Transcutaneous Computed Bioconductance Measurement in Lung Cancer

A Treatment Enabling Technology Useful for Adjunctive Risk Stratification in the Evaluation of Suspicious Pulmonary Lesions

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Abstract: Lung cancer is the number one cause of cancer deaths in North America and is rapidly increasing worldwide. Although there are advances being made in the multidisciplinary management and combined-modality therapies of lung cancers, most cases are still diagnosed in later noncurable stages. Early detection has hinged on clinical risk assessment and on the future possibility of screening by low-dose computed tomography of the chest; however, this will only vastly increase the number of indeterminate pulmonary lesions (IPLs) being detected. Given that the majority of radiographically detected lung lesions are benign, and tissue confirmation by various invasive biopsy tests has increased risks and costs, a noninvasive adjunctive test that can stratify likelihood of an indeterminate lung lesion as malignant or benign will be a useful treatment-enabling technology to speed up diagnosis and treatment of lung cancers at a more curable stage and defer unnecessary invasive procedures that have potential for harm. Measurement of transcutaneous bioconductance using the differential conductivity properties of cancerous versus benign tissue has been previously demonstrated on nonlung lesions. Thus, it has the potential of being a noninvasive, simple-to-perform and repeatable test that may be valuable in assessing lung lesions. In this prospective study of subjects with known thoracic malignancies, computed bioconductance measurements discriminated between malignant lesions (29 primary lung cancers) from benign pathology (12) across a range of IPL sizes (0.8 cm and greater) with a sensitivity of 89.7% (positive predictive value 96.3%) and specificity of 91.7% (negative predictive value 78.5%). The technology seems to be effective across a range of tumor thoracic locations, cell types, and stages. Additional cohorts of subjects will be used to validate testing and for refinement of the current algorithm, which at present has a test performance with a receiver operating characteristic of 90.7%. Noninvasive transcutaneous computed bioconductance measurement can become a standard risk assessment and therapy-enabling tool in the evaluation of IPLs.

Key Words: American Thoracic Society, Computed bioconductance, Computed axial tomography, Noncalcified nodules, Indeterminate pulmonary lesion, Receiver operating characteristic.

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Lung cancer is the most frequent cause of cancer deaths worldwide, which are greater in number than those caused by colorectal, prostate, and breast cancer combined.[1] In 2011 approximately 226,169 new cases of lung and bronchus cancer(totaling about 14% of new cancer diagnoses and 160,340 deaths or about 28% of all cancer deaths) are expected in the United States. [2] There are also more than 1.3 million lung cancer deaths annually worldwide.[3] Lung cancer is a disease for which there are currently no universally accepted screening methods, hence lung cancer cases are more often diagnosed clinically late in their course. Patients have a median survival of 6 to 12 months from the time of their diagnosis as more than half die within the first year of diagnosis.[1,2] The longer-term prognosis of patients diagnosed with lung cancer in the United States is also poor with a relative 5-year survival rate of only 15% with all stages combined.[2]

Spiral computed tomography (CT) is an important advance in imaging technology for a lung cancer workup as it is more sensitive than chest radiograph and is able to detect small, noncalcified nodules (NCNs).[4,5] The recently reported outcome from the National Lung Screening Trial in high-risk individuals found a 20.3% decrease in mortality, thus providing encouraging results for the possible value of low-dose helical CT in screening "high-risk" populations.[6] However, there are several impediments to the adoption of screening for lung cancer with low-dose CT. These include the risks associated with radiation exposure even with low-dose CT, and the

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problem of a large percentage of false-positive findings leading to invasive workups of lesions that are ultimately found to be benign.[7–9] Consequently, adjunctive technologies that could risk stratify subjects with an indeterminate pulmonary lesion (IPL) into a high or a low likelihood of having a true lung cancer will be very valuable therapy-enabling tools.

Electrical impedance is by definition the ratio of the voltage difference to the current across a circuit or a body (Ohm's law), and conductance is the inverse of impedance (1/impedance). The dielectrical properties of human cells and tissue are well recognized and are essential for several diagnostic procedures currently in use such as the electrocardiograph and electroencephalogram. The bioelectrical properties of cancerous tissue have been characterized in scientific and medical literature and shown to vary significantly from those of normal, benign tissue.[10–24] There is no broad consensus regarding the exact mechanism of action of this differential property. The mechanism has been attributed to the high content of water and sodium within cancerous tissues, with the movement of potassium, magnesium, and calcium out of the cell.[10–14] Other possible contributors include not only this altered membrane permeability but also changes in membrane composition, the nucleus-to-cytoplasm ratio, and alterations in cellular composition and density.[12,13]

Tissue-specific bioconductance has been reported to be valuable in the detection of various cancers including skin, thyroid, liver, cervix, and breast cancers.[14–24] Breast cancer has probably been the most extensively studied with bioconductance technology.[20–24] Investigators studying patients with sonographically or mammographically suspicious lesions have found significant differences in electrical conductance between normal and abnormal breast tissues.[20] By considering electrical conductance results in addition to ultrasound and mammography, the sensitivity of cancer detection increased from 86 to 95%.[21] In contrast, there is limited information regarding changes in lung bioconductivity associated with lung cancer although a few reports have suggested a relationship.[25–27]

Based on the above background information regarding differences in tissue bioconductance between normal and cancerous tissues, a study was performed at another medical center under an Institutional Review Board-approved study in 36 subjects, 18 with diagnosed primary lung cancers, and 18 age- and sex-matched controls using the noninvasive transcutaneous computed bioconductance (CB) measurement platform (Freshmedx, Salt Lake City, UT) . This study found a different bioconductance pattern between cancer and control cases.[28] This provided the basis for further pattern-algorithm development.

The purpose of the current investigation is to examine whether transcutaneous CB measurement data can be used to further develop an algorithm that discriminates between benign and malignant pulmonary lesions found on spiral chest CT scans.

PATIENTS AND METHODS

Subjects

The present research was conducted at a single institution—Johns Hopkins School of Medicine—and subjects were enrolled under an Institutional Review Board-approved protocol. Potential subjects were informed of the study's purpose and procedures, and signed the informed consent. The study subjects were recruited from those considered at risk for lung cancer, based on a presentation that included at least one suspicious clinical symptom and/or suspicious radiological finding. Suspicious clinical symptoms included persistent cough, hoarseness, shortness of breath, hemoptysis, fatigue, unexplained weight loss, recurrent pneumonia or bronchitis, and chest pain. All enrolled subjects had a minimum of one recent chest CT (obtained within and up to 14 days before the study date) that had demonstrated at least one NCN or lung lesion suspicious for lung cancer. Other inclusion criteria were subjects aged 18 or above, and if women, of nonchildbearing potential. Subjects were either to have a biopsy for tissue diagnosis within 60 days after the CB measurement or to be followed by short-term repeat chest imaging where appropriate.

Exclusion criteria included presence of a pacemaker or other implanted electronic devices; patients with known malignancy within the past 5 years except for nonmelanoma skin cancer; uncontrolled systemic diseases such as hypertension, diabetes, severe heart disease and or/autoimmune disease; use of systemic corticosteroid medication; patients having an invasive procedure involving the thoracic cavity within 30 days before measurement; those having alcohol or drug abuse that may interfere with reliable follow-up; an anomalous anatomical or physical condition that would preclude accurate cutaneous CB measurement; unusually strenuous exercise and other activities within 24 hours before measurement that may affect tissue bioconductance; patients having radiation or chemotherapy treatment within 30 days before measurement; and those receiving current therapy for a documented or suspected chest infection.

As a number of patients presenting with suspicious pulmonary lesions and identified as at-risk for lung cancer will be present or former smokers, obstructive airways disease may become a confounding factor. To help ascertain whether differential lung function may independently affect CB measurements, all study subjects will have had recent pulmonary function testing including spirometry ordered for clinical purpose. Otherwise, enrolled subjects performed spirometry as a part of the study according to standardized American Thoracic Society criteria.

Fifty-five subjects were enrolled in the study with 41 evaluable, as described in the Results section. The determination for subject inclusion or exclusion was made before completing the final statistical analysis. Patients were recruited sequentially and randomly from those who were eligible and agreed to participate in the study.

Medical Device

Subjects had a CB test on a single occasion with the transcutaneous Bioconductance Scan Platform (BSP; Freshmedx) (Fig. 1). Freshmedx's CB Test (CB Test), cleared by the Johns Hopkins Hospital's institutional biomedical engineering staff, delivers a safe current of less than 25 mA to measure bioconductance between reference electrodes placed on the patient's back or hands and a CB probe placed sequentially at 31 bilateral points on the skin surface. The operator views a computer screen that guides placement of the probe at these predefined anatomical locations across the thorax and other skin sites. The BSP device is designed to reduce measurement variability through a probe algorithm that

FIGURE 1. Freshmedx Bioconductance Scan Platform.

applies specified pressure to the measurement location that is independent of technician-applied force. In addition, the device software was designed with a quality check embedded in the system that checks the measurement and notifies the operator whether there is a degradation that could compromise accurate measurements. Measurements are obtained 25 times per second. Certain locations include diagnostic information whereas others provide control, baseline data that allow evaluation of technical performance but do not reflect disease state. The measurement session requires approximately 20 minutes per patient and is completed before any invasive diagnostic procedures. The operators (M.Y.Z., S.A.) did not participate in other aspects of the subject's clinical care. The acquired CB data were recorded onto a compact disk in a patient-anonymous manner, and mailed to a central data center for analysis.

Statistical Analysis

The purpose of this study and statistical analysis was to determine whether CB measurements could discriminate between malignant pulmonary lesions and benign pathology. In the sample size of $n = 41$ patients, 29 with malignant pulmonary lesions and 12 with benign pathology, it would be possible, by inspecting and taking advantage of chance patterns in the data, to derive an algorithm that combined the data in such a way that perfect discrimination could be achieved. Optimizing an algorithm, then, is intentionally avoided in this study. Instead, to establish feasibility, a completely prespecified approach was used rather than making decisions after examining the data.

The prespecified data analysis approach was programmed in Stata version 11 statistical software (StataCorp LP, College Station, TX), and validated using previously collected pilot data. The current study data were then passed through the program, without any interaction or decision by the biostatistician. This prespecified automated process included all steps of the analysis, including the validation step. Even though the biostatistician received data in an unblinded fashion, the automated data analysis approach provided protection against introducing statistician bias, which is similar to the protection that full blinding achieves.

The data consisted of CB measurements taken at 31 bilateral anatomical locations. CB measurements consist of various bioconductance data such as the maximum or minimum conductance value over a specified time period obtained at each anatomical location. These data coupled with the subject's final diagnosis were analyzed using weighted multivariable optimal data analysis (ODA).[29] The ODA approach selected cutoff points for CB measurements that were combined into a composite risk score that maximized discrimination accuracy. The composite risk score was calculated through a weighted binary approach that coded the best discriminating measurements based on their ODA cutoff points as 1 or 0 and then multiplied the binary codes by their respected weights that were derived in the ODA. That is, the composite risk score = ([1 if the first discriminating measurement is $\geq$ cutoff point, 0 otherwise] $\times$ [first weight] + [1 if the second discriminating measurement is $\geq$ cutoff point, 0 otherwise] $\times$ [second weight] + … + [1 if last discriminating measurement is $\geq$ cutoff point, 0 otherwise] $\times$ [last weight])/(sum of weights) $\times$ 100.

This composite score which ranged from 0 to 100 was then dichotomized into a binary diagnostic test with a cutoff point selected that maximized receiver operating characteristic (ROC) area. We refer to this as the CB test and report its test characteristics: area under the ROC curve, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Because the patient sample was a random sample, rather than a case-control or cohort sample, the estimates of these test characteristics are unbiased and do not need special adjustments for verification bias or selection bias.[30] The ROC area of a binary risk score is simply the average of sensitivity and specificity.[31]

With a sample size of 41 patients with measurements taken at 31 bilateral locations, the primary threat to the validity of the statistical analysis was overfitting, which occurs by having too many predictor variables for the given sample size, so that spurious or unreliable associations are detected in the data. Similarly, with many predictor variables, it is possible that some can seem to be discriminating simply from chance patterns in the data. Likewise, considering all possible cutoff points for each variable, again it is possible that chance patterns can arise. These three issues can all result in unreliable associations that may not hold up in future patients or data sets. The final critical step of the ODA approach, then, is the validation step, which corrects for overfitting and unreliable associations in the data. To validate the CB test, an internal bootstrap validation was performed.[32] The bootstrap-validated test characteristics are also reported in the next section.

RESULTS

Over 15 months, a total of 55 subjects were enrolled in the study and evaluated. Of these, 41 subjects (22 men and 19 women) aged 34 to 80 were considered evaluable whereas 14 were excluded in the final analysis. The reasons for the 14 exclusions were as follows: 4 subjects who had a diagnosed malignancy that was not a primary lung cancer (2 lymphomas, 1 pancreatic cancer, and 1 papillary cancer); 3 who were lost to follow-up without a definitive final diagnosis; 3 subjects where the lung biopsy was more than 60 days after the BSP measurement; 2 subjects who had recent illicit drug use (exclusion criteria); 1 subject who had a previous lobectomy (may have affected chest anatomy); and 1 who had a lung cancer within the previous 5 years. The performance of the

CB test was evaluated in 41 patients with the outcome of 29 malignant and 12 benign diagnoses.

The 12 patients with benign disease included three women and nine men, ranging in age from 34 to 77 years. The 29 patients with malignancy included 16 women and 13 men, ranging in age from 40 to 80 years. The benign group included 10 white and 2 black patients whereas the group with malignancies included 18 whites, 10 blacks, and 1 patient of Asian descent (Table 1).

The 12 benign cases had biopsy results for 9 patients that included 6 with benign or inflammatory respiratory epithelium, 1 with an epitheloid granuloma, 1 with granulomatous inflammation, and 1 with reactive respiratory epithelium and a fibrous scar. In three cases, the diagnosis of benignity resulted from follow-up CT scans that showed a decrease in lesion size in one patient at 2 months or a stable nodule in two patients at 12 months and 24 months on follow-up CTs. The lesion sizes in the benign group ranged from 0.4 to 3.9 cm with a median size of 2.2 cm. Most of the biopsies in the benign cases were performed with bronchoscopy. However, the patient with the fibrous scar had the largest benign lesion (3.9 cm) that was removed by a right upper lobectomy (Table 2).

The distribution of cell types from histology and the stage results for the 29 malignant cases are shown in Tables 3 and 4. There was one atypical carcinoid, two small-cell lung cancers, and 26 non–small-cell lung cancers. The lesions sizes for the 29 malignant cases ranged from 0.8 to 14.6 cm with a median size of 3.1 cm.

Spirometry was performed on all patients before the CB test; Table 5 shows the distribution within the benign and malignant cases. Normal was defined as forced expiratory volume in 1 second/forced vital capacity >70%. Overall, the patients with malignant disease exhibited more airflow obstruction with 10 of 28 (1 subject's results were erroneous) or 35.7% having moderate to severely reduced spirometric values.

All enrolled patients completed the CB testing without any observed or reported adverse events. The patients were also verbally administered a short questionnaire at the end of the testing session that asked the following four questions: (1) Did the device measurement cause any discomfort and if so, describe; (2) Did the testing time seem reasonable? (3) Would you agree to undergo measurement again? and (4) Do you have any suggestions for improvement? One patient responded a "little pressure" to the first question, and all responded that the testing time was acceptable. One patient responded "maybe" to undergoing repeat measurement and two subjects responded "no." Of the two "no" responses, one provided no reason and another cited

TABLE 1. Patient Demographics

Category	All	Benign (12)	Malignant (29)	Excluded (14)
Age (yr)				
Average	64	61	65	66
Range	34–84	34–77	40–80	48–84
Sex				
Female	26 (47%)	3 (25%)	16 (55%)	7 (50%)
Male	29 (53%)	9 (75%)	13 (45%)	7 (50%)
Race				
White	38 (69%)	10 (83%)	18 (62%)	10 (71%)
Black	15 (27%)	2 (17%)	10 (34%)	3 (21%)
Asian	2 (4%)	0 (0%)	1 (3%)	1 (7%)

TABLE 2. Lesion Distribution and Location

Category	All (%)	Benign (12) (%)	Malignant (29) (%)	Excluded (14) (%)
Size				
T1 (≤3 cm)	31 (56)	9 (75)	14 (48)	8 (57)
T2 (>3 cm ≤7 cm)	19 (35)	2 (17)	11 (38)	6 (43)
T3 (>7 cm)	4 (7)	0 (0)	4 (14)	0 (0)
Location				
Right upper lobe	20 (36)	5 (42)	10 (34)	5 (36)
Right middle lobe	5 (9)	1 (8)	3 (10)	1 (7)
Right lower lobe	10 (18)	1 (8)	6 (21)	3 (21)
Left upper lobe	9 (16)	1 (8)	5 (17)	3 (21)
Left lower lobe	11 (20)	4 (33)	5 (17)	2 (14)
Subjects with multiple lung lesions	8 (15)	1 (8)	5 (17)	2 (14)

TABLE 3. Histology Distribution in Malignant Group

Histology	Malignant (29) (%)
Atypical carcinoid	1 (3)
Minimally invasive or with predominantly lepidic features	3 (10)
Squamous cell	6 (21)
Adenocarcinoma	9 (31)
Metastatic adenocarcinoma	8 (27)
Small-cell carcinoma	2 (7)

TABLE 4. Stage Distribution in Malignant Group

Stage	Malignant (29) (%)
IA	7 (24)
IB	4 (14)
IIB	1 (3)
IIIA	3 (10)
III	3 (10)
IV	11 (38)

TABLE 5. Pulmonary Function Results

Spirometry Results	Benign (12) (%)	Malignant (29) (%)
Normal	9 (75)	12 (41)
Mildly reduced	2 (17)	6 (21)
Moderately reduced	0	4 (14)
Severely reduced	1 (8)	6 (21)

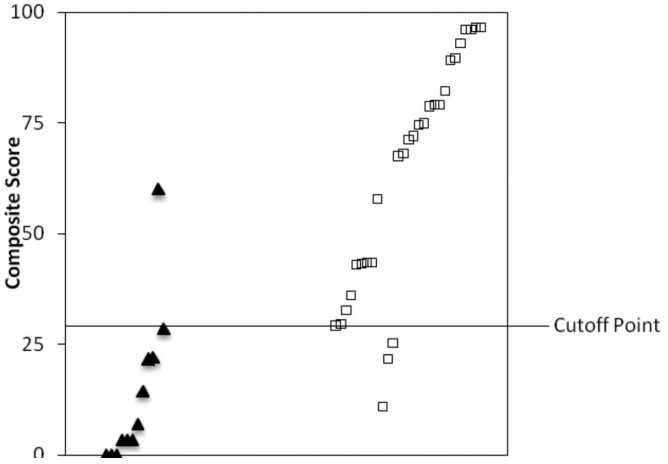

FIGURE 2. Patient computerized bioconductance test results.

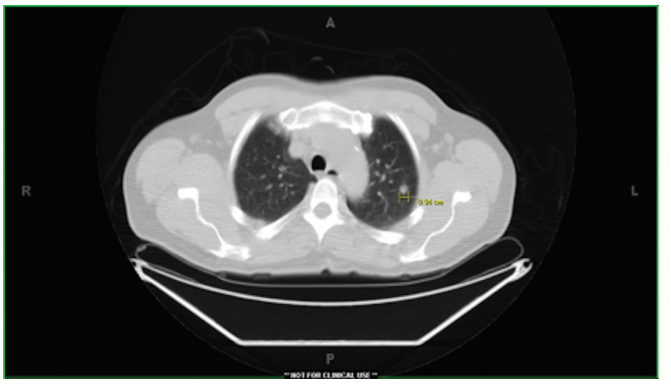

FIGURE 3. Computed tomography of a patient with a small lesion that pathology showed to be a moderately differentiated (G2) squamous cell carcinoma with a stage of T1N0Mx.

excessive travel from home to clinic. No suggestions for improvement were made.

Using the weighted multivariable ODA approach for analyzing the CB test data resulted in the scatter plot (illustrated in Fig. 2) for the 41 patients. As shown here, 11 of the 12 patients with benign lesions had composite risk scores that fell below the cutoff point. For the malignant cases, 26 of the 29 had composite risk scores above the cutoff point with 3 falling below it.

Thus, for the 12 benign cases, the CB data resulted in 1 false positive and 11 true negatives for a specificity of 91.7% and an NPV of 78.5%. After bootstrap validation, the specificity was 83.3%, 95% confidence interval (CI) (52.8–96.4%) and the NPV was 70.4%, 95% CI (41.2–88.9%). In the false-positive case, the patient underwent a lobectomy with a final diagnosis of a nonnecrotic granuloma.

For the 29 malignant cases, there were 26 true positives and 3 false negatives for a sensitivity of 89.7% and a PPV of 96.3%. After bootstrap validation, the sensitivity was 83.1%, 95% CI (65.5–93.3%) and the PPV was 92.9%, 95% CI (75.7–98.7%). In the three false-negatives cases, one was in the patient with atypical carcinoid cancer, whereas histologies from the other two malignant cases showed invasive squamous cell cancer with focal basaloid features for one and poorly differentiated adenocarcinoma for the other.

Further analysis evaluated BSP performance based on lesion size, which ranged from 0.4 to 14.6 cm based on the CT. The three cases with false-negative results had lesion sizes of 2.0, 4.0, and 7.5 cm, whereas the one false-positive case had a 2.2-cm mass that was resected by lobectomy. Among the cases correctly identified as malignant, there were two subjects with small masses of 0.8 cm each (Figs. 3 and 4), whereas the largest lesion with a benign diagnosis proven by lobectomy was 3.9 cm. The ROC area for the continuous composite risk score is illustrated in Figure 5, showing an ROC area of 94.5%. After dichotomizing the risk score, the binary CB test had an ROC of 90.7%. After bootstrap validation, the binary test ROC was 83.2%, 95% CI (71.0–95.3%). The lower bound of 71.0% of this bootstrap -validated 95% CI is well above 50%, thus demonstrating a statistically significant result (the null hypothesis value for a diagnostic test is ROC of 50%, where 50% indicates no discriminatory ability of the test).

A positive spiral CT showing an IPL was a key enrollment criterion for all subjects; Figures 3 and 4 show the images from two malignant cases.

DISCUSSION

The current study of a prospective automated evaluation of patients being assessed for possible lung cancer, using the present CB measurement system (Freshmedx BSP), has demonstrated distinct patterns of transcutaneous bioconductance measurements that can distinguish between individuals with primary lung cancers and those with a benign process. The study was "blinded" in that the CB measurements were taken before obtaining knowledge of whether the patient had benign or malignant lesions, and effectively blinded for the data analysis by using a fully prespecified and preprogrammed analysis that did not permit analysis decisions based on the data or malignancy status.

The need for noninvasive adjunctive techniques to risk stratify indeterminate pulmonary nodules for further evaluation is driven by several well-established facts: that lung cancer is the leading cause of cancer mortality in the United States and worldwide, and that it most commonly presents as radiographic abnormalities of the chest with or without clinical symptoms. Abnormalities in chest imaging, especially seen on CT scans of ever-improving resolution, are common findings.[4] Such findings, especially as NCNs, are most frequently benign in nature. However, with the present poor survival in incident lung cancer cases, and the worsened prognosis of larger cancers and higher-staged disease, watchful waiting is not always an option.[33] Although CT-guided needle biopsies, video-assisted or open surgical biopsies offer a higher diagnostic yield, they are much costlier in financial terms and in possible procedure-related morbidities.

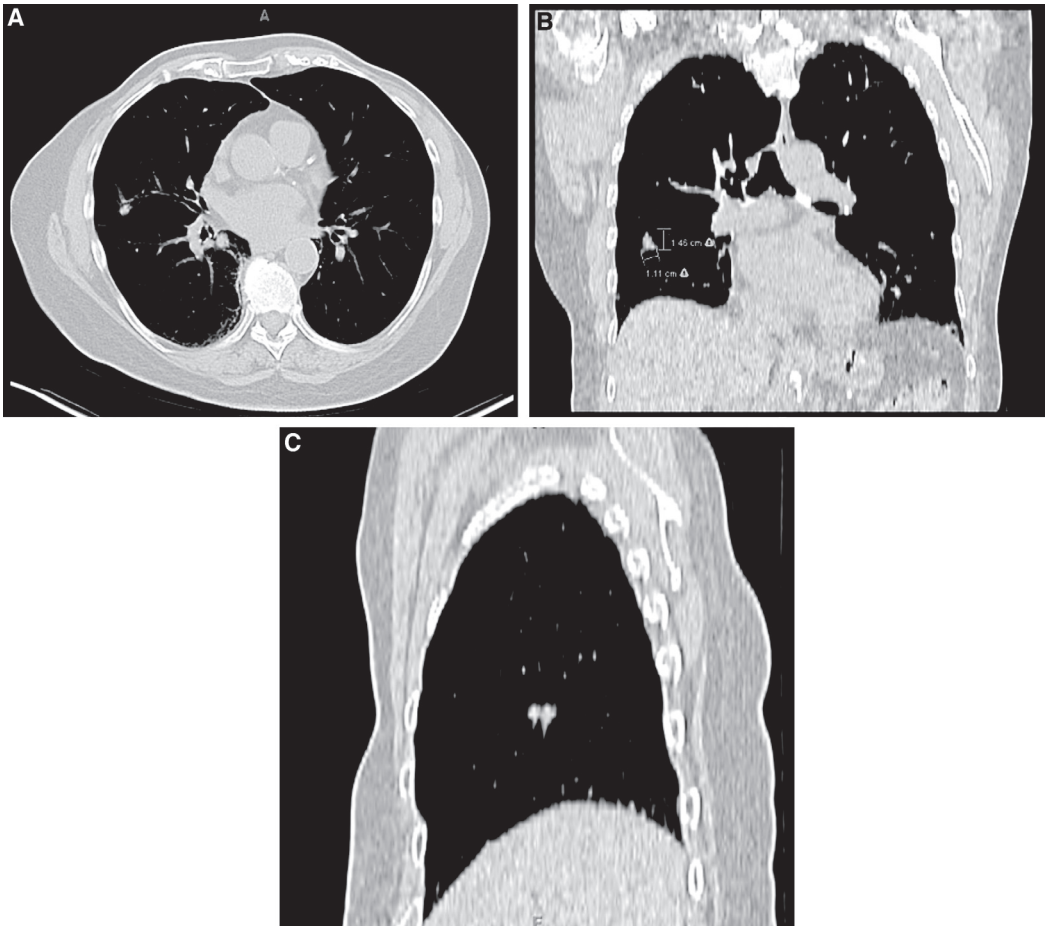

FIGURE 4. Panels A, B and C show computed tomography images of a patient with a small moderately differentiated (G2) adenocarcinoma with bronchoalveolar features. This patient was staged as T1N0M0.

In contrast, there is limited information regarding changes in lung bioconductivity associated with lung cancer with a few reports noting a relationship.[25–27] Kimura et al studied the extracellular and intracellular resistances and membrane capacitances in three groups of patients: those with lung cancers, metastatic cancers to the lung, and organizing pneumonias.[25] Measurements of the normal lung parenchyma were also obtained as each patient acted as his/her own control. This study involved an invasive approach of transthoracic insertion of a coaxial needle that is used as both the bioconductance measurement and tissue biopsy device. Although interesting observations can be made that a lung mass or consolidation (organizing pneumonia) has lower extracellular resistance than normal lung parenchyma, with a pneumonia having the lowest number, there were only 4 organizing pneumonias versus 49 cancers (44 lung primaries and 5 metastases); hence it is difficult to draw firm conclusions about difference in tissue conductance between these two groups. The authors concluded that a coaxial biopsy needle outfitted for bioconductance measurement may be useful in guiding biopsy, of when abnormal lung tissue is reached, hence it is really an adjunctive device for biopsy rather than for preinvasive assessment.

In a single, prior noninvasive study of bioconductance measurement in lung cancer subjects, the focus was on comparing bioelectric impedance vector analysis in patients with known advanced-stage (IIIB and IV) lung cancer (66) versus healthy controls (56).[26] The conclusion drawn in the study by Toso et al is that a distinct difference in transcutaneous bioimpedance (a combination of resistance and capacitance) can be seen between patients with advanced lung cancer and normal controls, and that in the advanced cancer cohort, regardless of their measured body mass index, one commonly used the index of nutrition, bioconductance measurement differences provided a better measurement of survival, and hence prognosis. No mention was made of how their technology or methodological approach may be used in the pretissue diagnostic realm. Finally, a third study used electrical impedance tomography to provide in vivo imaging before surgery in 22 patients with single-sided lung cancer and 7 healthy subjects.[27] These investigators found that images in 19 of the 22 affected lung cancer patients showed differences in conductivity that were statistically different from the average conductivity of a healthy lung.

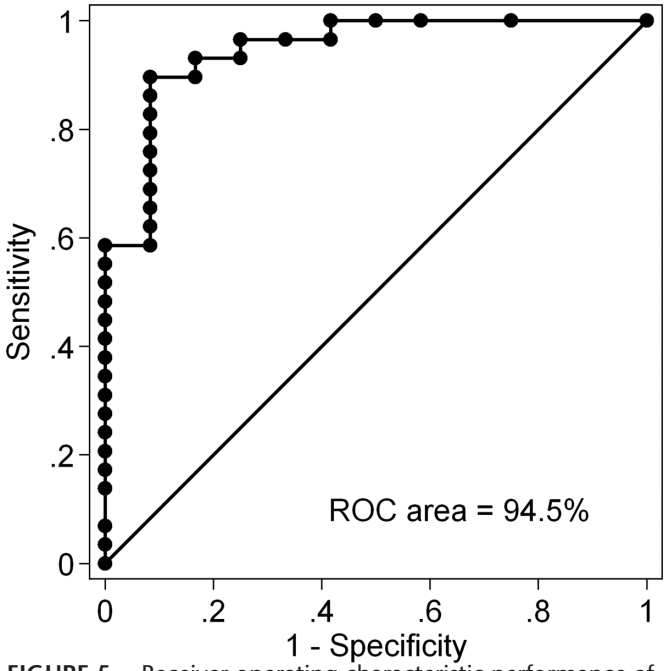

FIGURE 5. Receiver operating characteristic performance of the computed bioconductance test.

An earlier study of CB in 36 subjects (18 lung cancer proven and 18 age- and sex-matched control cohort) provided encouraging preliminary data, though using different equipment and measurement parameters by demonstrating a distinct pattern of bioconductance with a transcutaneous approach.[28] In the present study, using a prespecified risk score algorithm noted to be useful in distinguishing patients with cancer versus normal controls in the earlier study, the algorithm was applied to the current data to generate a continuous composite risk score. The "optimal" cutoff point for the composite score (Fig. 2) that produced a binary test correctly identifies 26 of 29 lung cancer cases as true positives (sensitivity 89.7%), and only 1 false positive (PPV 96.3%); the same cutoff point identified 11 of 12 benign lesions as true negatives (specificity 91.7%), but as there were 3 false negatives with this cutoff point, the NPV is 78.5%. The area under the curve of the ROC (Fig. 5) using the attributes chosen is a robust 94.5%, which remained high at 90.7% after converting to a binary test. It is possible to shift the cutoff point to further favor an increased sensitivity and higher NPV, but this will decrease the specificity. If used as a risk-stratifying test before tissue diagnosis, this will increase biopsies of benign lesions. It is recognized that the two cases considered in the benign categorization were based on follow-up CT results rather than biopsy, so their diagnosis is not completely definitive although consistent with current clinical practice.

Of the 29 proven lung cancers, 14 (48%) were T1 cancers, 11 (38%) were T2 and 4 (14%) were T3 (Table 2). The 3 false-negative cases (10.3%) were 2, 4.7, and 7.5 cm, whereas two 0.8 cm non–small-cell lung cancers were correctly identified by the combination score cutoff (Fig. 2), hence the size of primary cancer did not seem to affect usefulness of the CB composite risk score. Adenocarcinoma formed the majority (58%) cell type in the primary lung cancer cohort, perhaps not surprising because the subjects were selected on the basis of a visible peripheral lung mass. Of note, the three cases of adenocarcinoma classified as bronchioloalveolar cell were all accurately classified as cancer (Fig. 4).

The prior study by Kimura et al[25] of needle puncture into tissue observed the extracellular resistance and membrane capacitance differences between lung parenchyma and a lung mass, but no distinction was made between normal versus emphysematous versus fibrotic lung parenchyma. Because the majority of lung cancer patients continue to be active or ex-smokers who may have coexisting obstructive lung disease of varying severity, we collected spirometric measurements on all the patients (Table 5). There is no pattern of combination bioconductance measurements to suggest that the degree of airflow obstruction significantly affects the CB combination score that may mistakenly identify an epiphenomenon (airflow obstruction).

There are other noninvasive tests that have been used to further characterize an IPL to improve the discrimination of whether such a lesion is malignant or benign, but these are most commonly additional radiology studies that expose patients to higher and cumulative dosages of ionizing radiation. The use of timed contrast injection to measure nodule enhancement is useful for solid nodules and, with a minimum cutoff point of 15 Hounsfield unit (HU), has a high sensitivity (98%) and a high NPV in a study with 356 suspicious nodules. With this 15-HU threshold, the specificity is only 58%, and little is known about its utility for nonsolid lesions.[34] Instead, 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) metabolic scanning is ever more likely to be used as a follow-up imaging adjunct in the evaluation of the suspicious solitary pulmonary nodule, with sensitivities of 92 to 96% and specificities of 77 to 90%.[35,36]

There has been a prospective study of 42 nodules evaluated by both techniques, with the conclusion that 18-FDG PET scans offer a higher specificity of 90% and above with minimal loss of sensitivity .[37] The authors, all experts in this field, acknowledge the trade-off because contrast-enhanced CT is more easily available and cheaper to perform. Conversely, PET scans are costly, not widely available outside of North America, Western Europe, and the more developed larger cities on other continents. Furthermore, whereas 18-FDG-PET has an overall sensitivity of more than 90% in identifying the malignant pulmonary nodule, its diagnostic sensitivity falls in smaller (<1.0 cm) lesions and again in the nonsolid adenocarcinoma that are minimally invasive or presenting with a lepidic alveolar cell features. These smaller lesions and nonsolid lesions are also the ones that pose a bigger challenge in diagnosing with minimally invasive transthoracic needle or bronchoscopic techniques.

In our present study, all patients have high-resolution CT scans, most often with intravenous contrast, but we do not have a protocol for dynamic contrast enhancement with timed measurement of changes in the HU measurement of the nodule. This would entail multiple scans with attendant increase in exposure to ionizing radiation. A number of our subjects did have a 18-FDG-PET scan that had been ordered for the evaluation of the nodules. However, even though 36 of 55 subjects did have PET scans, these were performed at various facilities

with no standard methodology of reading or scoring uptake value, therefore we did not perform further subgroup analysis. This comparison can be of great interest if prospectively studied with standardized reading for the 18-FDG uptake.

We have not studied our patients with the BSP longitudinally with multiple CB in-series, as all patients were scheduled to have some form of tissue diagnosis on follow-up within 60 days, at which time the individual patient's study was considered complete. There were no device-related or study-associated adverse events, and only 2 of 55 subjects indicated "no" to repeat testing, citing inconvenience as the reason. It will be of interest to repeat measurement in all groups of patients, those with benign tissue diagnosis, and those who were followed to resolution of their suspicious pulmonary lesions; it is unknown whether the CB profile will remain static or change with radiographic findings. A separate pattern of change could be expected in patients with lung cancers who then underwent curative surgery, and of further interest and intrigue is whether a "cancer" profile should recur with cancer recurrence and/or development of a second primary lung cancer after surgical cure of the primary cancer. In the group of patients with nonsurgical lung cancer who are treated with standard combination of chemotherapy with and without radiation, it will be interesting to see whether serial measurements change as the disease responds or progresses, as is suggested in the Toso study.[26] The current cutoff point provides a binary response of risk assessment. Serial measurements of the same patient or larger study cohorts may provide a rationale to subdivide the combination score into subgroups of negative, low index, medium index, and high index of suspicion for lung cancer. A slope of serial combination score may be compared to currently accepted modes of serial assessment, Response Evaluation Criteria in Solid Tumors criteria, 18-FDG standard uptake values (SUV), and Eastern Cooperative Oncology Group functional status to determine whether it may provide prognostic information.

As discussed in the Statistical Analysis section, the CB test was a prespecified statistical analysis plan, with no effort made to maximize its performance. Review of patient-related factors such as age, sex, race, and body mass index as possible contributors to a subject's composite score did not show a clear correlation when examined in this relatively small patient population but may prove to be of value when larger patient groups are investigated. The sample size, particularly only having 12 benign cases, is a limitation of this study. Further clinical investigations are ongoing and refinement of the algorithm that discriminates between malignant and benign lesions continues to be in progress.

CONCLUSIONS

In this article, we are for the first time describing the use of transcutaneous CB measurements, which is noninvasive and does not expose the patient to ionizing radiation, that may offer a highly distinguishing signal between malignant and benign lesions. This test may be applied as a first-step risk-stratification adjunctive procedure in the evaluation of the IPL. Additional studies may include prospectively applying the presently developed algorithm of the CB test based on the present training set to new tests or validation sets of cohorts of patients with IPLs. There will be opportunity to further refine the present algorithm by inclusion of more patients with varying lung pathologies, malignant and benign. There will also be continued development by elimination of low-performance anatomic location measurement points, and by the testing of new measurement points that may further enhance the overall performance characteristic of CB measurement. Qualities such as ease of testing and repeatability open up potential future applications of this technology in specific high-risk populations for the early detection of disease recurrence after initial treatment response, emergence of second primary lung cancers, and as a potential technology for lung cancer screening.

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