Near Infrared Optical Contrast Endoscopy for Ventral Skull Base Tumors

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Disclosures

Introduction

- For the last two decades, fluorescent contrast agents have been used to intraoperatively label tumor tissues for better resection.
- 5-aminolevulinic acid has been commonly used for glioblastoma, but despite its benefits, limitations include poor signal penetration, autofluorescence of normal parenchyma, and limited success in patients with ventral skull base tumors.
- Intraoperative near-infrared (NIR) fluorescence imaging using high-dose indocyanine-green (Second Window ICG) has shown success in visualizing various intracranial neoplasms in open craniotomies.
- We hypothesized that Second Window ICG technique will demonstrate highly sensitive tumor visualization in endonasal endoscopic, ventral skull base surgery.
- In addition, we hypothesized that preoperative gadolinium enhancement will correlate with intraoperative NIR signal-to-background ratio.
Methods

NIR Contrast Agent and Visualization

- Based on our preclinical studies, patients received systemic infusions of ICG (5 mg/kg) 16-30 hours before surgery.

- All cases were imaged using an FDA-approved 4-mm endoscope NIR camera system capable of simultaneously imaging visible light and NIR views in real time.

Image Analysis

- Signal-to-background ratio (SBR) was calculated using the NIR signals from the tumor region and the adjacent background.

- T1-weighted, gadolinium-enhanced MRI scans were used to calculate preoperative tumor signal intensities compared to adjacent background (T1-to-normal).

- Gray Level Co-occurrence Matrix (GLCM) method was applied to analyze the heterogeneity of the tumor from the preoperative T1-weighted, gadolinium-enhanced MRI scans (Entropy).
**Results - Study design**

**Summary of patient and tumor characteristics**

- Total patient enrollment: n = 15
- 8 pituitary adenoma patients (mean age 54)
- 3 craniopharyngioma patients (mean age 64)
- 4 chordoma patients (mean age 52)

**Near-infrared signal to background ratio of primary tumor specimen**

(GLCM, gray level co-occurrence matrix; ICG, Indocyanine green; ID, study number; MRI, magnetic resonance imaging; SBR, signal-to-background ratio; SD, standard deviation)

- To understand the difference of fluorescence in these tumor types, we examined multiple variables: tumor size, T1-to-normal ratio, GLCM entropy, gender, BMI, time from injection to visualization, and tumor pathology.

- Using univariate linear regression to predict SBR, we identified tumor pathology, T1-to-normal, and gender as three variables with a p-value < .2.

- Prediction of SBR was performed using multivariate analysis, and the best predictor was T1-to-normal ratio (P=.0003).
Results – NIR intensity varies based on tumor type & MRI gadolinium enhancement

- All pituitary adenomas demonstrated NIR positivity with an average SBR of 3.9 ± .8.
- All craniopharyngiomas also demonstrated NIR positivity with average SBR of 4.1 ± 1.7, which was not statistically distinct from that of pituitary adenomas (Wilcoxon rank sum, P = .78).
- Chordomas had an average SBR of 2.1 ± .6, which was statistically weaker than patients with pituitary adenomas (Wilcoxon rank sum, P = .048).

- T1-to-normal increases by one point when SBR increases by 2.17 (A).
- T1-to-normal against the corresponding SBR for pituitary adenomas (B). Linear regression demonstrates that for every 1 full-point increase in T1-to-normal, the SBR increased by 1.53 times ($R^2 = .52$).
- For craniopharyngiomas, linear regression shows that for every 1 full-point increase in T1-to-normal, the SBR increased by 3.04 ($R^2 = .82$) (C).
- For chordomas, linear regression demonstrated that for every 1 full-point increase in T1-to-normal, the SBR increased by 6.02 times ($R^2 = .97$) (D).
Results – NIR fluorescence-guided endoscopic endonasal surgery

Second Window ICG provides intraoperative near-infrared optical contrast during endoscopic endonasal surgery

Patient ID 116 with pituitary adenoma

- (A, B) Preoperative T1-weighted, gadolinium-enhanced MRI scans.
- (C) Preoperative T1-weighted MRI scan without gadolinium-enhancement.
- (D, E, F) White light, NIR overlay, and NIR-only views, respectively, of the tumor region before dura removal.
- (G, H, I) White light, NIR overlay, and NIR-only views, respectively, of the fully exposed and isolated tumor tissue.
- (J, K, L) White light, NIR overlay, and NIR-only views, respectively, of a margin specimen detected by the NIR signal after primary debulking.
Results – NIR endoscope characterization and study statistics

Endoscope NIR demonstrates greater vignetting than white light

- (A) NIR intensity map overlaid on visible light view shows that NIR camera system using the endoscope demonstrates a focal light pattern towards the center of the ICG-enriched positive control medium.
- (B) NIR-only view more clearly demarcates the concentric ring pattern as well as the focal light pattern towards the center.
- (C) The distribution of white light from the endoscope is shown.
- (D) The yellow lines from (B) and (C) shows the slice that was used to calculate the intensity profile shown. Blue line shows the intensity profile for NIR-only view and the black line shows the profile from the white light view.

Second Window ICG is sensitive but not specific for residual pituitary adenoma

- Using tumor on final pathology as the gold standard compared to the surgeon’s impression from visible light alone, we calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), which were 90%, 100%, 100%, and 83%, respectively.
- In contrast, the sensitivity, specificity, PPV, and NPV of NIR intraoperative imaging for identifying tumor was 100%, 20%, 71% and 100%, respectively.
In contrast to the exoscope NIR camera system used in open craniotomies, we believe that the narrow profile of the endoscope limits more thorough spread of the excitation laser from the tip of the endoscope, thus increasing the relative focus of NIR excitation and emission towards the center of the view compared to the periphery.

Since such illumination profile is inherent to the system itself and not modifiable by the operator, it is important to consider different techniques to make NIR measurements consistent across different samples depending on the NIR endoscopic system used.

While tumor size did not correlate to SBR, we observed lower SBR for tumors with a more heterogeneous architecture based on the heterogeneity analysis of the T1 gadolinium-enhancement profile. The relative abundance of pockets of necrosis and limited vasculature demonstrated in chordomas may have limited ICG uptake and therefore produced a lower average NIR signal.

Although the mechanism of gadolinium enhancement in tumors does not rely on the enhanced permeability and retention as ICG, it does serve as a useful proxy for predicting the utility of NIR as a surgical adjunct.

ICG is not receptor specific, and at high doses, it will bind to plasma albumin and remain trapped within the extracellular matrix through the EPR effect. This phenomenon likely led to high false positive rates and thus low detection specificity.

While ICG has excellent sensitivity for detecting pituitary adenomas, no definitive analyses could be applied to the other two tumor types due to limited sample size.

the SBR is an arbitrary ratio and may not be a true reflection of tissue fluorescence, and the study was performed by a single surgeon and may be subject to selection bias and other limitations.
We demonstrated that Second Window ICG can provide sensitive and safe intraoperative near-infrared optical contrast using dual channel endoscope during endoscopic endonasal surgery of ventral skull base tumors.

Chordomas demonstrated the lowest SBR, suggesting that ICG may provide value in surgical resection of uniformly enhancing tumors such as pituitary adenomas and craniopharyngiomas.

While the utility of ICG is promising due to sensitive margin detection and in situ NIR signal correlation with gadolinium enhancement on MRI for all three tumor types, it is limited by low specificity.

Overall, we believe that intraoperative NIR tumor imaging may provide important guidance towards surgical decision-making and improved resection.