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Development of a Mobile Fluorescence Tomography-guided System for Pre-clinical Radiotherapy Research

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Abstract

We proposed to build a mobile fluorescence tomography (mFT) system as an image-guided platform for pre-clinical radiotherapy research. The mFT system is expected to localize functional target/tumor, guide irradiation, and provide longitudinal treatment assessment.

1. Introduction

Cone-Beam (CBCT) guided small animal radiation research platform (SARRP) has provided opportunities to test radiobiological hypotheses in a manner which closely parallel human treatment. The capabilities of these systems are particularly exciting where local radiation therapy (RT) can be used to elicit systemic antitumor response.

However, CBCT is less adept to localize soft tissue targets growing in a low image contrast environment and is not able to provide functional information for treatment assessment. With the increasing pool of reporters, fluorescence imaging allows important mechanistic study of various response pathways in vivo. To improve the functional imaging and target localization capability of the SARRP, it is compelling to incorporate 3D fluorescence tomography (FT) to the SARRP such that the response of a functional target can be assessed in accurate registration to the irradiated volume.

Current commercial fluorescence imaging systems are not optimized to guide irradiation due to lack of 3D target shape and precise image registration between the optical and SARRP CBCT images. To address these unmet needs and maintain the efficient use of both FT system and irradiators, a mobile FT (mFT) platform is proposed. The mFT is designed in a way such that it is flexible to adapt various choice of laser wavelength and filters for the reporters of interest and to integrate with other image modalities, as micro-CT and -MRI. The research potentials of FT are particularly significant when considering combinational molecular therapeutic strategies with radiation, such as immunotherapy.

2. Materials and Methods

The mFT system, originated from a previous bioluminescence tomography platform [1], and is designed with high flexibility allowing interchangeable components for different applications. The mFT includes three subsystems laser delivery, imaging system, and mouse bed (Fig. 1). A 2-axes galvo system directs the collimated laser to the animal surface. An imaging system collects emission wavelength data from the mouse, and the motorized mirror system can be rotated around the animal to support multi-view imaging. The mouse bed is designed to be moveable to transport imaged animal between optical and radiation system.

A 5 μm pinhole was placed in front of a laser diode at the focal length of a collimating optic to create low diverging rays. The laser spot size at two points along the laser path were measured to calculate full angle divergence. A linear relationship between galvo voltage input and CCD pixel location will be used to calibrate laser spot positioning on animal surface. To increase the available data points and improve FT reconstruction, additional mirrors will be added (example Fig 1b–c) to direct laser at anterior, posterior and lateral surface of imaged animal.

For initial testing, a rod with fluorescent quantum dot (QD800) placed on the tip will be inserted into the abdomen of a mouse phantom. FT localization accuracy will be tested by comparing reconstructed center of mass (CoM) locations of the optical sources with that of the physical source. To assess if the results will be improved with prior spatial information, the data will be re-analyzed by limiting the solution space to within the abdomen region to mimic in vivo situation where approximate target location is usually known. This phantom study will provide an initial knowledge of our mFT performance in terms of target localization.

In vivo studies will also be conducted to evaluate the mFT system and validate the accuracy of optical-guided SARRP irradiation. Orthotopic glioma model will be used for the study. To establish the model, 1.2×10^5 GL261 cells will be implanted into the left striatum of C57BL/6J mice. The GL261 is known to overexpresses EGFR [2], IRDye® 800CW EGF probe (LI-COR) 1 nmol will be used to label the tumor through i.v injection 48 hours before imaging acquisition [3], Prior spatial constraint will be placed in the region close to the cell implantation site. Secondary imaging contrast CT, and MRI will be used to confirm accuracy of the FT reconstruction for tumor location. The FT-guided irradiation will be validated by ex vivo pathological analysis.

3. Results

Our initial results show the full angle divergence is < 0.1 degrees for the laser delivery, and a spot size is < 0.5 mm within 370 mm from the laser source. Further study is needed to confirm dimensions of laser spot placed on the different surfaces of animal. Our calibration routine for the laser positioning gives a mean error of 1.3 ± 1.7 pixels, below set tolerance (10 pixels, ~ 1 mm at the image plane). Figure 2 shows CBCT image of mouse phantom, with QD800 placed inside the abdomen (red circle), overlapped with a color map of reconstructed emission absorption coefficient. Five laser positions at the mouse phantom

surface were used to collect emission data from its' posterior side. This initial study shows good correlation between reconstructed QD800 source and actual source location within 2 mm.

4. Conclusions

Functional imaging-guided SARRP system is currently unavailable to allow investigators to perform biology guided RT methods to support translational studies. The quantitative imaging information provided by FT is invaluable to understand the response of the target to treatment. The flexible mFT system, is expected to bring new advanced molecular optical imaging capabilities and enhance radiation research for SARRP users.

5. References

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Figure 1.
3D CAD model of mFT design (A) with sketch of initial laser delivery design for anterior (B) and lateral (C) scan of animal.

Figure 2. CBCT image of phantom (posterior (A), lateral (B), and proximal (C) view) with FT reconstruction of fluorescent QD800 source.