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Radiologic-Pathologic Correlation in Lung Cancer Presenting as a Subsolid Nodule: Room for Improvement?

Annemie Snoeckx[1], Pieter Reyntiens[1], Patrick Pauwels[2], Paul E. Van Schil[3], Maarten J. Spinhoven[1], Paul M. Parizel[1] and Jan P. van Meerbeeck[4]*

[1]Department of Radiology, Antwerp University Hospital and University of Antwerp, Wilrijkstraat, Belgium

[2]Department of Pathology, Antwerp University Hospital and University of Antwerp, Wilrijkstraat, Belgium

[3]Department of Thoracic and Vascular Surgery, Antwerp University Hospital and University of Antwerp, Wilrijkstraat, Belgium

[4]Department of Thoracic Oncology, Antwerp University Hospital and University of Antwerp, Wilrijkstraat, Belgium

Abstract

Pulmonary nodules are a common finding on Computed Tomography (CT) imaging studies. Nodules are becoming more frequently encountered in daily practice due to widespread use of CT and increasing interest in lung cancer screening by low dose CT. In 2011, the term bronchiolo-alveolar carcinoma was abandoned and the new IASLC/ATS/ERS classification system of lung adenocarcinoma and its precursors was introduced. In 2015, this new classification system was adopted by the World Health Organization (WHO). In this new classification findings on histopathology are correlated with imaging studies. This correlation holds imperfections, leaving room for improvement. A correct classification of pulmonary nodules into solid or subsolid is key to precise nodule management. Furthermore, morphological assessment of subsolid nodules is mandatory and essential for follow-up and assessing likelihood of invasiveness. A significant group of lesions that are pure ground glass without a solid component and hence suspicious for Atypical Adenomatous Hyperplasia (AAH) or Adenocarcinoma In Situ (AIS) on imaging grounds, turn out to be invasive adenocarcinoma. Other lesions that are part-solid on CT and suspicious for invasive adenocarcinoma turn out to be only AIS at resection. Moreover, nodule classification and morphological assessment are prone to variability among radiologists. Computer aided techniques and quantitative CT-analysis are on the rise. These techniques will create room for standardization and will make prospective studies regarding radiologic-pathologic correlation in subsolid nodules more precise and reliable. More accurate radiologic-pathologic correlation will lower the risk of over-/underdiagnosis and will aid in optimal patient selection for surgical treatment.

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****Correspondence:***

Annemie Snoeckx, Department of Radiology, Antwerp University Hospital and University of Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium, Tel: + 32 3 821 45 05; Fax: +32 3 821 45 32; E-mail: Annemie.snoeckx@uza.be

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Introduction

Pulmonary nodules are a common finding on Computed Tomography (CT) imaging studies of the chest, with adenocarcinoma being the most frequent encountered histological subtype of lung cancer presenting as pulmonary nodule [1,2]. Pulmonary adenocarcinomas consisted of a large and heterogeneous group of tumors with different types of histological growth patterns. In 2011, the term Bronchiolo-Alveolar Carcinoma (BAC) was abandoned and a new lung adenocarcinoma classification was published by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [3]. This new classification was officially adopted by the World Health Organization (WHO) in 2015 [4]. Although this new classification was mainly based on histological criteria, it was developed in collaboration with clinical, molecular and surgical colleagues as well as radiologists. In this new system, findings on histology were correlated with CT-imaging criteria.

Ground Glass Nodules (GGN) appear on thin section CT-images as hazy increased opacities of lung, with preservation of bronchial and vascular margins. Ground-glass is less opaque than consolidation in which bronchovascular margins are obscured [5]. On histological specimens, this correlates with a lepidic growth pattern, a pattern that is defined as tumor cells proliferating along the surface of intact alveolar walls without stromal or vascular invasion [6]. Lesions that only consist of ground glass are referred to as “pure GGN”. Lesions that include a combination of both ground-glass and solid components (with obscuring the lung architecture) are referred to as “part-solid GGNs”. Both pure GGNs and part-solid GGNs are considered and categorized as “subsolid”

Atypical adenomatous hyperplasia (AAH)	Adenocarcinoma in situ (AIS)	Minimally invasive adenocarcinoma (MIA)	Lepidic predominant adenocarcinoma (LPA)
Nodule size ≤ 5 mm Pure ground glass nodule	Nodule size 6-30 mm Pure ground glass nodue	Nodule size ≤ 30 mm Part-solid nodule with solid component ≤ 5 mm	Nodule size ≤ 30 mm Part-solid nodule with solid component > 5 mm

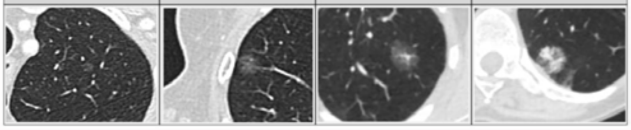

Figure 1: Overview of the radiologic-pathologic correlation of lung adenocarcinoma.

nodules [5].

The 2011, IASLC/ATS/ERS classification defines 4 types of lesions in the adenocarcinoma spectrum in relation to subsolid nodules with a maximum diameter of 3cm: Atypical Adenomatous Hyperplasia (AAH), Adenocarcinoma In Situ (AIS), Minimally Invasive Adenocarcinoma (MIA) and Lepidic Predominant Adenocarcinoma (LPA). Each of these adenocarcinoma subtypes has a CT-image correlate (Figure 1) AAH and AIS are believed to be pre-invasive lesions for lung adenocarcinoma, presenting on CT as pure ground glass lesions. AAH is usually smaller than 5mm and AIS larger than 5mm on any view of the CT image. Both AAH and AIS show no solid component on thin-section CT. AIS can be discretely more opaque than AAH. Neither AAH nor AIS are invasive on histopathology. Any pure ground glass lesion larger than 3cm is considered to be LPA. MIA represents a lesion smaller than 3cm with a solid component (on imaging) and invasive component (on histopathology) of 5mm or smaller. LPA is a subsolid lesion that is also not larger than 3cm with a solid or invasive component of more than 5mm [3,4].

Nowadays, ground glass and part-solid nodules are more frequently encountered in daily practice than years ago. It is unclear if this is only a perception or that this represents a real increase in incidence. The widespread use of CT in clinical practice and the use of multidectector CT-scanners with finer CT collimation certainly are important factors for the increase in detection of subsolid nodules. Furthermore, numerous large lung cancer screening trials have been initiated in the past 10 to 15 years. These trials have given more insight in the incidence, evolution and prognosis of these adenocarcinoma precursors. In the Early Lung Cancer Action Project (ELCAP), 2892 part-solid lesions were found among 5% of 57,496 participants [7]. In the National Lung Cancer Screening Trial (NLST), which is the largest randomized lung cancer screening trial, 9.4% of 26,722 participants presented with one or more subsolid nodules [8]. In the first round of the large Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON), 2.0% of the total of 8673 nodules found in 7557 participants were subsolid nodules (both pure ground glass and part-solid) [9]. Although the incidence of subsolid nodules is significantly lower than that of solid nodules and masses, these lesions cannot be ignored and pose future challenges.

A correct classification of pulmonary nodules is important since the likelihood of malignancy is larger in subsolid nodules compared to solid nodules [10]. Since subsolid nodules have a different prognosis than solid nodules, they require a different management approach. Moreover, invasive adenocarcinomas are more aggressive than adenocarcinoma precursor lesions [8,11]. The size (or absence) of a solid component on CT is correlated with the prevalence of an invasive component and is therefore crucial for clinical decision guidance. Furthermore survival in subsolid lesions depends on the invasive (or solid) component and not on the lepidic (or ground glass) component [12-16]. For this reason in the 8th edition of the TNM classification only the solid part is considered to measure the size of a lesion and determine the T descriptor [17]. The largest unidimensional size is measured using the lung window setting on chest CT scan.

Current guidelines for management and follow-up of subsolid lesions are fully based on CT-imaging criteria. When assessing the morphology of subsolid nodules, it is important to characterize these lesions on contiguous thin sections (preferably 1.0mm or less than 1.5mm) and to evaluate the evolution comparing the lesions with the oldest images available. In routine practice, the morphology of lesions is visually assessed by a radiologist and measurement of both the solid component and the lesion size is mainly done by manual electronic caliper measurement. The border of the whole lesion as well as the border between the solid component and ground glass component is often hazy, making measuring a difficult task and making reproducible measurements inaccurate.

To deal with the lack of detailed consideration of subsolid lung nodules in the 2005 Fleischner guidelines [18], specific recommendations for the management of subsolid pulmonary nodules detected at CT, were published in 2013 [19]. These guidelines were updated for both solid and subsolid nodules in 2017 [20]. The British Thoracic Society also incorporated specific recommendations for subsolid nodules in its guidelines for the investigations and management of pulmonary nodules, published in 2015 [21]. Furthermore, the 8th edition of the TNM staging classification of lung cancer, provides new criteria for cases presenting as multiple nodules with ground glass or lepidic features [22]. This new staging classification is based on CT-imaging findings of subsolid nodules. To address the need of a dedicated classification system for lung nodules in the era of lung cancer screening, the American College of Radiologists (ACR) proposed the Lung-RADS™ or lung imaging reporting and data system [23]. Subsolid nodules are incorporated in this management and follow-up scheme, which is widely used in the United States where – in contrast to Europe- lung cancer screening is already embedded in daily practice.

All these guidelines and criteria are based on the theoretical radiologic-pathologic correlation of this adenocarcinoma sequence, having a major impact on management of subsolid nodules.

Six years after the publication of the new IASLC/ATS/ERS classification guidelines, this new classification and the radiologic-pathologic correlation have certainly found their way into routine clinical practice. Numerous issues however remain of which some will be addressed in this article.

Theoretical Model

As discussed, there is a general correlation between imaging appearance and histopathologic diagnosis. This model however is theoretical, imperfect and not prospectively validated. Substantial overlaps of imaging features of AAH, AIS, MIA and invasive lung adenocarcinoma exist. To illustrate, we present 3 cases from a non-screening setting where the radiologic-pathologic correlation was not accurate and adenocarcinoma subtype on pathology was different than expected on imaging.

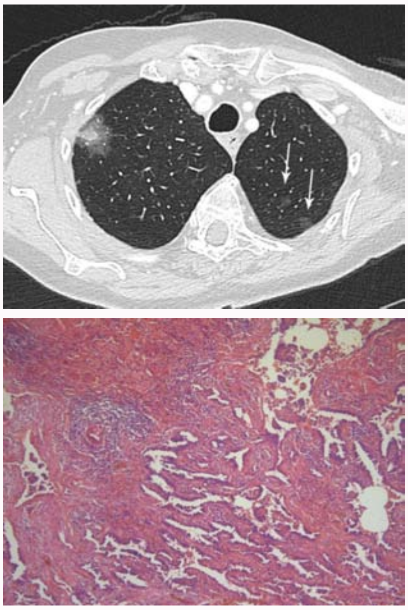

Figure 2: Axial CT in lung window setting (A) shows subsolid lesions in the upper lobes of both lungs. Note the large subsolid lesion in the right upper lobe and numerous pure ground glass nodules (white arrow) in the left upper lobe. Photomicrograph (B) shows predominantly adenocarcinoma in situ. However, fibrotic areas with individual acinar structures and a desmoplastic reaction suggest invasion (H-E stain; original magnification, x 20).

Case 1: An 82-year-old woman presented with a non-productive cough for more than 1 year. Chest CT (Figure 2) showed a subsolid nodule in the right upper lobe with a 17mm area of ground glass (with relatively high attenuation) and solid component of 14mm. Also note the small pure ground glass lesions in the left upper lobe (white arrows). The size and morphology of the subsolid lesion was suspicious for diagnosis of invasive adenocarinoma with lepidic component. The histopathology specimen after wedge excision showed findings consistent with minimally invasive adenocarcinoma. Both lesions in the left upper lobe correlate on imaging with AAH and AIS since they are pure ground glass nodules. Long term follow-up of these lesions is foreseen.

Case 2: A 70-year old man with previous surgery for a 1.3cm well-differentiated invasive adenocarcinoma (Figure 3A) in the right upper lobe presented during follow-up with a persistent subsolid lesion in the left upper lobe. CT examination 4 years after the initial surgery showed a 22mm large subsolid lesions with 18mm solid component and surrounding ground glass aspect (Figure 3B) in the left upper lobe. The imaging appearance of this new persistent subsolid lesion was suspicious for an invasive adenocarcinoma with lepidic growth. Histopathology after complete resection of the nodule could not reveal any invasive focus and diagnosis of Adenocarcinoma In Situ (AIS) was made.

Case 3: In a 63-year-old man in whom a chest CT was performed for persistent cough, a solid nodule (Figure 4) in the apex of the left lower lobe with minor lobulation and no clear spiculated morphology was discovered. Although this lesion did not show any ^{18}F-Fluorodexocyglucose (FDG) uptake on Positron Emission Tomography (PET), the multidisciplinary tumor board found it suspicious for primary lung cancer, mainly because of the pleural indentation (white arrow). Although the lesion had a complete solid appearance with absolutely no areas of ground glass, diagnosis of

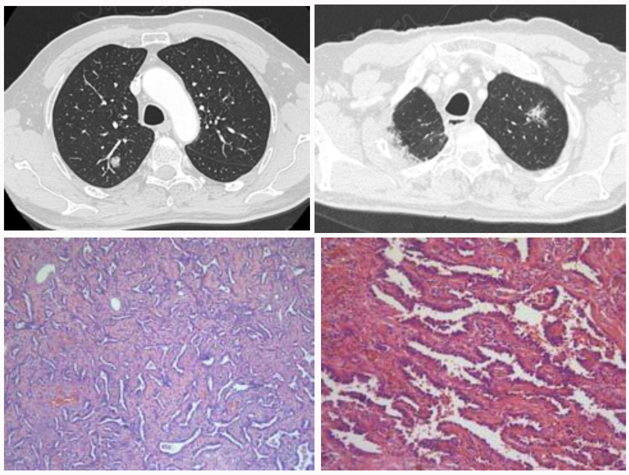

Figure 3: Axial CT in lung window setting (A) shows a solid nodule with discrete bubble like lucencies in the right upper lobe. Chest CT examination 4 years later shows a new but persistent subsolid nodule (B) in the left upper lobe. Photomicrograph (C,D) shows adenocarcinoma in situ with neoplastic cells that appear monotoneous, growing along intact alveolar septa. The nuclei are enlarged with mild cytologic atypica. The cells show nuclear overlapping. (H-E stain; original magnification, x 20 (C), x 40 (D)).

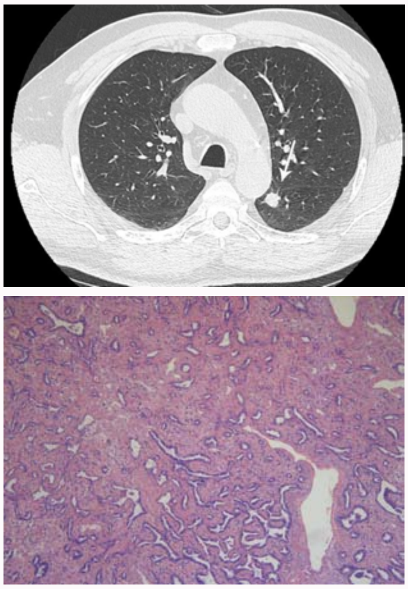

Figure 4: Axial CT in lung window setting (Figure 4A) shows a solid nodule in the apex of the left lower lobe. The nodule shows minor lobulation but no spiculation. The nodule is purely solid without signs of ground glass component. Photomicrograph (B) shows a predominant lepidic pattern (right part of the image) but areas of acinar growth are also present (left part of the image) (H-E stain; original magnification, x 20).

predominant lepidic adenocarcinoma was made after lobectomy.

Numerous studies have looked into the Radiologic-Pathologic Correlation (REF). Some of them correlate well with this model, others do not. In a group of 300 lesions, Honda “et al”. [24] found no invasive adenocarcinomas in the group of air-containing type nodules (nodules with AIS or MIA morphology on imaging): 20.8% of AIS lesions on pathology had a solid component on CT. In a retrospective study, 5mm was the highest solid component size threshold with a sensitivity of 100% [23]. This means that in patients undergoing resection for a ‘suspicious’ subsolid nodule, a solid component of less than 5mm enabled to rule out the presence

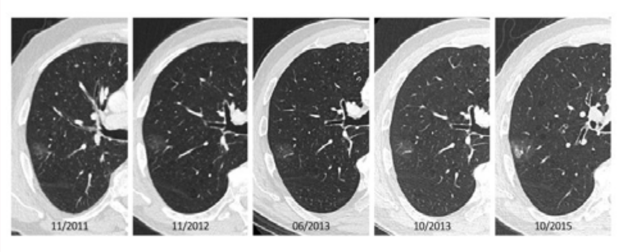

Figure 5: Four year follow-up in a 72-year-old man with a previous history of an oropharyngeal squamous cell carcinoma and lobectomy for 0.8cm invasive adenocarcinoma in the left upper lobe. Follow-up chest CT's show a pure ground glass lesion in the right upper lobe. Over a period of 3 years, the lesion did not change morphologically. After 4 years, suddenly the ground glass component enlarged and a solid component of 15mm was noted. Histopathology after resection showed a 21mm well-differentiated adenocarcinoma with areas of lepidic growth.

of invasive adenocarcinomas [25]. A retrospective study of surgically resected lesions showed in a white (non-Asian) population that in the group of pure ground glass lesions, 38.4% of lesions were invasive adenocarcinoma [24]. In the group of part-solid nodules (with significant solid component) 6.7% of lesions were adenocarcinoma in situ and 10.0% minimally invasive adenocarcinoma. In the group of pure solid lesions, 7.1% of lesions were in situ adenocarcinoma en 42.9% of lesions minimally invasive adenocarcinoma [26]. Eguchi "et al". [27] retrospectively investigated 101 pure ground glass lesions and found half of cases exhibited a pathological invasive area. Moreover a quarter of resected pure GGNs were diagnosed as invasive adenocarcinomas. These lesions were larger in size (>11 mm with sensitivity of 95.8%) and in general had an higher overall density. A small study by Lee "et al". [28] showed that MIA appeared as pure GGNs in one third of cases (5 out of 15) and presented as part-solid GGNs (with small central solid component) in two thirds of cases (10 out of 15).

So, a significant group of lesions that are pure ground glass without solid component, turn out to be invasive adenocarcinoma and some subsolid lesions turn out to be AIS and show no invasive focus.

Lack in Observer Agreement for Classifying Nodules

As mentioned, guidelines are based on morphologic criteria on CT. Once a nodule (solid or subsolid) is categorized, different guidelines and follow-up schemes apply. As nodule management is based on a visual assessment, how accurate is the radiologist in defining the morphology of a nodule? The factors that affected inter-and intra-observer agreement regarding the classification of pulmonary nodules on low-dose CT images were analyzed [27] in a retrospective series. A moderate overall interobserver agreement (mean κ, 0.51) to categorize nodules into solid, part solid with a solid component 5mm or larger of less than 5mm, and pure ground glass, was reported. Disagreement was mainly related to either the presence of a solid component in part-solid nodules or the size of this solid component relative to the 5mm threshold, which are all crucial criteria in different management protocols [29]. A retrospective study on NLST-data by Singh "et al". [30] also showed moderate to substantial reader agreement on nodule growth and screening result, and low reader agreement for changes in attenuation and margins. Penn "et al". [31] investigated the inter-reader variability of applying the Fleischner guidelines for potential subsolid lung nodules. They found only moderate inter-reader variability in particular regarding the fit of subsolid nodule criteria and whether a solid component was present. It may seem evident that expertise is important, but even among experienced thoracic radiologists, inter-and intra-observer agreement in differentiating solid from subsolid nodules on CT is variable [32].

Pathology is believed to be the 'golden standard', but if observer variability applies for radiologists, the same is true for pathologists. Thunnissen "et al". [33] provided strong evidence that in adenocarcinomas, a 'predominant pattern' for subtyping invasive adenocarcinoma could be reproduced with high concordance among pathologists [31]. Recognition of the adenocarcinoma in-situ pattern was more problematic [33]. On the contrary, a recent study showed good agreement between observers when classifying tumors as AIS, MIA and IA [32]. This study however was conducted in a large volume practice with dedicated sub specialization and high level of expertise in this subject [34]. It might be assumed that results would have been different when applied to a more general pathology practice.

Possible consequences

The preoperative prediction of invasiveness is crucial in the management of subsolid nodules, as these show different natural histories: some nodules grow, some remain stable and grow after a short period of time and others start to grow after many years (Figure 5). Until today, the behavior of these subsolid nodules remains unclear. In a prospective study, the natural course of subsolid nodules was evaluated. A total of 1229 subsolid nodules were included with a mean prospective follow-up period of 4.3 years. Among the 1046 pure GGNs, 1.2% developed into heterogeneous GGNs and 5.4% into part-solid nodules. Among the 81 heterogeneous GGNs, 19.8% developed into part-solid nodules. Invasive adenocarcinomas were diagnosed only among the part-solid nodules, corresponding to 1% of all 1229 subsolid nodules [35]. Lung cancers associated with these subsolid nodules have a high survival rate leading to concern about risk for overdiagnosis. Adenocarcinomas manifesting as subsolid nodules have longer volume doubling times compared to solid nodules. Currently, there are no validated biomarkers or imaging features available to predict growth or invasiveness. Lee "et al". [36] found that a history of prior lung cancer, a part-solid aspect and the diameter of subsolid nodules were significant predictors for the growth of subsolid nodules with solid parts smaller or equal than 5mm. Matsuguma "et al". [37] retrospectively correlated the growth of subsolid nodules with the type of subsolid nodule, initial nodule size and history of lung cancer. They found that a nodule size of more than 10mm and a history of prior lung cancer were significant predictive factors of growth in nonsolid nodules.

Some pure ground glass lesions might never become a part-solid nodule and some part-solid nodules might never evolve to an invasive carcinoma. This low radiologic-pathologic correlation of subsolid nodules hampers the search for biomarkers for growth and invasiveness.

In addition to a risk of overdiagnosis, there is also a risk of underdiagnosis. Part-solid nodules are prone to rigorous long-term follow-up. When a solid component of more than 5mm is seen and the lesion is evolving over time, surgery is recommended. In contrast, pure ground glass lesions are not generally resected but followed until they significantly grow or a solid component appears. As previously mentioned, there are pure ground glass lesions that are not AAH or AIS, but show an invasive component on pathological examination. There currently are no biomarkers to predict invasiveness in pure ground glass lesions. The clinical impact and impact on survival is unclear and difficult to estimate, especially since these lesions have an indolent nature.

Assessment of invasiveness is key to selection of management and patient selection for surgery [38]. Preoperative classification of the subtype is essential for patient management. Whereas lobectomy remains the standard of care for stage I invasive adenocarcinoma, lesser resections can be a valid alternative in patients presenting with part-solid nodules. Numerous uncontrolled studies have shown that for small adenocarcinomas, wedge excision or segmentectomy is equivalent to lobectomy in terms of cancer-specific survival [39-44]. Sparing lung parenchyma is vital in an elderly population with impaired lung function. Additionally patients presenting with these adenocarcinoma subtype lesions often have multiple ground glass nodules. Since these lesions are likely to become invasive, sparing lung parenchyma is important keeping in mind that future surgeries might be necessary [45]. Overdiagnosis of invasive adenocarcinoma that turns out to be MIA on pathology, will result in unnecessary lobectomies instead of wedge excisions.

Imaging solutions are on the way

What remains a challenge to the human eye and prone to variability might be solved by computer-aided technologies. In radiology, research in the field of quantitative analysis is expanding and certainly will be promising for the future. Correct classification of a nodule into solid or subsolid (pure ground glass or part-solid) is the first step in nodule management but is prone to variability. Jacobs "et al". [46] suggest a potential role for a Computer-Aided Diagnosis (CAD) system in classifying pulmonary nodules. The borders of nodules with a ground glass component are often hazy, making correct measurement challenging and prone to considerable variability. Decrease in dose will increase the noise, leading to an even larger increase in variability or measurement error. Semi-automatic segmentation of nodules and volumetric assessment of both ground glass and solid component might be a first step in standardization [47,48]. As mentioned, some pure ground glass nodules on imaging show an invasive component on histopathology. For the moment, visual assessment cannot differentiate pure GGNs with pathological invasiveness from GGNs that are AAH or AIS on histopathology. Eguchi "et al". [49] found that the mean CT attenuation could be useful in predicting invasive growth in pure GGN's. Nodule characteristics such as ground-glass opacity ratio and tumor disappearance rate might correlate better with the IASLC/ATS/ERS classification than the current radiologic-pathologic correlation. Quantitative analysis of CT imaging metrics such as mass, skewness/kurtosis, attenuation, texture parameters, might be able to differentiate invasive adenocarcinoma from AIS or MIA among lesions that appear as pure GGN with little solid component on CT [51,52]. Chae "et al". [53] showed that texture analysis could be promising to differentiate invasive adenocarcinomas from pre-invasive lesions in subsolid lesions. Iodine mapping may improve early recognition of invasive adenocarcinoma appearing as pure GGN or part-solid nodules with little solid component [54]. Assessing attenuation values might also be able to predict change or rate of growth in subsolid nodules [55]. Measurement of mass in subsolid nodules can enable detection of growth earlier than the human eye can detect discrete increase in density. Moreover, mass measurement is less prone to variability compared to visual assessment [56].

Computer-aided detection and classification, volumetric measurement, texturizing and mass measurement might overcome the problems of variability and are a good step towards a more standardized approach of radiologic-pathologic correlation.

Conclusion

Abandoning the confusing term BAC and introducing the 2011 IASLC/ATS/ERS classification system was a milestone in the standardization of classification lung adenocarcinoma and its precursors. The radiologic-pathologic correlation of subsolid nodules holds imperfections, certainly creating room for improvement. Computer aided techniques and quantitative CT analysis is on the rise and definitely will have an impact on characterization and management of subsolid nodules. Lowering variability and increasing standardization, will make prospective studies regarding radiologic-pathologic correlation in subsolid nodules more accurate and reliable. Computer-aided technologies might also give an insight in the natural course of progression, an area that upon today remains unresolved. Patient care will benefit from early recognition of invasiveness. More accurate radiologic-pathologic correlation will lower the risk of overdiagnosis, will aid in more optimal patient selection for surgical treatment as well as selection of the most beneficial and valid oncological surgical procedure. Quantification and standardization will be fundamental for answering the numerous remaining questions and addressing the uncertainties.

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