Current Research in Medical Sciences
ISSN 2958-0390
www.pioneerpublisher.com/crms
Volume 3 Number 1 March 2024

Advances in Diagnosis and Treatment of Neoplastic Ground-Glass Nodules

Sizhu Liu[1]

[1] Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China
Correspondence: Sizhu Liu, Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China.

doi:10.56397/CRMS.2024.03.11

Abstract

Lung cancer is a prevalent malignant tumor globally, carrying the highest mortality rate among all malignancies (Bray F, Ferlay J, Soerjomataram I, et al., 2018). Adenocarcinoma stands as the most frequent histological subtype (Hansell DM, Bankier AA, MacMahon H, et al., 2008). The widespread adoption of Low-dose Computed Tomography (LDCT) for lung cancer screening has led to a surge in lung nodule detection rates. Ground-glass nodules exhibit a higher malignancy rate compared to solid nodules, underscoring the significance of qualitative diagnosis. This plays a pivotal role in determining subsequent treatment modalities and patient prognosis. Distinguishing between neoplastic and non-neoplastic ground-glass nodules primarily hinges on their CT characteristics, including size, shape, lobulation, spiculation, and air bronchogram. Nevertheless, certain morphological features of GGNs pose challenges in differentiation, thereby complicating clinical diagnosis. As a result, this article conducts a review of pertinent prior studies and guidelines, encompassing the imaging attributes and discrimination of GGNs, neoplastic GGNs' pathological subtypes, and clinical management strategies.

Keywords: ground-glass nodules, lung adenocarcinoma, computed tomography

1. Definition of GGN

A ground-glass nodule (GGN) in the lung is defined as a nodule with increased density on thin-slice CT scans that does not obscure the underlying vessels and bronchi in the region (Kakinuma R, Muramatsu Y, Kusumoto M, et al., 2015). On mediastinal window images, depending on whether the ground-glass nodule contains internal solid components, it can be further categorized into pure ground-glass nodules (pGGN) and part-solid nodules (PSN); the latter can also be referred to as mixed GGNs (mGGN). GGNs are also referred to as sub-solid nodules (SSN). On lung window images, based on the uniformity of density in the pure ground-glass nodule, it can be further subcategorized into uniform pure ground-glass nodules and non-uniform pure ground-glass nodules (Fan L, Li Q, Xiao Y, et al., 2016). Research has indicated a higher incidence rate of early-stage lung adenocarcinomas presenting as ground-glass nodules in Asian countries (Hsu HT, Tang EK, Wu MT, et al., 2018), highlighting the need for special attention.

2. Imaging Differential Indicators of GGN

2.1 Size

Throughout the years, the size of GGNs has served as a reliable indicator for differentiation. Generally, smaller nodules are often benign, whereas larger nodules tend to be malignant. Wang et al. demonstrated a notable variance in the average diameter of benign and malignant ground-glass nodules, pinpointing an optimal threshold of 9.24mm (Wang YH, Chen CF, Lin YK, et al., 2020). Aberle et al. discovered that for nodules measuring 4-6mm in diameter, the positive predictive values were merely 0.3% and 0.7% (Aberle DR, DeMello S, Berg CD, et al., 2013). Horeweg et al. also proposed that there was no discernible difference in lung cancer risk between patients with nodules smaller than 5mm and those without nodules (Horeweg N, van Rosmalen J, Heuvelmans MA, et al., 2014). Moreover, both the Fleischner guidelines and the 2011 IASLC Lung Adenocarcinoma Classification Guidelines advocate for monitoring solely GGNs larger than 6mm, as benign lesions are prominently associated with smaller nodule diameters. As the volume of the nodules escalates, the invasiveness of lung adenocarcinoma manifesting as ground-glass nodules proportionately intensifies; thus, the nodule size can aid in distinguishing between pre-invasive lesions and invasive lesions (Lu J, Tang H, Yang X, et al., 2020).

2.2 Boundary

The boundary of a ground-glass nodule also holds significance in its differentiation, with indistinct borders being more prevalent in benign nodules compared to malignant ones. In the investigation conducted by He et al., 61.43% of benign SSNs exhibited indistinct borders, whereas only 44.47% of malignant SSNs displayed the same characteristic (He XQ, Li X, Wu Y, et al., 2022). Fu et al. similarly highlighted the disparity in borders between benign and malignant nodules (Fu BJ, Lv FJ, Li WJ, et al., 2021). Nevertheless, a notable number of benign GGNs may also feature well-defined borders, underscoring the variability in their border appearance. Thus, further exploration is imperative to assess the utility of borders in distinguishing nodules as benign or malignant.

2.3 Edge Features

Edge features, such as lobulation and spiculation, play a crucial role in the characterization of nodules. Lobulation in a nodule is primarily attributed to its uneven growth in various directions or obstruction by neighboring structures, resulting in a contour marked by multiple arcuate protrusions and concave notches between the arcs, giving rise to a lobulated appearance. This feature is strongly associated with malignant tumors (Gurney JW, 1993). In ground-glass nodules, a lobulated edge indicates invasiveness (Lee HJ, Goo JM, Lee CH, et al., 2009). However, in benign nodules, lobulation stems from the proliferation of adjacent fibrous tissue and scar contraction. On the other hand, spiculation refers to fine linear shadows emanating from the edge of a nodule into the surrounding lung parenchyma, without adhering to the pleura. The mechanism underlying spiculation involves the thickening of interlobular septa around the nodule and the infiltration of blood vessels or lymphatic vessels around the nodule by cancerous or inflammatory cells. Spiculation serves as a strong predictor of malignant tumors, with a notably high positive predictive value of up to 90% (Winer-Muram HT., 2006). Nodules exhibiting spiculation are more likely to be malignant in comparison to nodules with smooth edges (Seemann MD, Staebler A, Beinert T, et al., 1999). Benign conditions that can manifest with spiculation include infections, tuberculomas, inflammatory pseudotumor, localized lung collapse, and fibrosis. In ground-glass nodules, spiculation serves as a predictive indicator of nodule invasiveness (Lee SM, Park CM, Goo JM, et al., 2013).

2.4 Internal Features

Internal features include air cysts and air bronchogram sign. Air cysts refer to gas density or low-density shadows with a diameter of less than 5mm inside the nodule, which can be single or multiple. It is more common in malignant lesions and is caused by the specific growth pattern of the tumor, manifested as incomplete filling of the normal lung parenchyma, bronchial dilation, and enlargement of alveolar gaps (Fan L, Liu SY, Li QC, et al., 2011). A study involving 94 cases of non-neoplastic GGN and 1,840 cases of neoplastic GGN found that air cysts were more common in patients with neoplastic lesions (Yang W, Sun Y, Fang W, et al., 2018). In ground-glass nodules, the incidence of air cysts in invasive adenocarcinoma is slightly higher than in pre-invasive lesions (Lee SM, Park CM, Goo JM, et al., 2013). However, the diagnostic efficiency of this sign varies greatly in several studies, with some even suggesting that it cannot be used to differentiate GGN (Kohno N, Ikezoe J, Johkoh T, et al., 1993). Recent meta-analyses also indicate that further research is needed on the use of air cysts for nodule differentiation (Yang Y, Xu J, Wang W, et al., 2023). Air bronchogram sign refers to the imaging sign formed by the bronchus filled with gas against a background of non-luminous, non-air-containing lung tissue. The air bronchogram sign is a characteristic of lepidic growth lung adenocarcinoma, where proliferating tumor cells slowly fill the alveolar cavity without obstructing the terminal bronchioles, resulting in the imaging appearance of air bronchogram sign. Therefore, air bronchogram sign is more common in adenocarcinoma, especially those presenting as ground-glass nodules. Previous studies have shown that the air bronchogram sign is more common in malignant lesions than in benign lesions (Yang W, Sun Y, Fang W, et al., 2018). Fan et al. divided the air bronchogram sign into bronchi with a natural course and bronchi with dilation or distortion of their course, and their results showed that there was no significant difference in the occurrence rate of the two types in benign and malignant nodules (Fan L, Liu SY, Li QC, et al., 2012).

2.5 Adjacent Structure Features

Including the pleural indentation sign and the vascular convergence sign. The pleural indentation sign is characterized by a linear shadow extending from the nodule surface to the pleural surface, frequently observed in malignant lesions (Harders SW, Madsen HH, Rasmussen TR, et al., 2011). Research indicates that the pleural indentation sign in pure ground-glass nodules serves as a predictive indicator of invasiveness, with nodules exhibiting this sign more likely to be invasive adenocarcinomas rather than minimally invasive or in situ adenocarcinomas (Moon Y, Sung SW, Lee KY, et al., 2016). In cases where nodules do not directly contact the pleura, the presence of soft tissue components at the pleural end of the pleural indentation sign suggests potential invasion of the visceral pleura by the tumor (Hsu JS, Han IT, Tsai TH, et al., 2016). On the other hand, the vascular convergence sign pertains to adjacent blood vessels surrounding the lung nodule converging around the lesion. Typically, the diameter of lung blood vessels diminishes gradually. Abnormally dilated vessels present as segments of vessels within the nodule with a larger diameter than the proximal vessel segments, or vessels within the lesion conspicuously wider than other vessels at the same branch level. Vessels exhibiting deviation from the anticipated normal course are considered twisted or stiff. In the study by Gao et al., the relationship between GGN and its supplying vessels is categorized into four types: Type I, no branching supply to the lesion as vessels traverse the GGN; Type II, vessels passing through the lesion without significant alterations in path or size; Type III, vessels within the lesion displaying twisting or dilation; Type IV: irregular vessel dilation alongside the coexistence of vascular convergence signs. Fu et al. propose that the presence of vascular convergence signs within GGNs is predominantly linked to the nodule’s size and the distance between the nodule and the pleura, with vascular dilation or distortion within GGNs indicative of a higher likelihood of malignancy (Fu BJ, Lv FJ, Li WJ, et al., 2021).

3. The Relationship Between Neoplastic Ground Glass Nodules (GGNs) Imaging and Gene Mutations

Radiogenomics represents a burgeoning trend in clinical research that seeks to establish a connection between imaging characteristics and tumor biomarkers (Gillies RJ, Kinahan PE & Hricak H., 2016). As targeted therapy for lung cancer undergoes rapid advancement, the exploration of lung cancer driver genes is on the rise. While numerous studies have delved into lung cancer and gene mutations, data on adenocarcinomas in the form of pulmonary nodules are scarce and occasionally conflicting. In a study involving 38 cases of EGFR mutation and 42 cases of EGFR wild-type lung adenocarcinoma patients (Yano M, Sasaki H, Kobayashi Y, et al., 2006), the investigation centered on the correlation between CT morphology and EGFR gene mutations. Results from this study indicate that EGFR mutations are predominantly prevalent in peripheral small adenocarcinomas with a GGO ratio ≥50%, particularly in females. Kobayashi et al. (2015) conducted an evaluation on the clinical and pathological characteristics of 104 GGNs with ≥50% ground-glass components, examining their relationship with EGFR, KRAS, ALK, and HER2 mutations. Their findings suggest that EGFR mutation positivity correlates with GGN growth, defined as a diameter increase ≥2mm or an escalation in solid components. Furthermore, Takatoshi et al. (2012) analyzed 25 cases of lung adenocarcinoma exhibiting persistent GGNs, exploring the association between CT alterations and molecular biomarkers. Their study revealed that GGN-type lung adenocarcinomas commonly harbor EGFR mutations, with the emergence or augmentation of solid components potentially linked to p53 inactivation. Cai et al. (2023) delved into the correlation between CT imaging features, pathology, and genotypes of 465 GGNs, revealing EGFR gene mutations as the most prevalent, with the size of GGNs exhibiting a positive correlation with the mutation rate. Radiogenomics assumes a pivotal role in facilitating precise targeted therapy for patients, underscoring its paramount significance in clinical practice.

4. The Relationship Between Neoplastic GGNs Imaging and Pathology

The predominant pathological types of tumor-associated Ground Glass Nodules (GGNs) primarily consist of lung adenocarcinomas. In accordance with the new pathological classification of lung adenocarcinoma established by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society, lung adenocarcinoma is categorized into Atypical Adenomatous Hyperplasia (AAH), Adenocarcinoma in situ (AIS), Micro-invasive Adenocarcinoma (MIA), and Invasive Adenocarcinoma (IAC) (Travis WD, Brambilla E, Noguchi M, et al., 2011).

4.1 Atypical Adenomatous Hyperplasia (AAH)

Atypical Adenomatous Hyperplasia (AAH) serves as the precursor lesion of adenocarcinoma arising from pathologies within the terminal respiratory system (Nakahara R, Yokose T, Nagai K, et al., 2001). It is characterized by a localized small proliferation (≤5 mm) of atypical type II lung cells and/or lung alveolar walls and/or peripheral Clara cells on the wall of respiratory bronchioles, devoid of invasion. Typically manifesting as pure ground glass nodules, AAH nodules are oval or round in shape, with a diameter usually ≤5mm, occasionally exceeding 10mm. While AAH can manifest as isolated lesions, the majority are multifocal and bilateral. Owing to their low density and diminutive size, AAH nodules are challenging to detect even with thin-section CT scans.

4.2 Adenocarcinoma in Situ (AIS)

Adenocarcinoma in situ (AIS) represents a novel category of adenocarcinoma introduced in the 2011 IASLC/ATS/ERS classification, supplanting the previous bronchioloalveolar carcinoma. It is characterized as a small adenocarcinoma with localized growth along the alveolar walls in a lepidic pattern, devoid of interstitial, vascular, or pleural invasion. AIS, albeit rare, accounts for only 3% to 4% of all non-small cell lung cancers (NSCLC). Given its non-invasive nature, the 5-year survival rate post-surgery for AIS can attain 100% (Sakurai H, Dobashi Y, Mizutani E, et al., 2004). AIS typically exhibits a diameter larger than AAH, ranging from 5-20mm but <30mm. On CT scans, AIS manifests as pure ground glass nodules measuring 5-30mm. Nevertheless, in certain instances, partially solid or solid nodules may also represent AIS. The solid component within these nodules on CT images is linked to alveolar collapse and fibrosis (Yang ZG, Sone S, Takashima S, et al., 2001). Currently, distinguishing AIS from AAH in ground glass nodules hinges on the belief that AIS generally displays higher CT values and larger diameters (>5mm) compared to AAH. Nonetheless, there exists an overlap in CT characteristics among AAH, AIS, and MIA.

4.3 Micro-Invasive Adenocarcinoma (MIA)

Micro-invasive Adenocarcinoma (MIA) also emerged as a novel category of adenocarcinoma in 2011. It is characterized as a small adenocarcinoma predominantly exhibiting a lepidic growth pattern with an invasive focus of ≤5mm, typically presenting lesions smaller than 30mm. MIA is commonly solitary but may coexist with other lesions. With a favorable prognosis, the expected survival rate for MIA falls within the range of 98% to 100% (Tsuta K, Kawago M, Inoue E, et al., 2013). In the majority of instances, MIA is non-mucinous and is discernible on CT scans as partially solid nodules featuring pure ground glass or solid components measuring <5mm (Austin JH, Garg K, Aberle D, et al., 2013).

4.4 Invasive Adenocarcinoma (IAC)

IAC accounts for at least 70% of resected adenocarcinomas and is defined as a small adenocarcinoma with an invasive focus larger than 5mm. IAC can be histologically classified into lepidic, acinar, papillary, solid subtypes, and micropapillary. The prognosis varies among different subtypes: lepidic IAC has a high 5-year survival rate of up to 90% after resection. In contrast, the prognosis of micropapillary IAC is poorer (Yeh YC, Wu YC, Chen CY, et al., 2012). The CT features of IAC are diverse, ranging from pure ground glass nodules to partially solid or solid nodules. The size of the solid component is a key feature of invasive adenocarcinoma presented as partially solid nodules. A solid component smaller than 5mm is indicative of non-invasive adenocarcinoma, while a solid component larger than 9mm has 100% specificity for the diagnosis of invasive adenocarcinoma (Cohen JG, Reymond E, Lederlin M, et al., 2015). Therefore, it is currently believed that the size of the solid component may be more suitable for T staging compared to the size of the nodules (Aoki T, Tomoda Y, Watanabe H, et al., 2001).

5. Clinical Management Strategies for Neoplastic GGN

For neoplastic GGN, specific treatment options include: when the probability of malignant transformation is low, observation and follow-up, non-surgical biopsy, or surgical resection can be considered; when the probability of malignant transformation is high, surgery should be performed as soon as possible if conditions permit.

5.1 Follow-up Observation

In 2017, the Fleischner Society published guidelines for the management of pulmonary ground-glass nodules (pGGN) (MacMahon H, Naidich DP, Goo JM, et al., 2017) as follows: (1) For pGGNs <6mm, routine follow-up is not recommended. For nodules close to 6mm in size, with suspicious morphology or other risk factors, follow-up every 2-4 years is recommended. For pGGNs ≥6mm, follow-up every 6-12 months is recommended. (2) For subsolid nodules (PSN) <6mm, routine follow-up is not recommended. For PSNs ≥6mm with a subsolid component <6mm, follow-up every 3-6 months is recommended, followed by annual follow-up. For PSNs with a subsolid component ≥6mm, short-term follow-up is recommended to assess the persistence of the nodule. For nodules with high-risk factors, PET-CT, biopsy, or surgical resection are recommended. (3) In patients with multiple <6mm ground-glass nodules, infectious factors should be considered. If nodules persist on initial follow-up at 3-6 months, follow-up should be considered around 2 and 4 years, with the specific timing determined based on clinical factors. In patients with multiple ground-glass nodules, if at least one nodule is ≥6mm, the management should be based on the most suspicious nodule while also considering infectious factors. If nodules persist after 3-6 months, primary adenocarcinoma should be considered. Multiple nodules are generally more likely to be malignant than solitary nodules.

5.2 Non-Surgical Biopsy

Transthoracic needle biopsy and bronchoscopy are two common non-surgical biopsy methods for lung nodules. The selection between these approaches is influenced by various factors, including the nodule's location and the patient's tolerance. Peripheral lung nodules are typically better suited for transthoracic needle biopsy, while nodules near the airways are more effectively assessed through bronchoscopy. A meta-analysis (Han Y, Kim HJ, Kong KA, et al., 2018) revealed a higher positive diagnostic rate of 93% for transthoracic needle biopsy compared to 75% for bronchoscopy. However, transthoracic needle biopsy carries a relatively elevated risk of complications such as pneumothorax (26%) and bleeding (16%). Advancements in bronchoscopy techniques, including endobronchial ultrasound, electromagnetic navigation bronchoscopy, and robotic-assisted bronchoscopy, have notably enhanced the diagnostic efficacy of bronchoscopy while maintaining a lower complication rate. Another meta-analysis (Folch EE, Labarca G, Ospina-Delgado D, et al., 2020) reported a diagnostic rate of 77% for electromagnetic navigation bronchoscopy, with a pneumothorax risk of 2.0% and a major bleeding risk of 0.8%.

5.3 Surgical Treatment

For pure ground-glass nodules located in the outer third of the lung, wedge resection is recommended. For central pure GGNs, segmentectomy is recommended. Lymph node sampling should only be considered in high-risk patients. For partially solid nodules, a combination of lymph node dissection and segmentectomy is recommended. Minimally invasive surgery is the preferred method, and it is recommended to ensure a margin of at least 1 cm or a margin/tumor ratio of at least 1 to ensure complete resection. For multiple ground-glass nodules, the malignant risk of the primary lesion should be considered, and a lung parenchyma preservation strategy should be adopted.

6. Summary and Outlook

The diagnosis and treatment of neoplastic ground-glass nodules (GGNs) have always been a focus of attention. This article provides a review of the imaging features, pathological types, and clinical management of neoplastic GGNs by reviewing past relevant studies and guidelines. In current research, the diagnosis of neoplastic GGNs still poses challenges, as some morphological features are difficult to distinguish from non- neoplastic GGNs. Therefore, future research can focus on using more advanced imaging techniques and artificial intelligence algorithms to improve the accuracy of diagnosing neoplastic GGNs. Additionally, personalized treatment plans for different types of neoplastic GGNs are also a direction for future research. Through further research and clinical practice, it is believed that more effective strategies and methods can be provided for the diagnosis and treatment of neoplastic GGNs, thereby improving the treatment outcomes and prognosis for patients.

References

Aberle DR, DeMello S, Berg CD, et al. (2013). Results of the two incidence screenings in the National Lung Screening Trial. *N Engl J Med., 369*(10), 920-931.

Aoki T, Hanamiya M, Uramoto H, et al. (2012). Adenocarcinomas with predominant ground-glass opacity: correlation of morphology and molecular biomarkers. *Radiology, 264*(2), 590-596.

Aoki T, Tomoda Y, Watanabe H, et al. (2001). Peripheral lung adenocarcinoma: correlation of thin-section CT findings with histologic prognostic factors and survival. *Radiology, 220*(3), 803-809.

Austin JH, Garg K, Aberle D, et al. (2013). Radiologic implications of the 2011 classification of adenocarcinoma of the lung. *Radiology, 266*(1), 62-71.

Bray F, Ferlay J, Soerjomataram I, et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin., 68*(6), 394-424.

Cai Y, Chen T, Zhang S, et al. (2023). Correlation exploration among CT imaging, pathology and genotype of pulmonary ground-glass opacity. *J Cell Mol Med., 27*(14), 2021-2031.

Cohen JG, Reymond E, Lederlin M, et al. (2015). Differentiating pre- and minimally invasive from invasive adenocarcinoma using CT-features in persistent pulmonary part-solid nodules in Caucasian patients. *Eur J Radiol., 84*(4), 738-744.

Fan L, Li Q, Xiao Y, et al. (2016). How to Define and Display Solid Components within Ground-Glass Nodules and Differentiate Pure Ground-Glass Nodules from Mixed Ground-Glass Nodules?. *Radiology, 281*(1), 325-326.

Fan L, Liu SY, Li QC, et al. (2011). Pulmonary malignant focal ground-glass opacity nodules and solid nodules of 3cm or less: comparison of multi-detector CT features. *J Med Imaging Radiat Oncol., 55*(3), 279-285.

Fan L, Liu SY, Li QC, et al. (2012). Multidetector CT features of pulmonary focal ground-glass opacity: differences between benign and malignant. *Br J Radiol, 85*(1015), 897-904.

Folch EE, Labarca G, Ospina-Delgado D, et al. (2020). Sensitivity and Safety of Electromagnetic Navigation Bronchoscopy for Lung Cancer Diagnosis: Systematic Review and Meta-analysis. *Chest, 158*(4), 1753-1769.

Fu BJ, Lv FJ, Li WJ, et al. (2021). Significance of intra-nodular vessel sign in differentiating benign and malignant pulmonary ground-glass nodules. *Insights Imaging, 12*(1), 65. Published 2021 May 26.

Fu BJ, Lv FJ, Li WJ, et al. (2021). Significance of intra-nodular vessel sign in differentiating benign and malignant pulmonary ground-glass nodules. *Insights Imaging, 12*(1), 65.

Gao F, Sun Y, Zhang G, et al. (2019). CT characterization of different pathological types of subcentimeter pulmonary ground-glass nodular lesions. *Br J Radiol., 92*(1094), 20180204.

Gillies RJ, Kinahan PE, Hricak H. (2016). Radiomics: Images Are More than Pictures, They Are Data. *Radiology, 278*(2), 563-577.

Gurney JW. (1993). Determining the likelihood of malignancy in solitary pulmonary nodules with Bayesian analysis. Part I.

Theory. *Radiology, 186*(2), 405-413.

Han Y, Kim HJ, Kong KA, et al. (2018). Diagnosis of small pulmonary lesions by transbronchial lung biopsy with radial endobronchial ultrasound and virtual bronchoscopic navigation versus CT-guided transthoracic needle biopsy: A systematic review and meta-analysis. *PLoS One, 13*(1), e0191590. Published 2018 Jan 22.

Hansell DM, Bankier AA, MacMahon H, et al. (2008). Fleischner Society: glossary of terms for thoracic imaging. *Radiology, 246*(3), 697-722.

Harders SW, Madsen HH, Rasmussen TR, et al. (2011). High resolution spiral CT for determining the malignant potential of solitary pulmonary nodules: refining and testing the test. *Acta Radiol., 52*(4), 401-409.

He XQ, Li X, Wu Y, et al. (2022). Differential Diagnosis of Nonabsorbable Inflammatory and Malignant Subsolid Nodules with a Solid Component ≤5 mm. *J Inflamm Res., 15*, 1785-1796. Published 2022 Mar 11.

Horeweg N, van Rosmalen J, Heuvelmans MA, et al. (2014). Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. *Lancet Oncol., 15*(12), 1332-1341.

Hsu HT, Tang EK, Wu MT, et al. (2018). Modified Lung-RADS Improves Performance of Screening LDCT in a Population with High Prevalence of Non-smoking-related Lung Cancer. *Acad Radiol., 25*(10), 1240-1251.

Hsu JS, Han IT, Tsai TH, et al. (2016). Pleural Tags on CT Scans to Predict Visceral Pleural Invasion of Non-Small Cell Lung Cancer That Does Not Abut the Pleura. *Radiology, 279*(2), 590-596.

Kakinuma R, Muramatsu Y, Kusumoto M, et al. (2015). Solitary Pure Ground-Glass Nodules 5 mm or Smaller: Frequency of Growth. *Radiology, 276*(3), 873-882.

Kobayashi Y, Mitsudomi T, Sakao Y, et al. (2015). Genetic features of pulmonary adenocarcinoma presenting with ground-glass nodules: the differences between nodules with and without growth. *Ann Oncol., 26*(1), 156-161.

Kohno N, Ikezoe J, Johkoh T, et al. (1993). Focal organizing pneumonia: CT appearance. *Radiology, 189*(1), 119-123.

Lee HJ, Goo JM, Lee CH, et al. (2009). Predictive CT findings of malignancy in ground-glass nodules on thin-section chest CT: the effects on radiologist performance. *Eur Radiol., 19*(3), 552-560.

Lee SM, Park CM, Goo JM, et al. (2013). Invasive pulmonary adenocarcinomas versus preinvasive lesions appearing as ground-glass nodules: differentiation by using CT features. *Radiology, 268*(1), 265-273.

Lee SM, Park CM, Goo JM, et al. (2013). Invasive pulmonary adenocarcinomas versus preinvasive lesions appearing as ground-glass nodules: differentiation by using CT features. *Radiology, 268*(1), 265-273.

Lu J, Tang H, Yang X, et al. (2020). Diagnostic value and imaging features of multi-detector CT in lung adenocarcinoma with ground glass nodule patients. *Oncol Lett., 20*(1), 693-698.

MacMahon H, Naidich DP, Goo JM, et al. (2017). Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. *Radiology, 284*(1), 228-243.

Moon Y, Sung SW, Lee KY, et al. (2016). Pure ground-glass opacity on chest computed tomography: predictive factors for invasive adenocarcinoma. *J Thorac Dis., 8*(7), 1561-1570.

Nakahara R, Yokose T, Nagai K, et al. (2001). Atypical adenomatous hyperplasia of the lung: a clinicopathological study of 118 cases including cases with multiple atypical adenomatous hyperplasia. *Thorax, 56*(4), 302-305.

Sakurai H, Dobashi Y, Mizutani E, et al. (2004). Bronchioloalveolar carcinoma of the lung 3 centimeters or less in diameter: a prognostic assessment. *Ann Thorac Surg., 78*(5), 1728-1733.

Seemann MD, Staebler A, Beinert T, et al. (1999). Usefulness of morphological characteristics for the differentiation of benign from malignant solitary pulmonary lesions using HRCT. *Eur Radiol., 9*(3), 409-417.

Travis WD, Brambilla E, Noguchi M, et al. (2011). International association for the study of lung cancer/American thoracic society/European respiratory society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol., 6*(2), 244-285.

Tsuta K, Kawago M, Inoue E, et al. (2013). The utility of the proposed IASLC/ATS/ERS lung adenocarcinoma subtypes for disease prognosis and correlation of driver gene alterations. *Lung Cancer, 81*(3), 371-376.

Wang YH, Chen CF, Lin YK, et al. (2020). Predicting malignancy: subsolid nodules detected on LDCT in a surgical cohort of East Asian patients. *J Thorac Dis., 12*(8), 4315-4326.

Winer-Muram HT. (2006). The solitary pulmonary nodule. *Radiology, 239*(1), 34-49.

Yang W, Sun Y, Fang W, et al. (2018). High-resolution Computed Tomography Features Distinguishing Benign and Malignant Lesions Manifesting as Persistent Solitary Subsolid Nodules. *Clin Lung Cancer, 19*(1), e75-e83.

Yang Y, Xu J, Wang W, et al. (2023). Meta-analysis of the correlation between CT-based features and invasive properties of pure ground-glass nodules. *Asian J Surg, 46*(9), 3405-3416.

Yang ZG, Sone S, Takashima S, et al. (2001). High-resolution CT analysis of small peripheral lung adenocarcinomas revealed on screening helical CT. *AJR Am J Roentgenol., 176*(6), 1399-1407.

Yano M, Sasaki H, Kobayashi Y, et al. (2006). Epidermal growth factor receptor gene mutation and computed tomographic findings in peripheral pulmonary adenocarcinoma. *J Thorac Oncol., 1*(5), 413-416.

Yeh YC, Wu YC, Chen CY, et al. (2012). Stromal invasion and micropapillary pattern in 212 consecutive surgically resected stage I lung adenocarcinomas: histopathological categories for prognosis prediction. *J Clin Pathol., 65*(10), 910-918.