Higher-Dose Second Window Indocyanine-Green Provides Stronger Fluorescence and More Consistent Trans-Dural Visualization of Intracranial Metastases

Authors: Clare W. Teng, BA\textsuperscript{1,2}; Steve S. Cho, BS\textsuperscript{1,2}; Emma De Ravin, BS\textsuperscript{1,2}; Love Buch, BS\textsuperscript{1}; Steven Brem, MD\textsuperscript{1}; Sunil Singhal, MD, MBA\textsuperscript{3}, Edward Delikatny, PhD\textsuperscript{4}, John Y.K. Lee, MD, MSCE\textsuperscript{1}

1. Department of Neurosurgery at the Hospital of the University of Pennsylvania, Philadelphia, PA, USA

2. Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

3. Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

4. Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA
Disclosure

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Introduction

Metastases to the brain are the most common intracranial malignancies. One of the major challenges in the surgical management of brain metastases is the high local recurrence rate despite maximal safe resection. Even with adjunct radiotherapy, local recurrence rates is still close to 10%, leading to a median survival after diagnosis of brain metastasis of 3 to 27 months. When metastases are large, symptomatic, and oligometastatic, complete resection can extend survival.

A number of intraoperative technologies have emerged to improve resection rates, among which fluorescence-guided surgery (FGS) is slowly gaining favor. Fluorescence imaging utilizes contrast agents that selectively accumulate in neoplastic tissues through a number of mechanisms. We have previously demonstrated that the Second Window Indocyanine-Green (SWIG) technique using 5mg/kg dose of ICG leads to ICG accumulation in metastatic tumor tissue. This study aims to compare the effects of two doses of SWIG on fluorescence intensity and margin detection accuracy in patients with intracranial metastases.
Methods

Patients were prospectively enrolled in an IRB-approved trial of high dose, delayed ICG (aka SWIG) study. Patients received 5mg/kg ICG (n=25: 2014-2018) or 2.5mg/kg ICG(n=21:2018-2019) 24-hours preoperatively. Intraoperatively, near-infrared (NIR) imaging was performed using a dedicated NIR exoscope. Tumor fluorescence intensities were compared. Receiver Operative Characteristic (ROC) analysis and test characteristics at the surgical margins were calculated using neuropathology as the gold standard.
Results

1. Accurate Localization of Neoplasm
Among tumors <10mm below the cortex, accurate tumor localization through dura was accomplished in 91.3% (21/23) of the tumors in the 5mg/kg group and 52.9% (9/17) of the tumors in the 2.5mg/kg group (p=0.0047), demonstrating enhanced ability to visualize tumor through dura with the higher dose. Both doses allowed the surgeon to see through the normal cortex with equal likelihood (95.7% vs 88.2%, p=0.39).

2. NIR Fluorescence of Gross Tumors
Upon exposure of the tumor to direct visualization with no intervening cortex or dura, tumors in the 5mg/kg group showed similar signal-to-background ratio (SBR) (5.26±0.68) compared to the 2.5mg/kg group (4.45±0.44, p=0.34). On subgroup analysis, however, there was a significant improvement in SBR for lung metastases (SBR=7.98±1.24 and 4.70 ± 0.75, p=0.027).
To improve the specificity of NIR diagnostics by optimizing the SBR cutoff, comparative ROC curves between the two doses using SBR for margin specimens were drawn. The 2.5mg/kg group yielded a significantly greater area under the ROC curve (0.88±0.098) compared to the 5mg/kg group (0.57±0.12, p=0.049). Based on the ROC curves, an optimal SBR cutoff of 3 was selected to determine the presence of tumor under NIR signal, which changed the test characteristics compared to those based on surgeon’s impression in the OR (see Table). Using the new cutoff, both doses were able to detect margins with high sensitivity (83.3% and 85.7%), whereas the 2.5mg/kg dose led to higher specificity (57.1% vs 85.7%).
Discussion

Fluorescence-guided surgery (FGS) was developed with two main objectives: to quickly and accurately localize target lesions and to correctly identify infiltrative margins to improve the EOR. In this study, we demonstrate that high dose, delayed imaging of brain metastasis using the SWIG technique (regardless of dose) successfully demonstrates strong NIR fluorescence for brain metastasis regardless of histology with overall SBR = 4.89±0.42. 5mg/kg as compared to 2.5mg/kg provide improved ability to visualize tumor through dura. By identifying dye accumulation early, the dural incision can be customized to the location of the tumor. Despite overall lack of significant difference in NIR signal SBR, dose becomes a significant predictor of SBR of lung metastases. These results preliminarily suggest that brain metastasis from the lung may be more responsive to the dose of ICG.

Next, we demonstrated that when we reduced the dose of ICG, the specificity of the correct margin specimen identification increased without significantly sacrificing the sensitivity. Post hoc analysis found that SBR cutoff of 3 yielded that optimal test characteristics for correct margin identification. As this is higher than what has traditionally been used (SBR>2) as the criteria intraoperatively, it suggests that adjusting the camera signal parameters could potentially enhance the specificity of tumor distinction. However, we recognize that this analysis may have suffered from sampling bias between doses as there is fewer samples in the 2.5mg/kg cohort. Further margin specimen testing is required to corroborate sensitivity/specificity differences.
Summary Points

- Metastases are the most common intracranial malignancies and complete resection can significantly reduce recurrence rates.
- SWIG with 5mg/kg ICG demonstrated superior ability to localize tumor through dura compared to the 2.5mg/kg.
- Both doses allowed the surgeon to see through the normal cortex with equal likelihood.
- Upon exposure of the tumor to direct visualization, tumors in the 5mg/kg group showed similar signal-to-background ratio compared to the 2.5mg/kg group. However, there was a significant improvement in SBR for lung metastases with the higher dose.
- Increasing SBR cutoff for designating tissue as tumor under NIR imaging can increase specificity without reducing sensitivity of tumor margin detection.
- In order to capitalize on near-infrared imaging’s ability to fluoresce through multiple layers of normal tissue, we currently recommend 5mg/kg for SWIG. Further margin specimen testing is required to corroborate sensitivity/specificity differences.