Noninvasive Computed Tomography–based Risk Stratification of Lung Adenocarcinomas in the National Lung Screening Trial

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Abstract

Rationale: Screening for lung cancer using low-dose computed tomography (CT) reduces lung cancer mortality. However, in addition to a high rate of benign nodules, lung cancer screening detects a large number of indolent cancers that generally belong to the adenocarcinoma spectrum. Individualized management of screen-detected adenocarcinomas would be facilitated by noninvasive risk stratification.

Objectives: To validate that Computer-Aided Nodule Assessment and Risk Yield (CANARY), a novel image analysis software, successfully risk stratifies screen-detected lung adenocarcinomas based on clinical disease outcomes.

Methods: We identified retrospective 294 eligible patients diagnosed with lung adenocarcinoma spectrum lesions in the low-dose CT arm of the National Lung Screening Trial. The last low-dose CT scan before the diagnosis of lung adenocarcinoma was analyzed using CANARY blinded to clinical data. Based on their parametric CANARY signatures, all the lung

adenocarcinoma nodules were risk stratified into three groups. CANARY risk groups were compared using survival analysis for progression-free survival.

Measurements and Main Results: A total of 294 patients were included in the analysis. Kaplan-Meier analysis of all the 294 adenocarcinoma nodules stratified into the Good, Intermediate, and Poor CANARY risk groups yielded distinct progression-free survival curves ($P < 0.0001$). This observation was confirmed in the unadjusted and adjusted (age, sex, race, and smoking status) progression-free survival analysis of all stage I cases.

Conclusions: CANARY allows the noninvasive risk stratification of lung adenocarcinomas into three groups with distinct post-treatment progression-free survival. Our results suggest that CANARY could ultimately facilitate individualized management of incidentally or screen-detected lung adenocarcinomas.

Keywords: risk stratification; lung adenocarcinoma; image analysis; individualized medicine

Lung cancer is the most common cause of cancer-related deaths worldwide and in the United States. Despite significant advances in lung cancer treatment, the prognosis of

advanced lung cancer remains dismal with an overall 5-year survival of 16% (1). Although early stage lung cancer is curable with surgical resection, most patients

continue to be diagnosed with advanced disease.

A decrease in lung cancer–specific mortality of 20% was demonstrated in the

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At a Glance Commentary

Scientific Knowledge on the

Subject: Low-dose computed tomography (LDCT)-based lung cancer screening reduced mortality in the National Lung Screening Trial. However, LDCT screening seems to identify a subset of lung cancers in the adenocarcinoma spectrum with a more indolent clinical course, some of which may be overdiagnosed. Objective risk stratification of screen-detected adenocarcinomas is desirable.

What This Study Adds to the

Field: Using National Lung Screening Trial data, we validated a novel quantitative LDCT-based imaging tool that facilitates the risk stratification of lung adenocarcinomas detected on LDCT. This tool may have important future research and clinical implications.

National Lung Screening Trial (NLST) using low-dose computed tomography (CT) (2). However, lung cancer screening also identified suspicious lung nodules in 40% of participants, and 96% of these nodules were proven benign. Furthermore, approximately 20% of lung cancers diagnosed during screening may be overdiagnosed (3, 4). Although validated clinical prediction rules are used to distinguish benign from malignant nodules (5, 6), the identification and management of overdiagnosed lung cancers remain unclear. Indiscriminate treatment of these indolent cancers could result in increased mortality, morbidity, and healthcare costs, particularly in elderly patients and individuals with significant comorbidities. Interestingly, almost all indolent lung cancers belong to the adenocarcinoma spectrum and exhibit histologic features that correlate well with prognosis (7). However, comprehensive histologic assessment requires surgical resection and therefore cannot guide alternative treatment approaches. Noninvasive low-dose CT-based computer-aided risk stratification of lung adenocarcinomas therefore represents an attractive alternative.

Although most indolent lung adenocarcinomas present as subsolid

opacities, aggressive lesions and other histologic types of lung cancer almost exclusively present as solid lesions. Based on our prior analysis of two retrospective Mayo Clinic cohorts of patients with resected lung adenocarcinoma pulmonary nodules Computer-Aided Nodule Assessment and Risk Yield (CANARY), novel low-dose CT-based imaging software, may allow the noninvasive risk stratification of lung adenocarcinomas in three groups, correlating well with 5-year post-surgical progression-free survival (good, intermediate, and poor) (8, 9). In collaboration with the American College of Radiology Imaging Network (ACRIN) we independently evaluated the validity of the CANARY-based risk prediction model using the prospectively collected multiinstitutional NLST dataset.

Methods

Study Participants

The Mayo Clinic Institutional Review Board approved this study. NLST was a randomized controlled trial conducted at

33 U.S. screening centers (2). Institutional review boards approved the NLST protocol in all 33 participating centers. The study recruited asymptomatic high-risk individuals, aged 55–74 years, with an active or previous smoking history greater than or equal to 30 pack-years, having quit less than or equal to 15 years before randomization from August 2002 through April 2004. Individuals were screened for 3 years with either annual low-dose CT or chest radiography, and followed through December 31, 2009. A total of 26,722 individuals were randomized to the low-dose CT arm. All patients diagnosed with screen-detected (prevalent or incident) lung adenocarcinomas spectrum lesions (invasive, minimally invasive adenocarcinoma, and adenocarcinoma *in situ*, formerly bronchioloalveolar carcinoma) in the low-dose CT arm were included. Interval cancers were excluded.

Screening Using Low-Dose CT

Low-dose CT scans were obtained using less than or equal to 2.5-mm collimation meeting strict NLST requirements. Detailed low-dose CT criteria were previously published (10). Imaging data were transmitted electronically to Mayo Clinic

Figure 1. Consolidated Standards of Reporting Trials–style diagram outlining the cases included into the Computer-Aided Nodule Assessment and Risk Yield analysis. CT = computed tomography.

from the ACRIN and Lung Screening Study imaging core laboratories. The screening low-dose CT obtained before the diagnosis of lung adenocarcinoma was analyzed. The technical details of the included low-dose CT scans are summarized in Figure E1 in the online supplement.

Localization of Lung Adenocarcinoma and CANARY Analysis

Based on the information provided in the NLST dataset, the reported localization of all lung adenocarcinomas included in the study was confirmed by one radiologist (B.J.B.) and two pulmonologists (F.M. and T.P.) on the closest low-dose CT to the diagnosis of adenocarcinoma. Lesions were tagged electronically for CANARY analysis and segmented as previously described (8, 9). Cases without visible lesions, lesions that could not be separated from adjacent structures (mediastinum, diaphragm), or cases with missing clinical data were

excluded (Figure 1). All imaging data were analyzed blinded to all clinical outcome data. Stratification results were returned to the ACRIN statistician (F.D.) for survival analysis. Imaging and clinical data were obtained directly from NLST, ACRIN/LSS database, and the ACRIN and LSS core laboratories as part of an ACRIN Young Investigator Award (T.P.).

Nodule characterization and classification. Nodule characterization using CANARY has been previously described (8, 9). In summary, a total of 774 volumes of interest (9×9 voxels) were arbitrarily selected from 37 lung adenocarcinoma nodules ranging from pure groundglass to pure solid opacities on high-resolution CT (HRCT). Volumes of interest were compared using pairwise similarity metrics. Nine natural clusters of radiologically similar volumes of interest were identified using affinity propagation, an unsupervised clustering algorithm.

The most representative volume of interest within each cluster was identified as the exemplar. The nine identified exemplars were color-coded as violet, indigo, blue, green, yellow, orange, red, cyan, and pink to represent the radiologic building blocks of lung adenocarcinoma nodules. The characterization of a lesion consists of the sequential analysis of all voxels within the lesion. Each voxel with its surrounding 80 voxels (in a 9×9 voxel volume of interest) is compared with the nine exemplars using similarity metrics, and the color code of the most similar exemplar is assigned to the analyzed voxel. The process is repeated until all voxels have been assigned a color code. The distribution of the nine exemplars within the nodule represents its parametric signature. This parametric signature is represented as a glyph, the diameter of which is proportional to the volume of the nodules. The entire analysis

Table 1. Selected Baseline Characteristics of the Study Cohort Based on CANARY Risk Groups

	CANARY Risk Groups			Total Study Cohort Screen-detected Lung Adenocarcinomas in NLST Low-Dose CT Arm (n = 294)
	Good (n = 41)	Intermediate (n = 184)	Poor (n = 69)	
Age group, n (%)				
55–59	11 (27)	51 (28)	13 (19)	75 (26)
60–64	9 (22)	71 (39)	19 (28)	99 (34)
65–69	12 (29)	39 (21)	21 (30)	72 (24)
70–74	9 (22)	23 (12)	16 (23)	48 (16)
Sex, n (%)				
Male	18 (44)	91 (49)	37 (54)	146 (50)
Female	23 (56)	93 (51)	32 (46)	148 (50)
Race, n (%)				
White	41 (100)	172 (94)	63 (91.5)	276 (94)
Black or African American	0 (0)	8 (4)	3 (4)	11 (4)
Asian	0 (0)	3 (1.5)	1 (1.5)	4 (1)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	1 (1.5)	1 (0.5)
More than one race	0 (0)	1 (0.5)	1 (1.5)	2 (0.5)
Ethnicity, n (%)				
Hispanic or Latino	0 (0)	1 (0.5)	0 (0)	1 (0.5)
Neither Hispanic nor Latino	40 (98)	181 (98.5)	67 (97)	288 (98)
Unknown	1 (2)	2 (1)	2 (3)	5 (1.5)
Smoking status,* n (%)				
Former	27 (66)	90 (49)	25 (36)	142 (48)
Current	14 (34)	94 (51)	44 (64)	152 (52)
Pathologic stage,† n (%)				
Stage I	39 (95)	144 (78)	35 (50.5)	218 (74)
Stage II	0 (0)	11 (6)	11 (16)	22 (8)
Stage III	2 (5)	19 (10)	15 (22)	36 (12)
Stage IV	0 (0)	9 (5)	8 (11.5)	17 (6)
Unable to assess	0 (0)	1 (1)	0 (0)	1 (<0.5)

Definition of abbreviations: CANARY = Computer-Aided Nodule Assessment and Risk Yield; CT = computed tomography; NLST = National Lung Screening Trial.

* $P < 0.05$.

† $P < 0.001$.

takes less than 60 seconds. Parametric signatures have previously been shown to correlate well with the consensus histology of the lesion (Spearman correlation, $P < 0.0001$, $R = 0.89$) (8).

Nodule risk stratification. For risk stratification the parametric signatures (glyphs) of 170 consecutive surgical resected lung adenocarcinoma nodules at Mayo Clinic were compared using pairwise similarity metrics and affinity propagation (9). This process identified three natural nodule clusters, and the most representative nodule within each cluster was identified as the nodule exemplar. New adenocarcinoma nodules are compared with these three nodule exemplars and classified accordingly. We previously demonstrated that these nodule clusters demonstrate excellent correlation with 5-year progression-free survival and therefore were labeled as good (G), intermediate (I), and poor (P) CANARY classes, accordingly (9).

Statistical Methods

Survival analysis. Demographic characteristics were compared across CANARY class using chi-square and exact tests where counts were low. Kaplan-Meier curves with the log-rank test and Cox proportional hazards regression were used to examine lung-cancer progression-free survival (defined as time in months from initial lung cancer diagnosis to progression, including recurrence or lung cancer-related death) for the risk groups identified based on CANARY class. Deaths caused by clearly documented other causes, in absence of any evidence of recurrent disease, were censored at the time of death. The disease recurrence was identified based on imaging modality follow-up. In the Cox regression, potential confounders were adjusted for, including age, sex, race (white vs. nonwhite), smoking status (current vs. former), and pathologic stage (from I to IV) (one case with unknown stage was excluded for the analyses involving stage). The proportional hazards assumption was assessed through model diagnostics. The adjusted survival curves based on Cox regression estimates were also presented to graphically illustrate the survival differences among various risk groups, after averaging the values of other adjusted covariates (11). All analyses were completed using SAS (Cary, NC) and R statistical software (12).

Results

Study Participants

We reviewed all 352 cases of lung adenocarcinomas diagnosed in the low-dose CT arm of NLST. Three hundred and thirty-seven had available low-dose CT data. An additional 43 patients were excluded

because of absence of lesion on last screening low-dose CT, large hilar-mediastinal lesions, or missing outcome data (Figure 1). The demographic characteristics (age, sex, and race), smoking status, and pathologic staging of the patients with adenocarcinoma are summarized in Table 1.

Figure 2. The distribution of the Computer-Aided Nodule Assessment and Risk Yield (CANARY) patterns and parametric signature. Representative adenocarcinoma nodules quantitatively characterized using CANARY are shown for the three CANARY risk groups, Good (G), Intermediate (I), and Poor (P). (A) Raw computed tomography axial sections illustrating the nodule. (B) The computed tomography sections overlaid with CANARY pattern colors. (C) The three-dimensional rendering of the nodule. (D) Glyphs of the analyzed nodules.

CANARY Analysis

Low-dose CT datasets of 294 patients diagnosed with adenocarcinoma spectrum lesions during NLST and available outcome data were included in the blinded CANARY analysis (Figure 1). The parametric signatures of representative adenocarcinoma nodules shown as an unprocessed CT axial slice, overlay of voxel-wise exemplar-color patterns, and the extracted lesion and glyph representation are shown in Figures 2A–2D, respectively. The parametric signatures of the three previously identified nodule exemplars representing the Good (G), Intermediate (I), and Poor (P) survival groups are predominantly composed of blue–green–cyan, mixed, and violet–indigo–red–orange exemplar patterns, respectively.

Based on their similarity with these nodule exemplars, each NLST adenocarcinoma lesion was categorized as Good, Intermediate, or Poor (Figure 3). Thirty-five stage I and two stage III lung adenocarcinomas categorized as “Poor” or “Good,” respectively (Table 1).

Survival Characteristics

A total of 86 out of 294 CANARY-stratified adenocarcinoma lesions experienced recurrence ($n = 23$) or lung cancer–related deaths ($n = 63$). Fourteen patients (12 stage I, one stage II, and one stage III) died because of clearly documented other causes (see Table E1). Kaplan-Meier analysis of all 294 cases yielded distinct progression-free survival curves for the three CANARY risk groups ($P < 0.0001$) (Figure 4A). These results were confirmed in the progression-free survival curves for the subgroup of all stage I cases ($n = 218$) (Figure 4B). Kaplan-Meier plots for stage II, III, and IV patients did not reveal any significant differences between the CANARY risk groups (see Figures E2 and E3). The multivariate Cox regression hazard model of all 293 cases (one case was excluded because of unknown stage) predicting progression-free survival adjusted for the baseline variables, pathologic stage, and CANARY groups demonstrated significantly different hazard ratios comparing disease stages ($P < 0.001$), for CANARY risk groups Good versus Poor (hazard ratio, 0.09; 95% confidence limits, 0.01–0.70; $P = 0.02$) and CANARY groups Good versus

Figure 3. Montage of Computer-Aided Nodule Assessment and Risk Yield glyphs of the adenocarcinoma nodules stratified based on the identified three risk groups: Good (G), Intermediate (I), and Poor (P).

Intermediate (hazard ratio, 0.12; 95% confidence limits, 0.02–0.87; $P = 0.04$) (see Table E2).

Discussion

CANARY represents a novel quantitative imaging tool that allows the noninvasive risk stratification of lung adenocarcinomas into three groups with distinct progression-

free survival. These results validate our previous observations in a large independent prospective multicenter cohort of screen-detected lung adenocarcinoma spectrum lesions and confirm that CANARY-based risk stratification can predict patient outcomes and potentially facilitate individualized management of screen-detected lung adenocarcinoma lesions.

The comprehensive quantitative histologic assessment of resected lung

Figure 4. Progression-free survival based on Computer-Aided Nodule Assessment and Risk Yield Good, Intermediate, and Poor groups using low-dose computed tomography for patients diagnosed with adenocarcinoma during the National Lung Screening Trial. (A) All 294 cases. (B) All 218 pathologic stage I cases.

adenocarcinomas represents the basis for the recently updated classification of lung adenocarcinomas (13). Specific histologic features, such as visual estimates of tissue invasion and lepidic growth, correlate well with patient outcomes. Specifically, lesions classified as adenocarcinoma *in situ* and minimally invasive adenocarcinomas are

associated with an excellent (100%) 5-year post-surgical survival (7). Given their indolent behavior, alternative management strategies, such as limited resection, stereotactic radiation therapy, ablative techniques, or even watchful waiting compared with standard lobectomy, are being investigated in clinical trials.

Comprehensive histologic assessment of lung adenocarcinomas requires resection and consequently cannot be used to guide individualized patient management. Limited biopsy samples, such as HRCT-guided and bronchoscopic lung biopsies, do not allow this comprehensive assessment (14).

Although correlation of radiologic characteristics with histologic predictive features has been explored, it remains subject to substantial intraobserver and interobserver variability. Computer-aided diagnostic imaging tools have used morphology, calcification, spiculation, and nodule diameter to distinguish benign from malignant nodules; however, there are currently no validated tools for the noninvasive classification of pulmonary nodules of the lung adenocarcinoma spectrum (15–24).

Current semiquantitative analysis of pulmonary nodules of the lung adenocarcinoma spectrum depends on estimates of nodule size and distribution of two types of radiologic density: groundglass and solid opacity (17). However, in reality these nodules are composed of large numbers of individual voxels with a wide range of radiologic densities. Although the current semiquantitative analysis is clearly insufficient, voxel by voxel analysis is not feasible. CANARY-based risk stratification uses unsupervised clustering to reduce voxel density information to a manageable amount of data, successfully clustering lung adenocarcinomas into three clinically relevant groups. CANARY-based risk stratification seems to be valid across the most commonly used HRCT platforms and acquisitions protocols for lung cancer screening (see Figure E1).

Lung adenocarcinoma represents the most common type of non-small cell lung cancer, accounting for nearly half of incidentally and screen-identified lung malignancies. It is also the most common type of lung cancer in nonsmokers. The clinical course of a subgroup of these lesions seems to be more indolent and up to 20% of screen-detected lung adenocarcinomas may be overdiagnosed (3, 4). CANARY-based risk stratification identified 14% of all lung adenocarcinomas diagnosed in the low-dose CT arm of NLST as indolent (Good). Although ongoing clinical trials are assessing alternative management strategies for such indolent tumors, primarily based on lesion size (such

as largest diameter ≤ 2 cm) and semiquantitative estimates of groundglass and solid opacities, our data suggest that CANARY can facilitate more accurate assessment. Reliable differentiation of indolent (preinvasive or minimally invasive adenocarcinoma) from more aggressive type could help individualized patient management thereby minimizing excess morbidity, mortality, and healthcare costs associated with overdiagnosis and overtreatment. Alternatively, CANARY may also help identify those early stage (stage I) patients with the worst post-resection clinical outcomes (group Poor) who may benefit from adjuvant therapy despite a favorable surgical staging.

The strength of our study is the blinded validation of our retrospective single institution data in a large prospective cohort of screen-detected lung adenocarcinomas collected during the largest multicenter lung cancer screening trial. These data externally validate noninvasive CANARY-based risk

stratification for pulmonary nodules of the lung adenocarcinoma spectrum and clearly demonstrate its applicability across various HRCT platforms and acquisition protocols. One notable limitation of our study includes the reliance on post-treatment progression-free survival as a surrogate for the biologic behavior of lung adenocarcinoma. Although we recognize the challenges in extrapolating natural history from the behavior of treated lung cancers, this question requires a prospective study including watchful waiting as a management strategy, which depends on effective pretreatment risk stratification. CANARY offers this opportunity. In addition, we recognize that CANARY does not obviate invasive diagnostic methods to establish the diagnosis of adenocarcinoma, although most persistent subsolid opacities ultimately belong to the adenocarcinoma spectrum of disease.

In conclusion, CANARY represents a novel noninvasive tool for the accurate and reproducible risk stratification of lung adenocarcinoma nodules identified on HRCT. This approach was validated across the various HRCT platforms and acquisition protocols routinely used for lung cancer screening. CANARY-based risk stratification should be incorporated in future trials to individualize the management of HRCT-detected pulmonary nodules of the lung adenocarcinoma spectrum and may mitigate treatment-related morbidity, mortality, and increased healthcare costs associated with overtreatment. In addition, CANARY may help identify the most aggressive subgroup of patients with early stage lung adenocarcinomas and could guide the use of adjuvant treatment and ultimately better clinical outcomes for these individuals. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9–29.
2. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; 365:395–409.
3. Patz EF Jr, Pinsky P, Gatsonis C, Sicks JD, Kramer BS, Tammemägi MC, Chiles C, Black WC, Aberle DR; NLST Overdiagnosis Manuscript Writing Team. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med* 2014;174: 269–274.
4. Veronesi G, Maisonneuve P, Bellomi M, Rampinelli C, Durlì I, Bertolotti R, Spaggiari L. Estimating overdiagnosis in low-dose computed tomography screening for lung cancer: a cohort study. *Ann Intern Med* 2012;157:776–784.
5. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, Yasufuku K, Martel S, Laberge F, Gingras M, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med* 2013;369:910–919.
6. Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, Soylemez Wiener R. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143: e93S–e120S.
7. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, Beer DG, Powell CA, Riely GJ, Van Schil PE, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244–285.
8. Maldonado F, Boland JM, Raghunath S, Aubry MC, Bartholmai BJ, Deandrade M, Hartman TE, Karwoski RA, Rajagopalan S, Sykes AM, et al. Noninvasive characterization of the histopathologic features of pulmonary nodules of the lung adenocarcinoma spectrum using computer-aided nodule assessment and risk yield (CANARY)—a pilot study. *J Thorac Oncol* 2013;8:452–460.
9. Raghunath S, Maldonado F, Rajagopalan S, Karwoski RA, DePew ZS, Bartholmai BJ, Peikert T, Robb RA. Noninvasive risk stratification of lung adenocarcinoma using quantitative computed tomography. *J Thorac Oncol* 2014;9:1698–1703.
10. Aberle DR, Berg CD, Black WC, Church TR, Fagerstrom RM, Galen B, Gareen IF, Gatsonis C, Goldin J, Gohagan JK, et al.; National Lung Screening Trial Research Team. The National Lung Screening Trial: overview and study design. *Radiology* 2011;258: 243–253.
11. Nieto FJ, Coresh J. Adjusting survival curves for confounders: a review and a new method. *Am J Epidemiol* 1996;143:1059–1068.
12. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2014.
13. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger K, Yatabe Y, Powell CA, Beer D, Riely G, Garg K, et al.; American Thoracic Society. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: international multidisciplinary classification of lung adenocarcinoma: executive summary. *Proc Am Thorac Soc* 2011; 8:381–385.
14. Van Schil PE, Asamura H, Rusch VW, Mitsudomi T, Tsuboi M, Brambilla E, Travis WD. Surgical implications of the new IASLC/ATS/ERS adenocarcinoma classification. *Eur Respir J* 2012;39:478–486.
15. Dettlerbeck FC, Homer RJ. Approach to the ground-glass nodule. *Clin Chest Med* 2011;32:799–810.
16. Godoy MC, Naidich DP. Subsolid pulmonary nodules and the spectrum of peripheral adenocarcinomas of the lung: recommended interim guidelines for assessment and management. *Radiology* 2009;253: 606–622.
17. Naidich DP, Bankier AA, MacMahon H, Schaefer-Prokop CM, Pistolesi M, Goo JM, Macchiarini P, Crapo JD, Herold CJ, Austin JH, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. *Radiology* 2013;266:304–317.
18. Dettlerbeck FC, Gibson CJ. Turning gray: the natural history of lung cancer over time. *J Thorac Oncol* 2008;3:781–792.
19. Suzuki K, Koike T, Asakawa T, Kusumoto M, Asamura H, Nagai K, Tada H, Mitsudomi T, Tsuboi M, Shibata T, et al.; Japan Lung Cancer Surgical Study Group (JCOG LCSSG). A prospective

radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). *J Thorac Oncol* 2011;6: 751–756.

20. Roos JE, Paik D, Olsen D, Liu EG, Chow LC, Leung AN, Mindelzun R, Choudhury KR, Naidich DP, Napel S, *et al.* Computer-aided detection (CAD) of lung nodules in CT scans: radiologist performance and reading time with incremental CAD assistance. *Eur Radiol* 2010;20:549–557.
21. Ye X, Lin X, Dehmeshki J, Slabaugh G, Beddoe G. Shape-based computer-aided detection of lung nodules in thoracic CT images. *IEEE Trans Biomed Eng* 2009;56: 1810–1820.
22. Way T, Chan HP, Hadjiiski L, Sahiner B, Chughtai A, Song TK, Poopat C, Stojanovska J, Frank L, Attili A, *et al.* Computer-aided diagnosis of lung nodules on CT scans: ROC study of its effect on radiologists' performance. *Acad Radiol* 2010;17:323–332.
23. Kawata Y, Niki N, Ohmatsu H, Kusumoto M, Tsuchida T, Eguchi K, Kaneko M, Moriyama N. Quantitative classification based on CT histogram analysis of non-small cell lung cancer: correlation with histopathological characteristics and recurrence-free survival. *Med Phys* 2012;39:988–1000.
24. Tacelli N, Remy-Jardin M, Copin MC, Scherpereel A, Mensier E, Jaillard S, Lafitte JJ, Klotz E, Duhamel A, Remy J. Assessment of non-small cell lung cancer perfusion: pathologic-CT correlation in 15 patients. *Radiology* 2010;257:863–871.