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Original Article / Özgün Makale

A promising tool for T-staging of lung cancer: Is convex probe endobronchial ultrasound superior to computed tomography in detecting invasion of mediastinal and hilar vessels?

Akciğer kanserinin T evrelemesinde gelecek vadeden bir araç: Konveks prob endobronşiyal ultrason, mediastinal ve hiler damarların invazyonunu belirlemede bilgisayarlı tomografiden üstün müdür?

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ABSTRACT

Background: In the present study, we aimed to compare performance of convex probe endobronchial ultrasound and computed tomography in detecting vascular invasion of mediastinal and hilar lesions.

Methods: Medical data of a total of 55 patients (47 males, 8 females; mean age 59.6±7.7 years; range, 29 to 76 years) who underwent convex probe endobronchial ultrasound for diagnosis and staging of lung cancer in a tertiary care hospital between May 2016 and December 2017 were retrospectively analyzed. The presence of vascular invasion was determined according to two main criteria: visualization of the tumor tissue within the vessel lumen and loss of vessel-tumor hyperechoic interface. All available contrast enhanced computed tomography images were retrospectively re-evaluated by a blinded radiologist. The intra-rater agreement between convex probe endobronchial ultrasound and computed tomography was analyzed. The sensitivity, specificity, positive and negative predictive values, and accuracy of both modalities were calculated.

Results: A total of 65 vessel-tumor interface areas of 55 patients were analyzed. Almost all mediastinal and hilar vascular structures including pulmonary arteries and veins, aorta, superior vena cava and its branches, and left atrium with pulmonary veno-atrial junctions could be easily assessed by convex probe endobronchial ultrasound. The intra-agreement of both modalities in detecting vascular invasion was κ=0.268 (p=0.028). In nine patients with a surgical confirmation, the sensitivity, specificity, positive and negative predictive values, and accuracy values were 100%, 33.3%, 75.0%, 100%, and 77.7%, respectively for convex probe endobronchial ultrasound and 66.6%, 33.3%, 66.6%, 33.3%, and 55.5%, respectively for computed tomography.

Conclusion: Convex probe endobronchial ultrasound can be used to detect vascular invasion alone or in conjunction with contrast-enhanced computed tomography. Hence, a T_4 lesion would be better differentiated from T_3 in clinical staging of lung cancer.

Keywords: Computed tomography, convex probe endobronchial ultrasound, invasion, lung cancer.

ÖZ

Amaç: Bu çalışmada konveks prob endobronşiyal ultrason ve bilgisayarlı tomografinin mediastinal ve hiler lezyonların vasküler invazyonunu tespit etmedeki performansı karşılaştırıldı.

Çalışma planı: Mayıs 2016 - Aralık 2017 tarihleri arasında üçüncü basamak bir hastanede akciğer kanseri tanısı ve evrelemesi için konveks prob endobronşiyal ultrason yapılan toplam 55 hastanın (47 erkek, 8 kadın; ort. yaş 59.6±7.7 yıl; dağılım, 29-76 yıl) tıbbi verileri retrospektif olarak incelendi. Vasküler invazyonun varlığı başlıca iki kritere göre belirlendi: damar lümeni içinde tümör dokusunun görüntülenmesi ve damar-tümör hiperekoik arayüzünün kaybolması. Mevcut tüm kontrastlı bilgisayarlı tomografi görüntüleri, körleştirilen bir radyolog tarafından geriye dönük olarak yeniden değerlendirildi. Konveks prob endobronşiyal ultrason ve bilgisayarlı tomografinin gözlemci içi uyumu incelendi. Her iki yöntemin duyarlılığı, özgüllüğü, pozitif ve negatif öngördürücü değerleri ve doğruluğu hesaplandı.

Bulgular: Elli beş hastanın toplam 65 damar-tümör arayüz alanı incelendi. Pulmoner arterler ve damarlar, aort, superior vena kava ve dalları ve pulmoner veno-atriyal kavşakları olan sol atriyum dahil neredeyse tüm mediastinal ve hiler vasküler yapılar, konveks prob endobronşiyal ultrason ile kolaylıkla değerlendirilebildi. İki yöntemin vasküler invazyonu belirlemedeki gözlemci içi uyumu κ=0.268 idi (p=0.028). Cerrahi doğrulama yapılan dokuz hastada duyarlılık, özgüllük, pozitif ve negatif öngördürücü değerleri ve doğruluğu konveks prob endobronşiyal ultrason için sırasıyla %100, %33.3, %75.0, %100 ve %77.7 iken, bilgisayarlı tomografi için sırasıyla %66.6, %33.3, %66.6, %33.3 ve %55.5 idi.

Sonuç: Konveks prob endobronşiyal ultrason, vasküler invazyonu belirlemede tek başına veya kontrastlı bilgisayarlı tomografi ile birlikte kullanılabilir. Bu sayede, akciğer kanserinin klinik evrelemesinde bir T_4 lezyon T_3'ten daha iyi ayırt edilebilir.

Anahtar sözcükler: Bilgisayarlı tomografi, konveks prob endobronşiyal ultrason, invazyon, akciğer kanseri.

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Determination of a possible invasion of mediastinal and hilar vascular structures is an important component of the T descriptors of clinical staging of lung cancer. However, it is shown that the correctness of clinical staging seems to be low, despite the use of several diagnostic modalities in combination.[1,2] Regarding the pivotal role of contrast-enhanced computed tomography (CT) in the preoperative clinical staging and surgical evaluation of lung cancer through T descriptor, CT seems to be the main responsible for this inadequacy. As there is an unmet need in this field, it is reasonable to search an alternative approach to detect a vascular invasion.

Convex probe endobronchial ultrasound (CP-EBUS) is a near gold-standard modality in identifying the N component of lung cancer staging. However, its possible use in T component of clinical staging has not been well-studied, yet. Nonetheless, CP-EBUS may be a strong alternative with its superior resolution when introduced through tracheobronchial tree next to an affected vascular structure. The use of ultrasound in showing vascular invasion in pancreatic malignancies has been well-studied, although a similar function of CP-EBUS in lung cancer has not been clearly understood.

In the present study, we aimed to compare performance of EBUS and CT in detecting vascular invasion of mediastinal and hilar lesions.

PATIENTS AND METHODS

This retrospective study was carried out in a tertiary care hospital between May 2016 and December 2017. Medical data, still images, and vide files of patients who underwent CP-EBUS for the diagnosis and/or staging of mediastinal/hilar lesions were reviewed. All cases with available still images and video files showing the tumor-vessel interface were included, irrespective of the final diagnosis. Benign cases were also included, as they have a non-invasive nature, to serve as a contrast to invasive disease. Of 327 cases who underwent CP-EBUS procedure during the study period, 61 were included in the study. Six cases were excluded as the CT images were not adequate in quality to detect a possible invasion. Finally, 55 cases (47 males, 8 females; mean age 59.6±7.7 years; range, 29 to 76 years) were included in the study and 65 vessel-tumor interface areas were analyzed (two or three discrete areas were affected in some cases). A written informed consent was obtained from each patient. The study protocol was approved by the Dr. Suat Seren Chest Diseases and Thoracic Surgery Health Application and Research Center Ethics Committee (49109414-806.02.02-E.12813). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic and procedural data were collected. The presence of vascular invasion was determined according to two main criteria: visualization of tumor tissue within the vessel lumen and loss of vessel-tumor hyperechoic interface (Figure 1).[3] Power Doppler images were evaluated where available. All contrast-enhanced CT images were retrospectively re-evaluated by a radiologist who was blinded to all other data. Invasion was defined as an absence of fat plane between the tumor and vessel, distortion of vascular structures, irregularity of the vessel wall, and encasement of the aorta and superior vena cava with a contact of >90° and >180°, respectively. An agreement between CP-EBUS and CT was studied. In patients with a surgical confirmation, the diagnostic accuracies of the modalities were calculated.

All CP-EBUS procedures were done and re-evaluated by a single bronchoscopist. The EBUS-transbronchial needle aspiration was performed under deep sedation with midazolam, fentanyl, and propofol in the operating room. A CP-EBUS (BF-UC180F, Olympus, Tokyo, Japan) was used to examine the lymph nodes, and the ultrasound images were processed with a dedicated scanner (EU-ME1, Olympus, Tokyo, Japan).

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows® version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed in mean ± standard deviation (SD) for continuous variables and in number and frequency for categorical variables. The intra-rater agreement was computed and a kappa (κ) value was given. In cases with a surgical confirmation, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of CP-EBUS and CT were calculated to evaluate the diagnostic performance. A p value of <0.05 was considered statistically significant.

RESULTS

Data regarding the EBUS procedure are given in Table 1. The procedure was mostly performed for diagnosis and staging. The most commonly evaluated areas were the left main pulmonary artery, right main pulmonary artery, and right superior pulmonary vein. The most common histology was an epidermoid carcinoma.

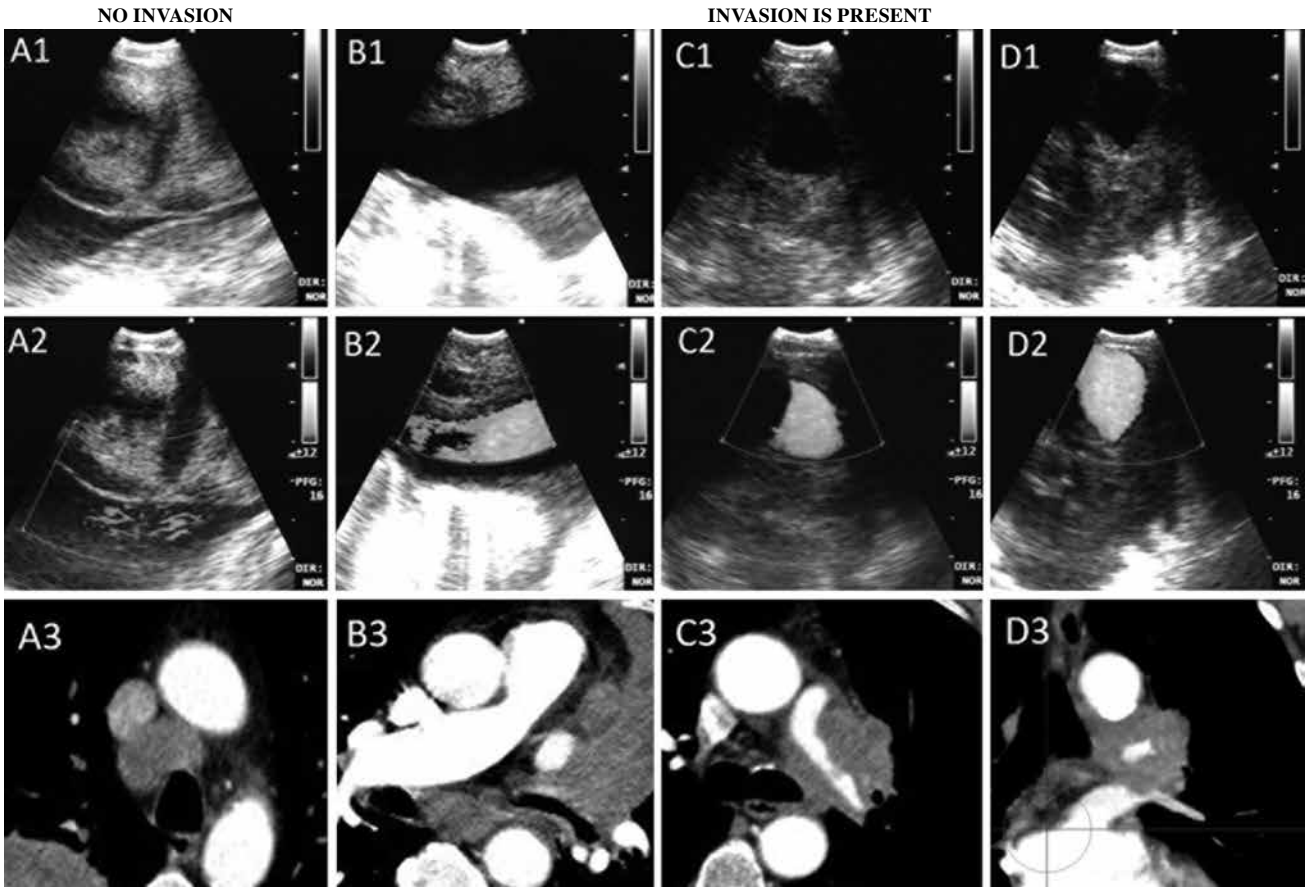

Figure 1. The figure shows several examples on the presence or absence of vascular invasion by tumor or lymph nodes. All figures are presented with their corresponding power Doppler images. **A1 and A2:** A distinct hyperechoic line is clearly and continuously seen between lesion and vessel (superior vena cava in this example). There is no sign of invasion. **B1 and B2:** The lesion invades left inferior pulmonary vein. The hyperechoic line cannot be seen thoroughly. **C1 and C2 (also in D1 and D2):** The lesion invades left main pulmonary artery. The hyperechoic line is vanished. Vessel wall becomes irregular by tumor cells protruding through the lumen. **A3 to D3:** Corresponding computed tomography images of the same patients. Note that scanning angle of EBUS may differ from the simple transverse and coronal/sagittal images of computed tomography.

The intra-rater agreement of CP-EBUS and CT in detecting vascular invasion was only fair (κ=0.268, p=0.028). Nine patients underwent surgical resection. These patients had a surgical confirmation, and the sensitivity, specificity, PPV, NPV, and accuracy values were 100%, 33.3%, 75.0%, 100%, and 77.7%, respectively for CP-EBUS and 66.6%, 33.3%, 66.6%, 33.3%, and 55.5%, respectively for CT.

DISCUSSION

The performance of ultrasound in identifying vascular invasion by pancreatic tumors has been studied by gastroenterologists for almost two decades. There are several published data regarding the performance of endoscopic ultrasound (EUS) in showing vascular invasion in pancreatic cancers.[3-8] In a single, head-to-head comparison study of EUS and CT, EUS showed a sensitivity and specificity of 61.1% and 90.3%, respectively which was higher than CT alone.[7] This finding was also confirmed by a systematic review, which yielded the area under the curve values of EUS and CT as 0.9379 and 0.8589, respectively.[8] However, in other meta-analyses and reviews, this superiority was not found.[4-6]

Invasion of great mediastinal/hilar vessels in lung cancer is an important issue in identifying T component of Tumor, Node, Metastasis (TNM) staging. To date, contrast-enhanced CT has been the main modality used for assessing vascular invasions. Besides the N component, the clinical staging of lung cancer with CT seems not to be fully accurate regarding the T component.[1,2,9] This brings this question to the fore:

Table 1. Data regarding endobronchial ultrasound procedure

	n	%
Indications (n=55)		
Diagnosis	7	12.7
Staging	15	27.3
Diagnosis and staging	33	60.0
Areas of interest (n=65)		
Left main pulmonary artery	25	38.4
Right main pulmonary artery	21	32.3
Right superior pulmonary vein	7	10.8
Others	12	18.5
Azygos vein	3	
Left inferior pulmonary vein	3	
Aorta	2	
Right inferior pulmonary vein	2	
Left atrium	1	
Superior vena cava	1	
Final diagnoses (n=55)		
Epidermoid carcinoma	24	43.7
Adenocarcinoma	15	27.3
Small cell lung cancer	8	14.6
Normal lymph node	3	5.4
Granulomatous inflammation	2	3.6
Lymphoma	1	1.8
Large cell carcinoma	1	1.8
Metastasis of thyroid papillary carcinoma	1	1.8

can CP-EBUS be a reliable alternative to CT in this issue?

Recently, Kuijvenhoven et al.[10] reported the value of EUS for detecting mediastinal invasion of centrally located lung tumors. This study is relevant, as they also used CP-EBUS introduced through esophagus which may limit some small, but considerable differences between EUS and EBUS devices, although the ratio of EBUS in total procedures was 4%. The authors included 74 cases in the final analysis. Six patients were judged to have a vascular invasion by EUS/EBUS. Of them, three were true-positives and the remaining three were false-positives. Moreover, EUS/EBUS failed to show an invasion in five patients in whom surgical resection confirmed the invasion. The EUS/EBUS has reached a sensitivity, specificity, PPV, NPV, and accuracy of 42%, 95%, 73%, 83%, and 81%, respectively. Computed tomography had a higher sensitivity in exchange with a lower specificity and a lower accuracy of 65%. The authors also analyzed the combined performance of two modalities and the corresponding sensitivity, specificity, PPV, NPV, accuracy values were found to be higher than both of the modalities alone which were 83%, 100%, 100%, 97%, and 97%, respectively. Although this study is clinically relevant, it has some issues to be addressed. Transesophageal assessment of several mediastinal vessels with EUS (and esophageal introduction of EBUS also) may be problematic, when normal course of esophagus behind the air-filled tracheal column is considered. However, CP-EBUS in tracheobronchial tree has a clear advantage while evaluating pulmonary arteries up to the proximal parts of lobar arteries and also intraparenchymal parts of both pulmonary veins. Aorta can be clearly seen all the way up to middle of the descending part. Azygos vein and upper parts of superior vena cava and innominate veins are also in the field and the left atrium can be clearly seen together with the pulmonary veno-atrial junctions.

Owing to its improved field control, CP-EBUS can be easily used to evaluate the presence of vascular invasions. There are several published data on the use of CP-EBUS in the diagnosis of vascular tumors and pulmonary embolism;[11] however, there is a limited number of data regarding its role in detecting vascular invasions. MacEachern et al.[12] reported a case in whom CP-EBUS demonstrated the vascular invasion and, hence, a T4 lesion. However, CT was unable to identify whether the mass invaded or compressed the adjacent vessel. Although this study confirms the capability of CP-EBUS, there is no other study since then.

Our study showed that a bronchoscopist could assess pulmonary arteries and veins, aorta, superior vena cava, and its branches and, also, left atrium with CP-EBUS. The intra-rater agreement of CP-EBUS and CT images was only fair. As CT alone is not a reliable modality to detect vascular invasion and CP-EBUS can yield different results, can we deem it as a superior performance? The only data come from a very limited number of cases having a surgical confirmation. The diagnostic accuracy of CP-EBUS is higher than CT (77.7% vs. 55.5%). However, our dataset is not large enough to give a proper accuracy on the combined performance of two modalities, as only nine cases had a surgical confirmation. When used in combination, all areas were found to be invasive; therefore, sensitivity and NPV could not be computed and accuracy was found to be 66.6% which was lower than CP-EBUS (data not shown).

Although the present study is of clinical importance, as it has provided new data to the literature, it has several limitations. First, this is a retrospective analysis. The video files were retrospectively analyzed according to the classification criteria. Second, although the blinded radiologist is essential in a robust methodology, it can be argued that if the areas of interest in CP-EBUS and CT images (and also surgical specimens) overlap. Third, interpretation of ultrasound images is highly operator-dependent. In our study, the procedures were done and re-evaluated by a single bronchoscopist who was intrinsically unable to be blinded to CT images. Finally, the number of cases with a surgical confirmation as gold standard was low. Therefore, the data on the diagnostic performance may not be reliable enough. Nonetheless, all these limitations have paved the way for the authors for a further, prospective study in surgically resected patients. A second bronchoscopist blinded to CT images is planned to be included to overcome the intra-rater variability. Also, a dedicated prospective method would be used to mark the areas of interest.

In conclusion, the agreement between convex probe endobronchial ultrasound and computed tomography was only fair for detecting vascular invasion of lung cancer. In a very limited number of surgically confirmed lesions, convex probe endobronchial ultrasound showed a superior diagnostic accuracy. Based on these findings, convex probe endobronchial ultrasound may be used to evaluate vascular invasion alone or in conjunction with other modalities. Nonetheless, future prospective studies are needed to properly position the place of convex probe endobronchial ultrasound in detecting T descriptor of lung cancer staging.

Declaration of conflicting interests

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