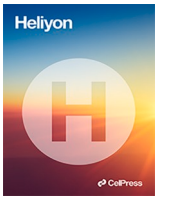
Heliyon 10 (2024) e28881

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Pulmonary mucinous adenocarcinoma: An overview of pathophysiology and advancements in treatment

Lihui Ge [a], Linlin Wang [b], Dongmei Pei [a,*]

[a] Department of Health Management, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China
[b] Department of Thoracic Surgery, Shenyang Tenth People's Hospital, Shenyang, Liaoning, China

ARTICLE INFO

Keywords:
Pulmonary mucinous adenocarcinoma
NSCLC
KRAS mutations
Targeted therapy
Prognostic

ABSTRACT

Pulmonary mucinous adenocarcinoma (PMA), a distinct subtype of non-small cell lung cancer (NSCLC), is characterized by an abundance of mucin-producing cells. Although this subtype comprises a relatively small fraction of lung adenocarcinomas, PMA stands apart due to its unique clinical, pathological, and molecular features. This review comprehensively discusses the pathophysiology and etiology, clinical features, diagnostic methods, treatment strategies, prognosis, and future directions for PMA, drawing from relevant literature and existing studies. Advances in PMA treatment includes surgical intervention, targeted therapy, immunotherapy, and adjuvant therapy. Particularly, we discussed factors influencing the prognosis of PMAs, such as molecular markers, pathological features, and the impact of the latest treatment advances on prognosis. Moreover, we intended this review to be a comprehensive reference for diagnosing, treating, and assessing the prognosis of PMA, providing valuable guidance for clinical practice.

1. Introduction

Pulmonary mucinous adenocarcinoma (PMA) stands out as a distinctive subtype among lung adenocarcinomas, falling within the broad category of non-small cell lung cancer (NSCLC) [1,2]. Characterized by the excessive production of mucin, a viscous, gel-like substance crucial for pathological identification, PMA significantly differs from other lung adenocarcinomas [3,4]. Mucin abundance serves as a diagnostic indicator and influences tumor biology, including invasiveness and metastatic potential. Additionally, PMA exhibits unique molecular and genetic traits, most notably an increased prevalence of specific Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations [5]. These distinct features suggest that PMAs may diverge from other subtypes regarding clinical presentation, treatment response, and overall prognosis. Despite representing a smaller fraction of lung adenocarcinomas, the unique clinical and molecular characteristics of PMAs underscore their significance in lung cancer research (see Fig. 1).

This review aimed to address key knowledge gaps in PMA, particularly in explaining the histological and molecular differences from other lung adenocarcinoma subtypes, exploring clinical characteristics and prognostic factors, summarizing treatment advances, and proposing future research directions to enhance understanding and treatment efficacy. By addressing these gaps, this review furnished a comprehensive reference for diagnosing, treating, and prognostically assessing pulmonary mucinous adenocarcinoma, guiding future research directions.

* Corresponding author. Department of Health Management, Shengjing Hospital of China Medical University, No. 36 Sanhao St., HePing District, Shenyang, Liaoning, 110004, China.
E-mail address: peidm1111@hotmail.com (D. Pei).

https://doi.org/10.1016/j.heliyon.2024.e28881
Received 17 January 2024; Received in revised form 21 February 2024; Accepted 26 March 2024
Available online 29 March 2024

1.1. Pathophysiology and etiology

Currently, adenocarcinoma is the most common histopathological type of lung cancer. In the 5th edition of the World Health Organization (WHO) classification of thoracic tumors (2021 edition), invasive mucinous adenocarcinoma (IMA) underwent reclassification and is acknowledged as a distinct histopathological type of lung adenocarcinoma (Table 1), rather than being categorized as a pathological subtype of invasive adenocarcinoma variants [6]. The pathogenesis and biological mechanisms of PMA exhibit significant differences from other lung cancer subtypes. The cellular and molecular mechanisms of PMA involve several key processes (Table 2). (1) Regulation of mucin production and secretion: excessive production and secretion of mucin is a hallmark of PMA. Compared to other lung cancer subtypes, mucinous adenocarcinoma cells may exhibit abnormalities in mucin production and

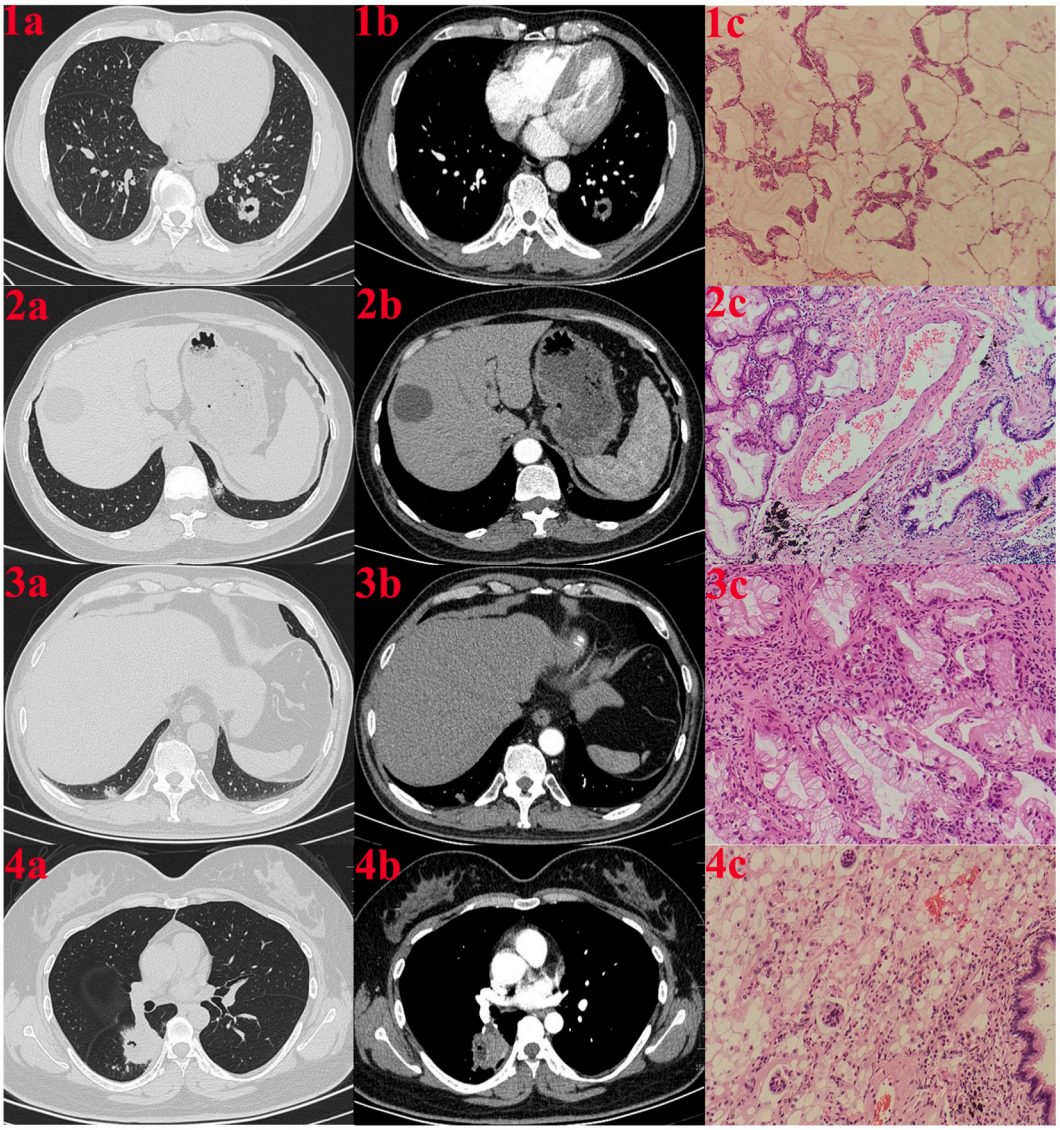


Fig. 1. **1a-b**: Chest CT showed a thick-walled, lobulated, and spiculated cavity measuring about 26 × 21 mm in the posterior basal segment of the left lower lobe. **1c**: Pathological examination indicated mucinous adenocarcinoma cells budding on the alveolar surface and filling the alveolar cavity with mucus. **2a-b**: Chest CT revealed a small, patchy, lobulated mass approximately 15 × 10 mm in size in the posterior basal segment of the left lower lobe. **2c**: Pathological analysis showed an acinar arrangement of goblet or tall columnar cells with mucus, with cancer cells at the base, alongside a cross-section of a vessel and a bronchiole. **3a-b**: Chest CT indicated a single, partially solid nodule about 13 mm in diameter with a bronchial shadow in the posterior basal segment of the right lower lobe. **3c**: Pathological examination revealed significant invasive growth of cancerous tissue in an acinar structure, with columnar cancer cells having nuclei at the base and mucus-filled cytoplasm. **4a-b**: Chest CT displayed a solid, lobulated, and spiculated nodule approximately 38 mm in diameter in the dorsal segment of the right lower lobe, with multiple small bubbles at the edge. **4c**: Pathological examination showed tumor cell clusters within the normal alveolar spaces adjacent to the tumor (spread through airspaces, STAS).

Table 1
2021 WHO classification of lung adenocarcinomas with ICD-O codes.

Adenocarcinomas	ICD-O codes
Minimally invasive adenocarcinoma	
Minimally invasive adenocarcinoma, nonmucinous	8256/3
Minimally invasive adenocarcinoma, mucinous	8257/3
Invasive nonmucinous adenocarcinoma	
Lepidic adenocarcinoma	8250/3
Acinar adenocarcinoma	8551/3
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma	8253/3
Mixed invasive mucinous and nonmucinous adenocarcinoma	8254/3
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric-type adenocarcinoma	8144/3

WHO, World Health Organization; ICD-O, International Classification of Diseases for Oncology.

secretion mechanisms. This may involve aberrant gene expression related to mucin production or dysregulation of signaling pathways, leading to excessive accumulation and uncontrolled mucin secretion [7]. (2) Differential expression of molecular markers: PMA may exhibit differences in the expression patterns of molecular markers compared to other lung cancer subtypes. For example, specific gene mutations (such as KRAS) may be more common in PMA, whereas other lung cancer subtypes may have different mutation spectra [8]. The differential expression of these molecular markers may affect the biological behavior of tumor cells and their treatment responses. (3) Changes in cell signaling pathways: unlike other lung cancer subtypes, the pathogenesis of PMA may involve aberrant activation or inhibition of cell signaling pathways [9]. Changes in these pathways may affect the proliferation, invasion, and metastatic abilities of tumor cells; thereby, influencing their pathological characteristics and clinical presentations. (4) Epithelial-to-mesenchymal transition (EMT): in certain cases, cells of mucinous adenocarcinoma undergo EMT, a process where epithelial cells acquire mesenchymal traits, contributing to increased invasiveness and metastatic capability [10,11]. (5) Influence of tumor microenvironment: excessive mucin production in PMA may have specific effects on the tumor microenvironment, including altering intercellular communication, affecting immune responses, and changing the physical properties [12,13]. These factors may present unique challenges and advantages in treating PMAs. Mucin overproduction in PMA may affect the functionality of T and B cells in the tumor microenvironment. T-cell infiltration is closely related to tumor immune evasion and prognosis. The accumulation of mucin, potentially forming a physical barrier, may be associated with immune evasion by hindering T-cell contact and killing of tumor cells [14]. Although the specific role of B cells in PMA has not been fully elucidated, they may play a role in regulating immune responses within the tumor microenvironment. Furthermore, the expression changes of chemokines like CXCL12 in the tumor microenvironment may affect the recruitment of immune cells and the behavior of tumor cells; thus, influencing the occurrence and progression of tumors and requiring further research.

The etiology and risk factors of PMA align with those of other lung cancers, although research on this specific subtype is limited because of its rarity. Smoking is the most significant risk factor for lung cancers, including PMA [15]. The risk increases with smoking duration and intensity. Exposure to environmental toxins increases the risk of developing lung cancer, including radon gas, asbestos, heavy metals like arsenic, and air pollution. Moreover, a genetic predisposition to lung cancer may exist. Individuals with a family history of lung cancer [16] may be at increased risk. Preexisting lung conditions such as chronic obstructive pulmonary disease and pulmonary fibrosis [17] are associated with a higher risk of lung cancer. Chronic inflammation and scarring of the lungs may

Table 2
Overview of pathophysiology.

Research area	Key processes and features	Examples of molecular pathways	Impact on tumor microenvironment and cellular communication
Mucin production and secretion	Pulmonary mucinous adenocarcinoma is characterized by overproduction and secretion of mucin.	Abnormal expression of genes such as MUC5AC and MUC5B.	Accumulated mucin may hinder intercellular signaling and immune cell infiltration.
Molecular marker expression	Pulmonary mucinous adenocarcinoma exhibits different molecular marker expression patterns compared to other lung cancer subtypes.	High prevalence of KRAS mutations.	Affects tumor cell proliferation, invasion, and treatment response.
Cellular signaling pathways	Abnormal activation or inhibition of cellular signaling pathways in pulmonary mucinous adenocarcinoma compared to other lung cancer subtypes.	EGFR and ALK gene rearrangements.	Alters tumor cell behavior and clinical presentation.
Epithelial-mesenchymal transition (EMT)	Mucinous adenocarcinoma cells may undergo EMT, enhancing invasion and metastatic capabilities.	Activation of the TGF-β signaling pathway.	Promotes tumor cell migration and invasion.
Tumor microenvironment	Excessive mucin in mucinous adenocarcinoma may specifically alter the tumor microenvironment.	Changes in chemokines such as CXCL12.	Affects intercellular communication, immune response, and physical properties of the tumor.

contribute to cancer development. The risk of lung cancer generally increases with age [18], and PMA is no exception. Although lung cancer rates have traditionally been higher in men, the gap has been narrowing, potentially because of changes in smoking patterns among women. Furthermore, individuals who previously had lung cancer are at a higher risk of developing a second lung cancer [19], including PMA.

1.2. Clinical features and diagnosis

PMA often presents with symptoms similar to those of other lung conditions, posing challenges in diagnosis. These symptoms encompass persistent cough, shortness of breath, chest pain, wheezing, recurrent respiratory infections, coughing up blood, and general systemic symptoms, such as unexplained weight loss, loss of appetite, and fatigue [20,21]. Owing to the similarity in symptoms with other lung diseases, PMA can be occasionally misdiagnosed as pulmonary actinomycosis [22].

Diagnosis relies on an integrated approach combining imaging and biopsy findings. Imaging modalities include chest radiography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans. Biopsies are obtained using bronchoscopy, CT-guided needle aspiration, endobronchial ultrasound, thoracentesis, and surgical methods. Moreover, histopathological evaluation is paramount for a definitive diagnosis. Histopathological examination is crucial for determining the type, grade, and stage of a tumor, thereby informing the development of an optimal treatment approach. Additionally, after histopathological examination, further molecular testing can be performed on tissue samples to identify specific mutations or biomarkers that may serve as treatment targets.

1.3. Treatment options (Table 3)

(1) Surgery: primary treatment for early-stage PMA typically involves surgical intervention, especially for localized operable tumors. Surgical options range from limited resections (e.g., wedge resections) to more extensive procedures like lobectomy or pneumonectomy, dictated by the tumor size and location. The recurrence rate and long-term survival depend on the stage at diagnosis and the thoroughness of resection. A notable study [23] comparing outcomes in IMA and non-mucinous invasive adenocarcinoma (NMA) in 20,914 patients showed that patients with PMA had an average survival time of 124 ± 34 months, with a 3-year survival rate of 73.8% (95% confidence interval [CI] 0.69–0.79) and a 5-year survival rate of 66.8% (95% CI 0.62–0.72). Although differences were observed in histological grading, tumor staging, and use of adjuvant therapy, no significant differences were noted in demographic characteristics or surgical aspects. A study [24] examining recurrence dynamics after curative surgery in patients with IMA indicated that morphological consolidation, higher T and N stages, smoking, and spread through alveolar spaces (STAS) are significant indicators of an increased risk of early recurrence or death in patients with IMA. However, the article did not specify the exact recurrence rates. (2) Chemotherapy: this treatment modality is employed in adjuvant, neoadjuvant, and advanced-stage scenarios. A significant study on palliative chemotherapy for advanced IMA [25] highlighted the frequent use of platinum-based regimens combined with pemetrexed and gemcitabine.

Table 3
Summary of different treatment modalities for pulmonary mucinous adenocarcinoma.

Treatment modality	Indications	Considerations	Subsets needing further research
Surgical treatment	Early-stage pulmonary mucinous adenocarcinoma (stages I and II).	Tumor size, location, patient's overall health; feasibility of surgical resection.	Optimizing surgical methods; long-term effects of minimally invasive surgery.
Chemotherapy	Advanced cases (stages III and IV) or as adjuvant post-surgery.	Drug choices (platinum-based, pemetrexed, gemcitabine); managing side effects; combination therapy strategies.	Personalized chemotherapy for specific patient groups; long-term effects of combination strategies.
Targeted therapy	Patients with specific genetic mutations (e.g., ALK, KRAS positive)	Mutation screening; drug selection and side effects; managing resistance.	Development and testing of new drugs for uncommon mutations; long-term effects and safety of targeted therapy.
Immunotherapy	Mainly for advanced-stage pulmonary mucinous adenocarcinoma.	Assessing PD-L1 expression levels; managing immune-related side effects; combination with chemotherapy or targeted therapy.	Effects of immunotherapy in specific genetic backgrounds; optimization of combination therapy strategies.
Radiotherapy	High-risk early-stage cases or inoperable advanced cases.	Choosing radiotherapy doses and schedules; combination with chemotherapy or surgery; managing radiotherapy-related side effects.	Studies on the effectiveness of new radiotherapy techniques (e.g., stereotactic radiotherapy); combination of radiotherapy with novel treatments.
Targeted adjuvant therapy	Patients positive for specific genetic mutations (e.g., EGFR mutation).	Target screening; drug selection and management; monitoring and managing resistance.	Treatment strategies for atypical or rare mutations; assessment of quality of life and effectiveness of long-term targeted therapy.
Supportive care	All stages of pulmonary mucinous adenocarcinoma.	Symptom management (pain, difficulty breathing, etc.); psychological and social support; improving quality of life.	Long-term impact of supportive care measures; importance of psychosocial support for treatment adherence and overall prognosis.
Personalized treatment plan	Customized according to patient's unique clinical presentation and genetic characteristics.	Combining individualized information to formulate a treatment plan; interdisciplinary collaboration; continuous monitoring and adjustment of the treatment strategy.	Application of precision medicine in the treatment of pulmonary mucinous adenocarcinoma; long-term effectiveness of personalized treatment plans.

(3) Targeted therapy: Tailored based on specific genetic mutations or biomarkers, targeted therapies are increasingly relevant, especially for KRAS mutations common in PMA. Promising results have been observed with sotorasib and adagasib in treating KRAS G12C metastatic lung cancer, as evidenced by phase I and II trials [26].
(4) Radiation therapy: Often adjunct to surgery and chemotherapy, radiation therapy is indicated for incomplete resection or high local recurrence risk. It serves as palliative care in the advanced stages. A study [27] identified postoperative radiotherapy (PORT) as an independent prognostic factor, suggesting benefits for patients with fewer than seven positive lymph nodes; however, chemotherapy might be more advantageous for those with more positive lymph nodes.
(5) Immunotherapy: the role of immunotherapy in PMA, particularly in patients with KRAS mutations, is under investigation. Xu et al. [28] reported differing responses to immunotherapy between IMA and NMA in advanced stages.

Distinct challenges in treating PMA necessitate tailored approaches. High mucoprotein levels can impede chemotherapy efficacy and radiation absorption. The tumor's spread along the airways and alveoli complicates surgical excision and heightens recurrence risk. KRAS mutations in PMA limit the effectiveness of targeted therapies applicable to other NSCLC subtypes. These factors, alongside tumor size, mucoprotein formation, and genetic mutations, influence prognosis and necessitate individualized treatment strategies.

1.4. Prognosis

In early-stage PMA (stages I and II), surgical intervention is typically prioritized as the primary option, carrying significant therapeutic importance, aiming for complete tumor tissue removal to achieve a cure. A study [29] on the treatment and prognosis of early-stage PMA (stage I) explored the effects of surgical methods and adjuvant chemotherapy (AC), indicating that compared to surgery alone, AC had a detrimental impact on overall survival (OS: 71.2 vs. 93.4 months) and cancer-specific survival (CSS: 74.9 vs. 101.1 months). Additionally, outcomes for patients with tumors smaller than 1 cm undergoing lobectomy and segmentectomy showed no significant difference in OS and CSS between the two surgical methods.

For advanced-stage PMA (stages III and IV), the treatment goals are often more focused on extending patient survival and alleviating symptoms rather than completely curing the tumor. A systematic review and meta-analysis [30] identified several prognostic factors for advanced-stage PMA, including sex, age, TNM staging, smoking history, lymph node metastasis, pleural metastasis, STAS, tumor size, pathological grade, and CT features. These factors significantly affect OS and disease-free survival (DFS). In treating advanced PMA, therapy selection often necessitates comprehensive consideration of multiple factors. Chemotherapy regimen choice is pivotal in advanced IMA prognosis. Common regimens include platinum with pemetrexed and platinum with gemcitabine. The efficacy of additional therapies, including immunotherapy (e.g., nivolumab, atezolizumab) and targeted therapies (e.g., EGFR TKI, ALK-TKI), varies in their impact on prognosis. In a study [16] investigating various palliative chemotherapy regimens, including new therapies, for patients with advanced IMA of the lungs, the median survival for patients was 20.1 months. Notably, patients treated with immunotherapy exhibited a longer OS, whereas no significant prognostic differences were noted among those receiving targeted therapy. Moreover, a study [31] specifically investigated the clinical course of patients with advanced-stage PMA and found that patients receiving non-tyrosine kinase inhibitor (non-TKI) chemotherapy showed no improvement in OS compared to untreated patients. However, among patients with NMA, TKI treatment resulted in the best OS among those with targetable mutations.

In a study [32] involving 294 patients with resected PMA, tumors were categorized into pure solid, partial solid, and pneumonic types based on imaging subtypes. The findings revealed that patients with the pneumonic type had a comparatively poor prognosis, with a 5-year recurrence-free survival (RFS) rate of only 23.7% and a 5-year OS rate of 44.7%. In contrast, the RFS rates for the pure and partial solid types were notably higher at 83.2% and 93.7%, respectively. Both types demonstrated 5-year OS rates of 100%. Yoon et al. [33] documented distinct recurrence patterns in patients with recurrent IMA, noting that those with pulmonary recurrence exhibited a favorable prognosis following local treatment, highlighting the potential importance of local interventions in resectable pulmonary recurrences of IMA.

In a study [34] on patients with multifocal invasive PMA, whole-exome sequencing was conducted in two to five distinct regions across seven patients, revealing mutations in KRAS, NKX2-1, TP53, and ARID1A genes identified as founder mutations. Another study [35] conducted whole-exome sequencing of 96 Chinese patients with PMA and uncovered specific genetic variations distinct from those in lung adenocarcinoma. This study found significant differences in the genomic and immune environments between PMA and common lung adenocarcinoma.

Additionally, a patient's overall health status significantly affects prognosis. Some patients may not tolerate aggressive treatments due to comorbidities or frailty, affecting treatment choices and outcomes. Therefore, clinicians must consider these factors and work with patients to develop the best treatment plan to maximize prognosis and quality of life.

2. Discussion

PMA, a distinctive subtype of adenocarcinoma within the NSCLC category, is characterized by an overproduction of mucin, a viscous substance produced by specific cells [36]. In PMA, the excessive mucin production by cancer cells results in the formation of mucin-filled spaces within the tumor [12]. These spaces, when observed microscopically, may resemble mucin vacuoles or pool-like structures. Excess mucin forms a viscous barrier [37] that physically impedes the penetration of chemotherapeutic drugs into tumor cells. This barrier restricts drug access and alters the tumor microenvironment, impacting drug efficacy [38]. Mucin can bind to and sequester drugs, reducing their availability to interact with cancer cells [13]. This sequestration reduces drug concentration within the tumor, diminishing its therapeutic effect. High mucin content can alter the tumor microenvironment, potentially inducing hypoxia, pH

fluctuations, and alterations in the extracellular matrix. These alterations can influence drug activity and cancer cell sensitivity to treatment. To overcome mucin-related drug resistance, several potential strategies can be employed. (1) Use of mucolytic agents [39]: drugs capable of degrading or dissolving mucin can reduce the barrier formed by mucin, enhancing the penetration of chemotherapeutic agents [40]. These mucolytic agents disrupt mucin structure, reduce its viscosity, and allow chemotherapy drugs to reach tumor cells more effectively. (2) Application of nanotechnology in drug delivery: nanoparticle-based drug delivery systems, developed using nanotechnology, may enhance penetration through the mucin barrier [41]. By adjusting the size and surface properties of nanoparticles, their ability to penetrate mucin can be enhanced; thereby, improving drug efficacy. (3) Use of combination therapies: combining mucolytic agents and standard chemotherapy drugs can improve the overall treatment effectiveness. Mucolytic agents are used to reduce the mucin barrier, followed by chemotherapeutic drugs to target more accessible cancer cells. (4) Development of targeted therapies against mucin production [42]: targeting molecular mechanisms involved in mucin production may decrease mucin content in tumors or alter their properties, enhancing drug penetration and efficacy. (5) Application of local hyperthermia: applying high temperatures to the tumor area can reduce the viscosity of mucin; thereby, enhancing the penetration of chemotherapeutic drugs. This method can be combined with chemotherapy to improve treatment outcomes [43].

Therefore, prioritizing urgent and decisive research areas in PMA is crucial. Special attention should be paid to the following aspects. (1) Molecular and genetic studies: research should focus on identifying specific biomarkers and genetic susceptibilities, utilizing biomarkers to guide personalized treatments, employing gene-editing technologies like CRISPR for directly repairing cancer-related genetic mutations, and developing CAR-T cell therapies and other cellular treatments, particularly for targeting challenging mutations. (2) Development of early diagnostic techniques: developing highly sensitive and specific screening and diagnostic methods is crucial for early detection of PMA. This may involve using liquid biopsies, imaging techniques, or bioinformatics tools. (3) Novel treatment approaches: searching and testing new treatment methods, such as targeted therapy, immunotherapy, and new combinations of chemotherapy, are crucial to improve treatment effectiveness and reduce side effects. Molecular subtyping initiatives for targeted drug development and identifying predictors of immunotherapy responses are crucial future milestones. (4) Study of drug resistance mechanisms: understanding the mechanisms underlying drug resistance in PMA is vital for developing new treatment strategies. (5) Improvement of patient quality of life: patient quality of life should be prioritized by focusing on pain management, offering psychological support, and addressing treatment-related quality of life issues. (6) Epidemiological research: studying the incidence, risk factors, and prevention strategies of PMA is essential for formulating public health strategies. (7) Interdisciplinary collaboration: interdisciplinary collaboration should involve experts in pulmonology, oncology, molecular biology, bioinformatics, and other fields to promote comprehensive research in this area.

3. Conclusions

Recent advances in genetic research and immunotherapy have facilitated personalized treatment approaches for PMA, a unique lung cancer subtype with high mucin content. Developments in targeted drugs and minimally invasive surgical techniques have improved patient prognoses. Despite the challenges in PMA treatment, ongoing research and the emergence of new treatment modalities contribute to the development of more effective and personalized patient care.

Data availability

No data was used for the research described in the article.

Ethics declarations

Review and/or approval by an ethics committee was not required for this study because it is a literature review and does not address the ethical considerations of animal, cell, and human experimentation.

CRediT authorship contribution statement

Lihui Ge: Writing – review & editing, Writing – original draft. **Linlin Wang:** Writing – review & editing, Writing – original draft, Conceptualization. **Dongmei Pei:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

No additional information is available for this study.

References

[1] W.C. Chang, Y.Z. Zhang, A.G. Nicholson, Pulmonary invasive mucinous adenocarcinoma, Histopathology 84 (1) (2024) 18–31.
[2] D. Zhu, Q. Zhang, Z. Rui, S. Xu, Pulmonary invasive mucinous adenocarcinoma mimicking pulmonary actinomycosis, BMC Pulm. Med. 22 (1) (2022) 181.
[3] Y. Wang, Y. Gao, Z. Zhang, Z. Zhang, A. Wang, K. Zhao, M. Zhang, S. Zhang, M. Li, J. Sun, D. Guo, Z. Liang, Claudin18.2 expression in pulmonary mucinous adenocarcinoma, J. Cancer Res. Clin. Oncol. 149 (14) (2023) 12923–12929.
[4] J. Zhang, L. Hao, M. Qi, Q. Xu, N. Zhang, H. Feng, G. Shi, Radiomics nomogram for preoperative differentiation of pulmonary mucinous adenocarcinoma from tuberculoma in solitary pulmonary solid nodules, BMC Cancer 23 (1) (2023) 261.
[5] K. Tomoshige, W.D. Stuart, I.M. Fink-Baldauf, M. Ito, T. Tsuchiya, T. Nagayasu, T. Yamatsuji, M. Okada, T. Fukazawa, M. Guo, Y. Maeda, FOXA2 cooperates with mutant KRAS to drive invasive mucinous adenocarcinoma of the lung, Cancer Res. 83 (9) (2023) 1443–1458.
[6] A.G. Nicholson, M.S. Tsao, M.B. Beasley, A.C. Borczuk, E. Brambilla, W.A. Cooper, S. Dacic, D. Jain, K.M. Kerr, S. Lantuejoul, M. Noguchi, M. Papotti, N. Rekhtman, G. Scagliotti, P. van Schil, L. Sholl, Y. Yatabe, A. Yoshida, W.D. Travis, The 2021 WHO classification of lung tumors: impact of advances since 2015, J. Thorac. Oncol. 17 (3) (2022) 362–387.
[7] J.C. Chang, M. Offin, C. Falcon, D. Brown, B.R. Houck-Loomis, F. Meng, V.A. Rudneva, H.H. Won, S. Amir, J. Montecalvo, P. Desmeules, K. Kadota, P. S. Adusumilli, V.W. Rusch, S. Teed, J.K. Sabari, R. Benayed, K. Nafa, L. Borsu, B.T. Li, A.M. Schram, M.E. Arcila, W.D. Travis, M. Ladanyi, A. Drilon, N. Rekhtman, Comprehensive molecular and clinicopathologic analysis of 200 pulmonary invasive mucinous adenocarcinomas identifies distinct characteristics of molecular subtypes, Clin. Cancer Res. 27 (14) (2021) 4066–4076.
[8] R. Buettner, Invasive mucinous adenocarcinoma: genetic insights into a lung cancer entity with distinct clinical behavior and genomic features, Mod. Pathol. 35 (2) (2022) 138–139.
[9] Y. Haga, Y. Sakamoto, K. Kajiya, H. Kawai, M. Oka, N. Motoi, M. Shirasawa, M. Yotsukura, S.I. Watanabe, M. Arai, J. Zenkoh, K. Shiraishi, M. Seki, A. Kanai, Y. Shiraishi, Y. Yatabe, D. Matsubara, Y. Suzuki, M. Noguchi, T. Kohno, A. Suzuki, Whole-genome sequencing reveals the molecular implications of the stepwise progression of lung adenocarcinoma, Nat. Commun. 14 (1) (2023) 8375.
[10] K.V. Odarenko, M.A. Zenkova, A.V. Markov, The nexus of inflammation-induced epithelial-mesenchymal transition and lung cancer progression: a roadmap to pentacyclic triterpenoid-based therapies, Int. J. Mol. Sci. 24 (24) (2023) 17325.
[11] Y. Lou, L. Diao, E.R. Cuentas, W.L. Denning, L. Chen, Y.H. Fan, L.A. Byers, J. Wang, V.A. Papadimitrakopoulou, C. Behrens, J.C. Rodriguez, P. Hwu, I.I. Wistuba, J.V. Heymach, D.L. Gibbons, Epithelial-mesenchymal transition is associated with a distinct tumor microenvironment including elevation of inflammatory signals and multiple immune checkpoints in lung adenocarcinoma, Clin. Cancer Res. 22 (14) (2016) 3630–3642.
[12] S. Kishikawa, T. Hayashi, T. Saito, K. Takamochi, S. Kohsaka, K. Sano, N. Sasahara, K. Sasa, T. Kurihara, K. Hara, Y. Suehara, F. Takahashi, K. Suzuki, T. Yao, Diffuse expression of MUC6 defines a distinct clinicopathological subset of pulmonary invasive mucinous adenocarcinoma, Mod. Pathol. 34 (4) (2021) 786–797.
[13] Y. Ning, H. Zheng, Y. Zhan, S. Liu, Y. Yang, H. Zang, J. Luo, Q. Wen, S. Fan, Comprehensive analysis of the mechanism and treatment significance of Mucins in lung cancer, J. Exp. Clin. Cancer Res. 39 (1) (2020) 162.
[14] X. Xu, N. Li, D. Wang, W. Chen, Y. Fan, Clinical relevance of PD-L1 expression and CD8+ T cells' infiltration in patients with lung invasive mucinous adenocarcinoma, Front. Oncol. 11 (2021) 683432.
[15] L. Shan, L. Zhang, X. Zhu, Z. Wang, S. Fang, J. Lin, J. Wang, N. Li, H. Liu, X. Zhang, Y. Feng, J. Liu, J. Pan, G. Ye, X. Yu, A. Tufman, A. Katalinic, T. Goldmann, F. Petersen, J. Jiang, G. Geng, X. Yu, Chinese never smokers with adenocarcinoma of the lung are younger and have fewer lymph node metastases than smokers, Respir. Res. 23 (1) (2022) 293.
[16] L. Ang, C.P.Y. Chan, W.P. Yau, W.J. Seow, Association between family history of lung cancer and lung cancer risk: a systematic review and meta-analysis, Lung Cancer 148 (2020) 129–137.
[17] B. Mehić, L. Duranović Rayan, N. Bilalović, D. Dohranović Tafro, I. Pilav, Lung adenocarcinoma mimicking pulmonary fibrosis-a case report, BMC Cancer 16 (1) (2016) 729.
[18] T. Saito, K. Tsuta, O. Honda, M. Ishida, R. Yamaka, N. Tanaka, K. Ishida, T. Utsumi, N. Maru, H. Matsui, Y. Taniguchi, H. Hino, T. Kurata, T. Murakawa, Prognostic impact of mucin spread, tumor cell spread, and invasive size in invasive mucinous adenocarcinoma of the lung, Lung Cancer 146 (2020) 50–57.
[19] M.K. Thakur, J.J. Ruterbusch, A.G. Schwartz, S.M. Gadgeel, J.L. Beebe-Dimmer, A.J. Wozniak, Risk of second lung cancer in patients with previously treated lung cancer: analysis of surveillance, epidemiology, and end results (SEER) data, J. Thorac. Oncol. 13 (1) (2018) 46–53.
[20] Y. Liu, H.L. Zhang, J.Z. Mei, Y.W. Guo, R.J. Li, S.D. Wei, F. Tian, L. Yang, H. Wang, Primary mucinous adenocarcinoma of the lung: a case report and review of the literature, Oncol. Lett. 14 (3) (2017) 3701–3704.
[21] X. Xu, W. Shen, D. Wang, N. Li, Z. Huang, J. Sheng, A.J. Rucker, W. Mao, H. Xu, G. Cheng, Clinical features and prognosis of resectable pulmonary primary invasive mucinous adenocarcinoma, Transl. Lung Cancer Res. 11 (3) (2022) 420–431.
[22] G.D. Xie, Y.R. Liu, Y.Z. Jiang, Z.M. Shao, Epidemiology and survival outcomes of mucinous adenocarcinomas: a SEER population-based study, Sci. Rep. 8 (1) (2018) 6117.
[23] D. Cui, S. Xie, Q. Liu, Postoperative survival of pulmonary invasive mucinous adenocarcinoma versus non-mucinous invasive adenocarcinoma, BMC Pulm. Med. 23 (1) (2023) 9.
[24] H.J. Yoon, J. Kang, H.Y. Lee, M.A. Lee, N.Y. Hwang, H.K. Kim, J. Kim, Recurrence dynamics after curative surgery in patients with invasive mucinous adenocarcinoma of the lung, Insights Imaging 13 (1) (2022) 64.
[25] Y.J. Jang, D.G. Hyun, C.M. Choi, D.H. Lee, S.W. Kim, S. Yoon, W.S. Kim, W. Ji, J.C. Lee, Optimizing palliative chemotherapy for advanced invasive mucinous adenocarcinoma of the lung, BMC Cancer 21 (1) (2021) 731.
[26] M. Araghi, R. Mannani, A. Heidarnejad Maleki, A. Hamidi, S. Rostami, S.H. Safa, F. Faramarzi, S. Khorasani, M. Alimohammadi, S. Tahmasebi, R. Akhavan-Sigari, Recent advances in non-small cell lung cancer targeted therapy; an update review, Cancer Cell Int. 23 (1) (2023) 162.
[27] Y. Gu, H. Zhu, J. Deng, J. Zhang, T. Chen, S. Lai, Comparison of treatment strategies for resectable locally advanced primary mucinous adenocarcinoma of the lung, Cancer Med. 12 (8) (2023) 9303–9312.
[28] M. Xu, Y. Hao, H. Zhou, Z. Shi, J. Si, Z. Song, Comparison of the immunotherapy efficacy between invasive mucinous and non-mucinous adenocarcinoma in advanced lung cancer patients with KRAS mutation: a retrospective study, Med. Oncol. 40 (7) (2023) 198.
[29] J. Liu, S. Zhang, J. Luo, Prognosis of early stage pulmonary mucinous adenocarcinoma with different treatments, Transl. Cancer Res. 9 (9) (2020) 5182–5189.
[30] T. Zhao, J. Yi, D. Luo, J. Liu, X. Fan, Q. Wu, W. Wang, Prognostic factors for invasive mucinous adenocarcinoma of the lung: systematic review and meta-analysis, World J. Surg. Oncol. 22 (1) (2024) 41.
[31] Y.J. Cha, H.R. Kim, H.J. Lee, B.C. Cho, H.S. Shim, Clinical course of stage IV invasive mucinous adenocarcinoma of the lung, Lung Cancer 102 (2016) 82–88.
[32] W. Li, Y. Yang, M. Yang, N. Song, Z. Wan, Q. Lu, J. Shi, Clinicopathologic features and survival outcomes of primary pulmonary mucinous adenocarcinoma based on different radiologic subtypes, Ann. Surg Oncol. 31 (1) (2024) 167–177.
[33] D.W. Yoon, S. Hwang, T.H. Hong, Y.L. Choi, H.K. Kim, Y.S. Choi, J. Kim, Y.M. Shim, J.H. Cho, Distinct recurrence pattern and survival outcomes of invasive mucinous adenocarcinoma of the lung: the potential role of local therapy in intrapulmonary spread, Ann. Surg Oncol. 31 (1) (2024) 201–212.
[34] M. Kim, J. Hwang, K.A. Kim, S. Hwang, H.J. Lee, J.Y. Jung, J.G. Lee, Y.J. Cha, H.S. Shim, Genomic characteristics of invasive mucinous adenocarcinoma of the lung with multiple pulmonary sites of involvement, Mod. Pathol. 35 (2) (2022) 202–209.
[35] C. Zhang, K. Wang, W. Liu, J. Lin, Z. Li, H. Wang, C. Zhao, Y. Chen, S. Wu, A. Yang, J. Wu, H. Wang, Whole exome sequencing in Chinese mucinous pulmonary adenocarcinoma uncovers specific genetic variations different from lung adenocarcinoma, Front. Oncol. 12 (2022) 1054845.
[36] S.K. Lai, Y.Y. Wang, D. Wirtz, J. Hanes, Micro- and macrorheology of mucus, Adv. Drug Deliv. Rev. 61 (2) (2009) 86–100.
[37] F. Azari, G. Kennedy, A. Chang, B. Nadeem, N. Sullivan, I. Marfatia, A. Din, C. Desphande, J. Kucharczuk, E.J. Delikatny, S. Singhal, Presence of non-Newtonian fluid in invasive pulmonary mucinous adenocarcinomas impacts fluorescence during intraoperative molecular imaging of lung cancer, Eur J Nucl Med Mol Imaging 49 (13) (2022) 4406–4418.

[38] R. Beatson, J.M. Burchell, A mucin degrader for cancer therapy, Nat. Biotechnol. (2023 Oct 9), https://doi.org/10.1038/s41587-023-01984-5. Epub ahead of print. PMID: 37813982.
[39] K. Pedram, D.J. Shon, G.S. Tender, N.R. Mantuano, J.J. Northey, K.J. Metcalf, S.P. Wisnovsky, N.M. Riley, G.C. Forcina, S.A. Malaker, A. Kuo, B.M. George, C. L. Miller, K.M. Casey, J.G. Vilches-Moure, M.J. Ferracane, V.M. Weaver, H. Läubli, C.R. Bertozzi, Design of a mucin-selective protease for targeted degradation of cancer-associated mucins, Nat. Biotechnol. 3 (2023 Aug), https://doi.org/10.1038/s41587-023-01840-6. Epub ahead of print. PMID: 37537499.
[40] A.K. Dilly, B.D. Honick, R. Frederick, A. Elapavaluru, S. Velankar, H. Makala, T.K. Hitchens, L.M. Foley, J. Guo, J.H. Beumer, L.H. Rigatti, Y.J. Lee, D.L. Bartlett, H.A. Choudry, Improved chemosensitivity following mucolytic therapy in patient-derived models of mucinous appendix cancer, Transl. Res. 229 (2021) 100–114.
[41] C. Butnarasu, P. Petrini, F. Bracotti, L. Visai, G. Guagliano, A. Fiorio Pla, E. Sansone, S. Petrillo, S. Visentin, Mucosomes: intrinsically mucoadhesive glycosylated mucin nanoparticles as multi-drug delivery platform, Adv Healthc Mater 11 (15) (2022) e2200340.
[42] D.H. Lee, S. Choi, Y. Park, H.S. Jin, Mucin1 and Mucin16: therapeutic targets for cancer therapy, Pharmaceuticals 14 (10) (2021) 1053.
[43] F. Shi, D. Luo, X. Zhou, Q. Sun, P. Shen, S. Wang, Combined effects of hyperthermia and chemotherapy on the regulate autophagy of oral squamous cell carcinoma cells under a hypoxic microenvironment, Cell Death Discov 7 (1) (2021) 227.