Nanotechnology Enabled Image Guided Therapeutics in Lung Cancer

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Personalizing Cancer Medicine in 2015

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Lung Cancer

• Lung cancer remains the leading cause of cancer death in the Western world

• Early detection is key to improved survival

• The detection rate of early-stage lung cancer is anticipated to increase with the introduction of CT screening
Lung Cancer – New Problems

• How can we efficiently localize small lung cancer during MIS?

• What are other minimally invasive therapeutic options for high risk pts with lung cancer?

2009 2011 2012
Diagnostic Approach to Pulmonary Nodules

• Minimally Invasive Biopsy
  • Bronchoscopic biopsy
  • CT guided FNA

• Surgical biopsy
  • VATS
  • Thoracotomy
Bronchoscopic Biopsy

- Transbronchial biopsy

- EBUS-GS

- Electromagnetic Guidance

- Virtual Navigation
VATS (Video-assisted thoracoscopic surgery)

• Procedure of choice for surgical biopsy of peripheral pulmonary nodule

• Limitation
  • Identification of the nodule
  • Lack of digital palpation in small, non-solid deep nodules
  • May require conversion to thoracotomy
Localizing Techniques - VATS

• Intraoperative imaging
  • CT
  • Thoracic ultrasound

• Preoperative CT guided marking
  • Liquid material (contrast media, colored adhesive agents, dyes)
  • Radionuclides
  • Wires (hookwires, microcoils)

• Preoperative bronchoscopic marking
  • Dye
  • Fiducials

Radiology 2002; 225: 511-518
Wire Localization - Microcoil Localization

73/75 (97%) 4-24-mm nodules successfully removed low rate of intervention (3%) for procedural complications

Radiology 2009; 250: 576-585
Microcoil Localization

1. CT guided micro coil placement
2. VATS microcoil detection
3. Fluoroscopy guided VATS wedge resection
4. Confirmation of microcoil
Microcoil Localization – Toronto Experience

• First case October 2008
• 64 cases
• Complete resection with VATS in 62/64 cases (97%)
• 100% diagnostic yield
GTx (Guided Therapeutics) Program
GTx Surgery Overview

TRIGOR = Translation Research Image Guided OR
TRIGOR A Capabilities

Cone-Beam CT

Dual Source- Dual Energy CT

MIS, Endoscopic Technology
TRIGOR A - GTx OR
Multi-Modality Surgical Guidance

Pre-Operative Imaging

Intraoperative CBCT

Surgical Tool Tracking

Surgical Planning

Optical Imaging

Intraoperative localization

Image assistance during MIS/Robotic Surgery

Real time monitoring of minimally invasive thoracic intervention
Optical Surgical Navigation

1. Preoperative CT imaging
2. Cone-beam CT nodule localization
3. Image registration with surgical navigation

Pre-Operative Imaging
Intraoperative CBCT
Surgical Tool Tracking
GTx OR – Image guided Transbronchial Interventions
GTx OR – VATS localization
ICG and Near Infrared (NIR) Imaging

Indocyanine green

![Indocyanine green molecule](image)

M.W: 775

![Molar extinction coefficient graph](image)

Surv Ophthalmol, 2000

NIR thoracoscope

SPY scope, Novadaq Technologies™
ICG - SPY Localization
Image-guided Localization Platform for Minimally Invasive Lung Cancer Surgery
Multi-modal liposomal nanoparticle (C800) - ICG Liposome

The phospholipid nanoparticle, coated with polyethylene glycol, encapsulates ICG and CT contrast (iohexol, labelled IOX).

The prolonged intravascular half-life allows for longitudinal CT and NIR imaging.
Administered CF800 continuously remains in both vasculature and the tumor in a rabbit, allowing for successful 3D reconstruction even at 3 days post injection.
NIR imaging of Lung Cancer

4 days post-injection of CF800
Ultra-minimally Invasive multi-modal image guided phothermal ablation of lung cancer
Porphysomes: Liposomes like bilayer porphyrin-phospholipid

Porphysome nanovesicles generated by porphyrin bilayers for use as multimodal biophotonic contrast agents

Jonathan F. Lovell\textsuperscript{1,2}, Cheng S. Jin\textsuperscript{1,2}, Elizabeth Huynh\textsuperscript{2,3}, Honglin Jin\textsuperscript{2,3}, Chulhong Kim\textsuperscript{4}, John L. Rubinstein\textsuperscript{3,5}, Warren C. W. Chan\textsuperscript{1}, Weiguo Cao\textsuperscript{6}, Lihong V. Wang\textsuperscript{4} and Gang Zheng\textsuperscript{1,2,3, *}

Works as both fluorophore and photo-enhancer
EPR effect; Enhanced Permeability and Retention Effect

Cancer vasculature

Normal vasculature

Porphyrome distribution in Orthotopic lung cancer Xenograft models

A549

H460

H520

White-light Image

Maestro Fluorescence Image
Porphysome thermal effect on resected VX2 tumor tissue (ex-vivo)
Development of prototype bronchoscope for visualization of porphysome fluorescence

**Emission (bronchoscope side):**
- A long pass filter: 678-1000nm

**Exitation (light source side):**
- Red diode of 10 mW output
- A band-pass filter: 650-670nm
In-vivo model

Prototype fluorescence bronchoscope

WL  0 time  24hr  48hr
Experimental Design

Day 0

Bronchoscopic VX2 inoculation

Day 3

CT

Day 8

- Confirming Tumor growth by bronchoscope & Radial EBUS
- Systemic administration of porphysomes Fluorescent bronchoscope

Day 10

- Fluorescent bronchoscope & PTT

Tumor-growth

Bronchoscope  Radial-EBUS  Bronchoscope  Radial-EBUS
Porphysome enhanced transbronchial PTT

Laser Control

R160

Lung Slide

H&E staining

NADH staining

*Ablated area: < 2 mm diameter

Porphysome-PTT

R167

H&E Staining

NADH Staining

Ablated area: 6 mm x 5 mm

Ablated volume
Ultra-minimally invasive multi-modal image guided phothermal ablation of lung cancer
Summary

• Advances in nanotechnology and image guidance will enable intraoperative localization of small peripheral nodule and also assist surgeons during MIS

• New transbronchial ablation technologies are in development and can potentially be used for minimally invasive treatment of early stage lung cancer
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