are reactive histiocytic cells.

It is widely accepted that PGCT has an epithelial origin from a ductal adenocarcinoma with a subsequent sarcomatous transformation [31, 35]. In 1988 Silverman reported the first series of four cases of PGCT with immunohistochemical study [42]. All cases were positive for vimentin while only half of the specimens stained with cytokeratins.

PGCs frequently express mesenchymal markers such as vimentin, but rarely histiocytic markers such as CD68 [27, 30, 31]. Furthermore, PGCs show immunoreactivity for epithelial markers such as low-weight cytokeratins or CEA in a significant number of cases [30, 31] (**Figure 2**). These data support the hypothesis that PGCs are undifferentiated neoplastic cells deriving from epithelial elements with a subsequent sarcomatous transformation, expression of the epithelial-mesenchymal transition [43]. In rare cases PGCs are negative for both epithelial and mesenchymal markers; these findings are compatible with an extreme tumor dedifferentiation [35, 36]. At the same time, PGCs share many cellular features with spindle-shaped cells: they have an analogous immunohistochemical profile and a similarity in the aneuploidy-hyperploidy in chromosomal analysis. These cytological features have suggested some Authors hypothesized an origin of PGCs from spindle cells [30].

As expected, MGCT shows both histological characteristics, sowing doubts on the real independent origin of PGCT and OGCT. The concomitant presence of these two cell lines led several investigators to suppose a possible overlap in the origin of these tumors: OGCs and PGCs may derive from a unique cellular precursor capable of generating different neoplastic histotypes [27, 31, 35, 37]. Consequently, OGCT and PGCT could be two ends of a biological spectrum of a single neoplasm [27].

IMMUNOHISTOCHEMISTRY AND MOLECULAR PATHOLOGY

In the last decades, several studies focused on the immunohistochemical profiles of the different cell types of UPC [30, 32, 33]. OGCs constantly show a positive staining for the histiocytic marker CD65 and less frequently for antibody against vimentin and cathepsin D [16, 27, 30, 31, 33]; CD45 and lysozyme are not constantly expressed [27, 31, 33, 37]. At the same time, OGCs are always negative for epithelial markers such as ketarins (AE1/AE3, CAM 5.2), epithelial membrane antigen (EMA) and CEA [12, 17]. Moreover, these cells usually present negative immunohistochemical staining to desmin, smooth muscle actin, and rarely positive to A1ACT [11, 30, 31, 32]. Also p53 is always negative in OGCs [12].

PGCs present immunoreactivity for keratins and CEA in a significant number of cases; EMA is less frequently positive [11, 17, 28, 30]. PCCs may show positive staining for mesenchymal markers such as vimentin [31, 33, 37], while histiocytic markers, such as CD68 or CD45, are weakly positive in rare cases [11, 27, 30, 31]. In the majority of cases p53 is moderately to strongly reactive in this cell type [11, 12].

Spindle-shape cells invariably express epithelial markers like keratins (AE1/AE3, CAM 5.2, and CEA) but are less frequently positive for vimentin [16, 31, 35]. Positive immunohistochemical staining for A1ACT and smooth muscle actin is also described [30,31]. These cell types are usually negative for histiocytic markers [16].

INI-1 protein, a recently identified marker specific for UPC, is frequently expressed in PGCs and mononuclear cells [17]; S100, chormogranin A, and synaptophysin are usually negative in all cellular types [11, 17].

The progression from dysplastic epithelium to invasive pancreatic carcinoma is currently well defined due to the extensive genetics studies on somatic mutations of oncogenes and tumor suppressor genes. In the majority of PDACs four driver genes are involved: KRAS, CDKN2A, TP53, and SMAD4 [44, 45]. KRAS and CDKN2A are the more frequent genetic alterations: activating mutations of KRAS oncogene are found in 90% of patients and inactivation of CDKN2A suppressor gene is present in about 95% of cases. Moreover TP53 alterations are found in 50-80% and SMAD4 mutations are found in 30-60% of PDACs [46].

While the sequence of genetic alteration is well studied in PDAC, much less is known about mutations occurring in UPC [4]. In OGCT, the KRAS mutation is well documented in several studies [11, 30, 35]. In a recently published study the entire exome sequencing was performed on 8 cases of OGCTs [14]. As in conventional PDAC, OGCT presented somatic mutations in the four driver genes. All eight cases showed alterations in KRAS oncogene and seven cases in TP53 suppressor gene. Two OGCTs had mutation in CDKN2A and one presented a mutation of SMAD4 gene. In this analysis also sporadic alterations were detected in PTEN, BAP1 and SERPINA3 genes [14]. The

study suggested that, despite their histologic differences, conventional PDAC and UPC could share a common origin.

PROGNOSIS

The UPC has a poor prognosis: recent series show that UPC survival is worse than the ordinary pancreatic ductal adenocarcinoma [11, 13]. The median overall survival is 3-6 months and the 5-year survival rate is 8% [10, 13]. Furthermore, PGCT is characterized by a poor prognosis with a mortality rate of about 85% at 1 year- follow-up [13].

Discrepant data about OGCT prognosis were reported in the recent literature. Early reports, based on single cases, suggested that it might have a better outcome than ordinary ductal carcinoma [37, 47, 48]. However in a series of 9 cases all patients except one died within 1 year from diagnosis [16]. Conversely, in a retrospective analysis of 15 patients affected by UPC, all long-term survivors presented a neoplasm containing OGCs [13]. In a more recent large population study, the OGCT showed a better prognosis compared to others type of UPC [10]. It is interesting to note that in two small series the presence of a high proportion of pleomorphic cells into OGCT was associated to shorter survival [30, 49]. These series highlight how OGCT could be slower to metastasize and less often associated with lymph nodes involvement [12, 32]. It also seems to show a better fairly good response to surgery and chemotherapy. On the other hand, PGCT shows a fatal evolution in short time. This can be attributed to early lymph nodal invasion and rapid formation of distant metastasis [32, 36]. The mixed type seems to have an intermediate prognosis characterized by a very uncertain behavior. Nevertheless, its behavior seems more benign than the classic PGCT.

Definitely UCP is characterized by a poor prognosis; however, case series from medical literature highlight that long-term survival is possible in patients affected by OGCT. In a patient with this type of pancreatic carcinoma, an accurate histopathological diagnosis could predict different behavioral pathways in terms of tumor progression and prognostic profile.

CONCLUSION

The nosological classification of the UPC is difficult due to the uncertain origin of its histological variants. It is important to underline how, due to the rarity of the pathology, all these findings are based on small case-series and case reports, leading to the lack of consistent survival data. Currently UPC is classified into three histotypes in the recent literature: OGCT, PGCT, and MGCT. In particular, as we know, of the mixed type less than 50 cases have been published in literature, and its true characteristics and behavior are still uncertain; in particular, the mixed type variant could be the missing link between PGCT and OGCT. Nevertheless, the three different types of GCT seem to show different behavioral pathways in terms of metastatic invasion and long term survival.

ACKNOWLEDGEMENTS

We thank Dr. Gerardo Cioffi, native speaker, for reviewing the English language.

Conflicts of Interest

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

REFERENCES

1. 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:30207593]
2. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. *N Engl J Med* 2014; 371:1039-1049. [PMID: 25207767]
3. Hidalgo M. Pancreatic cancer. *N Engl J Med* 2010; 362:1605-1617. [PMID:20427809]
4. Luchini C, Capelli P, Scarpa A. Pancreatic ductal adenocarcinoma and its variants. *Surg Pathol Clin* 2016; 9:547-560. [PMID:27926359]
5. Bruzoni M, Johnston E, Sasson AR. Pancreatic incidentalomas: clinical and pathologic spectrum. *Am J Surg* 2008; 195:329-332. [PMID: 18308040]
6. Sachs T, Pratt WB, Callery MP, Vollmer CM Jr. The incidental asymptomatic pancreatic lesion: nuisance or threat? *J Gastrointest Surg* 2009; 13:405-415. [PMID: 19130153]
7. Chiarelli M, Gerosa M, Tagliabue F, Fumagalli L, Guttadauro A, Gabrielli F, et al. Left-sided pancreatic incidentalomas treated with laparoscopic approach: a report of 20 cases. *World J Surg Oncol* 2016; 14:204. [PMID: 27487847]
8. WHO Classification of Tumours Editorial Board. *Digestive System Tumours*, Lyon (France): International Agency for research on Cancer; 2019 (WHO classification of tumors series, 5th edn; vol 1).
9. Sommers SC, Meissner WA. Unusual carcinomas of the pancreas. *AMA Arch Pathol* 1954; 58:101-111. [PMID: 13170907]
10. Clark CJ, Graham RP, Arun JS, Harmsen WS, Reid-Lombardo KM. Clinical outcomes for anaplastic pancreatic cancer: a population-based study. *J Am Coll Surg* 2012; 215:627-634. [PMID: 23084492]
11. Paal E, Thompson LD, Frommelt RA, Przygodzki 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]
12. Muraki T, Reid MD, Basturk O, Jang KT, Bedolla G, Bagci P, et al. Undifferentiated carcinoma with osteoclastic giant cell of the pancreas. Clinicopathologic analysis of 38 cases highlights a more protracted clinical course than currently appreciated. *Am J Surg Pathol* 2016; 40:1203-1216. [PMID:27508975]
13. Strobel O, Hartwig W, Bergmann F, Hinz U, Hackert T, Grenacher L, et al. Anaplastic pancreatic cancer: Presentation, surgical management, and outcome. *Surgery* 2011; 149:200-208. [PMID: 20542529]
14. Luchini C, Pea A, Lionheart G, Mafficini A, Nottegar A, Veronese N, et al. Pancreatic undifferentiated carcinoma with osteoclast-like giant cells is genetically similar to, but clinically distinct from, conventional ductal adenocarcinoma. *J Pathol* 2017; 243:148-154. [PMID: 28722124]
15. Lukás Z, Dvorák K, Kroupová I, Valásková I, Habanec B. Immunohistochemical and genetic analysis of osteoclastic giant cell tumor of the pancreas. *Pancreas* 2006; 32:325-329. [PMID: 16628090]
16. Molberg KH, Heffess C, Delgado R, Albores-Saavedra J. Undifferentiated carcinoma with osteoclast-like giant cells of the pancreas and periampullary region. *Cancer* 1998; 82:1279-1287. [PMID: 9529019]
17. Reid M, Muraki T, HooKim K, Memis B, Graham RP, Allende D, et al. Cytologic features and clinical implications of undifferentiated carcinoma with osteoclastic giant cells of the pancreas: an analysis of 15 cases. *Cancer Cytopathol* 2017; 125:563-575. [PMID: 28371566]

18. Low G, Panu A, Millo N, Leen E. Multimodality imaging of neoplastic and non-neoplastic solid lesions of the pancreas. *Radiographics* 2011; 31:993-1015. [PMID: 21768235]
19. Leighton CC, Shum DT. Osteoclastic giant cell tumor of the pancreas: case report and literature review. *Am J Clin Oncol* 2001; 24:77-80. [PMID: 11232955]
20. Chiarelli M, Guttadauro A, Gerosa M, Marando A, Gabrielli F, De Simone M, et al. An indeterminate mucin-producing cystic neoplasm containing an undifferentiated carcinoma with osteoclast-like giant cells: a case report of a rare association of pancreatic tumors. *BMC Gastroenterol* 2015; 15:161. [PMID: 26581412]
21. Maksymov V, Khalifa MA, Bussey A, Carter B, Hogan M. Undifferentiated (anaplastic) carcinoma of the pancreas with osteoclast-like cells showing various degree of pancreas duct involvement. A case report and literature review. *JOP* 2011; 12:170-176. [PMID: 21386647]
22. Tanaka M, Fernandez del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatol* 2012; 12:183-197. [PMID: 22687371]
23. Kalb B, Sarmiento JM, Kooby DA, Adsay NV, Martin DR. MR imaging of cystic lesions of the pancreas. *Radiographics* 2009; 29:11749-1765. [PMID: 19959519]
24. Larghi A, Petrone MC, Galasso D, Arcidiacono PG. Endoscopic ultrasound in the evaluation of pancreaticobiliary disorders. *Dig Liv Dis* 2010; 42:6-15. [PMID: 19665951]
25. Moore JC, Bentz JS, Hilden K, Adler DG. Osteoclastic and pleomorphic giant cell tumors of the pancreas: A review of clinical, endoscopic, and pathologic features. *World J Gastrointest Endosc* 2010; 2:15-19. [PMID: 21160673]
26. Sakhi R, Hamza A, Khurram MS, Ibrar W, Mazzara P. Undifferentiated carcinoma of the pancreas with osteoclast-like giants cells reported in an asymptomatic patient: a rare case and literature review. *Autops Case Rep* 2017; 7:51-57. [PMID: 29259932]
27. Martin A, Texier P, Bahnini JM, Diebold J. An unusual epithelial pleomorphic giant cell tumour of the pancreas with osteoclast-type cells. *J Clin Pathol* 1994; 47:372-374. [PMID: 7517956]
28. Loya AC, Ratnakar KS, Shastry RA. Combined osteoclastic giant cell and pleomorphic giant cell tumor of the pancreas: a rarity. An immunohistochemical analysis and review of the literature. *JOP* 2004; 5:220-224. [PMID: 15254351]
29. Wada T, Itano O, Oshima G, Chiba N, Ishikawa H, Koyama Y, et al. A male case of an undifferentiated carcinoma with osteoclast-like giant cells originating in an indeterminate mucin-producing cystic neoplasm of the pancreas. A case report and review of the literature. *World J Surg Oncol* 2011; 9:100. [PMID: 21902830]
30. Deckard-Janatpour K, Kragel S, Teplitz RL, Min BH, Gumerlock PH, Frey CF, et al. Tumors of the pancreas with osteoclast-like and pleomorphic giant cells: an immunohistochemical and ploidy study. *Arch Pathol Lab Med* 1998; 122:266-272. [PMID: 9823867]
31. Watanabe M, Miura H, Inoue H, Uzuki M, Noda Y, Fujita N, et al. Mixed osteoclastic/pleomorphic-type giant cell tumor of the pancreas with ductal adenocarcinoma: histochemical and immunohistochemical study with review of the literature. *Pancreas* 1997; 15:201-208. [PMID: 9260206]
32. Lewandrowski KB, Weston L, Dickersin GR, Rattner DW, Compton CC. Giant cell tumor of the pancreas of mixed osteoclastic and pleomorphic cell type: evidence for a histogenetic relationship and mesenchymal differentiation. *Hum Pathol* 1990; 21:1184-1187. [PMID: 2227926]
33. Gatteschi B, Saccomanno S, Bartoli FG, Salvi S, Liu G, Pugliese V. Mixed pleomorphic-osteoclast-like tumor of the pancreas. Light microscopical, immunohistochemical, and molecular biological studies. *Int J Pancreatol* 1995; 18:169-175. [PMID: 8530833]
34. Rosai J. Carcinoma of pancreas simulating giant cell tumor of bone. Electron-microscopic evidence of its acinar cell origin. *Cancer* 1968; 22:333-344. [PMID: 5660199]
35. Sakai Y, Kupelioglu AA, Yanagisawa A, Yamaguchi K, Hidaka E, Matsuya S, et al. Origin of giant cells in osteoclast-like giant cell tumors of the pancreas. *Hum Pathol* 2000; 31:1223-1229. [PMID: 11070115]
36. Chadha MK, LeVea C, Javle M, Kuvshinov B, Vijaykumar R, Iyer R. Anaplastic pancreatic carcinoma. A case report and review of literature. *JOP* 2004; 5:512-515. [PMID: 15536293]
37. Ezenekwe AM, Collins BT, Ponder TB. Mixed osteoclastic/pleomorphic giant cell tumor of the pancreas: a case report. *Acta Cytol* 2005; 49:549-553. [PMID: 16334035]
38. Alguacil-Garcia A, Weiland LH. The histologic spectrum, prognosis, and histogenesis of the sarcomatoid carcinoma of the pancreas. *Cancer* 1977; 39:1181-1189. [PMID: 912652]
39. Goldberg RD, Michelassi F, Montag AG. Osteoclast-like giant cell tumor of the pancreas: immunophenotypic similarity to giant cell tumor of bone. *Hum Pathol* 1991; 22:618-622. [PMID: 1864595]
40. Fischer HP, Altmannsberger M, Kracht J. Osteoclast-type giant cell tumour of the pancreas. *Virchows Arch A Pathol Anat Histopathol* 1988; 412:247-253. [PMID: 3124345]
41. Wong M, See JY, Sufyan W, Diddapur K. Splenic infraction. A rare presentation of anaplastic pancreatic carcinoma ad review of the literature. *JOP* 2008; 9:493-498. [PMID: 18648141]
42. Silverman JF, Dabbs DJ, Finley JL, Geisinger KR. Fine-needle aspiration biopsy of pleomorphic (giant cell) carcinoma of the pancreas. Cytologic, immunocytochemical, and ultrastructural findings. *Am J Clin Pathol* 1988; 89:714-720. [PMID: 3369361]
43. Ishida K, Yamashita R, Osakabe M, Uesugi N, Yamada N, Nitta H, et al. Expression of epithelial-mesenchymal transition proteins in pancreatic anaplastic (undifferentiated) carcinoma. *Pancreas* 2019; 48:36-42. [PMID: 30451796]
44. Biankin AV, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* 2012; 491:399-405. [PMID: 23103869]
45. Felenstein M, Hruban R, Wood LD. New developments in the molecular mechanisms of pancreatic tumorigenesis. *Adv Anat Pathol* 2018; 25:131-142. [PMID: 28914620]
46. Hosoda W, Wood LD. Molecular genetics of pancreatic neoplasms. *Surg Pathol Clin* 2016; 9:685-703. [PMID: 27926367]
47. Jeffrey I, Crow J, Ellis BW. Osteoclast-type giant cell tumour of the pancreas. *J Clin Pathol* 1983; 36:1165-1170. [PMID: 6619312]
48. Baniel J, Konichezky M, Wolloch Y. Osteoclast-type giant cell tumor of the pancreas. Case report. *Acta Chir Scand* 1987; 153:67-69. [PMID: 3577570]
49. Moore JC, Hilden K, Bentz JS, Pearson RK, Adler DG. Osteoclastic and pleomorphic giant cell tumors of the pancreas diagnosed via EUS-guided FNA: unique clinical, endoscopic, and pathologic findings in a series of 5 patients. *Gastrointest Endosc* 2009; 69:162-166. [PMID: 19111699]