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Iodine quantification to characterize primary lesions, metastatic and non-metastatic lymph nodes in lung cancers by dual energy computed tomography: An initial experience

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ABSTRACT

Purpose: To investigate whether dual energy computed tomography (CT) with iodine quantification can characterize primary lesions and metastatic lymph nodes from non-metastatic ones in non-small cell lung cancer (NSCLC).

Materials and methods: Sixty-one patients with NSCLC confirmed by pathology underwent chest contrast CT scan with dual energy computed tomography before surgery. The Iodine concentration (IC) and normalized iodine concentration (NIC) values of the primary lesions, 20 metastatic and 20 non-metastatic lymph nodes were measured, respectively. The differences between the primary lesions, metastatic and non-metastatic lymph nodes were statistically analyzed.

Results: For the IC and NIC values of the primary lesions and their metastatic lymph nodes, there were no significant differences between lung squamous cell carcinomas and adenocarcinomas, respectively ($P > 0.05$), while significant differences existed between metastatic and non-metastatic lymph nodes, respectively ($P < 0.05$). The IC of 29.32 100 μg/cm^3 and NIC value of 0.4328 of a lymph node represented the optimal threshold to discriminate metastatic from non-metastatic lymph nodes and yielded the following: sensitivity, 80% and 75%; specificity, 65% and 75%; PPV, 70% and 75%; NPV, 76% and 75%; accuracy, 73% and 75%, respectively.

Conclusion: Although its value in distinguishing primary lesions and their metastatic lymph nodes in NSCLC needs to be verified in further studies, dual energy CT with iodine quantification may be used to differentiate metastatic from non-metastatic lymph nodes in NSCLC.

1. Introduction

Lung cancer is the most common cancer in both men and women, and is also the leading cause of cancer death throughout the world. Non-small cell lung cancer (NSCLC) accounts for 85–90% of all lung cancer. Adenocarcinoma and squamous carcinoma are the main histological subtypes of NSCLC. The benefits of oncology treatment including chemotherapy, radiotherapy and targeted therapy rely on the tumor's histologic type, stage and molecular markers. Therefore, initial staging of disease extent is important in patients with newly diagnosed NSCLC, in order to select the most appropriate therapeutic option and to derive prognostic information.

Because of advanced stage and/or comorbidities at presentation, most lung cancers are nonresectable. It is therefore advantageous to diagnose and stage the patient's tumor with small biopsies or cytologic examination rather than with surgical resection specimens. However, some patients cannot be performed the biopsies due to the tumor location or other reasons. Furthermore, staging of lung cancer including the analysis of the lymph nodes is second in importance only to the pathologic determination of cell type. Accurate staging provides prognostic information and stage determines treatment strategies for all types of lung cancer. Imaging is playing an important role in discrimination both subtypes of NSCLC and tumor staging. In the past decades, computed tomography (CT) has been employed as a main imaging modality for NSCLC diagnosis and staging [1]. Morphologic assessment of tumor has been the mainstay of conventional CT imaging evaluation in clinical practice. Recently, a new dual-energy CT technique based on the switching between high- and low-energy data sets from view to view is intro-

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duced. This technique enables registration of data sets for creation of material-decomposition images (e.g., water- and iodine-based material-decomposition images) for quantitative iodine measurement. The CT scanning method has been added and demonstrated its benefits in clinical applications such as differentiating metastatic from non-metastatic lymph nodes in rectal cancer, clear cell from papillary renal cell carcinoma and benign from malignant solitary pulmonary nodule [2–4].

However, to the best of our knowledge, there are few studies about the value of dual energy CT with iodine quantification in the differentiation and staging of NSCLC. It is possible for post-contrast dual energy CT imaging technology to determine and quantify iodine-related attenuation with the assumption of a correlation with perfusion parameters and the degree of malignant tissue vascularization. The aim of our study was to investigate whether dual energy CT with iodine quantification could characterize primary lesions and their metastatic lymph nodes between lung adenocarcinomas and squamous carcinomas, and discriminate metastatic lymph nodes from non-metastatic ones.

2. Material and methods

2.1. Patients

This retrospective study was approved by our institutional review board for human research and thus written informed consent was obtained from all patients. From January 2012 to December 2014, seventy-one patients suspected of primary peripheral lung cancer appearing as nodules or masses on the non-enhanced CT images underwent enhanced chest dual energy CT scanning before operation. All pulmonary lesions and lymph nodes were subsequently confirmed by surgical resection. Of the 71 patients, we excluded 10 patients because of the histological results of small cell lung carcinoma and the limited case number. Therefore, 61 patients (37 men, 24 women; mean age, 59.5 ± 8.7 years) were ultimately included in the present research. The body mass index (BMI) of the patients ranged from 18.4 to 22.3. A preoperative therapy (radiotherapy and/or chemotherapy) was not performed in any patient. All patients underwent surgical resection within two weeks (ranging from 2 to 14 days) after CT examinations. Each patient had one primary lesion. All patients had the complete CT images and the detailed surgical and pathological records, which were retrospectively reviewed.

2.2. Dual energy CT imaging

All patients were scanned in supine position with hands above the head. Chest contrast-enhanced scans were performed on a High Definition CT system (Discovery CT750HD, GE Healthcare, Milwaukee, Wisconsin, USA). The nonionic contrast media iohexol (Omnipaque) 300 (GE Healthcare, USA) at the dose of 1.2 mL/kg weight was injected with power injector at a rate of 2.5 mL/s through the median cubital vein. This was followed by 20 mL saline flushing at a rate of 3.0 mL/s. The spectral imaging was obtained when the attenuation in distal thoracic aorta increased to a default threshold (100HU) after contrast material injection which was measured by a dedicated monitoring system [5]. The GSI scan parameters included helical, instantaneous switch between voltages of 140 kVp and 80 kVp, display field of view (DFOV) of 40 cm, a section thickness of 1.25 mm, a reconstruction interval of 1.25 mm, a pitch of 1.375:1, a gantry rotation speed of 0.8 s, and a scan range from apex to base of lung.

2.3. Image analysis

Image reconstruction and data analysis were performed using the Advanced Workstation (AW 4.5; GE Healthcare, USA) with a special gemstone spectral imaging (GSI) viewer. A circular region of interest (ROI) was placed to cover the solid portion of the primary lesion. In homogeneous lesions, the ROIs were placed at the level of the largest axial diameter of the lesion while avoiding the edges where volume averaging can occur. In heterogeneous lesions (i.e., tumors with extensive areas of necrosis), ROIs encompassed only as much of the most avidly enhanced areas of the lesion as possible in order to avoid the inclusion of necrotic parts. The iodine concentration (IC, 100 $\mu g/cm^3$) of a primary lesion was automatically calculated from the iodine-based material decomposition images by the GSI viewer software package. In order to minimise variations in patients, the iodine concentration in the primary lesion was normalized to the iodine concentration of the aorta at the same level on the same iodine-based material decomposition image to derive a normalized iodine concentration (NIC). The NIC was calculated as the following formula: $NIC = IC_{lesion}/IC_{artery}$.

For the measurement of lymph nodes, the selection of lymph nodes was according with the surgical record and histological result. The pulmonary hilar and mediastinal lymph nodes were only enrolled in the present study and the lymph nodes with the short axis diameters less than 5 mm were excluded from analysis because it is technically challenging to position the circular ROI in these small lymph nodes. The measurement of lymph nodes was similar to that of primary lesions.

The image analysis was performed by two radiologists (X. Li and X. Meng) with 5 years and 3 years of experience in thoracic imaging, respectively. The inter-observer agreement for the measurements was assessed by using intraclass correlation coefficient (ICC). Measurements from the two radiologists were averaged to produce the final values for analysis.

2.4. Statistical analysis

All statistical calculations were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and MedCalc Version 16.2.1 statistical softwares. The inter-observer agreement for the measurements was assessed by using intraclass correlation coefficient (ICC). ICC values were categorized into 5 categories: 0.0–0.20 poor; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 good; 0.81–1.00 excellent. Quantitative variables were expressed as mean ± standard deviation (SD). All reported P values were two sided, and $P < 0.05$ was considered to indicate a statistically significant difference.

The independent two-sample t-test was performed to compare the differences of IC and NIC of the primary lesions, and between metastatic and non-metastatic lymph nodes. The receiver operating characteristic (ROC) curves were generated to help establish the threshold values and the diagnostic capabilities for the parameters in differentiating the metastatic and non-metastatic lymph nodes.

3. Results

The patients in the present analysis were divided into 27 patients with squamous cell carcinomas and 34 patients with adenocarcinomas, all of them were peripheral non-small cell lung cancer. The inter-observer agreement between the two readers in the measurements was excellent. The ICC for the IC and NIC measurements in primary lesions was 0.83 and 0.86, respectively. The ICC for the IC and NIC measurements in lymph nodes was 0.94 and 0.93, respectively. The mean IC and mean NIC of primary lesions were 21.29 100 $\mu g/cm^3$ and 0.34 for squamous cell carcinoma and 21.98 100 $\mu g/cm^3$ and 0.34 for adenocarcinoma, respectively. There