Second Window Indocyanine Green for Oropharyngeal Tumors: A Retrospective Case Series and Comparison of Near-Infrared Camera Systems

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5 Key Points:

- Prior studies demonstrated a failure to identify and localize head and neck cancers via near-infrared (NIR) imaging of indocyanine green (ICG) with a robot-integrated platform. However, our group demonstrated success in visualization of neoplasms using a commercially available dedicated NIR camera system and a technique called second window ICG (SWIG), in which ICG is injected 24 hours pre-operatively.
- We aimed to evaluate the SWIG technique in patients undergoing transoral robotic surgery (TORS) for oropharyngeal squamous cell carcinoma (OPSCC) and compare two NIR camera systems.
- System 1 showed poor tumor-margin delineation with no fluorescence in 4/6 cases (66.7%) and only minimal fluorescence in the remaining 2 cases (33.3%).
- System 2 showed marked fluorescence in 5/6 cases (83.3%), with good margin definition in 4 cases (66.7%). In 2 cases (33.3%), System 2 also identified tumor that was not visible under white light.
- In this preliminary case series, we found that System 2 outperforms System 1 in NIR imaging with SWIG during TORS for oropharyngeal tumor resection.

Introduction

Negative margin status is the most important prognosticator in the surgical treatment of oropharyngeal squamous cell carcinoma (OPSCC), but can be challenging to achieve with tumors in poorly visualized regions.[1]This can be magnified in transoral robotic surgery (TORS) where haptic feedback is limited. Fluorescence molecular imaging (FMI) using near-infrared (NIR) fluorophores has been increasingly used to augment margin definition and residual tumor detection *in vivo* for achieving tumor-free margins.

The NIR dye indocyanine green (ICG), routinely used for FMI, accumulates in areas of disrupted, permeable endothelium (i.e. neoplastic tissue) via the enhanced-permeability-and-retention (EPR) effect.[2]Additionally, ICG accumulates within tumors due to poorly developed tumoral lymphatics.

Recently, TORS has advanced the surgical treatment of OPCSCC.[3]Unfortunately, prior studies found that ICG failed to identify head and neck lesions and achieve tumor-free margins during TORS.[4] Our group previously demonstrated that NIR imaging of ICG injected 24 hours preoperatively, a novel technique called Second Window ICG (SWIG), with the VisionSense Iridium^{TM} platform, could be used for intraoperative identification of head and neck lesions and regional metastasis.[5]The current study's objective was to compare a surgical robot-integrated NIR system to a dedicated NIR imaging platform for intraoperative imaging with SWIG.

Methods

Study Design, Setting, and Participants

This prospective case series was performed at the University of Pennsylvania following Institutional Review Board approval. Patients were eligible for this study if they were >18 years old and undergoing TORS resection of a biopsy-proven p16-positive OPSCCC with or without neck dissection between February 2016 and January 2018. All patients provided informed consent. Patients with a history of radiation, chemotherapy, or recurrent malignancy were excluded.

Near-Infrared Technology

For the da Vinci Xi Firefly^{TM} endoscope platform (Intuitive Surgical Inc., Sunnyvale, California, USA), henceforth called System 1, a 736nm NIR laser excitation source was used and emission signals were collected from 600-900nm. The VisionSense Iridium^{TM} exoscope system (VisionSense, Philadelphia, Pennsylvania, USA), henceforth called System 2, has demonstrated high NIR sensitivity in prior studies[6]and uses a 785nm laser excitation source and a high-sensitivity NIR camera with an 800-835nm filter. Real-time videos were captured in 720p and displayed at 1080p.

Study Procedure and Outcomes

Patients presented 24 hours prior to surgery for intravenous infusion of 5mg/kg ICG (Akorn Pharmaceuticals, Illinois, USA). At the time of TORS, an endoscope attachment was used for primary tumor evaluation under white light. Tumors were coded yes/no for visualization under white light based on the surgeon's impression. The primary lesion was then imaged using both the systems. Videos of tumor resection were recorded and analyzed postoperatively. Cases were evaluated for the presence/absence of NIR signal and tumor margin delineation as visualized by the two platforms.

This case series has been reported in line with the PROCESS Guideline.[7]

Results

Six patients were included in this study, with an average age of 59 (range [48-67]). Demographics and tumor characteristics are included in Table 1. Notably, all patients were Caucasian and male. Primary tumor sites included tonsil (2/6), tongue base (1/6), and glossotonsillar sulcus (3/6).

System 1 showed poor tumor-margin definition with no fluorescence in 4 of 6 cases (66.7%) and only minimal fluorescence in the remaining 2 cases (33.3%) (Fig. 1). In contrast, System 2 showed marked fluorescence in 5 of 6 cases (83.3%), with good definition of margins in 4 cases. In two cases, the oropharyngeal lesion was poorly visualized by the surgeon *in vivo* , but showed marked ICG fluorescence when visualized using System 2 (Fig. 2).

Discussion

Negative margins are associated with improved survival and progression-free survival in surgically-treated OPSCC.[1]FMI with NIR fluorophores has added to surgeons' armamentarium to achieve negative margins and has been successfully implemented in glioma, breast cancer, and ovarian cancer.[2,8,9]Prior studies demonstrated that ICG failed to localize head and neck neoplasms and their margins during TORS.[4]However, our group demonstrated that SWIG imaging with the VisionSense Iridium^{TM} can be used for intraoperative visualization of head and neck tumors and identification of regional metastasis to aid surgical resection.[5]The present study is the first evaluation and comparison of SWIG imaging with the VisionSense Iridium^{TM} to the da Vinci-integrated Firefly^{TM} NIR platform during TORS resection of OPSCC.

While the robot-integrated platform (System 1) only demonstrated NIR fluorescence in 2 of 6 (33%) lesions, the dedicated NIR exoscope system (System 2) visualized 5 of 6 (83%) lesions, and identified 2 additional tumors that had not been visible under white light alone. These results suggest that System 2 outperforms System 1, which may be explained by differences in imaging processing software or detector sensitivity between the two systems.[6]System 1 requires additional refinement to improve its efficacy in aiding TORS resection. Additionally, given that some cases were better visualized with ICG than white light, this technology

could be beneficial in evaluation of head and neck carcinoma of an unknown primary.

Limitations to this study include its small sample size and homogenous sample population, which included only male, Caucasian patients. For further evaluation, larger sample sizes with more diverse patient characteristics should be utilized.

Conclusion

Achieving negative surgical margins is associated with improved survival for OPSCC, and the development of minimally invasive approaches such as TORS has led to decreased surgical morbidity.[1,3,10]To improve negative oncologic margin rates, techniques such as FGS have emerged as rapid and cost-effective methods of real-time intraoperative tumor visualization. In this study, we compared the performance of a surgical robot-integrated NIR camera system to a dedicated NIR imaging platform for SWIG imaging during TORS for OPSCC. The combination of NIR FMI and TORS could aid in achieving negative surgical margins, but additional development is required to improve the technology currently available in the robot-integrated system.

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Figure Legends Figure 1.

Figure 1A. Intraoperative, *in vivo* photograph of primary right tonsil lesion poorly visualized under white light.

Figure 1B. Representative image using System 1 demonstrating mild fluorescence of the right tonsil lesion.

Figure 2. Intraoperative, *in vivo* photograph of right glossotonsillar lesion poorly visualized with both white light (A) and System 1 (not shown). Representative image of tumor fluorescence with System 2 *in vivo* (B) and *ex vivo* (C).

Table 1. Demographics and tumor characteristics of the study population.

Demographics and tumor characteristics of the study population.

Variable	**Number (%)**
Age (mean (SD))	59.5 (6.4)
Sex	
Male	6 (100)
Female	0 (0)
Race	
Caucasian	6 (100)
Black	0 (0)
Asian	0 (0)
Hispanic	0 (0)
Location of Primary Tumor	
Tonsil	2 (33)
Tongue base	1 (17)
Glossotonsillar sulcus	3 (50)
Pathologic T stage	
T1	5 (83)
T2	1 (17)