ARCHIVOS DE BRONCONEUMOLOGIA

Original Article

Real-time prediction of mediastinal lymph node malignancy by endobronchial ultrasound[☆]

Hanaa Shafiek,[a,c] Federico Fiorentino,[a] Alejandro David Peralta,[a] Enrique Serra,[b] Blanca Esteban,[b] Rocío Martinez,[a] Maria Angels Noguera,[a] Pere Moyano,[e] Ernest Sala,[a,d] Jaume Sauleda,[a,d] Borja G. Cosío[a,d,*]

[a] Departamento de Medicina Respiratoria, Hospital Universitario Son Espases, Palma de Mallorca, Spain
[b] Departamento de Anatomía Patológica, Hospital Universitario Son Espases, Palma de Mallorca, Spain
[c] Departamento de Enfermedades del Tórax, Facultad de Medicina, Universidad de Alejandría, Alejandría, Egypt
[d] Ciber de Enfermedades Respiratorias (Ciberes), Spain
[e] Departamento de Anestesiología, Hospital Universitario Son Espases, Palma de Mallorca, Spain

A B S T R A C T

Objective: To evaluate the utility of different ultrasonographic (US) features in differentiating benign and malignant lymph node (LN) by endobronchial ultrasound (EBUS) and validate a score for real-time clinical application.
Methods: A total of 208 mediastinal LNs acquired from 141 patients were analyzed. Six different US criteria were evaluated (short axis $\geq$10 mm, shape, margin, echogenicity, central hilar structure [CHS], and presence of hyperechoic density) by two observers independently. A simplified score was generated where the presence of margin distinction, round shape and short axis $\geq$10 mm were scored as 1, and heterogeneous echogenicity and absence of CHS were scored as 1.5. The score was evaluated prospectively for real-time clinical application in 65 LNs during EBUS procedure in 39 patients undertaken by two experienced operators. These criteria were correlated with the histopathological results and the sensitivity, specificity, and positive and negative predictive values (PPV and NPV) were calculated.
Results: Both heterogenicity and absence of CHS had the highest sensitivity and NPV ($\geq$90%) for predicting LN malignancy with acceptable inter-observer agreement (92% and 87% respectively). On real-time application, the sensitivity and specificity of the score >5 were 78% and 86% respectively; only the absence of CHS, round shape and size of LN were significantly associated with malignant LN.
Conclusions: A combination of different US criteria can be useful for the prediction of mediastinal LN malignancy and valid for real-time clinical application.

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Predicción en tiempo real de la malignidad de ganglios linfáticos mediastínicos mediante ecografía endobronquial

R E S U M E N

Objetivo: Evaluar la utilidad de diferentes características ecográficas para diferenciar los ganglios linfáticos (GL) benignos y malignos mediante ecografía endobronquial (EBUS) y validar una puntuación para una aplicación clínica *en tiempo real.*
Métodos: Se analizaron 208 GL mediastínicos procedentes de 141 pacientes. Dos observadores evaluaron de manera independiente 6 criterios ecográficos diferentes (eje menor $\geq$10 mm, forma, margen, ecogenicidad y estructura hiliar central [EHC] y presencia de densidad hiperecogénica). Se generó una puntuación simplificada en la que a la presencia de márgenes bien definidos, la forma redondeada y el eje menor

≥10 mm se les asignaba una puntuación de 1 y a la ecogenicidad heterogénea y la ausencia de EHC se les asignaba una puntuación de 1,5. La puntuación se evaluó prospectivamente para la aplicación clínica *en tiempo real* en 65 GL durante la EBUS llevada a cabo por 2 operadores experimentados en 39 pacientes. Estos criterios se correlacionaron con los resultados histopatológicos, y se calcularon la sensibilidad, la especificidad y los valores predictivos positivo (VPP) y negativo (VPN).

Resultados: La heterogeneidad y la ausencia de EHC fueron los parámetros que mostraron la máxima sensibilidad y VPN (≥90%) en la predicción de la malignidad de los GL, con una coincidencia interobservadores aceptable (92 y 87%, respectivamente). En la aplicación *en tiempo real*, la sensibilidad y la especificidad de la puntuación >5 fueron del 78 y del 86%, respectivamente; tan solo la ausencia de EHC, la forma redondeada y el tamaño de los GL mostraron una asociación significativa con la malignidad de estos.

Conclusiones: La combinación de diferentes criterios ecográficos puede ser útil en la predicción de la malignidad de los GL mediastínicos y válida para una aplicación clínica *en tiempo real*.

Introduction

Lymph node (LN) biopsy is essential for accurate staging of lung cancer. Endobronchial ultrasound (EBUS) is a technique that combines endoscopic visualization with high frequency ultrasound imaging.[1] EBUS is useful for visualizing both mediastinal and hilar LN[3] and for guiding needle aspiration during the cytological and histological biopsy procedure.[2,4,5]

In the last decade, many studies have evaluated sonographic observations that may suggest malignant LN infiltration in head and neck, breast, uterine cervix and esophageal cancer.[2,6–9] In a recent retrospective study in lung cancer, Fujiwara et al.[10] described 4 sonographic features of value for predicting the malignant infiltration of mediastinal LN (round shape, distinct margin, heterogeneous echogenicity and the presence of coagulation necrosis sign). Schmid-Bindert et al.[11] proposed a score that combined the following ultrasound criteria for predicting malignancy in mediastinal LN: round shape, well-defined margins, echogenicity, the absence of any central hilar structure (CHS), short axis ≥1 cm and color power Doppler index grade 2 or 3. The authors concluded that if less than 3 of the specified criteria were present, the LN had a very low probability of being malignant.[11] However, these criteria are retrospective and may have a subjective component, since no prospective validation was made and some of the criteria used are difficult for experienced operators to determine in real time.

In an attempt to validate the clinical utility of the foregoing criteria, the hypothesis was proposed that some LN ultrasound criteria could be useful for predicting malignant LN infiltration and thus could be used as a guide for selecting LNs for aspiration, leading to improved bronchogenic staging. Consequently, the objectives of this study were, firstly, to evaluate retrospectively which EBUS sonographic features were the most accurate for differentiating benign involvement from malignant involvement in both mediastinal and hilar LNs, after correlating these features with the histopathological results; and secondly, to prospectively analyze the previously proposed score for a combination of these ultrasound criteria for real-time clinical application.

Methods

Design and study patients

The study was divided into 2 parts. The first was a descriptive study for which 176 patients with mediastinal/hilar LN undergoing EBUS in the Hospital Universitario Son Espases between 2009 and 2012 for lung cancer staging or investigation of suspected malignant LN infiltration were screened. Of these patients, 141 were included in the study, and 2 raters who were unaware of the final diagnosis independently analyzed the 208 LN images. The second part was a prospective study for which 39 consecutive patients were recruited and two raters predicted the probability of malignant LN involvement in real time on the basis of the previously validated criteria. Consecutive patients scheduled to undergo EBUS to study mediastinal/hilar LN observed on a computed tomography (CT) of the chest or hypermetabolic LN identified in a positron emission tomography with fluorodeoxyglucose (PET-FDG) were included.

The indication for performing invasive mediastinum staging by EBUS, endoscopic ultrasound (EUS), or a combination of both techniques is established by a local multidisciplinary lung cancer committee, according to the following standardized criteria[12]: (a) enlarged discrete mediastinal LN with PET uptake; (b) PET activity in a mediastinal LN and nodes with normal appearance on CT, and (c) suspected N2,3 involvement with a radiographically normal mediastinum (determined by CT and PET) and a central or N1 tumor. Patients with any contraindication for bronchoscopy according to the recommendations of the American Thoracic Society[13] or a high anesthetic risk (American Society of Anesthesiologists physical status >3)[14] were excluded. A full clinical history was obtained and chest CT and PET-FDG images were analyzed by a multidisciplinary lung cancer committee that established the indication for performing EBUS with transbronchial needle aspiration (TBNA) or transtracheal aspiration (TTA), following international guidelines.[15] Patients were then evaluated by the anesthesiology team before the intervention. Informed consent was obtained from all patients.

EBUS + TTA/TBNA procedure

EBUS was performed using an EB-1970UK (Pentax, 10.0-5.0 MHz, Tokyo, Japan) endoscope and the Hitachi Digital Ultrasound Scanner EUB-7000HV. The procedure was performed via the oral route under deep sedation with propofol, midazolam and fentanyl with anesthesiologist-controlled spontaneous ventilation in all study patients. The intervention was performed as described by Yasufuku et al.[2] Enlarged LNs (greater than 5 mm) were identified by the measurements made in the digitally captured ultrasound images. Fixed images were captured for subsequent analysis. Blood vessels were confirmed with the Doppler modality. For TBNA and/or TTA, a 22-caliber needle was used. The needle was introduced via the working channel of the EBUS through the bronchial wall, and the LN was aspirated under ultrasound guidance to obtain a tissue biopsy. A smear of the aspirated material was prepared on a glass slide, air-dried and immediately stained with standard hematoxylin and eosin for rapid on-site evaluation (ROSE) by a cytopathologist. Three consecutive biopsies of a reactive LN were considered negative for malignant disease. The aspirated materials were also collected in liquid formol, and the cell block underwent a final histological evaluation by the pathologist. The final pathological diagnosis was the standard reference for positive malignant LN infiltration. Patients with negative pathology