Near Infrared (NIR) Image-guided Lymphatic Mapping for Adequate Nodal Staging in Esophageal Cancer

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Disclosures

• I have no equity, ownership, stock, options or any interest in any company
• I do not consult for any company

We gratefully acknowledge Novadaq for the generous loan of the Pinpoint system. There has been no data preview or monetary sponsorship for this collaboration

Use of ICG for NIR-imaging of SLN is NOT FDA-approved
Why is this clinical trial important?

- 5-year survival: <40% (node positive)
  - High prevalence of nodal disease even with T1 lesions (16-36%)
  - Locoregional nodal recurrence rates: ~5-20%

- Robust lymphadenectomy (LAD) for prognostic staging
  - Esophageal lymphatics: local (en bloc with the specimen) and regional (separate from the specimen)

- No established techniques to determine which regional nodes are most critical for removal and analysis

Hypothesis

We hypothesize that identifying regional LNs at greatest risk for metastases for focused histologic analysis is safe and feasible via NIR lymphatic mapping with potential to improve clinical outcomes
Near Infrared (NIR) Lymphatic Mapping

- NIR dye Indocyanine Green (ICG) emission range: 750-950nm
- ICG signal detection using a near-infrared videoscopic camera
- Visualization of merged and single channel real-time images

Video of Real-time Merged Images

Light Source (color, NIR fluorescence excitation)

NIR Camera

Color Video Camera

Surgical Field

Courtesy of J Frangioni at BIDMC.
Trial Aims

- Assess the safety and feasibility of intra-operative, minimally invasive, Near Infrared (NIR) image-guided lymphatic mapping of regional LNs in esophageal cancer

- Compare the feasibility of lymphatic mapping with Near Infrared dye Indocyanine Green (ICG) alone or premixed with human serum albumin (ICG:HSA)
Methods: Patient Selection

Pilot “first-in-human” clinical trial

- Ten patients with early stage adenocarcinoma
  - T1 (n=2); T2 (n=2); T3 (n=6)

- Standard preoperative clinical work up:
  - EUS, CT, PET/CT

- 8 of 10 patients had preoperative chemoradiation
Methods: Intraoperative Protocol

Eligible pt in OR

Endoscopy

Endoscopic peritumoral, submucosal injection of ICG (2.5mg ICG in 1cc of sterile water or albumin)

Minimally invasive esophagectomy + NIR imaging (during laparoscopy + VATS)

Identification of NIR+ LN in vivo

Ex vivo NIR imaging of all specimens

Routine LN Pathologic analysis
Results

- In vivo NIR imaging was feasible in all cases (n=10)
- NIR imaging revealed 2-6 NIR+ tumor-draining regional LNs per patient (n=6) (fig).
- NIR+ LNs detected from 30 mins – 3.5 hrs after ICG injection.

NIR image-guided identification of a tumor-associated paraesophageal LN
### Results

- **ICG:HSA** – superior tracer

**NIR+ regional LNs** identified:
  - 4/4 ICG:HSA
  - 2/5 ICG alone

<table>
<thead>
<tr>
<th>Pt #</th>
<th>ICG carrier</th>
<th>Regional LNs (NIR+/total)</th>
<th>Total LNs sampled</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ICG:HSA</td>
<td>6/10</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>ICG:HSA</td>
<td>2/2</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>ICG alone</td>
<td>0/11</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
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<td>0/3</td>
<td>28</td>
</tr>
<tr>
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<td>0/2</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td><em>ICG:HSA</em></td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>ICG alone</td>
<td>1/5</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>ICG:HSA</td>
<td>2/8</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>ICG:HSA</td>
<td>3/7</td>
<td>25</td>
</tr>
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<td>31</td>
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### Results

- ICG:HSA – superior tracer

- NIR+ regional LNs identified:
  - 4/4 ICG:HSA
  - 2/5 ICG alone

- Mean total number of LNs resected:
  - T1: 21.5 (+/- 4.95)
  - T2/T3: 29.3 (+/- 5.99)

#### NIR+ LNs as a Function of ICG Carrier

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Results

- High NIR background on the specimen limits identification of distinct NIR+ “local” nodes.
- No adverse events.
**Location of NIR+ Regional LNs**

**Frequency of NIR+ LN by Station**

- **Subcarinal (7)**: 16.7% (1)
- **Lower paraesophageal (8L)**: 16.7% (1)
- **Paracardial (16)**: 83.3% (5)
- **Left gastric (17)**: 33.3% (2)
- **Celiac Axis (20)**: 16.7% (1)

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**NIR+ Regional LN Locations and Prevalence in GEJ and Lower Esophageal Cancers**

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Rate of LN Metastasis by Station*:
- Subcarinal: ~5-12%
- Lower paraesophageal: ~22-30%
- Paracardial: ~13-59%
- Left gastric: ~19-36%
- Celiac Axis: ~14-19%

NIR+ Regional LN Locations and Prevalence in GEJ and Lower Esophageal Cancers:

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Results

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<tr>
<th>Pt #</th>
<th>Regional LNs # metastatic/total</th>
<th>Local en bloc LNs #metastatic/total</th>
</tr>
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<tbody>
<tr>
<td>3*</td>
<td>0/11</td>
<td>1/15</td>
</tr>
<tr>
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<td>0/5</td>
<td>1/28</td>
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* ICG alone cohort, all others ICG:HSA

- Pathologic status of NIR+ regional LNs is consistent with that of other regional LNs
- Metastatic LNs were found only en bloc with the esophageal specimen
This is the first study to examine lymphatic mapping of regional LNs in esophageal cancer using intra-operative minimally invasive NIR imaging.

- NIR imaging is safe and feasible in esophageal cancer.
- Distribution of NIR+ LNs appears to mimic known LN metastatic patterns.

Targeted NIR-guided removal of tumor-associated nodes may serve as a minimally invasive staging tool and assist in adequate nodal sampling during lymphadenectomy.
Future Directions

- **Optimize NIR imaging of local LNs:**
  - dose de-escalation to minimize background

- **Other innovative imaging techniques for nodal assessment**
Thank you