Review Article

A current knowledge of the undifferentiated carcinoma of the pancreas with osteoclast-like giant cells: a narrative review

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Background and Objective: Undifferentiated carcinoma of the pancreas with osteoclast-like giant cells (UCOGC) is a rare variant of malignant pancreatic tumor. There is still no standardized treatment for this uncommon subtype, as surgical resection with lymphadenectomy is the only potentially curative treatment so far. In this paper, we describe the current knowledge of this very rare specific subtype of pancreatic cancer (PC) as a narrative review.

Methods: For this review, we did not specify the time range of studies referred to due to limited data availability. Our inclusion criteria comprised previous studies, which specifically focused on the rare UCOGC subtype of PC as a confirmed histopathology, either pure or present together with other subtypes. We disregarded the studies involving any other PC subtype but not UCOGC, including undifferentiated and anaplastic carcinomas without osteoclast-like giant cell components.

Key Content and Findings: The limited available data precludes a definitive assessment of the efficacy of both neoadjuvant and adjuvant chemotherapy in the treatment of UCOGC. Monoclonal antibody pembrolizumab has been proven to be effective in metastatic cases. Multiple cases demonstrate a better overall survival rate for patients with UCOGC only versus those having UCOGC as a component with a pancreatic ductal adenocarcinoma (PDAC) histopathological subtype. The same conclusion can be also drawn comparing the survival rate of patients having pure UCOGC versus UCOGC with associated PDAC. Programmed cell death ligand-1 expression has been shown to be an important determinant, which shortens the survival period of patients diagnosed with UCOGC.

Conclusions: The rarity of UCOGC limits data for clinical courses and treatment plans. We need more data to better understand the relationship between pathogenic mutations, histological subtypes, and prognosis in PC, including UCOGC. Understanding UCOGC's molecular, clinical, radiological, and pathological characteristics can lead to earlier, more accurate diagnoses and better management.

Keywords: Pancreatic neoplasms; carcinoma, undifferentiated; therapeutics; review

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Introduction

Ranked as the sixth most common cause of cancer-related deaths, pancreatic cancer (PC) was a cause of 467,005 deaths worldwide in 2022 (1). The current relative survival rate of PC including all races and ethnicities is 13% in the USA, which places it last in the list of cancers with the lowest survival rates (2). The mortality rate of PC in the USA is estimated to surpass that of breast and colorectal cancer by 2030 (3).

About 90% of pancreatic tumors are of exocrine origin, with pancreatic ductal adenocarcinoma (PDAC), an infiltrating neoplasm harboring glandular differentiation being the most common subtype (4,5). There is also a subset of PC with largely opposite features, an undifferentiated PC, which lacks glandular differentiation and comprises prominent histiocyte and osteoclast-like giant cell infiltration (6). Undifferentiated PC demonstrates poor cohesion as well as hypercellularity with sparse stroma (7). According to the World Health Organization (WHO), there is a further division within the group of undifferentiated PCs, covering undifferentiated osteoclast-like giant cell (OGC) [undifferentiated carcinoma of the pancreas with osteoclast-like giant cells (UCOGC)], rhabdoid, and sarcomatoid types, and their combinations (8).

UCOGC is an uncommon PC subtype representing less than 1% of all PCs (9). The main feature of this rare variant comprises pleomorphic neoplastic mononuclear cells mixed with large non-neoplastic multinucleated giant cells. This histological category contains three subtypes within itself: osteoclastic, pleomorphic, and a mixture of the two (4). The latest classification of the malignant epithelial tumors of the pancreas by the WHO is summarized in *Figure 1* (10). The UCOGC is more frequently diagnosed within the 6th and 7th decades of life, and appears to affect males and females equally (11,12). In this paper, we will focus on the genetic background, histology, immunohistochemistry, possible treatment options, and the clinical course of the UCOGC. We will describe the current knowledge of this very rare specific subtype of PC as a narrative review. We present this article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-780/rc).

Methodology

All the studies referred for this review have been searched via the National Library of Medicine (NIH), PubMed, with the keywords "undifferentiated carcinoma of the pancreas with osteoclast-like giant cells", "genetic background of UCOGC", "histopathology of UCOGC", "immunohistochemistry of UCOGC", "treatment of UCOGC", and "clinical course of UCOGC". A visual tool Connected Papers (www.connectedpapers.com) and reference manager software Mendeley (www.mendeley.com) served for proper citation and access to the studies regarding the abovementioned aspects of UCOGC. For this review, we did not specify the time range of studies referred due to insufficiency in number. Our inclusion criteria comprised previous studies, which specifically focused on the rare UCOGC subtype of PC as a confirmed histopathology, either pure or present together with other subtypes. We disregarded the studies involving any other PC subtype but not UCOGC, including undifferentiated and anaplastic carcinomas without OGC component. The search strategy is summarized in *Table 1*.

The genetic background of UCOGC

Luchini *et al.* demonstrated a remarkable similarity between the PDAC and UCOGC regarding their genetic alterations (6). By the whole exome sequencing of the UCOGC specimens, they found mutations in tumor suppressor genes or oncogenes *KRAS*, *CDKN2A*, *TP53*, and *SMAD4* with already demonstrated roles in formation of conventional PDAC. Their findings about genetic alterations suggest the classification of the UCOGC as a PDAC variant (6). This suggestion is further supported by Hrudka *et al.* (13). After the next generation panel sequencing of the histologically confirmed 13 UCOGC samples, they also detected a spectrum of mutations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4* similar to those observed in sequenced PDAC specimens (13).

KRAS mutations have also been reported by the other studies involving UCOGC (*Table 2*) (6,15-17). One of these studies demonstrated a mutational analysis for microdissected UCOGC samples, showing that they harbor *KRAS* mutations. They suggested the presence of *KRAS* mutations in the osteoclast-like giant cells of these microdissections as a reflection of their propensity for phagocytosis of surrounding tumor cells. They further suggested ductal epithelium as an origin of UCOGC by documenting the base changes at codon 12 of *KRAS*, which were the same as those detected in the corresponding ductal epithelial proliferation (16). This contradicts the findings of Lewandrowski *et al.* from the

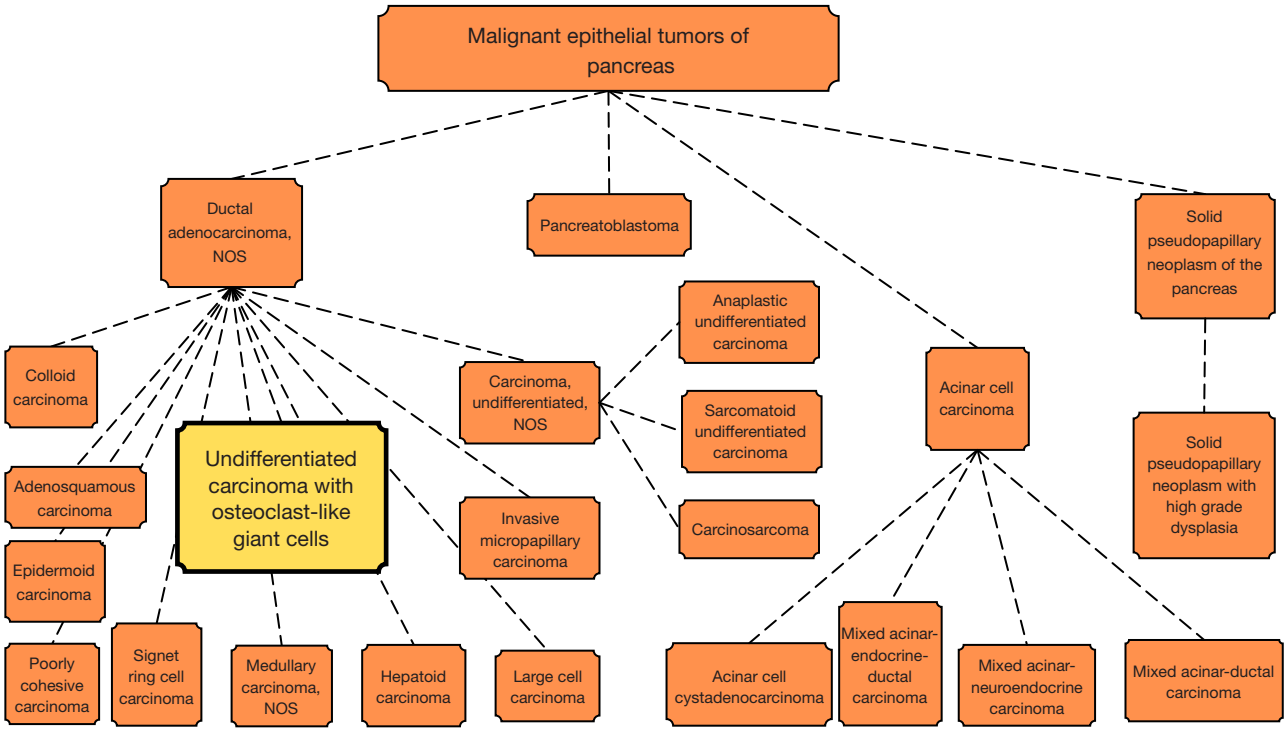

Figure 1 Malignant epithelial tumors of the pancreas according to the latest classification by WHO (10). NOS, not otherwise specified; WHO, World Health Organization.

Table 1 The summary of the search strategy for this narrative review

Items	Specification
Date of search	1 April 2024 to 1 June 2024
Database and other sources searched	National Library of Medicine, PubMed
Search terms used	"undifferentiated carcinoma of the pancreas with osteoclast-like giant cells", "genetic background of UCOGC", "histopathology of UCOGC", "immunohistochemistry of UCOGC", "treatment of UCOGC", and "clinical course of UCOGC"
Timeframe	No specific timeframe
Inclusion and exclusion criteria	Studies which specifically focused on the rare UCOGC subtype of pancreatic cancer, either pure or present together with other subtypes were included
	Studies focused on any other pancreatic cancer subtype but not UCOGC, including undifferentiated and anaplastic carcinomas without OGC component were excluded
Selection process	Author E.G. conducted the literature selection. M.O. and P.S. supervised the search strategy
Additional considerations	Connected Papers (www.connectedpapers.com) and Mendeley (www.mendeley.com) served for proper citation and access to the studies

previous century, who showed the absence of epithelial features in both mononuclear and osteoclast-like giant cells under the electron microscope (18).

Programmed cell death ligand-1 (PD-L1) expression is another important point worth mentioning, as it seems to negatively affect the clinical course of patients with UCOGC, which will be discussed later in the treatment clinical course section. Luchini *et al.* demonstrated the expression of PD-L1 in numerous UCOGC tumor cells in 17 of 27 cases in total (*Table 2*) (14).

Table 2 The summary of the studies discussed in this narrative review regarding the genetic background of UCOGC

Study	Type of study	Focus of study	Observation	Reference
Luchini *et al.*	Mutational analysis	Clinical and pathological features of 22 UCOGC specimens, of which 8 samples were subject to the whole exome sequencing	Inactivation mutations in *KRAS*, *CDKN2A*, *TP53*, and *SMAD4*, which are already known to have a role in conventional PDAC	(6)
		Investigating the expression of PD-1, PD-L1, and CD163 in a series of UCOGC	The expression of PD-L1 in numerous UCOGC tumor cells	(14)
Hrudka *et al.*	Mutational analysis	Molecular genetic analysis of 13 UCOGC cases to compare the spectrum of oncogenic DNA mutations to PDAC	A spectrum of mutations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4* similar to those observed in the sequenced PDAC specimens	(13)
Imai *et al.*	Mutational analysis	Molecular as well as immunohistochemical analysis of three cases of giant cell carcinoma of the pancreas	All cases contained a mutation in *KRAS* (codons 12, 13), but neither *p53* (exons 5–8) nor *p16INK4* (exons 1, 2) mutations were found in any case	(15)
Westra *et al.*	Mutational analysis	Analyzing each individual UCOGC specimen for mutations at codon 12 of the *KRAS* oncogene	The base changes at the codon 12 of *KRAS*, which were the same as those detected in the corresponding ductal epithelial proliferations	(16)

UCOGC, undifferentiated carcinoma of the pancreas with osteoclast-like giant cells; PDAC, pancreatic ductal adenocarcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand-1.

Histopathology and immunohistochemistry of UCOGC

The preferential location of UCOGC includes the tail and the head of the pancreas (19). UCOGC can be present pure or together with other PC subtypes, such as cystadenocarcinoma, pancreatic mucinous cystic neoplasm, adenosquamous carcinoma, and PDAC (6,20-22). The growth pattern of the UCOGC has been microscopically observed as endoluminal/polypoid with pushing border (23). The histopathological examination reveals the UCOGC as a combination of osteoid and glandular elements, resembling the giant cell tumors of bone with benign appearance, and containing the osteoclast-like eosinophilic multinucleated cells with 5 to 20 nuclei located centrally with ovoid or spindle mononuclear cells (11,23). The mononuclear cells demonstrate varying degrees of cytological atypia, together with the true osteoclasts lacking significant mitotic activity or pleomorphism (16). Manduch *et al.* microscopically observed the foci of osteochondroid differentiation predominantly consisting of chondroid differentiation with some peripheric osteoid formation with remarkable OGC rimming. Their immunohistochemical results suggest the origins as epithelial and histiocytic for mononuclear and osteoclast-like giant cells, respectively (24). Areas of chondromyxoid differentiation, irregular calcifications, and numerous foamy macrophages, which resemble lipoblasts, have also been evident in some cases (25,26). Studies involving the immunohistochemistry of UCOGC specimens for mononuclear cells, associated malignant epithelial cells, and OGC are summarized in *Table 3* (23,26-33).

Treatment options and the clinical course of UCOGC

The treatment strategy for the UCGOC has never been standardized due to the scarcity of this PC subtype. Such a challenge also applies to confirming a diagnosis, complicated by the lack of specific symptoms and accurate biomarkers in blood (34,35). The definitive role of EUS for PC remains incompletely characterized by currently available guidelines (36). The primary treatment for localized UCOGC is radical R0 resection with lymphadenectomy when possible (37,38). While the efficacy of chemotherapy for UCOGC remains under investigation, established chemotherapeutic regimens for PC, including FOLFIRINOX and gemcitabine have been adopted for UCOGC due to its classification as a variant of ductal adenocarcinoma of the pancreas (39). In a randomized phase II–III trial of patients with PDAC, FOLFIRINOX therapy

Table 3 Summary of positive immunohistochemistry results for the components of UCOGC

Immunohistochemical staining for	Mononuclear cells (histiocyte-like, atypical)	Associated malignant epithelial cells	Osteoclast-like giant cells
A1ACT	√		√
Actin	√		
Carcinoembryonic antigen	√		
CK AE1/AE3	√	√	
CK CAM 5.2		√	
CK7		√	
CK19		√	
CK20		√	
CD163	√		
CD31			√
CD34	√		
CD68	√		√
EMA		√	
HAM 56 (macrophage marker)	√		
Ki-67	√		
LCA	√		√
Lysozyme	√	√	√
p53	√		
pCNA		√	
Vimentin	√		√

Data from literature (23,26-33). AE1/AE3, panepithelial keratin; CD, cluster of differentiation; CK, cytokeratin, EMA, epithelial membrane antigen; Ki-67, antigen Kiel 67; LCA, leukocyte antigen; pCNA, proliferating cell nuclear antigen; UCOGC, undifferentiated carcinoma of the pancreas with osteoclast-like giant cells.

was associated with a median increase in overall survival of 4.3 months (40). In a phase III trial of patients with resected PC, the median overall survival for the gemcitabine plus capecitabine group was 28 months [95% confidence interval (CI): 23.5–31.5], compared with 25.5 months (95% CI: 22.7–27.9) in the gemcitabine alone group (P=0.032) (41). The combination of gemcitabine and albumin-bound paclitaxel has also been approved for treating metastatic cases of PC (42). Randomly designed phase III study of the efficacy and safety of this combination versus gemcitabine monotherapy revealed the median overall survival of 8.5 months in the nab-paclitaxel-gemcitabine group, versus 6.7 months in the gemcitabine group (P<0.001) (43). Similarly, as in PDAC cases, FOLFIRINOX neoadjuvant chemotherapy followed by conversion surgery is reserved for borderline and advanced tumors in patients with good performance status (44,45).

A comprehensive meta-analysis of survival rates of UCOGC cases was conducted by Mylonakis *et al*. The analysis revealed that surgical resection was the predominant treatment strategy, employed in 88.4% of patients. Following surgical resection, 19 patients received adjuvant chemotherapy, consisting of either gemcitabine or FOLFIRINOX. The 1-, 3-, and 5-year survival rates were determined to be 58%, 44.7%, and 37.3%, respectively. The study revealed that the administration of adjuvant chemotherapy, either gemcitabine or FOLFIRINOX, did not significantly improve survival outcomes for patients with UDOGC (46). A comparison of survival rates between patients who underwent surgery alone and those who

received both surgery and adjuvant treatment demonstrated no statistically significant difference (P=0.518). Furthermore, the limited use of neoadjuvant chemotherapy in only three out of 67 cases (4.4%) precluded a definitive assessment of its impact on survival (46).

Igarashi *et al.* presented a case of UCOGC that underwent conversion surgery after receiving neoadjuvant FOLFIRINOX chemotherapy. Notably, the patient exhibited a 6-month disease-free survival period following the surgery (47). A comprehensive review of the existing literature revealed no prior reports of conversion surgery for UCOGC performed after neoadjuvant FOLFIRINOX therapy. Consequently, the efficacy of neoadjuvant chemotherapy followed by conversion surgery in UCOGC warrants further clinical investigation.

A multicenter retrospective cohort study involving 17 institutions in Japan was undertaken to compare the outcomes of different chemotherapeutic approaches for unresectable cases of undifferentiated carcinoma (UC) of the pancreas, including UCOGC (48). The study retrospectively collected clinical and treatment data from patients with unresectable UC. The results demonstrated a significant improvement in overall survival (OS) for patients receiving a paclitaxel-containing first-line regimen compared to those treated with non-paclitaxel-based regimens (6.94 *vs.* 3.75 months; P=0.041). Notably, the positive association between paclitaxel-containing regimens and OS persisted even after adjusting for potential confounding factors (P=0.006). Based on these findings, the utilization of a paclitaxel-containing regimen was considered a reasonable therapeutic strategy for patients with unresectable UC by Imaoka *et al.* (48).

The lack of treatment standardization also applies to the metastatic cases of UCOGC. However, pembrolizumab, a humanized monoclonal antibody against programmed cell death protein 1 (PD-1) has been effective against the lung metastases of UCOGC in the case of a 66-year-old man, presented by Obayashi *et al.* The patient demonstrated no cancer recurrence 6 months postoperatively, without adjuvant treatment (49). A marked response to pembrolizumab monotherapy has also been demonstrated in another case report of UCOGC distantly spreading to lungs and brain. In total, 46 cycles of pembrolizumab resulted in a continuous reduction of UCOGC lesions in pancreas and brain, as well as a complete elimination of lung metastases (*Table 4*) (50).

Various studies reported a significantly better prognosis for cases involving UCOGC versus those with PDAC (*Table 4*) (6,27). A large study with 38 patients has been done involving the comparison between the survival rates of patients with UCOGC versus PDAC. A 5-year overall survival rate in patients suffering from UCOGC was 59.1% with a median survival period of 7.67 years, which was significantly better than for those with PDAC, 15.7% with 1.59 years of median survival period (P=0.0009) (27). Luchini *et al.* also compared the survival rates of patients suffering from either pure or PDAC-associated UCOGC. They demonstrated a significantly longer survival period for patients having pure UCOGC with median overall survival being 36 months versus 15 months for UCOGC with associated PDAC (P=0.04) (6). Another case report of pure UCOGC demonstrated a >7-year disease-free survival after curative surgery, suggesting a significantly better prognosis for UCOGC lacking ductal adenocarcinoma component (52). Another case of a 71-year-old patient with UCOGC, who underwent curative surgery and four cycles of adjuvant gemcitabine, showed 10-year period without metastasis or any other signs of tumor recurrence (53).

A meta-analysis conducted by Kobayashi *et al.* identified several other patient characteristics associated with shorter-term survival in UCOGC. These factors include older age, male gender, and positive lymph node metastasis (54). On the other hand, the presence of osteoclast-like giant cells, small tumor size and encapsulation have been associated with increased survival period for UCOGC cases (55). The presence of PD-L1 expression is another important factor for the clinical course according to the study done by Luchini *et al.*, demonstrating a worse prognosis for patients with PD-L1-positive UCOGCs compared to PD-L1-negative ones (14). Hrudka *et al.* also observed a significantly shorter median survival period of 9 months in patients with PD-L1 expression (P=0.0042) (*Table 4*) (51).

Conclusions & discussion

In the clinical setting, we encounter UCOGC very rarely. However, due to better prognosis, different histological and molecular characteristics, and possible targeted treatment options, it is important to be aware of this rare subtype with the goal of personalized medicine.

Histological reports from multiple cases demonstrate the UCOGC as a combination of pleomorphic neoplastic mononuclear cells with large non-neoplastic multinucleated giant cells. The mononuclear cells exhibit cytological atypia with varying degrees. On the other hand, true osteoclasts show the absence of significant mitotic activity and

Table 4 Summary of studies discussed in this narrative review regarding the treatment and clinical course of UCOGC

Study	Type of study	Focus of study	Observation	Reference
Mylonakis *et al.*	Meta-analysis	Survival rate of patients suffering from UCOGC following surgical resection, either alone or with adjuvant chemotherapy	1-, 3-, and 5-year survival rates were 58%, 44.7%, and 37.3% Administration of adjuvant chemotherapy, either gemcitabine or FOLFIRINOX, did not significantly improve survival outcomes (P=0.518)	(46)
Igarashi *et al.*	Case report	Treatment of a patient suffering from UCOGC	A 6-month disease-free survival period following the conversion surgery with neoadjuvant FOLFIRINOX chemotherapy	(47)
Imaoka *et al.*	Retrospective cohort study	Comparing the outcomes of different chemotherapeutic approaches for unresectable cases of undifferentiated carcinoma of the pancreas	Significant improvement in overall survival for patients receiving a paclitaxel-containing first-line regimen compared to those treated with non-paclitaxel-based regimens (6.94 *vs.* 3.75 months; P=0.041) Positive association between paclitaxel-containing regimens and overall survival even after adjusting for potential confounding factors (P=0.006)	(48)
Obayashi *et al.*	Case report	Treatment of a patient suffering from metastatic UCOGC	Pembrolizumab has been effective against the lung metastases of UCOGC	(49)
Besaw *et al.*	Case report	Treatment of a patient suffering from UCOGC with lung metastases	46 cycles of pembrolizumab resulted in a continuous reduction of UCOGC lesions in pancreas and brain, as well as complete elimination of lung metastases	(50)
Luchini *et al.*	Case report, expression analysis	Clinical and pathological features of 22 UCOGC specimens	A longer survival period for patients having pure UCOGC versus UCOGC with associated PDAC	(6)
	Expression analysis	Investigating the expression of PD-1, PD-L1, and CD163 in a series of UCOGC	Worse prognosis for patients with PD-L1-positive UCOGCs compared to PD-L1-negative ones	(14)
Muraki *et al.*	Clinical and pathological analysis	Investigating the clinicopathologic characteristics of 38 resected UCOGCs versus 725 resected PDAC	A 5-year overall survival rate in patients suffering from UCOGC was significantly better than those with PDAC (P=0.0009)	(27)
Hrudka *et al.*	Expression analysis	The expression of the PD-L1 and several other potential therapeutic and predictive markers in 13 UCOGC specimens	Significantly shorter median survival period in patients with PD-L1 expressing UCOGCs	(51)

FOLFIRINOX, folinic acid, fluorouracil, irinotecan, oxaliplatin; PD-L1, programmed cell death ligand-1; UCOGC, undifferentiated carcinoma of the pancreas with osteoclast-like giant cells; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma.

pleomorphism.

A spectrum of mutations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4* reminds of the genetic similarity to PDAC specimens in two different studies discussed before. Considering the expression and mutational analysis, ductal epithelium seems to be the most probable origin of this rare subtype, which is also in accordance with the current classification by the WHO. This similarity, coupled with a better prognosis, may give researchers hope for more effective treatment for PDAC. In other words, while the mutations are similar, the prognoses differ. This can be revealed by omics cross-match analyses of whole genome,

exome, and RNA sequencing data of common PDAC and rare subtypes of PC.

So far there is no standardized treatment for UCOGC. The primary treatment of choice is surgical resection. The limited available data precludes a definitive assessment of the efficacy of both neoadjuvant and adjuvant chemotherapy in the treatment of UCOGC, necessitating further clinical investigation. While the efficacy of chemotherapy remains unclear, established chemotherapeutic regimens for PC, including FOLFIRINOX, have been adopted for UCOGC due to its classification as a PDAC subtype. For unresectable cases, the utilization of a paclitaxel-containing regimen has been considered a reasonable therapeutic option. Pembrolizumab seems to be effective in metastatic cases of UCOGC. In one particular case, it significantly reduced the size of UCOGC lesions in the pancreas and brain and eliminated metastases in lung. Multiple cases demonstrate a better overall survival rate for patients with pure UCOGC versus those having simultaneously a PDAC component or solely PDAC. Furthermore, PD-L1 expression has been shown to be an important determinant, which shortens the overall survival period of patients diagnosed with UCOGC. As our understanding of the molecular drivers of UCOGC deepens, personalized medicine approaches, such as targeted therapies and immunotherapy, hold the potential to revolutionize the treatment landscape for this rare and aggressive disease.

Our review provides a fair overview of current knowledge about UCOGC. However, due to limited available data, our conclusions may be broad. Nonetheless, this review contributes to the field and informs future research. The rarity of UCOGC limits data for clinical courses and treatment plans. We need more data to better understand the relationship between pathogenic mutations, histological subtypes, and prognosis in PC, including UCOGC. Clinical research will collect more cases and long-term follow-up data, refining our approach. Understanding UCOGC's molecular, clinical, radiological, and pathological characteristics can lead to earlier, more accurate diagnoses and better management.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-780/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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