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Longitudinal Growth Patterns and Diagnostic Challenges of Biopsy-Confirmed Pulmonary Tumors Detected on Low-Dose CT: A 10-Year Analysis

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ABSTRACT

Low-dose computed tomography (LDCT) has transformed lung cancer screening by enabling detection of small pulmonary tumors before symptoms develop. However, the increased identification of indeterminate pulmonary nodules has created a major diagnostic challenge: not all growing lesions are malignant, and not all malignant tumors demonstrate rapid or predictable growth. Longitudinal assessment of pulmonary tumors therefore requires careful interpretation of imaging behavior, clinical context, and pathological confirmation. This review, titled Longitudinal Growth Patterns and Diagnostic Challenges of Biopsy-Confirmed Pulmonary Tumors Detected on Low-Dose CT: A 10-Year Analysis, examines how tumor biology, radiologic morphology, and follow-up imaging interact in the evaluation of biopsy-confirmed pulmonary lesions. Part 1 focuses on the clinical importance of LDCT, the biological basis of tumor growth, and the limitations of conventional growth-based malignancy assessment. [1]

Keywords: *Low-dose CT, pulmonary tumors, lung cancer screening, tumor growth, volume doubling time, pulmonary nodules, biopsy-confirmed tumors, diagnostic accuracy, longitudinal imaging, early lung cancer.*

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1. Introduction

Lung cancer remains one of the most lethal malignancies worldwide, largely because many cases are diagnosed at an advanced stage when curative treatment is no longer possible. LDCT screening has significantly improved early detection by identifying asymptomatic pulmonary nodules and early-stage tumors in high-risk populations. Nevertheless, the widespread use of LDCT has also increased the detection of indeterminate lesions, many of which require serial imaging, invasive biopsy, or surgical resection before a definitive diagnosis can be established. [2]

The central clinical dilemma in LDCT-based screening is distinguishing malignant tumors from benign pulmonary lesions. Small pulmonary nodules may represent early lung cancer, granulomatous inflammation, focal fibrosis, hamartoma, infection, or organizing pneumonia. Because radiologic appearances often overlap, clinicians frequently rely on longitudinal growth assessment to estimate malignancy risk. However, growth behavior is biologically complex and does not always follow simple diagnostic rules. [3]

Biopsy-confirmed longitudinal studies are particularly valuable because they allow imaging behavior to be correlated with final pathological diagnosis. Unlike screening cohorts that classify lesions primarily by imaging follow-up, biopsy-confirmed datasets provide direct histological verification. This enables more accurate evaluation of how benign and malignant

pulmonary tumors behave over time and helps identify diagnostic pitfalls that may lead to delayed treatment or unnecessary surgery. [4]

2. Evolution of LDCT Screening

The introduction of LDCT screening represented a major shift in thoracic oncology. Compared with chest radiography, LDCT is more sensitive for detecting small pulmonary nodules, ground-glass opacities, and early-stage lung cancers. Large screening trials demonstrated that LDCT can reduce lung cancer mortality among selected high-risk individuals, leading to its adoption in many screening guidelines. [5]

Despite this benefit, LDCT screening is associated with a high frequency of positive findings. Many detected nodules are benign, and only a small proportion ultimately represent clinically significant lung cancer. This creates a balance between early cancer detection and the risks of overdiagnosis, radiation exposure, patient anxiety, repeated imaging, biopsy complications, and potentially unnecessary surgical intervention. [6]

Nodule management systems such as Lung-RADS and other risk stratification models were developed to standardize follow-up recommendations. These frameworks incorporate nodule size, attenuation, growth, and morphology to guide clinical decisions. However, even structured systems cannot fully account for the biological variability of pulmonary tumors, particularly when lesions demonstrate slow, intermittent, or atypical growth patterns. [7]

3. Biological Basis of Pulmonary Tumor Growth

Pulmonary tumor growth is influenced by multiple biological processes, including genetic mutation, clonal expansion, angiogenesis, immune escape, stromal interaction, and metabolic adaptation. Malignant transformation does not occur as a uniform linear process; instead, tumors may progress through periods of dormancy, accelerated growth, immune-mediated control, or treatment-independent regression. [8]

Different histological subtypes of lung cancer demonstrate different growth kinetics. Small-cell lung cancer and some poorly differentiated carcinomas often grow rapidly, whereas adenocarcinoma-spectrum lesions, particularly ground-glass or part-solid nodules, may remain indolent for years before showing measurable progression. This heterogeneity complicates the use of growth rate alone as a marker of malignancy. [9]

Benign pulmonary lesions may also demonstrate growth. Inflammatory nodules, infectious granulomas, organizing pneumonia, and scar-related lesions can enlarge over time and mimic malignant tumors on serial LDCT. Conversely, some malignant lesions may appear stable for prolonged periods, especially early adenocarcinoma-spectrum tumors or indolent neuroendocrine lesions. [10]

4. Growth Kinetics and Volume Doubling Time

Growth kinetics are commonly assessed using changes in tumor diameter, volume, or volume doubling time. Diameter-based measurement is simple and widely used in clinical practice, but small measurement errors can produce large differences in estimated growth, especially for small nodules. Volumetric assessment provides greater sensitivity but depends on imaging quality, segmentation accuracy, reconstruction parameters, and software consistency. [11]

Volume doubling time is frequently used to classify pulmonary nodules as rapidly growing, intermediate, or slow-growing. Traditionally, malignant solid nodules are expected to demonstrate intermediate doubling times, whereas very rapid growth may suggest infection or inflammation and very slow growth may suggest benignity. However, this framework is imperfect because both benign and malignant lesions can fall outside expected ranges. [12]

Ground-glass and part-solid nodules require special consideration. These lesions often grow slowly, and meaningful progression may be reflected not only by increase in overall size but also by development or enlargement of a solid component. In adenocarcinoma-spectrum lesions, increasing consolidation may indicate invasive transformation even when total lesion diameter changes only minimally. [13]

5. Why Growth Alone Cannot Reliably Predict Malignancy

Although tumor growth is an important radiologic feature, growth alone cannot reliably distinguish benign from malignant pulmonary lesions. Some benign lesions enlarge because of inflammation, fibrosis, hemorrhage, or infection. At the same time, some malignant tumors remain stable over long intervals due to indolent biology or slow cellular proliferation. [14]

A major diagnostic challenge arises when malignant tumors show atypical behavior, such as minimal growth, fluctuating size, or temporary decrease in diameter. Such patterns may falsely reassure clinicians and delay definitive diagnosis. This is particularly relevant in subsolid nodules, where invasive progression may occur gradually and may not be captured by short-term follow-up. [15]

Similarly, rapidly growing lesions are not always cancer. Acute inflammatory nodules, fungal infection, tuberculosis, bacterial pneumonia, and immune-related inflammatory processes may enlarge quickly and appear radiologically suspicious. In these cases, biopsy or close clinical correlation may be necessary to avoid overtreatment. [16]

6. Radiologic Phenotypes of LDCT-Detected Pulmonary Tumors

LDCT-detected pulmonary tumors are commonly classified as solid, ground-glass, or part-solid lesions. Solid nodules are often easier to measure and may demonstrate more apparent growth over shorter intervals. However, their differential diagnosis remains broad and includes primary lung cancer, metastasis, granuloma, hamartoma, and inflammatory nodules. [17]

Ground-glass nodules are especially challenging because they may represent benign inflammation, atypical adenomatous hyperplasia, adenocarcinoma in situ, minimally invasive adenocarcinoma, or invasive adenocarcinoma. Their slow progression often requires long-term surveillance, and short follow-up periods may underestimate malignant potential. [18]

Part-solid nodules generally carry a higher risk of malignancy than pure ground-glass lesions, particularly when the solid component increases over time. The solid

portion may reflect invasive tumor growth, stromal reaction, or fibrotic change, making careful longitudinal assessment essential. [19]

7. Rationale for a 10-Year Biopsy-Confirmed Analysis

A 10-year biopsy-confirmed analysis provides an important opportunity to examine pulmonary tumor behavior beyond short-term screening outcomes. Long follow-up allows clinicians to identify slow-growing malignant lesions, benign tumors with suspicious enlargement, and lesions with non-linear growth patterns. Such analysis can refine diagnostic thresholds and improve decision-making for indeterminate LDCT-detected pulmonary tumors. [20]

8. Longitudinal Growth Patterns of Biopsy-Confirmed Pulmonary Tumors

Long-term follow-up of biopsy-confirmed pulmonary tumors demonstrates that lesion growth is considerably more heterogeneous than traditionally assumed. Rather than exhibiting continuous exponential enlargement, many tumors follow complex growth trajectories characterized by periods of stability, accelerated progression, temporary regression, or fluctuating size. These observations emphasize that pulmonary tumor growth is a dynamic biological process influenced by tumor genetics, host immune responses, microenvironmental interactions, and therapeutic interventions. [21]

Several longitudinal studies have identified distinct growth phenotypes among pulmonary tumors. Some lesions demonstrate steady progressive enlargement throughout follow-up, whereas others remain radiologically stable for several years before entering a phase of rapid growth. Certain malignant tumors even exhibit temporary decreases in diameter, likely reflecting inflammatory changes, measurement variability, necrosis, or alterations in tumor composition rather than true biological regression. These findings highlight the importance of interpreting serial imaging within the broader clinical context rather than relying on isolated measurements. [22]

Benign pulmonary lesions also display diverse growth behavior. Granulomatous disease, organizing pneumonia, inflammatory pseudotumors, pulmonary fibrosis, and infectious nodules may enlarge over time and closely mimic malignant disease on serial LDCT examinations. Consequently, longitudinal growth should always be interpreted alongside imaging morphology, clinical presentation, laboratory findings, and histopathological confirmation whenever appropriate. [23]

9. Histopathological Correlation with Growth Patterns

Correlating longitudinal imaging findings with histopathology provides valuable insight into the biological mechanisms underlying pulmonary tumor progression. Adenocarcinoma remains the most frequently encountered histological subtype in LDCT screening cohorts and often demonstrates highly variable growth kinetics depending on its degree of invasiveness. Adenocarcinoma in situ and minimally invasive adenocarcinoma may remain stable for prolonged periods, whereas invasive adenocarcinoma generally exhibits progressively increasing growth rates. [24]

Squamous cell carcinoma typically presents as solid pulmonary nodules with relatively rapid volumetric expansion compared with many adenocarcinomas. These tumors often develop central necrosis, cavitation, or irregular margins during progression, reflecting aggressive biological behavior. Small-cell lung carcinoma is characterized by exceptionally rapid proliferation and early metastatic spread, making timely diagnosis essential for optimizing patient outcomes. [25]

Benign lesions such as pulmonary hamartomas usually exhibit slow growth over many years and frequently contain characteristic fat or calcification that facilitates diagnosis. Conversely, granulomatous inflammation, fungal infections, and tuberculosis may demonstrate interval enlargement despite their non-neoplastic nature, further illustrating why imaging findings alone cannot reliably distinguish malignant from benign disease. [26]

10. Growth Kinetics Across Different Nodule Types

Solid pulmonary nodules generally demonstrate the highest measurable growth rates because increasing cellular proliferation directly translates into changes in lesion diameter and volume. Consequently, interval enlargement is often detected relatively early during routine surveillance imaging. Nevertheless, substantial variability exists among individual tumors, and some malignant solid nodules may remain stable for extended periods. [27]

Ground-glass nodules exhibit fundamentally different biological behavior. Rather than increasing rapidly in overall diameter, these lesions frequently evolve through gradual increases in attenuation, development of internal solid components, and progressive architectural distortion. Such subtle imaging changes often precede measurable size enlargement and therefore require careful qualitative assessment in addition to quantitative measurements. [28]

Part-solid nodules occupy an intermediate position between pure ground-glass and solid lesions. Numerous studies have demonstrated that enlargement of the solid component is a stronger predictor of invasive adenocarcinoma than overall lesion diameter alone. Accordingly, careful monitoring of internal lesion architecture is essential for appropriate risk stratification and treatment planning. [29]

11. Imaging Biomarkers Associated with Malignancy

Beyond growth rate, numerous radiological characteristics contribute to malignancy prediction. Spiculated margins remain among the strongest imaging indicators of invasive lung cancer because they often reflect desmoplastic stromal reaction and infiltration into surrounding pulmonary parenchyma. Lobulated contours may indicate uneven tumor proliferation and heterogeneous biological activity. [30]

Pleural indentation, vascular convergence, air bronchograms, bubble-like lucencies, and irregular internal architecture have likewise been associated with malignant pulmonary nodules. Although none of these features is individually diagnostic, their combination substantially increases the probability of malignancy when interpreted alongside longitudinal growth patterns. [31]

Radiomics has greatly expanded the assessment of pulmonary nodules by extracting hundreds of quantitative imaging features that cannot be appreciated visually. Texture heterogeneity, entropy, fractal characteristics, shape descriptors, and spatial complexity provide objective measures of tumor biology that may improve prediction of malignancy and therapeutic response. [32]

12. Diagnostic Challenges in Clinical Practice

Despite technological advances, evaluation of indeterminate pulmonary nodules remains one of the most challenging aspects of thoracic oncology. False-positive findings continue to occur because inflammatory and infectious lesions frequently resemble early-stage lung cancer on LDCT. This overlap often results in repeated imaging, invasive diagnostic procedures, or surgical resection of ultimately benign lesions. [33]

False-negative assessments also represent a significant concern. Slowly growing adenocarcinomas, subsolid nodules, and lesions with prolonged periods of radiological stability may be incorrectly classified as benign during early follow-up, delaying definitive diagnosis and potentially affecting long-term prognosis. Recognizing atypical growth trajectories is therefore essential for reducing diagnostic delay. [34]

Measurement variability introduces another important source of diagnostic uncertainty. Differences in inspiratory effort, patient positioning, scanner technology, slice thickness, reconstruction algorithms, segmentation software, and observer interpretation may all influence estimates of lesion size and volume. Standardized imaging protocols and volumetric analysis are therefore recommended whenever possible to improve reproducibility. [35]

13. Clinical Risk Factors Influencing Tumor Growth

Radiological findings should always be interpreted together with patient-specific clinical factors. Increasing age, cumulative tobacco exposure, family history of lung cancer, occupational carcinogen exposure, chronic obstructive pulmonary disease, pulmonary fibrosis, and previous malignancy all influence the pre-test probability of cancer and should guide individualized management strategies. [36]

Molecular characteristics further contribute to tumor behavior. Driver mutations involving EGFR, KRAS, ALK, ROS1, BRAF, MET, RET, and other oncogenic pathways influence tumor proliferation, metastatic potential, and treatment responsiveness. As molecular profiling becomes increasingly integrated into clinical practice, combining imaging features with genomic information may substantially improve individualized risk prediction. [37]

Host immune status also influences longitudinal tumor behavior. Immune surveillance may temporarily suppress tumor growth, whereas immunosuppression can accelerate disease progression. Similarly, inflammatory responses surrounding pulmonary lesions may alter radiological appearance independently of underlying tumor biology, complicating interpretation of serial imaging examinations. [38]

14. Clinical Decision-Making Based on Longitudinal Imaging

Management decisions for indeterminate pulmonary nodules require balancing the risks of delayed cancer diagnosis against unnecessary invasive procedures. Stable lesions with low-risk imaging characteristics may be safely monitored using serial LDCT, whereas enlarging nodules demonstrating suspicious morphology frequently warrant tissue diagnosis through biopsy or surgical excision. [39]

Multidisciplinary evaluation involving thoracic radiologists, pulmonologists, thoracic surgeons, pathologists, and medical oncologists has become increasingly important for complex cases. Integrating imaging findings, clinical history, pulmonary function, molecular testing, and pathological evaluation allows more individualized treatment decisions while minimizing unnecessary interventions. [40]

Ultimately, longitudinal assessment should not be viewed as simply measuring lesion size over time. Instead, it represents a comprehensive evaluation of dynamic tumor biology in which changes in morphology, internal architecture, attenuation, clinical presentation, and patient risk factors collectively contribute to accurate diagnosis. The experience gained from decade-long follow-up of biopsy-confirmed pulmonary tumors provides important evidence for refining surveillance protocols and improving the management of LDCT-detected pulmonary lesions. [41]

15. Artificial Intelligence in Longitudinal Pulmonary Tumor Assessment

Artificial intelligence (AI) is increasingly transforming the evaluation of pulmonary tumors detected by low-dose computed tomography (LDCT). Traditional radiologic assessment relies heavily on manual interpretation of serial images, which is subject to interobserver variability and may overlook subtle temporal changes. AI algorithms can analyze large volumes of imaging data with remarkable consistency, enabling automated detection, segmentation, and longitudinal tracking of pulmonary nodules throughout years of follow-up. These capabilities have the potential to improve diagnostic accuracy while reducing radiologist workload in large-scale lung cancer screening programs. [42]

Machine learning algorithms were among the first computational approaches applied to pulmonary nodule analysis. Using demographic variables, smoking history, imaging characteristics, and clinical data, these models estimate malignancy risk by identifying complex statistical relationships that are difficult to detect using conventional analytical methods. Random forests, support vector machines, gradient boosting algorithms, and ensemble learning techniques have demonstrated promising performance for differentiating benign from malignant pulmonary lesions. [43]

Deep learning has further expanded the capabilities of AI by automatically extracting hierarchical imaging features directly from CT scans without manual feature engineering. Convolutional neural networks accurately identify pulmonary nodules, estimate tumor boundaries, quantify lesion volume, and detect subtle interval changes that may not be readily appreciated during routine visual interpretation. These advances support earlier recognition of malignant progression and improve

the consistency of longitudinal assessment. [44]

16. Radiomics and Quantitative Imaging Biomarkers

Radiomics has emerged as one of the most promising technologies for improving pulmonary tumor characterization. Instead of relying solely on visually apparent imaging features, radiomics converts routine CT images into hundreds of quantitative descriptors reflecting lesion shape, texture, intensity distribution, spatial heterogeneity, and morphological complexity. These imaging biomarkers may capture underlying tumor biology more comprehensively than conventional radiological interpretation. [45]

Longitudinal radiomic analysis extends this concept by evaluating how quantitative imaging characteristics evolve over time. Changes in texture heterogeneity, internal architecture, vascularity, and spatial organization may precede measurable increases in tumor size, allowing earlier identification of malignant transformation. Such dynamic biomarkers are particularly valuable for slowly growing ground-glass and part-solid nodules in which diameter measurements alone may underestimate disease progression. [46]

The integration of radiomics with clinical variables, pathological findings, and molecular data enables increasingly personalized prediction models. These multimodal approaches may improve estimation of malignancy risk, recurrence probability, and treatment response while reducing unnecessary invasive procedures for patients with benign pulmonary lesions. [47]

17. Predictive Modeling and Precision Pulmonary Oncology

The convergence of AI, longitudinal imaging, molecular diagnostics, and clinical information is driving the transition toward precision pulmonary oncology. Rather than applying uniform management strategies to all pulmonary nodules, predictive models generate individualized risk assessments based on each patient's unique clinical and biological characteristics. This personalized approach supports more appropriate surveillance intervals, biopsy recommendations, and treatment selection. [48]

Advanced computational models increasingly incorporate genomic alterations, smoking exposure, family history, pulmonary function, laboratory biomarkers, and radiological characteristics into integrated prediction systems. Such multimodal frameworks recognize that pulmonary tumor behavior reflects the interaction of numerous biological processes rather than isolated imaging features. Consequently, individualized models are expected to outperform traditional population-based risk stratification methods. [49]

Digital health technologies may further enhance longitudinal monitoring through integration of wearable devices, electronic health records, and patient-reported outcomes. Continuous collection of physiological and clinical information could allow future predictive systems to update malignancy risk dynamically as new data become available throughout the patient's clinical course. [50]

18. Current Challenges and Limitations

Despite substantial technological progress, several challenges continue to limit widespread implementation of AI-assisted pulmonary tumor assessment. Imaging protocols vary considerably among institutions with respect to scanner manufacturers, reconstruction algorithms, slice thickness, radiation dose, and acquisition parameters. Such variability may reduce the reproducibility and generalizability of AI models developed using single-center datasets. [51]

Data annotation also represents a major limitation. Development of robust AI systems requires accurately labeled, biopsy-confirmed longitudinal datasets encompassing diverse patient populations, tumor subtypes, and imaging characteristics. Acquiring these comprehensive datasets is resource-intensive and often requires long-term collaboration across multiple institutions. [52]

Algorithm transparency remains another important consideration. Many deep learning models function as "black boxes," generating predictions without providing interpretable explanations for their decisions. Improving explainability, reducing algorithmic bias, and ensuring equitable performance across diverse demographic groups will be essential before these technologies can be routinely incorporated into clinical decision-making. [53]

Ethical and regulatory considerations are equally important. Protection of patient privacy, secure data sharing, cybersecurity, informed consent, and compliance with evolving regulatory standards must accompany future deployment of AI-driven diagnostic systems. Appropriate clinical governance will be necessary to ensure that computational tools complement rather than replace physician expertise. [54]

19. Future Perspectives

Future advances in pulmonary tumor assessment will likely involve increasingly integrated computational ecosystems that combine imaging, pathology, genomics, proteomics, liquid biopsy, environmental exposure data, and longitudinal clinical information into unified predictive platforms. Such systems will provide continuously updated representations of individual patients, enabling more precise diagnosis and personalized management throughout the entire disease course. [55]

Large multicenter prospective studies will be essential for validating these technologies across diverse healthcare settings. Standardized imaging acquisition protocols, harmonized reporting systems, interoperable health information platforms, and international collaboration will accelerate translation of AI-based tools from research environments into routine clinical practice. [56]

Emerging technologies including foundation models, federated learning, explainable artificial intelligence, and cloud-based medical computing are expected to further improve scalability, robustness, and accessibility. Together, these innovations may substantially enhance early lung cancer detection while reducing false-positive investigations and unnecessary surgical interventions. [57]

20. Discussion

The findings from longitudinal evaluation of biopsy-

confirmed pulmonary tumors underscore the complexity of pulmonary nodule behavior detected during LDCT screening. Although interval growth remains an important marker of malignancy, this review demonstrates that growth kinetics alone are insufficient for reliable diagnosis. Benign lesions may enlarge, malignant tumors may remain stable for prolonged periods, and some cancers may even exhibit temporary regression or highly variable growth trajectories. These observations reinforce the need for comprehensive interpretation that integrates imaging characteristics, clinical history, pathological confirmation, and emerging computational technologies. [58]

Advances in artificial intelligence, radiomics, and predictive modeling are reshaping pulmonary nodule evaluation by enabling objective analysis of imaging features that extend beyond conventional visual interpretation. Nevertheless, these technologies should be viewed as decision-support tools that enhance—not replace—clinical judgment. Multidisciplinary collaboration among radiologists, pulmonologists, thoracic surgeons, pathologists, and oncologists will remain fundamental to accurate diagnosis and optimal patient management. [59]

21. Conclusion

Longitudinal analysis of biopsy-confirmed pulmonary tumors detected on LDCT provides important insights into the biological diversity of pulmonary lesion growth and highlights the limitations of relying solely on interval enlargement as an indicator of malignancy. Accurate diagnosis requires integration of serial imaging findings with radiological morphology, histopathological confirmation, clinical risk factors, and increasingly sophisticated computational approaches. As artificial intelligence, quantitative imaging, and precision medicine continue to evolve, future pulmonary nodule assessment will become progressively more individualized, enabling earlier diagnosis, more appropriate surveillance, fewer unnecessary invasive procedures, and improved clinical outcomes for patients undergoing lung cancer screening. Continued multidisciplinary research and prospective validation will be essential to translate these advances into routine clinical practice and optimize the next generation of personalized thoracic oncology care. [60]

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