ELSEVIER

Seminars in
ULTRASOUND
CT and MRI

Spectrum of Lung Adenocarcinoma

Barry D. Hutchinson, MD,* Girish S. Shroff, MD,† Mylene T. Truong, MD,† and Jane P. Ko, MD*

Lung cancer remains the most common cause of cancer death in the United States of America and worldwide despite continued advances in lung cancer screening as well as surgical, medical, and radiation oncological treatments. Adenocarcinoma is the most common histological subtype of primary lung cancer and has recently been reorganized into a spectrum ranging from preinvasive lesions to invasive adenocarcinoma. An understanding of the pathology, diagnosis, and management of the spectrum of lung adenocarcinoma is more important than ever, considering the central role of the radiologist. The aim of this review is to describe the subtypes of the lung adenocarcinoma spectrum in terms of histological and imaging features, their pattern of growth on imaging, management, staging, and evolving knowledge of tumor genetics.
Semin Ultrasound CT MRI 40:255-264 © 2018 Published by Elsevier Inc.

Lung Adenocarcinoma

Adenocarcinoma is now the most common histological subtype of primary lung cancer[1,2] accounting for greater than 40% of cases,[3] and its relative frequency is increasing.[4] The most recent World Health Organization (WHO) Classification of Tumors[5] published in 2015 heralded a different approach to lung adenocarcinoma relative to previous editions.[6] Various histological subtypes of adenocarcinoma are now organized into a spectrum ranging from indolent preinvasive lesions to aggressive forms of invasive adenocarcinoma with a poor prognosis.[2,6] Increasing emphasis has been placed on the integration of molecular and genetic analysis of adenocarcinomas into the diagnosis and treatment of lung adenocarcinoma owing to the proliferation of novel targeted therapies.[6] A correlation between imaging findings in lung adenocarcinoma and histologic features and/or prognosis has been demonstrated by numerous studies.[7-9] In the 20th century, squamous cell carcinoma (SCC) was the most common histological subtype of primary lung cancer in men accounting for nearly half of all cases in the 1970s.[3] Since the 1980s, the relative frequency of SCC has declined with adenocarcinoma becoming the most common subtype by 1998-2002.[4] This shift has been attributed to a number of factors including: (1) the production of filtered cigarettes with lower tar content allowing deeper inhalation and more peripheral distribution of cigarette smoke, (2) increasing air pollution, and (3) earlier cessation of smoking. Improved attitudes toward the risks of cigarette smoking have increased the proportion of adenocarcinomas relative to other histologic subtypes of lung cancer, given SCC and small cell carcinoma have a more positive linear relationship with smoke inhalation than adenocarcinoma.[4,10] Overall rates of lung cancer in men, including adenocarcinoma, have been declining since the 1980s for these reasons.[3] Adenocarcinoma has always been the most common subtype of primary lung cancer in women, thought to be due

Abbreviations: WHO, World Health Organization; SCC, Squamous Cell Carcinoma; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; pGGN, Pure Ground-Glass Nodule; PSN, Part-Solid Nodule; I-ELCAP, International Early Lung Cancer Action Program; HRCT, High Resolution Computed Tomography; GGO, Ground-Glass Opacity; MRP, Multiplanar Reformations; AAH, Atypical Adenomatous Hyperplasia; INV, Invasive Adenocarcinoma; AIS, Adenocarcinoma *in Situ*; MIA, Minimally Invasive Adenocarcinoma; IMA, Invasive Mucinous Adenocarcinoma; STAS, Spread Through Air Spaces; LPA, Lepidic Predominant Adenocarcinoma; KRAS, Kirsten Rat Sarcoma Viral Oncogene; EGFR, Epidermal growth factor receptor; TKI, Tyrosine Kinase Inhibitor; ALK, Anaplastic Lymphoma Kinase; ROS1, Encoding Tyrosine-Protein Kinase ROS; MET, Mesenchymal-Epidermal Transition Oncogene; BRAF, v-Raf Murine Sarcoma Viral Oncogene; PD-L1/P-1, Programmed Death-Ligand 1/Programmed Cell Death Protein 1; NSCLC, Non-Small Cell Lung Carcinoma; TNM, Tumor, Node and Metastasis; SCIS, Squamous Cell Carcinoma *in situ*; LCSG, The Lung Cancer Study Group

*Department of Radiology, NYU Langone Medical Center, NYU School of Medicine, New York, NY.

†Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX.

Address reprint requests to Barry D. Hutchinson, MD, Department of Radiology, NYU Langone Medical Center, 660 First Ave, New York, NY 10016. E-mail: barry.hutchinson@nyulangone.org

https://doi.org/10.1053/j.sult.2018.11.009
0887-2171/© 2018 Published by Elsevier Inc.

to later adoption of smoking by women.[3,4] In contrast to men, the overall incidence of lung cancer and relative frequency of adenocarcinoma have continued to rise in women until recently when decline has been seen in some populations.[3,4]

Understanding of adenocarcinoma progression was reported by Noguchi et al., who described 6 stages of tumor development in a seminal study on the growth pattern of small peripheral lung adenocarcinomas and its correlation with prognosis.[11] The first 3 stages (Types A-C) were characterized by lepidic growth, which is replacement of Clara cells and type II pneumocytes that usually line the alveolar walls with neoplastic cells, progressing to more solid growth with increasing levels of fibrosis, alveolar collapse, and dedifferentiation.[11] A lepidic growth pattern in resected specimens correlated with a better prognosis than the latter fibrosing pattern.[11] This work served as the basis of a new classification of primary lung adenocarcinoma issued by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society[12] and was later adopted by the WHO.[5] This system is based on the accumulated knowledge pertaining to molecular features of adenocarcinoma and the stepwise continuum of lung adenocarcinoma tumorigenesis characterized by the progression from preinvasive, to minimally invasive, and ultimately to overtly invasive pulmonary adenocarcinoma with a lepidic pattern.[12,13] (Fig. 1). This classification integrated radiology and/or pathology correlation knowledge from studies.[12,14]

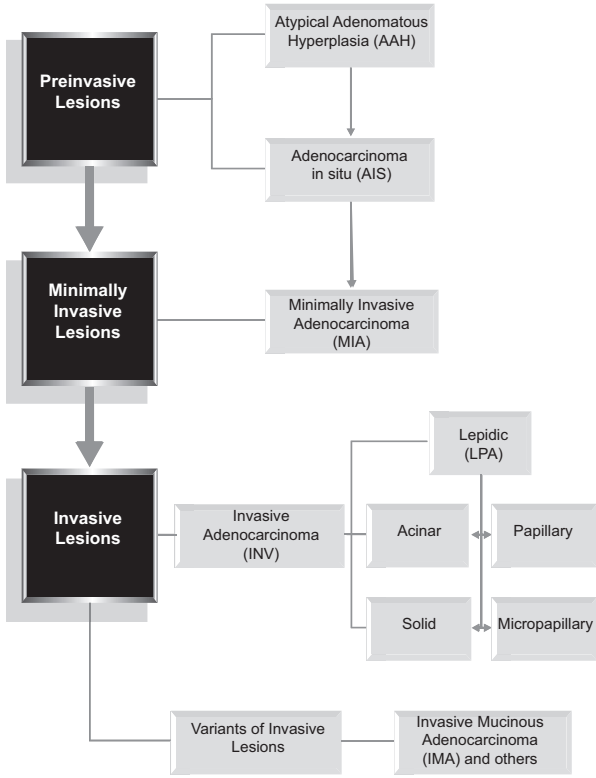


Figure 1 Flow chart depicting the spectrum of pulmonary adenocarcinoma from preinvasive to invasive lesions.

Technique and Terms

Pulmonary nodules, defined as rounded lung parenchymal opacities measuring less than 30mm, can be divided into solid and subsolid nodules.[15] Solid nodules completely obscure the lung parenchyma.[16] Subsolid nodules comprise (1) pure ground-glass nodules (pGGNs), which are focal areas of increased lung attenuation within which the margins of any normal structures, such as vessels and airways remain outlined[16] and (2) part-solid nodules (PSNs) which are nodules containing both solid and ground-glass components (Figs. 2 and 3).[12,15,16] Pulmonary masses measure 30mm or greater and may also have solid or subsolid attenuation.[15]

Subsolid nodules are less common than solid nodules. Subsolid nodules were seen in 9.2% of the 57,946 patients enrolled in the International Early Lung Cancer Action Program, whereas solid pulmonary nodules were identified in 30.2% of the same cohort.[17] When persistent, subsolid nodules have a high association with malignancy, particularly the adenocarcinoma spectrum. In the International Early Lung Cancer Action Program cohort, 34% of sampled persistent subsolid nodules were malignant, versus 7% of persistent solid pulmonary nodules in the same study.[18]

Ground-glass opacity (GGO) seen on computed tomography (CT) corresponds histologically to partial filling of airspaces; interstitial thickening due to fluid, cells, or fibrosis; partial collapse of alveoli; increased capillary blood volume; or a combination of these. The common factor is partial replacement of lung air.[14] When seen in the context of the adenocarcinoma spectrum, ground-glass opacity has been shown to correspond to lepidic tumor growth, while invasive solid tumor appears as a solid opacity on CT.[2,9,14,19-21]

For evaluating lung nodules on CT scans of the thorax, a standard imaging protocol is recommended. Images should be reconstructed with contiguous thin sections (usually 1mm) and with coronal and sagittal multiplanar reformations to enable accurate characterization of small pulmonary nodules.[22] The routine use of intravenous contrast media has not been recommended for the characterization of pulmonary nodules[23] but may be useful in assessing mediastinal structures.[20] Use of a similar technique, particularly section thickness and reconstruction kernel,[22] minimizes variability in measurement and assessment of nodule morphology on follow-up imaging.

In 2017, the Fleischner Society issued guidelines directed toward standardizing measurement of incidental pulmonary nodules.[24] Measurement of nodule diameter with electronic calipers is currently the most widely used approach.[24] For small (3-10mm) nodules, measurement should be the average of long- and short-axis diameters, rounded to the nearest whole millimeter, which are acquired typically in the axial plane on thin section images using lung windows and a high spatial frequency (sharp) filter.[24] The long-axis diameter can be measured in the coronal or sagittal plane if the nodule is largest in these dimensions, although this should be specified in the report.[22] The long-axis diameter of the nodule should be determined first, and then the short axis is to be

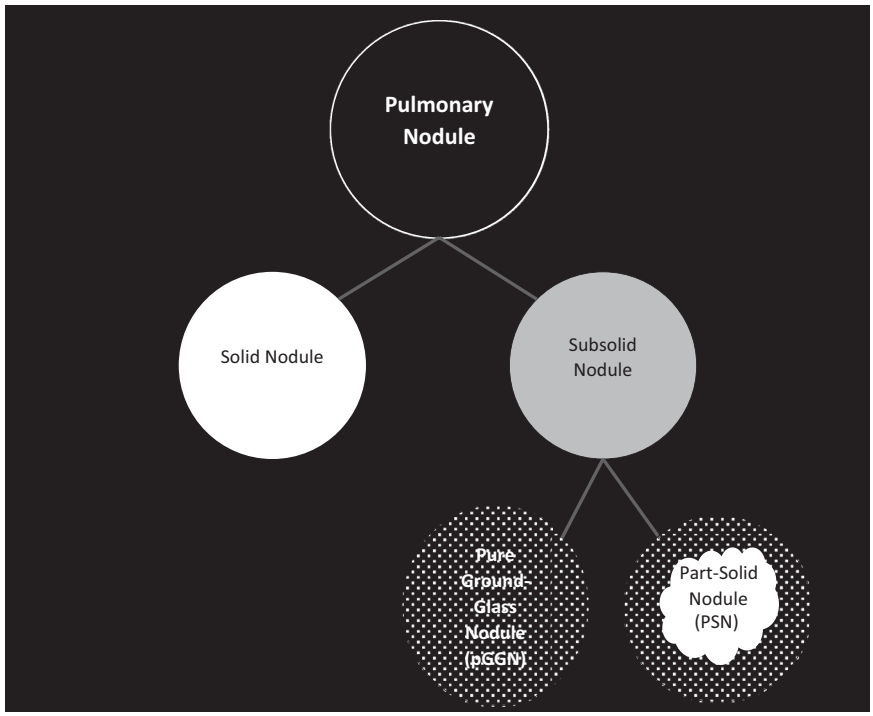


Figure 2 Nomenclature of pulmonary nodules by CT appearance.

measured perpendicular to the long axis.[24] For larger nodules (>10mm) and masses, both long and short axis measurements should be recorded and can be measured on thicker reconstructions (Fig. 3).[24]

Measurement of nodule volume by using software that detects nodule boundaries has shown to reduce interobserver variability when compared with standard bidimensional diameter measurement.[25] This can serve as a more sensitive test for growth in both solid and subsolid nodules.[24] Investigational computer software has also been developed to assist in segmentation of PSNs into fractions of solid and ground-glass components.[21,26] This method has been shown to have a correlate with the quantity of invasive component at histology[21] and to help stratify between preinvasive and invasive lesions.[21,26]

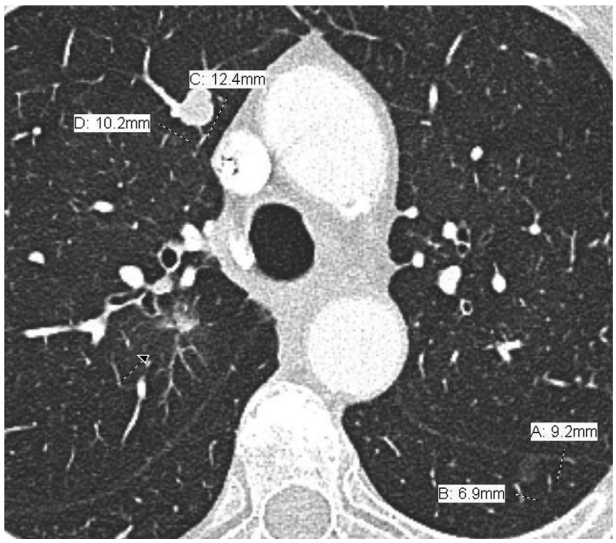


Figure 3 74-year-old woman with a history of multiple adenocarcinoma spectrum lesions as well as metastatic colon cancer with examples of solid, part-solid, and pure ground-glass nodules, all on the same image. Solid (anterior right upper lobe, calipers), PSN (posterior right upper lobe, arrow) and pGGN are all present (left lower lobe superior segment, calipers). Note, the solid nodule should be recorded as 12 × 10mm, but the pGGN has an average diameter of 8mm.

Agreement between experienced readers on whether a nodule is a dense pGGN or PSN has been shown to be low.[27] Furthermore, due to the progression from lepidic to solid components, adenocarcinoma spectrum lesions can grow by increasing in size and/or attenuation and even by contracting and/or decreasing in size.[9,28] For this reason, quantitative measures such as nodule mass that incorporate density and volume (volume × CT number), as proposed by de Hoop and colleagues, may detect earlier growth of subsolid nodules with improved interobserver agreement.[28] Other morphological features frequently described with adenocarcinoma spectrum lesions are bubble lucencies (small spots of round or ovoid air attenuation present within a subsolid nodule, Fig. 4) and pleural indentation and/or retraction.[29-31]

Atypical Adenomatous Hyperplasia

Atypical adenomatous hyperplasia (AAH) is a small focus of noninvasive proliferation of type II pneumocytes with mild to moderate cellular atypia, which line pre-existing alveolar walls and sometimes respiratory bronchioles (lepidic growth).[12,13] The term field "cancerization" describes changes occurring on the surface of tissues that are exposed

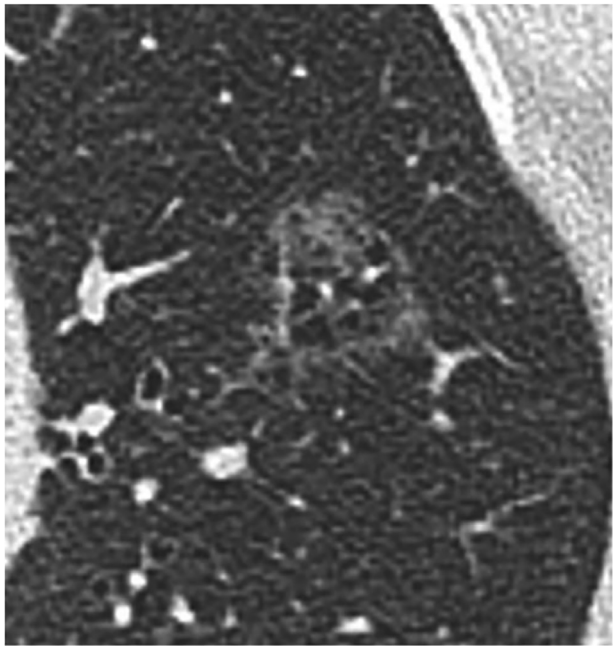


Figure 4 82-year-old woman with part-solid nodule in the left lower lobe that is composed of mainly ground-glass attenuation. This demonstrates bubble lucencies. This was diagnosed to be a micropapillary predominant adenocarcinoma by resection.

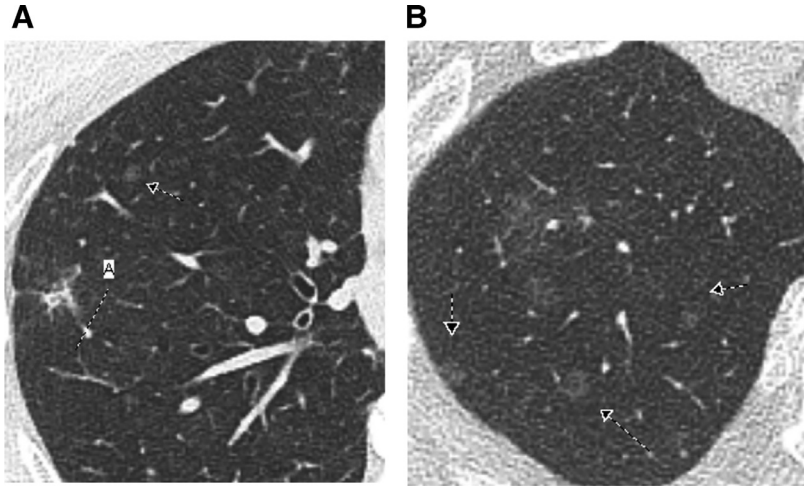
to carcinogens for an extended period of time.[32] AAH is frequently found in the vicinity of invasive adenocarcinoma (INV)[33] (Fig. 5A) which is thought to be an indication of field cancerization, that is lung tissue is at risk of developing adenocarcinoma because it possesses genetic features that make the tissue vulnerable to the development of AAH, which is often followed INV.[13] This observation, along with the isolation of specific genetic abnormalities in areas of AAH that are also frequently found in INVs, suggests a carcinogenic sequence pathway.[11,13,33] However, observed progression of AAH to INV is very uncommon.[22,34] AAH, like all members of the adenocarcinoma spectrum, are usually peripheral lesions.[12] AAH is seen more commonly in patients with multiple synchronous primary INVs than in those with a single lesion.[33]

Being the earliest member of the adenocarcinoma histopathologic spectrum, AAH is also the earliest adenocarcinoma spectrum lesion detectable by thin-section CT.[12] AAH is not always visible on CT but when seen, it is characterized by purely lepidic growth and appears as a pGGN having the lowest density of all of the ground-glass lesions of the adenocarcinoma spectrum.[14] AAH lesions are usually well-circumscribed with smooth round margins (Fig. 5B).[20,29] AAH is often bilateral and usually located in the upper lobes.[33] While it is described as typically measuring less than 5mm at histology,[12] the lesions can measure greater than 5mm on CT. In a study comparing imaging and histologic findings of 60 pGGNs by Si et al., the mean diameter of AAH lesions (17/60) was 7.6 ± 2.5mm.[29] None of these lesions demonstrated spiculation or pleural indentation.

Adenocarcinoma *in Situ*

Adenocarcinoma *in situ* (AIS) was adopted by the WHO for the first time in the 2015 classification of lung tumors.[5] Like AAH, AIS demonstrates purely lepidic growth of neoplastic type II pneumocytes or Clara cells along intact septae and lacks stromal, vascular, and pleural invasion.[12] AAH and AIS are a morphologic continuum, with AIS demonstrating more cellular and structural atypia than AAH, but their histologic distinction can be challenging.[13] While AIS can be mucinous, virtually all cases are nonmucinous.[12] The diagnosis of AIS can only be made in a completely resected specimen that enables exclusion of any invasive foci in the entire lesion.[6]

AIS is larger than AAH histologically, usually measuring between 5mm and 3cm,[12] although mean diameter of AIS



Figured 5 **A** 56-year-old man who underwent right upper lobectomy for a part-solid nodule (calipers) which was an acinar-predominant invasive adenocarcinoma at histology. A pure ground-glass nodule adjacent to it (arrow) was found to be atypical adenomatous hyperplasia. **B.** Multiple similar pure ground-glass nodules (arrows) in the right lung apex were also found to be atypical adenomatous hyperplasia at histology.

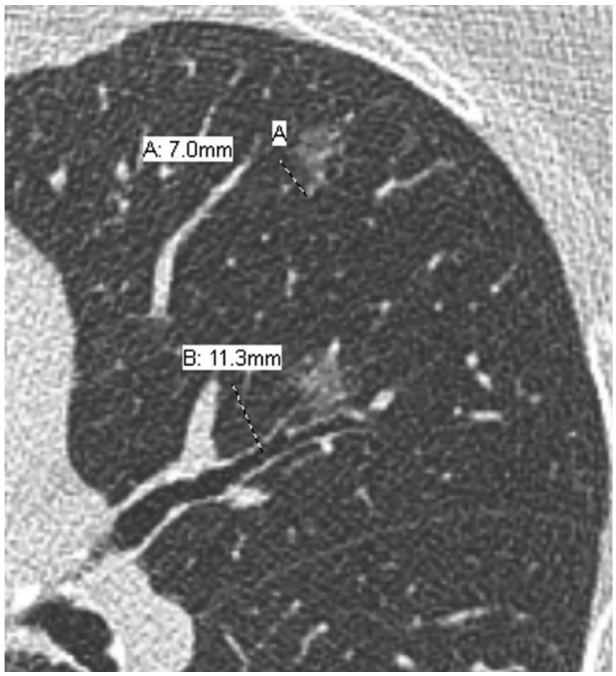


Figure 6 74-year-old woman with pGGNs measuring 7mm and 11mm in the lingula. At histology, the smaller lesion was AIS and the larger MIA. AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma.

on CT (9.0 ± 3.2mm) has not been shown to be statistically significantly different from AAH.[29] Like AAH, AIS usually appears as a pGGN on CT,[12,14,29] but the attenuation of the ground-glass is often higher than that of AAH, likely due to differences in the amount of cellular components in the alveolar airspaces or the thickness of alveolar walls (Fig. 6).[14] Nonmucinous AIS can demonstrate a small solid component, owing to collapse of alveolar walls or a benign scar,[14,35] but as a general rule, nonmucinous AIS should not have a solid component greater than 0.5cm on imaging.[35] AIS, like AAH, is more frequently smoothly-marginated in contour than MIA and INV.[36] Lesion size is the only significant discriminator between preinvasive lesions and INVs with a pGGN morphology.[36] Using cut-off value of 10mm in pGGNs is shown by one investigation to have a specificity of 100%. This means that a size smaller than 10-mm favors preinvasive lesions rather than INVs.[36]

Minimally Invasive Adenocarcinoma

Minimally Invasive Adenocarcinoma (MIA), like AIS, is comprised of predominantly lepidic tumor growth, measures 3cm or less, and has a 100% 5-year survival when fully resected.[11,12,37,38] It is distinguished from AIS by the presence of a focus or foci of invasive adenocarcinoma measuring less than 5mm.[5] Histologic invasion is defined as tumor cellular arrangement in acinar or papillary tubular structures or solid nests in a fibroblastic stroma, often accompanied by collagenization.[14,39]

The small focus of invasion in MIAs can be seen on CT as a solid component within a PSN, which typically is predominantly ground−glass attenuation (Fig. 6). PSNs with a solid component smaller than 6mm have been shown to typically represent either AIS or MIA.[22] The solid component in a MIA can appear larger than 5mm on CT due to scar, collapse of alveoli, macrophages filling alveolar sacs, and intra-alveolar hemorrhage.[14] Alternatively, foci of invasion of 5mm or smaller in MIA and even those of greater than 5mm in INV commonly manifest as a pGGN on CT because of the limited resolution of thin-section CT (0.2-0.3mm).[14,30] In a large prospective study of subsolid nodules performed by Kakinuma et al., 977 pGGNs were examined, and 35 of these were resected. These 35 pGGNs were 10 MIA, 21 AIS, and 5 AAH lesions.[40] MIA has been shown to be significantly larger than AAH and AIS when presenting as a pGGN. In a study of 60 pGGNs with histologic correlation, using a diameter of 7.5mm as a cutoff, yielded a sensitivity of 100% in distinguishing MIA from the preinvasive lesions.[29] Therefore, the most common presentation of MIA on CT is a pGGN of greater than 10mm in diameter without an internal solid component[14,30] (Fig. 6), but a significant minority appears as a PSN with a small solid component (Fig. 7).[41] Bubble lucency can be seen in MIAs[41] but has not been shown to reliably distinguish them from preinvasive lesions.[29]

INV

Unlike AIS and MIA, INVs are strictly nonmucinous and a separate diagnosis from invasive mucinous adenocarcinoma (IMA). INVs contain a focus of invasion greater than 5mm in diameter.[5] It is important to note that the histologic distinction between MIA and early INV is subject to interobserver variation. In a study of 296 resected pulmonary adenocarcinoma spectrum lesions, there was disagreement between a diagnosis of MIA and INV in 45 cases (15%).[42] Invasive components may be arranged in an acinar, papillary, solid or micropapillary histologic patterns, with infiltration of stroma and infiltration of blood vessels or structures such as the visceral pleura.[5] An

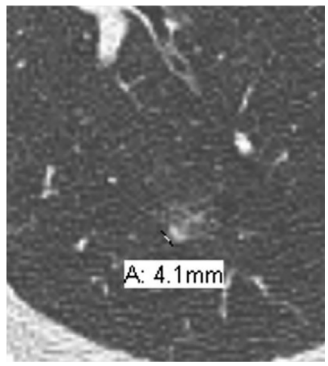


Figure 7 78-year-old man with a part-solid nodule containing a 4mm peripheral solid component and predominant GGO. This was found to be MIA at histology. Note that the sold component is measured in its longest dimension. GGO, ground-glass opacity.

additional pattern of tumor invasion called "spread through air spaces" (STAS) has also recently been described. It is characterized by the spread of lung cancer tumor cells into air spaces in the lung parenchyma adjacent to the main tumor and has been associated with a significantly higher rate of recurrence.[43] In the majority of cases of INV, these tumors are composed of a complex, heterogeneous mixture of histologic subtypes including lepidic adenocarcinoma.[12] Since the 2015 WHO classification of lung tumors, INVs are classified by their predominant subtype.[5] Another change in the latest classification pertains to the reporting in 5% increments of all adenocarcinoma subtypes present in the lesion,[12] for example, a diagnosis of "invasive adenocarcinoma 40% Lepidic, 35% Acinar, 25% Papillary" would be rendered. The histologic heterogeneity of adenocarcinoma is associated with a wide variation in prognosis depending on the varying amounts of each subtype. Three distinct prognostic groups have emerged in resected Stage 1 INVs: Lepidic predominant adenocarcinoma (LPA), acinar and/or papillary predominant adenocarcinoma, and solid and/or micropapillary predominant adenocarcinoma.[8,44]

Intuitively, INV prognosis correlates with the proportion of lepidic component. LPAs with more than 50% lepidic component have demonstrated a 0% 5-year recurrence rate,[37] and in one large study, the 5-year survival rate for all LPAs was 90%.[8] With poorer prognosis than for LPA, papillary and acinar predominant adenocarcinoma has a 5-year disease-free survival of 83% and 84%[8], respectively, and the overall survival for both is 70%.[44,45] Solid and micropapillary predominant adenocarcinomas have the worst prognosis with a 5-year disease free survival of 70% and 67%,[8] respectively, and an overall survival rate of 55% for both.[45] The significant clinical impact of these latter subtypes was underscored by recent studies which have shown that the presence of minor components of micropapillary and/or solid subtypes of lung adenocarcinoma correlate with lymph node metastasis and poor prognosis (Fig. 4).[46]

Like their histology and prognosis, imaging findings of INV at CT are highly variable, typically a part-solid nodule or completely solid nodule and/or mass although can be a pGGN (Fig. 8). Like all the adenocarcinoma spectrum lesions described, INVs are most commonly peripheral in location.[12] INVs are often accompanied by additional earlier adenocarcinoma spectrum lesions including AAH, AIS, and MIA (Figure 5A).[47] When appearing as a pGGN, nodule size has been shown to be a significant discriminator between INV and AIS and/or MIA. In a study of 46 resected pGGNs, a cut-off of 16.4mm was shown to reliably discriminate INV from AIS and/or MIA.[30] In another study of 83 resected pGGNs, the mean nodule diameter of the 17 patients (20.5%) diagnosed with INV was 19mm, significantly larger than that of the 66 cases of AIS and/or MIA (79.5%) which averaged 12mm in diameter.[48] The pGGN size has also been shown to correlate significantly with size and number of histologically invasive foci.[49] Density and/or mass of a pGGN have been reported as reliable discriminators of INV from AIS and/or MIA in several studies.[30,50]

As described, the presence of small solid components does not necessarily indicate the existence of invasive foci. However, solid components measuring greater than 5mm in a PSN have been shown to correlate with a substantial likelihood of local invasion and as a method to distinguish INV from AIS and/or MIA.[22] In the large study by Kakinuma et al., the mean maximal diameter of the solid component in the mediastinal window was 3.3mm for MIAs and 5.5mm for INVs; this difference in the mean diameter of the solid component was statistically significant.[40] The relative proportions of solid to ground-glass components in a PSN, when measured with investigational segmentation software, have been shown to not only distinguish INV from AIS and/or MIA but also LPA from other more invasive forms of INV. The mean percentage solid volume of nonlepidic INVs was 35.4%, higher than the 14.5% for LPA and 8.2% for AIS and/or MIA.[26] Lastly pleural retraction is more commonly seen in INV than AIS and/or MIA and other nonmalignant lesions,[50] seen in 76.5% of cases of INVs in one study vs 15.2% for non-INVs.[48]

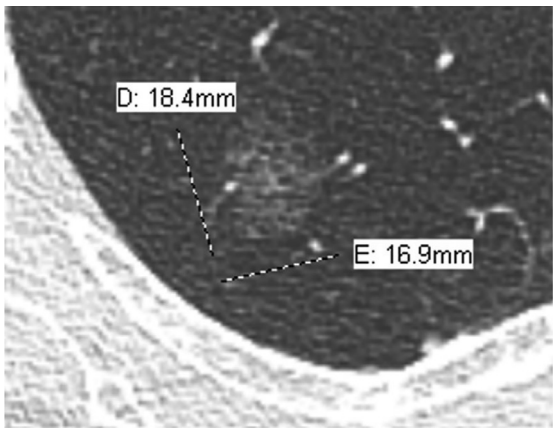


Figure 8 72-year-old woman with pGGN measuring 18 × 17 mm in the right upper lobe. This was LPA with an invasive focus of papillary adenocarcinoma at histology. LPA, lepidic predominant adenocarcinoma.

Variants of INV

Variants of INV include IMA as well as colloid, fetal, and enteric subtypes.[12] IMA was formally classified as separate from non-mucinous INV in the most recent adenocarcinoma classification[5] due to their major clinical, radiological, pathologic, genetic, and staging differences.[12] IMA tumor cells are goblet or columnar cells and contain intracytoplasmic mucin.[12] Biopsy can be nondiagnostic, as the alveolar spaces at the tumor periphery can be filled entirely with mucin and therefore no cells.[51] A lepidic growth pattern with microscopic skip lesions is a characteristic of IMAs, which may show the same heterogeneous mixture of lepidic, acinar, papillary, micropapillary, and solid growth patterns as INVs.[51] IMAs also have distinct molecular make-ups. Kirsten rat sarcoma (KRAS) viral oncogene driver mutations are seen in up to 86%.[51] Conversely, epidermal growth factor receptor (EGFR) mutations are very rare.[12] At imaging, IMAs can present with multicentric opacities in one lobe or multiple lesions in one or both lungs. IMAs may appear as solid,

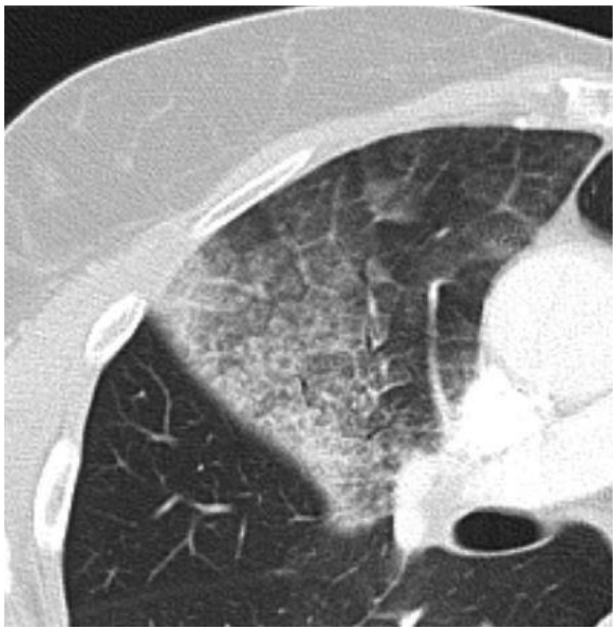


Figure 9 36-year-old woman with IMA appearing as airspace opacity, both GGO and consolidation. IMA, invasive mucinous adenocarcinoma.

subsolid nodules, or as airspace opacities, and they can mimic pneumonia (pneumonic-type adenocarcinomas, Fig. 9).[51,52] IMAs have been associated with a high recurrence rate[8] which has been hypothesized to be due to tumor cells traveling through the abundant mucin in a pattern similar to STAS.[51] The "CT angiogram" sign, which is the ability to see

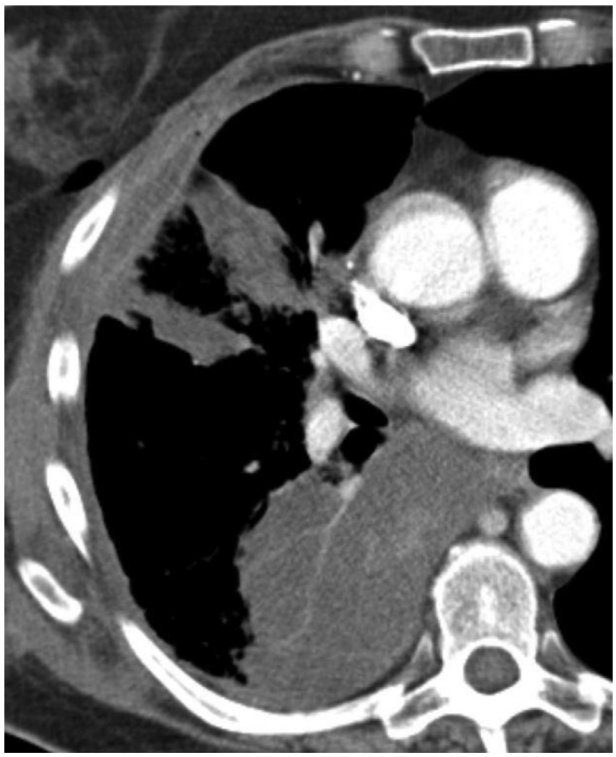


Figure 10 68-year-old woman with IMA. Right lower lobar consolidation demonstrates the "CT angiogram sign" with enhancing vessels seen in the consolidation.

normal pulmonary vasculature within parenchymal consolidations (Fig. 10) was initially thought to be specific for IMA,[53] but subsequent studies found it unhelpful in distinguishing IMA from other causes of airspace opacities including infectious pneumonia, postobstructive pneumonitis, passive atelectasis, and pulmonary lymphoma.[54]

Colloid adenocarcinomas (which also contain abundant amounts of mucin), fetal, and enteric subtypes of invasive adenocarcinoma are rare and do not have well-described distinguishing imaging features.[12]

Genomics

While smoking is the main risk factor for lung cancer, up to 25% of lung cancer patients are never-smokers; this is especially evident in women with adenocarcinoma.[32] In these patients, other risk factors including genetic alterations play a major role. Genetic alterations are necessary for all oncogenesis. These alterations may be inherited or acquired through errors in copying DNA, also known as "somatic genomic alterations".[32] Those somatic genomic alterations that are causing carcinogenesis are known as "driver" alterations, whereas those that are not, are called "passenger" alterations.[32] Recent progress in gene sequencing technologies has led to the identification of several driver genes which play a significant role in lung carcinogenesis.[55] Of note, many of these genetic alterations are seen in AAH, AIS, and MIA and support the hypothesis of a stepwise continuum for lung adenocarcinoma.[13] Molecular-targeted therapies against driver gene aberrations have dramatically changed the treatment strategies for malignant tumors and are considered first-line agents when these drivers are identified.[55]

The EGFR gene encodes proteins that belong to the cell-surface tyrosine kinase receptor family. In 2004, EGFR mutations were described which lead to activation of oncogenic signaling pathways.[10] EGFR is mutated in 10%-16% of cases of lung adenocarcinoma and is more prevalent in Asian populations and nonsmoking women, present in up to 60% of cases of adencarcinoma.[32] A majority of EGFR mutations sensitize tumors to first generation tyrosine kinase inhibitors (TKI) erlotinib and gefitinib.[10] Gene rearrangements involving anaplastic lymphoma kinase and encoding tyrosine-protein kinase ROS1, as well as mutations of mesenchymal-epidermal transition oncogene, are susceptible to the TKI Crizotinib.[10,32,55] These are rare but exclusively found in lung adenocarcinoma and enriched in young female light smokers.[10] Genetic alterations in Kirsten rat sarcoma viral oncogene (the earliest described lung cancer driver), v-Raf murine sarcoma viral oncogene, and others are potential targets for targeted molecular therapy and are currently being investigated.[55] Currently, it is recommended that all patients with advanced lung adenocarcinoma should undergo testing for *EGFR* mutations, anaplastic lymphoma kinase,[6] and encoding tyrosine-protein kinase ROS1 rearrangements irrespective of smoking history.[10] Further molecular testing can also be performed in individual cases, for example young nonsmokers with lung adenocarcinoma.[10]

Another type of targeted therapy called immunotherapy blocks immune checkpoint proteins such as programmed death-ligand 1/programmed cell death protein 1 (PD-L1/PD-1).[10] PD-L1/PD-1 limit the body's immune system to avoid excessive tissue damage from T cells.[32] PD-1 is an inhibitory receptor expressed on activated T cells. PD-L1 that is overexpressed by tumors binds PD-1 preventing an inflammatory response and thereby protecting the tumor from the immune system.[32] PD-L1/PD-1 inhibitor drugs target this pathway. Three of these medications have been approved for the treatment of advanced-stages of nonsmall cell lung carcinoma (NSCLC): Nivolumab, pembrolizumab, and atezolizumab.[32]

Radiogenomics is an area in clinical research that aims to correlate the imaging appearance of tumors with molecular markers with the goal of identifying targeted therapies without the need for invasive samples, but the field is still in its early stages.[20]

Progression Through the Adenocarcinoma Spectrum

Adenocarcinoma spectrum lesions, particularly when presenting as pGGNs on CT, are frequently slow-growing[56] with volume-doubling times between 265 and 887 days.[34] Follow-up imaging over a prolonged timeframe[22] and surgical treatment of a potentially indolent disease have raised the question of overdiagnosis.[57] However, a subset of adenocarcinoma spectrum lesions that demonstrate early imaging appearances similar to indolent lesions will progress more rapidly and be associated with a worse prognosis.[8]

The imaging characteristics that predict the likelihood of growth in a suspected adenocarcinoma lesion are namely size and solid components.[58] The pGGNs measuring 5mm or less, often thought to represent small foci of AAH, have a very low likelihood of growth.[22] In a study of 438 solitary pGGNs measuring 5mm, 10% grew and 1% developed into MIA or INV over a mean follow-up of 3.6 years.[34] The Fleischner society does not recommend routine follow-up imaging for solitary pGGNs or PSNs measuring less than 6mm.[22] PSNs with a solid component of 5mm or less have been found to have a probability of growth of 17% and 48% at 2 and 5 years, respectively. While lesions in this group that grow are likely to be MIA or INV, no survival disadvantage has been demonstrated with a "follow-up until interval growth" approach. A study compared outcomes in patients with PSNs containing a solid component of 5mm or less who had immediate resection vs those who had resection after a period of imaging surveillance during which the nodule grew. No significant difference in the recurrence-free survival and overall survival was identified,[58] and this study also found that pGGN nodule size of >10mm and PSN size of >8mm were associated with a higher likelihood of growth.[58] PSNs with a solid component greater than 5mm have the highest likelihood of growth.[22]

Staging and Tumor Measurement

Recently, the International Association for the Study of Lung Cancer made a number of proposals for changes to T categories in subsolid nodules for the eighth edition of the Tumor, Node, and Metastasis (TNM) Classification of Lung Cancer, partly to address several new entities described in the most recent WHO classification of adenocarcinoma.[59] Proposals are as follows. The T descriptor of Tis (AIS) for AIS should be used to distinguish it from TIS (SCIS), now that lung *in situ* carcinoma can be either AIS or squamous cell carcinoma *in situ* (SCIS).[59] In addition, MIA of the lung should be classified as T1mi. Use of the size of the invasive component to determine the T descriptor size is recommended.[59] While the Fleischner Society recommends using an average diameter,[24] for T staging purposes, the TNM system uses the single largest dimension measured on thin CT sections and multiplanar reconstructions. For pathologic TNM assessment, although 3-dimensional measurements are frequently recorded in pathology reports, the single maximum diameter is traditionally (Fig. 7). For a PSN, the solid component if >3mm should also be recorded.[59] As CT features are not definitive for diagnosis or measurement of a tumor, the suspected diagnosis and clinical staging should be regarded as a preliminary assessment that is subject to revision after pathologic evaluation.[59]

Mucinous adenocarcinomas (including mucinous AIS, MIA, IMA, and colloid adenocarcinoma) are addressed separately. IMAs appear as pneumonic-type adenocarcinomas with multilobar involvement and poorly-demarcated borders.[35] New proposals recommend using standard size measurements if there is one site of pulmonary involvement in a single lobe. Lesions are considered T3, if the disease is difficult to measure but confined to a single lobe; T4, if multiple lobes of the same lung are involved; and M1a, if involving both lungs.[35,59]

Surgery

Lobectomy and mediastinal node dissection have been considered the gold standard for the treatment of all stage 1A for NSCLC as a result of the only randomized controlled trial performed by The Lung Cancer Study Group (LCSG) in 1995 comparing lobectomy and limited resection (wedge resection or anatomical segmentectomy) in patients with T1N0 NSCLC. They found a significantly reduced 5-year survival rate (56%vs 73%), a lower freedom from recurrence rate (62%vs 78%), and 3-fold increase in local recurrence rates (5.4%vs 1.9%) in the limited resection arm.[60,61] Limited resections have the advantage of preservation of lung function in patients with poor pulmonary function tests and synchronous or metachronous adenocarcinoma spectrum lesions.[61] Recently, there has been a trend toward sublobar resections based on improved techniques, better understanding of tumor biology and retrospective studies showing similar outcomes for both lobectomy and sublobar resection.[62] A study of 2008 patients over 65 years of age who had resection of T1a lung adenocarcinoma showed similar outcomes

for lobectomy and segmentectomy.[63] However, those who had wedge resections had worse outcomes.[63]

Radiologists can play a role in surgical planning with precise description of tumor size, location, and relevant anatomical considerations. While segmentectomy can be performed for central tumors, most tumors evaluated in studies supporting sublobar resections have been peripherally located within the outer third of the lung.[62] Tumors considered for segmentectomy should be confined to the anatomic segmental boundaries without crossing intersegmental planes.[62] There is no clear consensus on this topic[64] for many reasons, for example, histological factors that may not be recognized before resection such as the presence of STAS[65] or small amounts of micropapillary pattern of tumor[66] have been shown to significantly increase the likelihood of recurrence in those undergoing sublobar resections compared to lobectomy. Randomized trials are currently in progress to clarify this issue.[67,68]

Conclusion

The study of the lung adenocarcinoma spectrum has undergone dramatic changes. Various histological subtypes of adenocarcinoma are now organized into a spectrum ranging from indolent preinvasive lesions to aggressive forms of INV with poor prognosis. Research has focused on the integration of molecular and genetic analysis of adenocarcinomas into the diagnosis and treatment of lung adenocarcinoma resulting in the proliferation of novel targeted therapies. Studies have shown correlation between imaging findings in lung adenocarcinoma, histologic features, and patient prognosis. A good understanding of the pathologic subtypes of the lung adenocarcinoma spectrum in terms of histological and imaging features, their pattern of growth on imaging, management, staging and tumor genetics is essential in the diagnosis and treatment of patients with lung adenocarcinoma.

References

1. Torre LA, Siegel RL, Jemal A: Lung cancer statistics. Adv Exp Med Biol 893:1-19, 2016
2. Travis WD, Brambilla E, Noguchi M, et al: International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: International multidisciplinary classification of lung adenocarcinoma: Executive summary. Proc Am Thorac Soc 8:381-385, 2011
3. Meza R, Meernik C, Jeon J, et al: Lung cancer incidence trends by gender, race and histology in the United States, 1973-2010. PloS One 10: e0121323, 2015
4. Lortet-Tieulent J, Soerjomataram I, et al: International trends in lung cancer incidence by histological subtype: Adenocarcinoma stabilizing in men but still increasing in women. Lung Cancer 84:13-22, 2014
5. Travis WD: Cancer IAfRo. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. International Agency for Research on Cancer, 2015
6. Travis WD, Brambilla E, Nicholson AG, et al: The 2015 World Health Organization classification of lung tumors: Impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac oncol 10:1243-1260, 2015
7. Vazquez M, Carter D, Brambilla E, et al: Solitary and multiple resected adenocarcinomas after CT screening for lung cancer: Histopathologic features and their prognostic implications. Lung Cancer 64:148-154, 2009
8. Yoshizawa A, Motoi N, Riely GJ, et al: Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: Prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Mod Pathol 24:653-664, 2011
9. Aoki T, Tomoda Y, Watanabe H, et al: Peripheral lung adenocarcinoma: Correlation of thin-section CT findings with histologic prognostic factors and survival. Radiology 220:803-809, 2001
10. Sholl L: Molecular diagnostics of lung cancer in the clinic. Transl Lung Cancer Res 6:560-569, 2017
11. Noguchi M, Morikawa A, Kawasaki M, et al: Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer 75:2844-2852, 1995
12. Travis WD, Brambilla E, Noguchi M, et al: International Association for the Study Of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 6:244-285, 2011
13. Inamura K: Clinicopathological characteristics and mutations driving development of early lung adenocarcinoma: Tumor initiation and progression. Int J Mol Sci 19(4):1259, 2018
14. Lee HY, Choi YL, Lee KS, et al: Pure ground-glass opacity neoplastic lung nodules: Histopathology, imaging, and management. AJR Am J Roentgenol 202:W224-W233, 2014
15. Hansell DM, Bankier AA, MacMahon H, et al: Fleischner Society: Glossary of terms for thoracic imaging. Radiology 246:697-722, 2008
16. Godoy MC, Naidich DP: Subsolid pulmonary nodules and the spectrum of peripheral adenocarcinomas of the lung: Recommended interim guidelines for assessment and management. Radiology 253:606-622, 2009
17. Yankelevitz DF, Yip R, Smith JP, et al: CT Screening for lung cancer: Nonsolid nodules in baseline and annual repeat rounds. Radiology 277:555-564, 2015
18. Henschke CI, Yankelevitz DF, Mirtcheva R, et al: CT screening for lung cancer: Frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 178:1053-1057, 2002
19. Suzuki K, Asamura H, Kusumoto M, et al: "Early" peripheral lung cancer: Prognostic significance of ground glass opacity on thin-section computed tomographic scan. Ann Thorac Surg 74:1635-1639, 2002
20. Cohen JG, Reymond E, Jankowski A, et al: Lung adenocarcinomas: Correlation of computed tomography and pathology findings. Diagn Interv Imaging 97:955-963, 2016
21. Cohen JG, Goo JM, Yoo RE, et al: Software performance in segmenting ground-glass and solid components of subsolid nodules in pulmonary adenocarcinomas. Eur Radiol 26:4465-4474, 2016
22. MacMahon H, Naidich DP, Goo JM, et al: Guidelines for management of incidental pulmonary nodules detected on CT images: From the Fleischner Society 2017. Radiology 284:228-243, 2017
23. Henschke CI, Yankelevitz DF, McCauley DI, et al: Guidelines for the use of spiral computed tomography in screening for lung cancer. Eur Respir J Suppl 39:45s-51s, 2003
24. Bankier AA, MacMahon H, Goo JM, et al: Recommendations for measuring pulmonary nodules at CT: A statement from the Fleischner Society. Radiology 285:584-600, 2017
25. Goodman LR, Gulsun M, Washington L, et al: Inherent variability of CT lung nodule measurements in vivo using semiautomated volumetric measurements. AJR Am J Roentgenol 186:989-994, 2006
26. Ko JP, Suh J, Ibidapo O, et al: Lung adenocarcinoma: correlation of quantitative CT findings with pathologic findings. Radiology 280:931-939, 2016
27. van Riel SJ, Sanchez CI, Bankier AA, et al: Observer variability for classification of pulmonary nodules on low-dose CT images and its effect on nodule management. Radiology 277:863-871, 2015
28. de Hoop B, Gietema H, van de Vorst S, et al: Pulmonary ground-glass nodules: Increase in mass as an early indicator of growth. Radiology 255:199-206, 2010
29. Si MJ, Tao XF, Du GY, et al: Thin-section computed tomography-histopathologic comparisons of pulmonary focal interstitial fibrosis, atypical

adenomatous hyperplasia, adenocarcinoma in situ, and minimally invasive adenocarcinoma with pure ground-glass opacity. Eur J Radiol 85:1708-1715, 2016
30. Lim HJ, Ahn S, Lee KS, et al: Persistent pure ground-glass opacity lung nodules >/= 10 mm in diameter at CT scan: histopathologic comparisons and prognostic implications. Chest 144:1291-1299, 2013
31. Kim TJ, Goo JM, Lee KW, et al: Clinical, pathological and thin-section CT features of persistent multiple ground-glass opacity nodules: Comparison with solitary ground-glass opacity nodule. Lung Cancer 64:171-178, 2009
32. Chalela R, Curull V, Enriquez C, et al: Lung adenocarcinoma: From molecular basis to genome-guided therapy and immunotherapy. J Thorac Dis 9:2142-2158, 2017
33. Nakahara R, Yokose T, Nagai K, et al: Atypical adenomatous hyperplasia of the lung: A clinicopathological study of 118 cases including cases with multiple atypical adenomatous hyperplasia. Thorax 56:302-305, 2001
34. Kakinuma R, Muramatsu Y, Kusumoto M, et al: Solitary pure ground-glass nodules 5mm or Smaller: Frequency of growth. Radiology 276:873-882, 2015
35. Raptis CA, Robb CL, Bhalla S: Tumor staging of lung cancer: Essential concepts for the radiologist. Radiol Clin North Am 56:391-398, 2018
36. Lee SM, Park CM, Goo JM, et al: Invasive pulmonary adenocarcinomas versus preinvasive lesions appearing as ground-glass nodules: Differentiation by using CT features. Radiology 268:265-273, 2013
37. Kadota K, Villena-Vargas J, Yoshizawa A, et al: Prognostic significance of adenocarcinoma in situ, minimally invasive adenocarcinoma, and nonmucinous lepidic predominant invasive adenocarcinoma of the lung in patients with stage I disease. Am J Surg Pathol 38:448-460, 2014
38. Behera M, Owonikoko TK, Gal AA, et al: Lung adenocarcinoma staging using the 2011 IASLC/ATS/ERS classification: A pooled analysis of adenocarcinoma in situ and minimally invasive adenocarcinoma. Clin Lung Cancer 17:e57-e64, 2016
39. Fujita A, Kameda Y, Goya T: Clinicopathology of stromal invasion in lung adenocarcinoma. Pathol Int 59:1-6, 2009
40. Kakinuma R, Noguchi M, Ashizawa K, et al: Natural history of pulmonary subsolid nodules: A prospective multicenter study. J Thorac Oncol 11:1012-1028, 2016
41. Lee SM, Goo JM, Lee KH, et al: CT findings of minimally invasive adenocarcinoma (MIA) of the lung and comparison of solid portion measurement methods at CT in 52 patients. Eur Radiol 25:2318-2325, 2015
42. Boland JM, Froemming AT, Wampfler JA, et al: Adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive pulmonary adenocarcinoma—analysis of interobserver agreement, survival, radiographic characteristics, and gross pathology in 296 nodules. Hum Pathol 51:41-50, 2016
43. Kadota K, Nitadori J-i, Sima CS, et al: Tumor spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I lung adenocarcinomas. J Thorac Oncol 10:806-814, 2015
44. Borczuk AC: Prognostic considerations of the new World Health Organization classification of lung adenocarcinoma. Eur Respir Rev 25:364-371, 2016
45. Duhig EE, Dettrick A, Godbolt DB, et al: Mitosis trumps T stage and proposed International Association for the Study Of Lung Cancer/American Thoracic Society/European Respiratory Society classification for prognostic value in resected stage 1 lung adenocarcinoma. J Thorac Oncol 10:673-681, 2015
46. Zhao Y, Wang R, Shen X, et al: Minor components of micropapillary and solid subtypes in lung adenocarcinoma are predictors of lymph node metastasis and poor prognosis. Ann Surg Oncol 23:2099-2105, 2016
47. Hattori A, Matsunaga T, Takamochi K, et al: Oncological characteristics of radiological invasive adenocarcinoma with additional ground-glass nodules on initial thin-section computed tomography: Comparison with solitary invasive adenocarcinoma. J Thorac Oncol 11:729-736, 2016
48. Moon Y, Sung SW, Lee KY, et al: Pure ground-glass opacity on chest computed tomography: Predictive factors for invasive adenocarcinoma. J Thorac Dis 8:1561-1570, 2016
49. Heidinger BH, Anderson KR, Nemec U, et al: Lung adenocarcinoma manifesting as pure ground-glass nodules: Correlating CT size, volume, density, and roundness with histopathologic invasion and size. J Thorac Oncol 12:1288-1298, 2017
50. Zhang Y, Shen Y, Qiang JW, et al: HRCT features distinguishing preinvasive from invasive pulmonary adenocarcinomas appearing as ground-glass nodules. Eur Radiol 26:2921-2928, 2016
51. Cha YJ, Shim HS: Biology of invasive mucinous adenocarcinoma of the lung. Transl Lung Cancer Res 6:508-512, 2017
52. Akira M, Atagi S, Kawahara M, et al: High-resolution CT findings of diffuse bronchioloalveolar carcinoma in 38 patients. AJR Am J Roentgenol 173:1623-1629, 1999
53. Im JG, Han MC, Yu EJ, et al: Lobar bronchioloalveolar carcinoma: "Angiogram sign" on CT scans. Radiology 176:749-753, 1990
54. Shah RM, Friedman AC: CT angiogram sign: incidence and significance in lobar consolidations evaluated by contrast-enhanced CT. AJR Am J Roentgenol 170:719-721, 1998
55. Saito M, Suzuki H, Kono K, et al: Treatment of lung adenocarcinoma by molecular-targeted therapy and immunotherapy. Surg Today 48:1-8, 2018
56. Hasegawa M, Sone S, Takashima S, et al: Growth rate of small lung cancers detected on mass CT screening. Br J Radiol 73:1252-1259, 2000
57. Patz EF Jr., Pinsky P, Gatsonis C, et al: Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med 174:269-274, 2014
58. Lee JH, Park CM, Kim H, et al: Persistent part-solid nodules with solid part of 5mm or smaller: Can the 'follow-up and surgical resection after interval growth' policy have a negative effect on patient prognosis? Eur Radiol 27:195-202, 2017
59. Travis WD, Asamura H, Bankier AA, et al: The IASLC lung cancer staging project: Proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. J Thorac Oncol 11:1204-1223, 2016
60. Ginsberg RJ, Rubinstein LV: Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung cancer study group. Ann Thorac Surg 60:615-622, 1995. discussion 622-613
61. Fiorelli A, Loizzi D, Santini M: Lobar or sublobar resection for stage I lung cancer: That is (still) the question!. J Thorac Dis 10:38-41, 2018
62. D'Andrilli A, Rendina EA: POINT: Should segmentectomy rather than lobectomy be the operation of choice for early-stage non-small cell lung cancer? Yes. Chest 153:590-592, 2018
63. Veluswamy RR, Ezer N, Mhango G, et al: Limited resection versus lobectomy for older patients with early-stage lung cancer: Impact of histology. J Clin Oncol 33:3447-3453, 2015
64. Bertolaccini L, Solli P: COUNTERPOINT: Should segmentectomy rather than lobectomy be the operation of choice for early-stage non-small cell lung cancer? No. Chest 153:592-595, 2018
65. Eguchi T, Kameda K, Lu S, et al: Lobectomy is associated with better outcomes than sublobar resection in spread through air spaces (STAS)–positive T1 lung adenocarcinoma: A propensity score–matched analysis1. J Thorac Oncol: official publication of the International Association for the Study of Lung Cancer 14(1):87-98, 2019
66. Nitadori J-i, Bograd AJ, Kadota K, et al: Impact of micropapillary histologic subtype in selecting limited resection vs lobectomy for lung adenocarcinoma of 2cm or smaller. J Natl Cancer Inst 105:1212-1220, 2013
67. Fox N, Bauer T: CALGB 140503: A randomized phase III trial of lobectomy versus sublobar resection for small (< 2 cm) peripheral non-small cell lung cancer. Oncol Issue 23:20-21, 2008
68. Nakamura K, Saji H, Nakajima R, et al: A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). Jpn J Clin Oncol 40:271-274, 2010