Fluorescence Guidance Improves the Diagnostic Yield of Stereotactic Biopsy: A Proof of Principle Study

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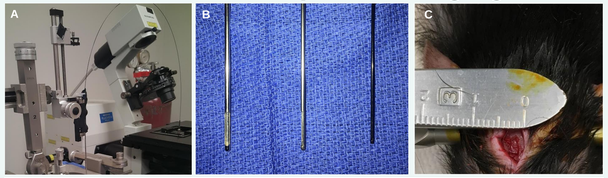
Introduction

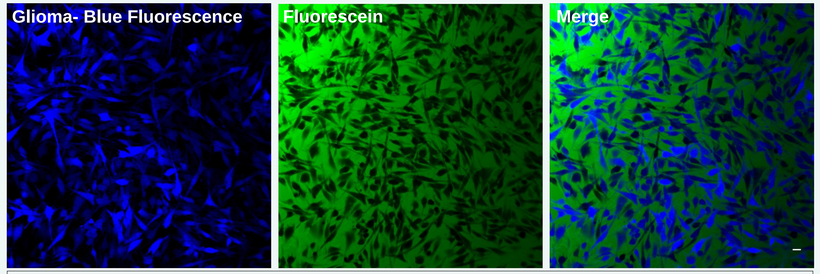
The incidence of primary and metastatic brain tumors is increasing. As systemic cancer therapies continue to improve, the incidence of small intracranial lesions found on routine screening is expected to continue to increase. Though metastatic brain lesions occur more frequently than primary brain tumors, ten-percent of patients with a systemic cancer may present with a primary brain lesion. Treatments for metastatic and primary brain neoplasms differ, therefore it is often imperative to obtain a histopathologic diagnosis by direct tissue sampling. Stereotactic biopsy (STB) is the method of choice for sampling tissue from these lesions. However, this technique fails to obtain diagnostic tissue in 10-24% of cases. Failure to obtain diagnostic tissue delays initiation of personalized treatment plans and may result in further invasive procedures for patients. This project evaluates if coupling a novel *in vivo* optical imaging system with a STB system can verify acquisition of diagnostic tissue at the time of biopsy.

Microendoscope and Imaging



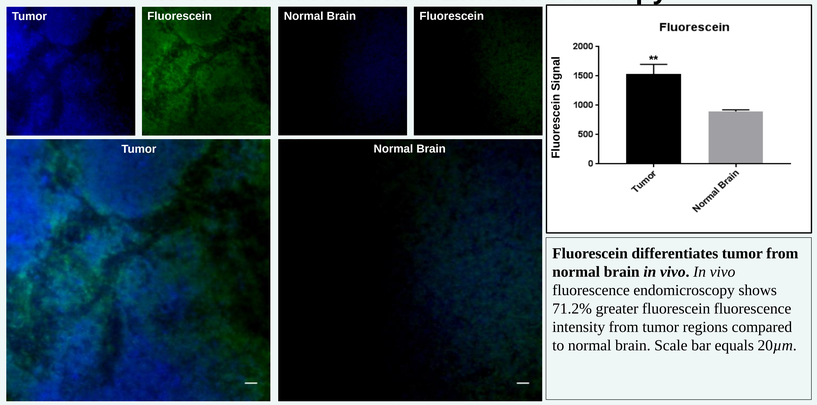
Minimally invasive *in vivo* imaging. A) The imaging platform with a 0.65mm diameter fiber optic microendoscope. B) Our microendoscope fits within the inner diameter of standard stereotactic biopsy needles. C) *In vivo* imaging and biopsies performed through miniature craniotomies in animal models.

Genetically Modified Human Glioma Cells in Culture



Molecular imaging of fluorescent glioma cells and fluorescein contrast. Confocal microscopy confirms expression of blue fluorescent protein in modified human glioma cells. Fluorescein contrast delineates glioma cell bodies. Scale bar equals 20μm.

In Vivo Fluorescence Endomicroscopy



Fluorescein differentiates tumor from normal brain *in vivo*. *In vivo* fluorescence endomicroscopy shows 71.2% greater fluorescein fluorescence intensity from tumor regions compared to normal brain. Scale bar equals 20μm.

Methods

A fiberoptic imaging system was developed by coupling a 0.65mm diameter coherent fiberoptic bundle to an Olympus FLUOView 1000 microscope. Human U251 glioma cells expressing blue fluorescent protein (U251-BFP) were visualized with fluorescein contrast in *in vitro* and *in vivo* experiments. For animal experiments, a rodent was intracranial implanted with U251-BFP cells and administered fluorescein contrast 5 weeks post-implantation. A STB needle containing our 0.65mm imaging fiber was passed through a small cranial burr hole into the rodent's brain. Fluorescence images from tumor and normal brain were obtained and quantitatively evaluated.

Results and Conclusions

Fluorescein demarcated the location of tumor cells *in vitro*. *In vivo*, fluorescein fluorescence intensity was 71.2% greater from tumor regions compared to contralateral normal brain regions (1532.0 ± 52.47 vs. 895 ± 9.349 RFU, $p<0.001$).

Increasing the diagnostic yield of stereotactic biopsies may expedite and improve the overall care of neuro-oncology patients. We found that fluorescence imaging during STB can provide direct visualization of neoplastic tissue in an animal brain tumor model. This technique may complement clinical STB systems by providing a simple technique for verifying neoplastic tissue during biopsy.

References

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