Risk stratification for lung nodules: Size isn't everything

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With the demonstration of the efficacy of low-dose computed tomography (CT) screenings for lung cancer in the National Lung Screening Trial, the detection of early-stage lung cancer is expected to increase.¹ Small lung cancers ≤ 2 cm (T1a in the seventh edition of the tumor, node, and metastasis [TNM] classification) have been categorized further into T1a (≤ 1 cm) and T1b (> 1 to ≤ 2 cm) in the upcoming eighth edition.² This change was based on prognostic data from a multinational cohort of the International Association for the Study of Lung Cancer (IASLC), which is considered the reference standard for overall survival for patients with non-small cell lung cancer (NSCLC). The TNM classification is a simple and clinically useful prognosticator. Increasing patient age, however, is associated with more comorbidities and high competing risks³; therefore, the consideration of multiple available treatment options (sublobar vs lobar resection, or stereotactic ablative radiotherapy) and risk stratification beyond tumor size are required in the management of both solitary lung nodules and early-stage lung cancers.

More than 80% of all lung cancers are NSCLC, among which adenocarcinoma (ADC) is the most common histologic subtype, and its incidence is increasing. In an effort to better prognosticate lung ADC beyond the use of the T component of the TNM staging classification, a multidisciplinary group composed of experts from the IASLC, American Thoracic Society (ATS), and European Respiratory Society (ERS) proposed a new classification. The foundation of this new classification was the evidence that histologic subtype can predict tumor behavior and malignancy.⁴ The World Health Organization adopted this system in 2015, after validation in independent cohorts.⁵

In this classification, 4 major concepts were recommended: (1) histologic patterns are recorded in 5% increments, and the predominant histologic pattern subsequently is determined (lepidic [LEP], acinar, papillary, micropapillary [MIP], and solid [SOL]); (2) MIP pattern was added as a major histologic subtype, owing to its association with poor

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Central Message

Beyond tumor size, the presence of high-risk features on radiologic imaging, preoperative biopsy, and postoperative histologic subtype should be considered in the risk stratification of small lung nodules.

See Editorial Commentary page 1563.

prognosis; (3) 2 new subtype categories were added, adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA); and (4) mucinous bronchioloalveolar carcinoma was reclassified as invasive mucinous adenocarcinoma (IMA). This histologic classification had implications for the Fleischner Society recommendations for the management of sub-solid pulmonary nodules detected by CT scan.⁶ Additionally, the IASLC Lung Cancer Staging Project addressed the correlation between radiologic part-solid nodules and the histologic components of ADC by proposing the revised T categories and tumor size assessment in the eighth edition of the TNM classification.⁷

Herein, to address the pressing need to manage small lung nodules detected on CT scans, we summarize the published evidence and discuss key issues related to diagnostic and staging workup, choice of resection type (lobectomy vs sublobar resection), and postoperative risk assessment. After the recorded decrease in cigarette smoking, the incidence of squamous cell carcinoma has declined. Squamous cell carcinoma accounts for $< 20\%$ of all early-stage NSCLC tumors³; therefore, the article is focused primarily on the management of lung ADC.

AT PRESENTATION OF A LUNG NODULE: FURTHER WORKUP OR FOLLOW-UP?

Pure ground-glass nodules identified on first presentation are followed with further imaging.⁶ Solid and sub-solid nodules detected by CT scans require further work-up. The Fleischner Society and,⁶ after considering new data from the National Lung Screening Trial and other trials, the National

FIGURE 1. Risk stratification for small nodules.^{3,4,6,8-21} §Persistent solid component ≥6 mm in the follow-up CT scan. *Adequate tissue is needed for both histologic and molecular testing. #EBUS is the preferred first choice on the basis of invasiveness, sensitivity, and the relative cost of mediastinoscopy. ¶High-grade subtypes: MIP, SOL, or colloid-predominant subtypes, or invasive mucinous adenocarcinoma. CT, Computed tomography; LC, lung cancer; COPD, chronic obstructive pulmonary disease; PET, positron emission tomography; SUVmax, maximum standardized uptake value; Sublobar, sublobar resection; C/T ratio, consolidation to tumor ratio; ADC, adenocarcinoma; TDR, tumor disappearance ratio; MIP, micropapillary; SOL, solid; PFT, pulmonary function test; FEV1, forced expiratory volume in the first second; DLCO, diffusion capacity of the lungs for carbon monoxide; STAS, spread through air spaces; LVI, lymphovascular invasion.

Comprehensive Cancer Network recently published guidelines for lung cancer screening and workup of lung nodules.⁸ On the basis of these guidelines and other published evidence, we propose an algorithmic management of CT-detected solitary lung nodules (Figure 1).^{3,4,6,8-21}

Initial diagnostic work-up with positron emission tomography/CT should be considered for any nodule that has a solid component ≥ 8 mm or for sub-solid nodules with a persistent solid component ≥ 6 mm.⁸ The results of this imaging—along with patient risk factors for lung cancer (eg, passive/active smoking, occupational exposure, smoking-related other cancer history, family history, and chronic obstructive pulmonary disease)—are used to determine whether the nodule is highly suspicious for lung cancer, which would necessitate further workup/treatment, or not suspicious for lung cancer, which would allow for management with close follow-up only.⁶

TO PERFORM THE PREOPERATIVE BIOPSY OR NOT?

Preoperative Diagnostic Biopsy

Patients for whom there is strong clinical and radiologic suspicion of stage I disease, on the basis of lung cancer risk assessment, may not require a diagnostic biopsy before resection, unless intraoperative diagnosis appears to be difficult or risky⁹ and/or preoperative histologic information influences the type of surgical resection. Because of the therapeutic implications of the recent advances in histologic subtyping, diagnostic core-needle biopsy²² is substantive enough to allow for both histologic and molecular testing.²³ Patients for whom there is suspicion of lung cancer and who are being considered for nonsurgical therapy require histologic confirmation before initiation of treatment.⁹

In the ongoing multicenter Cancer and Leukemia Group B (CALGB) 140503 trial, Kohman and colleagues¹⁰ investigated the factors preventing the intraoperative randomization of patients with clinical stage IA NSCLC ≤ 2 cm to be treated with lobectomy or sublobar resection. Of 637 preregistered patients, only 61% were randomized. Of the nonrandomized patients (39%), $>80\%$ were found to be misdiagnosed (benign nodules) or understaged. The reasons for nonrandomization ($n = 208$) were (1) NSCLC not confirmed (benign or other malignancy) by intraoperative frozen-section analysis (58%); (2) NSCLC confirmed but patient ineligible because of advanced stage (23%); (3) technical reasons (6%); and (4) other reasons (14%). There was a statistically significant increase in successful randomization (50% vs 23%) among patients who had preoperative diagnostic biopsies. This study concluded that preoperative biopsy for radiologically suspected small NSCLC would reduce the number of nontherapeutic or unnecessary thoracic procedures.

Preoperative Invasive Mediastinal Staging

Intraoperative mediastinal node staging is recommended before planned resection (during the same anesthetic event)

for all patients diagnosed with clinical stage I or II lung cancer, except those with radiologically solid tumors < 1 cm or pure nonsolid tumors ≤ 3 cm, because of the low likelihood of positive mediastinal lymph nodes.⁹ Preoperative staging is recommended when there is strong clinical suspicion of N2 or N3 nodal disease. The utility of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and/or mediastinoscopy in detecting occult nodal metastasis in clinical stage I lung cancer is an ongoing focus of investigation.²⁴

Czarnecka-Kujawa and colleagues¹¹ conducted a retrospective, cost-effectiveness analysis of mediastinal lymph node staging in NSCLC and compared 4 strategies on the basis of cost, sensitivity, and risk of pN2 in clinical N0 patients: (1) no invasive staging before surgery; (2) EBUS-TBNA; (3) mediastinoscopy; and (4) EBUS-TBNA followed by confirmatory mediastinoscopy. This study concluded that, in patients with low pN2 risk ($< 2.5\%$) invasive mediastinal staging was not cost-effective, in moderate-risk patients (2.5%-57%) EBUS-TBNA was cost-effective when used as the only staging modality, and in high-risk patients ($> 57\%$) confirmatory mediastinoscopy should be considered in cases of negative EBUS-TBNA.

We reported previously that the histologic presence of MIP pattern and the absence of LEP pattern were independent predictors of occult mediastinal lymph node metastasis in patients with clinical N0-1 lung ADC (tumor size ≤ 5 cm).²⁵ In this consecutive case study cohort, 11% of all patients had occult N2 disease and the risk of occult N2 disease increased as the percentage of MIP pattern increased (MIP pattern: $< 5\%$, 5%-39%, and $\geq 40\%$; occult N2: 6%, 13%, and 26%, respectively). The presence of SOL pattern also was associated with a high risk of occult N2 disease. According to the risk-specific mediastinal staging strategy reported by Czarnecka-Kujawa and colleagues,¹¹ if presence of MIP and/or SOL pattern is recognized on preoperative tumor biopsy specimens, preoperative EBUS-TBNA would be appropriate on the basis of the high risk of positive N2 nodes. A combination of high-risk clinical and radiologic features, together with the presence of MIP and/or SOL histologic pattern on preoperative biopsy, necessitates preoperative EBUS-TBNA.

RESECTION TYPE: LOBECTOMY OR SUBLOBAR?

The standard treatment for stage I NSCLC is lobectomy with mediastinal lymph node evaluation.²⁶ An analysis of Surveillance, Epidemiology, and End Results data between 2001 and 2007, however, demonstrated that, among elderly patients (≥ 66 years of age), only 59% had undergone lobectomy, with this percentage decreasing as age increased.²⁷ Despite concerns about the adequacy of sublobar resection as a curative option,²⁸ its use has been increasing. Sublobar resection (segmentectomy and wedge

resection) was considered an alternative treatment for (1) elderly patients ≥ 75 years of age²⁶; (2) patients with poor pulmonary reserve or other major comorbidities that contraindicate lobectomy⁹; and (3) patients with peripheral nodules ≤ 2 cm with pure AIS histologic pattern, $\geq 50\%$ ground-glass appearance on CT scan, or surveillance-confirmed long doubling time (≥ 400 days).⁹ Data from ongoing randomized clinical trials (CALGB 140503 and Japan Clinical Oncology Group [JCOG] 0802) assessing the outcomes of sublobar versus lobar resection of small (≤ 2 cm) tumors can add to the accuracy of individual lung cancer-specific prognostic risk assessment.

Preoperative Radiologic Risk Assessment

JCOG 0201 prospectively investigated the utility of thin-section CT to predict pathologically noninvasive tumors. In 545 radiology and pathology evaluations, the use of 2 radiologic criteria—consolidation/tumor (C/T) ratio ≤ 0.25 in lung ADC tumors ≤ 2 cm and C/T ratio ≤ 0.5 in lung ADC tumors 2 to 3 cm—was able to predict excellent prognosis in patients after lobectomy.¹² A separate multi-institution retrospective study showed that C/T ratio ≤ 0.25 was associated with excellent prognosis in lobectomy-tolerant patients (≤ 75 years of age) who had undergone sublobar resection, thus suggesting that tumors with a C/T ratio ≤ 0.25 are good candidates for sublobar resection.²⁹ Shimada and colleagues¹³ investigated the predictive value of radiologic tumor disappearance ratio for pathologic invasiveness in cT1a (≤ 2 cm) N0M0 NSCLC. The prognostic value of tumor disappearance ratio was validated subsequently in a prospective trial.

Okada and colleagues¹⁴ investigated the prognostic predictive value of maximum standardized uptake value (SUVmax) from positron emission tomography scans and reported that, in addition to CT findings, SUVmax (optimal cutoff ≥ 2.5) was useful in predicting high-grade pathologic features (lymphovascular/pleural invasion and lymph node metastasis) and worse prognosis after lung resection in patients with clinically diagnosed T1N0M0 lung ADC. Our group reported that C/T ratio of 0.25 and SUVmax of 2.2 (median of the cohort) were useful markers in stratifying the risk of recurrence after sublobar resection in patients with cT1a (≤ 2 cm) N0M0 lung ADC.³⁰ Nakamura and colleagues³¹ reported a close association between SUVmax and predominant histologic subtypes based on the new classification—the highest SUVmax was observed in MIP, followed by SOL, IMA, acinar, papillary, LEP, MIA, and AIS.

Risk Assessment Based on Preoperative Biopsy or Intraoperative Frozen-Section Analysis

Histologic subtyping using cytologic specimens is challenging. Ferretti and colleagues³² reported that CT-guided transthoracic core-needle biopsy specimens would be useful for both histologic subtyping and molecular testing for

lung ADC in accordance with the new IASLC/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification system. Liu and colleagues¹⁵ conducted a retrospective investigation of the ability of intraoperative frozen-section analysis to distinguish AIS and MIA versus invasive ADC in patients with peripheral small lung ADC. They reported high concordance with the final pathologic assessment (84%). Because invasive ADC includes different histologic predominant subtypes of variable prognostic significance, we investigated the utility of frozen-section analysis in predicting each specific histologic subtype and found that, for detecting the presence of MIP and SOL patterns, frozen-section analysis has high specificity (94% and 96%, respectively) but low sensitivity (37% and 69%, respectively).¹⁶

Competing Noncancer Risk Assessment

Among solid tumors, lung cancer carries a relatively high risk of competing cancer and noncancer events because more than two-thirds of patients with lung cancer are ≥ 65 years of age at the time of diagnosis, one half of whom are ≥ 75 years of age.³ Among elderly patients, particularly those with early-stage disease, overall survival, disease-free survival, and recurrence-free survival are affected by competing events, which underlines the need to perform competing risks analysis during preoperative assessment.³ As age increases, the risk of competing events, such as death from noncancer diseases, also increases. Noncancer risk factors for poor outcomes include increased age, comorbidities (such as chronic obstructive pulmonary disease and cardiovascular disease), and poor pulmonary function, as determined by forced expiratory volume in the first second and diffusion capacity of the lungs for carbon monoxide.

POSTRESECTION PATHOLOGIC RISK ASSESSMENT

The new classification of lung ADC recommends that pathologists report predominant subtypes in 5% increments for all subtypes. Colloid-predominant, MIP, SOL, and IMA tumors were classified as high-grade on the basis of clinicopathologic analysis of patients with stage I lung ADC and were validated subsequently in separate international cohorts.

In addition to predominant subtype, the presence of any high-grade subtypes, such as MIP or SOL, has been reported to be associated with worse prognosis after lung resection.^{17,18} We investigated the procedure-specific prognostic impact of presence of MIP ($\geq 5\%$) in small (≤ 2 cm) lung ADC and found that presence of MIP was associated with a greater incidence of recurrence in patients who had undergone sublobar resection but not in those who had undergone lobectomy.¹⁷

Other than histologic subtype, pathologic prognosticators include tumor spread through air spaces (STAS), which we defined as tumor cells within alveolar spaces in the lung parenchyma beyond the edge of the main tumor. This is a recently recognized pattern of tumor invasion in lung cancers and has been reported to be associated with worse prognosis in patients after lung resection.¹⁹ We reported the procedure-specific prognostic impact of tumor STAS in patients with small (≤ 2 cm) lung ADC—the poor prognostic influence of STAS was more significant in patients who had undergone sublobar resection.³³ We also recently reported the incidence of tumor STAS in lung squamous cell carcinoma and its prognostic impact on recurrence and lung cancer-specific survival in a competing risks analysis.³⁴ Additionally, microscopic lymphovascular invasion has been shown to be associated with worse prognosis, and cellular findings, such as mitotic count, are considered useful prognosticators in resected lung cancer.^{20,35} Finally, we reported that *KRAS* mutation in early-stage lung ADC was a strong predictor of greater recurrence and worse survival, especially for patients with SOL-predominant tumors.²¹ Risk assessment based on molecular testing also can be performed preoperatively with biopsy specimens.³⁶

Aside from the aforementioned strategies, molecular-based risk assessments, such as cell cycle progression score³⁶ and immune microenvironment-based risk assessments (tumor-infiltrated T cells, tumor-associated Tregs, and tumoral cytokine receptor expression),³⁷ have been reported to be useful in risk assessment; their utility and integration in clinical practice have yet to be validated. Although the significance of emerging biomarkers in the therapeutic management of high-risk, early-stage lung ADC remains undefined, these patients should be reviewed in a multidisciplinary setting for potential benefits of additional therapies.

Summary

The high rate of misdiagnosis and/or understaging of solitary small lung nodules despite best management practices, combined with the high rates of recurrence seen in a subgroup of early-stage patients undergoing curative-intent resection, necessitates risk stratification beyond tumor size in the management of small-sized lung nodules. Our algorithmic summarization of the published evidence can help identify and stratify subgroups of patients who have a greater risk of recurrence or death. Furthermore, it can assist in individualizing treatment plans that include different treatment modalities (surgery or stereotactic ablative radiotherapy), different surgical procedures (lobectomy or sublobar resection), and additional postsurgical therapies (completion lobectomy, adjuvant chemotherapy, or observation).

Conflict of Interest Statement

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