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^{68}Ga-citrate PET/CT is Valuable for Abdominal Lymphoma Imaging

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***Abstract*—Introduction: Although ^{67}Ga-citrate has been used in scintigraphic imaging for lymphoma, the long physical half-life of ^{67}Ga and inferior resolution of SPECT scanner limited the wide-spread application of this agent. In contrast, the ideal physical half-life of ^{68}Ga and superior resolution of PET scanner push us to test lymphoma imaging potential of ^{68}Ga-citrate.** Materials: **Sodium citrate was added into newly eluted ^{68}Ga and incubated at room temperature for 15min for ^{68}Ga-citrate preparation. Three patients with abdominal lymphoma were retrospectively analyzed after ^{68}Ga-citrate PET/CT imaging.** Results: **^{68}Ga-citrate was labeled with >99% yield and purity within 15 minutes. ^{68}Ga-citrate PET/CT revealed rapid progression of bowel diffuse large B-cell lymphoma in one patient; ^{68}Ga-citrate revealed more lesion than ^{18}F-FDG in another diffuse large B-cell lymphoma patient; ^{68}Ga-citrate imaging was negative in an enteropathy-associated T cell lymphoma patient.** Conclusion: **A simplified method to prepare ^{68}Ga-citrate without nuclide pre-purification is available. ^{68}Ga-citrate can be used for lymphoma imaging and further evaluation is warranted.**

***Index Terms*—^{68}Ga-Citrate, Diffuse large B-cell Lymphoma, PET, imaging.**

INTRODUCTION

Lymphoma is a type of cancer that occurs when B or T lymphocytes divide faster or live longer than they should be. Lymphoma often originate in lymph nodes and may develop in the lymph nodes, spleen, bone marrow, blood or extranodal sites including tonsils, skin, brain, bowels and bone and eventually they form a tumor [1, 2] . Lymphoma presents with certain non-specific symptoms such as swelling of lymph nodes, fever, night sweats, weight loss, anorexia, fatigue, dyspnea, itching, and etc. Lymphoma is definitively diagnosed by a lymph node biopsy, further characterized by immunophenotyping, flow cytometry, FISH testing, and finally divided into different categories according to whether or not it is a Hodgkin lymphoma, the site that the cell arises from, whether the cell that is replicating is a T cell or B cell or natural killer cell [3,4]. Indolent lymphoma is compatible with a long life even without treatment, whereas aggressive lymphoma causes rapid deterioration and death [5]. However, Most of the aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL) and enteropathy-associated T-cell lymphoma (EATL) respond well to treatment and are curable [6]. The correct diagnosis and classification of the disease is very important to the prognosis. DLBCL is aggressive lymphoma often occurred outside lymph nodes in all ages, but most commonly in older adults with overall 5-year survival of 60%. Its relative incidence in adults is 40 to 50% of lymphomas. Most DLBCL resemble B cells of large germinal centers and express CD20 on cell surface [7]. EATL, a peripheral T-cell lymphoma, accounted for 9% of gastrointestinal lymphomas [8].

^{67}Ga-citrate has been used in scintigraphic imaging for lymphoma and was valuable for prognosis [9-12]. ^{67}Ga scintigraphy is an excellent predictor of residual tumor viability in DLBCL patients and that persistent positivity of the scan predicts poor outcome and may justify a change in treatment [13].However, the long physical half-life of ^{67}Ga (78h) limited the wide-spread application of this agent because the injection dose is relatively low, which result in low image quality. The gamma spectrum of ^{67}Ga varies from 92 to 300keV, which lower the quality and resolution of the final image and increase the radiation dose to patient and clinical staff. In recent years, ^{68}Ga has been produced successfully and is commercially available. The ideal physical half-life of ^{68}Ga (68min) makes ^{68}Ga-citrate can be administered with high dose. The positron emitted by ^{68}Ga can be used for PET imaging with high resolution and high image quality. Interestingly, ^{68}Ga-citrate has been successfully in the diagnosis of osteomyelitis, diskitis and intra-abdominal infection but not in lymphoma [14, 15]. Also, the relatively complex procedure of ^{68}Ga-citrate preparation in the literature makes the routine use of ^{68}Ga-citrate difficult [14, 16]. In this study, we try a simplified method to label citrate with ^{68}Ga and test its imaging potential in lymphoma patients.

EXPERIMENTAL SECTION

Materials

^{68}Ge/^{68}Ga generator was provided by ITG (Isotope Technologies Garching GmbH, Germany). ^{68}Ga was eluted with 0.05N HCl from the generator. Sodium citrate was produced by Xinning pharmaceutical (Guangdong, China).

^{68}Ga-citrate labeling and quality control

Sodium citrate of 0.1mol/L was prepared with Millipore water (18MΩ). Aliquoting 0.2ml citrate into 0.6ml of

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^{68}Ga(370MBq) to final pH of 4.0 and incubating at room temperature for 15min. The mixture was diluted with 5ml saline and filtered with 0.22μm membrane for quality control and imaging. Instant thin layer chromatography (ITLC) was used for ^{68}Ga-citrate quality control. The radiochemical purity was determined by ITLC-SG strips (Pall) with methanol and glacial acetic acid (v:v=9:1) as mobile phase.

PET Imaging

^{68}Ga-Citrate (148 MBq) was injected intravenously in two DLBCL patients and one EATL (Type II) patient. The images were acquired 60 minutes post-injection.

RESULTS

Quality control of ^{68}Ga-citrate

The radiochemical purity and yield of ^{68}Ga-citrate was over 99%. The Rf of ^{68}Ga-citrate was 1 (Fig 1A) while that of ^{68}Ga was 0 (Fig 1B) in mobile phase glacial acetic acid and methanol (1:9). This result indicated that the ^{68}Ga directly eluted from ^{68}Ge/^{68}Ga generator can be used for citrate labeling without pre-purification by ion exchange resin.

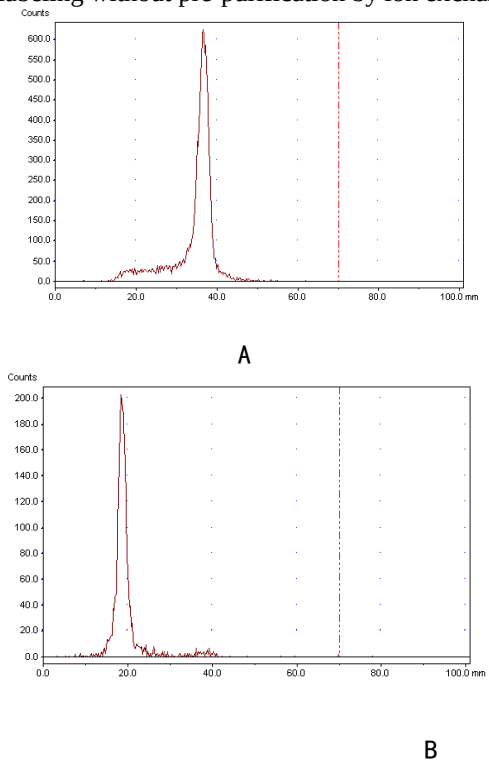

Fig 1. Radiochemical purity determination of ^{68}Ga-citrate by ITLC-SG with mobile phase glacial acetic acid and methanol.（A. ^{68}Ga-citrate, Rf=1; B. free ^{68}Ga, Rf=0）

^{68}Ga-citrate PET/CT revealed rapid progression of DLBCL

We here present a case of a 45-year-old male patient with DLBCL. He underwent ^{68}Ga-citrate PET/CT, which clearly showed that ileocecal region of the colon was abnormal (Figure 2 top). About one month later, the patient situation became worse, intestinal obstruction symptom appeared. ^{68}Ga-citrate PET/CT were repeated, expanded ^{68}Ga-citrate accumulation was found in the previous ileocecal region of the colon (Figure 2 bottom). The lesion was removed by surgery and the biopsy of the lesion confirmed DLBCL (Figure 3). This case indicated that ^{68}Ga-citrate PET/CT should be used as routine procedure for diagnosis of bowel lymphoma.

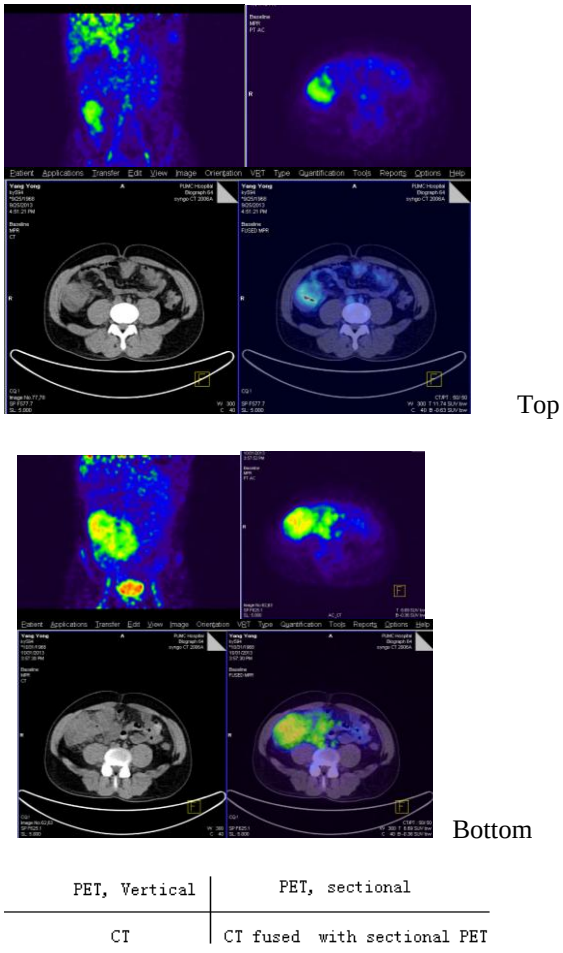

Fig 2. ^{68}Ga-citrate PET imaging revealed rapid progression of DLBCL. (The top PET images were acquired 90min after intravenous 3mCi dose administration demonstrated the colon wall accumulated ^{68}Ga-citrate significantly higher than the background on Sep 25, 2013; simultaneous CT demonstrated that the colon wall thickened. The bottom PET image demonstrated the colon wall accumulated ^{68}Ga-citrate further wider than before On Oct 31, 2013; simultaneous CT demonstrated the colon wall further thickened.

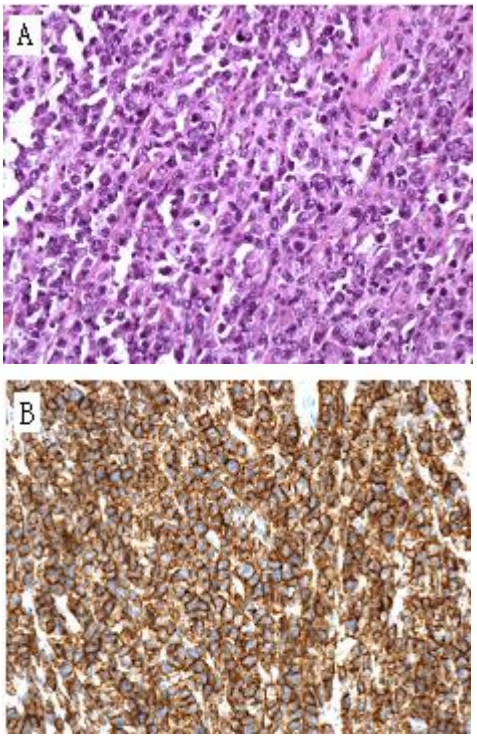

Fig 3. The Surgery biopsy of the colon lesion display large atypical lymphoid cells with prominent nucleoli (A, H&E staining). The tumor cells was positive for CD20, a pan B cell marker (B, peroxidase staining)

^{68}Ga-citrate revealed more lesion than ^{18}F-FDG in DLBCL

We here present another case of a 73-year-old female patient with DLBCL. She underwent ^{68}Ga-citrate PET/CT and then ^{18}F-FDG PET/CT in consecutive day. ^{68}Ga-citrate PET/CT revealed DLBCL lesions in omentum majus, ileocecal junction, and ileum (Figure 4 right). ^{18}F-FDG PET/CT only revealed DLBCL lesion in omentum majus (Figure 4 left). The lesions were removed by surgery and DLBCL in ileum, ileocecal junction and omentum majus were confirmed by pathological staining.

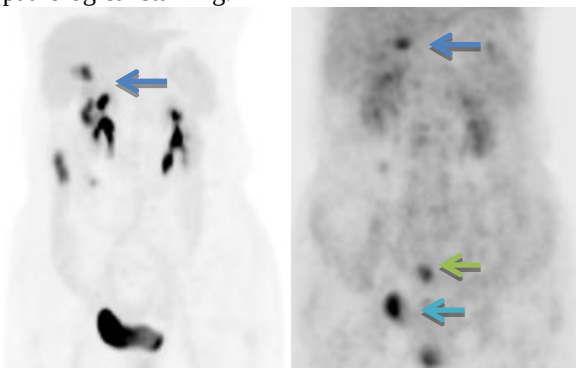

Fig 4. ^{68}Ga-citrate detected ileac DLBCL lesion, but ^{18}F-FDG did not. Omentum majus (blue arrow), ileum (green arrow), ileocecal junction (brilliant blue arrow)

^{68}Ga-citrate imaging was negative in an EATL patient

We here present another case of an 82-year-old male patient with EATL (Type II) in ascending colon. He underwent ^{68}Ga-citrate PET/CT (Figure 5 right) and ^{18}F-FDG PET/CT (Figure 5 left) in consecutive day. Although both tracers show negative accumulation in ascending colon, the biopsy demonstrated that EATL lesion was present in ascending colon.

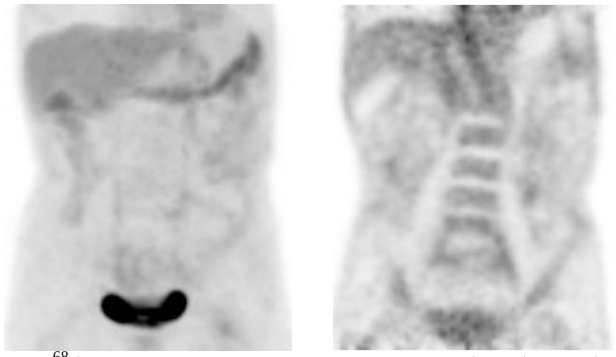

Fig 5. ^{68}Ga-citrate imaging was negative in one EATL (Type II) patient (right) while ^{18}F-FDG imaging was also negative (left).

DISCUSSION

Primary colorectal lymphoma is rare gastrointestinal lymphomas (3%) and DLBCL is the most common histological subtype of colorectal lymphoma [17, 18]. EATL is also rare gastrointestinal lymphomas (9%) while Type II EATL represents only approximately 10% to 20% of all EATL [19]. It has been reported that ^{18}F-FDG PET/CT was applicable in detecting DLBCL and EATL [20-22] but ^{68}Ga-citrate PET/CT was not reported in DLBCL and EATL.

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The literature reported that the pre-purification of ^{68}Ga was needed before citrate labeling. The procedure consisted of eluting ^{68}Ga from generator with diluted hydrochloric acid, loading ^{68}Ga on cationic exchange resin, washing with low acidic acetone to remove impurities such as Ti, Zn, Fe and ^{68}Ge. The final purified ^{68}Ga was eluted with higher concentration of acidic acetone and residual acetone was evaporated with 1 min boiling [14]. Dawson firstly described colorectal lymphoma in 1961 [23], but till now the lack of specific symptoms usually lead to delayed diagnosis in large part of patients. In this study, ^{68}Ga eluted from generator was directly added into sodium citrate for citrate labeling. The labeling efficiency is high enough for imaging without further purification. Three abdominal lymphoma cases reported here proved that ^{68}Ga-citrate PET/CT is valuable for diagnosis of abdominal lymphoma. The site most commonly involved in colon lymphoma is the ileocecal region due to the proliferation of lymphoid tissue (Peyer's patches) in this area [24]. In one patient, rapid progression of DLBCL was revealed by ^{68}Ga-citrate PET/CT. In another DLBCL, ^{68}Ga-citrate revealed more lesion than ^{18}F-FDG. The SUVmax in the lymphoma of ^{68}Ga-citrate is lower than that of ^{18}F-FDG. The reason for negative imaging of ^{68}Ga-citrate in an EATL patient is unknown. The mechanism of ^{68}Ga-citrate imaging is its transferrin receptor binding. Since some lymphomas are transferrin receptor negative, the lesions displayed on ^{68}Ga-citrate may be false negative [20]. Early detection with ^{18}F-FDG PET/CT, combined with ^{68}Ga-citrate PET/CT, may be beneficial for suspected lymphoma patients. The imaging of ^{18}F-FDG is based on glucose utilization, so the lesion displayed on ^{18}F-FDG image may be inflammation, which results in false positive. The balance reading between the ^{18}F-FDG and ^{68}Ga-citrate image is helpful for diagnosis of suspected lymphoma patients before biopsy. However, only a few cases were presented in this study, further evaluation of ^{68}Ga-citrate with more cases in lymphoma imaging is needed in the future.

CONCLUSION

In summury, ^{68}Ga-citrate without nuclide pre-purification is prepared in our facility. ^{68}Ga-citrate can be used for lymphoma imaging and ^{68}Ga-citrate PET/CT is proved to be valuable for abdominal lymphoma imaging. Further ^{68}Ga-citrate PET/CT evaluation in lymphoma detection is warranted.

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