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Research article

Value of contrast-enhanced ultrasound and PET/CT in assessment of extramedullary lymphoma

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ABSTRACT

Objective: The aim of the study was to evaluate clinical value of contrast-enhanced ultrasonography (CEUS) and PET/CT for assessment of extramedullary lymphoma, using histopathology as reference standard.

Method: A total of 63 patients with histopathologically-confirmed extramedullary lymphoma who had underwent CEUS and PET/CT examinations of suspicious lymph nodes included in the study. CEUS patterns and parameters (arrival time, peak time and intensity, base intensity, area under the time-intensity curve, ascending and descending slopes) and PET/CT parameters including maximum standardized uptake value, mean standardized uptake value, and metabolic tumor volume (MTV) were evaluated. Patients were classified into Hodgkin lymphomas (HL), non-Hodgkin lymphomas (NHL), early (stage I and II) and advanced (stage III and IV) lymphoma, B cells and T cells lymphoma, and aggressive and indolent lymphoma. The differences between the two independent samples were compared using non-parametric rank and inspection, $P < 0.05$ was considered statistically significant. The optimal cut-off value for parameters was used to predict the staging and pathology using Receiver Operating Characteristic (ROC) curve analysis.

Result: In the early and advanced group, the differences between $\triangle$T and ascending slope (AS) were statistically significant ($p = 0.010$, $0.024 < 0.05$). Hodgkin lymphomas (HL) or non-Hodgkin lymphomas (NHL) results were determined by optimal cut-off value of AT and TP ($p = 0.001$, $0.001 < 0.05$). Aggressive or indolent lymphoma were determined by optimal cut-off values of Color Doppler flow resistance index ($P = 0.001 < 0.05$) and SUVmax ($p = 0.001 < 0.05$). There was no statistically significant difference between B and T cell lymphoma. And there was no statistically significant difference among the qualitative indexes. The optimal cutoff value for statistically significant indicators was calculated by ROC.

Conclusion: The quantitative parameters of CEUS and SUVmax of PET/CT are proven useful in assessment of different clinical and pathologic patterns of extramedullary lymphoma.

1. Introduction

Lymphoma is malignancy of unclear etiology that originates in the lymph nodes or other lymphoid organs. In recent years, an increase in the incidence of malignant tumor up to 3%–4% [1] was registered worldwide. Lymphoma is divided into two categories: Hodgkin lymphoma (HL) and non-Hodgkin's lymphoma (NHL), with the latter one accounting for 80%–90% [2] out of total incidence. Whole organ and organism tissue can be infringed because of the distribution of lymphatic system. Therefore, although common clinical manifestations can occur, there are remarkable differences with reference to tumor position and size in view of different pathological types. The application of PET/CT in lymphoma has been widely accepted, as it can detect lesions that could easily be ignored during traditional imaging examination. Conversely, PET/CT can be used to effectively distinguish the residual fibrosis or tumor tissue. Additionally, some initial PET/CT data, such as metabolism of tumor volume, have shown to contribute to evaluation of prognosis [3].

Abbreviations: CEUS, contrast-enhanced ultrasonography; PET, positron emission tomography; CT, computed tomography; MTV, metabolic tumor volume; ROC, receiver operating characteristic; HL, Hodgkin lymphomas; NHL, non-Hodgkin lymphomas; CDFI, color doppler flow imaging; TIC, time intensity curve; RI, resistance index; LN, lymph node

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Sonography is a well-known diagnostic imaging technique. It has been shown to possess a higher sensitivity in the detection of superficial enlarged lymph nodes compared to palpation [4,5]. Gray-scale sonography assesses the nature of lymph node based on different aspects such as shape, size and echotexture. Color Doppler Flow Imaging (CDFI) is used to evaluate the blood flow such as the resistance index. Elastography, a useful method for reflecting tissue hardness, provides reference information for distinguishing between benign and malignant lymph nodes. Contrast-enhanced ultrasound with (CEUS), used to detect microflow perfusion, is superior to CDFI for detection of tumor vascularity, as it improves diagnostic levels of sonography [6,7]. The microbubble concentration is related to blood perfusion following contrast agent injection. Furthermore, CEUS, as a real-time dynamic imaging, can be used to evaluate the blood flow of lymph nodes via enhancement patterns, and to analyze perfusion features of lymph nodes more objectively and comprehensively via time intensity curve (TIC) analyses.

In patients with lymphoma, the flow perfusion of inflammatory and malignant of lymph nodes often overlaps. Therefore, it is difficult to evaluate the flow features of enlarged lymph nodes purely based on imaging enhancement morphology. The aim of the study was to explore clinical value of contrast-enhanced ultrasonography (CEUS) and PET/CT for differential diagnosis of extramedullary lymphoma using histopathology as reference standard. In order to explore the value of CEUS and PET/CT, different histopathological patterns and staging of lymphoma were analyzed using qualitative and quantitative methods among different groups.

2. Materials and method

2.1. Patients

During the period between October 2015 and March 2017, 63 patients with extramedullary lymphoma who had underwent CEUS and PET/CT examinations of the suspicious lymph nodes and subsequently subjected to ultrasound-guide biopsy or surgical removal of the nodes for histopathology were included in this study. Due to CEUS contraindications, exclusion criteria included: men < 18 years old, pregnant women, and patients with potential allergy of contrast agent material. Forty-two patients were male and 21 female, and their age ranged between 20 and 74 (median age of 50 years). Sixty-four patients had suspicious lymph nodes in the neck, 10 in the inguinal region and 14 in axillary. This study was approved by the Institutional Ethics Committee, and informed consent was obtained from all patients.

2.2. CEUS examination

All patients were examined with GE Logic E8 ultrasound system using a 9L high-frequency linear array transducer by two ultrasound specialists with at least 5 years of experience in the field, who were blinded to the patients' histopathology information before the first circle of chemotherapy. Suspicious enlarged lymph nodes in the cervical, axillary or inguinal regions were selected for CEUS examination. The diameter of lymph nodes, resistance index of flow and value of elastricity were recorded by the gray-scale imaging,CDFI, and elastography. The plane with the richest blood flow was selected for CEUS evlauation. Whenever possible, the selected plane attempted to include the region of lesion and surrounding normal tissue. All patients read signed the informed consent for intravenous administration of the contrast agent SonoVue (Bracco, Milan, Italy). For contrast imaging, 2.4 mL of the SonoVue was administrated via peripheral vein in a bolus fashion. The machine parameters were adjusted so that mechanical index was 0.11 and gain was 30–40 dB. Continuous imaging lasted for 90 s and it was performed immediately before and after injection and recorded for 90 s. No parameter was changed during the examination. Patients were instructed supposed to breathe slowly and evenly during imaging acquisition and recording.

2.3. PET/CT examination

18F-FDG PET/CT scanning was performed within the same week of CEUS study before first cycle of chemotherapy in all enrolled patients. Patients fasting for 4–6 h, with blood glucose levels between 4.5–8.2 mL/l were injected with 0.015–0.18 mCi/kg of 18F-FDG tracer at a resting state and were asked to rest for ~60 min after injection to avoid muscular uptake. Imaging was performed using Discovery ST PET/CT scanner (GE Healthcare); and all patients were scanned from the skull base to the upper thigh after micturition. The CT data and PET imaging were transmitted to workstation (Xeleris, GE Healthcare) which was used for imaging display and analysis, as well as for attenuation correction and measurement.

2.4. CEUS imaging analysis

The intensity of node enhancement was classified as intense enhancement (higher than surrounding normal tissue), moderate enhancement (equal to the surrounding normal tissue) and weak enhancement (lower than surrounding normal tissue). The characteristics of node enhancement were classified as homogeneous (global or diffuse enhancement) and heterogeneous (partial filling defect). The pattern of enhancement in lymph nodes comprises central enhancing (enhanced from peripheral to the center) and centrifugal enhancing (global and diffuse enhancement or enhanced from the hilum to peripheral). The anatomical boundaries of lymph node were defined as clear (more than 50% with well-defined circumference) and unclear (blurred border, lobulated and angulate appearance or less than 50% with well-defined circumference).

The remarkable and rapidly enhanced region of interest (ROI) was selected for measurement of dynamic parameters of CEUS [8]. ROI was drawn around the margin of lesion in the lymph node lesion an electronic-cursor, avoiding the surrounding tissue. For each patient, all measurements were performed three times, and the mean ROI value was considered as the final value for data analysis. A time-intensity curve (TIC) for the selected ROI was derived automatically by the scanner software, which provided time and enhancement parameters, including **1**) arrival time (AT): defined as the time of first detection of micro bubbles within the lesion; **2**) Peak time (TTP): peak intensity detected post- agent injection; **3**) $\triangle$T = TTP-AT; **4**) Base intensity (BI): defined as the base intensity of the TIC; **5**) Peak intensity (PI): defined as the maximum intensity of the TIC; **6**) Area under the TIC (AUC): proportionated to the total volume of blood in ROI; **7**) Ascending slope (AS): defined as the maximum wash-in velocity of the contrast medium; **8**) Descending slope (DS): defined as the maximum wash-out velocity of the contrast medium.

2.5. PET/CT imaging analysis

The maximum standardized uptake value (SUVmax) and total lesion glycolysis (TLG) of ROI which the same lymph node and area performed CEUS was calculated according the following formula: *TLG = SUVmean * MTV* (standardized uptake value mean, SUVmean; metabolic tumor volume, MTV) [9]. We can automatic sketch interesting area firstly, which over 30% threshold uptake values by visual analysis, then manual sketch the boundary of the original site combing the morphological presentation from CT imaging. Finally, volume of each imaging layer was measured using the following formula: *area of each layer * layer thickness*; while MTV was calculated by accumulation algorithm.

2.6. Study design

According to the clinical staging and pathological type of extramedullary lymphoma, patients were classified into: Hodgkin