GGN.[359] Optimal evaluation of subsolid nodules requires thin-section CT scans (≤3 mm thickness) to assess the solid versus ground-glass components.[359,360]

Radiologic Spectrum According to Histologic Subtype

AAH is the earliest preinvasive lesion for lung adenocarcinoma detectable by thin-section CT. It appears as a small (usually ≤5 mm), GGN (Figure 11).[19,23,129,361–365] AAH characteristically appears as a very faint pure GGN usually measuring ≤5 mm.[130,366] The pure GGN of AAH can be single or multiple.[129,365,367]

AIS is best demonstrated at CT (preferably thin section) and sometimes can be seen on chest radiography. It is a noninvasive lesion and nonmucinous AIS presents typically as a pure GGN (Figure 12) but sometimes as a part solid or occasionally a solid nodule.[19,23,128,131,362,367–370] AIS can be bubble like.[131,365,370,371] Mucinous AIS can appear as a solid nodule or consolidation (Figure 13). The pure GGN of AIS usually appears at thin-section CT as slightly higher attenuation than the very faint GGN of AAH.[130,366,367] AIS also can be single or multiple.[19,128,131,365,370]

MIA is variable in its imaging presentation and is, as yet, not fully described, but a provisional description of the nonmucinous type at thin-section CT is a part-solid nodule consisting of a predominant ground-glass component and a small central solid component measuring 5 mm or less (Figure 14).[47,58] Mucinous MIA (Figure 14) is less common than nonmucinous MIA and appears as a solid or part-solid nodule.[52,93,126] There is an overlap among imaging features of AAH, AIS, and MIA.

Radiology Recommendation 1

When an opacity in the lung adenocarcinoma spectrum is either a pure GGN or part-solid nodule with a predominant ground-glass component, we recommend that the term BAC no longer be used. These tumors should be classified by the new terms: AIS, MIA, and LPA (strong recommendation, low-quality evidence).

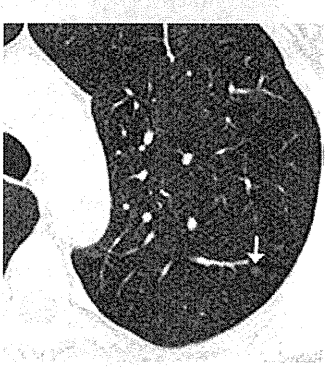

FIGURE 11. CT of preinvasive lesion (AAH or AIS). Axial 2-mm image through the left upper lobe shows a 5 mm pure ground-glass nodule (GGN), which has remained stable for 8 years (arrow). AAH and AIS can be single or multiple. AIS, adenocarcinoma in situ; CT, computed tomography.

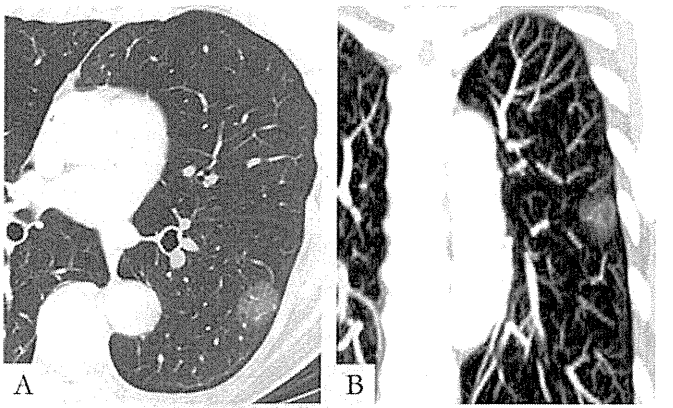

FIGURE 12. CT of a peripheral 2 cm nonmucinous AIS. *A*, Axial CT section. *B*, Coronal maximal intensity projection (MIP) image shows a pure GGN in the left lower lobe. Vessels and lung architecture are seen through the nodule. AIS, adenocarcinoma in situ; CT, computed tomography; GGN, ground-glass nodule.

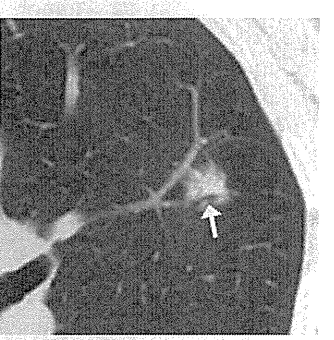

FIGURE 13. CT of mucinous adenocarcinoma in situ; 2 cm predominantly solid nodule with air bronchogram (arrow) is noted in the left upper lobe. CT, computed tomography.

Invasive adenocarcinoma is usually a solid nodule (Figure 15) but may also be part solid (Figure 16) and occasionally a GGN.[23,58,103,125,129–134,367,370–372] A lobar pattern of ground-glass opacity (GGO) may occur (Figure 17). Bubble-like or cystic lucencies in stage IA adenocarcinoma have been described as correlating with well-differentiated tumors[131,132,370,371,373,374] and slow growth.[132,374] Thick (≥2 mm) coarse spiculation has been associated with lymph node metastasis, vascular invasion, and decreased survival post resection.[23,375] For stage IA adenocarcinoma presenting as a part-solid nodule, an extensive ground-glass component suggests a favorable prognosis.[18,20,23,103,105,376–388] Histologically, the ground-glass component typically corresponds to a lepidic pattern and the solid component to invasive patterns. An intratumoral air bronchogram usually indicates a well-differentiated tumor.[132,370,375,387] Absence of pleural retraction for stage IA adenocarcinoma is also a favorable prognostic sign.[375,389] In solid adenocarcinomas, the presence of notches, or concave cuts on thin section CT, has been associated with poor differentiation on histology and adverse outcome.[390]

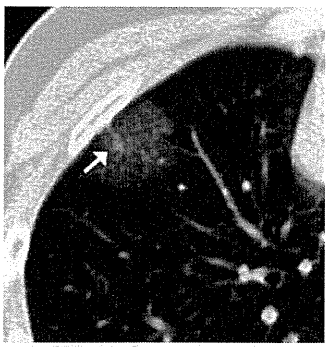

FIGURE 14. CT of nonmucinous minimally invasive adenocarcinoma. Axial 2-mm CT section shows a peripheral, predominantly ground-glass, part-solid nodule in the right upper lobe that includes a 4 × 3 mm solid component (arrow), which corresponded to invasion by pathology. CT, computed tomography.

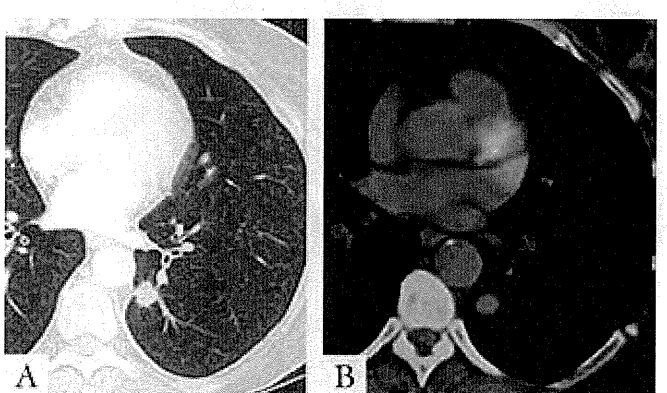

FIGURE 15. CT and FDG-PET of invasive adenocarcinoma. *A*, Axial CT image and (*B*) FDG-PET images show a 2-cm spiculated hypermetabolic solid nodule in the left lower lobe. CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography.

Invasive mucinous adenocarcinoma, formerly called mucinous BAC, characteristically presents in imaging studies as a range of nodules to lobar replacement by a spectrum of patterns including GGO, mixed GGO/solid foci, or consolidation,[126,128] but intraalveolar mucus may make the CT appearance solid or nearly solid (Figs. 18 and 19).[125,391] The mucoid component may appear as homogeneous consolidation with soft-tissue attenuation that is lower than that of muscle. After administration of an intravenous iodinated contrast agent, vessels are well shown traversing these regions (CT angiogram sign).[126,125,133,391] Overlap does occur between imaging features of mucinous and nonmucinous invasive adenocarcinomas.

Radiology Recommendation 2

For overtly invasive adenocarcinomas previously classified as mucinous BAC, we recommend they be separated from nonmucinous adenocarcinomas and be classified as invasive mucinous adenocarcinoma (strong recommendation, moderate quality evidence).

Remark: At CT, this entity is usually solid or mostly solid, has frequent air bronchograms, shows a lobar or multilobar distribution, and frequently consists of multiple nodular or consolidative opacities (former term multicentric BAC).

Size and Growth Rate of Lesions

AAH characteristically is ≤5 mm but in a minority of cases may be up to 12 mm.[19,276,129,363,364,368] Growth is very slow. Although it has been suggested that a pure GGN less than 5 mm is so unlikely to become a cancer that it needs no follow-up,[359] optimal frequency and duration of CT follow-up of a GGN of any size are as yet unclear.

AIS is variable in size, but most are 2 cm or less. Growth is very slow. Suspicious GGNs, i.e., ≥5 mm diameter, are usually followed by at least annual follow-up CT examination, and an increase in size or attenuation is regarded as a sign of probable progression to invasive disease.[359] For sizes more than 10 mm, closer follow-up is indicated with CT every 6 months to 1 year. Nevertheless, all recommendations for following suspicious GGNs to date have been based on data from small observational studies and need further evaluation.[131,361,368,372,387,392–394]

MIA has not yet been well defined in terms of imaging findings, in part, because the histopathologic definition is difficult, and little is known about size and growth rates, but most MIA are less than 2 cm.[58] Invasive adenocarcinomas of the lung are variable in size and growth rates. For adenocarcinoma less than 2 cm, the smaller the tumor, the less likely there is to be vascular invasion.[373] Size of an adenocarcinoma does predict metastatic disease to the central nervous system: for a node-negative adenocarcinoma of 2 to 6 cm, the probability of metastatic disease to the central nervous system has been reported as 0.14 for a 2 cm tumor, increasing linearly to 0.72 for a 6 cm tumor.[395,396]

For small solid nodules suspicious for lung cancer at CT, the recommendations for follow-up per Fleischner Society guidelines are currently widely recognized.[397–399] Nevertheless, these guidelines do not specifically address GGNs and part-solid nodules, as discussed by Godoy and Naidich.[359]

Because the sizes of many of the clinically problematic nodular lesions at CT are small, how size is measured is especially important. Differences in CT scanners, window settings, and inter- and intraobserver performance are common and may impact critically on assessments of size, especially in the CT follow-up of nodular lesions.[400–405]

Multiple Primary Lung Cancers

Multifocal lung adenocarcinomas are not uncommon, being found in up to 8 to 22% in surgically resected adenocarcinomas[406,407] and 18% of adenocarcinomas detected in screening programs.[64] Multiple lung adenocarcinomas can occur in the setting of multiple AAH, AIS, and invasive adenocarcinoma (Figure 20).[365] Similarities or differences in attenuation may provide clues regarding the relative percentage of lepidic versus solid histologic components.[359] Subsolid nodules are very rarely metastatic.[408]

Positron Emission Tomography (Scanning)

Elevated standard uptake values (SUVs) on fluorodeoxyglucose positron emission tomography (PET) correlate

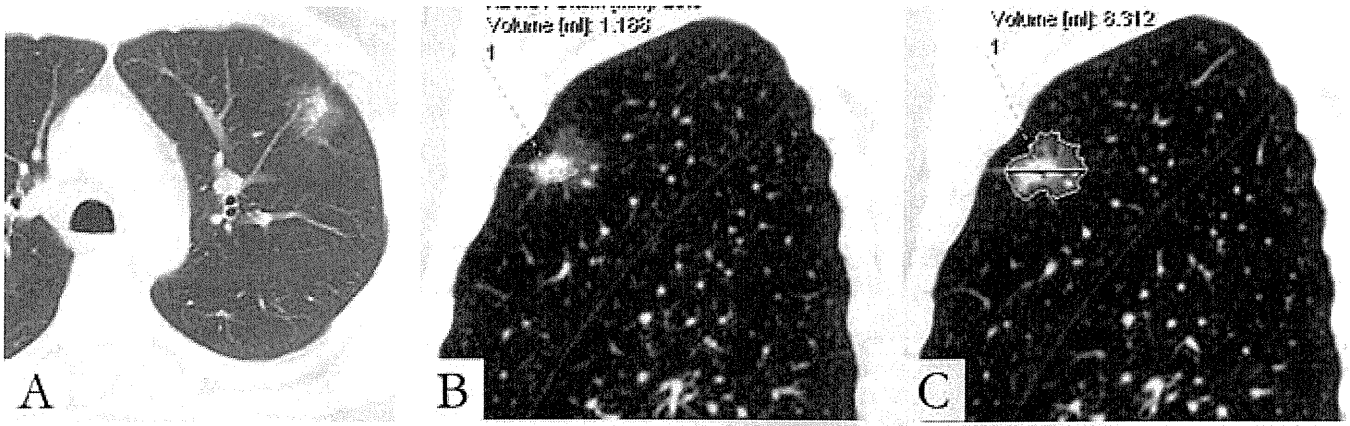

FIGURE 16. Invasive adenocarcinoma. *A*, Axial CT image shows a part-solid nodule in the left upper lobe. *B*, Corresponding sagittal CT images show automated estimation of the volume of (*B*) the solid component (1.188 cm^3) and (*C*) the entire lesion (8.312 cm^3). In this case, if tumor size were measured only by the invasive component, the size T factor would change from T2a (3.2 cm) to T1a (1.8 cm). Recording of total and invasive sizes are suggested until it is known whether invasive size predicts prognosis better than total size. CT, computed tomography.

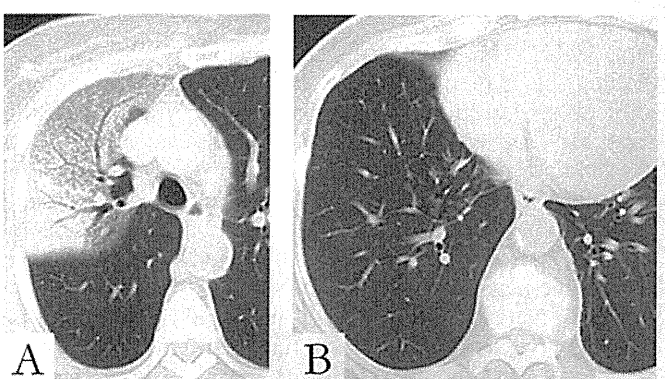

FIGURE 17. CT of nonmucinous lepidic predominant adenocarcinoma. CT images show (*A*) predominantly GGO in the right upper lobe and (*B*) multiple GGN in the right lower lobe. CT, computed tomography; GGN, ground-glass nodule.

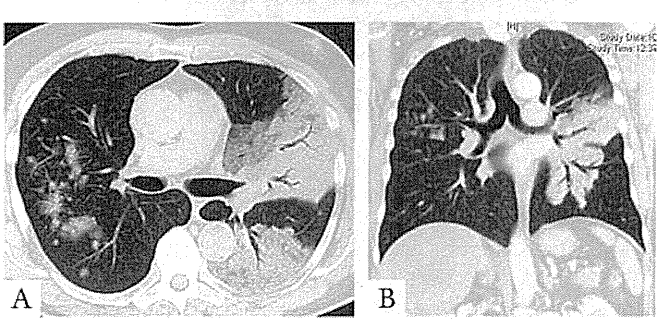

FIGURE 18. CT of invasive mucinous adenocarcinoma. *A*, Axial and (*B*) coronal CT images show multilobar consolidation and nodules mixed with GGO. Air bronchograms are present. CT, computed tomography; GGO, ground-glass opacity.

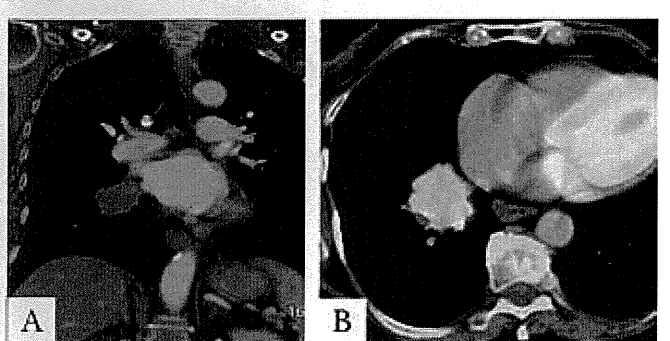

FIGURE 19. CT and FDG PET of invasive mucinous adenocarcinoma. *A*, Coronal CT and (*B*) FDG-PET images show a hypermetabolic hypodense solid 4 cm mass in the right lower lobe. CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography.

with cellular proliferation and aggressiveness of the primary cancer (Figures 15 and 19).[369,409–417] Sensitivity of PET for AIS is usually very low.[410,414] PET is commonly used for staging and follow-up of invasive adenocarcinoma, and for lesions of 7 mm or larger, SUV for adenocarcinoma of the lung tends to be lower than for other histologic types of lung cancer and correlate inversely with survival.[416,418,419] PET may be more accurate than CT for assessing response to chemotherapy, although more studies are needed.[420,421] For mucinous versus nonmucinous adenocarcinoma, after adjusting for size of the lesion, no significant difference in SUV has been found.[125] For a small, well-differentiated adenocarcinoma of low fluorodeoxyglucose avidity (e.g., maximum SUV <2.5), follow-up PET to assess change in SUV as a diagnostic tool unfortunately seems to be of only limited value.[422]

Magnetic Resonance

Magnetic resonance has been investigated as a method for differentiating among small AIS, mixed invasive adenocarcinoma/AIS, and invasive adenocarcinoma.[285,423] In the studies by Ohno et al. and Tanaka et al.,[285,423] for the distinction of AIS/lepidic predominant (former BAC) from

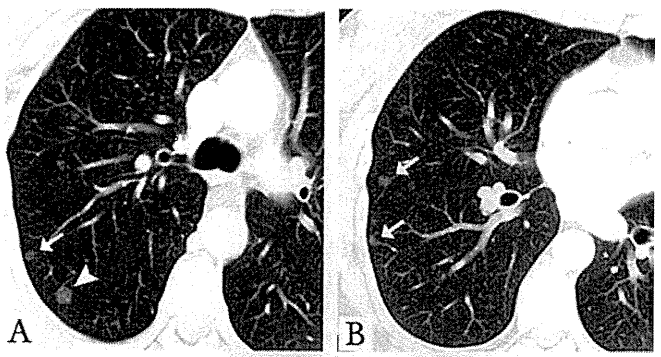

FIGURE 20. CT of multicentric GGNs of AIS/AAH. *A* and *B*, Multiple subsolid nodules (arrows) on axial 3-mm CT images show differing sizes and attenuation. These were presumed to represent preinvasive lesions (AAH and AIS). Because the dominant nodule in the right upper lobe posteriorly near the fissure in part *A* (large arrowhead) appears somewhat dense, it was excised surgically and found to be nonmucinous AIS. AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; CT, computed tomography; GGN, ground-glass nodule.

invasive adenocarcinoma, sensitivity was 86% and 97%, and specificity was 100% and 77%, respectively.

Imaging-Guided Percutaneous Needle Biopsy for Molecular and Immunohistochemical Correlations

Percutaneous imaging-guided needle biopsy, whether obtained by aspiration or as a core, allows molecular characterization from even minimal samples.[200,201,203]

Radiology Recommendations

1. When an opacity in the lung adenocarcinoma spectrum is either a pure GGN or part-solid nodule with a predominant ground-glass component, we recommend that the term BAC no longer be used. These tumors should be classified by the new terms: AIS, MIA, and LPA (strong recommendation, low-quality evidence).
2. For overtly invasive adenocarcinomas previously classified as mucinous BAC, we recommend they be separated from nonmucinous adenocarcinomas and be classified as invasive mucinous adenocarcinoma (strong recommendation, moderate quality evidence).

Remark: At CT, this entity is usually solid or mostly solid, has frequent air bronchograms, shows a lobar or multilobar distribution, and frequently consists of multiple nodular or consolidative opacities (former term multicentric BAC).

Radiology Considerations for Good Practice

1. Radiologists performing biopsies should obtain sufficient tissue not only for traditional microscopic analysis but also for immunohistochemical and molecular analysis.
2. Thin-section CT technique should be used for part-solid lesions, to record the size of (a) the solid component and (b) total tumor size, including both solid and ground-glass components (Figure 16).
3. Changes in shape, size, and attenuation help determine follow-up and when intervention is appropriate.

Radiology Research Recommendations

1. What is the natural history of single and multiple GGNs? The frequency of invasive transformation of these lesions is unknown.
2. How should tumor size be measured: single largest diameter, bidimensional, volume? For part-solid lesions, size of both the entire lesion and solid component should be mentioned, because prognosis as a function of size is not yet well established in terms of the dimensions of the solid component. Correlation of the measurement of the solid component of part-solid lesions and size of the invasive component at histopathologic assessment is also needed. Careful attention to thin-section CT technique to assess changes over time in sizes of small adenocarcinomas of the lung is warranted. Inter- and intraobserver differences among radiologists for measurements of the size of a nodule remain an important arena for inquiry.[400,402] Volumetric measurements also offer promise for assessing changes in size of indeterminate nodules, but error—both human and computer—remains an issue for small GGN, including identifying a possible solid component (Figures 17*B, C*).[405,424,425]
3. What is the CT attenuation according to the newly proposed lung adenocarcinoma histologic subtypes? CT histogram analysis suggests that attenuation characteristics may differ among AAH, AIS, and MIA.[366] Further investigations of these lesions using quantitative analysis are in order.
4. In the setting of multiple adenocarcinomas, can careful description of the attenuation (e.g., relative extent of ground glass versus solid components) for each nodule assist in the determination whether the nodules are metastases versus synchronous or metachronous primary carcinomas, similar to the way comprehensive histologic subtyping is helpful pathologically?[102]
5. How can this new classification impact CT screening? Screening may reveal small cancers early in their natural history,[64,372,426–434] and cost/benefit issues, both medical and economic, remain an arena of active current research.[424,435–439]
6. What molecular correlations can be made with the spectrum of radiologic patterns of lung adenocarcinoma? Not many studies have attempted correlation of imaging and molecular findings. *EGFR* mutations have been described as correlating with more than 50% GGO,[271,440,441] with size less than 3.5 cm[440,442] and with a high SUV level at PET of advanced-stage disease.[440,443] Ki-67 has been described as associated with high SUV levels at PET[444,445] and with dedifferentiation of the tumor.[445]

SURGICAL FEATURES

The newly proposed adenocarcinoma classification, particularly introduction of the concepts of AIS and MIA, raises surgical issues to which no definite answer is available yet. This relates to sublobar resection for early-stage lung cancer, role of chest CT in selecting patients for sublobar resection, specific surgical approach for these lesions, extent of lymph node dissection, the role of frozen section analysis, and the treatment of multiple small lung cancers.

Is Sublobar (Limited) Resection Adequate Oncologic Treatment for Some Early Adenocarcinomas?

One of the main reasons for defining the concepts of AIS and MIA in this classification is to raise the question whether these diagnoses can be anticipated by a GGO appearance on CT when presenting as a small, solitary lesion and whether limited resection may be effective therapy for such lesions. Lobectomy is still considered standard surgical treatment for tumors 2 cm or less in size, which have a solid appearance on CT, because such tumors are invasive carcinomas. Whether there can be any change in this standard care for lesions that present with a GGO appearance on CT awaits the results of two randomized trials (Japan Clinical Oncology Group, JCOG 0802 in Japan and CALGB 140503 in North America) that randomize such patients to either lobectomy or sublobar resection. Recently, there have been numerous retrospective studies that have suggested that sublobar (limited) resection for early lung cancers may be adequate surgical treatment; however, these are not randomized trials.[24–26] Most reports showed no difference in survival or in locoregional recurrence between lobectomy and sublobar resection for tumors 2 cm or less in size. Tumors with a GGN (GGO) appearance on CT are reported to have 100% disease-free survival at 5 years after complete resection.[18–21]

Can CT be Used to Select Patients for Sublobar Resection?

In performing sublobar resections, several important factors affect the appropriateness of this intervention. These include the location (peripheral versus central), appearance (ground glass versus solid), and size (T1a versus T1b versus T2) of the tumor. CT images, especially obtained by high-resolution CT scan with thin slices, are indispensable to evaluate these factors, and recent studies show rather good image-pathological correlations.[359] In recent studies correlating CT findings of GGOs with histopathology, many of these lesions, though not all, correspond to preinvasive, noninvasive, or early forms of neoplastic growth, especially those of adenocarcinoma lineage.[18–23,359,424]

Is There a Difference in Outcome between Video-Assisted Thoracoscopic surgery versus Thoracotomy in the Treatment of Early-Stage Lung Adenocarcinoma?

Several series suggest that there is no difference in overall survival between patients who have lobectomies performed by video-assisted thoracoscopic surgery (VATS) versus those performed by thoracotomy for clinical stage I non-small cell lung cancer.[446,447] Morbidity seems to be lower with the VATS approach. VATS is a standard approach for peripheral wedge resections; VATS segmentectomy is much less widely performed and requires further evaluation.[448]

What can be Expected of Pathologists at Frozen Section?

For a limited resection to be adequate oncologically, a precise pre- and intraoperative diagnosis is critical. The accuracy of intraoperative frozen section analysis in determining whether small lung adenocarcinomas have an invasive component still needs to be defined. The predictive value of frozen section ranges from 93 to 100% but not all articles clearly report the accuracy of frozen section analysis.[65–67,449]

Evaluation of margins by frozen section may be problematic, especially when stapler cartridges have been used on both sides. Scraping or washing of staple lines with subsequent cytological analysis has been attempted.[450,451] When a sublobar resection is performed, frozen section analysis of an interlobar, hilar, or any suspicious lymph node is a useful staging evaluation, and when positive nodes are found, a lobectomy is indicated when there is no functional cardiopulmonary limitation.

Should a Systematic Lymph Node Dissection be Performed in Every Early-Stage Adenocarcinoma?

The necessity of systematic hilar and mediastinal lymph node dissection is based on the fact that approximately 20% of pulmonary adenocarcinomas ≤20 mm and 5% of cases ≤10 mm in size are reported to have nodal metastases.[452–454] Lobe-specific nodal dissection, which limits dissection to the primary nodal regions draining the involved lobe, has been shown to be a potentially adequate alternative to complete systematic nodal dissection.[26,455,456] A recently reported multicenter prospective clinical trial randomizing patients with intraoperatively staged T1–2N0 nonhilar N1 NSCLC to lymph node sampling versus systematic nodal dissection showed that systematic nodal dissection identified occult disease in 3.8% of patients but was not associated with a benefit in overall survival.[457] These results should not be generalized to higher stage tumors. Recent studies also show that in some specific subsets of very early-stage adenocarcinoma, especially GGO lesions, systematic lymph node dissection is not always required.[458]

Multiple Lesions

In the setting of multifocal lung adenocarcinomas, when there is no evidence of mediastinal lymph node invasion, multiple nodules are not a contraindication for surgical exploration.[64,459] A standard treatment algorithm for multiple lesions has not yet been established. Several factors have to be taken into consideration: number and size of the different nodules, synchronous versus metachronous lesions, ipsilateral versus contralateral, primary versus metastatic lesions, and specific nature (AAH, AIS, and MIA).

Surgery Research Recommendations

1. The precise role of limited resection has not been determined yet because of a lack of randomized prospective trials.
2. The extent of lymph node dissection remains controversial.
3. The accuracy of frozen section in assessing the presence of invasive adenocarcinoma and the accuracy of frozen section or cytology of resection margins in sublobar resections need to be investigated further, and specific guidelines for frozen section analysis should be developed to guide intraoperative decisions.
4. Treatment of multiple lesions has not been standardized.

CLASSIFICATION IN A LOW-RESOURCE SETTING

Although this lung adenocarcinoma classification is written to incorporate special stains and molecular techniques, it is understood that some patients will need to be managed without immunohistochemical or molecular data. This may occur in parts of the world where resources are limited, or it may happen in academic centers where the additional tissue required for special studies is not available. This section briefly outlines how this classification can be applied in such situations.

Pathologic Classification

In the absence of molecular, immunohistochemical, or histochemical testing, the diagnosis and subclassification of lung adenocarcinoma are based purely on light microscopic evaluation of pathologic material.

Resection Specimens

For resection specimens, the two situations where special stains may be useful include solid adenocarcinoma, for which mucin stains can help in the distinction from large cell carcinoma, and for which NE markers can help diagnose LCNEC. In the former situation, if an adenocarcinoma shows a pure solid pattern without acinar, papillary, or lepidic patterns, sometimes intracytoplasmic mucin can be seen on H&E stains. If this cannot be detected, the tumor should be classified as large cell carcinoma, mentioning that it was not possible to perform special stains. If a non-small cell carcinoma shows NE morphology and NE immunohistochemical markers cannot be performed, the tumor should be classified as large cell carcinoma with NE morphology and a specific comment should be made that the tumor could be LCNEC but that material was not available to confirm this immunohistochemically.

Small Biopsies and Cytology

For small biopsies, if clear glandular or squamous differentiation is seen morphologically, the tumor can be classified as adenocarcinoma or squamous cell carcinoma, respectively. If there is some level of uncertainty, this can be reflected by the phrase: poorly differentiated non-small cell carcinoma, favor adenocarcinoma (or squamous cell carcinoma), mentioning in a comment that special stains were not available, and this diagnosis is based purely on light microscopic morphology. If no morphologic features of glandular or squamous differentiation are seen, the tumor should be classified as poorly differentiated NSCLC-NOS.

Clinical, Radiologic, and Surgical Approach to Aid Management of Patients in the Absence of Molecular or Immunohistochemical Data

Evaluation of patients with lung adenocarcinoma should be no different if the diagnosis is established in the absence of special techniques.

Whenever possible, a chest CT extending to adrenals and liver should be used for radiologic evaluation of such patients. In a low resource setting, chest radiography may reveal the primary lung cancer, pleural effusions, and involvement of lymph nodes or bones; however, given the much lower resolution with radiographs compared with CT, an attempt to obtain a chest CT examination should be made for accurate diagnosis and staging of tumor when possible.

If patients diagnosed in low resource settings may subsequently have tissue tested with molecular or immunohistochemical studies, tissue should be managed appropriately to make this possible.

Clinical management of lung adenocarcinoma patients without information about molecular status such as *EGFR* or *KRAS* mutations consists of standard surgical and chemotherapeutic approaches based on tumor, node, and metastasis (TNM) staging.

IMPLICATIONS OF THIS CLASSIFICATION FOR TNM STAGING

There are several important implications of this new adenocarcinoma classification for staging that need to be considered for the next revision of the TNM classification. The changes relating to the concepts of AIS, MIA, and LPA parallel classification criteria and terminology currently used in breast cancer,[460] but they would not be applicable to other histologic types of lung cancer. In addition, the comprehensive histologic subtyping approach to assessing invasive adenocarcinomas in this classification provides a useful approach to staging multiple adenocarcinomas.

1. AIS would be classified as Tis. Nevertheless, because carcinoma in situ (CIS) can occur with both lung squamous cell carcinoma and adenocarcinoma, these should be specified as Tis (squamous) or Tis (adenocarcinoma), similar to breast cancer where there is Tis for ductal CIS and Tis for lobular CIS.
2. MIA would be classified as T1mi, similar to microinvasive breast cancer, which defined as an invasive carcinoma with no focus measuring greater than 1 mm; however, the size for MIA is not greater than 5 mm.
3. Also, similar to breast cancer, the size T factor for adenocarcinomas with an in situ or lepidic component may best predict prognosis according only to the size of the invasive component rather than the way it is currently done including total tumor size including both the invasive and the lepidic or in situ components. In

early-stage tumors, the tumor size T factor may need to be adjusted from total tumor size to only the size of the invasive component. This needs to be tested radiologically and pathologically by comparing survival according to total tumor size (GGO plus solid components by CT versus invasive versus in situ/lepidic components pathologically) compared with analysis only by the size of the solid or invasive component by CT and pathology examinations, respectively.

4. For multiple lung adenocarcinomas, comprehensive histologic subtyping can help in distinguishing intrapulmonary metastasis versus synchronous or metachronous primaries.[102] The role of molecular testing in this setting is promising but needs further study.[331]

Many of these concepts need to be tested vigorously in the next 5 years in both early- and advanced-stage lung adenocarcinoma to determine whether they are robust enough to warrant changes in the 8th Edition TNM classification.

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Clinicopathological findings of non-small-cell lung cancer with high serum progastrin-releasing peptide concentrations

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ABSTRACT

Although progastrin-releasing peptide (proGRP) is used as a serum tumor marker for small cell lung cancer (SCLC), high serum pro-GRP concentrations are observed in some non-small-cell lung cancers (NSCLCs). The characteristics of these NSCLCs are not well known. To determine the clinicopathological features of NSCLC in patients with elevated serum proGRP concentrations, serum proGRP values were assessed in 654 advanced lung cancer patients, and positive (>46 pg/mL) NSCLC specimens were subjected to cytological and histopathological reevaluation. Serum proGRP concentrations were positive in 34 of 421 NSCLC patients (8.1%) and 186 of 233 SCLC patients (80%). Histological subtypes of the 34 NSCLC patients at diagnosis were 20 adenocarcinomas, 5 squamous cell carcinomas, 4 large cell carcinomas, and 5 large cell neuroendocrine carcinomas. Six of 27 cytology specimens contained characteristic neuroendocrine morphology. Immunohistochemical analysis showed that 11 of 17 tumors were positive for neuroendocrine markers (64.7%). Twenty of 34 serum proGRP-positive NSCLC patients received platinum-based chemotherapy, and the response rate was 55.0%. These results suggest that serum proGRP-positive NSCLCs may have neuroendocrine differentiation. In addition, serum proGRP-positive NSCLCs may have clinical characteristics that are different from other NSCLCs.

1. Introduction

Lung cancer is the leading cause of cancer death worldwide. In 2005, the number of deaths due to lung cancer in Japan exceeded 60,000 [1]. Conventionally, lung cancer is classified into small cell lung cancer (SCLC) and non-small-cell carcinoma (NSCLC). Because SCLC has neuroendocrine features, it has a poorer prognosis and shows greater sensitivity to chemotherapy than NSCLC. Although NSCLC is subclassified into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, some NSCLCs have neuroendocrine differentiation. In 1999, the World Health Organization categorized large cell neuroendocrine carcinoma (LCNEC) as a variant of large cell carcinoma [2]. LCNEC has been reported to have a poor prognosis, even for early-stage disease [3,4]. Different types of NSCLCs differ in their clinical behavior according to the presence or absence of neuroendocrine differentiation. Neuroendocrine differentiation in a tumor is generally determined by immunohistochemistry and/or electron microscopy, which reveal the characteristic neuroendocrine morphology [2,5]. However, it is difficult to obtain sufficient tissue by biopsy, and limited tumor tissue sampling may make it difficult to diagnose neuroendocrine differentiation in NSCLC. Therefore, the development of a sensitive serum marker for the detection of neuroendocrine differentiation is greatly desired to facilitate the diagnosis of NSCLCs and neuroendocrine tumors.

Progastrin-releasing peptide (proGRP) is a signal peptide that is produced by small cell lung cancer cells (SCLC). Serum proGRP is considered to be a sensitive tumor marker for SCLC. The sensitivity and specificity of serum proGRP as a tumor marker for SCLC is 60–70% and 96%, respectively [6]. Elevated serum proGRP concentrations have been observed in some NSCLC patients, especially LCNEC patients [6,7], suggesting that serum proGRP is a potentially good marker not only for SCLC but also for NSCLC with neuroendocrine features. However, the clinical and pathological characteristics of NSCLCs with elevated serum proGRP concentrations have not been well studied. In the present study, serum proGRP levels were measured in 654 lung cancer patients and the clinical characteristics of serum proGRP-positive NSCLC patients

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were analyzed; the histopathology of the surgical or biopsy specimens of the positive patients were also evaluated.

2. Patients and methods

Serum proGRP concentrations were measured in 654 patients who were diagnosed with lung cancer by histology or cytology at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research between April 1998 and April 2006.

An enzyme-linked immunosorbent assay (ELISA) kit (serumlabo ProGRP; Fujirebio Diagnostics Inc., Tokyo, Japan) was used to determine serum proGRP concentrations, and samples were considered positive when their values exceeded 46 pg/mL [8].

The clinical characteristics of serum proGRP-positive NSCLC patients were retrospectively analyzed, including age at diagnosis, gender, smoking history, and TNM stage. Response to platinum-based chemotherapy in serum proGRP-positive NSCLC patients was determined according to RECIST criteria (without confirmation).

In addition, the cytological and histological findings of the surgical or biopsy specimens of these patients were reevaluated. Immunohistochemical (IHC) staining was used to evaluate neuroendocrine differentiation in the tumors. Formalin-fixed paraffin-embedded sections were stained for a panel of epithelial markers, including thyroid transcription factor-1 (TTF-1; Dako EnVision+, Saitama, Japan) and carcinoembryonic antigen (CEA; Nichirei, Tokyo, Japan), and neuroendocrine markers, including chromogranin A (CGA) (Dako EnVision+, Saitama, Japan), synaptophysin (Dako EnVision+, Saitama, Japan), CD56 (neural cell adhesion molecule [NCAM]) (Clone 1B6; Novocastra, and proGRP (Advanced Life Science Institute Inc., Saitama, Japan). IHC staining was performed according to standard protocols with EnVision kits (Dako EnVision+, Saitama, Japan). IHC results were grouped into 3 categories – strongly positive, weakly positive, or negative – by well-trained pathologists (WH and NM).

Statistical calculations were performed using StatView version 5.0 for Windows XP (SAS Institute, Cary, NC). Associations between categorical variables and serum proGRP concentrations were evaluated using Student's *t* test. Survival was measured from the start of chemotherapy to the last follow-up evaluation or death, and survival rates were estimated using the Kaplan–Meier method.

3. Results

3.1. Patient characteristics

Of a total of 654 patients, 421 were diagnosed with NSCLC and 233 with SCLC. Serum proGRP samples were positive in 220 of 654 patients, of which 34 (8.1%) had NSCLC and 186 (80%) had SCLC.

The clinical characteristics of serum proGRP-positive and negative NSCLC patients are shown in Table 1. There were no significant differences in the clinical characteristics between the serum proGRP-positive and -negative NSCLC patients.

In serum ProGRP-positive NSCLC patients, the median age of these patients was 67 years (range, 49–77). There were 22 males and 12 females, and 65% of the patients were heavy smokers (smoking index > 400). Most of the patients (94%) had advanced NSCLC. Serum creatinine concentrations were less than 1.6 mg/dL in all 34 serum proGRP-positive NSCLC patients.

The histological subtypes of the 34 serum proGRP-positive NSCLCs at diagnosis were as follows: 20 adenocarcinomas, 5 squamous cell carcinomas, 4 large cell carcinomas, and 5 LCNECs. The rates of positive serum proGRP in each histological subtype were as follows: 7.7% in 260 adenocarcinomas, 5.9% in 85 squamous cell carcinomas, 9.3% in 43 large cell carcinomas, and 44.4% in 11 LCNECs.

Table 1
Clinical characteristics of NSCLC patients.

Characteristics	ProGRP-positive NSCLC patients	ProGRP-negative NSCLC patients
Total no. of patients	34	387
Age, years		
Median (range)	67 (49–77)	62 (29–87)
Sex		
Male/female	22/12	261/126
Smoking index		
Mean (range)	807.5 (0–1400)	661 (0–3000)
Never/≤400/>400	10/2/22	121/29/237
Histological subtype at diagnosis		
Adenocarcinoma	20	240
Squamous cell carcinoma	5	80
Large cell carcinoma	4	48
LCNEC	5	6
Adenosquamous	0	2
Other	0	11
Stage		
I/II	2	56
IIIA	7	63
IIIB	6	106
IV	16	144
Recurrent	3	18

LCNEC: large cell neuroendocrine carcinoma, ProGRP: progastrin-releasing peptide, NSCLC: non-small-cell lung cancer.

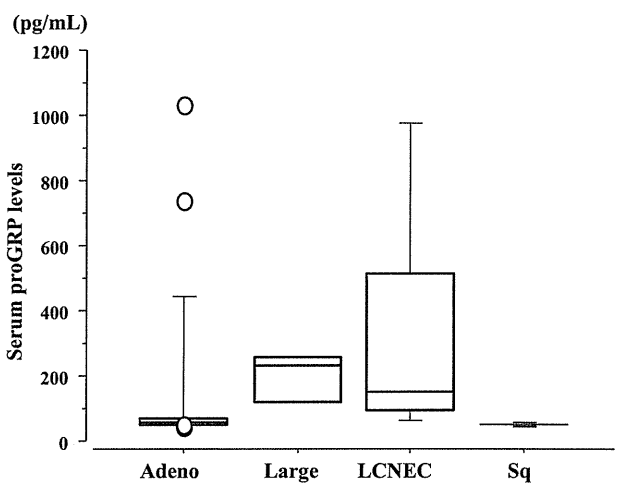

Fig. 1. Serum progastrin-releasing peptide (proGRP) concentrations of 34 non-small-cell lung cancer patients with elevated proGRP. Adeno: adenocarcinoma, Large: large cell carcinoma, LCNEC: large cell neuroendocrine carcinoma, Sq: squamous cell carcinoma.

The median serum proGRP concentration of the 34 NSCLC patients was 60.7 pg/mL and the range was 46.0–973.0 pg/mL. The serum proGRP concentrations in these 34 NSCLC patients were significantly lower than the serum concentrations in proGRP-positive SCLC patients (median, 469 pg/mL; range, 47.1–344,000 pg/mL) ($P < 0.05$).

Fig. 1 shows the serum proGRP concentrations for each histological subtype of serum proGRP-positive NSCLC. The mean serum proGRP concentration in LCNECs was 147 pg/mL and the range was 78.6–973 pg/mL. These concentrations are relatively high compared to other NSCLCs. On the other hand, serum proGRP concentrations were relatively low, even in serum proGRP-positive squamous cell carcinoma patients (median, 47.4 pg/mL; range, 46–56.7 pg/mL).

Table 2
Immunohistochemistry results of non-small-cell lung cancer with elevated serum progastrin-releasing peptide concentrations.

	Serum proGRP (pg/dL)	Histological subtype at diagnosis	Specimen	Stage	IHC					
					TTF-1	CEA	CGA	Synapto-phisin	NCAM	proGRP
1	973	Large	TBLB	IV	–	++	++	++	+	–
2	363	LCNEC	TBLB	IV	++	–	++	++	++	++
3	269	LCNEC	TBLB	IV	++	++	++	++	++	+
4	229	Large	TBLB	IV	–	–	–	–	–	–
5	78.6	Large	TBLB	IV	–	–	–	–	–	–
6	60.3	Adeno	TBLB	IV	++	–	–	–	–	–
7	56.7	Sq	Surgery	Rec	–	+	–	+	++	–
8	56.0	Adeno	Surgery	Rec	++	–	–	+	–	–
9	55.3	Adeno	TBLB	IIIB	++	–	–	+	+	–
10	54.7	Adeno	TBLB	IV	++	–	–	+	–	–
11	53.1	Adeno	Surgery	IB	++	–		+	–	–
12	51.8	Adeno	TBLB	IV	++	+	++	++	++	+
13	51.4	Adeno	Surgery	IB	++	++	++	++	++	++
14	48.3	Sq	TBLB	IB	–	++	–	–	–	–
15	47.4	Sq	Surgery	IIIA	–	++	–	–	–	–
16	47.3	Sq	TBLB	IIIA	–	–	–	+	–	–
17	46	Sq	TBLB	IIIB	–	++	–	–	–	–

IHC: immunohistochemistry, proGRP: progastrin-releasing peptide, TTF-1: thyroid transcription factor 1, CEA: carcinoembryonic antigen, CGA: chromogranin A, NCAM: neural cell adhesion molecule, Adeno: adenocarcinoma, Sq: squamous cell carcinoma, Large: large cell carcinoma, LCNEC: large cell neuroendocrine carcinoma, TBLB: transbronchial lung biopsy, –: negative, +: weakly positive, ++: strongly positive.

3.2. Cytological and histological examination

Cytological specimens corresponding to 27 of the 34 serum proGRP-positive NSCLCs were reevaluated. All 5 cytology specimens diagnosed as LCNEC contained typical neuroendocrine features such as rosette-like and palisading patterns. A rosette-like formation was found in only 1 cytology specimen diagnosed as squamous cell carcinoma, and the other 21 specimens did not contain the typical cytological features of neuroendocrine differentiation.

IHC staining was performed on 17 histological specimens of the 34 serum proGRP-positive NSCLCs (7 adenocarcinomas, 5 squamous cell carcinomas, 3 large cell carcinomas, and 2 LCNECs) to examine neuroendocrine differentiation (Table 2). Four of 17 specimens (24%) showed positive staining (2 weakly and 2 strongly positive) for proGRP, and some neuroendocrine markers were positive in 11 of 17 specimens (64.7%). In particular, 2 of 7 adenocarcinomas, 1 of 3 large cell carcinomas, and 2 of 2 LCNECs showed strongly positive staining for at least 2 out of the 3 neuroendocrine markers CGA, synaptophysin, and NCAM. None of the squamous cell carcinomas showed strongly positive staining for at least 2 out of the 3 neuroendocrine markers CGA, synaptophysin, and NCAM. One of 5 squamous cell carcinomas showed strongly positive staining for NCAM. One of 5 squamous cell carcinomas showed strongly positive staining for NCAM. There was no significant relationship between serum proGRP concentrations and proGRP immunoreactivity.

3.3. Response to chemotherapy

Twenty of 34 serum proGRP-positive NSCLC patients received platinum-based chemotherapy (Table 3). There were 11 partial responses, 4 stable diseases, and no responses observed in the 5 patients. The objective response rate was 55.0%. The median survival of the 20 patients was 11 months, and the 1-year survival rate was 48%.

On the other hand, 232 of 387 serum proGRP-negative NSCLC patients received platinum-based chemotherapy. There were 82 partial responses, 97 stable diseases, and no complete responses observed in the 53 patients. The objective response rate was 35.0%, the median survival was 11.5 months, and the 1-year survival rate was 49.1%.

Table 3
Platinum doublet regimens administered to serum proGRP-positive and -negative patients.

Regimens	ProGRP-positive NSCLC patients (n=20)		ProGRP-negative NSCLC patients (n=232)	
	n	%	n	%
CBDCA/PTX	9	45	141	60.7
CBDCA/GEM	0	0	16	7
CBDCA/VP16	1	5	5	2
CDDP/DOC	3	15	53	23
CDDP/S-1	2	10	4	1.8
CDDP/VNR	2	10	1	0.5
CDDP/VP16	1	5	0	0
CDDP/CPT11	2	10	2	1
CDDP/GEM	0	0	10	4

CBDCA: carboplatin, CDDP: cisplatin, PTX: paclitaxel, GEM: gemcitabine, VP16: etoposide, DOC: docetaxel, VNR: vinorelbine, CPT11: irinotecan, ProGRP: progastrin-releasing peptide.

4. Discussion

In the present study, the positive rate of serum proGRP concentration in NSCLC patients was 8.1% (34/421), and histological neuroendocrine features were detected in 11 of 17 (64.7%) serum proGRP-positive NSCLC specimens. Several studies have examined serum proGRP concentrations in lung cancer, and all of these studies reported that serum proGRP was a specific tumor marker for SCLC [6,9]. The sensitivity and specificity for SCLCs were around 70% and 99%, respectively, and serum proGRP was superior to NSE [10].

Although increases in serum ProGRP concentration have been observed in some NSCLC patients in previous studies, the reported positive rates of serum proGRP in NSCLCs demonstrated a wide range of variability (3–30%) [6,11]. The 8% positive rate found in the present study was relatively higher than in previous studies, with the exception of 2 reports (the Takada study used a lower cutoff for positive, at 34 pg/mL, and the Molina study included a higher proportion of renal failure patients) [11,12]. Although several studies have reported that serum proGRP values were elevated in NSCLC patients, there have been few studies examining the clinicopathological characteristics of serum proGRP-positive NSCLC patients [13]. Only 1 study examined the clinicopathological