Three-dimensional radiopharmaceutical-excited fluorescence imaging of lymph nodes

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***Abstract*—Optical imaging techniques have been developed for localizing lymph nodes before surgical resection due to the non-invasion and high sensitivity. However, its attendant penetrability limitations and auto-fluorescence effect have greatly limited the spatial resolution and imaging precision. In this study, a novel technique radiopharmaceutical-excited fluorescence imaging (REFI) was adopted to image lymph nodes, which use gamma-ray and Cerenkov radiation from radioisotopes to excite lanthanide europium oxide (EO) nanophosphors and boost the light intensity. An effective adaptive-steepest-descent-projection onto convex sets (ASD-POCS) reconstruction algorithm and the anatomic structure information were used to three-dimensionally image lymph nodes in mice models. The results indicate that REFI can greatly boost the light intensity and accuracy of three-dimensional imaging of lymph node with location deviation less than 1.03 mm.**

***Index Terms*—radiopharmaceutical-excited fluorescence imaging, lymph nodes imaging, 3D reconstruction.**

I. Introduction

As a noninvasive molecular imaging mode, optical molecular imaging can real-time visualized of biochemical events at the cellular and molecular level within living animals [1]. Optical imaging techniques such as intraoperative image-guided surgery based on fluorescence molecular imaging (FMI) has also enhanced the way clinicians investigate complex pathological phenomena [2]. To date, near-infrared fluorescence contrast agents specific for many different targets have been used for lymph node mapping in surgical navigation with high sensitivity [3]. However, its inherent poor tissue penetration ability and auto-fluorescence effect of FMI have greatly limited the spatial resolution and imaging precision. To address these issues, in this study, a three-dimensional optical molecular imaging technique named as radiopharmaceutical-excited fluorescence imaging (REFI) was developed for imaging lymph nodes in mice models by combining an effective 3D reconstruction algorithm.

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II. Method

REFI combines the merits of Cerenkov luminescence imaging (CLI) and FMI which use gamma-ray and Cerenkov radiation from radioisotopes to excite Rare-earth nanophosphors and boost the light intensity [4].

A. Spectrophotometry of EO

The lanthanide europium oxide (EO) nanoparticle (Eu2O3, 99.9% metal basis, molecular weight=351.91) was purchased from the Aladdin Chemistry Co. Ltd. The excitation and emission profile of EO nanoparticles were measured using a fluorospectrophotometer (Hitachi, FL9000). The excitation profile was obtained using a 620 nm emission filtre. The fluorescence profiles were obtained with excitation at 400 and 535 nm.

B. REFI VS CLI

In order to compare the optical signal of REFI and CLI, the xenogen in vivo imaging system (IVIS) (Caliper Life Sciences) was used for these studies. In REFI, 100 mCi ^{18}F-FDG was mixed with EO nanoparticles ($10mg$) and filled in 1.5 ml tubes. While in CLI, only 100 mCi ^{18}F-FDG was used. The imaging parameters were binning: 4, exposure: 5 min and aperture: f1, unless otherwise indicated.

C. Light transport in biological tissue

In general, When Rare-earth nanophosphor was excited by radioisotopes, the photons' propagation at near-infrared wavelengths can be described by diffusion equation. Coupled with Robin-type boundary condition, which can be expressed as [5]:

$$\begin{cases} -\nabla \cdot (D(r)) + \mu_a(r)\Psi(r) = S(r), (r \in \Omega) \\ \Psi(r) + 2A(r)D(r)(\nu(r) \cdot D(r)) = 0, (r \in \partial\Omega) \end{cases} \quad (1)$$

Where $\Psi(r)$ denotes the light fluence rate at position $r \in \Omega$. $S(r)$ is the nanoparticle distribution. $D(r)$=$1/3(\mu_a(r) + (1-g)\mu_s(r))$ is the diffusion coefficient with $\mu_a(r)$ and $\mu_s(r)$

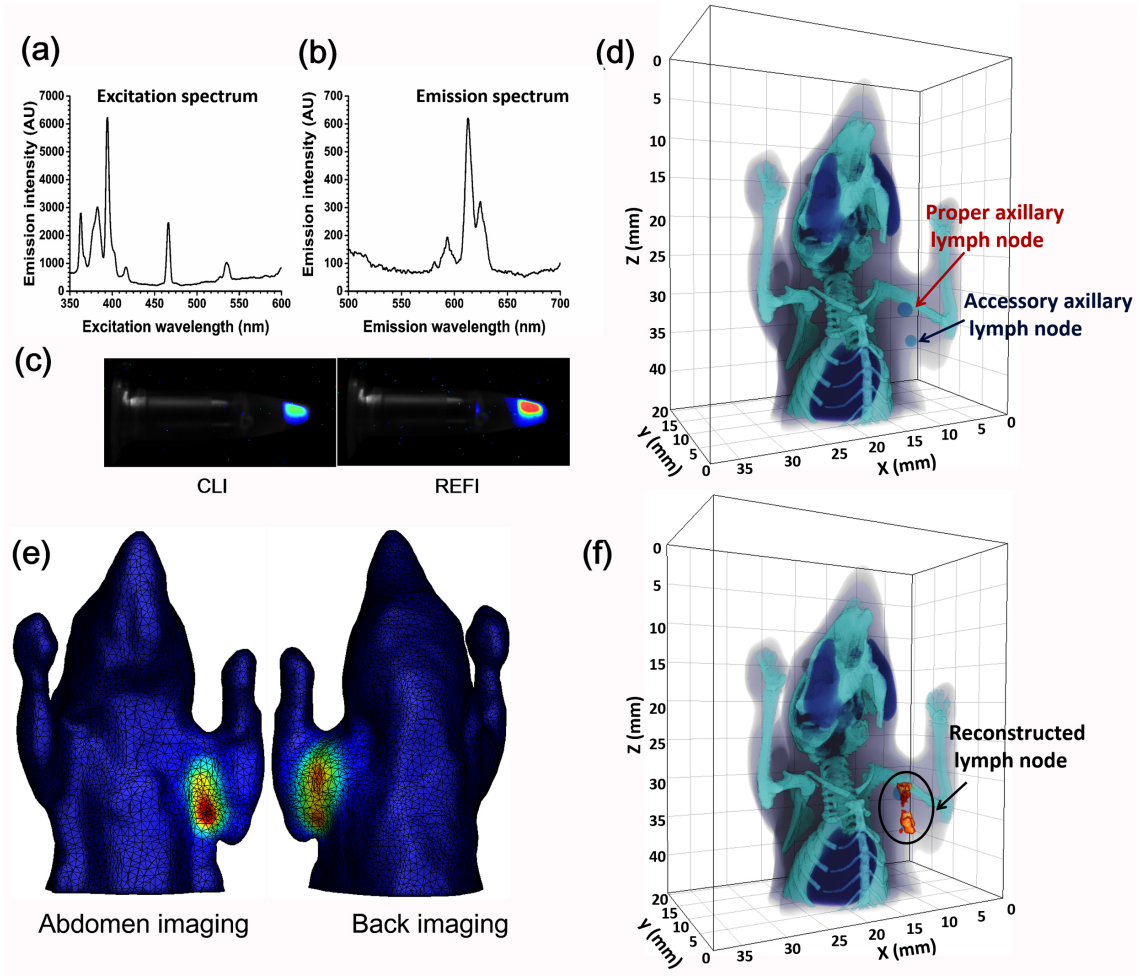

Fig. 1. The results of three-dimensional radiopharmaceutical-excited fluorescence imaging of lymph nodes. (a) the excitation spectrum of EO nanophosphors; (b) the emission spectrum of EO nanophosphors; (c) comparison result of REFI and Cerenkov luminescence imaging; (d) 3D digital mouse atlas and simulated lymph nodes; (e) surface fluorescence images in abdomen and back view; (f) reconstructed lymph nodes by ASD-POCS reconstruction algorithm.

being the absorption coefficient and scattering coefficient, and g is the anisotropy coefficient. $A(r)$ is the boundary mismatch factor accounting for different refractive indices across the boundary $\partial\Omega$, $\nu(r)$ denotes the unit outer normal. In the finite element method (FEM) framework, a linear relationship between the unknown nanoparticle distribution and the detected surface partial photon flux fluence rate can be obtained as [6]:

$$\Gamma X = \Psi \tag{2}$$

Where Γ is the symmetric matrix, X is the unknown nanoparticle distribution, Ψ is the surface detected photon flux.

D. lymph nodes 3D reconstruction

Due to the strong scattering property of biological tissues and the limited boundary measurements, the radiopharmaceutical-excited fluorescence tomography (REFT) reconstruction is an ill-posedness inverse problem. To improve the imaging accuracy, the anatomic structure information was used to build the system equation of the light transport in biological tissue. And a lymph nodes reconstruction algorithm named adaptive-steepest-descent-projection onto convex sets (ASD-POCS) reconstruction algorithm was proposed. ASD-POCS was based on total variation (TV) regularization and minimized the TV objective function using adaptive steepest descent and the data fidelity error using projection onto convex sets (POCS). The lymph nodes 3D reconstruction experiment was conducted in a common used 3D digital mouse atlas [7]. And only the head section of the mouse with a height of 40mm was selected and divided into bone, muscle, etc. In forward simulation, the surface REFI distribution was calculated by FEM.

III. RESULTS

The excitation and emission profile of EO nanophosphors were shown in Fig. 1(a) and Fig. 1(b). The excitation spectrum included six characteristic absorption peaks (365, 384, 396, 424, 467, 536 nm). The spectral characteristic indicated that REFI could shift spectral from blue to red (620 nm), when using ultraviolet to blue spectrum to excite EO. Fig. 1(c) showed the comparison result of REFI and Cerenkov luminescence imaging (CLI). Where the Cerenkov luminescent signal was generated by ^{18}F-FDG decay; and in REFI, the EO was excited by gamma-ray photon and Cerenkov radiation,

and these two energy components were all produced by 18F-FDG decay. The comparison result showed that REFI was able to greatly boost the light intensity. Fig. 1(d) was a common used 3D digital mouse atlas. In this study, the proper axillary lymph node and accessory axillary lymph node were regard as radiopharmaceutical-excited fluorescence source. And these two lymph nodes were simulated by two different size spheres with diameter of 2 mm and 1.6 mm. Fig. 1(e) showed the finite element mesh and surface fluorescence image in abdomen and back views which were employed to reconstruct lymph nodes. Fig. 1(f) was the reconstructed lymph nodes by our proposed ASD-POCS algorithm. The location deviation of the proper axillary lymph node and accessory axillary lymph node were $1.03mm$ and $0.89mm$, respectively.

IV. Conclusion

This study demonstrates a novel three-dimensional lymph nodes imaging technique by combing REFI and the effective ASD-POCS reconstruction algorithm. The results indicate that REFI can greatly boost the light intensity and accuracy of three-dimensional imaging of lymph node with location deviation less than 1.03 mm.

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