CHEST

Noninvasive Tissue Characterization of Lung Tumors Using Integrated Backscatter Intravascular Ultrasound

An Ex Vivo Comparative Study With Pathological Diagnosis

Fumitaka Ito, MD; Masanori Kawasaki, MD, PhD; Yasushi Ohno, MD, PhD; Sayaka Toyoshi, MD; Megumi Morishita, MD; Daizo Kaito, MD; Komei Yanase, MD; Norihiko Funaguchi, MD, PhD; Masahiro Asano, MD; Junki Endo, MD, PhD; Hidenori Mori, MD, PhD; Kazuhiro Kobayashi, MD; Kazuhiko Nishigaki, MD, PhD; Tatsuhiko Miyazaki, MD, PhD; Genzou Takemura, MD, PhD; and Shinya Minatoguchi, MD, PhD

BACKGROUND: Endobronchial ultrasonography (EBUS) facilitates a lung cancer diagnosis. However, qualitative tissue characterization of lung tumors is difficult using EBUS. Integrated backscatter (IBS) is an ultrasound technique that calculates the power of the ultrasound signal to characterize tissue components in coronary arteries. We hypothesized that qualitative diagnosis of lung tumors is possible using the IBS technique. The aim of the present study was to elucidate whether the IBS technique can be used in lung tissue diagnoses.

METHODS: Thirty-five consecutive patients who underwent surgery for lung cancer were prospectively enrolled. Surgical specimens of the lung and the tumor tissue were obtained, and the IBS values were measured within 48 h after surgery. Histologic images of lung and tumor tissues were compared with IBS values, and the relative interstitial area according to results of Masson's trichrome staining were determined by using an imaging processor.

RESULTS: The IBS values in tumor tissue were significantly lower than those in normal lung tissue (−50.9 ± 2.6 dB and −47.6 ± 2.6 dB, respectively; $P < .001$). The IBS values of adenocarcinomas associated with a good 5-year survival rate were higher than those of non-adenocarcinomas (−48.1 ± 1.6 dB and −52.6 ± 1.4 dB; $P < .001$). There were significant correlations between the IBS values and the relative interstitial area or micro air area in tumor ($r = 0.53$ and $r = 0.67$; $P < .01$). After combining normal lung tissue and adenocarcinomas with a good prognosis, the sensitivity and specificity for establishing the presence of lung tumors were 84% and 85%.

CONCLUSIONS: Qualitative diagnosis of lung tumors was possible, with a sensitivity of 84% and a specificity of 85%, using the ultrasound IBS technique.

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KEY WORDS: endobronchial ultrasonography; integrated backscatter ultrasound; lung tumor; tissue characterization

ABBREVIATIONS: EBUS = endobronchial ultrasonography; IBS = integrated backscatter; IVUS = intravascular ultrasound; ROI = regions of interest

AFFILIATIONS: From the Department of Respirology (Drs Ito, Ohno, Toyoshi, Morishita, Kaito, Yanase, Funaguchi, Asano, Endo, and Mori), Department of Cardiology (Drs Kawasaki, Nishigaki, Takemura, and Minatoguchi), and the Pathology Division (Drs Kobayashi and Miyazaki), Gifu University Graduate School of Medicine, Gifu, Japan.

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CORRESPONDENCE TO: Masanori Kawasaki, MD, PhD, Department of Cardiology, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan; e-mail: masanori@ya2.so-net.ne.jp

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The bronchoscope is a primary and a promising diagnostic device for lung tumors. Because different stages of the disease respond differently to the offered treatment, accurate diagnosis and staging of lung cancer are important to improve the prognosis.[1] Transbronchial lung biopsy is a technique for obtaining tissue for histologic diagnosis in many pulmonary disorders. Although this technique is relatively safe,[2] complications such as pneumothorax and bleeding are not negligible. Endobronchial ultrasonography (EBUS) during bronchoscopy enables diagnosis of lung tumors. However, qualitative tissue characterization of lung tumors is difficult using conventional EBUS. In vivo evaluation of the tissue characteristics of lung tumors using ultrasonography is the ultimate goal in establishing a noninvasive lung cancer diagnosis.

We previously reported that ultrasonic integrated backscatter (IBS) values obtained by intravascular ultrasound (IVUS) reflect the tissue characteristics of human coronary arterial plaques, with high sensitivity and specificity (90%-95%).[3-5] The IBS value was calculated as the average power of the ultrasound backscattered signal from a small volume of tissue using fast Fourier transform measured in decibels; different tissues had their own IBS values. The reliability and usefulness of IBS IVUS have been established in many previous reports.[6-8]

The hypothesis of the present study was that the qualitative diagnosis of lung tumors is possible by using the IBS technique. The goal was to elucidate whether the IBS technique can be used to diagnose lung cancer.

Materials and Methods

Study Protocol

For the ex vivo study, we prospectively enrolled patients who underwent surgery for lung cancer after a diagnostic medical examination. Surgical specimens of the lung and the tumor tissue were obtained, and the IBS values were measured within 48 h after surgery. The IBS values at the sites 1.5 mm from the ultrasound probe in saline were measured and compared with the histologic images.

The present study was approved by the ethics committee of Gifu University (approval number, 19-149), and all patients provided written informed consent prior to participation.

Acquisition of IBS Values From Lung Tissue and Tumor

The IBS ultrasound method is based on analysis of the backscattered signals. We previously reported tissue characterization of human carotid and coronary arterial plaques in vivo using an IBS ultrasound.[3-5] These studies found that IBS measurements accurately reflect the tissue characteristics of human carotid and coronary arterial plaques, and that the values recorded just after the excision at autopsy or after fixation were precisely correlated with tissue characteristics.[5] We previously reported the details of this system.[6,7] Briefly, the IBS IVUS system (IB-IVUS; YD Co, Ltd) was connected to an IVUS imaging system (Clear View; Boston Scientific) with radiofrequency, signal trigger, and video image output to obtain the radiofrequency signals. Ultrasound IBS signals were acquired by using a 40 MHz mechanically rotating IVUS catheter (Atlantis; Boston Scientific), digitized and subjected to spectral analysis. IBS values for each tissue component were calculated by using a fast Fourier transform of the frequency component of the backscattered signal from a small volume of tissue; the values were expressed in decibels. Conventional ultrasound images, IBS color-coded maps, and IBS values were displayed side-by-side on a monitor. Tissue IBS values were calibrated by subtracting the values from the previously measured values of stainless steel placed at a distance of 1.5 mm from the catheter.

Our definition of IBS values for each tissue component in "coronary plaques" was determined by comparing the histologic images reported in our previous study.[3] Color-coded maps consist of four colors (blue for lipid pools in the coronary plaque, $-73 < \text{IBS value} \leq -63$ dB; green for fibrosis in the coronary plaque, $-63 < \text{IBS value} \leq -55$ dB; yellow for dense fibrosis in the coronary plaque, $-55 < \text{IBS value} \leq -30$ dB; and red for calcification in the coronary plaque, $-30 < \text{IBS value} \leq -23$ dB). However, these cutoff values for coronary plaques cannot be applied to the lung tissues. The size of the regions of interest (ROI) was the same as that of the previous study (0.3 mm × 0.3 mm) (Fig 1). A total of 141 ROIs were compared. We used three or four ROIs for one specimen from one patient and used average IBS values. ROIs were set evenly covering the images at the sites 1.5 mm from the ultrasound probe.

Lung segments obtained during surgery were subjected to ultrasound imaging in saline at 37°C. After measuring IBS values, specimens were embedded with paraffin and cut into 4-μm sections, and then stained with hematoxylin-eosin and Masson's trichrome. Histologic images of Masson's trichrome staining were digitized, and the areas that were stained blue (collagen fibers, mucus, and basophils) were automatically selected by a multipurpose image processor (LUZEX F; Nireco Co) and defined as an interstitial area. The relative interstitial area (interstitial area/entire ROI area) was automatically calculated by using the LUZEX F system. A nontissue area was also automatically selected by the LUZEX F system and defined as a micro air area. The relative micro air area (micro air area/entire ROI area) was automatically calculated by the LUZEX F system.

Reproducibility and Reliability of Data

We previously determined intercatheter variability of IBS values in the same ROI in 18 recordings that were measured by one observer using five randomly selected catheters of IB-IVUS.[6] The intercatheter variability of IBS values in the same ROI was 4.1% ± 3.2%. Likewise, we determined the intracatheter variability of IBS values in the same ROI in 18 images that were measured three times by one observer using one catheter selected at random. The intracatheter variability of the lipid pool cross-sectional area and fibrous cross-sectional area was 2.6% ± 1.7% and 0.73% ± 0.38%, respectively.

Interobserver variability of IBS values were determined in the same image in 18 recordings that were measured by two observers. We also determined the intra-observer variability of IBS values in the same image in 18 recordings that were measured twice by one observer during a 7-day interval.