Evolution and Results of Handheld Confocal Endomicroscopy for Brain Tumors During a 6 Years Experience

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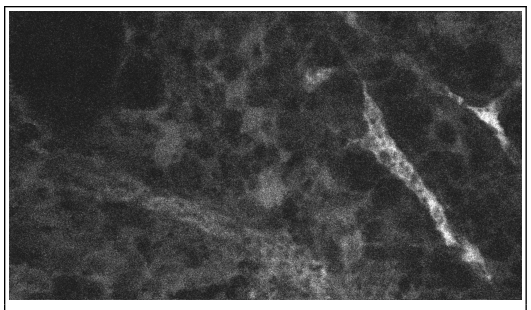
Introduction

Handheld confocal laser endomicroscopy (CLE) allows real-time "optical biopsy" at a cellular level without tissue processing. We document the evolution of this technology and present results of over 6 years clinical and experimental experience with CLE for diagnosis and visualization of various brain pathologies, but especially to assess imaging of tumor border regions.

Methods

Animal CLE feasibility studies included rodents injected with GL261, C6 glioma and human-derived GBM, swine and rodent brain injury models. CLE guided biopsies and resections of tumors for patients and experimentally in animals. Fluorophores included: fluorescein sodium(FNa), acridine orange, acriflavine, sulforhodamine-101, 5-ALA, cresyl violet, and ICG. Selected experimental gliomas had specific antibody labeling. Our clinical experience with CLE includes 237 patients examined ex-vivo and in-vivo using a Generation 1 CLE and 34 patients using a Generation 2 CLE.



Vasculature in rodent GBM with intraoperative fluorescein sodium

Results

CLE-FNa clinical imaging produced 77.7±46.2(average) images/optical biopsy location. A first diagnostic image was identified within seconds of CLE use clinically (within 7-14 images). CLE specificity/sensitivity during FNa-guided surgery was equal or better than frozen section (94%/91% for gliomas, 93%/97% for meningiomas). Gliomas and brain injuries with visible FNa extravasation were distinguished in over 90% of CLE locations imaged (Sensitivity=0.86, Specificity=0.96, PPV=0.97, NPV=0.78). Generation 2 CLE showed improved resolution and glioma resection using 5-ALA revealed detectable tumor signal. Animal and human CLE, including specific antibody labeling, provided clear identification of tumor cells, tumor border, and invading cells (even around and into blood vessels).

Conclusions

Utilization of CLE during FNa surgery is an effective tool for intraoperative detection and differentiation of tumor tissue in order to improve surgical resection accuracy and extent. CLE provides rapid intraoperative information on tissue architecture and atypical cellular features and could significantly improve the surgery-pathology workflow. Future avenues regarding precision or theranostics-based surgical management of tumors may involve CLE imaging with specific fluorescent targeted markers.

Learning Objectives

Confocal laser endomicroscopy allows for rapid intraoperative tissue diagnosis in human and experimental tumor tissues in -vivo and ex-vivo.

Confocal laser endomicroscopy allows differentiation of fluorescein sodium in tumor and injured normal brain.

Individual cells and intracellular structures may be visualized using CLE with various fluorophores.

Confocal Laser Endomicroscopy may allow for visualisation of 5-ALA induced PpIX in gliomas at cellular resolution.

Future potential application for confocal laser endomicroscopy includes fluorescent targeted tumor specific markers.

References

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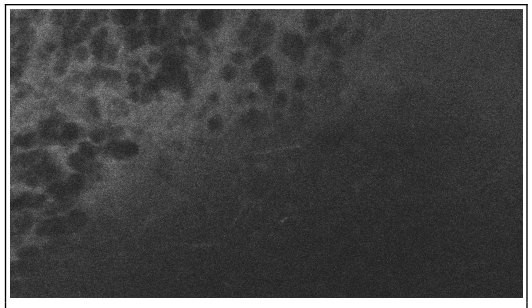
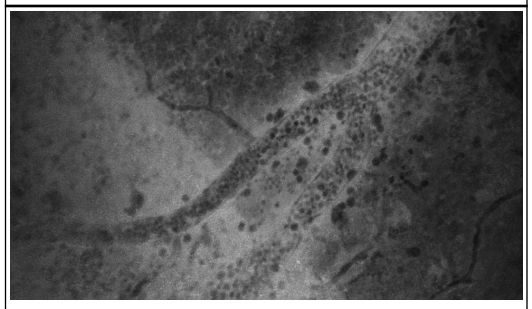
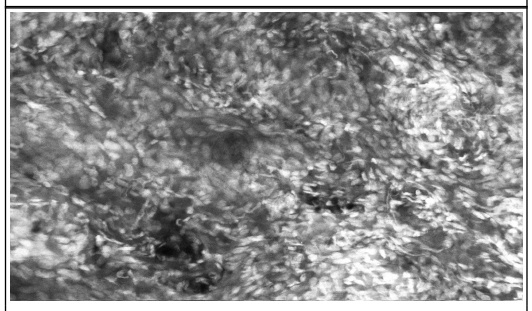


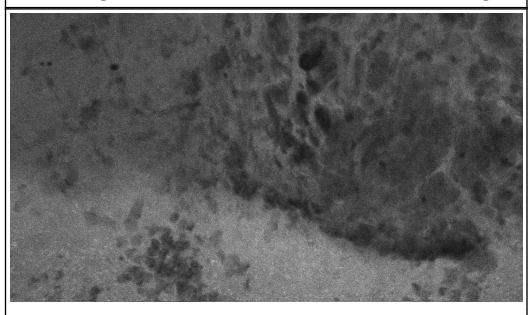
Rodent GBM bordering normal brain



Perivascular tumor cells (Rodent GBM)



Meningioma stained with acridine orange



Human GBM with fluorescein sodium