Review

Understanding Polyploid Giant Cancer Cells: From Molecular Mechanisms to Clinical Implications

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Review

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Simple Summary

Polyploid giant cancer cells (PGCCs) are characterized by abnormal enlargement and considerable polyploidy. Although these cells have been documented in tumors for decades, they remain poorly understood, especially in clinical practice, due to diagnostic challenges and confusion regarding synonyms for PGCCs. Emerging evidence suggests that PGCCs play crucial roles in tumor progression, facilitating metastatic spread via asymmetric cell division and genomic instability. Their presence in tumor tissue has been associated with marked treatment resistance and a poor prognosis across multiple solid tumor types, suggesting their potential utility as a prognostic indicator.

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Although no established treatments exist, emerging targeted therapies targeting specific pathways in PGCCs represent potential strategies to improve clinical outcomes for patients with PGCC-containing tumors. This review integrates insights from basic research and clinical studies to enhance understanding of the complex biology and clinical implications of PGCCs.

Abstract

Polyploid giant cancer cells (PGCCs) are characterized by abnormal enlargement and considerable polyploidy. Though the presence of giant cancer cells has been documented for decades, they remain not fully understood, especially in clinical practice, due to diagnostic challenges, and confusion regarding synonyms for PGCCs still exists. Thus, understanding PGCCs may be a key clue to overcoming them. This review offers a comprehensive overview of PGCCs, integrating insights from basic research and clinical studies to enhance understanding of their complex biology and clinical implications. In basic research, PGCCs are known to emerge under various stressors, including chemotherapy exposure, radiation, viral infection, and hypoxic environments. These cells play crucial roles in tumor progression through multiple mechanisms: enhancing genetic diversity, and facilitating metastatic spread via asymmetric cell division and genomic instability. In clinical studies, PGCC-containing tumors have been shown to exhibit marked treatment resistance and are associated with a poor prognosis across multiple solid tumor types, including prostate, lung, and pancreatic cancers. Despite these therapeutic challenges, paclitaxel-containing regimens have shown promising results in PGCC-containing tumors, such as pleomorphic carcinoma of the lung and undifferentiated carcinoma of the pancreas. Furthermore, emerging targeted therapies directed at specific pathways in PGCCs, particularly those involving TP53, represent potential strategies to improve clinical outcomes of patients with PGCC-containing tumors.

Keywords: polyploid giant cancer cell; polyaneuploid cancer cell; pleomorphic cancer cell; osteoclast-like giant cell; multinucleated giant cancer cell; undifferentiated carcinoma; cancer-associated macrophage-like cell; polyploidization; dormancy

1. Introduction

Polyploid giant cancer cells (PGCCs) are a type of cancer cell observed in various cancers, including prostate, lung, and pancreatic cancers [1]. Morphologically, the nuclei of PGCCs are usually irregular and large; Zhang defined PGCC nuclei as being ≥ three times greater than regular-sized diploid tumor cell nuclei [2].

Across all types of cancer, PGCCs are thought to be associated with more aggressive behavior and a poorer prognosis. One reason is the cancer stem cell-like characteristics of PGCCs. Normal cells proliferate by symmetric division, but PGCCs generate progeny cells through asymmetric division other than normal mitosis. PGCCs can express cancer stem cell-related markers (CD44 and CD133) [3] and epithelial-mesenchymal transition (EMT)-related proteins to promote invasion and migration [4]. In addition, PGCCs can be related to chemoresistance and tumor recurrence. These characteristics resemble cancer stem cells [5] and are thought to contribute to the malignant phenotype of PGCCs.

Today, PGCCs are the focus in translational fields. However, the clinical significance of PGCCs is not well recognized in clinical practice. PGCCs are not uncommon in tumors, but they represent only a small fraction of the total cells [6,7]. These facts make the diagnosis of PGCCs in clinical practice difficult and hinder understanding of the entity of PGCCs and their clinical application, including targeted therapy for them. In this review, current knowledge about PGCCs is outlined. First, a simple overview of PGCCs in basic research is provided. Second, the clinical implications of PGCCs based on clinical studies are reviewed. Although there are various terms for numerical chromosomal abnormalities [8], hyperdiploid and polyploidy have been treated synonymously in many studies and are followed here. Most aneuploid tumors exhibit chromosomal gains [9]. Therefore, in this review, aneuploidy is considered to be near-polyploid. PGCCs have been predominantly described

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in solid tumors. Notably, polyploidy is not limited to solid tumors. Tetraploid/near-tetraploid acute myeloid leukemia and polyploid diffuse large B-cell lymphoma have also been associated with poor prognosis [10,11]. Although the morphological features and underlying biological mechanisms of polyploidy in hematologic malignancies may differ from those of PGCCs in solid tumors, these findings support the notion that genomic polyploidization represents a common pathway contributing to tumor progression and therapeutic resistance across diverse cancer types. However, the present review focuses primarily on PGCCs in solid tumors, where their distinct morphological and functional characteristics have been more extensively investigated.

2. Polyploidization and Dormancy

The multinucleated morphology of PGCCs is considered the outcome of polyploidization and dormancy. PGCCs undergo polyploidization and enter a dormant state in response to stressors such as chemotherapy, radiation, viral infection, and a hypoxic microenvironment [3,12,13]. Consequently, polyploidy and dormancy cause a poor prognosis for tumors by promoting tumor evolution through the accumulation of chromosomal instability, acquisition of therapeutic resistance, and metastasis (**Figure 1**).

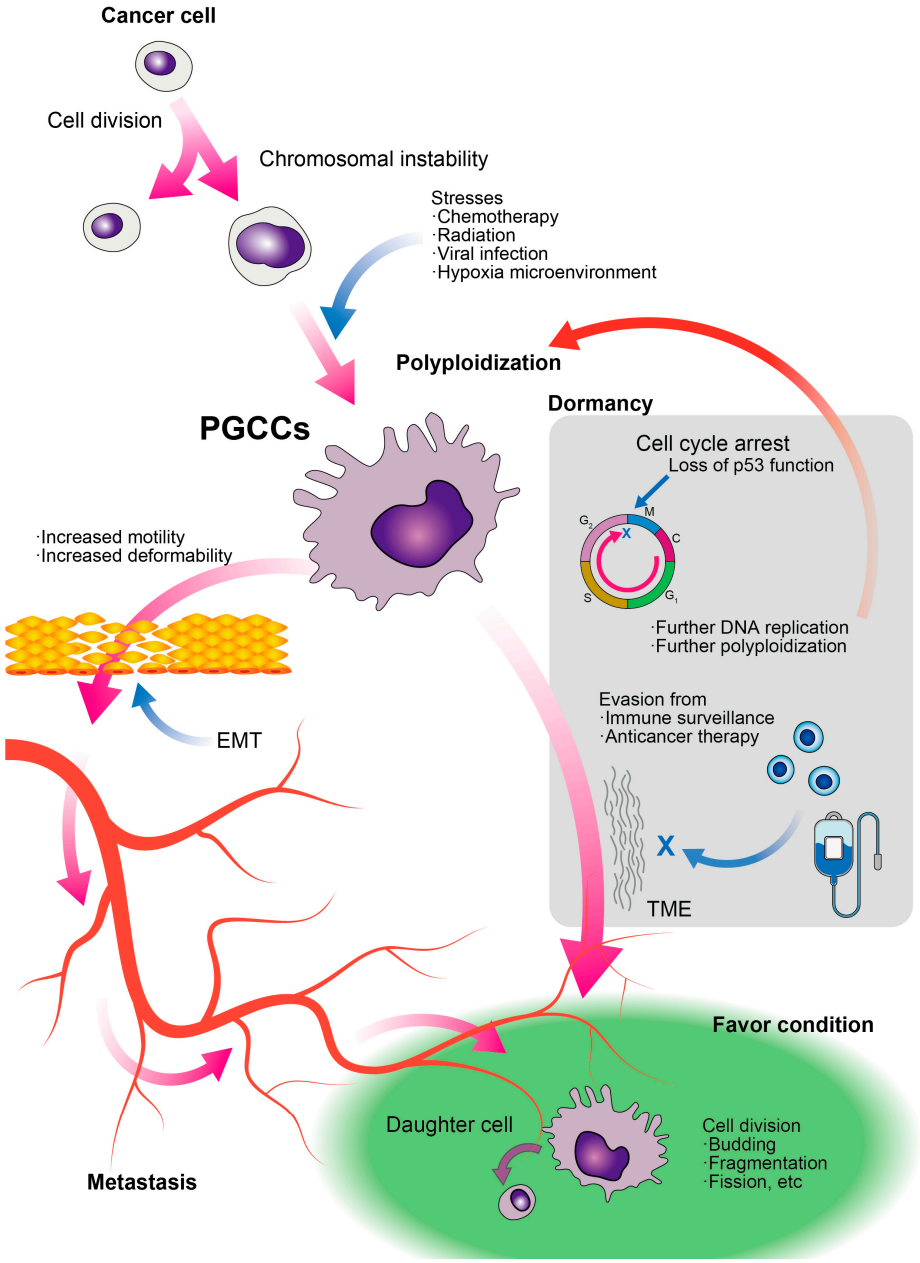

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Figure 1. Comprehensive overview of the formation and functions of PGCCs. PGCCs, polyploid giant cancer cells; EMT, epithelial-mesenchymal transition; TME, tumor microenvironment.

2.1. Polyploidization

Polypoidization is the process by which a cell gains one or more extra sets of chromosomes, leading to polyploidy, which is a genetic condition in which cells have more than two complete sets of chromosomes. Normal cells have two sets of chromosomes (2n), with one set inherited from each parent (diploid). In contrast, polyploid cells have three or more complete sets of chromosomes (3n, 4n, etc.). These cells are common in plants but are uncommon in most humans except for specific human cell types: hepatocytes (4n) and megakaryocytes (up to 64n). In cancers, polyploidization is a relatively common phenomenon and plays a significant role in tumor evolution and progression.

In the nuclei of PGCCs, increased DNA content has been observed using various DNA analysis techniques [14]. Pan-cancer genomic analysis has shown that a high proportion of human solid tumors (28.2–37%) have experienced at least one round of polyploidization during their evolution [15,16]. Chromosome missegregation during cell division leads to uneven distribution of chromosomes between daughter cells. Such polyploidization promotes chromosomal instability, an abnormality in chromosomal number or structure, which in turn facilitates cancer evolution by generating genetic diversity [17]. Thus, polyploidy was considered to be mainly caused by an abnormality in cell division. However, recent studies suggest that polyploidization can occur early in cancer development after oncogenic driver events, such as TP53 dysfunction and cell cycle arrest (see Section ***Dormancy*** for further details) [15].

2.2. Dormancy

Dormancy is a temporary, reversible state in which cells stop dividing and enter quiescence while remaining viable. Simply put, cells go into a “sleep mode” in which they maintain minimal metabolic activity but can “wake up” and resume normal function when conditions become favorable. Dormant cancer cells share several identical characteristics and signaling pathways with cancer stem cells, including recurrence and the ability to metastasize and evade the immune system [18,19]. To maintain dormancy, tumor cells suppress genes required for DNA synthesis or cell division and promote the expression of anti-apoptotic, anti-aging, and anti-differentiation genes [20,21]. Dormancy can allow cancer cells to undergo different cellular states (migration, quiescence) and evade anticancer therapies and immune surveillance [22–24]. Dormant PGCCs are usually in a non-proliferative state, the toxic effects of systemic therapies are evaded, and residual PGCCs later reactivate and proliferate, leading to tumor recurrence [13].

PGCCs have two major characteristics similar to dormant cancer cells: cell cycle arrest and high migratory ability. Cell cycle arrest is caused by disruption of the cell cycle checkpoint. In normal cells, this cell cycle checkpoint monitors the process of the cell cycle and pauses or inhibits its progression if abnormalities are detected. This checkpoint mechanism is disrupted in PGCCs, and the cell cycle is arrested [25,26]. Essentially, cell cycle arrest refers to the halting of the cell cycle and DNA replication in response to detected damage, allowing time for repair before mutations can occur. However, during cell cycle arrest in PGCCs, these cells undergo further DNA replication and polyploidization in the nucleus, known as endoreplication. They are survival strategies dormant PGCCs adopt to adapt to harsh environmental conditions. Cell cycle arrest in PGCCs consists of the following four steps [27]. First, multiple stresses can induce cell cycle arrest in cancer cells, leading to the formation of PGCCs for survival after anti-mitotic treatment [28,29]. Second, PGCCs replicate chromosomes without mitosis, which allows tumor cells to grow in a polyploid state. In this state, PGCCs evade this checkpoint through loss of p53 function and continue proliferating even with abnormal DNA levels [28,29]. Third, PGCCs generate daughter cells distinct from conventional mitosis through processes via alterations in aurora kinases A and B, which regulate chromosome segregation: budding (where small cells emerge from the PGCC surface and eventually separate to form independent daughter cells), fragmentation, and fission (where PGCCs divide their nuclear content

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into smaller nuclei, facilitating cellular division) [28,30]. Furthermore, PGCCs activate autophagy pathways to maintain survival and proliferative capacity under stressful conditions. Finally, daughter cells acquire new genomes and resume mitosis [28,30].

Another major characteristic of PGCCs similar to dormant cancer cells is high migratory ability. PGCCs exhibit increased motility and deformability mediated by increased mesenchymal-related protein expression and show increased metastatic potential. It is reported that PGCCs have thicker and longer actin fibers with abnormal overexpression of actin components compared with diploid cancer cells [31]. This mechanism allows PGCCs to be highly motile and metastatic. Furthermore, dormancy of tumor cells is an essential stage of tumor metastasis since it allows dormant cells to survive during dissemination, remain dormant until favorable conditions, and adapt to circumstantial conditions. Dormant PGCCs can be activated by external signals such as growth factors and cytokines from the microenvironmental [32]. These signals promote cell proliferation, causing dormant tumor cells to re-enter the cell cycle and initiate metastasis [33].

PGCCs exit dormancy and produce daughter cells via asymmetric division. Still, this asymmetric division leads to the loss of genetic material in the mononuclear daughter cells, thereby increasing their genetic instability and heterogeneity [2]. Metastatic capabilities of PGCCs and their daughter cells, such as proliferation, migration, and invasion, are enhanced through the high expression of EMT-related proteins [34]. Of these EMT-related proteins, vimentin is highly expressed in both PGCCs and their daughter cells, facilitating their migration and invasion abilities. This elevated vimentin expression enables these cells to readily metastasize to lymph nodes and distant organs while promoting migratory persistence [35].

3. Treatment-Resistance of PGCCs

PGCCs demonstrate resistance to various treatments, including anti-cancer drugs and radiotherapy. Several cytotoxic agents and radiotherapy exert anti-cancer effects by blocking mitosis. Thus, these treatments cannot effectively target dormant PGCCs. In addition, multiple mechanisms underlying PGCC treatment resistance have been suggested.

Several research has indicated that cytokine-PGCC crosstalk critically drives cancer progression and promotes chemotherapy resistance [36,37]. Cancer tissues typically feature fibrosis-rich stroma, creating a tumor microenvironment (TME) that impedes chemotherapeutic agent penetration, shields tumors from immune responses, and enhances tumor growth through growth factor expression. Migration inhibitory factors, cytokines primarily secreted by immune cells, modulate immune responses by inhibiting macrophage migration. However, PGCC-derived migration inhibitory factors facilitate immune evasion by suppressing T-cell function and promoting the expression of immune checkpoint molecules like PD-L1 within the TME [38]. Further, PGCC-derived IL-6 stimulates fibroblasts to increase collagen production, enrich cancer-associated fibroblast (CAF) subpopulations, and enhance vascular endothelial growth factor expression. These reprogrammed CAFs promote angiogenesis and metastasis and modify the TME to favor PGCC survival [39,40].

Polyploidy enables short-term metabolic adaptations to cope with oxidative stress. Once cancer cells acquire this capability, they can survive and respond to various stressors in TME [41,42]. The dormancy of PGCCs allows for efficient energy conservation and redistribution under poor environmental conditions [43], thereby contributing to long-term survival. It has been reported that PGCCs are rich in mitochondria, which play a crucial role in sustaining their survival by generating adenosine triphosphate through oxidative phosphorylation [44]. In addition, increased lipid droplet formation has been observed in PGCCs, suggesting that lipids are vital energy reservoirs that help these cells endure metabolic and environmental stresses [45]. The accumulation of lipids may also support membrane remodeling that facilitates PGCCs' adaptation and persistence in the TME.

Intriguingly, Bukkuri et al. suggested that post-therapy PGCC-derived recurrent populations develop cross-resistance to multiple therapies with distinct mechanisms using mathematical modeling. The authors proposed that this may be due to PGCC memory. Though their result was theoretical and needs to be validated, it is interesting to consider treatment resistance in PGCCs [46].

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4. Confusion of Terminology for PGCCs

The terminology for PGCCs has varied, and polyaneuploid cancer cells, pleomorphic cancer cells, osteoclast-like giant cells (OGCs), cancer-associated macrophage-like cells, and multinucleated giant cancer cells are often regarded as synonymous [41]. However, the diagnoses for these terms were based solely on morphological findings, so confusion exists (**Figure 2**).

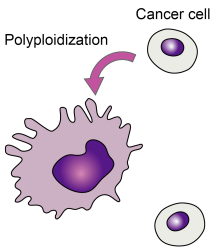
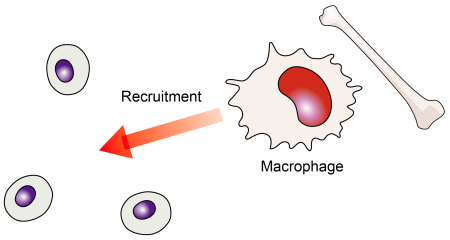
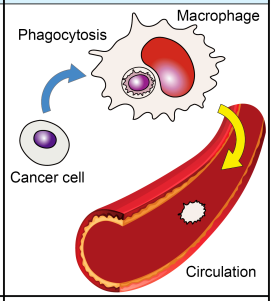
	Cancer-derived giant cells	Inflammatory giant cells		
	Polyploid giant cancer cells / Polyaneuploid cancer cells / Peomorphic cancer cells	Osteoclast-like giant cells	Multinucleated giant cancer cells	Cancer-associated macrophage-like cells
Mechanism				
Cancer stem cell markers e.g., SOX2, OCT4, and CD44	○	X	X	X
Pan-macrophages markers e.g., CD68	X	○	○	○
M1 macrophages markers e.g., CD11c, HLA-DR	X	X	○	X
M2 macrophages markers e.g., CD163, CD206	X	X	X	○
TAM markers e.g., CD14	X	X	X	○
Prognosis	Poor	Relatively good	Relatively good	Poor

Figure 2. Key differences between cancer-derived giant cells (e.g., PGCCs) and inflammatory giant cells. TAM, tumor-associated macrophage.

Polyaneuploid cancer cells and pleomorphic cancer cells are considered cancer-derived giant cells synonymous with PGCCs. Polyaneuploid cancer cells are known to have undergone whole-genome duplication, resulting in at least twice the complement of the original aneuploid genomic content. These unusually large aneuploid cancer cells have been well documented in the cancer literature since 1858, when Virchow first described them [47]. These cells have been observed across multiple fields of study, including aneuploidy, stem cell biology, genetic instability, tumor cell heterogeneity, senescence, and quiescence [41], and they are considered synonymous with PGCCs. This entity has been well documented in the prostate.

Pleomorphic carcinoma of the lung is a rare, poorly differentiated non–small cell lung cancer (NSCLC) that contains at least 10% spindle and/or giant cells and is currently categorized as a subtype of sarcomatoid carcinomas of the lung by the WHO classification of thoracic tumors [48]. These spindle and giant tumor cells are now considered part of the same clonal neoplasm. In the pancreas, pleomorphic carcinoma, also known as anaplastic carcinoma, is a rare subtype of undifferentiated carcinoma. The tumors consist of pleomorphic mononuclear cells admixed with bizarre-appearing giant cells with eosinophilic cytoplasm and lack gland formation [49] (**Figure 3**). These PGCC-containing tumors are reported to be marked treatment-resistant and associated with a poor prognosis (see Section **Clinical Implications of PGCCs** for further details).

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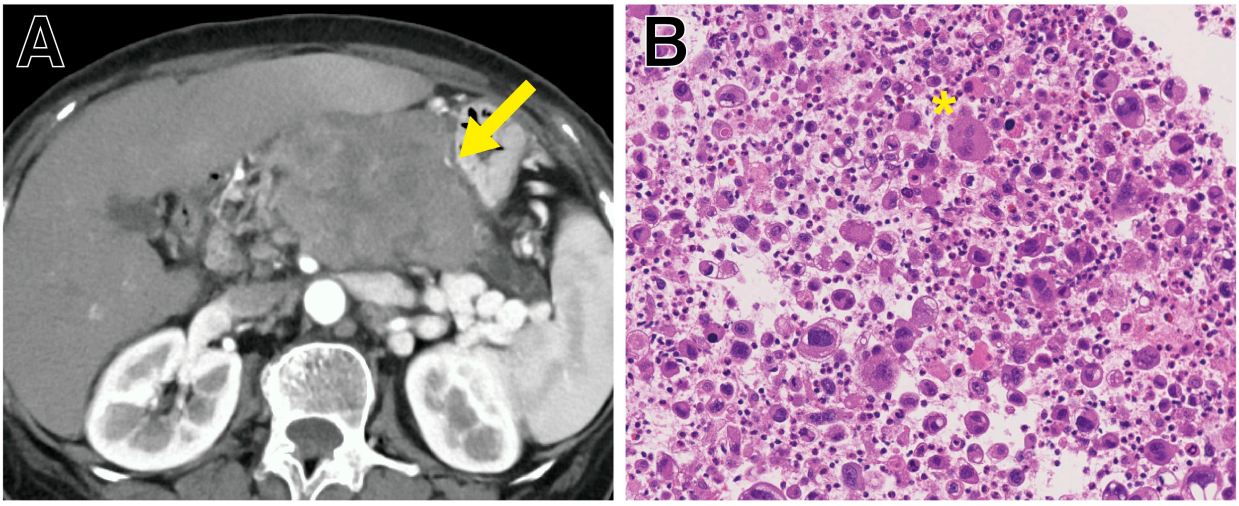

Figure 3. Imaging and histological findings of PGCC-containing tumors of the pancreas (undifferentiated carcinoma defined by the WHO classification). **(A)** Contrast-enhanced computed tomography showed a large tumor with poor contrast effect in the body of the pancreas (→). **(B)** Histologically, the cancer cells with irregular and large nuclei are seen (*).

In contrast, OGCs, multinucleated giant cancer cells, and cancer-associated macrophage-like cells consist of non-neoplastic cells, which are considered inflammation-derived giant cells. These giant cells are all thought to be derived from macrophages and have been induced in response to tumors. The cells are morphologically similar but different entities from PGCCs.

OGCs have been documented in various organs, particularly the pancreas, and they are classified as undifferentiated carcinoma with OGCs. Pathologically, they contain neoplastic pleomorphic cells (high Ki-67 index, positive for epithelial markers) and multi-nucleated OGCs (few mitoses, positive for macrophagic marker CD68, negative for epithelial markers) (**Figure 4**). These findings suggest that OGCs are reactive cells from macrophages rather than neoplastic cells. Studies by Strobel et al. and Muraki et al. indicate that patients with undifferentiated carcinoma with OGCs have significantly longer overall survival (OS) than those with undifferentiated carcinoma or conventional pancreatic cancer [50,51].

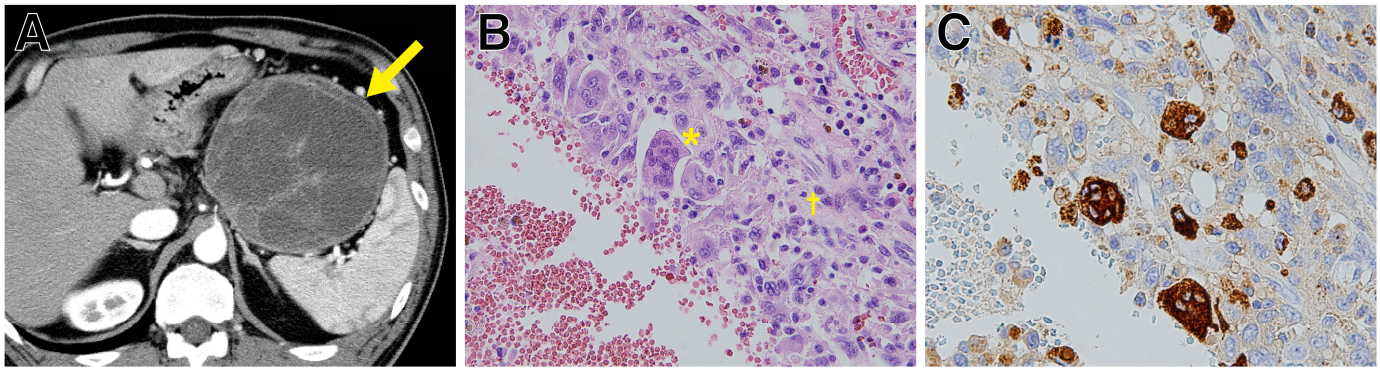

Figure 4. Imaging and histopathologic findings of osteoclast-like giant cells of the pancreas (undifferentiated carcinoma with osteoclast-like giant cells defined by the WHO classification). **(A)** Contrast-enhanced computed tomography showed a large tumor with a round shape, and marked cystic degeneration is seen in the pancreatic tail (→). **(B)** Pathological findings of the resected specimen. A mixture of pleomorphic mononuclear tumor cells (†) and non-neoplastic osteoclastic multinucleated giant cells (*) were seen. **(C)** Multinucleated osteoclast-like giant cells were immunohistochemically positive for CD68.

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Cancer-associated macrophage-like cells (CAMLs) are generally larger than circulating tumor cells, ranging from 25 to 300 μm. They have atypical or multiple nuclei and contain phagocytosed tumor protein epitopes in the cytoplasmic vesicles. CAMLs express the macrophage protein CD14 on their cell surfaces, so they are believed to represent tumor-associated macrophages that have phagocytosed tumor cell material locally and have disseminated [52]. The prognostic significance of circulating CAMLs has also been reported in various types of cancers [53]. In a study by Adams DL et al. [52], circulating CAMLs were detected in 93% of solid tumor patients but not in healthy volunteers; furthermore, tumor cell diameter and polyploidy increased with tumor progression. Large CAMLs (>50 μm, particularly >110 μm) were significantly associated with poor PFS and OS. The authors suggested that tumor microenvironmental stimuli induce polyploidization of myeloid-derived hematopoietic stem cells and monocytic cells into PGCCs, a fraction of which disseminate into the circulation as CAMLs.

Multinucleated giant cells typically occur in granulomatous diseases, including infections, vasculitis, immunological disorders, and cancer. They are formed by the fusion of circulating monocytes, progenitors of macrophages, infiltrating into local tissues. These cells display surface markers (CD11c+, HLA-DR+, CD163-, CD206-) similar to M1 macrophages, indicating that these cells are anti-tumor M1 macrophages [54,55].

5. Diagnostic Approaches for PGCCs

Currently, there is no established gold standard for the diagnosis of PGCCs. The diagnostic process often requires both pathological and genetic approaches, and these facts make diagnosing PGCCs difficult and hinder their understanding and application in clinical practice.

In pathological approaches, Zhang defined PGCC nuclei as ≥ three times larger than regular-sized diploid tumor cell nuclei [2]. Although a simple and applicable definition, PGCCs represent a relatively small fraction (5–20%) of tumor cells in various cancers [56]. Furthermore, a careful cytomorphological analysis is required to distinguish true PGCCs from other giant cells, since chronic infections and inflammations also induce giant cells and can circulate in patients without cancer [57] (**Figure 2**) (see Section **Confusion of terminology for PGCCs** for further details). In such situations, immunohistochemistry and special staining are necessary for differential diagnosis. Immunohistochemical cancer stem cell markers (e.g., SOX2, OCT4, and CD44) [58] and Feulgen staining, used for semi-quantitative evaluation of DNA, can aid in the diagnosis of PGCCs.

In genetic approaches, various methods, such as karyotyping, flow cytometry, fluorescence in situ hybridization (FISH), and single-cell next-generation sequencing (NGS), have been used. Karyotyping is a classic method to evaluate quantitative or structural chromosomal abnormalities. Still, it is technically complex and time-consuming due to the reduced mitotic activity of PGCCs, requiring specialized expertise. In contrast, flow cytometry and FISH offer methodological simplicity and rapid results through direct analysis of cellular DNA content without requiring cell division. Thus, they are popular methods in PGCC research. Single-cell NGS is a new and beneficial technique because it provides not only PGCC ploidy and chromosomal copy numbers, but also detailed information on genomic alterations. However, it has the disadvantage of high cost.

Currently, new approaches for the diagnosis of PGCCs are being investigated. Chinen et al. examined circulating PGCCs in blood samples from patients with six types of cancer (colon, gastric, lung, breast, anal canal, and kidney). Of these patients, PGCCs were identified in 46 (20.18%) of 228 patients, including 14.47% of 152 non-metastatic cases and 29.85% of 67 metastatic cases [59]. Several studies have used machine learning for risk stratification of various solid tumor types based on morphological findings of cancer cells [60–63]. These studies indicated that the presence of PGCCs was a poor prognostic factor; however, detailed information about polyploid cancer cells was often not provided.

6. Clinical Implication of PGCCs

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As described above, basic research has shown that PGCCs can drive cancer progression and promote chemotherapy resistance. PGCCs are potentially associated with more aggressive behavior and a poorer prognosis. In fact, several clinical studies have reported the clinical characteristics of PGCC-containing tumors and suggested their association with more aggressive behavior in various types of solid tumors (**Table 1**).

Table 1. Summary of prognosis of polyploid giant cancer cell-containing solid tumors.

Author (year)	Population	No. of patients	Survival metric	Median survival time	Comparison	Survival comparison summary
Prostate cancer						
Trabzonlu (2023) [65]	Prostate cancer with PGCCs with intermediate- or high-risk	239	Metastasis-free survival	–	Prostate cancer with PGCCs vs. control prostate cancer	HR, 2.00 (95% CI, 1.40–2.87)*
Lung cancer						
Chen (2022) [68]	Registry data	461	OS	9 months		
Pancreas						
Clark (2012) [76]	Registry data	353	OS	3 months	Undifferentiated carcinoma vs. control pancreatic cancer	HR, 1.9 (95% CI, 1.7–2.1)
Imaoka (2020) [77]	Treated with chemotherapy	50	OS	4.08 months		
Hepatocellular carcinoma						
Matsuura (2023) [81]	HCC with PGCCs	20	OS	–	HCC with PGCCs vs. near-diploid HCC	log-rank p=0.013
Colorectal cancer						
Chinen (2024) [59]	Presence of circulating PGCCs	9	OS	–	Presence of circulating PGCCs vs. absence of circulating PGCCs	log-rank p=0.033 (5-years OS rate 76% vs. 96%)
Urothelial carcinoma						
Portugal-Gaspar (2024) [84]	High-grade urothelial carcinoma	21	OS	–	Urothelial carcinoma with PGCCs vs. conventional urothelial carcinoma	HR, 2.22 (95% CI, 1.126–4.384)
Angiosarcoma Tan (2021) [85]	Treated with chemotherapy	22	OS	9.6 months	Presence of PGCCs vs. absence of PGCCs	HR, 2.20 (95% CI, 1.17–4.15)

For consistency, all survival time have been converted to months in this review. HR > 1 indicates that PGCC-containing tumors have a poorer prognosis. *HR per 1 PGCC increase. HR, hazard ratio; CI, confidence interval; OS, overall survival; HCC, hepatocellular carcinoma; PGCCs, polyploid giant cancer cells.

6.1. Prostate Cancer

If a predominant proportion of the tumor consists of PGCCs, pleomorphic carcinoma of the prostate is diagnosed. This rare and highly aggressive variant of prostate cancer is characterized by marked pleomorphism. Comprehensive data on the frequency of this cancer are limited, and as a

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result, the molecular mechanisms and optimal treatment strategies remain poorly understood. However, several studies have reported a poor prognosis for this cancer. Alharbi et al. reported 30 patients with pleomorphic carcinoma of the prostate. The PGCC components were focal (<5%) but indicated aggressive disease, rapid progression, and a poor prognosis. All patients had the usual acinar prostatic adenocarcinoma with a Gleason score of 9–10. In patients with no prior prostate cancer diagnosis and >1-year follow-up, 37% died within a median of 8 months. In those with recurrent disease, 57% died within a median of 7 months [64]. Trabzonlu et al. also reported that PGCCs are a significant prognostic factor for metastatic-free survival in a case-cohort of intermediate- or high-risk men who underwent radical prostatectomy. The number of PGCCs was a significant prognostic factor for metastasis-free survival (hazard ratio [HR] per 1 PGCC increase, 2.00; 95% confidence interval [CI], 1.40–2.87) [65]. Schmidt et al. analyzed bone marrow aspirates from 44 patients with advanced prostate cancer and found that the presence of circulating large nuclei tumor cells (CTCs) with increased genomic content was significantly associated with poorer progression-free survival (log-rank p=0.0095) [66]. In addition, single-cell copy number profiling of CTCs with increased genomic content showed clonal origins shared with typical CTCs, suggesting complete polyploidization. These findings are consistent with the features of PGCCs.

6.2. Lung Cancer

In the lung, pleomorphic carcinoma is defined by the WHO classification as tumors with ≥10% PGCCs (pleomorphic or spindle giant cell) components. These rare tumors (0.4–1.6% of lung malignancies) primarily affect heavy-smoking men, respond poorly to chemotherapy, and have worse outcomes than other NSCLCs [67]. One epidemiological study analyzed 461 patients with pleomorphic carcinoma from 2004 to 2014. The median OS was 9 months, and multivariate Cox analysis revealed that elderly patients (>66 years) and advanced disease were predictors of poor prognosis in terms of OS. Surgery significantly improved OS in patients with localized and regional stages, but had little impact on those with distant-stage disease. Conversely, chemotherapy reduced the risk of death in distant-stage patients, but did not benefit those with localized or regional-stage disease. Radiation therapy had no significant effect on OS [68]. Regarding chemotherapy, small, retrospective studies have reported that pleomorphic carcinoma of the lung responded poorly to chemotherapy, mainly cytotoxic agents, and patient prognosis remained poor [69,70]. EFGR is one of the most important treatment targets in NSCLC. Several studies reported that the frequency of *EGFR* mutation is approximately ≤20%, almost equivalent to conventional NSCLC. However, the effect of EGFR inhibitors on pleomorphic carcinoma with *EGFR* mutation has been limited [71–73].

Genomic and immunohistochemical analyses of pleomorphic carcinoma of the lung showed key molecular characteristics. A sequencing study of 78 specimens from 52 patients identified *TP53* (71%) as the most frequently mutated gene, followed by *KRAS* (27%) and *EGFR* (8%) [73]. Both epithelial and sarcomatoid components shared activating driver mutations, with no significant differences in tumor mutational burden. Another study analyzing PD-L1, EMT-related proteins (E-cadherin, vimentin, ZEB-1), and c-MET in 16 surgically resected pleomorphic carcinoma patients found PD-L1 expression in 88% of carcinomatous areas, with 56% showing high expression [74]. PD-L1 expression in sarcomatous areas was comparable to that in carcinomatous areas; notably, high expressions of PD-L1, ZEB-1, and c-MET in sarcomatous areas correlated with a poor prognosis.

6.3. Pancreatic Cancer

If a predominant proportion of the tumor consists of PGCCs, undifferentiated carcinoma of the pancreas is diagnosed. It accounts for 0.3–7% of malignant pancreatic tumors. According to the WHO classification [75], undifferentiated carcinomas are classified into three subtypes: anaplastic undifferentiated carcinoma, sarcomatoid undifferentiated carcinoma, and carcinosarcoma. PGCCs correspond to anaplastic undifferentiated carcinoma, and the other two subtypes are extremely rare and not discussed here.

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In one report using registry data, the median age at diagnosis was 62.0 years, and undifferentiated carcinoma showed a male predominance (71.4%). Thus, undifferentiated carcinoma shares characteristics with its counterpart, pancreatic cancer. In contrast, patients with undifferentiated carcinoma showed significantly shorter OS than those with pancreatic cancer (HR, 1.9; 95% CI, 1.7–2.1) [76]. Undifferentiated carcinoma is recognized as a chemoresistant disease. A retrospective cohort study showed limited efficacy, with an objective response rate of 10% and median progression-free survival of 1.84 months for first-line treatment [77]. Genomic alterations in *KRAS*, *TP53*, *CDKN2A/B*, and *SMAD4* are commonly observed in undifferentiated carcinoma. Of them, *KRAS* mutations are the most frequent, occurring in 60–80% of patients, supporting the concept that undifferentiated carcinoma originates from pancreatic cancer. In addition, EMT-related changes, characterized by E-cadherin downregulation and upregulated expression of Slug, Twist1, and ZEB-1, are frequently observed on immunohistochemistry [49].

6.4. Hepatocellular Carcinoma

Typically, polyploidy is associated with cancer and increases in various liver diseases that promote tumorigenesis. However, various studies have shown that the relationship between hepatocyte polyploidy and tumorigenesis in hepatocellular carcinoma (HCC) is more complicated. Lin et al. showed that polyploid hepatocytes maintain the ability to regenerate liver tissues during chronic damage without generating mitotic errors, and higher polyploidy can protect them, developing fewer HCCs following chronic liver injury [78]. Meanwhile, Matsumoto et al. demonstrated that polyploid hepatocytes are not fully protected from oncogenesis, and ploidy reduction can promote cancer initiation through multipolar mitosis, inducing chromosomal instability [79]. Binuclear polyploid hepatocytes comprise the majority of polyploid cells in normal human liver tissue, but Bou-Nader et al. showed that binuclear polyploid hepatocytes were significantly decreased during HCC progression. In comparison, mononuclear polyploid hepatocytes increased. They suggested that mononuclear polyploid hepatocytes are associated with low differentiation, high proliferation, and a poor prognosis in HCC, particularly amplified in poorly differentiated tumors with *TP53* mutations [80]. In cancer cells, Matsuura et al. found that polyploidy was detected in 36% of HCCs and identified an aggressive subset of HCC [81]. The polyploid HCCs frequently exhibited large nuclei and were associated with elevated serum alpha-fetoprotein levels, poor differentiation, and a worse prognosis than near-diploid HCCs. These characteristics suggest that polyploid HCCs share features with PGCCs.

6.5. Colorectal Cancer

The pathological presence of PGCCs is associated with poor differentiation, invasion, metastasis, and, consequently, a poor prognosis in colorectal carcinoma (CRC). Zhang et al. investigated the clinicopathological characteristics of PGCCs in CRC [82]. More PGCCs were observed in poorly differentiated CRC than in well-differentiated CRC (well-differentiated, 27.5%; moderately differentiated, 50%; poorly differentiated, 90.2%), and PGCCs have a high predictive value for lymph node metastasis in poorly differentiated CRC. In CRC, pathological micropapillary carcinoma patterns and tumor budding (isolated small groups of cancer cells from the invasive tumor margin) are known to be factors associated with a poor prognosis. PGCCs were observed in most micropapillary carcinoma patterns and tumor budding [83]. Chinen et al. indicated that the presence of PGCCs had a negative impact on patient prognosis. They showed that CRC patients with PGCCs had a significantly shorter OS than those without ($p=0.033$) using circulating PGCCs in blood samples [59].

As in vitro data, clinical studies of locally advanced rectal cancer have indicated that neoadjuvant chemoradiotherapy (nCRT) can induce the formation of PGCCs, whose daughter cells exhibit strong migratory, invasive, and proliferative abilities. Fei et al. analyzed 304 samples from patients treated with nCRT and 301 paired samples from those without nCRT [12]. The number of PGCCs was significantly higher in tumor tissues from patients who underwent nCRT than in those

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who did not. In addition, more PGCCs were observed in anastomotic recurrent rectal cancer after nCRT than before treatment.

6.6. Urothelial Carcinoma

In urothelial carcinoma, PGCCs (pleomorphic giant cells) are an aggressive variant and are associated with poor prognosis. Portugal-Gaspar et al. reported the clinicopathological characteristics [84], indicating that all cases were associated with high-grade urothelial carcinoma. The presence of PGCCs was an independent factor associated with poor OS (HR, 2.222; 95% CI, 1.126–4.384).

6.7. Other Types of Cancer

PGCCs have been identified as a factor associated with poor OS in various cancers. In angiosarcoma, PGCCs exhibit genomic similarities to regular-sized cells. They were detected in 41.4% of patient samples and were associated with poor chemotherapy response rates (25.0% vs. 73.3%, p=0.0213). In addition, PGCCs independently contributed to worse OS (HR, 2.20; 95% CI, 1.17–4.15) [85]. Similarly, one study of laryngeal cancer demonstrated that high PGCC expression was associated with worse OS [86].

Although no survival data were presented, a higher number of PGCCs was detected in more advanced stages of various cancers. In malignant melanoma, PGCC numbers were significantly higher in larger tumors than in smaller ones and in tumors with lymph node metastasis than in those without metastasis [87]. This trend was also observed in glioma, where higher malignant grades exhibited increased PGCCs [88,89]. Similarly, in breast cancer, PGCC numbers correlated with malignancy grade: metastatic disease showed the highest PGCC numbers compared with primary breast cancer with lymph node metastasis, without lymph node metastasis, and benign disease [90].

Emerging evidence suggests that cytomegalovirus (CMV) may play a role in oncogenesis, particularly in breast cancer and high-grade serous ovarian cancer. CMV infection induces PGCC formation in these CMV-associated cancers. Recent studies have demonstrated strong correlations among CMV, PGCCs, and EZH2 expression in CMV-associated cancers, highlighting that oncogenic CMV strains induce polyploidy through EZH2 and Myc upregulation [91,92].

7. Treatment

In translational research, prevention of the formation of PGCCs by several agents, such as tocilizumab, mTOR inhibitors, zoledronic acid, and aurora kinase inhibitors, has been reported [40,44,93,94]. However, the efficacy of these agents against PGCCs in clinical settings remains questionable based on clinical data. For example, the aurora kinase inhibitor alisertib, which potentially mediates cellular division of PGCCs, failed to demonstrate an antitumor effect against peripheral T-cell lymphoma in a phase 3 trial [95]. Similarly, tocilizumab and zoledronic acid have not been shown to have antitumor effects.

Despite advances in research on PGCCs, no clear evidence for targeted treatments has been established. Furthermore, treatment data for patients with PGCCs are limited. However, retrospective studies indicated that a paclitaxel-containing regimen is a reasonable option for the treatment of patients with PGCC-containing tumors. In PGCC-containing tumor of the lung (pleomorphic carcinoma), one small retrospective study reported that the paclitaxel-containing regimen, carboplatin plus paclitaxel, or carboplatin plus nab-paclitaxel, offered a high objective response rate of 60.0% and a median OS of 16.7 months [96]. Similarly, in PGCC-containing tumor of the pancreas (undifferentiated carcinoma), a paclitaxel-containing regimen was associated with a significant OS benefit in patients with advanced disease (HR, 0.221; 95% CI, 0.076–0.647) [77]. Although retrospective in nature, these results indicated that a paclitaxel-containing regimen for PGCC-containing tumors may provide promising results. Thus, we are currently conducting a phase 2 clinical trial of gemcitabine plus nab-paclitaxel for them (jRCTs031220099).

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Today, immune checkpoint inhibitors (ICIs) have emerged as a new treatment paradigm for patients with many types of cancer [97]. High microsatellite instability is considered a biomarker for predicting the efficacy of immune checkpoint inhibitors. Notably, tumors tend to exhibit either chromosomal instability or high microsatellite instability [98], indicating that tumors with chromosomal instability typically display low microsatellite instability. Although there are no data examining the efficacy of ICIs, PGCCs with chromosomal instability may not respond to ICIs based on these findings.

As previously described, p53 is a tumor suppressor protein and a key regulator of PGCCs. Thus, p53 is a potential therapeutic target. Recently, a novel p53 reactivator, Rezatapopt, showed a promising antitumor effect on *TP53 Y220C*-mutated tumors [99]. This small molecule binds to the *TP53 Y220C* mutant p53 protein, restoring its tumor-suppressor activity. Although this drug's development is still in the early stages, it has the potential to be effective against PGCCs. Another potential therapeutic target is EZH2, which plays a critical role in the polyploidization of CMV-associated cancer cells. Recent studies have shown that EZH2 inhibition reduces malignant transformation in CMV-associated breast cancer and high-grade serous ovarian cancer [91,92], suggesting that EZH2 is a promising therapeutic target for CMV-associated malignancies. The EZH2 inhibitor, tazemetostat, showed encouraging results in follicular lymphoma [100] and advanced epithelioid sarcoma with loss of INI1/SMARCB1 in phase 2 trials [101].

8. Conclusion

Despite decades of documentation, PGCCs remain clinically challenging due to diagnostic difficulties. PGCC-containing tumors exhibit marked treatment resistance and are associated with a poor prognosis across multiple solid tumor types, including prostate, lung, and pancreatic cancers. Despite these therapeutic challenges, paclitaxel-containing regimens have shown promising results in PGCC-containing tumors. Furthermore, emerging targeted therapies directed at specific pathways in PGCCs represent potential strategies to improve clinical outcomes in PGCC-containing tumors. Further understanding of PGCCs may be a key clue to overcoming cancer.

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