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Advances in Radiological Characterization of Lung Cancer and Lung Nodules

By Jessica C. Sieren, PhD and John D. Newell, Jr., MD, FACR, FCCP, FASER

Recent advances in computed tomography (CT) have progressively increased spatial resolution and decreased acquisition times, making it possible for high-resolution, 3-dimensional, isotropic images of the whole lung to be acquired in less than 10 seconds. This has expanded capabilities for the early detection of small pulmonary nodules. It is believed that early detection of lung cancer will result in earlier treatment at lower stages of the disease, thereby improving the 5-year survival rate, which has remained relatively constant at 15% for the last 30 years.[1] Early nodule detection and characterization are required to separate the large number of non-cancerous nodules from malignant lesions that require treatment. The lung cancer scientific and medical community is currently trying to meet this challenge.

Lung cancer screening with CT scans

The National Lung Screening Trial (NLST) compared the efficacy of chest radiography to low-dose chest CT (LDCT) for the purpose of screening high-risk individuals for lung cancer. In 2011, the NLST published the results of the study that showed a 20% relative reduction in lung cancer mortality and an accompanying 6.7% relative reduction in all-cause mortality[2,3] when LDCT was compared to chest radiography. The trial included over 50,000 participants at high risk for developing lung cancer: current or former (quit within 15 years) heavy smokers (≥30-pack-years) between 55 and 74 years of age at randomization. These findings have prompted support for LDCT screening for lung cancer in at-risk individuals from the National Comprehensive Cancer Network (NCCN),[4] the American Lung Association,[5] and the American Cancer Society.[6]

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Although there was a significant reduction in lung cancer mortality in the LDCT arm of the NLST, 96.4% of the nodules found by LDCT were non-cancerous.[2] The critical step now is to distinguish malignant nodules from the majority of non-cancerous nodules in a timely and resource-efficient manner. The American College of Radiology (ACR) supports techniques that reduce lung cancer mortality. However, official guidelines from the ACR will not be released prior to publication of the NLST cost-effectiveness evaluation, which is expected to come out in 2013. A preliminary lung cancer screening cost-benefit analysis from the NCCN estimates that lung cancer screening with LDCT would add an expense of $240,000 per cancer death avoided, with an anticipated 8,000 cancer deaths avoided annually.[7] This study acknowledged the potential to optimize the cost/benefit ratio by maintaining tight control of the target population for screening, ensuring adherence to follow-up management plans, and, in order to gain support for screening from insurers, eliminating insurance coverage for expensive, late-stage interventions with minimal proven health benefits.

Detecting pulmonary nodules with CT scans

The superior spatial resolution and volumetric data presentation of LDCT imaging permits the early detection of very small (4 mm) pulmonary lesions. Early detection and treatment of lung cancer is essential in improving lung cancer mortality rates. However, LDCT generates significantly more image data per exam than chest radiography, thus requiring more time and effort for radiology interpretation. Computer aided detection (CAD) systems are computer analysis approaches that serve as a secondary or adjunct reader to radiologists. They can highlight specific areas of interest for the radiologist to interpret as pulmonary lesions or as false positives.

The performance of CAD systems varies widely with respect to sensitivity and specificity, due to the diversity in algorithmic approaches. Recent studies have reported improved sensitivity with an associated increase in false positives when CAD is incorporated into radiologist assessment of CT data. Roos et al. reported a 16% increase in sensitivity, accompanied by a 26% increase in the false positive rate from 1.15 per patient to 1.45 per patient when CAD was combined with radiologist assessment.[8] Godoy et al. addressed the question of performance for solid, part-solid and ground glass nodules (GGNs) incorporating both thin- and thick-slice CT data and independent CAD performance, radiologist performance, and radiologist with CAD performance.[9] Again, improvements in sensitivity (19% improvement for thin-slice CT; 31% for thick-slice CT) were achieved by incorporating CAD, but at a cost of increased false positives per case (0.64 vs 0.90 for thin-slice CT; 1.19 vs 1.26 for thick-slice CT).

Challenges in CAD development include uncertainty in 'ground truth' with regards to true positive nodules. True positive nodules are nodules that are identified with CAD and are known to be physically present. With regards to cancer detection, histopathological diagnosis achieved by resection or biopsy is utilized as 'ground truth' diagnosis. Unfortunately, for identification of small pulmonary nodules, there is no conclusive way to physically determine presence or absence of the identified nodule. The typical approach used to establish a surrogate for 'ground truth' for CAD development is to have data independently read by multiple radiologists followed by a majority or consensus vote to determine nodules present within a training dataset. Establishing reliable and consistent 'ground truth' for nodule presence is vital to the training of CAD systems and ultimately the performance on test cases. In addition, the reported performance statistics for alternative CAD approaches are not directly comparable because the CT data incorporated into the studies are highly diverse and complex. The Lung Image Database Consortium was established to create an open access database of annotated CT datasets for the development and cross-comparison of pulmonary lesion CAD systems and is a highly valuable tool for advancing CAD applications.[10-13] CAD for pulmonary nodule detection is an exciting technology with powerful potential to assist with the data volume increases expected as lung cancer screening becomes broadly implemented.

Management of CT-detected pulmonary nodules

Low-dose chest CT is a critical tool for detecting and assessing pulmonary nodules. Utilization of LDCT is likely to expand in the future with the expansion of lung cancer

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Table 1: Recommendations for the Management of Small Pulmonary Lesions Detected on CT[a]

Radiological appearance		Nodule Size (mm)	Patient Risk[c]	Initial CT (months)	Surveillance CT (months)	Additional Testing
Solitary	Pure GGN	≤5	All	None	None	
		>5	All	3 (confirm presence)[b]	Every 12 for 36	
	Part Solid GGN	<5 (solid component)	All	3 (confirm presence)[b]	Every 12 for 36	
		>5 (solid component)	All	3 (confirm presence)[b]	Additional testing recommended	PET/CT (>10mm), biopsy, surgical resection
	Solid	≤4	Low	None	None	
			High	12	None	
		>4-6	Low	12	None	
			High	6-12	18-24	
		>6-8	Low	6-12	18-24	
			High	3-6	9-12 and then 24	
		>8	All	3	9 and then 24	PET/CT, biopsy
Multiple	Pure GGN	≤5	All	24	24	
		>5 (no dominant lesion)	All	3 (confirm presence)[b]	Every 12 for 36	
	Solid or Part Solid (dominant lesion)		All	3 (confirm presence)[b]	Additional testing recommended	Surgical resection

***Abbreviations**: CT, computed tomography; GGN, ground-glass nodule; PET, positron emission tomography.*
a Adapted from recommendations from the Fleischner Society.[14,15]
b Confirmation of presence is required because benign GGNs may resolve in this period. If completely resolved, surveillance is not required.
c Low Risk: minimal or absent smoking history and other known risk factors. High Risk: history of smoking and/or other known risk factors.

screening programs. To maximize diagnostic benefit and decrease costs of clinical management, the Fleischner Society released recommendations for the assessment of solid and subsolid pulmonary nodules <10 mm in diameter that are detected by thin-section LDCT.[14,15] These recommendations are summarized in ***Table 1***. They define subsolid lesions as pure GGNs or part-solid GGNs that contain both ground glass and solid components.

The number of subsolid lesions detected is increasing for two reasons: the incidence of lung adenocarcinoma in the population is rising, and the quality and resolution of chest CT data acquired in the clinical environment is improving.

A more specific histopathological classification of lung adenocarcinoma was recently established[16] that further subtypes lung adenocarcinoma based on survival and treatment options. However, the ability to sub-classify the *radiological appearance* of lung adenocarcinoma is less well defined. A larger amount of solid component within a part-solid GGN, as measured by high-resolution CT, has been associated with a poor prognosis, recurrence, and lymph node metastasis.[17,18] In solid lesions, size, shape, boundary, and calcification on CT are used to assess the likelihood of cancer. Calcifications that follow a diffuse, central, laminated, or popcorn pattern on CT are associated with decreased risk of malignancy. Larger size (>3 cm), spiculated boundaries,[19] and the presence

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of an air bronchogram[20] suggest possible malignancy.[21,22]

Monitoring lung nodules for stability

Monitoring temporal changes in the size and morphology of pulmonary nodules is essential for early risk stratification of patients with small lung nodules, as well as for assessment of treatment response in confirmed cases of lung cancer. The Fleischner Society management guidelines use repeated LDCT imaging as a key component of characterizing lung cancer risk for patients with small pulmonary nodules. Defining the criteria for stability is important so that we know when it is acceptable to discontinue follow-up chest CT studies. Solid lesions that exhibit no detectable increase in size or change in morphology on chest CT over a follow-up period of 2 years are currently considered stable.[23] Change in subsolid lesions can be more challenging to detect over time by chest CT, therefore these lesions are followed for 3 years.[15] An initial, short follow-up period of 3 months is recommended for subsolid lesions in order to detect those that resolve in a short period of time and to remove patients from the regular follow-up schedule, thus minimizing their anxiety and radiation exposure.[15] In order to have comparable CT image data on follow-up studies, it is important to standardize protocols across CT models and manufacturers. Patients must also be coached to achieve the same level of inspiration (typically total lung capacity) during the studies.

An important area of active research in lung nodule assessment using chest CT is to identify additional image-based phenotypic markers. CT data captures a large amount of information about the shape, boundary, attenuation, and texture of pulmonary nodules. However, the primary quantitative image-based phenotypic marker utilized clinically for nodule evaluation is diameter, as measured in the Response Evaluation Criteria in Solid Tumors (RECIST).[24] The field of radiogenomics is focused on correlating quantified imaged-based phenotypic markers (nodule sphericity, for example) with cancer diagnosis, survival, and/or genetics.[25] We have examined a small cohort of benign and malignant lung lesions (6-30 mm), extracting hundreds of quantified measures of texture and shape from both the solid lesion and the surrounding parenchyma and achieved an accuracy of 93%, with 100% sensitivity and 88.2% specificity, in distinguishing benign from malignant lesions.[26] New phenotypic markers could potentially minimize the duration of the follow-up period for chest CT screening in nodules with a benign phenotype and hence reduce radiation dose exposure. They could also provide a way to intervene earlier in lesions that have image phenotypes that are suspicious for malignancy.

Assessing lung cancer risk

In lung cancer screening, there are two important challenges related to risk: (1) how to assess patient cancer risk in order to most precisely target the appropriate population for imaging-based lung cancer screening, and (2) once imaging is complete, how to utilize CT data to efficiently and accurately segregate nodules into "likely malignant" and "likely benign" groups, with appropriate follow-up procedures to improve the specificity of CT lung cancer screening.

The NLST lung cancer screening criteria focused on subjects between 55 and 74 years of age with a ≥30 pack-year smoking history and <15 years since smoking cessation. These broad criteria provided a valuable dataset and statistically significant findings with regards to mortality. However, they may not be the optimal criteria for clinical implementation of lung cancer screening because they exclude other known lung cancer demographic risk factors. Tammemagi et al. used a modified risk factor model developed for the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial to incorporate a larger set of demographic data into the selection of subjects for screening.[27] The model incorporated age, race, education, body mass index, chronic obstructive pulmonary disease (COPD), personal and family history of cancer, smoking intensity, and duration and time since smoking cessation. Compared to the NLST criteria, the modified risk model criteria for selecting subjects who received a diagnosis of lung cancer had increased sensitivity (71.1% vs 83.0%, P<.001), specificity (62.7% vs 62.9%, P=.54), and positive predictive value (3.4% vs 4.0%, P=.01). In addition, the NLST criteria excluded more subjects from screening who ended up with a diagnosis of lung cancer compared to the risk model criteria (0.85% vs 0.50%, P<.0001).

To maximize the clinical benefit of CT imaging for lung cancer, there is a critical need to improve the specificity of CT through effective identification of pertinent structural risk factors for lung cancer. Because COPD is associated with an increased incidence of lung cancer, important insight

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may be gained through targeting pulmonary structural changes associated with this disease. Associations have been reported between lung cancer risk and airflow obstruction in COPD, as measured by spirometry.[28,29] In COPD, the physical properties of the lung that contribute to airflow obstruction include airway wall remodeling, emphysema, or a combination of these changes. These structural changes may be relatively homogeneous and diffuse throughout the lung, or they may be present with a heterogeneous dispersion of severity across the lung lobes. Spirometry relies heavily on patient effort and does not provide details about the underlying structural cause of airflow obstruction or distribution across sub-lobar regions. The connection between COPD, lung cancer, and emphysema has been previously explored in studies using chest CT,[28-30] in which subjective assessment was used to quantify CT evidence of emphysema. Gierada and colleagues performed a quantitative assessment of both emphysema and airway wall measurements using chest CT.[31] They found an association between lung cancer and emphysema, but no association with airway wall measurements. We examined the location of pulmonary nodules relative to local smoking-induced structural changes assessed by CT and found statistically significant associations between nodule position and several localized, quantitative measures of emphysema, air-trapping, and airway wall remodeling.[32]

Lowering radiation dose

Increased utilization of CT imaging and concerns about cumulative medical radiation exposure over a lifetime have pushed manufacturers to address radiation dose reduction. Iterative reconstruction techniques, as opposed to the standard filtered back projection (FBP) method, have been developed to minimize noise in the CT image and have achieved comparable reconstructed image quality for CT data acquired with radiation dose reductions of ≥50%.[33-35] FBP reconstruction is the standard, single step reconstruction method used to create image data from multiple projections. In contrast, iterative reconstruction is a multi-step, iterative process that is more computationally expensive but superior in reducing image noise. Comprehensive investigations into the impact of iterative reconstruction approaches on quantitative pulmonary assessment are still required. Yanagawa and colleagues recently reported that incorporating iterative reconstruction can improve lung nodule CAD sensitivity, although this was accompanied by more false positive findings.[36] Iterative reconstruction techniques have been shown to significantly impact quantitative measurements for emphysema and air trapping in COPD. Mets et al. found a reduction in CT-measured emphysema (3.81% vs 0.57%, P<.001) and air trapping (24.3% vs 14.4%, P<.001) when they compared FBP reconstruction to iterative reconstruction.[37] These changes in quantitative CT measures of emphysema and air-trapping using iterative reconstruction techniques could also impact the assessment of nodules, particularly subsolid nodules. Hence, we need to exercise care in the temporal assessment of changes in pulmonary nodule size and morphology as we transition to newer CT technologies.

Genetic mutations and radiological appearance

Advances in personalized oncological medicine have led to the development of targeted agents for treating lung cancers with specific genetic mutations. Epidermal growth factor receptor (EGFR) mutations are common in non-small cell lung cancer. Testing for this mutation can successfully identify tumors that can be treated with tyrosine kinase inhibitors. The rapid growth of knowledge in this area is driving researchers to examine the correspondence between molecular markers (particularly EGFR) and the CT appearance of pulmonary nodules.

EGFR mutations are associated with an increased ratio of solid component to ground glass opacity in malignant pulmonary nodules. Chung et al. studied 24 patients with multiple subsolid nodules using chest CT and testing for EGFR mutations.[38] Stratifying by CT appearance, EGFR mutations were seen in 38% of the pure-GGNs, 42% of the part-solid GGNs with <50% solid component, and 50% of the part-solid GGNs with >50% solid component. The authors also discovered different EGFR mutational profiles in synchronous subsolid nodules that indicated independent development of multifocal lesions, as opposed to metastasis from a primary lesion. Similarly, in a larger study of 162 patients, Hsu et al. found that EGFR mutations were significantly more frequent in nodules that had less ground glass and more solid components.[39]

There is also evidence that certain mutations are associated with interval change in the radiographic appearance of lung adenocarcinomas. In a retrospective study of both EGFR and

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p53 mutations in subsolid lesions, Aoki et al. found that p53 staining was negative in GGNs that were stable over time, but p53 staining was positive in GGNs that developed new or enlarging areas of solid component within the nodule.[40] EGFR mutations were found in approximately 50% of cases with no correlation to patterns of CT change.

Conclusion

The transformation of medical imaging from a qualitative interpretive science to a quantitative biomarker science is evident in the latest lung cancer and radiology research. The quantitative analysis of lung nodules has evolved from use of RECIST criteria to the application of sophisticated texture measures and correlation of image-based biomarkers with lung cancer genetics. These advances form the basis of radiogenetics and will enhance CAD approaches to lung cancer imaging. Rapid progress in this area is expected in the near future.

Disclosures

Dr. Sieren and Dr. Newell submitted ICMJE Disclosures Forms to ***Lung Cancer Frontiers***. Dr. Sieren reports no relationships with any companies or organizations whose products or services are discussed in this article. Dr. Newell reports the following relevant financial activities outside this article: VIDA Diagnostics (consultancy, patent pending, stock options); Siemens Health (research grants, travel).

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Selections from the Peer-Reviewed Literature

By Kendra Hammond, MD and Ali I. Musani, MD, FCCP

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Complications, consequences, and practice patterns of endobronchial ultrasound-guided transbronchial needle aspiration: results of the AQuIRE registry

Eapen GA, Shah AM, Lei X, Jimenez CA, Morice RC, Yarmus L, Filner J, Ray C, Michaud G, Greenhill SR, Sarkiss M, Casal R, Rice D, Ost DE; American College of Chest Physicians Quality Improvement Registry, Education, and Evaluation. *Chest* 2013; 143:1044-53.

BACKGROUND: Few studies of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) have been large enough to identify risk factors for complications. The primary objective of this study was to quantify the incidence of and risk factors for complications in patients undergoing EBUS-TBNA.

METHODS: Data on prospectively enrolled patients undergoing EBUS-TBNA in the American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education (AQuIRE) database were extracted and analyzed for the incidence, consequences, and predictors of complications.

RESULTS: We enrolled 1,317 patients at six hospitals. Complications occurred in 19 patients (1.44%; 95% CI, 0.87%-2.24%). Transbronchial lung biopsy (TBBx) was the only risk factor for complications, which occurred in 3.21% of patients who underwent the procedure and in 1.15% of those who did not (OR, 2.85; 95% CI, 1.07-7.59; P=.04). Pneumothorax occurred in seven patients (0.53%; 95% CI, 0.21%-1.09%). Escalations in level of care occurred in 14 patients (1.06%; 95% CI, 0.58%-1.78%); its risk factors were age >70 years (OR, 4.06; 95% CI, 1.36-12.12; P =.012), inpatient status (OR, 4.93; 95% CI, 1.30-18.74; P=.019), and undergoing deep sedation or general anesthesia (OR, 4.68; 95% CI, 1.02-21.61; P=.048). TBBx was performed in only 12.6% of patients when rapid on site cytologic evaluation (ROSE) was used and in 19.1% when it was not used (P=.006). Interhospital variation in TBBx use when ROSE was used was significant (P<.001).

CONCLUSIONS: TBBx was the only risk factor for complications during EBUS-TBNA procedures. ROSE significantly reduced the use of TBBx.

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EDITORIAL COMMENT: The diagnosis and staging of lung cancer has evolved significantly with the advent of positron emission tomography (PET) scanning and EBUS-TBNA. EBUS-TBNA has been shown to significantly improve diagnostic yields when compared to conventional TBNA. When compared to the historical gold standard of mediastinoscopy, EBUS-TBNA appears to have comparable diagnostic yields in accessible lymph node stations. The most recent American College of Chest Physicians guidelines for invasive mediastinal staging of lung cancer have integrated EBUS-TBNA into the staging algorithm, and studies have shown its utility in reducing unnecessary thoracotomies. However, to date, the EBUS-TBNA literature has focused primarily on diagnostic yields rather than on complications. In this article, Eapen et al. utilized the AQuIRE Registry (a database of EBUS-TBNA procedures performed at 6 academic centers) to evaluate the complications and safety of EBUS-TBNA.

Eapen et al. examined data from prospectively enrolled patients undergoing EBUS-TBNA, which included 1,317 patients over an approximately 18 month period. The overall complication rate was quite low at 1.44% (total of 19 complications). A significantly higher rate (3.21% vs 1.15%, P=.04) of complications occurred when concomitant transbronchial biopsies were performed because the results of EBUS-TBNA samples were not conclusive. Thus, EBUS-TBNA, in and of itself, had minimal complications. The use of ROSE with EBUS-TBNA resulted in a significantly less frequent use of transbronchial biopsies (12.6% versus 19.1%, P=.006). Inpatient status, the use of deep sedation/anesthesia, and age >70 years did not increase the risk for complications such as pneumothorax or bleeding. However, these factors were associated with an increased risk for escalation of care, such as hospital admission or transfer to a higher level of care if already hospitalized, when complications did occur.

In addition to evaluating complications, this study also highlighted general patterns of use of EBUS-TBNA. For example, 63% of the procedures were performed on an outpatient basis with deep sedation or general anesthesia, although approximately 37% of the procedures were done with moderate sedation alone. Interestingly, 43% of the procedures were performed to sample lymph nodes ≤1 cm in size, which would be considered at most only borderline enlarged. The majority of procedures also involved sampling multiple lymph node stations. The duration of the bronchoscopy was noted to be over 30 minutes in the majority of patients (78%).

This study highlights the overall safety of the EBUS-TBNA procedure, which had previously only been assumed, based on the relatively low numbers of complications reported in previous case series and small studies evaluating its diagnostic efficacy. In comparison, other diagnostic alternatives, such as conventional TBNA and mediastinoscopy have major complication rates of 0.3% and 1.07%, respectively (*Thorax* 2005;60:949-55; *Ann Thorac Surg* 2006;82:1185-90). These complication rates must also be viewed in the context of diagnostic yield, which has been clearly shown, at least in the case of conventional TBNA, to be higher with EBUS-TBNA (*Chest* 2004;125:322-5).

The study is limited by the low total complication rate, which hindered univariate and multivariate analyses. In addition, the results should be viewed within the context of the procedures being performed in predominantly academic settings by operators experienced with EBUS-TBNA. The registry included all patients who underwent TBNA at these institutions, many of which are referral centers, and these subjects likely do not reflect the patient population in a community pulmonary practice. Although fellows were involved in over 80% of EBUS-TBNA procedures, their involvement did not appear to increase the complication rate. Lastly, the complication rates only reflect events occurring within 24 hours of the procedure; delayed complications, such as infections, were not captured. Although infections following EBUS-TBNA appear to be quite rare, they have been reported in multiple case reports. Despite these weaknesses, this study complements prior studies and provides further support for the increased use of EBUS-TBNA in the mediastinal staging of patients with lung cancer.

Natural history of pure ground-glass opacity lung nodules detected by low-dose CT scan

Chang B, Hwang JH, Choi YH, Chung MP, Kim H, Kwon OJ, Lee HY, Lee KS, Shim YM, Han J, Um SW. *Chest* 2013; 143:172-8.

BACKGROUND: Although focal ground-glass opacity (GGO) lung nodules are generally reported to grow slowly, their natural course is unclear. The purpose of this study was to elucidate the natural course of screening-detected pure GGO lung nodules in patients with no history of malignancy.

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METHODS: We retrospectively reviewed the database of subjects who had undergone screenings involving low-dose CT scans. We included patients with pure GGO lung nodules who were followed for >2 years after the initial screening.

RESULTS: Between June 1997 and September 2006, 122 pure GGO nodules were found in 89 patients. The median nodule size was 5.5 mm (range, 3-20 mm) in the largest diameter on initial low-dose CT scan. The median follow-up period per patient was 59 months. On a per-person basis, the frequency of growth was 13.5% (12 of 89 patients). On a per-nodule basis, the frequency of growth was 9.8% (12 of 122 nodules). Nodule growth was significantly associated with initial size and new development of an internal solid portion. The median volume doubling time was 769 days for growing pure GGO nodules. A total of 11 growing nodules were surgically validated, and all lesions were confirmed as primary lung cancer.

CONCLUSIONS: About 90% of the screening-detected pure GGO lung nodules did not grow during long-term follow-up in subjects with no history of malignancy and most growing nodules had an indolent clinical course. A strategy of long-term follow-up and selective surgery for growing nodules should be considered for pure GGO lung nodules.

EDITORIAL COMMENT: The Fleischner Society published original guidelines for the follow up of small pulmonary nodules in 2005 (*Radiology* 2005; 237:395-400). With new data supporting the use of screening CT scans to detect lung cancer, the issue of newly identified pulmonary nodules has become more complex, and it could have repercussions on the US health care system. Although the data regarding solid pulmonary nodules has grown more robust, less is known about the malignant potential of GGO nodules.

Ground glass nodules are areas of increased density in which one can visualize bronchovascular structures and normal lung parenchyma. It is difficult to determine whether a GGO nodule is a benign area of inflammation or an early stage malignancy. The important questions about GGO nodules are: (1) which characteristics are associated with malignancy? and (2) what is their natural history? Answers to these questions could help clinicians predict which GGO lesions are likely to be so indolent that they are not clinically relevant.

Earlier this year, the Fleischner Society published an additional set of guidelines that focus on GGO nodules, or, as they term them, "subsolid nodules" (*Radiology* 2013; 266:304-17). The guidelines recommend no additional follow up for GGO lesions <5 mm. Lesions with solid components should be considered to have a high probability for malignancy. Lesions in the third category — pure GGO nodules >5mm — have a less clear natural history. These are the lesions that Chang et al. focused on in their study.

Chang et al. performed a single center, retrospective study involving 89 subjects (122 total nodules) with a median follow-up time of 59 months. Subjects with persistent, pure GGO nodules were identified in a database of screening low-dose CT scans. Subjects with transient nodules, solid or mixed lesions, history of prior malignancy, or concern for interstitial lung disease were excluded. Of the 491 subjects who were screened and had follow up CT scans for >2 years, nearly half of these (N=197) had transient lesions and were excluded from the study. Lesions >10 mm in diameter or which demonstrated a solid component were considered for biopsy, while lesions <10 mm and without a solid component were followed initially with repeat CT scans at 3 months and 9 months after the initial scan, then with annual scans.

The majority (89%) of lesions in this study were >5 mm, with 71% between 5 and 7 mm in diameter. Subjects were predominantly male (82%), with a mix of current (39%), former (27%), and never (34%) smokers. The frequency of nodule growth was low (9.8%, 12 of 122 nodules). Predictors of growth were initial nodule size, especially initial nodule size of <8mm, and development of a solid component. The median doubling time noted for the 12 lesions that grew was 769 days. Review of the individual growth patterns demonstrated significant variability in the latency period prior to, and overall pattern of, growth. All but one of the enlarging lesions were biopsied, and all biopsied lesions demonstrated primary lung cancer. Age, smoking history, number of lesions, and sex were not found to predict growth.

This study provides added support for classification of GGO nodules >10 mm with or without solid components as being high risk for malignancy. The high variability in individual growth patterns and lag times before growth further highlight the difficulty in developing guidelines for appropriate management of GGO nodules. The limitations of this study are its small size, retrospective design, and exclusion of transient lesions. Additional long-term studies are needed to

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clarify the behavior of these lesions.

Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: The TIME2 randomized controlled trial

Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, Davies CW, Grayez J, Harrison R, Prasad A, Crosthwaite N, Lee YC, Davies RJ, Miller RF, Rahman NM. *JAMA* 2012; 307:2383-9.

CONTEXT: Malignant pleural effusion causes disabling dyspnea in patients with a short life expectancy. Palliation is achieved by fluid drainage, but the most effective first-line method has not been determined.

OBJECTIVE: To determine whether indwelling pleural catheters (IPCs) are more effective than chest tube and talc slurry pleurodesis (talc) at relieving dyspnea.

DESIGN: Unblinded randomized controlled trial (Second Therapeutic Intervention in Malignant Effusion Trial [TIME2]) comparing IPC and talc (1:1) for which 106 patients with malignant pleural effusion who had not previously undergone pleurodesis were recruited from 143 patients who were treated at 7 UK hospitals. Patients were screened from April 2007-February 2011 and were followed up for a year.

INTERVENTION: Indwelling pleural catheters were inserted on an outpatient basis, followed by initial large volume drainage, education, and subsequent home drainage. The talc group were admitted for chest tube insertion and talc for slurry pleurodesis.

MAIN OUTCOME MEASURE: Patients completed daily 100-mm line visual analog scale (VAS) of dyspnea over 42 days after undergoing the intervention (0 mm represents no dyspnea and 100 mm represents maximum dyspnea; 10 mm represents minimum clinically significant difference). Mean difference was analyzed using a mixed-effects linear regression model adjusted for minimization variables.

RESULTS: Dyspnea improved in both groups, with no significant difference in the first 42 days with a mean VAS dyspnea score of 24.7 in the IPC group (95% CI, 19.3-30.1 mm) and 24.4 mm (95% CI, 19.4-29.4 mm) in the talc group, with a difference of 0.16 mm (95% CI, −6.82 to 7.15; P=.96). There was a statistically significant improvement in dyspnea in the IPC group at 6 months, with a mean difference in VAS score between the IPC group and the talc group of −14.0 mm (95% CI, −25.2 to −2.8 mm; P=.01). Length of initial hospitalization was significantly shorter in the IPC group with a median of 0 days (interquartile range [IQR], 0-1 day) and 4 days (IQR, 2-6 days) for the talc group, with a difference of −3.5 days (95% CI, −4.8 to −1.5 days; P< .001). There was no significant difference in quality of life. Twelve patients (22%) in the talc group required further pleural procedures compared with 3 (6%) in the IPC group (odds ratio [OR], 0.21; 95% CI, 0.04-0.86; P=.03). Twenty-one of the 52 patients in the catheter group experienced adverse events vs 7 of 54 in the talc group (OR, 4.70; 95% CI, 1.75-12.60; P=.002).

CONCLUSION: Among patients with malignant pleural effusion and no previous pleurodesis, there was no significant difference between IPCs and talc pleurodesis at relieving patient-reported dyspnea.

EDITORIAL COMMENT: Malignant pleural effusion (MPE) can have a significant and negative impact on a patient's quality of life. The most common etiology of MPE is lung cancer, however, breast cancer and lymphoma are also common. The development of MPE usually portends a poor prognosis, with a life expectancy ranging from 3 to 12 months. The majority of these effusions will be symptomatic, with most patients experiencing dyspnea. Because survival time following diagnosis is typically short, management of a symptomatic MPE should focus on the palliation of symptoms.

In 2010, the British Thoracic Society published new guidelines on the treatment of MPEs (*Thorax* 2010; 65:ii32-ii40). In that report, intercostal tube placement with pleurodesis is the preferred treatment modality for MPE in patients with a life expectancy greater than one month. The guidelines suggest that IPCs be used in the presence of a trapped lung and to minimize hospital days for patients with limited expected survival. The study by Davies et al. provides additional knowledge in this area by being only the second randomized controlled trial comparing IPC to pleurodesis for MPE. It is also the only trial to compare IPC with talc pleurodesis.

Davies et al. performed a multicenter, randomized controlled

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study comparing the relief of dyspnea provided by IPCs with that achieved with chest tube placement and talc pleurodesis. One hundred and six subjects with MPE with a life expectancy of ≥3 months and no prior pleurodesis attempts were enrolled. Dyspnea was graded daily using a 100 mm visual analog scale score for the first 42 days after the procedure, then every 4 weeks from week 10 to week 26, and finally at 9 and 12 months.

Dyspnea was the primary end point. Improvement in dyspnea scores over the first 42 days were similar between the IPC and chest tube plus talc pleurodesis groups, with both groups demonstrating improvements from their pre-procedure baselines. Six month follow-up data, however, did show a statistically significant improvement (P=.01) in dyspnea in the IPC group compared to the chest tube group.

Secondary endpoints included hospital length of stay, which was significantly shorter in the IPC group (median 0 days, compared to 4 days for the chest tube group). No significant differences between groups were found in quality of life, as measured with the QLQ-30 questionnaire. Adverse events were more frequent in the IPC group (40% vs 13%, P=.002) and mainly consisted of pleural infection, cellulitis, and catheter blockage. None of the IPCs required removal for infection. The spontaneous pleurodesis rate in the IPC group was 51%.

Six percent of the IPC group required additional pleural procedures, compared to 22% in the chest tube plus talc pleurodesis group, a statistically significant difference (P=.03).

This study demonstrates that placement of an IPC is a viable option for treating MPEs and should be offered to patients as an alternative to chest tube placement with talc pleurodesis. Unfortunately, this study does not address which patients may benefit most from an IPC. At this time, patient preference, after discussion of the pros and cons of both methods, should drive the final decision.

Disclosures

Dr. Hammond and Dr. Musani submitted ICMJE Disclosure Forms to ***Lung Cancer Frontiers***. Dr. Hammond reports no relationships with any companies or organizations whose products or services are discussed in this article. Dr. Musani discloses the following relevant financial activities outside this article: Aeris Medical (grants/grants pending); Boehringer Ingelheim (travel/expenses); Boehringer Laboratories (royalties); Boston Scientific (consultancy, paid lectures, travel/expenses); CareFusion (paid lectures, travel/expenses); Covidien (paid lectures); Intuitive Surgical (paid lectures, travel/expenses); National Jewish Health (patent/patent pending); Olympus USA (consultancy, paid lectures, travel/expenses); superDimension (paid lectures).

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