Use of a cathepsin-activatable fluorescent agent to rapidly distinguish tumor versus normal tissue in multiple tumor types

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Background

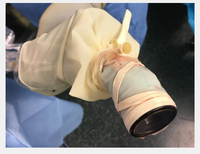
- Obtaining tumor free specimen margins is critical for most surgical oncology procedures
  - Frozen sections are slow and not feasible for many procedures
- Tools are needed for accurate, real time identification of residual tumor during cancer surgery
- We assessed the LUM2.6 Imaging System and the, cathepsin-activatable fluorescent dye, LUM015 for distinguishing tumor from normal tissue in a variety of tumor types

Methods

I. Sarcoma and Breast Pilot Study[1] performed at Duke University Medical Center
   - Dose (0.5, 1.0, 1.5 mg/kg LUM015) and time point study
   - Specimen were imaged ex vivo; areas of high signal were compared to standard histopathology

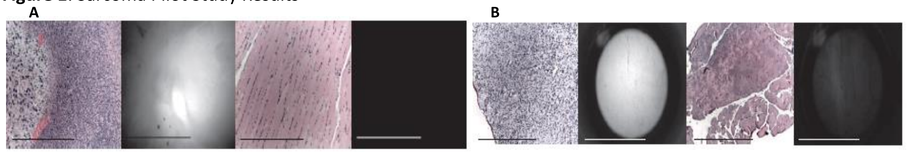
II. Breast Feasibility Study performed at the Massachusetts General Hospital (MGH)
   - Injection with LUM015 at 1.0 mg/kg 4±2 hours prior to surgery
   - Breast lumpectomy cavity walls were imaged in vivo and breast specimens examined ex vivo
     - In vivo areas of high signal were identified and excised
     - In vivo and ex vivo areas of fluorescent signal were compared with standard histopathology

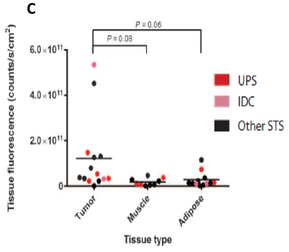
III. GI Feasibility Study[2,3] performed at MGH
   - Injection with LUM015 at 0.5, 1.0 and 1.5 mg/kg 4±2 hours prior to resection
   - Esophageal, pancreatic and colorectal cancers were imaged with the LUM system ex vivo



Results

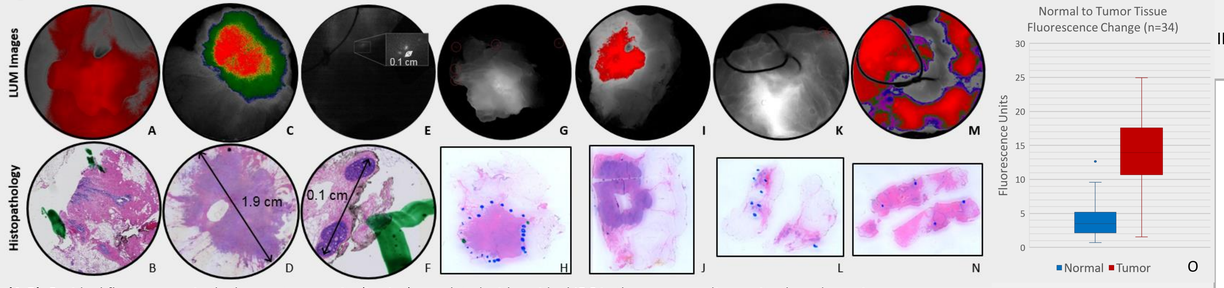
Figure 1: Sarcoma Pilot Study Results[1]





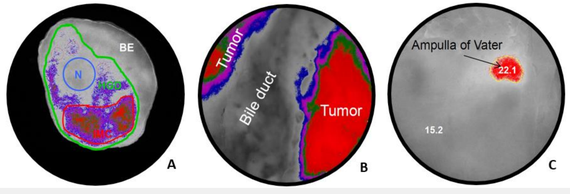
(A-B): Representative human subjects with UPS of the thigh (A) and myxofibrosarcoma of the thigh (B). From left to right: H&E histology of imaged tumor tissue, fluorescence image of tumor tissue obtained with the LUM device, H&E staining of imaged normal muscle, fluorescence image of normal muscle obtained with the LUM device.
(C): Distribution of tumor, normal muscle, and adipose tissue fluorescence across all patients from Pilot study.

Figure 2: Breast Feasibility Results



(A-B): Residual fluorescence in the lumpectomy cavity (in vivo) correlated with residual IDC in the corresponding cavity shaved margin
(C-D): High fluorescence in a 1.9 cm region from an ex vivo lumpectomy transection correlated with tumor configuration on histopathology
(E-F): Two sub-millimeter spots of high fluorescence separated by 0.1 cm identified by an ex vivo LUM image corresponded to 2 foci of DCIS
(G-H): High fluorescence in a 0.9cm region from an ex vivo lumpectomy transection correlated with IDC configuration on histopathology
(I-J): High fluorescence in a 1.3cm region from an ex vivo lumpectomy transection correlated with IDC and DCIS with prominent lymphocytic infiltrate on pathology
(K-L): Ex vivo image of the marginal side of a shaved cavity margin with correlated with DCIS, necrosis, calcifications and cancerization of lobules
(M-N): Ex vivo image of the marginal side of a shaved cavity margin with correlated with DCIS (spanning up to 0.7cm) , necrosis and calcifications
(O): Normal and Tumor fluorescence histogram measured from ex vivo lumpectomy transection LUM images

Figure 3: GI Feasibility Preliminary Results[2,3]



(A): Ex vivo LUM image of esophageal nodule. Comparison with histopathology revealed outlined areas, BE: Barrett's Esophagus. HGD: High Grade Dysplasia. IMC: Intramucosal Carcinoma. N: Nodule
(B): Ex vivo image of an uninvolved bile duct surrounded by pancreatic adenocarcinoma mass
(C): Ex vivo image of pancreatic carcinoma protruding through Ampulla of Vater in a background of normal small intestinal mucosa

I. Sarcoma: tumor (T) was distinguished from normal tissue (N) for multiple histologies (Figure 1)[1]
   - Malignant cancers were visualized (peripheral nerve sheath tumor, metastatic clear cell sarcoma, spindle cell carcinoma, myxofibrosarcoma, myxoinflammatory fibroblastic sarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma (UPS) and well differentiated liposarcoma)
   - T:N ratio was on average 4.3 ± 2.4 after 17.9 hours (n=12)

II. Breast: (Figure 2[‡])
   - Invasive ductal (IDC), invasive lobular (ILC) and ductal carcinoma in situ (DCIS) lesions were distinguished from surrounding normal tissue
   - T:N ratio was on average 4.3 ± 3.2 after 4.6 hours (n=34)
   - The LUM Imaging System correctly predicted residual tumor in 8 of 8 patients with positive margins on standard histopathology (6 true positives and 2 true negatives)
   - No positive margins containing invasive tumor or DCIS were missed by the LUM Imaging System

III. GI: preliminary evidence is promising (Figure 3[‡])[2,3]

[‡]LUM Imaging software reports high fluorescence with multicolored signaling. Ex vivo images may not have LUM System signaling as thresholding differs from in vivo

Conclusions

- **The LUM Imaging System can distinguish tumor from normal tissue in a wide variety of carcinomas and sarcomas.**
- The 2.6 cm diameter field and image acquisition in 1 second allows rapid assessment of a large specimen or in vivo surgical bed.
- Further clinical trials are underway to assess the ability of the LUM Imaging System to reduce positive margin rates in breast cancer lumpectomies compared with standard surgery (NCT03321929)
- Additional studies are under way to assess the performance of the LUM Imaging System in a variety of GI tumor types (NCT02584244)

References

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