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OBJECTIVE

To investigate the potential of near-infrared dye indocyanine green (ICG) in localization of HPV+ oropharyngeal cancer in order to:

- 1. Improve visualization of tumors undergoing resection
- 2. Assist with delineation of intraoperative surgical margins

INTRODUCTION

- Indocyanine green (ICG) is an FDA-approved, near infrared fluorescent dye used for its fluorescent properties that has been used in several other applications, including identifications of tumors within thoracic, hepatic and renal surgery.
- Previously published feasibility studies have shown that ICG can be utilized for head and neck cancer, but this is the first study looking at its use in transoral robotic surgery (TORS) for HPV+ oropharyngeal cancer.
- ICG is a promising option for oropharyngeal cancer because:
 - 1. Fluorescent visualization of tumoral tissue may improve tumoral identification and demarcation of tumor margins
 - 2. Readily available fluorescent imaging technology is incorporated into the da Vinci robot (Firefly)

METHODS

- Inclusion criteria: patients with a diagnosis of HPV+ oropharyngeal squamous cell carcinoma undergoing TORS as per standard of care.
- After obtaining informed consent, patients are pre-operatively injected with ICG (25mg) 4-6 hours prior to surgery.
- Surgery is performed as per standard-of-care. Imaging obtained prior to tumor resection and post-resection examination of wound bed. After tissue collection, IVIS imaging is performed to quantify fluorescence of tissue.
- Measures:
 - Intra-operative imaging
 - Surgeon survey re: intra-operative visualization
 - Post-operative tissue specimen IVIS imaging
 - Correlation of intra-operative findings with final histology

RESULTS

Thus far, 10 patients have been recruited to participate in the study. ICG injection results in enhanced visualization of HPV+ oropharyngeal cancers (**Figure 1**). IVIS is able to quantifiably measure visualized ICG-related fluorescence under the da Vinci Firefly system (**Figure 2**). After systemic injection of ICG, IVIS is able to both visualize and quantifiably measure the amount of ICG-fluorescence in pathologically positive tissue in both primary tumor and regional nodal metastases (**Figure 3**).

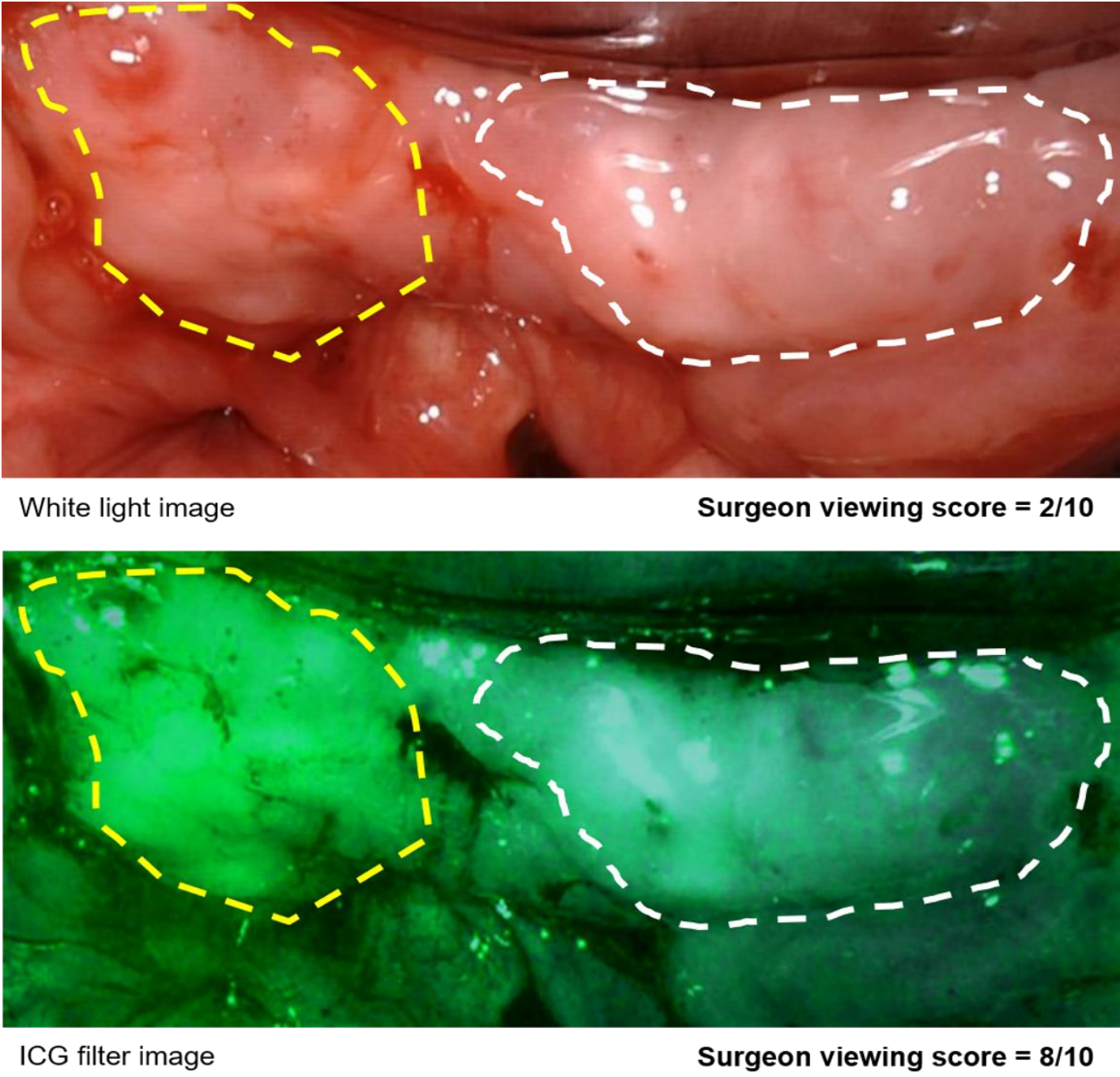


Figure 1. Improved visualization of tumoral tissue after systemic ICG injection. Yellow dashes represented histopathologically positive tumor tissue, white dashes represent normal tissue. Surgeon viewing score improved from 2/10 to 8/10 under the da Vinci Firefly filter.

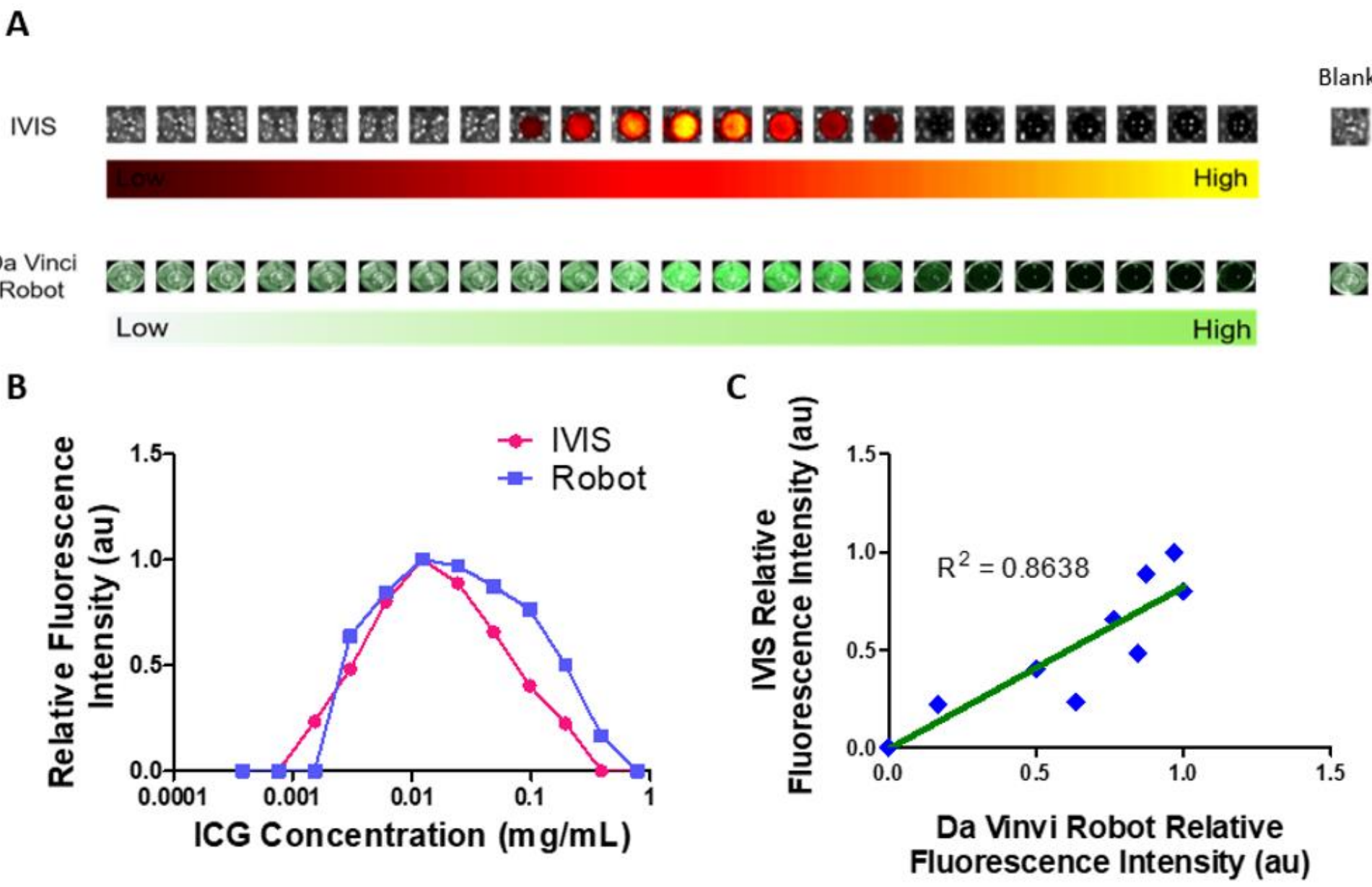


Figure 2. Demonstration of IVIS's ability to quantify ICG-related fluorescence. A) Sequentially increasing concentrations of ICG demonstrate correlated fluorescence in both the IVIS imaging system and da Vinci Firefly system. B) Relative fluorescence intensity in both the IVIS and da Vinci Firefly systems was determined to be optimized at 0.012 mg/ml from both systems. C) Linear correlation of fluorescence intensity between the IVIS and da Vinci Firefly system.

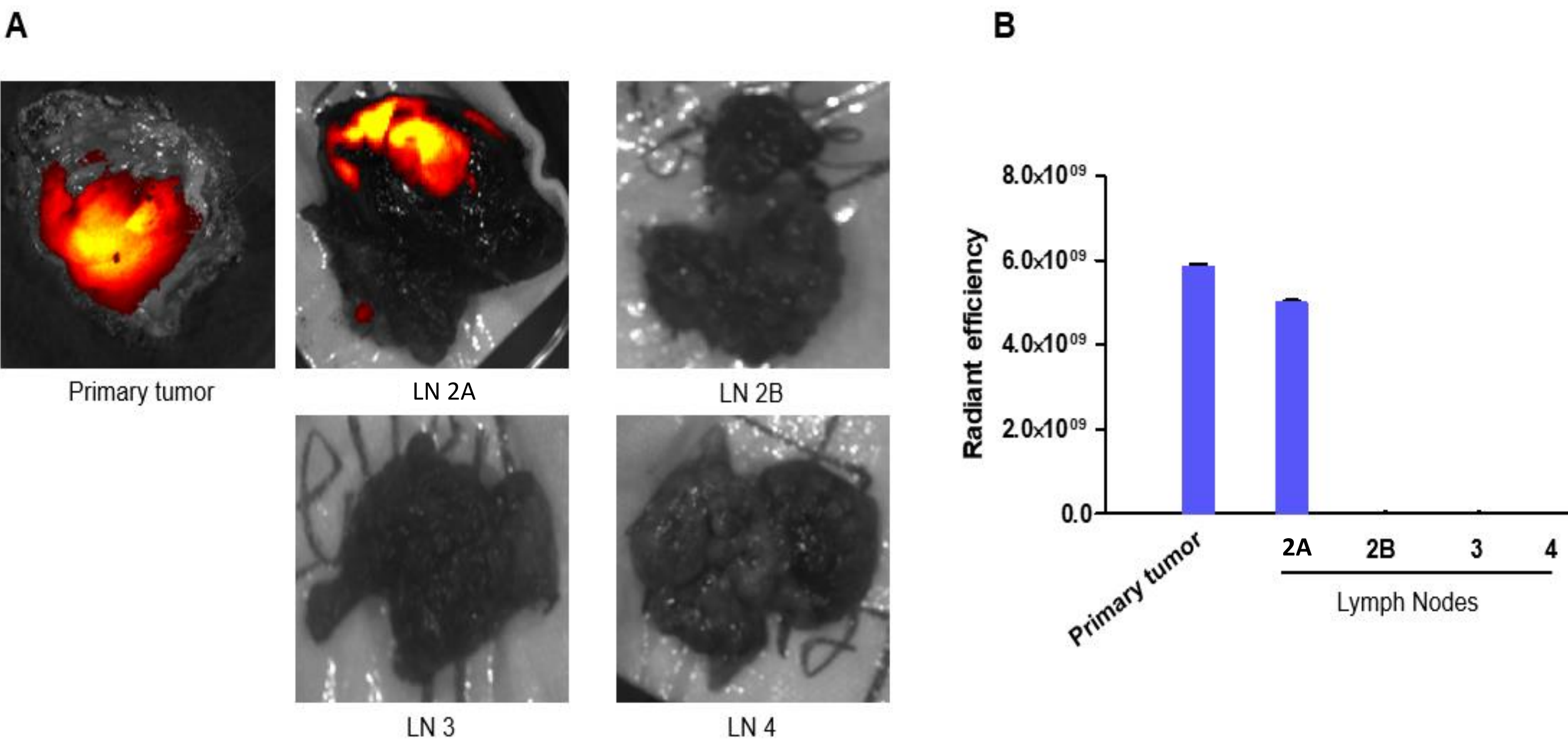


Figure 3. Quantifiable analysis of ICG fluorescence after systemic injection using the IVIS system. A) Primary tumor and nodal packets of levels 2A, 2B, 3, and 4 imaged via IVIS for fluorescence. Only level 2A had a single pathologic lymph node with evidence of metastatic squamous cell carcinoma. B) The fluorescence radiant efficiency of the primary site and nodal packets measured using IVIS correlate with image findings.

DISCUSSION

- Systemic injection of ICG results in accumulation of fluorescence in primary tumors and positive lymph nodes for HPV+ oropharyngeal cancer, which can be effectively visualized with the da Vinci Firefly system and quantified using the IVIS imaging system.
- The preferential accumulation of ICG in tumoral tissue is likely secondary to the enhanced permeability and retention effect, which is based on ICG's ability to associate with albumin. Healthy tissue rapidly clears proteins while enhanced tumoral permeability and increased retention leads to preferential accumulation of ICG in tumoral tissue.
- The use of ICG in TORS for HPV+ oropharyngeal cancer is a promising technique to help identify unknown primary tumors and delineate surgical margins, with the overall goal of reducing morbidity and improving clinical outcomes among TORS patients.
- Further research is needed to investigate the underlying biochemical properties responsible for ICG accumulation in these tumors to ultimately allow for improved ICG delivery design.