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

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Introduction: Pulmonary nodules of the adenocarcinoma spectrum are characterized by distinctive morphological and radiologic features and variable prognosis. Noninvasive high-resolution computed tomography–based risk stratification tools are needed to individualize their management.

Methods: Radiologic measurements of histopathologic tissue invasion were developed in a training set of 54 pulmonary nodules of the adenocarcinoma spectrum and validated in 86 consecutively resected nodules. Nodules were isolated and characterized by computer-aided analysis, and data were analyzed by Spearman correlation, sensitivity, and specificity and the positive and negative predictive values.

Results: Computer-aided nodule assessment and risk yield (CANARY) can noninvasively characterize pulmonary nodules of the adenocarcinoma spectrum. Unsupervised clustering analysis of high-resolution computed tomography data identified nine unique exemplars representing the basic radiologic building blocks of these lesions. The exemplar distribution within each nodule correlated well with the proportion of histologic tissue invasion, Spearman $R = 0.87$, $p < 0.0001$ and 0.89 and $p < 0.0001$ for the training and the validation set, respectively. Clustering of the exemplars in three-dimensional space corresponding to tissue invasion and lepidic growth was used to develop a CANARY decision algorithm that successfully categorized these pulmonary nodules as “aggressive” (invasive adenocarcinoma) or “indolent” (adenocarcinoma in situ and minimally invasive adenocarcinoma). Sensitivity, specificity, positive predictive value, and negative predictive value of this approach for the detection of aggressive lesions were 95.4, 96.8, 95.4, and 96.8%, respectively, in the training set and 98.7, 63.6, 94.9, and 87.5%, respectively, in the validation set.

Conclusion: CANARY represents a promising tool to noninvasively risk stratify pulmonary nodules of the adenocarcinoma spectrum.

Key Words: Computer-aided image analysis, Lung adenocarcinoma, Pulmonary nodules, Risk stratification.

Lung cancer remains the leading cause of cancer-related deaths in the United States and worldwide.1,2 Although early diagnosis offers a chance of cure, in the absence of effective screening, most patients present with advanced stage disease associated with poor outcomes.3 Recently, the National Lung Screening Trial (NLST) demonstrated that annual screening using low-dose chest high-resolution computed tomography (HRCT) reduces lung cancer–specific mortality by 20% in high-risk individuals. Unfortunately, computed tomography (CT) screening was positive in 39.1% of all participants and 24.2% of all screening CT scans. The false-positive rate was 96.4% among all positive screening CTs.4

Data from previous single-arm observational studies of lung cancer screening suggest that some HRCT–detected lung cancers may be more indolent than their clinically detected counterparts. The majority of these lesions belong to the recently reclassified lung adenocarcinoma spectrum.5–7 The radiologic manifestations of these lesions range from pure ground glass opacities (GGO) to sub-solid opacities (SSO) and solid pulmonary nodules (SPN). Although GGO and SSO typically progress slowly as evidenced by prolonged volume-doubling times of frequently more than 400 days, SPN of the adenocarcinoma spectrum often grow faster.5
Histologically, GGO and SSO are usually characterized by various combinations of lepidic growth (malignant growth along the intact alveolar structures), tissue invasion, and associated desmoplasia. Therefore, depending on the presence and size of invasive foci, they are classified as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA, invasion ≤ 5 mm), or invasive adenocarcinoma (IA, invasion > 5 mm). In contrast, enlarging solid areas and SPN on HRCT typically represent IA. Although the clinical outcomes of patients with surgically resected AIS and MIA are excellent (approaching 100% disease-specific survival at 10 years), patients with IA have a more guarded prognosis.\textsuperscript{b,11} This spectrum of biological behavior highlights the value of a comprehensive histologic examination of these lesions to predict patient outcomes and forms the basis of the recent histologic reclassification of the lung adenocarcinoma spectrum. Because alternative therapeutic strategies to standard lobectomy (such as sublobar resections) are currently being investigated, the noninvasive risk stratification of these nodules will facilitate individualized patient management. Currently, this assessment requires surgical resection of the lesion with histopathologic examination of the entire lesion, which cannot be reliably performed on nonsurgical tissue biopsies. Because of the widespread availability and utilization of HRCT in clinical practice and lung cancer screening programs, HRCT-based risk stratification would be ideal for this task. Unfortunately, currently available HRCT-based strategies remain suboptimal. Computer-aided lung informatics for pathology evaluation and rating (CALIPER) is a HRCT-based image analysis tool developed at Mayo Clinic, Rochester, Minnesota. CALIPER has demonstrated considerable potential for automatic, rapid, and reliable lung parenchymal isolation and tissue classification in patients with diffuse lung diseases such as diffuse interstitial pneumonias and emphysema.\textsuperscript{12} On the basis of these observations, we hypothesized that CALIPER could facilitate the noninvasive radiologic–pathologic correlation of pulmonary nodules of the adenocarcinoma spectrum. Herein, we report the development of computer-aided nodule assessment and risk yield (CANARY)—an adjunct tool for the characterization and categorization of pulmonary nodules (Fig. 1).

**MATERIALS AND METHODS**

**Participants**

Between 2008 and 2010, patients with surgically resected lesions of the pulmonary adenocarcinoma spectrum (search terms “bronchioloalveolar carcinoma (BAC),” “adenocarcinoma with BAC features,” and “adenocarcinoma”) were identified from the Mayo Clinic Epidemiology and Genetics of Lung Cancer Study database as a training set. An independent validation set of 86 pulmonary nodules of the adenocarcinoma spectrum consecutively resected from 80 patients (from January 1, 2006 to December 31, 2007) pulmonary nodules of adenocarcinoma spectrum meeting the same inclusion criteria as the training set were identified from the Mayo Clinic Thoracic Surgery Registry. All patients without a signed research authorization were excluded.

**Histology Review**

Two independent expert pulmonary pathologists (J.B. and E.S.Y.) blindly (without clinical or radiologic information) reviewed all available hematoxylin and eosin slides of the enrolled cases. Because the proportion of lepidic growth was found to be technically easier to estimate the proportion of invasion, they estimated the proportion of lepidic growth. In addition, the presence or absence of stromal, vascular, and/or pleural invasion was assessed, and the diameter of the largest area of invasion, including surrounding scar, was measured. All measurements were adjusted to the nearest millimeter.

On the basis of the largest focus of tissue invasion, all cases were also categorized as absent invasion (AIS), less than or equal to 5 mm invasion (MIA), or greater than 5 mm invasion (IA), as previously described.\textsuperscript{11} When there was disagreement between invasive category (AIS, MIA, and IA), the consensus invasive category was determined by the third pathologist (M.C.A.). The consensus value for the proportion of lepidic growth was determined using the following algorithm (all values in cases where lepidic growth was <90% were rounded up to the nearest 10%): For cases less than 50% lepidic growth by either pathologist, the results were averaged if the discrepancy was less than or equal to 20%. Otherwise, a third pathologist reviewed the case, and the two closest lepidic growth values were averaged. For cases between 50 and 90% lepidic growth, the results were averaged if the discrepancy was less than or equal to 10%. Otherwise, a third pathologist reviewed the case, and the two closest lepidic growth values were averaged. Cases greater than or equal to 90% lepidic growth were categorized as 90, 95, 99, or 100% by two pathologists. Any discrepant cases were reviewed by a third pathologist and categorized based on the two closest values.

**CT Imaging**

Chest CT scans were performed on a variety of scanners. The scanners were all multidetector scanners ranging from 8 to 64 detectors. Preoperative (≤ 3 months) thin section images were required in all cases. Collimation ranged from 1.25 to 2.5 mm. Reconstruction algorithms varied by scanner and included both smoothing and high-resolution algorithms based on the vendor algorithms.

**Radiology Review**

All preoperative CT scans included in the training set were reviewed independently in a blinded fashion by two thoracic radiologists (A.M.S. and T.E.H.). Both readers subjectively categorized each case as aggressive or indolent and measured the tumor/consolidation (C/T) ratio as previously described.\textsuperscript{13}

**Lung Parenchymal Characterization and Nodule Extraction**

**Lung parenchymal isolation and classification**

The lung parenchyma was isolated by segmentation of preoperative HRCT data using an adaptive density-based morphology approach involving threshold optimizing, region
growing, and hole filling. Lung parenchymal classification was based on the previously identified exemplars representing five radiologic lung tissue types: normal, emphysema, reticular, ground glass, and honeycomb change. An exemplar represents the most central region of interest (ROI) within a natural cluster of ROIs and constitutes the basic building block for the CALIPER-based lung parenchymal classification. These exemplars were derived based on the statistical analysis of representative HRCT data of patients with various parenchymal lung diseases that were selected from the Lung Tissue Research Consortium. Consequently, each lung parenchymal voxel was assigned to one of these five primal lung parenchymal HRCT patterns using CALIPER (See Supplemental Figures 1 [Supplemental Digital Content 1, http://links.lww.com/JTO/A389] and 2 [Supplemental Digital Content 2, http://links.lww.com/JTO/A390] and Supplemental Table 1 [Supplemental Digital Content 3, http://links.lww.com/JTO/A391]).

Nodule extraction
The location of all surgically resected nodules was known a priori. Hence, the nodule of interest was extracted with a supervised approach using constrained seeded region growing. Because GGO, SSO, and SPN nodules are composed of reticular and ground glass patterns, the region growing was constrained to include only those voxels connected to the seed voxel and classified as reticular or ground glass.

Statistical Analysis
Multinomial logistic regression was used to generate equations predictive of the degree of histologic invasion (see Results section).
Because of the lack of a Gaussian distribution of the data for AIS and invasion, nonparametric Spearman correlation was used to analyze the relationship between histopathologic and radiologic invasion as determined by CANARY. The sensitivity, specificity, and the positive and negative predictive value for CANARY to distinguish histopathologically “aggressive” from “indolent” lesions were calculated. A $p$ value of less than 0.05 was considered statistically significant. Cohen's kappa was calculated as a statistical measure of the inter-rater agreement between the thoracic radiologists. The Prism software package (GraphPad, San Diego, CA) was used for the statistical analysis.

The Mayo Foundation Institutional Review Board approved the study.

RESULTS

Subjects
For the training set, 139 of the 208 identified cases were excluded because of the lack of an appropriate preoperative HRCT scan. Of the remaining 70 patients, 16 patients with lung masses (>3 cm) were excluded. Fifty-four patients with surgically resected pulmonary nodules of the adenocarcinoma spectrum were included in the analysis as the training set.

For the independent validation set, 86 nodules (80 patients) of consecutively resected pulmonary nodules with similar inclusion criteria as the training set were included in the analysis. The demographic characteristics, tumor, node, metastasis stage, pathologic nodule size, and consensus histopathology diagnoses for these patients are included in Table 1 and Supplemental Figure 3 (Supplemental Digital Content 4, http://links.lww.com/JTO/A392).

Radiologic nodule analysis and development of CANARY
Conventional characterization of lung nodules on HRCT consists of semiquantitative estimates of the solid and ground glass components by a trained radiologist. However, these nodules are represented by a complex combination of numerous contiguous voxels with a broad range of densities. Consequently, reducing this information to only two categories, solid or ground glass, likely results in the loss of potentially useful diagnostic information. Using CANARY, we were able to successfully reduce this complex pattern of voxel densities to a limited number of representative exemplars, hypothesized to represent the essential building blocks of lung nodules of the adenocarcinoma spectrum. These exemplars were generated using the following approach. An expert thoracic radiologist (B.J.B.) arbitrarily selected 774 ROI (size = 9 × 9 voxels, Fig. 2) spanning the radiologic spectrum of these lesions across the HRCT scans of 37 randomly selected cases (37 of the 54 included cases). Natural clusters among these ROIs were identified by comparing all ROIs to one another using affinity propagation (an unsupervised clustering technique) and pairwise similarity metrics. This unsupervised analysis yielded nine unique natural clusters of ROIs. The most

| TABLE 1. Patient Demographics, Tumor Stage, Nodule Size, and Histology |
|-----------------|-------------------|-------------------|
| Demographics    | 54 patients       | 80 patients       |
| Age at diagnosis (years: median (range)) | 68 (40–89) | 68 (35–91) |
| Gender (n (%))  |                   |                   |
| Women           | 35 (65)           | 48 (60)           |
| Smoking (n (%)) |                   |                   |
| Never           | 17 (31)           | 9 (11)            |
| TNM stage (n (%)) |                 |                   |
| IA              | 42 (76)           | 42 (52)           |
| IB              | 1 (2)             | 12 (15)           |
| IIA             | 0                 | 4 (5)             |
| IIIB            | 8 (16)            | 7 (9)             |
| IIIA            | 1 (2)             | 8 (10)            |
| IV              | 2 (4)             | 7 (9)             |
| Nodule size mm ± SD | 16.7 ± 0.69 | 17.2 ± 0.61 |
| Histopathologic classification (n (%)) |       |                   |
| AIS             | 2 (6)             | 1 (1)             |
| MIA             | 20 (36)           | 10 (12)           |
| IA              | 32 (58)           | 75 (87)           |

AIS, adenocarcinoma in situ; IA, invasive adenocarcinoma; MIA, minimally invasive adenocarcinoma; TNM, tumor, node, metastasis.
central ROI within each cluster was chosen as the exemplar, or essential building block, of the lesions (see Supplemental Material, Supplemental Digital Content 5, http://links.lww.com/JTO/A393). These exemplars were color coded as Violet (V), Indigo (I), Blue (B), Green (G), Yellow (Y), Orange (O), Red (R), Cyan (C), and Pink (P). These color-coded exemplars form the basic building blocks for the analysis and risk stratification of pulmonary nodules of the adenocarcinoma spectrum by CANARY (Fig. 2).

To characterize an extracted lung nodule, each voxel within the nodule was compared with all nine exemplars. The most similar exemplar was computed using the pairwise comparison of histograms of the $9 \times 9$ voxel neighborhood of each voxel to the respective exemplars. The color code of the most similar exemplar was assigned to each individual voxel of the analyzed nodule. This approach resulted in a specific combination of exemplars (and color pattern) for each nodule. This distribution of exemplars within the nodule (signature) was visualized yielding concentric color-coded areas (Fig. 3A). Hence, CANARY signatures were established without clinical input, solely based on radiologic characteristics.

CANARY-based assessment of the relative contributions of tissue invasion and lepidic growth in pulmonary nodules of the adenocarcinoma spectrum

To investigate the face validity of the CANARY lung nodule signatures, we attempted to determine whether specific signatures (combination of exemplars) would correlate with distinct histologic characteristics. We elected to compare these radiologic signatures to a histologic measure of invasion defined as 100%—lepidic growth %. Sixteen nodules spanning the entire spectrum of invasion (from 0 to 100% as assessed by consensus pathology) were included in a multinomial logistic regression analysis to generate equations to radiologically predict the proportion of histologic tissue invasion. These predictive equations were then validated on the
remaining 38 nodules. In addition, the excellent correlation between CANARY and consensus histopathology was confirmed in an independent validation set (Fig. 4).

With the exception of two cases, correlation between CANARY and consensus histopathology was excellent (Spearman $R = 0.87$, 95% confidence intervals [CI]: 0.78–0.92; $p < 0.0001$) among the 38 cases of the training set and even better, Spearman $R = 0.89$, CI: 0.83–0.93; $p < 0.0001$, in the independent validation set of 86 nodules from 80 patients (Fig. 4).

The two discrepant cases were reviewed in detail. For one case, CANARY determined the lesion to be 100% invasive, whereas consensus histologic assessment found no invasion. For the second case, CANARY measured 80% invasion compared with 20% by consensus histology. These cases were...
found to be solid opacities radiologically, although characterized by minimal invasion on histopathologic evaluation, explaining the discordant results between CANARY assessment and histopathology.

CANARY-based noninvasive radiologic risk stratification of pulmonary nodules of the adenocarcinoma spectrum

Subsequently, multidimensional scaling was used to understand the three-dimensional distribution of the nine adenocarcinoma exemplars. The space partitioned into three natural exemplar clusters corresponding to the V-I-R-O, Y-P, and B-G-C exemplars. The quantitative distribution of the different exemplars and the rule-based CANARY decision algorithm were used to categorize each of the pulmonary nodules. On the basis of the observation that V-I-R-O and B-G-C groups correlated predominantly with invasion and lepidic growth, respectively, a rule-based CANARY decision algorithm was developed to categorize every nodule as AIS, MIA, or IA. (Figs. 3B and 5)

Patients with AIS and MIA share a similarly favorable postsurgical prognosis. This contrasts with the worse postoperative survival of patients with IA. Consequently, we classified all cases as either Group 1 histology aggressive (n = 32, training set and n = 75, validation set; IA) or Group 2 histology indolent (n = 22, training set and n = 11, validation set; AIS and MIA) based on predominance of the VIRO (aggressive), YP (moderately aggressive), or the BGC (indolent) cluster. Sensitivity, specificity, positive predictive value, and negative predictive value for the detection of histopathologic aggressive lesions using the CANARY decision algorithm were calculated. The sensitivity was 95.4% (95% CI: 75.1–99.7%) and 98.7% (95% CI: 91.8–99.9%), the specificity was 96.8% (95% CI: 82–99.8%) and 63.6% (95% CI: 31.6–87.6%), the positive predictive value was 95.4% (95% CI: 75.1–99.7%) and 94.9% (95% CI: 86.7–98.3%), and the negative predictive value was 96.8% (95% CI: 82–99.8%) and 87.5% (95% CI: 46.7–99.3%) in the training and validation set, respectively (Fig. 6).

None of the indolent cases identified by CANARY in the training or validation sets presented with locally advanced or metastatic disease. In the validation set, lung cancer–specific postsurgical survival of the indolent and aggressive CANARY groups mirrored that of the AIS/MIA and IA groups identified by consensus histopathology (Fig. 7).

Semiquantitative Review of the Training Set

On the basis of the case review by the treating physician, the assessment of the clinical radiologist, and patient preferences, all 140 nodules included in the training and validation sets were judged to be worrisome enough to be resected. All 54 preoperative CT scans analyzed by CANARY in the training set were reviewed independently in a blinded fashion by two thoracic radiologists (A.M.S. and T.E.H.). Both readers subjectively categorized each case as aggressive (IA) or indolent (AIS or MIA). There was moderate agreement with a $\kappa$ of 0.49 (95% CI: 0.21–0.78). On the basis of consensus histology, 36 cases were correctly categorized by both radiologists. In 10 cases, the readers disagreed and eight cases were incorrectly classified by both. Seven cases were classified as aggressive as opposed to indolent and one case as indolent as opposed to aggressive. Representative cases misclassified by both radiologists but correctly identified by CANARY are shown in Figure 8.

A

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<tr>
<td>Total</td>
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FIGURE 5. Rule-based CANARY decision algorithm based on the distribution of exemplar clusters (%): violet–red–orange (VIRO), yellow–pink (YP), and blue–green–cyan (BGC) within each lesion. CANARY, computer-aided nodule assessment and risk yield.

FIGURE 6. Two by two contingency table of CANARY’s diagnostic performance (rows) to predict consensus histopathologic tissue invasion (columns). (A) Training set (n = 54). (B) Validation set (n = 86). CANARY, computer-aided nodule assessment and risk yield.
Using a C/T ratio of less than or equal to 0.25 to classify the pulmonary nodules as indolent (≤0.25) or aggressive (>0.25), we observed better agreement (substantial agreement), \( \kappa = 0.78 \) (95% CI: 0.60–0.96) between the two readers. In the training set, a C/T ratio less than or equal to 0.25 by consensus or average between the two readers detected invasion with a sensitivity of 91% (95% CI: 74–98%) and a specificity of 55% (95% CI: 33–75%).

**DISCUSSION**

The ever-increasing utilization of HRCT imaging of the lungs has led to a substantial increase in the number of detected pulmonary nodules. In addition, the results of the recently published NLST will almost certainly prompt the implementation of comprehensive HRCT screening programs for high-risk individuals. This strategy has already been endorsed by some of the major medical societies.\(^4,16\) Pulmonary nodules of the adenocarcinoma spectrum represent the majority of HRCT-detected lung cancers, and the biological behavior of a subgroup of these lesions seems to differ significantly from their clinically detected counterparts, although arguably the data regarding the natural history of these lesions are limited.\(^5\) Radiologically, these lesions often present as solitary or not uncommonly multiple SSO or pure GGO, for which the optimal management strategies are suboptimally defined. Consequently, the indiscriminate implementation of a mass HRCT screening program and routine utilization of standard surgical therapy (lobectomy) as opposed to currently available alternatives such as limited resection or stereotactic body radiation therapy would potentially result in excess mortality, morbidity, and health care cost. This paradigm shift in our understanding of lung cancer will require the urgent development and implementation of new noninvasive strategies for the risk stratification and guidance of the individualized management of HRCT-detected pulmonary nodules.\(^13\)

Unsupervised CANARY-based analysis of HRCT data identified nine exemplars across the spectrum of pulmonary nodules of the lung adenocarcinoma spectrum. These exemplars segregate into three clusters that seem to visually correspond to the predominant histopathology of the lesion. Although the B-G-C cluster represents lepidic growth, the VI-R-O cluster correlates with tissue invasion. By providing additional HRCT descriptors beyond well-established categories such as GGO and consolidation, CANARY-based analysis facilitates the individualized characterization of pulmonary nodules of the lung adenocarcinoma spectrum. On the basis of the CANARY analysis and the consensus histopathology of the lesion, we successfully designed and optimized a decision algorithm for the noninvasive risk stratification into aggressive.
(IA) and indolent lesions (AIS and MIA). Through automated volumetric quantitation of the lesions, CANARY provides the opportunity for the noninvasive preoperative characterization and risk stratification of pulmonary nodules of the lung adenocarcinoma spectrum. If validated in future prospective studies, CANARY could ultimately become a valuable tool to assist in the individualized management of these lesions (e.g., limited surgical resection versus standard of care).

Other investigators have successfully demonstrated the value of comprehensive histologic assessment to predict the postsurgical disease-specific survival (biological behavior) of these pulmonary nodules. In this context, pure lepidic growth (AIS) and less than or equal to 5 mm invasion (MIA) are associated with significantly better patient outcomes than lesions with greater than 5 mm invasion (IA).10,18–23 These observations are reflected in the revised 2011 histologic classification of pulmonary adenocarcinomas.11 Unfortunately, comprehensive histologic tumor tissue analysis requires the surgical removal of the lesion and is not feasible for preoperative treatment planning. In contrast, HRCT allows the comprehensive and noninvasive characterization of pulmonary nodules. However, the accurate and reproducible assessment of pulmonary nodules, including solid opacities and SSO, remains challenging. Difficulties include large interobserver variability in the assessment of simple variables such as variation of size over time to estimates of volume-doubling times. Despite previous reports demonstrating some correlation between lepidic growth and tissue invasion with GGO and SSO by HRCT, in the process of investigating the differences in the CANARY protocols for the CT scans, because of the retrospective nature of our study, we have an influence on our results. We are currently in the process of investigating the differences in the CANARY signatures caused by different CT scanners and determine the optimal reconstruction algorithm. Another limitation of our study is that the natural history of screen-detected SSO of the adenocarcinoma spectrum remains unknown. However, the postsurgical biological behavior of these lesions seems to correlate well with the histologic predictors of outcomes that correlated to CANARY.

Although this pilot study is restricted to cases of histologically confirmed adenocarcinomas, we hope to expand the use of CANARY to classify screening-detected pulmonary nodules. We are currently investigating whether a CANARY-based approach can classify screening-detected pulmonary nodules into benign and malignant lesions and identify clinically aggressive lesions of the adenocarcinoma spectrum using the NLST data set.

In conclusion, after further validation, the CANARY-based noninvasive risk stratification of pulmonary nodules of the adenocarcinoma spectrum using a preoperative HRCT could be applied to guide the individualized management of these lesions and may offer valuable insight into the biology of this type of lung cancer. Furthermore, future use of CANARY

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for the assessment of serial imaging studies to highlight both qualitative and quantitative longitudinal changes across serial imaging studies might improve its diagnostic yield beyond that of the current single time point evaluation.

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