

Review Article

Comprehensive review of undifferentiated carcinoma of the pancreas: from epidemiology to treatment

Hiroshi Imaoka^{1,*}, Masafumi Ikeda¹, Kumiko Umemoto², Yu Sunakawa², Makoto Ueno³, Hideki Ueno⁴, Masato Ozaka⁵, Takamichi Kuwahara⁶, Naohiro Okano⁷, Masashi Kanai⁸, Terumasa Hisano⁹, Yuko Suzuki¹⁰, Akinori Asagi¹¹, Kazuhiko Shioji¹², Akiko Todaka¹³, Kunihiro Tsuji¹⁴, Kenji Ikezawa¹⁵, Ikuya Miki¹⁶, Yoshito Komatsu¹⁷, Noriyuki Akutsu¹⁸, Tatsuya Yamashita¹⁹, Hiroyuki Okuyama²⁰, Junji Furuse³ and Hiroaki Nagano²¹

¹Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan,

²Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan, ³Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan, ⁴Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan, ⁵Hepato-Biliary-Pancreatic Medicine Department, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan, ⁶Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan, ⁷Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan,

⁸Department of Medical Oncology, Kyoto University Hospital, Kyoto, Japan, ⁹Department of Hepato-Biliary-Pancreatology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan,

¹⁰Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan, ¹¹Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, ¹²Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan, ¹³Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, ¹⁴Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan, ¹⁵Department of Hepatobiliary and Pancreatic Oncology, Osaka International Cancer Institute, Osaka, Japan, ¹⁶Department of Gastroenterological Oncology, Hyogo Cancer Center, Akashi, Japan, ¹⁷Department of Gastroenterology, Hokkaido University Hospital, Sapporo, Japan, ¹⁸Department of Gastroenterology and Hepatology, Sapporo Medical University School of Medicine, Sapporo, Japan, ¹⁹Department of Gastroenterology, Kanazawa University Hospital, Kanazawa, Japan, ²⁰Department of Medical Clinical Oncology, Kagawa University Hospital, MikiKagawa, Japan and ²¹Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine, Ube, Japan

¹⁹Department of Gastroenterology, Kanazawa University Hospital, Kanazawa, Japan, ²⁰Department of Medical Clinical Oncology, Kagawa University Hospital, MikiKagawa, Japan and ²¹Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine, Ube, Japan

²⁰Department of Medical Clinical Oncology, Kagawa University Hospital, MikiKagawa, Japan and ²¹Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine, Ube, Japan

²¹Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine, Ube, Japan

²¹Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine, Ube, Japan

*For reprints and all correspondence: Hiroshi Imaoka, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. E-mail: hiimaoka@east.ncc.go.jp

Received 16 May 2023; Editorial Decision 25 May 2023; Accepted 27 May 2023

Abstract

Undifferentiated carcinoma (UC) of the pancreas is a rare subtype of pancreatic cancer displaying no definitive direction of differentiation. UC has been reported as a highly aggressive malignant neoplasm, with a median overall survival of <1 year, except for several surgical series. On the other hand, UC tissue sometimes contains non-neoplastic osteoclast-like giant cells (OGCs), and such cases have been reported to have relatively longer survival. Thus, the World Health Organization (WHO) classification histologically distinguishes UC with OGCs (UCOGCs) from UC, and UCs were

subclassified into three subtypes: anaplastic UC, sarcomatoid UC and carcinosarcoma. However, still less is known about UC due to its rarity, and such situations lead to further difficulties in treatment for UC. To date, only surgical resection can offer curative treatment for patients with UC, and no clear evidence for chemotherapy exists for them. However, a retrospective cohort study and case reports showed that relatively promising results paclitaxel-containing regimens for treatment of patients with unresectable UC. Furthermore, high programmed cell death protein 1 expression has been reported in sarcomatoid UCs and UCOGCs, and promising responses to anti-programmed death-ligand 1 therapy have been described in case reports of UCOGCs. Recent advances in chemotherapeutic agents and molecular technologies are opening up the possibilities for expanded treatments.

Key words: osteoclast-like giant cells, carcinosarcoma, sarcomatoid undifferentiated carcinoma, anaplastic carcinoma, undifferentiated carcinoma

Introduction

Epithelial malignant tumours of the pancreas are categorized into exocrine neoplasms arising from exocrine glands and neuroendocrine neoplasms arising from endocrine glands. Pancreatic cancer (PC) is classified as an exocrine neoplasm, and it accounts for nearly 90% of pancreatic neoplasms (1). The prognosis of PC is poor, and Siegel et al. reported that the 5-year survival rate of PC patients was only 12%, the lowest of all cancer types (2).

Undifferentiated carcinoma (UC) of the pancreas, also known as anaplastic carcinoma of the pancreas, is a rare subtype of PC. UC is a neoplasm displaying no definitive direction of differentiation. Unlike conventional PC (ductal adenocarcinoma), UC is poorly cohesive and hypercellular, with scant stroma (3). The frequency of UC in malignant neoplasms of the pancreas varied from 0.3 to 7% in the previous reports (3–6). UC has basically been considered more aggressive than PC (4, 5, 7). On the other hand, UC tissue sometimes contains non-neoplastic osteoclast-like giant cells (OGCs), and such cases have been reported to have relatively long survival (5, 8). Based on these findings, although UCs were classified into three subtypes (pleomorphic type, spindle cell type and anaplastic carcinoma with OGCs) in the Japanese classification of pancreatic cancer (9), the WHO classification histologically distinguishes UC with OGCs (UCOGC) from UC. Furthermore, UCs were subclassified into three subtypes based on recent reports of UC variants with molecular analysis: anaplastic UC, sarcomatoid UC and carcinosarcoma (10).

So far, though there have been relatively many case reports of UC (11), only a few studies have systematically reported its clinical and molecular features. Such situations lead to further difficulties in our understanding of UC. However, recent developments in molecular technologies such as next-generation sequencing open up the possibility of understanding and treatment for UC. In this review, the current knowledge of the epidemiology, clinical features, diagnosis, prognosis, histological findings and treatment of UC of the pancreas are outlined. Furthermore, the molecular features of UC, which may lead to new therapeutic strategies for the treatment of them, are considered.

Epidemiology

The frequency of UC in malignant neoplasms of the pancreas varied from 0.3 to 7% in the previous reports (3–6). Recent studies reported that the frequency of UC was 2–3%. The most reliable epidemiological data were reported based on SEER registry data by Clark

et al (4). Of a total 6212 patients with PC, 353 patients (5.7%) were diagnosed with UC, and 11 patients (0.2%) were diagnosed with UCOGC. The age-adjusted incidence of UC was 0.027 per 100 000 persons [95% confidence interval (CI), 0.023–0.031]. There are many case reports of UC. However, epidemiological reports by Clark et al. indicate that these are biased data, and that the actual frequency is extremely rare.

In the incidence of UC, no racial difference has been reported (4), and the median age at diagnosis is around the 1960s, being slightly more common in male than in female patients. Clark et al. reported that the proportion of male patients with UC was slightly higher (57.5%) than that of female patients, and the median age at diagnosis was 67 years, with no significant difference both in sex and age compared with PC (4). Paal et al. also reported 35 cases of UC using registry data retrieved from the Armed Forces Institute of Pathology (7). In their reports, the median age at diagnosis was 62.0 years, and UC showed male predominance (71.4%). Thus, UC shares characteristics with its counterpart PC. On the other hand, a younger, female predominance has been reported in UCOGCs. Muraki et al. reported 38 cases of UCOGCs (8), and the mean age at diagnosis was 57.9 years, with a range from 29 to 86 years, and UCOGCs showed slight female predominance (62.9%).

Clinical features

Size and tumour location

Reflecting its highly aggressive behaviour, UC tends to show larger size. The median tumour size was reported to be 60–90 mm, with larger tumours than PC (4, 7, 8), but there was no significant difference in tumour size amongst subtypes of UC (7). The tumour was less frequently located in the head of the pancreas in UC than in PC (43.4% vs. 67.5%, $P < 0.001$) (4).

Symptoms

Due to their large size, UCs are often accompanied by some clinical symptoms. These symptoms commonly include abdominal pain and weight loss, but no specific symptoms have been reported in both UC and UCOGCs. In the report by Paal et al., patients reported abdominal pain (51.4%), weight loss, loss of appetite (14.3%), nausea and/or vomiting (11.4%), fatigue (5.7%) and diarrhoea (5.7%) (7). In UCOGCs, Muraki et al. reported that presenting symptoms included abdominal or back pain (62%), weight loss (38%), nausea (28%), tarry stool and jaundice (14%) in four patients each and diabetes mellitus (10%) in three.

The patients with UC were in poor condition at the time of diagnosis due to its aggressive behaviour (12). We reported that the Eastern Cooperative Oncology Group performance status (ECOG PS) was ≥ 1 for 80% and ≥ 2 for 20% at the time of diagnosis.

Diagnosis

Tumour markers

Both carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are commonly used tumour markers for PC. However, they were mostly not elevated in UC. We reported CEA and CA19-9 levels in both UC and UCOGCs at an advanced stage (12). The median [interquartile range (IQR)] CEA and CA19-9 levels were 3.5 (2.0–6.9) and 35.7 (16.4–556.0) U/ml in UC and 2.1 (1.7–3.1) ng/mL and 22.8 (5.0–131.0) U/mL in UCOGCs, respectively. Gao et al. reported 13 patients with UCOGCs (13), and the commonly used tumour markers of CEA, CA19-9 and AFP were mostly not elevated. The median (IQR) CEA, CA19-9 and AFP levels were 3.0 (2.4–11.8) ng/ml, 34.0 (11.5–62.0) U/ml and 2.0 (1.2–2.3) ng/ml, respectively. Notably, on the other hand, NSE levels were elevated in 66% of patients with UCOGC (median, 23.0 ng/ml; IQR, 21.5–26.0 ng/ml). On the other hand, other tumour markers such as DUPAN-2 and Span-1 are known to be useful in the diagnosis of PC, but there have been no reports of their usefulness for UC.

Radiological modalities

In most cases of UC, computed tomography (CT) is sufficient to identify the tumour. However, since UC is a variant of PC, it has similar imaging features to those of PC. Ishigami et al. reported that multidetector-row CT showed a hypovascular tumour with upstream main pancreatic duct dilatation (14). On the other hand, due to its highly aggressive behaviour, haemorrhagic necrosis was present within tumours. Furthermore, intraductal tumour growth in the main pancreatic duct and tumour thrombus were often observed, and these findings may support the imaging diagnosis of UC.

Endoscopic ultrasound-guided tissue acquisition

As previously described, there are no tumour markers or radiological findings useful for the diagnosis of UC. Thus, pathological examination is mandatory for diagnosis. One of the reasons why UC is reported mainly in surgical series is that it is difficult to obtain a tissue diagnosis of UC preoperatively. Chadha et al. reported the utility of pathological diagnosis of biopsy specimens in exploratory laparotomy or from liver metastases (15). However, a less invasive approach is demanded for the diagnosis of UC.

Recently, advances in diagnostic modalities are facilitating the diagnosis of pancreatic neoplasms (16–19). This enables us to acquire more accurate pathological diagnoses of UC even in cases of unresectable disease (12). We reported the clinical courses of advanced-stage UC patients retrospectively. Of the total 55 patients, 14 (25.5%) were diagnosed via Endoscopic ultrasound-guided tissue acquisition (EUS-TA) (20). Currently, EUS-TA is vital for the diagnosis of UC, especially in the advanced stage.

The diagnosis of UCOGC requires inclusion of OGCs in the small specimens obtained by EUS-TA. However, EUS-TA is a useful approach in the diagnosis of UCOGC. Reid et al. examined 15 cases of UCOGC that underwent EUS-TA, and 6 (40%) could be diagnosed (21). EUS-TA specimens showed specific components to UCOGC (neoplastic pleomorphic mononuclear cells, OGCs and spindle cells) and adenocarcinoma components in the sample. Furthermore, they reported that immunostaining of specimens obtained by EUS-TA

for the macrophage and monocyte marker CD68 and the epithelial differentiation marker epithelial membrane antigen (EMA), may help in the diagnosis. Similarly, the utility of EUS-TA for the diagnosis of UCOGC has been reported in some case series (22, 23).

Regarding the diagnosis of UC via EUS-TA, the most important issue is the differentiation of UC from conventional PC. Therefore, obtaining a tissue sample including neoplastic cells specific to UC, such as neoplastic pleomorphic mononuclear cells and OGCs, is fundamental to making a diagnosis of UC with EUS-TA. Newer endoscopic ultrasound-guided fine needle biopsy (EUS-FNB) needles potentially allow higher histological yield and enable immunohistochemical staining and even next-generation sequencing (19, 24–26). The use of EUS-FNB needles may help in the diagnosis.

Prognosis

UC has been believed to be more aggressive than PC (Table 1). However, there are only a few systematic reports on its prognosis due to its rarity. Furthermore, these data were based primarily on surgical series. Considering that it has been reported that ~80% of PC patients were diagnosed in unresectable stages (27, 28), these data were potentially biased. However, most studies reported that median overall survival (OS) of UC was poor, at <1 year, except for several surgical series (Table 2). Clark et al. compared the prognosis between UC and PC in their population-based study (4). The median OS was 3 months in patients with UC and 11 months in patients with PC. OS was significantly worse for patients with UC than for patients with PC [hazard ratio (HR), 1.9; 95% CI, 1.7–2.1]. Strobel et al. also reported a case-control study of surgically resected cases of UC (5). In their report, there were no significant differences in OS between UC and PC (7.1 vs. 16.5 months, respectively). However, this is possibly due to the small sample size.

On the other hand, UCOGCs have been reported to have relatively long survival compared with UC. Strobel et al. compared OS between UCOGC and UC (5), and survival was significantly longer for UCOGC patients than for UC patients (2-year OS rate in UCOGC patients, 57.1%; median OS, 3.3 months in UC patients; $P = 0.0477$). Muraki et al. compared OS of UCOGC and PC (8), and the median OS was significantly longer for UCOGC patients than for PC patients (7.67 vs. 1.59 years, $P = 0.0009$).

Meanwhile, the difference in OS was attenuated in the advanced stage (12, 21). We reported the prognosis of 55 UC patients with the advanced stage (12). The median OS in all patients with unresectable UC was 3.95 months, and there was no significant difference in OS between the UCOGC group and the UC without OGC group (5.36 vs. 3.58 months, respectively). The possible reasons for this poor prognosis of UC in the advanced stage have been suggested to be poor response to chemotherapy and publication bias. We also evaluated prognostic factors for unresectable UC (12), and age, ECOG PS and C-reactive protein were independent prognostic factors of OS.

Pathological findings

UC is also called anaplastic carcinoma. ‘Anaplastic’ denotes the characteristics of cells or tissues that have lost their mature or specialized features, and it is used to describe neoplastic cells that divide rapidly and show no similarity to normal cells. Thus, UC is defined as a malignant, epithelial neoplasm displaying no particular differentiation, such as glandular formation, mucin production or keratinization. Typically, neoplastic cells are poorly cohesive and hypercellular, and they have only scant stroma. According to the

Table 1. Overview of undifferentiated carcinoma

Epidemiology	<ul style="list-style-type: none"> • The frequency in malignant neoplasms of the pancreas is 0.3–7% • The median age at diagnosis is around the 60s. • There is a slight male predominance.
Clinical features	<ul style="list-style-type: none"> • Tend to show larger size (the median size was reported to be 60–90 mm). • Slightly more frequently seen in the pancreatic body/tail. • No specific symptoms are seen.
Diagnosis	<ul style="list-style-type: none"> • Both CEA and CA19-9 are mostly not elevated. • CT shows similar imaging features to pancreatic cancer. • EUS-TA is essential for the diagnosis, especially in the advanced stage.
Prognosis	<ul style="list-style-type: none"> • UC patients have significantly shorter survival compared with PC patients. • UCOGCs have been reported to have relatively long survival compared with UC.
Pathological findings	<p>Anaplastic UCs</p> <ul style="list-style-type: none"> • Pleomorphic mononuclear cells admixed with bizarre-appearing giant cells with eosinophilic cytoplasm are present. Neoplastic cells are non-cohesive and lack gland formation. <p>Sarcomatoid UCs</p> <ul style="list-style-type: none"> • Spindle-shaped cells mimicking sarcomas are present. <p>Rhabdoid UCs</p> <ul style="list-style-type: none"> • A rare subtype of sarcomatoid UCs. Neoplastic cells have rhabdoid inclusions. <p>Carcinosarcomas</p> <ul style="list-style-type: none"> • Admixture of both roundish epithelioid cells and spindle sarcomatous cells. <p>UCOGCs</p> <ul style="list-style-type: none"> • Admixture of neoplastic pleomorphic mononuclear cells and multinucleated OGCs. OGCs are positive for leucocyte markers and considered non-neoplastic.
Molecular features	<ul style="list-style-type: none"> • Similar to pancreatic cancer, <i>KRAS</i>, <i>TP53</i>, <i>CDKN2A/B</i> and <i>SMAD4</i> are commonly observed. <p>Anaplastic UCs</p> <ul style="list-style-type: none"> • EMT-related proteins are highly expressed. <p>Sarcomatoid UCs</p> <ul style="list-style-type: none"> • PD-L1 is highly expressed. <p>Rhabdoid UCs</p> <ul style="list-style-type: none"> • Genomic alterations in SWI/SNF complex subunits are frequently observed. <p>Carcinosarcomas</p> <ul style="list-style-type: none"> • Both carcinomatous and sarcomatous components share identical alterations of <i>KRAS</i> and <i>TP53</i>. <p>UCOGCs</p> <ul style="list-style-type: none"> • PD-L1 is highly expressed.
Treatment	<ul style="list-style-type: none"> • Basically, only surgical resection can offer curative treatment for patients with UC. • To date, no clear evidence exists for chemotherapy for UC. <p>Anaplastic UCs</p> <ul style="list-style-type: none"> • A retrospective cohort study and case reports indicate that a paclitaxel-containing regimen is a reasonable option for the treatment of patients with unresectable UC. <p>UCOGCs</p> <ul style="list-style-type: none"> • Promising responses to ICIs for UCOGCs have been described in case reports.

CT, computed tomography; EUS-TA, endoscopic ultrasound-guided tissue acquisition; UC, undifferentiated carcinoma; OGCs, osteoclast-like giant cells; UCOGCs, UC with OGCs; EMT, epithelial–mesenchymal transition; PD-L1, programmed death-ligand 1; SWI/SNF, SWI/SNF/Sucrose Non-Fermentable; ICIs, immune checkpoint inhibitors.

WHO classification 5th edition, UC is currently categorized into two different types: UC (with three subtypes: anaplastic UC, sarcomatoid UC and carcinosarcoma) and UCOGC (10, 29). The details follow.

Anaplastic UCs

Anaplastic UCs are composed of pleomorphic mononuclear cells admixed with bizarre-appearing giant cells with eosinophilic cytoplasm and lack gland formation. Neoplastic cells are non-cohesive,

and a neutrophilic inflammatory infiltrate may be prominent, with emperipolesis of neutrophils within the cytoplasm of the cells (Fig. 1).

Sarcomatoid UCs

On histological examination, sarcomatoid UCs are characterized by a predominance of spindle-shaped cells, accounting for ~80% of the cells without gland formation. These spindle-shaped cells mimic

Table 2. Summary of prognosis of undifferentiated carcinoma

Author (year)	No. of patients	Median OS	Extent of disease		Initial treatment		
			Metastatic	Localized (resectable or unresectable)	Curative resection	Chemotherapy/chemoradiotherapy	Best supportive care
Any subtype							
Clark (2012) (4)	353	3 months	204	127	81 (2-year OS rate, 30.7%)	–	–
Strobel (2011) (5)	18	5.7 months	5	13	13 (median OS, 7.1 months)	–	–
Imaoka (2021) (12)	55	3.95 months	47 (median OS, 3.95 months)	8 ^a (median OS, 2.83 months)	0	44	11
<i>Imaoka (2020) (20)</i>	50	4.08 months	44	6	0	50	0
Anaplastic UCs							
Strobel (2011) (5)	11	3.3 months	–	–	8 (median OS, 3.9 months)	–	–
Sarcomatoid UCs							
Gkoutakos (2022) (41)	7	21 months	2	5	5	–	–
Rhabdoid UCs							
Sano (2014) (30)	6	<3 months	6	0	0	2	4
Carcinosarcomas							
Li (2020) (31)	6	14 months	0	6	6	0	0
UCOGCs							
Clark (2012) (4)	11	(2-year OS rate, 50.0%)	–	–	10	–	–
Strobel (2011) (5)	7	(2-year OS rate, 57.1%)	–	–	5 (2-year OS rate, 80%)	–	–
Muraki (2016) (8)	38	7.67 years	0	38	38	0	0
Luchini (2017) (47)	16	20 months	0	16	16	0	0
Imaoka (2021) (12)	13	5.36 months	10	3 ^a	0	11	2
Gao (2022) (13)	13	13 months	0	13	13	0	0

OS, overall survival.

^aAll patients were diagnosed with locally advanced disease.

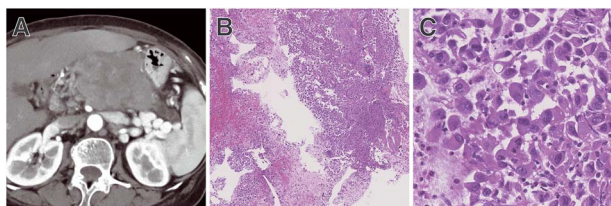


Figure 1. Representative case of anaplastic undifferentiated carcinoma (UC). (A) Computed tomography (CT) showing a hypovascular tumour at the body of the pancreas with upstream main pancreatic duct dilatation. (B) Tissue sample obtained by endoscopic ultrasound-guided tissue acquisition showing neoplastic cells, necrosis with neutrophil infiltration. In the high-powered field, (C) pleomorphic mononuclear neoplastic cells admixed with bizarre-appearing giant cells with eosinophilic cytoplasm were present.

sarcomas, but they demonstrate epithelial derivation without specific mesenchymal differentiation.

Rhabdoid UCs. Rhabdoid UCs are a very rare subtype of sarcomatoid UCs. Much like sarcomatoid UCs, they have abundant pleomorphic

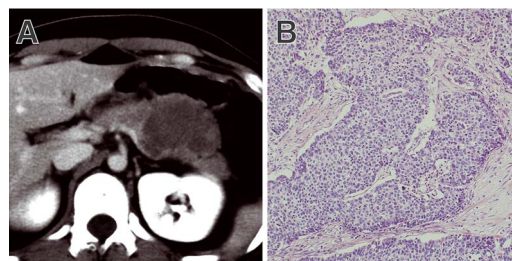


Figure 2. Representative case of rhabdoid UC. (A) CT showing a hypovascular tumour at the tail of the pancreas. In the surgical specimen, (B) abundant pleomorphic neoplastic giant cells with rhabdoid inclusion were present.

neoplastic giant cells with abundant eosinophilic cytoplasm (Fig. 2). However, unlike sarcomatoid UCs, they have rhabdoid inclusions (30).

Carcinosarcomas

Carcinosarcoma refers to a neoplasm composed of an admixture of both roundish epithelioid cells and spindle sarcomatous cells.

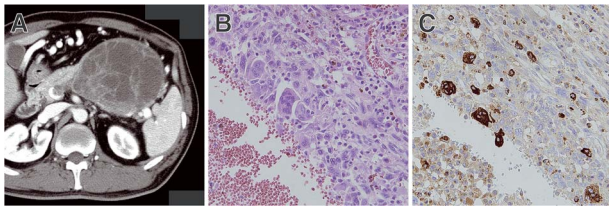


Figure 3. Representative case of UC with osteoclast-like giant cells. (A) CT showing a large tumour at the tail of the pancreas. (B) Tissue sample obtained by EUS-TA showing a mixture of neoplastic pleomorphic mononuclear cells and multinucleated OGCs. (C) Multinucleated OGCs were immunohistochemically positive for CD68.

Each component should arbitrarily constitute 30% of the neoplasm to qualify as carcinosarcoma. Carcinosarcoma is found the most frequently in the uterus and has also been reported in other organs, including the pancreas (31).

Undifferentiated carcinoma with osteoclast-like giant cells

UCOGCs are pathologically characterized by the mixture of neoplastic pleomorphic mononuclear cells and multi-nucleated OGCs (Fig. 3). Neoplastic mononuclear cells have a high Ki-67 proliferation index. Immunohistochemically, they are positive for epithelial markers such as CEA, EMA and AE1/AE3, suggesting epithelial differentiation. On the other hand, OGCs show few mitoses, and immunohistochemistry shows low positivity for proliferation markers such as Ki-67. They are also positive for leucocyte markers CD45 and CD68 but negative for epithelial markers. These findings suggest that OGCs are not neoplastic but reactive cells derived from macrophages (histiocytes) (32).

Molecular features

Pathologically, UC is an epithelial tumour that originates from the pancreas, but the direction of differentiation is unknown. However, genomic alterations *KRAS*, *TP53*, *CDKN2A/B* and *SMAD4* are also commonly observed in UCs (33–35). Of these, *KRAS* mutations are the most frequently observed genomic alterations, in 60–80%. This fact supports the concept that UCs are subtypes of PC. Molecular features of UCs are summarized in Table 3.

Anaplastic UCs

Previously, associations between UC and epithelial–mesenchymal transition (EMT) have been suggested. EMT is a complex process by which epithelial cells lose their cell polarity and cell–cell adhesion via inhibition of E-cadherin, and they gain migratory and invasive properties of mesenchymal cells. By EMT, cancer cells in a primary tumour break through the basement membrane with increased invasive properties and enter the bloodstream through intravasation. EMT is known to be associated with a poor prognosis in various cancers, and this fact may contribute to the aggressive clinical course of UCs. Furthermore, some research suggests that pleomorphic pathological findings of UC similar to mesenchymal phenotype are the result of EMT (36). It has been well known that loss of E-cadherin is frequently observed in UC. Yonemasu et al. compared UC with PC, and E-cadherin expression was completely lost in seven of eight UC cases, whereas half the PCs showed strong reactivity for E-cadherin immunohistochemically (37). Winter et al. evaluated E-cadherin protein expression by immunohistochemistry

Table 3. Summary of molecular features of undifferentiated carcinoma

Author (year)	KRAS mutation	KRAS amplification	TP53 mutation	SMAD4	CDKN2A	EMT-related marker expression		Predictive biomarkers for ICIs			SWI/SNF complex subunits	
						Loss of E-cadherin	Snai2	Twist1	MSI-high	TMB-high	SMARCB1 (INI1)	ARID1A (SMARCF1)
Anaplastic UCs												
Hoorens (1998) (33)	59%											
Paal E (2001) (7)	67% ^a		71%									
Marttilo (2021) (40)						60% ^a	100% ^a	30% ^a	0%	0%		8%
Sakakida (2023) (35)	76%		68%	8%	40%				0%	0%		
Sarcomatoid UCs												
Gkoutakos (2022) (41)	100%		90%	10%	60%							
Faber (2023) (42)	86%		86%	10%	18%				63% ^a	2%		29% ^a
Rhabdoid UCs												
Agaimy (2015) (43)	54%											
UCOGCs												
Hoorens (1998) (33)	50%											
Lehrke (2017) (49)									80% ^a			
Hrudka (2020) (50)									76.9% ^a	0% ^a		
Marttilo (2021) (40)			69.2% ^a			31.3% ^a	50% ^a	25% ^a				

EMT, epithelial–mesenchymal transition; ICIs, immune checkpoint inhibitors; SWI/SNF, SWI/SNF complex; SMARCB1, SMARCB1; ARID1A, ARID1A; MSI, microsatellite instability; TMB, tumour mutation burden; UC, undifferentiated carcinoma.
^a Assessed by immunohistochemistry.

in pancreaticobiliary cancers with a non-cohesive histological phenotype, predominantly UC (38). Interestingly, most UCs showed complete loss of E-cadherin expression, and they were characterized by either abnormal cytoplasmic accumulation or complete loss of β -catenin expression, suggesting a deficient adherens junction. They showed that E-cadherin inactivation via hypermethylation of *CDH1*, encoding for E-cadherin, may be involved in the process of dedifferentiation in PC, based on its known function as a transmembrane protein within the adherens junction and its central role in the EMT of tumour progression. Ishida et al. immunohistochemically assessed E-cadherin and three other EMT-related proteins, Slug (zinc finger protein *SNAI2*), Twist1 (Twist-related protein 1) and Zeb1 (zinc finger E-box-binding homeobox 1), in resected specimens. Increased Zeb1 expression and the complete loss of E-cadherin expression affect the progression of UC through the development of EMT (39). On the other hand, Mattiolo et al. compared the immunohistochemical expressions of three EMT-related markers (E-cadherin, *Snai2* and Twist1) between UC and UCOGCs. They found that EMT was more frequently activated in UC than in UCOGC (40). Furthermore, among UCOGCs, EMT was more frequently activated in cases with PC components.

Sarcomatoid UCs

Advances in sequencing technology have shown that the genomic profile of sarcomatoid UCs is similar to that of PC. Gkoutakos et al. reported that the most frequently observed genomic mutations were *KRAS* (100%), *TP53* (90%) and *CDKN2A* (60%) (41). They reported that, unlike in PC, *SMAD4* mutations were rare (10%), and *KRAS* amplification was more frequent in sarcomatoid UCs. Faber et al. also reported the genomic profiling of sarcomatoid UCs compared with PC patient samples (42). The most frequently observed genomic mutations were *KRAS* (86%), *TP53* (86%) and *CDKN2A* (18%), with similar prevalences to PC. Programmed death-ligand 1 (PD-L1) was significantly highly expressed in sarcomatoid UCs compared with PC (63% vs. 16%, respectively), but there were no significant differences both in the frequency of microsatellite instability-high/mismatch repair (MMR)-deficient (2% vs. 1%, respectively) and tumour mutation burden-high (2% vs. 2%, respectively).

Rhabdoid UCs. Rhabdoid UCs are considered a rare subtype of sarcomatoid UCs. Unlike UCs and UCOGCs, the rhabdoid subtype is unique in having a low frequency of *KRAS* mutation and a high frequency of *KRAS* amplification. Agaimy et al. reported that the frequencies of *KRAS* amplification and *KRAS* mutation in this rare subtype were 38 and 54%, respectively (43).

On the other hand, high frequencies of SWI/SNF chromatin remodelling complex subunit deficiencies were reported in UCs of the gastrointestinal tract, especially with rhabdoid features (44). The SWI/SNF complex plays significant roles in the regulation of gene expression. On the other hand, alterations in SWI/SNF complex subunits, such as *SMARCA4*, *SMARCB1* (*INI1*) and *ARID1A* (*SMARCF1*), can cause a loss of function of the subunit as a tumour suppressor. Furthermore, SWI/SNF subunits can also be required for tumour maintenance or even play an oncogenic role in certain disease contexts (45). Agaimy et al. reported that strong correlation between *KRAS* alterations and intact *SMARCB1* expression, and loss of *SMARCB1* expression correlated with the absence of *KRAS* alterations (43). Based on *KRAS* alterations and immunohistochemical *SMARCB1* expression status, they also classified sarcomatoid UCs into two subtypes: the pleomorphic subtype (*KRAS* alterations and intact

SMARCB1) and the monomorphic subtype (*KRAS* wild-type and loss of *SMARCB1*). Recently, SWI/SNF complex subunits have been highlighted as therapeutic targets, and multiple novel agents are currently being tested in several phase I–II trials (46): tazemetostat for loss of *SMARCB1* (NCT02601950) and berzosertib for *ARID1A* (NCT02059265).

Carcinosarcoma

Although carcinosarcoma is composed of an admixture of both epithelial and sarcomatous components, each component is immunophenotypically similar to its pure counterpart. Li et al. reported the result of genomic and molecular analyses of carcinosarcoma, using laser-captured microdissection both in carcinomatous and sarcomatous components (31). These two components shared identical alterations of *KRAS* and *TP53*. In addition, the expression statuses of *TP53*, *ARID1A* and *KDM6A* were consistent between carcinomatous and sarcomatous tissues. In this study, genomic and molecular analyses showed the monoclonal origins of the carcinomatous and sarcomatous components.

Undifferentiated carcinoma with osteoclast-like giant cells

The results of whole exome sequencing of UCOGCs have been reported, and the genetic alterations of UCOGCs are quite similar to those of PC, including *KRAS*, *CDKN2A*, *TP53* and *SMAD4* (47). Despite unique pathological findings of UCOGCs, these results support the classification of UCOGC as a PC variant and suggest that somatic mutations are not the determinants of its phenotype.

Recently, a predictive biomarker for immune checkpoint inhibitors (ICIs), PD-L1, has been highlighted. Currently approved ICIs target immune checkpoint proteins: cytotoxic T-lymphocyte-associated antigen 4, programmed cell death protein 1 (PD-1) and PD-L1. The anti-PD-1 antibody pembrolizumab binds to PD-1 on the T cells and inhibits the interaction of PD-1 with the PD-L1 expressed on the cancer cells (48). This causes immunosuppressive signals to T cells to be blocked, which allows T cells to attack cancer cells. In UCOGCs, Lehrke et al. examined the expressions of PD-L1, CD3, CD20, CD68 and DNA MMR proteins in 24 patients with UC immunohistochemically (16 cases were anaplastic UC, 5 were UCOGCs, 1 was sarcomatoid UC and 5 were rhabdoid UC) (49). In their comparison with PC, PD-L1 expression was more frequently observed in UC than in PC (63% vs. 15%, $P < 0.05$). Of the total five UCOGCs, four expressed PD-L1. On the other hand, 8.3% (2/24) UCs were MMR-deficient, and they were positive for PD-L1, with more than 10% positive tumour cells. Hrudka et al. also compared PD-L1 expression between UCOGC and PC, and PD-L1 was significantly highly expressed in UCOGC compared with PC (76.9% vs. 12.5%, $P < 0.001$) (50). Among UCOGC patients with high or low expression levels of PD-L1, the median OS was 5.7 months and not reached, respectively. However, the difference was not significant mainly due to the small sample size, and high expression of PD-L1 may possibly impact negatively on survival of UCOGC patients. On the other hand, high expression of PD-L1 can potentially be a therapeutic target for ICIs (see [Treatment](#)).

Treatment

Surgical resection

Only surgical resection can offer curative treatment for patients with UC, and surgical resection such as the Whipple procedure, pylorus-preserving pancreatoduodenectomy, distal pancreatectomy

or total pancreatectomy is performed depending on the primary site and extension of the lesion, as in the case of PC. In the population-based study by Clark et al., pancreatic resection was an independent prognostic factor for OS (HR = 0.3; 95% CI, 0.2–0.5; $P = 0.001$) (4). Strobel et al. also reported the prognosis of UC based on a surgical database (5). The study showed that curative resection significantly improved OS compared with palliative surgery (7.1 vs. 2.2 months, $P = 0.0094$). This difference was even more evident in terms of the presence of OGCs, and median OS in patients with curatively resected UCOGCs was significantly longer than in those without OGCs (not reached vs. 3.9 months, $P = 0.0104$). They also reported that adjuvant chemotherapy was not associated with longer OS in UC. Recent progress in adjuvant chemotherapy for PC may potentially benefit such UC patients treated with surgical resection (51–53), but there is no evidence for its use.

Chemotherapy

To date, no clear evidence exists for chemotherapy for UC. Furthermore, treatment data for patients with unresectable UC are lacking, as previous reports were based primarily on surgical series or registry data. However, a retrospective cohort study and case reports indicate that a paclitaxel-containing regimen is a reasonable option for treatment of patients with unresectable UC. We analysed a total of 50 UC patients treated with chemotherapy (20). The efficacy of chemotherapy was limited, with an objective response rate (ORR) of 10% and a median progression-free survival (PFS) of 1.84 months for first-line chemotherapy. However, gemcitabine plus nab-paclitaxel as first-line chemotherapy showed relatively promising results, with an ORR of 33.3% and a median PFS of 4.60 months. A paclitaxel-containing, first-line regimen significantly improved OS compared with a non-paclitaxel-containing regimen (6.94 vs. 3.75 months, $P = 0.041$). After adjustment, use of a paclitaxel-containing regimen in any line was still an independent predictor of OS (HR, 0.221; 95% CI, 0.076–0.647; $P = 0.006$). They also reported that the presence of OGCs did not affect chemotherapeutic effects. King et al. published a case report of rhabdoid UC with complete response achieved by gemcitabine plus nab-paclitaxel after failure of FOLFIRINOX (54). Wakatsuki et al. also reported a case of complete response to paclitaxel based on chemosensitivity testing (55). These reports suggest that gemcitabine plus nab-paclitaxel is a reasonable option in the treatment for UC.

ICIs have emerged as a new treatment paradigm for patients with many types of cancer (56, 57). ICIs bind to immune checkpoint proteins or their ligands and block these immunosuppressive signals in cancer cells (58). Only a limited number of cancer patients have been shown to derive benefit from ICIs; however, promising responses to ICIs for UCOGCs have been described in case reports (59, 60). Although biomarkers for predicting the efficacy of ICIs are not fully understood, the utility of PD-L1 expression has been demonstrated in non-small-cell lung cancer (57). Several studies showed high PD-L1 expression in UCOGCs, and ICIs may potentially benefit such patients with UCOGCs.

The most problematic issue is treatment for UC. Such rare cancers are generally under-represented, resulting in delays in the establishment of treatments, with little progress in research and development. As a result, UC patients lack access to appropriate treatment, resulting in poor treatment outcomes (61). However, because of their rarity, there are few ongoing clinical trials, and we do not expect any company-led therapeutic developments in the future. Based on previous retrospective data (20), we are currently

conducting a phase II clinical trial of gemcitabine plus nab-paclitaxel for UC (jRCTs031220099).

Conclusion

UC of the pancreas is an aggressive epithelial neoplasm with a poor prognosis, but still less is known about it due to its rarity. However, recent advances in diagnostic modalities and genomic sequencing technologies are opening up the possibilities for diagnosis and expanded treatments. Deepening our understanding and accumulating knowledge of UCs are necessary to establish treatment for them.

Conflict of Interest statement

Hiroshi Imaoka has received honoraria from Yakult Honsha. Masafumi Ikeda has received research funding from Eli Lilly Japan, Yakult, Pfizer and Takeda and honoraria from Eli Lilly Japan, Yakult Honsha, Taiho Pharmaceutical and Takeda. Kumiko Umemoto has received honoraria from Yakult Honsha. Makoto Ueno has received research funding from Taiho Pharmaceutical, AstraZeneca, Merck Biopharma, MSD, Astellas Pharma, Eisai, Ono Pharmaceutical, Incyte, CHUGAI PHARMACEUTICAL, DFP, Daiichi Sankyo, Novartis, Boehringer Ingelheim and J-pharma and honoraria from Taiho Pharmaceutical, AstraZeneca, Yakult Honsha, MSD, Nihon Servier, Ono Pharmaceutical, Incyte, CHUGAI PHARMACEUTICAL, Boehringer Ingelheim and J-pharma. Masato Ozaka has received honoraria from Taiho Pharmaceutical, Yakult Honsha, MSD, Ono Pharmaceutical, Nihon Servier, Bayer and Pfizer. Naohiro Okano has received honoraria from Taiho Pharmaceutical, Eli Lilly Japan, Eisai, Bayer Yakuhin, Chugai Pharma, Ono Pharmaceutical, Takeda, Daiichi Sankyo and AstraZeneca and is a member of Data Safety Monitoring Board or advisory board for GlaxoSmithKline. Kenji Ikezawa has received research funding from ASKA Pharmaceutical and honoraria from Taiho Pharmaceutical, Yakult Honsha, Ono Pharmaceutical, MSD, Myriad Genetics, Asahi Kasei Pharma and Incyte Biosciences Japan. Junji Furuse has received research funding from Taiho Pharmaceutical and Daiichi Sankyo and honoraria from Eli Lilly, Yakult Honsha, Taiho Pharmaceutical and Daiichi Sankyo and is a member of Data Safety Monitoring Board or advisory board for Taiho Pharmaceutical.

References

1. Fitzgerald TL, Hickner ZJ, Schmitz M, Kort EJ. Changing incidence of pancreatic neoplasms: a 16-year review of statewide tumor registry. *Pancreas* 2008;37:134–8.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin* 2023;73:17–48.
3. Tschang TP, Garza-Garza R, Kissane JM. Pleomorphic carcinoma of the pancreas: an analysis of 15 cases. *Cancer* 1977;39:2114–26.
4. 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;215:627–34.
5. Strobel O, Hartwig W, Bergmann F, et al. Anaplastic pancreatic cancer: presentation, surgical management, and outcome. *Surgery* 2011; 149:200–8.
6. Morohoshi T, Held G, Klöppel G. Exocrine pancreatic tumours and their histological classification. A study based on 167 autopsy and 97 surgical cases. *Histopathology* 1983;7:645–61.
7. 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;5:129–40.

8. Muraki T, Reid MD, Basturk O, et al. Undifferentiated carcinoma with osteoclastic giant cells of the pancreas: clinicopathologic analysis of 38 cases highlights a more protracted clinical course than currently appreciated. *Am J Surg Pathol* 2016;40:1203–16.
9. Japan Pancreas Society. *Classification of pancreatic carcinoma*, 4th English edn. Kanehara & Co., Ltd., Tokyo, 2017.
10. Hruban RH, Adsay NV, Esposito I, et al. *Pancreatic ductal adenocarcinoma. World Health Organization classification of tumours digestive system tumours*, 5th edn. IARC Press, Lyon, 2019; 322–32.
11. Shihara M, Higuchi R, Izumo W, Furukawa T, Yamamoto M. A comparison of the pathological types of undifferentiated carcinoma of the pancreas. *Pancreas* 2020;49:230–5.
12. Imaoka H, Ikeda M, Maehara K, et al. Risk stratification and prognostic factors in patients with unresectable undifferentiated carcinoma of the pancreas. *Pancreatol* 2021;21:738–45.
13. Gao Y, Cai B, Yin L, et al. Undifferentiated carcinoma of pancreas with osteoclast-like Giant cells: one Center's experience of 13 cases and characteristic pre-operative images. *Cancer Manag Res* 2022;14:1409–19.
14. Ishigami K, Nishie A, Yamamoto T, et al. Imaging features of undifferentiated carcinoma of the pancreas. *J Med Imaging Radiat Oncol* 2019;63:580–8.
15. Chadha MK, LeVea C, Javle M, Kuvshinoff B, Vijaykumar R, Iyer R. Anaplastic pancreatic carcinoma. A case report and review of literature. *JOP* 2004;5:512–5.
16. Hebert-Magee S, Bae S, Varadarajulu S, et al. The presence of a cytopathologist increases the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration cytology for pancreatic adenocarcinoma: a meta-analysis. *Cytopathology* 2013;24:159–71.
17. Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. *Gastrointest Endosc* 2012;75:319–31.
18. Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA. How good is endoscopic ultrasound-guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass?: a meta-analysis and systematic review. *Pancreas* 2013;42:20–6.
19. Imaoka H, Sasaki M, Hashimoto Y, Watanabe K, Ikeda M. New era of endoscopic ultrasound-guided tissue acquisition: next-generation sequencing by endoscopic ultrasound-guided sampling for pancreatic cancer. *J Clin Med* 2019;8:1173.
20. Imaoka H, Ikeda M, Maehara K, et al. Clinical outcomes of chemotherapy in patients with undifferentiated carcinoma of the pancreas: a retrospective multicenter cohort study. *BMC Cancer* 2020;20:946.
21. Reid MD, Muraki T, HooKim K, 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; 125:563–75.
22. 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.
23. Sekulic M, Gilles S, Amin K, Stewart J III. Undifferentiated (anaplastic) carcinoma with osteoclast-like giant cells of the pancreas: a series of 5 cases with clinicopathologic correlation and cytomorphologic characterization. *J Am Soc Cytopathol* 2016;5:321–30.
24. Facciorusso A, Wani S, Triantafyllou K, et al. Comparative accuracy of needle sizes and designs for EUS tissue sampling of solid pancreatic masses: a network meta-analysis. *Gastrointest Endosc* 2019;90:893–903 e7.
25. Crino SF, Le Grazie M, Manfrin E, et al. Randomized trial comparing fork-tip and side- fenestrated needles for EUS-guided fine-needle biopsy of solid pancreatic lesions. *Gastrointest Endosc* 2020;92:648–58 e2.
26. Karsenti D, Palazzo L, Perrot B, et al. 22G acquire vs. 20G Procore needle for endoscopic ultrasound-guided biopsy of pancreatic masses: a randomized study comparing histologic sample quantity and diagnostic accuracy. *Endoscopy* 2020;52:747–53.
27. Latenstein AEJ, van der Geest LGM, Bonsing BA, et al. Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma. *Eur J Cancer* 2020;125:83–93.
28. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *The Lancet* 2011;378:607–20.
29. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020;76:182–8.
30. Sano M, Homma T, Hayashi E, et al. Clinicopathological characteristics of anaplastic carcinoma of the pancreas with rhabdoid features. *Virchows Arch* 2014;465:531–8.
31. Li J, Wei T, Zhang J, et al. Carcinosarcoma of the pancreas: comprehensive clinicopathological and molecular characterization. *HPB* 2020;22:1590–5.
32. Hruban RH, Pitman MB, Klimstra DS. *Adenocarcinoma variants. Tumors of the pancreas*. Washington, DC: American Registry of Pathology, 2007; 165–90.
33. Hoorens A, Prenzel K, Lemoine NR, Kloppel 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.
34. Bazzichetto C, Luchini C, Conciatori F, et al. Morphologic and molecular landscape of pancreatic cancer variants as the basis of new therapeutic strategies for precision oncology. *Int J Mol Sci* 2020;21.
35. Sakakida T, Ishikawa T, Doi T, et al. Genomic landscape and clinical features of rare subtypes of pancreatic cancer: analysis with the national database of Japan. *J Gastroenterol* 2023;58:575–85.
36. Demetter P, Maréchal R, Puleo F, et al. Undifferentiated pancreatic carcinoma with osteoclast-like giant cells: what do we know so far? *Front Oncol* 2021;11:630086.
37. Yonemasu H, Takashima M, Nishiyama KI, et al. Phenotypical characteristics of undifferentiated carcinoma of the pancreas: a comparison with pancreatic ductal adenocarcinoma and relevance of E-cadherin, alpha catenin and beta catenin expression. *Oncol Rep* 2001;8:745–52.
38. Winter JM, Ting AH, Vilardell F, et al. Absence of E-cadherin expression distinguishes noncohesive from cohesive pancreatic cancer. *Clin Cancer Res* 2008;14:412–8.
39. Ishida K, Yamashita R, Osakabe M, et al. Expression of epithelial-mesenchymal transition proteins in pancreatic anaplastic (undifferentiated) carcinoma. *Pancreas* 2019;48:36–42.
40. Mattiolo P, Fiadone G, Paolino G, et al. Epithelial-mesenchymal transition in undifferentiated carcinoma of the pancreas with and without osteoclast-like giant cells. *Virchows Arch* 2021;478:319–26.
41. Gkoutakos A, Mafficini A, Lou E, et al. Genomic characterization of undifferentiated sarcomatoid carcinoma of the pancreas. *Hum Pathol* 2022;128:124–33.
42. Faber E, Krause H, Walker P, et al. Genomic profiling of rare undifferentiated sarcomatoid subtypes of pancreatic carcinomas for potential response to immunotherapy. *J Clin Oncol* 2023;41:741.
43. Agaimy A, Haller F, Frohnauer J, et al. Pancreatic undifferentiated rhabdoid carcinoma: KRAS alterations and SMARCB1 expression status define two subtypes. *Mod Pathol* 2015;28:248–60.
44. Chang B, Sheng W, Wang L, et al. SWI/SNF complex-deficient undifferentiated carcinoma of the gastrointestinal tract: Clinicopathologic study of 30 cases with an emphasis on variable morphology, immune features, and the prognostic significance of different SMARCA4 and SMARCA2 subunit deficiencies. *Am J Surg Pathol* 2022;46:889–906.
45. Andrades A, Peinado P, Alvarez-Perez JC, et al. SWI/SNF complexes in hematological malignancies: biological implications and therapeutic opportunities. *Mol Cancer* 2023;22:39.
46. Mittal P, Roberts CWM. The SWI/SNF complex in cancer - biology, biomarkers and therapy. *Nat Rev Clin Oncol* 2020;17:435–48.
47. Luchini C, Pea A, Lionheart G, et al. Pancreatic undifferentiated carcinoma with osteoclast-like giant cells is genetically similar to, but clinically distinct from, conventional ductal adenocarcinoma. *J Pathol* 2017;243:148–54.
48. Francisco LM, Salinas VH, Brown KE, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. *J Exp Med* 2009;206:3015–29.
49. Lehrke HD, Graham RP, McWilliams RR, et al. Undifferentiated pancreatic carcinomas display enrichment for frequency and extent of PD-L1 expression by tumor cells. *Am J Clin Pathol* 2017;148:441–9.
50. Hrudka J, Lawrie K, Waldauf P, Ciprová V, Moravcová J, Matěj R. Negative prognostic impact of PD-L1 expression in tumor cells of undifferentiated (anaplastic) carcinoma with osteoclast-like giant cells of the

- pancreas: study of 13 cases comparing ductal pancreatic carcinoma and review of the literature. *Virchows Arch* 2020;477:687–96.
51. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013;310:1473–81.
 52. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med* 2018;379:2395–406.
 53. Unno M, Motoi F, Matsuyama Y, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP-05). *J Clin Oncol* 2019;37:189.
 54. King DA, Rahalkar S, Bingham DB, Fisher GA. Pancreatic INI1-deficient undifferentiated rhabdoid carcinoma achieves complete clinical response on gemcitabine and nab-paclitaxel following immediate progression on FOLFIRINOX: a case report. *J Gastrointest Oncol* 2021;12:874–9.
 55. Wakatsuki T, Irisawa A, Imamura H, et al. Complete response of anaplastic pancreatic carcinoma to paclitaxel treatment selected by chemosensitivity testing. *Int J Clin Oncol* 2010;15:310–3.
 56. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–23.
 57. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016;375:1823–33.
 58. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science* 2011;331:1565–70.
 59. Obayashi M, Shibasaki Y, Koakutsu T, et al. Pancreatic undifferentiated carcinoma with osteoclast-like giant cells curatively resected after pembrolizumab therapy for lung metastases: a case report. *BMC Gastroenterol* 2020;20:220.
 60. Besaw RJ, Terra AR, Malvar GL, Chapman TR, Hertan LM, Schlechter BL. Durable response to PD-1 blockade in a patient with metastatic pancreatic undifferentiated carcinoma with osteoclast-like giant cells. *J Natl Compr Cancer Netw* 2021;19:247–52.
 61. Casali PG, Bruzzi P, Bogaerts J, Blay JY. Rare Cancers Europe Consensus P. Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper. *Ann Oncol* 2015;26:300–6.