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Research Progress on Biomarkers for Differential Diagnosis of Benign and Malignant Pulmonary Nodules

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Abstract: Pulmonary nodules may serve as early manifestations of lung cancer, and accurate differentiation between benign and malignant lesions directly influences clinical diagnosis and treatment strategies. Traditional imaging features provide fundamental morphological references, yet their application is prone to subjective bias and exhibits significant limitations in detecting microlesions. Breakthroughs have been achieved in research on quantitative functional imaging metrics, radiomics information, AI-assisted models, and circulating tumor cells (CTCs). Multimodal and multi-parameter fusion-based discriminant models have demonstrated enhanced efficiency in nodule characterization, emerging as a core research trend in this field.

Keywords: Pulmonary nodule; Benign-malignant differentiation; Biomarker; Radiomics; Artificial intelligence

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1. Introduction

High-resolution CT has seen increasingly widespread application in early lung cancer screening, leading to higher clinical detection rates of pulmonary nodules, most of which are benign lesions. Although puncture biopsy and postoperative pathological examination serve as gold standards for diagnosis, their invasive nature hinders widespread adoption during screening stages. While traditional imaging evaluation remains the preferred approach, it relies heavily on physician experience, resulting in insufficient diagnostic accuracy for small nodules and atypical lesions. With continuous advancements in quantitative imaging analysis techniques and molecular biology, novel biomarkers have opened new pathways for precise differentiation of pulmonary nodules. This article provides a comprehensive review of research progress on relevant biomarkers.

2. Traditional imaging characteristics as morphological biomarkers

2.1. Size and morphological characteristics of nodules

The diameter of pulmonary nodules serves as the most intuitive morphological indicator for distinguishing benign from

malignant lesions. Research by Lin Lili (2025) demonstrated that high-resolution CT can clearly visualize nodule size, with significantly higher detection rates of malignancy in large-diameter nodules compared to micro-sized nodules [1]. Ning Xianpu (2025) reviewed that malignant risk increases when nodule diameter exceeds specific thresholds, which also constitutes a risk factor for malignant solid pulmonary nodules [2]. For smaller subcentimeter nodules, benign and malignant lesions may overlap in size, making diameter alone unreliable for malignancy prediction. A comprehensive evaluation combining size characteristics with other imaging features is essential to enhance diagnostic reliability. Variations in diameter threshold definitions across studies correlate with sample composition and inclusion criteria, necessitating clinical application based on individual cases rather than rigid application of fixed cutoff values.

2.2. Edge and adjacent structural signs

The morphological characteristics of pulmonary nodule margins and their correlation with adjacent structures provide critical diagnostic clues. Ning Xianpu (2025) synthesized multiple studies revealing that lobulation features manifest as multiple arcuate protrusions at nodule margins, which exhibit higher detection frequency in malignant nodules and are pathologically associated with heterogeneous tumor cell proliferation rates [2]. Spiculation refers to radiating fibrous strands extending from nodule margins into surrounding lung tissue, demonstrating a strong correlation with peripheral lung cancer and higher prevalence in malignant nodules. Pleural depression results from traction of visceral pleura by internal tumor scar tissue, presenting as linear or triangular high-density shadows between nodules and pleura, a hallmark imaging feature of malignant pulmonary nodules. Vascular bundle formation indicates abnormal tumor uptake of local blood supply, offering diagnostic value in clinical evaluation.

2.3. Limitations of traditional biomarker forms

Morphological characteristics possess certain reference values, but their independent use as biomarkers remains significantly limited. Ning Xianpu (2025) pointed out that conflicting conclusions often emerge regarding the diagnostic value of similar features across different studies [2]. Benign lesions such as tuberculomas and inflammatory pseudotumors may also exhibit imaging features resembling malignant lesions, including lobulation, spiculation, and pleural depression, leading to substantial overlap in lesion imaging characteristics. Traditional radiographic interpretation heavily relies on clinicians' subjective experience, with judgment processes demonstrating pronounced subjectivity and no unified quantitative evaluation criteria established within the field [3]. Lin Lili (2025) noted that pulmonary nodules with small diameters and atypical morphological features remain difficult to accurately characterize even with high-resolution CT examinations [1]. Cui Kai and Zhang Xiaoju (2021) highlighted in their review that single morphological biomarkers demonstrate limited diagnostic efficacy, while combining novel biomarkers can improve the accuracy of pulmonary nodule differentiation [4]. The independent use of traditional morphological biomarkers fails to meet clinical precision diagnostic demands. Integrating functional imaging and molecular-level information into diagnostic reference systems provides more reliable evidence for distinguishing benign from malignant pulmonary nodules.

3. Functional imaging and quantitative parameter biomarkers

3.1. PET/CT metabolic parameters

Fluorodeoxyglucose PET/CT reflects tissue glucose metabolic activity, providing functional biomarkers independent of morphological features. Ning Xianpu (2025) noted in a relevant review that standardized uptake values serve as commonly used semi-quantitative indicators in clinical practice, with malignant nodules typically exhibiting hypermetabolic manifestations, and uptake levels showing a strong correlation with tumor cell proliferation activity [2]. The specificity of PET/CT is susceptible to infectious lesions; benign lesions such as inflammatory granulomas and active tuberculosis may demonstrate false-positive hypermetabolic signals, particularly in high-infection-endemic regions. The interpretation of metabolic parameters must be integrated with clinical context and epidemiological characteristics and should not be used

as the sole diagnostic criterion. Optimal cutoff values vary across studies, and standardized clinical application remains subject to certain limitations.

3.2. MRI functional parameters

Magnetic resonance imaging (MRI) does not emit ionizing radiation, making it highly suitable for patients with pulmonary nodules requiring long-term follow-up examinations. Ning Xianpu (2025) reviewed advancements in related fields, demonstrating that diffusion-weighted imaging can quantitatively assess tissue cell density based on apparent diffusion coefficients [2]. Malignant nodules with more dense cellular arrangements often exhibit diffusion limitation manifestations. Imageomics features extracted from specific sequences demonstrate reliable efficacy in distinguishing benign from malignant pulmonary lesions. The integration of multi-parameter MRI with machine learning algorithms provides a viable approach for differential diagnosis of pulmonary pathologies.

4. Novel imaging biomarkers: Imagingomics and artificial intelligence

4.1. Feature extraction and model construction for imaging omics

Imagingomics utilizes medical images to achieve high-throughput feature extraction, obtaining quantitative information that is difficult to capture through conventional visual interpretation, thereby overcoming the boundary limitations inherent in traditional imaging analysis. Ning Xianpu (2025) reviewed the research landscape in related fields, noting that imagingomics encompasses morphological parameters, first-order gray-level statistics, texture information, and higher-order representations, enabling numerical expression of tumor internal heterogeneity [2]. Prediction models constructed by integrating imagingomics with deep learning features demonstrate superior diagnostic performance compared to models relying solely on single features. The combined use of imagingomics metrics with conventional imaging findings enhances the accuracy of lesion differentiation. Imagingomics analysis provides reliable quantitative evidence for pulmonary nodule risk stratification, maintaining stable diagnostic performance under both low-dose CT and standard-dose CT scanning conditions, making it suitable for early lung cancer screening.

4.2. Application and limitations of artificial intelligence-assisted diagnostic systems

Artificial intelligence deep learning models can automatically identify pulmonary nodules and extract imaging features, thereby improving radiographic review efficiency. Research by Ye Hongda (2025) demonstrates that such systems can reduce average per-case review time, exhibit outstanding sensitivity for small nodules, and minimize missed diagnoses caused by visual fatigue [3]. However, standalone AI diagnosis faces challenges of high sensitivity but insufficient specificity, often misclassifying normal or benign structures such as vascular cross-sections, pleural thickening, and bronchial mucus plugs as malignant nodules. It cannot directly replace physicians in qualitative diagnosis, has a low threshold for identifying malignant pulmonary nodules, and is prone to false positives.

4.3. Diagnostic advantages of multi-source information fusion models

The integration of radiomics features with clinical parameters and conventional imaging characteristics to construct a multi-source information fusion model can further enhance diagnostic accuracy. Ning Xianpu (2025) summarized that models combining radiomics features with conventional imaging features demonstrate improved efficacy in differentiating the benign and malignant nature of solid pulmonary nodules [2]. Clinical factors such as the spiculation sign and age exhibit superior diagnostic performance when combined with radiomics features. Ye Hongda (2025) confirmed that the combined use of artificial intelligence and physician-based diagnosis achieves higher accuracy than either approach alone, with good consistency with pathological results [3]. Shi Jie et al. (2021) demonstrated that combined detection of cytokines and tumor markers improves the differential diagnostic efficacy for solitary pulmonary nodules, with the established multi-index fusion model showing superior area under the curve performance compared to individual detection metrics [5]. Multimodal

strategies integrate complementary information from biomarkers across different dimensions: radiomics captures microscopic textural heterogeneity, conventional features present macroscopic morphological information, clinical parameters reflect host background risk levels, and decision curve analysis confirms that multimodal fusion models deliver clinical net benefits across a wide threshold probability range, demonstrating reliable clinical applicability.

5. Liquid biomarkers and their application in the differentiation of pulmonary nodules

5.1. Circulating tumor cells

Circulating tumor cells (CTCs) originate from the detachment of the primary lesion and enter the peripheral blood, representing a significant direction for liquid biopsy development. Research by Ning Xianpu (2025) revealed that CTCs fundamentally differ from imaging biomarkers, directly reflecting tumor biological behavior rather than indirectly indicating morphological changes, thereby possessing unique diagnostic value [2]. In differentiating benign from malignant solid pulmonary nodules, CTCs serve as a critical risk factor; when combined with CT imaging features, they enhance the accuracy of early lung cancer diagnosis and provide supplementary insights for nodules with atypical imaging manifestations. CTC detection technologies include positive-enrichment and negative-enrichment methods, though their sensitivity and standardization still require improvement. Significant inter-platform variability exists among detection results, and CTC testing has not yet been incorporated into routine clinical practice.

5.2. Traditional serum tumor markers

Serum tumor markers have gained widespread clinical application due to their ease of detection, but their value in distinguishing benign from malignant pulmonary nodules remains relatively limited. Ning Xianpu (2025) noted that conventional indicators such as carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and cytokeratin 19 fragments (CK19) exhibit suboptimal sensitivity and specificity in early lung cancer screening, demonstrating weak practical utility for benign/malignant differentiation of solid pulmonary nodules [2]. Single tumor markers lack organ-specific or tumor-specific specificity and cannot serve as standalone diagnostic biomarkers. Pei Dongfang et al. (2021) demonstrated that low-dose spiral CT combined with multiple tumor markers, including CEA, squamous cell carcinoma antigen (SCCA antigen), gastrin-releasing peptide precursor (GRP-P), and NSE, optimizes the differential diagnosis of solitary pulmonary nodules, with the combined approach showing superior diagnostic sensitivity and accuracy compared to single CT imaging [6]. Zhu Zhengxin et al. (2025) corroborated that chest CT imaging combined with serum tumor marker testing provides more reliable evidence for nodular malignancy assessment, serving as an effective diagnostic supplement for atypical imaging features [7].

5.3. Multimodal combined diagnostic strategy

The reliance on a single biomarker has inherent limitations, making multimodal integration the prevailing consensus in current research. Ye Hongda (2025) demonstrated that artificial intelligence combined with physician-based manual diagnosis achieves high consistency with pathological results, highlighting the advantages of computer-assisted screening integrated with human decision-making [3]. Ning Xianpu (2025) emphasized that the fusion of traditional imaging features, clinical characteristics, and radiomics features enhances the diagnostic accuracy for solid pulmonary nodules [2]. A review by Shi Jie et al. (2021) noted that incorporating cytokines alongside conventional tumor markers into diagnostic models compensates for the limitations of single serological indicators, providing richer biological dimension information for pulmonary nodule risk stratification [5]. The combined application of imaging biomarkers and liquid biomarkers holds promising prospects. Future efforts should focus on developing comprehensive predictive models that integrate radiomics, functional imaging parameters, serum markers, and clinical risk factors, with multicenter prospective studies validating the models' generalizability.

6. Conclusion

Research on biomarkers for the differential diagnosis of benign and malignant pulmonary nodules has expanded from single morphological indicators to a multidimensional system comprising functional imaging parameters, radiomics features, artificial intelligence models, and liquid biomarkers. Radiomics and artificial intelligence can enhance feature extraction and improve efficiency, yet they cannot replace clinical decision-making by physicians. Circulating tumor cells (CTCs) in liquid biomarkers provide unique biological information. Each biomarker has its own limitations, and multimodal, multi-parameter integrated models represent an effective approach to improving diagnostic accuracy.

Disclosure statement

The authors declare no conflict of interest.

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