status) was associated with worse survival (HR: 1.9, 95% CI: 1.1–3.4) and a better response to erlotinib ($p = 0.005$), after controlling for race, performance status, weight loss, smoking history, prior treatment, and response to prior treatment.[236] In a second-line, chemotherapy controlled phase III study (INTEREST) comparing gefitinib with docetaxel, overall survival was similar in the two arms, and there were no statistically significant interactions between treatment and EGFR copy number, protein expression, or mutation status.[234] The results of all three of these studies may be influenced by inclusion of large numbers of patients with histologies other than adenocarcinoma and should be regarded as exploratory.[234–236]

For treatment of advanced NSCLC, response and outcome to EGFR-TKIs have been demonstrated in most studies to be better predicted by *EGFR* mutation testing rather than copy number or immunohistochemistry. In a phase II study of erlotinib-treated patients, multivariate analysis of molecular predictors showed that *EGFR* mutations, but not copy number, was predictive of response to erlotinib with a response of 83% in patients with *EGFR* mutations versus 7% in those without ($p < 0.01$).[198] In this study, immunohistochemistry was not predictive of response.[198] Another study by Sholl et al.[237] found *EGFR* mutation status, but not FISH, CISH, or immunohistochemistry, was useful for predicting response and PFS for TKI therapy. The recent development of new mutation-specific antibodies for *EGFR* exon 19 deletion and L858R mutation seems to be much more reliable in predicting *EGFR* mutation status, and these need to be evaluated in future clinical trials.[238–240] In the Iressa Pan Asian Survival Study, in FISH+ patients, gefitinib was worse than chemotherapy if those patients lacked *EGFR* mutations.[241] All these studies used RECIST to measure response to therapy.[8–11,198,234–236,241]

More recently, investigators have noted that all NSCLC histologies other than squamous cell carcinoma seem to garner more benefit from two drugs, pemetrexed for efficacy and bevacizumab for avoidance of toxicity. Nevertheless, most of the analyses are subgroup analyses with the known shortcomings. Pemetrexed, a multitargeted antifolate agent, seems to have greater activity in NSCLCs with nonsquamous histology (adenocarcinoma and NSCLC-NOS), with the greatest proportion of benefit observed in patients with adenocarcinomas as demonstrated in two phase 3 trials.[12–15] In a phase 3 trial, comparing cisplatin/pemetrexed with cisplatin/gemcitabine, preplanned subgroup analysis, revealed median overall survival was significantly better for patients with adenocarcinoma (12.6 versus 10.9 months, HR = 0.81, 95% CI: 0.71–0.99, $p = 0.03$) and large cell carcinoma (would be called NSCLC-NOS by the current proposal), overall survival of 10.4 versus 6.7 months (HR = 0.67; CI: 0.48–0.96), whereas no benefit was seen with squamous cell carcinoma or with all histologies combined.[13] Follow-up analysis of the same patients from this phase 3 study but focusing on those without grade 3 or 4 drug toxicity, a similar benefit for overall survival was found in patients with nonsquamous histology comparing cisplatin pemetrexed with cisplatin/gemcitabine (median survival of 5.6 months versus 2.8 months, respectively, HR = 0.64, 95% CI: 0.56–0.72, $p < 0.001$).[12] Ciuleanu et al. showed in a phase 3 trial comparing pemetrexed versus placebo, where prespecified analysis for histology were performed, that patients with adenocarcinoma histology had better median PFS (4.5 versus 1.5 months, HR = 0.511; CI: 0.38–0.68; $p < 0.0001$) and median overall survival (16.8 versus 11.5 months; HR = 0.73; CI: 0.56–0.96; $p < 0.026$). The benefit was also significant for nonsquamous carcinomas classified as other, and for nonsquamous cell carcinoma overall, but not for large cell carcinomas or squamous cell carcinomas.[14] Several phase II studies have also shown a benefit for pemetrexed in patients with advanced NSCLC with nonsquamous histologic subtypes.[242,243] Nevertheless, a recent phase III trial, with primary end point as the assessment of quality of life, observed similar outcomes for patients treated with pemetrexed/carboplatin regardless of histology.[244] Patients with adenocarcinoma or NSCLC-NOS (nonsquamous NSCLC histology) are the only patients who have been demonstrated to benefit from bevacizumab in combination with chemotherapy.[245] Indeed, patients with squamous cell carcinoma are at greater risk of adverse events, and therefore, such patients have been excluded from receiving this drug by the Food and Drug Administration,[17] but they are eligible for adjuvant therapy in ongoing trials.[16]

Very recently, a new predictive biomarker has been identified in patients with NSCLC, the *EML4/ALK* translocation. This translocation leads to an oncogenic constitutive activation of ALK.[220,246,247] A recent study of 82 patients with NSCLC confirmed to have ALK fusion by FISH demonstrated a 57% overall response rate to crizotinib (PF-02341066), an inhibitor of MET and ALK, and the estimated 6-month PFS was 72%.[248] De novo resistance mutations in the kinase domain of *EML4-ALK* have been reported to develop during ALK inhibitor therapy.[249]

Clinical Implications of Histology and Molecular Testing

Accurate histologic subtyping and *EGFR* mutation testing are important and should be included in the initial work-up of patients with advanced lung adenocarcinoma because it may guide treatment decisions. Whether other EGFR tests should be recommended (i.e., immunohistochemistry and FISH) and/or *KRAS* mutation as an indicator of TKI resistance is not yet clear.[250,251] In addition to *EGFR* mutation analysis, additional molecular tests are in development and may be more useful when further clinical data support their use.

Surgically Resectable NSCLC

Twenty to 30% of patients with NSCLC are diagnosed with stage I to stage IIIA disease and, thus, may be amenable to surgical resection. Patients who undergo resection have differing prognoses based on pathologic stage. The recent IASLC staging project has demonstrated overall 5-year survival of 73% for stage IA, 58% for stage IB, 46% for stage IIA, 36% for stage IIB, 24% for stage IIIA, and 9% for stage IIIB.[252,253] The introduction of adjuvant cisplatin-based chemotherapy represented a major step forward with a 5% increase in cure rate.[254] Still, 27% of patients with stage IA

disease and 42% of patients with stage IB NSCLC eventually recur and die of their disease; there is no accurate way to predict which of these patients have poor-risk disease and are likely to recur. Similarly, 41% of patients with stage II NSCLC are cured by surgery alone and do not need any adjuvant therapy.[252,253] Thus, an urgent need to identify factors, which will select patients for adjuvant therapy, exists. Several predictive factors for better efficacy of adjuvant chemotherapy have been described in retrospective analyses of phase III randomized adjuvant studies. An example is low expression of the DNA repair genes excision repair cross-complementation group 1 for greater benefit from cisplatin-based chemotherapy, although this needs further validation.[207] Based on initial data showing striking differences in survival predicted by histologic subtyping according to this proposed classification of lung adenocarcinomas in resected specimens,[44] it is possible in the future that histology will play an important role in selecting patients for adjuvant therapy.

Clinical Recommendation

In patients with advanced lung adenocarcinoma, we recommend testing for *EGFR* mutation (strong recommendation, moderate quality evidence).

Remarks: This is a strong recommendation because potential benefits clearly outweigh harms. This recommendation assumes that correct classification by *EGFR* mutation status is associated with important benefit based on randomized phase 3 clinical trials of EGFR-TKI therapy, which demonstrate a predictive benefit for response rate and PFS, but not overall survival, and subset analyses of multiple additional studies.

Clinical Consideration for Good Practice

1. If molecular testing is planned, appropriate biopsy methods should be used to obtain sufficient tissue for both pathologic diagnosis and molecular analyses, and the specimens should be handled appropriately.

Clinical Research Recommendations

1. How can this histological and/or molecular classification improve our ability to estimate prognosis and optimize the selection of patients for a specific therapy?
2. What is the relative importance of histologic versus molecular data for identifying prognostic or predictive markers based on small biopsies and cytology versus resected specimens?
3. Is immunohistochemical testing using *EGFR* mutation-specific antibodies as predictive of response to EGFR-TKIs as *EGFR* mutations?
4. In advanced lung adenocarcinomas, are the prognostic and therapeutic implications of histology any different if the pathologic diagnosis is based on a combination of histology and immunohistochemistry (i.e., TTF-1 and/or p63) versus conventional light microscopy alone which is the basis for current data?
5. In metastatic lung adenocarcinomas, what are the clinical implications of any potential differences in molecular or histologic features compared with primary tumors?
6. What are the clinical, epidemiological, molecular, and histologic characteristics of never smokers with lung adenocarcinoma?

MOLECULAR FEATURES

There are several molecular observations that have important implications for lung adenocarcinoma patients: (1) *EGFR* mutation is a validated predictive marker for response and PFS with EGFR-TKIs in the first-line therapy in advanced lung adenocarcinoma.[8,215–218] (2) Tumors with an *EGFR* mutation have been associated with a more indolent course.[8,234] (3) *EGFR* and *KRAS* mutations are virtually mutually exclusive.[236,255] (4) *EGFR/KRAS* mutation-negative cases may have detectable fusion of *EML4-ALK*.[153,220]

Histogenetic Origins of Lung Adenocarcinoma Subtypes

Normal lung tissues, from which lung cancers arise, can be anatomically divided into two major components, the air-conducting system and the peripheral lung parenchyma where gases are exchanged. After generation of the two embryologic lung buds, repeated branching morphogenesis results in conducting airways and the subsequent development of the terminal sac and alveoli. During the later stages, the regulatory TTF-1 is ubiquitously expressed in the peripheral lung epithelial cells such as small bronchioles and alveoli.[256] TTF-1 is potentially a lineage-specific survival oncogene of some lung adenocarcinomas.[257,258] The peripheral bronchioloalveolar compartment (terminal bronchioles, alveolar ducts, and alveoli) also contains two potential tumor cells of origin, the Clara cells and type II pneumocytes,[259] which together comprise the terminal respiratory unit (TRU) and give rise to tumors expressing TTF-1. These often manifest as a GGN on CT. The central conducting airways (bronchi) contain two potential candidate progenitor cells that give rise to tumors: the bronchial basal cells and the mucous cells.[259,260] These tumors are TTF-1 negative and demonstrate a solid appearance on CT. Hierarchical clustering analysis of lung adenocarcinoma based on the expression profile demonstrated two major clusters, which correspond to TRU and non-TRU-type adenocarcinomas and thus two major subsets of adenocarcinoma with distinct histogenetic origins.[261]

It is hypothesized that a subset of lung adenocarcinomas undergoes progression from AAH to AIS to invasive carcinoma and that this may be a stepwise process triggered by multiple genetic changes that supplement those responsible for initiation of the malignant phenotype.[4,77,262,263] Although *EGFR* and *KRAS* mutations are observed from the earliest stages including normal epithelium[264,265] and AAH, to invasive adenocarcinoma, EGFR gene copy number changes become widespread later at the stage of invasion and metastases.[266,267] *EGFR*, *KRAS*, and *TTF-1* amplification are characteristic of this progression.[258,266,268] *p53* mutation is more often found in invasive compared with noninvasive adenocarcinomas.[48,269–273] Nevertheless, *p53* mutation has not been identified as a reliable prognostic marker or a therapeutic target.

Histologic Molecular Correlations

High-throughput analysis of DNA mutations has reshaped the molecular landscape of lung adenocarcinomas.[98] DNA sequencing of 623 known cancer-related genes in 188 adenocarcinomas identified 1013 somatic mutations.[98] In addition to confirmation of known tumor suppressor genes *p53*, *P16*^{INK4}, and *STK11/LKB1*, newly described mutations in *NF1* and *RB1* were detected at a frequency of 10% each. There were two other important findings: (1) mutations were often detected in the tyrosine kinase gene family members *EGFR*, *KRAS*, *ERBB4*, *EPHA4*, *EPH3*, *KDR*, and *FGFR4* that are potentially targetable by tyrosine-kinase inhibitors and (2) mutual exclusivity was demonstrated in several gene mutation pairs including *EGFR/KRAS*, EGFR/*STK11*, and *NF1* and *p53/ATM*.[98,274] Mutation frequency showed negative correlations between acinar, papillary, and BAC subtypes with mutations in LRP1B, p53, and INHBA.[98] Nevertheless, these mutations showed significant positive correlations with the solid subtype (Table 5).[98]

Many publications have studied the prevalence and specificity of *KRAS* and *EGFR* alterations in lung adenocarcinoma (Table 5). The frequency of *KRAS* and *EGFR* mutations is each 10 to 30% with higher *EGFR* mutation frequency in Asians, never smokers, and nonmucinous tumors, whereas *KRAS* mutations are most common in non-Asians, smokers, and in invasive mucinous adenocarcinoma.[140] Mu-

TABLE 5. Adenocarcinoma Histologic Subtypes, Molecular, and Radiological Associations

Histological Subtype Predominant	Molecular Features	CT Scan Appearance	Gene Pathways Associated	References
Nonmucinous AIS and MIA	TTF-1 + (100%) *EGFR* mutation never smokers: 10–30% *KRAS* mutation smokers: 10–30%	GGN, part-solid nodule	Not known	141, 261, 275–277
Lepidic (nonmucinous)	TTF-1 + (100%) *EGFR* mutation never smokers: 10–30% *EGFR* amplification: 20–50% *KRAS* mutation smokers: 10% *BRAF* mutations: 5%	Part solid nodule GGN or solid nodule	Low cell cycle stimulatory[278] High Wnt	69, 261, 266, 276, 279–283
Papillary	TTF-1 + (90–100%) *EGFR* mutation: 10–30% *EGFR* amplification: 20–50% *KRAS* mutation 3% (lack of *KRAS*) *ERBB2* mutations: 3% *p53* mutations: 30% *BRAF* mutations: 5%	Solid nodule	Low cell cycle[278] stimulatory High EGFR High notch	69, 98, 264, 266, 279, 280–282, 284–286
Acinar	TTF-1 + or − *KRAS* mutation in smokers (20%) *EGFR* mutations <10% nonsmokers *EGFR* amplification: 10% *EML4/ALK* translocation: >5% *P53* mutations: 40%	Solid nodule	High PDGF[278] Low EGFR Low angiogenesis	69, 98, 269, 287
Micropapillary	*KRAS* mutations (33%) *EGFR* mutations (20%) *BRAF* mutations (20%)	Unknown	Unknown	69, 95, 283
Solid	TTF-1 (70%) MUC1 positive *KRAS* mutation smokers: 10–30% *EGFR* mutation never smokers: 10–30% *EGFR* amplification: 20–50% *EML4/ALK* translocation >5% *p53* mutation: 50% *LRP1B* mutations *INHBA* mutations	Solid	High cell cycle stimulatory+[278] High angiogenesis High JAK-STAT Low notch	69, 98, 125, 269, 287, 288
Invasive mucinous adenocarcinoma	TTF-1 (0–33% positive) *KRAS* mutation: 80–100% No *EGFR* mutation MUC5+ MUC6+ MUC2+	Consolidation, air bronchograms; less often GGO	Not known	123, 125, 126, 137, 140–142, 286, 289–291

AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; GGN, ground-glass nodule; EGFR, epidermal growth factor receptor; TTF, thyroid transcription factor.

tations in *EGFR* mainly affect the adenosinetriphosphate-binding pocket within the tyrosine kinase domain. The most common mutations result in an arginine for leucine substitution at amino acid 858 and in-frame deletions at exon 19. *EGFR* mutation status has been reported to be significantly associated with AIS, LPA, papillary, and micropapillary adenocarcinoma subtypes, although *EGFR* mutations can be seen in tumors with other histologic subtypes (Table 5). A large cohort of 806 NSCLC specimens showed a correlation between the presence of *EGFR* mutation and adenocarcinomas formerly classified as BAC or with BAC features (probably including AIS, MIA, and LPA),[275] but another study with pathology review of 97 adenocarcinomas showed no difference.[274] Predominant solid subtype has been shown to be significantly associated with *KRAS* mutations[288] but not in all studies.[69] V600E *BRAF* mutations, occur in less than 5% of cases, and they have been associated with papillary, micropapillary, and lepidic components of invasive lung adenocarcinomas.[95,279] Other less common types of *BRAF* mutations are reported such as V599E in a patient with a "well differentiated adenocarcinoma" (no subtyping information)[292] and two cases with missense mutations in exon 11 (G465V) and in exon 15 (L596R) where no histologic subtyping was reported.[293]

Table 5 summarizes our present knowledge on the molecular features associated with predominant patterns of adenocarcinoma. The only example of a strong correlation between a histologic subtype and a set of molecular and biologic features is that of invasive mucinous adenocarcinoma (former mucinous BAC), which typically have *KRAS* mutations and lack of *EGFR* mutation.[55,140,141–144] Most of these tumors are negative for TTF-1, and they may express MUC 2-5-6 because of their derivation from bronchiolar mucinous goblet cells.[146,289]

EGFR mutation is a specific target for therapy by EGFR-TKIs and is a validated biomarker of treatment response based on three recent phase 3 trials (see detailed explanation in Clinical Recommendation section)[8–11] and multiple phase 2 trials.[228–233] Recently described mutation-specific antibodies for the *EGFR* exon 19 deletion and *L858R* mutation seem to be much more reliable in predicting *EGFR* mutation status than previous antibodies, but they require further testing and validation in clinical trials.[238–240] Specific acquired *EGFR* mutations such as T790M as well as, other genetic alterations in MET (amplification), ERBB3 (overexpression), and epiregulin (autocrine loop activation), account for approximately 50% of cases of TKI resistance.[236,250,294–299]

Lung Cancers with ALK Translocations

A minority of lung tumors harbor a small inversion within chromosome 2p giving rise to the transforming fusion gene *EML4-ALK*. No activating mutations in the kinase domain are observed; the dimerization of the fusion protein causes its activation.[246] Epidemiological characteristics include prevalence in 5% of lung adenocarcinomas. Younger age, male gender, and never or light smokers may identify a population of patients with greater chance of harboring this aberration.[153,220,248,300] A variety of histologic features are reported including acinar, papillary, cribriform, mucin production (intra- and extracytoplasmic), and signet-ring patterns.[153,220,300–304]

It is still at issue whether other histological types such as squamous cell carcinoma and mucoepidermoid carcinoma also contain *EML4-ALK* translocations. Detection of the *EML4-ALK* translocations can be difficult and can be approached with several methods including immunohistochemistry, FISH, and reverse transcription-polymerase chain reaction.[153,248,249,300–303,305] Immunohistochemistry requires use of antibodies and methods that are validated to correspond well to *EML4-ALK* translocations, and it may serve as a useful screening method.[153,302,306–308] Most tumors with *EML4-ALK* translocations are positive for TTF-1 and may be p63 positive.[301,303] Tumors with *EML4-ALK* translocations seem to be mutually exclusive with *EGFR* and *KRAS* mutations and have a lower frequency of *p53* mutations.[153,247,300,301,303] Another ALK translocation involving *KIF5B-ALK* fusion has been recently identified in lung adenocarcinomas; however, at present, insufficient data exist to define its specific histological nature.[302] De novo resistance mutations in the kinase domain of *EML4-ALK* have been reported to develop during ALK inhibitor therapy.[249]

Lung Adenocarcinoma Gene Expression Analyses

The messenger RNA genomic profiling of tumors can provide important information about pathogenesis, patient prognosis, and prediction of response to therapy in a fashion that complements histological evaluation. Unsupervised clustering analysis consistently shows three distinct groups of adenocarcinomas associated with tumor morphology[69,261,309,310] and with lung developmental pathways. Beer et al.[309] showed that tumors within the three clusters were significantly correlated with differentiation, stage, and morphology as classified by bronchial-derived or lepidic morphology. Borczuk et al.[310] showed that invasive features were associated with the cluster containing more aggressive tumors. The three groups consisted of noninvasive and minimally invasive tumors (≤5 mm); mixed-invasive and lepidic pattern tumors; and solid-invasive cancers. Motoi et al.[69] demonstrated that the three clusters correlated strongly with former BAC, solid, and papillary subtypes, respectively. Takeuchi et al.[261] showed that expression profile-defined adenocarcinoma subtypes were correlated with morphology and with normal lung developmental pathways. Morphologic analysis revealed two branches consisted of TRU-type adenocarcinomas, which are based on lepidic pattern and expression of TTF-1 and surfactant proteins, and non-TRU adenocarcinomas that lack these characteristics. TRU tumors were further divided into TRU-a and TRU-b classes. Functional annotation showed retention of normal peripheral differentiated lung features in the TRU types, which contrasted with the cell cycling and proliferation enriched annotation of genes associated with the non-TRU tumors.

Although *EGFR* mutations are found in association with papillary predominant adenocarcinomas (Table 5)[69,98] and TRU-a tumors, whereas *KRAS* mutations are more frequent in the solid and TRU-b tumors, it is clear that oncogene mutation status is not a primary determinant of the molecular

subtypes as defined by gene expression profiling.[311] Taken together, unsupervised clustering defines three morphologically distinct groups of lung adenocarcinomas. These include (1) AIS and MIA; (2) invasive nonsolid adenocarcinoma; and (3) invasive adenocarcinoma, predominantly solid.[69,261,309,310] Thus, these molecular profiles provide biological plausibility for the proposed classification scheme that creates separate categories based on evaluation of lepidic pattern and other components, including solid pattern.

Recently Bryant et al.[278] used the lung adenocarcinoma gene expression data from Shedden et al.[99] together with complete pathological review to examine associations between 27 known cancer-related pathways and the adenocarcinoma subtype, clinical characteristics, and patient survival. Unsupervised clustering of adenocarcinoma and gene expression enrichment analysis reveals three main clusters and that cell proliferation is the most important pathway separating tumors into subgroups.[278] Further, adenocarcinomas with increased cell proliferation demonstrate significantly poorer outcome and an increased solid subtype component. Interestingly, tumors with any solid component have decreased survival, when compared with tumors without a solid component. Significant associations between specific histologic subtypes, gene expression pathways, and clusters were also reported, some of these are included in Table 5. The consistency of these findings was demonstrated using two independent lung adenocarcinoma cohorts from Japan ($N = 87$) and France ($N = 89$) using the identical analytic procedures.[278]

Tumor messenger RNA profiling is emerging as a source of clinically significant information regarding patient outcome after resection. Several predictors have been developed based on methodologically sound approaches that include independent validation.[312–324] The results of these studies are heterogeneous in terms of the number of genes both in the predictors and in the specific genes included in each signature. This heterogeneity is expected given differences in study design, assay platform, tumor histology, and patient selection. A large, multicenter, blinded evaluation of eight independently derived genomic signatures of prognosis in 442 adenocarcinomas demonstrated that the addition of clinical covariates enhanced the performance of the signatures, relative to using gene expression alone.[99] A method that relied on the correlated expression of 100 gene clusters to predict subject outcome produced relatively good performance with several other methods showing similar performance.[99] Relatively higher expression of a cluster of 545 genes enriched for cell proliferation was associated with poor outcome. This study is a model for the careful handling of challenges inherent in translational cancer genomic studies and for its vast repository of clinical and pathologically annotated data. Independent prospective evaluation of the predictive accuracy of these signatures, prospective clinical trials, and application to small biopsy specimens[200–203] will be required to extend this area of research.

Copy Number Analyses of Lung Adenocarcinoma Subtypes

Multiple studies have defined lung adenocarcinoma subtypes by using techniques to assess DNA copy number changes.[41,69,257,280,284,325–327] Adenocarcinoma subtype was examined in a comprehensive analysis using CGH by Aviel-Ronen et al.,[326] who contrasted former BAC and invasive mixed-type adenocarcinoma with former BAC features, most of which would probably be classified as invasive adenocarcinoma with predominant lepidic growth in the new classification. A large number of specific chromosomal alterations were detected such as gain at 1p, 2q, 5p, 7p, 11p, 11q, 12q, 16p, 16q, 17q, 20q, and 21q in both former BAC and the adenocarcinomas with lepidic growth. Although both types had similar chromosomal changes, the invasive adenocarcinomas with lepidic growth showed greater variability and frequency of chromosomal changes and with longer segmental alterations and deletions. Deletions were also more common in adenocarcinomas with lepidic growth and were observed mainly on 3p and 5q and to a lesser extent on 4q and 6q. The genomic profile of former BAC seems to be distinguishable from that of invasive adenocarcinoma with lepidic growth, with the latter displaying greater genomic aberrations. This demonstrates a progression at the genomic level from former BAC to the invasive areas of adenocarcinoma with lepidic growth.

Weir et al.[257] found the most common focal amplification event in lung adenocarcinoma involved chromosome 14q13.3 in 12% of cases and TTF-1, also known as NKX2-1 was identified in this region. Barletta et al.[41] examined histologic correlations with amplification of the *TTF-1* gene, and six cases demonstrated *TTF-1* amplification among the 49 acinar, papillary, and solid subtypes but not in tumors classified formerly as BAC.

EGFR gene amplification was examined using FISH by Hirsch et al.,[284] who demonstrated that *EGFR* gene copy number detected by FISH is associated with improved response to gefitinib therapy in patients with advanced-stage former BAC and in adenocarcinomas with lepidic growth. A strong relationship between mutation and *EGFR* amplification was also reported by Cappuzzo et al.[328] Conde et al.[280] reported similar results with a higher percentage of mutations among adenocarcinomas with former BAC and papillary morphologies relative to adenocarcinomas without these features. Chang et al.[327] used CISH and found that TKI responsiveness was significantly associated with *EGFR* mutation and adenocarcinoma morphology but only marginally with increased *EGFR* gene copy number. Other studies report similar findings, but the relationship between adenocarcinoma subtype and *EGFR* copy number changes is often not indicated.[195,198,287] Motoi et al.[69] was one of the first studies to examine this and found no strong correlations between adenocarcinoma subtype and *EGFR* amplification using CISH.

EGFR copy number analysis during the progression of adenocarcinomas has been examined.[264,267] *EGFR* mutations precede copy number abnormalities. *EGFR* copy number heterogeneity was greater in the primary tumor than in corresponding metastases.[264] *EGFR* amplification correlated with high histologic grade and/or invasive growth and was rare in the precursor lesions AAH and former BAC.[267] Thus, tumors with these changes appear more aggressive. Zhu et

al.[236] showed that using a multivariate Cox model, high *EGFR* copy number was both a significant prognostic factor for poor survival (HR: 1.93, CI: 1.09–3.44, $p < 0.025$) and a significant predictive factor of an erlotinib effect on survival (HR: 0.33, CI: 0.15–0.71, $p < 0.005$). The amplification of *MET* may be one possible mechanism associated with tumor resistance to erlotinib.[267] Finally, the application of these types of FISH analyses to small diagnostic samples was examined by Zudaire et al.[201] They found that more than 90% of cases of paraffin-embedded transthoracic FNA samples were suitable for FISH for both *EGFR* and *c-MYC* analyses. These studies suggest that even when limited tumor material is available, copy number analyses may provide prognostic information for *EGFR* amplification and an explanation for resistance to EGFR-TKIs for *MET* amplification. Nevertheless, *EGFR* mutation is more predictive of response to EGFR-TKIs than amplification.[198,241]

Multiple Pulmonary Nodules

Several techniques have been tested to distinguish metastases from synchronous primary tumors including DNA microsatellite analysis,[329,330] CGH,[331] DNA mutation sequencing,[332–336] immunohistochemistry,[337] and gene expression analysis. The utility of these assays is enhanced by their potential application to small biopsy specimens. These approaches have not been prospectively validated; thus, their performance and efficacy in routine clinical practice remain to be established. Nevertheless, these molecular techniques offer promising new ways to help in the distinction of synchronous primary tumors from metastases in patients with multiple adenocarcinoma nodules, which is critical for accurate tumor staging, determination of prognosis, and for planning treatment.[338,339]

Molecular Differences in Metastases versus Primary Tumors

There may be important differences between the primary tumor and metastases of lung adenocarcinoma both with respect to morphology and biomarker expression; however, more study of this problem is needed.[340] The mutation status of metastases can be the same[341,342] or different from that of the primary tumor and also among metastases, so a multidisciplinary approach is needed.[343,344] The available data regarding *EGFR* mutations is mainly from tumor material collected at the time of diagnosis (either from the primary tumor or from metastases) and not from the point in time at which treatment with EGFR inhibitors is given.

Molecular Prognostic Factors

Biomarkers that can predict patient prognosis have been extensively sought during the past 20 years. Immunohistochemical markers for which meta-analyses have been done include EGFR,[345] TTF-1,[346] p21ras,[347] HER2,[348] p53,[349,350] Ki67,[351] *Bcl*II,[352] and cyclooxygenase 2.[353] All but EGFR, p21 ras, and cyclooxygenase 2 were statistically significant by meta-analysis. Nevertheless, the magnitude of the association is generally weak with HRs that range from 1.13 to 1.57.

Meta-analyses[347,349,350] showed that although prognostic impact of mutations of *p53* or *KRAS* gene might be statistically significant, their impact was not strong enough to be recommended for routine clinical use. In contrast, there is a suggestion that patients who underwent surgical resection for lung adenocarcinomas that have *EGFR* mutations seem to have better prognosis in the absence of EGFR-TKI therapy than those without, based on two retrospective observational studies.[354,355]

Molecular Research Recommendations

1. More investigation is needed of copy number variation, genomic, and proteomic markers for their relationship to clinical and pathologic variables.
2. *EML4-ALK* fusion gene needs further study, particularly in *EGFR/KRAS*-negative cases.
3. We recommend that research studies of molecular markers be based on well-annotated clinical and pathologic datasets, with adenocarcinomas diagnosed according to this classification.
4. MicroRNAs need further evaluation to determine whether they can be helpful in lung adenocarcinoma risk stratification and outcome prediction.[356,357] There is limited information regarding correlation with adenocarcinoma subtype classification.
5. Investigations combining both genomic and proteomic studies are needed to determine whether they can provide more accurate subclassification of NSCLC and adenocarcinoma, and more precise information regarding the risk stratification, outcome prediction, and treatment selection for different subtypes of adenocarcinoma.

RADIOLOGIC FEATURES

A number of terms have been used to describe lung adenocarcinomas by CT imaging. In particular, for tumors that present as small nodules, the terms used have reflected the various ground glass (nonsolid), solid, or part-solid appearances that can occur. Largely based on the Fleischner Society glossary of terms[358] and the recently suggested guidelines by Godoy and Naidich[359] for subsolid nodules, we propose the following definitions: (1) a pure GGN (synonym: nonsolid nodule) as a focal area of increased lung attenuation within which the margins of any normal structures, e.g., vessels, remain outlined, (2) a solid nodule as a focal area of increased attenuation of such density that any normal structures, e.g., vessels, are completely obscured, and (3) part-solid nodule (synonym: semisolid nodule) as a focal nodular opacity containing both solid and ground-glass components.[358,359] The Fleischner Society glossary of terms for thoracic imaging defines a nodule on a CT scan as "a rounded or irregular opacity, well or poorly defined, measuring up to 3 cm in greatest diameter" in any plane.[358] If the opacity is greater than 3 cm, it is referred to as a mass.[358] The ≤3 cm cutoff is in keeping with our concept of the maximum accepted size for the pathologic diagnosis of AIS and MIA. The term subsolid nodule has also entered common radiologic usage, referring to both part-solid nodules and pure

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).

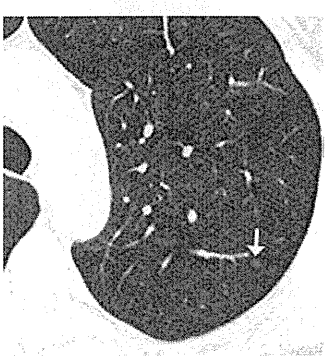

FIGURE 11. CT of preinvasive lesion (AAH or AIS). Axial 2-mm image through the left upper lobe shows a 5 mm pure ground-glass nodule (GGN), which has remained stable for 8 years (arrow). AAH and AIS can be single or multiple. AIS, adenocarcinoma in situ; CT, computed tomography.

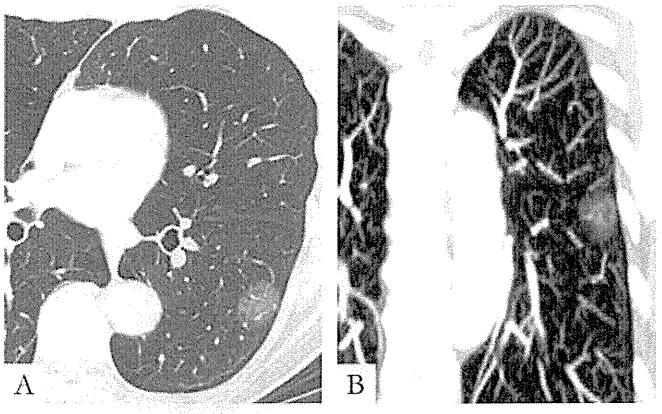

FIGURE 12. CT of a peripheral 2 cm nonmucinous AIS. *A*, Axial CT section. *B*, Coronal maximal intensity projection (MIP) image shows a pure GGN in the left lower lobe. Vessels and lung architecture are seen through the nodule. AIS, adenocarcinoma in situ; CT, computed tomography; GGN, ground-glass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

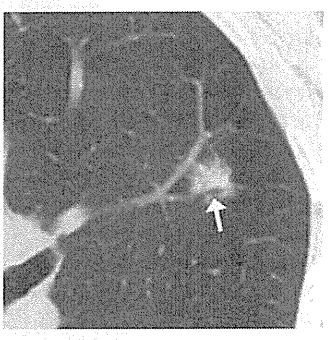

FIGURE 13. CT of mucinous adenocarcinoma in situ; 2 cm predominantly solid nodule with air bronchogram (arrow) is noted in the left upper lobe. CT, computed tomography.

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]

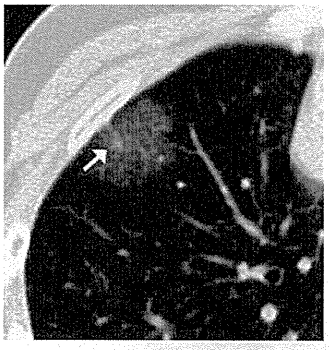

FIGURE 14. CT of nonmucinous minimally invasive adenocarcinoma. Axial 2-mm CT section shows a peripheral, predominantly ground-glass, part-solid nodule in the right upper lobe that includes a 4 × 3 mm solid component (arrow), which corresponded to invasion by pathology. CT, computed tomography.

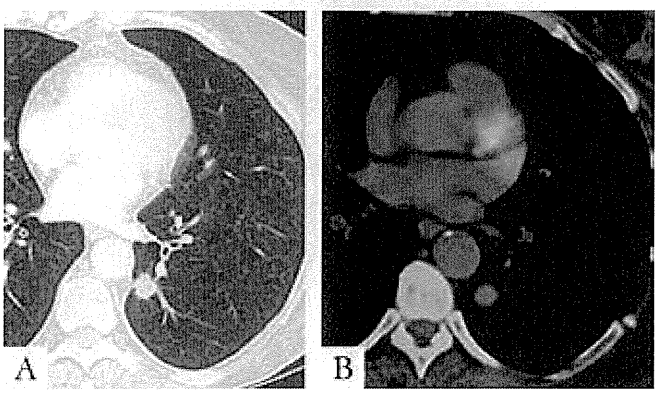

FIGURE 15. CT and FDG-PET of invasive adenocarcinoma. *A*, Axial CT image and (*B*) FDG-PET images show a 2-cm spiculated hypermetabolic solid nodule in the left lower lobe. CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography.

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

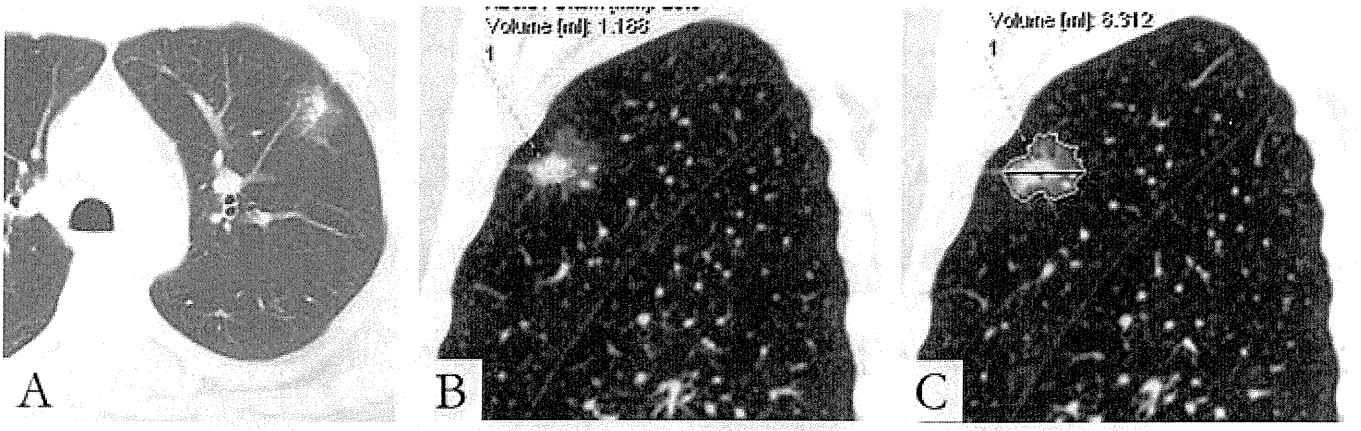

FIGURE 16. Invasive adenocarcinoma. *A*, Axial CT image shows a part-solid nodule in the left upper lobe. *B*, Corresponding sagittal CT images show automated estimation of the volume of (*B*) the solid component (1.188 cm^3) and (*C*) the entire lesion (8.312 cm^3). In this case, if tumor size were 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.

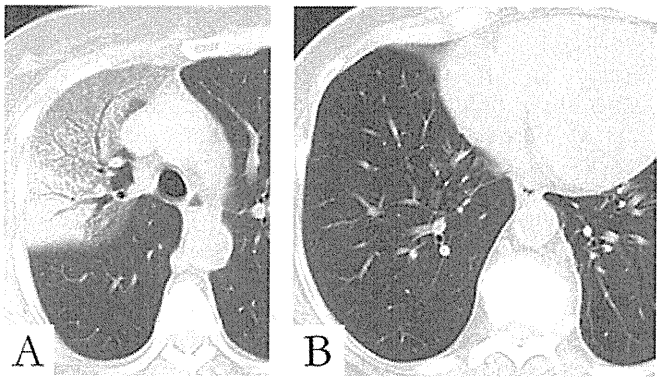

FIGURE 17. CT of nonmucinous lepidic predominant adenocarcinoma. CT images show (*A*) predominantly GGO in the right upper lobe and (*B*) multiple GGN in the right lower lobe. CT, computed tomography; GGN, ground-glass nodule.

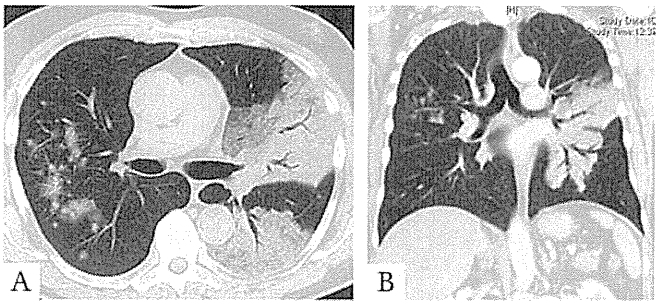

FIGURE 18. CT of invasive mucinous adenocarcinoma. *A*, Axial and (*B*) coronal CT images show multilobar consolidation and nodules mixed with GGO. Air bronchograms are present. CT, computed tomography; GGO, ground-glass opacity.

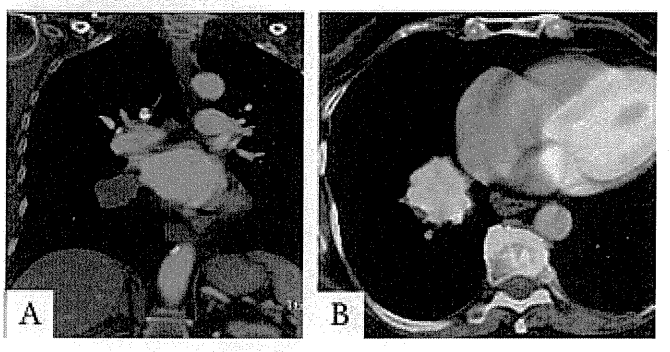

FIGURE 19. CT and FDG PET of invasive mucinous adenocarcinoma. *A*, Coronal CT and (*B*) FDG-PET images show a hypermetabolic hypodense solid 4 cm mass in the right lower lobe. CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography.

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

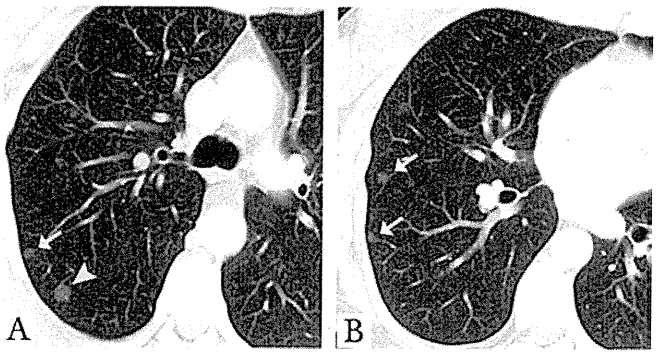

FIGURE 20. CT of multicentric GGNs of AIS/AAH. *A* and *B*, Multiple subsolid nodules (arrows) on axial 3-mm CT images show differing sizes and attenuation. These were presumed to represent preinvasive lesions (AAH and AIS). Because the dominant nodule in the right upper lobe posteriorly near the fissure 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).
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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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