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Fluorescent guided surgery for sinonasal tumors

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Abstract

Near-infrared fluorescence is increasingly finding utility in surgery. The ease of administering contrast agents, the ability to image in real-time, and the lack of tissue disruption are features of fluorescence imaging which have contributed to its use in the operating room. In this review, we examine fluorescence-guided surgery in the context of sinonasal tumors, evaluate currently available contrast agents and their targets, and discuss future applications of fluorescence in endoscopic sinus surgery.

Keywords: Near-infrared fluorescence, surgical navigation, molecular imaging, tumor imaging, sinonasal cancer

INTRODUCTION

Sinonasal cancers pose a formidable challenge for resection due to the narrow endonasal corridor, intricate adjacent anatomy, proximity to critical structures, and need to reconstruct the skull base following the procedure. The endonasal corridor also presents unique opportunities for utilization of fluorescent-guided techniques given the enclosed space, relatively uniform lighting conditions, and consistent utilization of endoscopic imaging which can enable overlays of different visual inputs. Recent technological advancements in surgical visualization have the potential to inform several aspects of surgical treatment for sinonasal tumors.

TUMOR IDENTIFICATION

With regard to non-targeted fluorescence techniques, indocyanine green (ICG) fluorescence imaging has been demonstrated to have diverse applications in the surgical resection of sinonasal tumors. ICG is a water-soluble tricarbocyanine dye with excellent safety profile that fluoresces when exposed to wavelengths of light in the near-infrared (NIR) spectrum (peak excitation at 805 nanometers).

When ICG is infused preoperatively via an intravenous line (IV), it can highlight tumor tissue during surgery, leveraging the differential vascular perfusion patterns between cancer tissue and normal tissue. Tumor tissue is often characterized by vascular damage and increased permeability, which results in increased retention of ICG compared to normal tissue[1]. By visualizing tumor with fluorescence, surgeons can ensure a more precise and complete resection, minimizing the risk of leaving residual cancerous tissue. This technology has been validated in benign skull base tumors such as pituitary adenomas[2,3]. One series demonstrated that an IV infusion of ICG 24 h prior to surgery generated a significantly high signal-to-background ratio between tumor tissue and normal tissue for chordomas, craniopharyngiomas, and pituitary adenomas[4]. This study found that tumors with high signal intensity on magnetic resonance imaging (MRI) T1 sequence with gadolinium contrast were the single best predictor of the signal-to-background ratio. While ICG has been shown to facilitate intraoperative identification of squamous cell carcinoma and adenoid cystic carcinoma in the head and neck[5], currently no studies investigate the efficacy of ICG to highlight tumor tissue specifically in sinonasal malignancy.

TARGETED FLUORESCENCE

Targeted fluorescence approaches capitalize further on tumor-specific biomarkers to provide signal contrast during surgery. These approaches, also referred to as "molecular imaging", are the subject of numerous trials in oncologic surgery, which are now beginning to expand into sinonasal tumors.

Certain tumors overexpress folate receptors, which has led to the development of folate analogs conjugated to fluorescent antibodies. For example, pituitary adenomas have demonstrated up to 20-fold overexpression of folate receptor alpha[6]. OTL38 is a folate analog conjugated to ICG to allow for fluorescence in NIR. Among skull base tumors, OTL38 can be used to distinguish pituitary adenomas from normal tissue intraoperatively, when administered intravenously 4-6 hours preoperatively[6]. Pre-operative confirmation of target receptor content is not typically feasible due to limited tissue biopsy, and as such, targeted imaging typically relies on preclinical validation of target receptor content. While folate receptors have not been investigated specifically for sinonasal malignancy, in squamous cell carcinoma of the head and neck, tumors do contain a high population of macrophages that express folate receptors, suggesting that folate-conjugated fluorescent dyes may be able to specifically target tumor tissue[7].

Another molecular target of interest is vascular endothelial growth factor (VEGF), which is overexpressed in sinonasal papilloma. This target can be identified using the antibody-dye conjugate, bevacizumab-IRDye800CW. Using a fluorescent grid to quantify fluorescence within a tumor sample, *ex vivo*, Vonk *et al.* calculated the signal-to-background ratio and demonstrated a significantly higher mean fluorescence signal in SNP compared to normal tissue [77.54 (IQR 50.47-112.30) *vs.* 35.99 (IQR 21.48-57.81), $P < 0.0001$][8]. However, despite the higher levels of fluorescence, the authors conclude that clinical utility is limited, because this higher fluorescence signal could not be detected during endoscopic surgery. VEGF is also uniquely overexpressed in pituitary neuroendocrine tumors, and is the subject of a clinical trial using bevacizumab-IRDye800CW (NCT04212793)[9].

The epidermal growth factor receptor (EGFR) is another target that has been the focus of study in sinonasal surgery. EGFR is commonly overexpressed in head and neck cancer, and several trials utilizing Panitumumab-IRDye800 have demonstrated utility in intraoperative margin assessment, residual tumor identification, and mapping of nodal disease. A preclinical study of Pan800 in a sinonasal tumor model was able to demonstrate the feasibility of endoscopic targeted NIR imaging; further translational studies are necessary to evaluate the utility of Pan800 in sinonasal cancer[10].

The 5-aminolevulinic acid (5-ALA) has been investigated as another potential agent for fluorescence-guided surgery. Administered orally 2-4 h preoperatively, 5-ALA is absorbed by cells and transformed into protoporphyrin IX (PpIX), a fluorescent compound. PpIX has been shown to have an affinity for rapidly dividing cells, such as those found in cancer[11]. Intraoperatively, PpIX can be visualized using 405 nm wavelength blue light. The compound 5-ALA has Food and Drug Administration (FDA) approval for use in high-grade gliomas[11] and has recently been shown to have utility in head and neck squamous cell carcinoma for identifying positive margins, perineural invasion, and metastatic nodal disease[12]. However, in endonasal surgery, the utility of 5-ALA may be limited. A recent multicenter study of sinonasal tumors investigating 28 sinonasal benign and malignant tumors found that SCC, esthesioneuroblastoma, and plasmacytoma did not demonstrate any 5-ALA fluorescence[13,14]. This fluorescence was only observed in two of the tumors (7%): a pituicytoma and a meningioma.

PRESERVATION OF CRITICAL STRUCTURES

Sinonasal cancers often encroach upon critical neurovascular structures of the skull base. Intraoperative use of fluorescent agents can allow for real-time enhanced visualization of structures, allowing surgeons to navigate and preserve them more effectively.

The internal carotid artery can be reliably identified in endoscopic sinonasal and skull base surgery within a few seconds after intraoperative administration of ICG, with a strong fluorescent signal[15]. ICG can also be used to assess patency of the cavernous sinus. Furthermore, angiography can also aid in identification of critical perforators of the brain, optic apparatus, and pituitary gland[16]. In resection of skull base tumors, ICG has been utilized to assess and preserve vascular perfusion of the optic nerve with excellent vision outcomes[17,18].

Intravenous administration doses can range from 12.5 to 50 mg. A NIR endoscope can then be used to visualize vascular structures within one minute of administration. Examples of ICG administration to visualize skull base vascular anatomy can be seen in Figure 1.

PERFUSION ASSESSMENT IN RECONSTRUCTIVE FLAPS

ICG fluorescence angiography provides real-time feedback on blood flow dynamics, enabling surgeons to make informed decisions regarding tissue viability and the potential need for vascularized flaps in reconstructive procedures.

Necrosis of a reconstructive flap poses the potential complication of meningitis. While MRI with gadolinium contrast is considered the standard method to assess for flap perfusion, this can often only be performed in the postoperative setting. Flap necrosis can potentially be avoided through utilization of intraoperative ICG angiography to assess viability of reconstructive flaps[19-21]. A systematic review assessed 104 cases of patients undergoing skull base reconstruction with nasoseptal flaps, lateral nasal wall flaps, pericranial flaps, and microvascular free flaps, and found that intraoperative ICG perfusion was strongly associated with flap perfusion as assessed by postoperative MRI[22]. Intraoperative administration of ICG can help confirm the perfusion of nasoseptal flap pedicles in real time, through fluorescence in the region of the posterior septal artery [Figure 2].

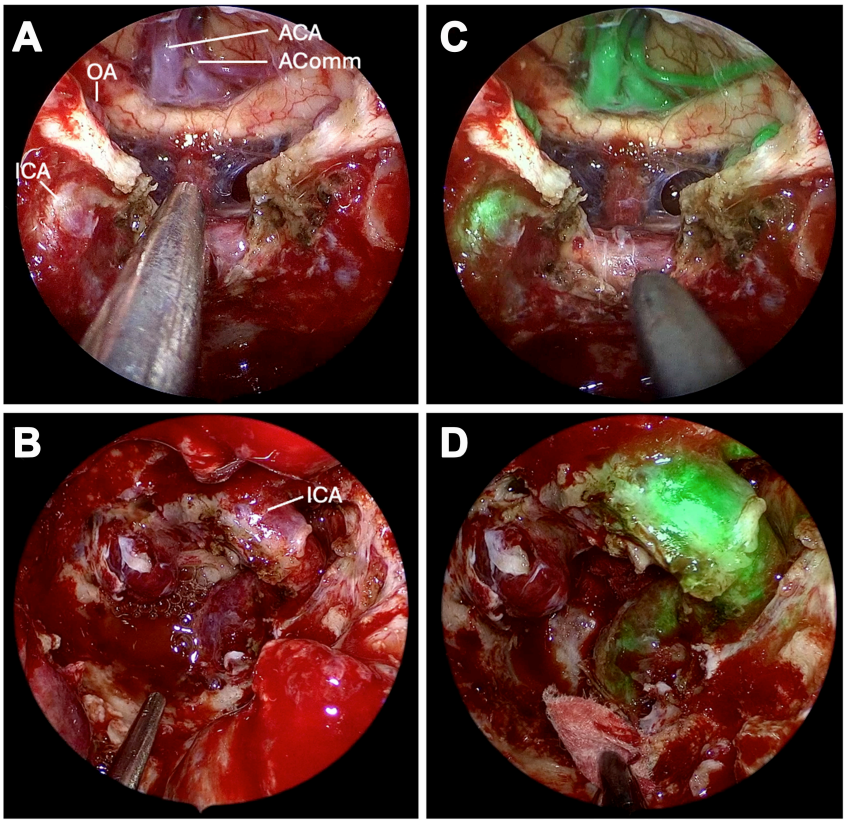

Figure 1. Visualization of critical vascular anatomy at the skull base with white light endoscopy (A and B) and enhanced with ICG fluorescence angiography (C and D). Source: Author's operative case (M.C.). Patients images were obtained with informed consent as part of IRB-approved study. ACA: Anterior cerebral artery; AComm: anterior communicating artery; ICA: internal carotid artery; OA: ophthalmic artery; ICG: indocyanine green.

VISUALIZATION OF CSF

Short wave infrared (SWIR) endoscopy is another type of alternative wavelength visualization of specific tissues with potential future application in sinonasal surgery. SWIR visualization technology has offered enhanced visualization of cerebrospinal fluid (CSF). In the context of skull base surgery reconstruction, where visualization of CSF is crucial, this technology provides clear and real-time images, enabling surgeons to confirm the presence or absence of a CSF leak[23]. The shortwave infrared technology may facilitate the identification of potential leaks and allow for prompt intervention, ultimately improving patient outcomes and minimizing the risk of complications related to reconstruction failures.

INFORMING INTRA-ARTERIAL CHEMOTHERAPY TREATMENT

One study aimed to evaluate the feasibility of ICG fluorescence technique during intra-arterial chemotherapy for recurrent sinonasal cancers. Seven patients were included in the study. While computed tomography angiography (CTA) alone detected blood supply in three cases, the addition of endoscopic ICG fluorescence imaging confirmed perfusion in all cases, informing intraoperative targeting of arteries for drug administration[24].

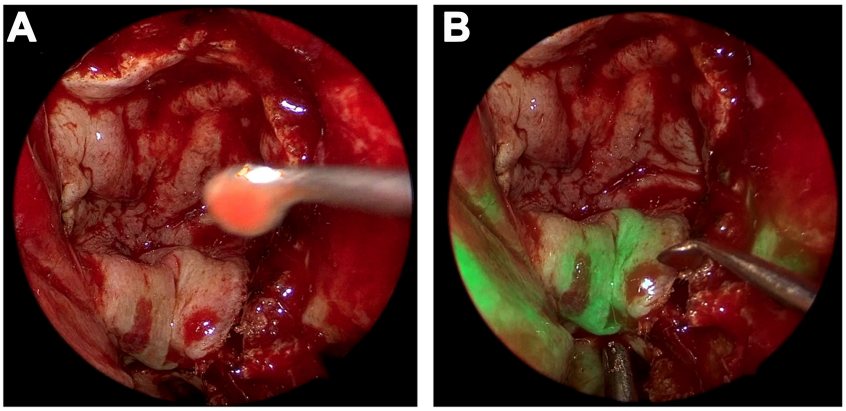

Figure 2. Skull base reconstruction with nasoseptal flap viability assessed in (A) white light endoscopy and (B) near-infrared fluorescence angiography. Source: Author's operative case (M.C.). Patients images were obtained with informed consent as part of IRB-approved study.

FUTURE DIRECTIONS AND CHALLENGES

While the use of non-targeted fluorescent techniques in endonasal surgery has shown promising results, ongoing research aims to refine their applications further. Much of the existing evidence supporting potential applications is derived from cases with benign tumor pathology. These technologies require validation for malignant pathologies, particularly when it comes to tumor margins and nodal metastases. Additional challenges include optimizing imaging systems, standardizing protocols, and addressing cost-benefit considerations. Furthermore, fluorescent tracers, despite their potential benefits in surgical applications, may not be readily available worldwide due to varying regulatory constraints. Nonetheless, the integration of these fluorescence imaging techniques into sinonasal cancer surgery has the potential to enhance surgical visualization, precision, and outcomes.

To address limitations in depth of signal detection of NIR probes, the NIR-II or "second window" has been explored with promising results. These wavelengths are typically defined between 1,000-1,700 nm, and imaging in the NIR-II window has demonstrated increased depth sensitivity and improved image contrast[25]. Along with the development of new fluorescence dyes, conjugates and their applications, there has been a concomitant increase in fluorescence imaging devices. Since the introduction of the handheld SPY Imaging System (Novodaq Industries) in 2005, several hardware developments have increased imaging capabilities into microscopic, robotic and endoscopic approaches. Currently, the only clinically-available rigid NIR endoscopes are the Karl Storz Hopkins Rubina scopes (0, 30, 45 degrees; 5 and 10 mm outer diameter) and the Scholly NIR FI (0, 30 degrees; 10 mm outer diameter). However, there is intense research into expanding endoscopic technologies, including narrower, flexible endoscopes and multiplexed endoscopic fluorescence imaging[26,27].

The integration of artificial intelligence (AI)-based computer vision has the potential to significantly enhance fluorescent-guided surgery by improving the accuracy and efficiency of surgical field analysis. Machine learning algorithms can be trained on large datasets of fluorescence images to recognize patterns and nuances that may be imperceptible to surgeons. While fluorescence is typically a qualitative assessment or based on relative signal-to-background ratios, there is potential for AI to guide surgical decision-making based on quantitative numerical cutoffs which is particularly feasible in controlled ambient light environments, such as endoscopic surgery. Computer vision algorithms can automate the identification of tumor boundaries and the differentiation between cancerous and normal tissues, as well as process and

analyze real-time fluorescence signals in other applications pertaining to tissue perfusion or anatomical structures. The synergy of these technologies has significant potential to change surgical treatment in the coming years.

CONCLUSION

Fluorescence technology has the potential to impact sinonasal surgery by improving identification of sinonasal tumors and enhancing the detection of vital anatomic structures. Additional studies on the clinical implementation of these technologies, and the continued development of contrast agents and imaging devices will be crucial to achieving this impact.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Chang M, Baik F

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

This study was reviewed and approved by the Institutional Review Board (IRB) at Stanford University (Administrative Panel on Human Subjects in Medical Research, No. 64018). Informed consent to participate was obtained from all patients.

Consent for publication

Not applicable.

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