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TITLE: Electromagnetic-Optical Coherence Tomography Guidance of Transbronchial Solitary Pulmonary Nodule Biopsy

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14. ABSTRACT

We present a novel high-resolution multimodality imaging platform utilizing CT and electromagnetic (EM) navigation for spatial guidance to targeted lung nodules, and OCT for microscopic volumetric imaging. The OCT optic fiber probe and EM sensor were incorporated into a single flexible catheter. The catheter was designed to be compatible with a custom peripheral transbronchial aspiration needle to enable both imaging and specimen collection. The EM sensor guides the catheter and biopsy needle to the spatial location of the pulmonary nodules and OCT images are obtained to microscopically assess the tissue.

15. SUBJECT TERMS

Electromagnetic Optical Coherence Tomography, Biopsy Guidance, Lung Cancer, Optical Microscopy

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1. INTRODUCTION

Lung cancer is the leading cause of cancer related death accounting for more deaths than breast, prostate and colon combined. Early diagnosis is critical to patient survival, however the vast majority of lung malignancies are detected only once symptoms arise and the cancer has spread, at which time patients have little chance of cure. Macroscopic imaging modalities including CT and bronchoscopy have made significant strides in increasing early detection, however they do not have the required specificity to diagnose malignancy. Diagnosis must be made on the microscopic level, which at present can only be accomplished with excisional biopsy. Unfortunately, low-risk bronchoscopic techniques for retrieving biopsy samples are hampered by low diagnostic yields, and trans-thoracic and surgical approaches carry higher intrinsic risk of complications. Given the very high false positive rates of these macroscopic imaging platforms it is imperative that high-risk procedures are avoided and the diagnostic accuracy of lower-risk approaches are greatly improved. In this proposal we aim to dramatically increase the diagnostic yield of low-risk bronchial biopsy using a novel multimodality electromagnetic and optical coherence tomography (EM-OCT) biopsy guidance platform to provide not only macroscopic spatial guidance to the lesion (using CT and EM) but to additionally confirm the needle placement within the lesion on the microscopic scale (OCT) ensuring that the needle is positioned within the target lesion prior to biopsy acquisition. Specifically we will (Aim 1) develop and fabricate an EM-OCT catheter, rotary junction and system software to facilitate real-time 3D imaging of, and navigation to, SPN for transbronchial biopsy, and (Aim 2) conduct a preclinical study to demonstrate the feasibility of EM-OCT biopsy guidance of artificial SPN (aSPN) in living swine.

2. KEYWORDS

Electromagnetic Navigation, Biopsy Guidance, Optical Microscopy, Optical Coherence Tomography, Lung Cancer, Optical needle.

3. OVERALL PROJECT SUMMARY

***Aim 1:* Develop and fabricate an EM-OCT catheter, rotary junction, and system software to facilitate real-time 3D imaging of, and navigation to, peripheral pulmonary lesions for transbronchial biopsy.**

Task 1: Construct and electro-optical rotary junction (months 1-6)

1a: Design and fabricate a high speed, high signal throughput optical rotary junction including electrical slip rings to convey the EM sensor information (months 1-6)

Completed

We successfully designed and fabricated an electro-optical rotary junction to maintain continuous optical and electrical connection between a rotating imaging catheter and the stationary EM-OCT system. We encountered issues relating to noise from cross-talk however, we were able to successfully overcome this by repositioning the DC motors at a greater distance from the electrical-optical rotating joint.

1b: Design and fabricate the rapid-connect joint to attach the EM-OCT catheter to the electro-optical rotary junction. (months 2-6)

Completed

We successfully designed and fabricated an elegant rapid-connect joint for the catheter.

Task 2: Design and construct EM-OCT catheters that are compatible with standard TBNA (months 3-9)

2a: Fabricate a number of optical imaging cores based on our existing ball lens design (month 3)

Completed

The optical parameters of our most recent EM-OCT catheters is as follows.

- *Current prototype optical parameters: ball lens radius: r_s=106 µm, r_t=136 µm; Focus length: f_s=791 µm, f_t=868 µm; Spot size: D_s=17.8 µm, D_t=16.5 µm; Polished angle: 41 degree; Optical length: 2070 mm; Output power: 29 mW*

2b: Assemble the EM-OCT catheter ensuring accurate sensor positioning distal to the imaging optics (month 4-9)

Completed

The inner core of the catheter consists of a fiber optical core together with the electrical wires for the positioning sensor, which are located within a torque coil. The optical ball lens and positioning sensor are located at the distal end of the catheter.

Although our developed prototypes met all the electrical-optical specifications, we encountered a number of issues relating to the clinical utility of the original catheter design with the needle causing damage to the catheter polyimide sheath. After a number of iterations we successfully overcame this design challenge and created the first clinically viable flexible transbronchial OCT needle catheter, and the first clinically viable flexible EM-OCT needle catheter.

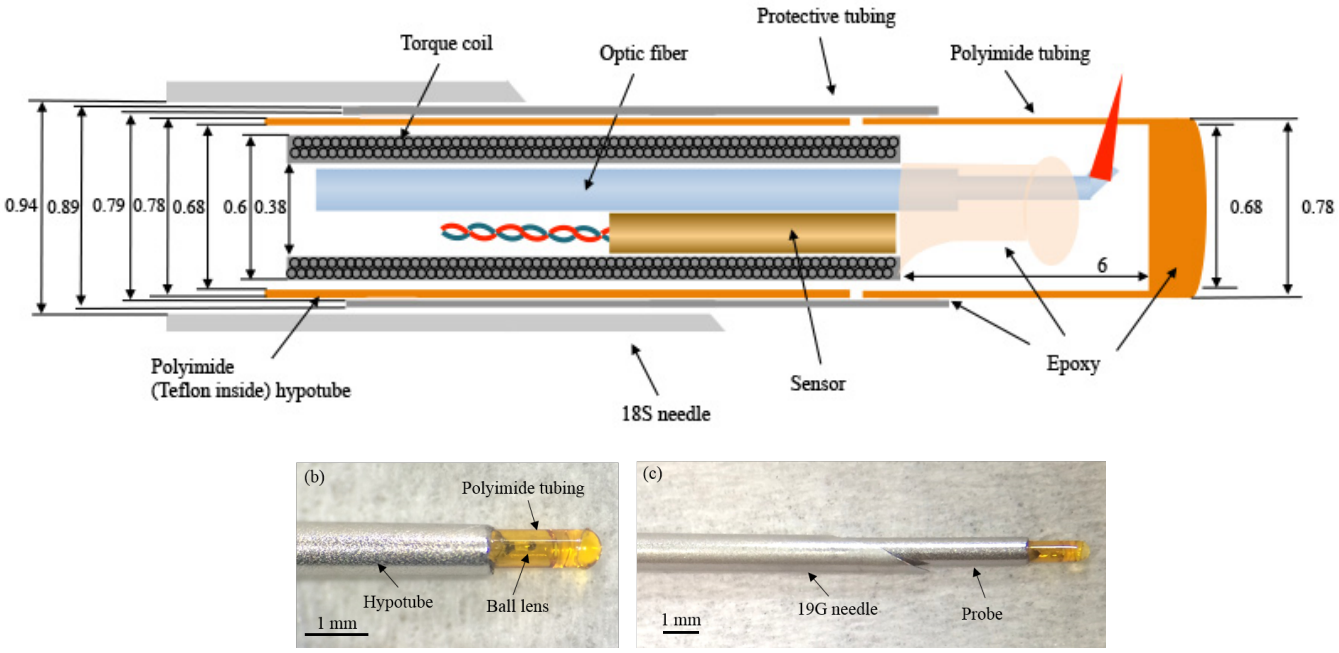
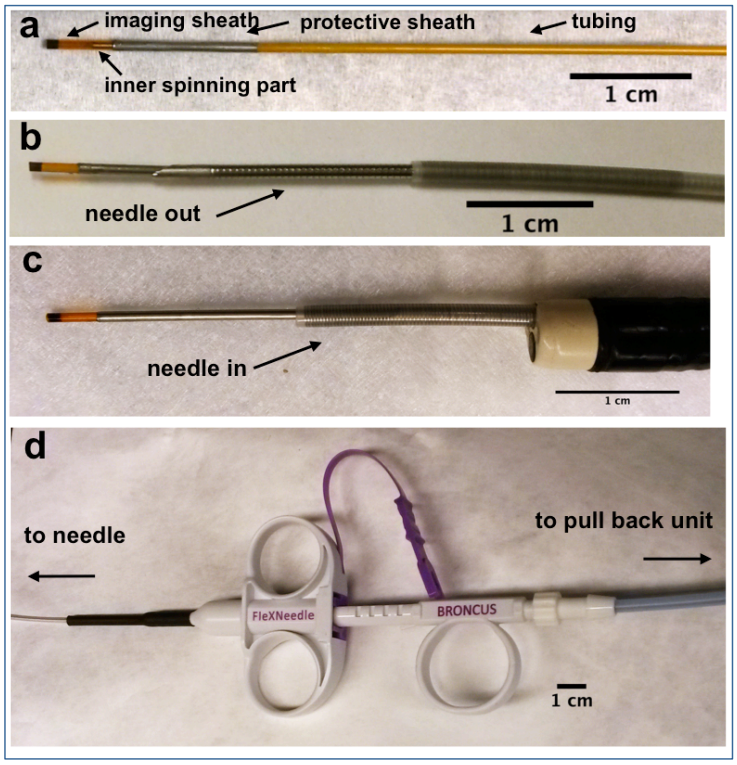


Figure: Schematic of EM-OCT probe design at the distal end, both the sensor and fiber optic probe were incorporated inside a double layer torque coil for rotational scanning. Stainless steel hypotube was used to protect the probe, and a sealed polyimide tubing was epoxied to hypotube as optical window. (b) Photograph of the distal end of the probe, the ball lens is visible through the polyimide tubing. (c) Photograph of the distal end of the probe inside 19G TBNA needle. (unit: mm)

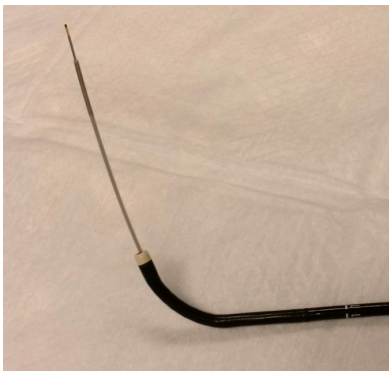


EM-OCT catheter including transbronchial needle aspiration (TBNA) and bronchoscope

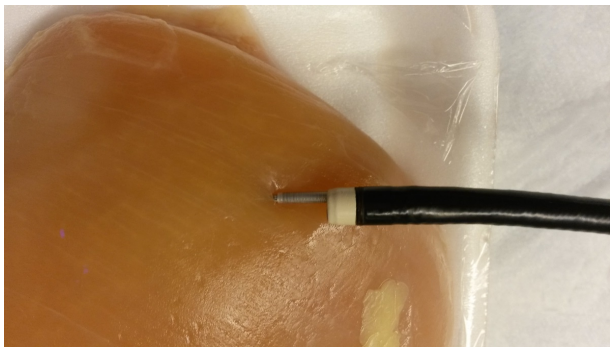
a) The EM-OCT catheter consists of the inner spinning part and the outer tubing's. At the distal end the transparent imaging sheath is connected to the protective sheath that prevents the needle to cut through the tubing. b) Photograph of catheter and pull back until including TBNA. b) The catheter inserted through the TBNA, with needle outside. c) The catheter inserted through the TBNA and bronchoscope, with needle inside. d) TBNA handle with the connection to the pull back unit.

2c: Test the optical and electrical performance and calibrate the precise optical viewing angle and EM sensor position for each catheter (month 4-9)

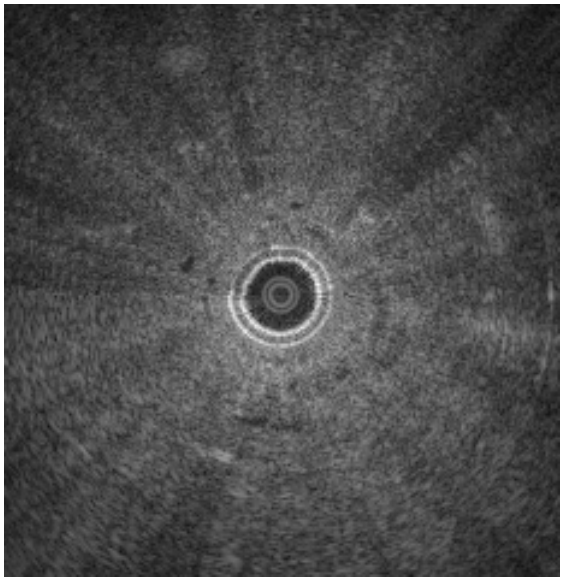
Completed



Photograph of the EM-OCT catheter extending out of the TBNA needle through the bronchoscope.

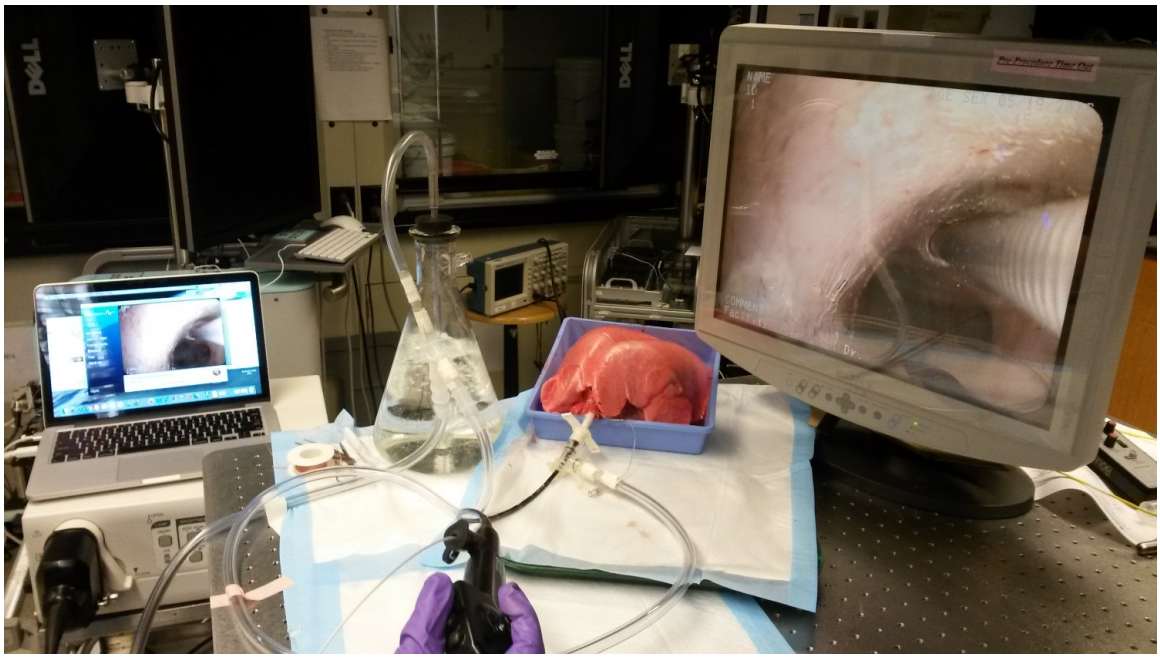


Testing the OCT image quality of the catheter in solid tissue

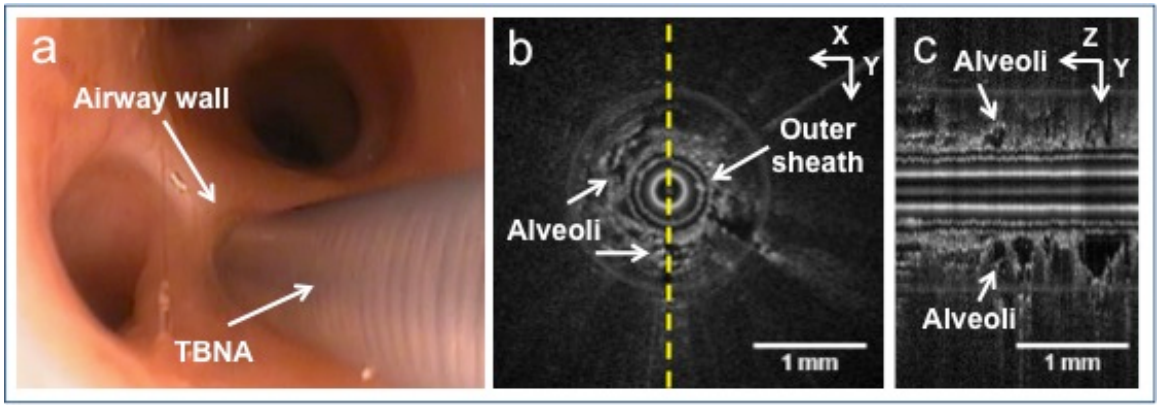


OCT image showing visualization of tissue structure (raw chicken breast to simulate solid pulmonary nodule)

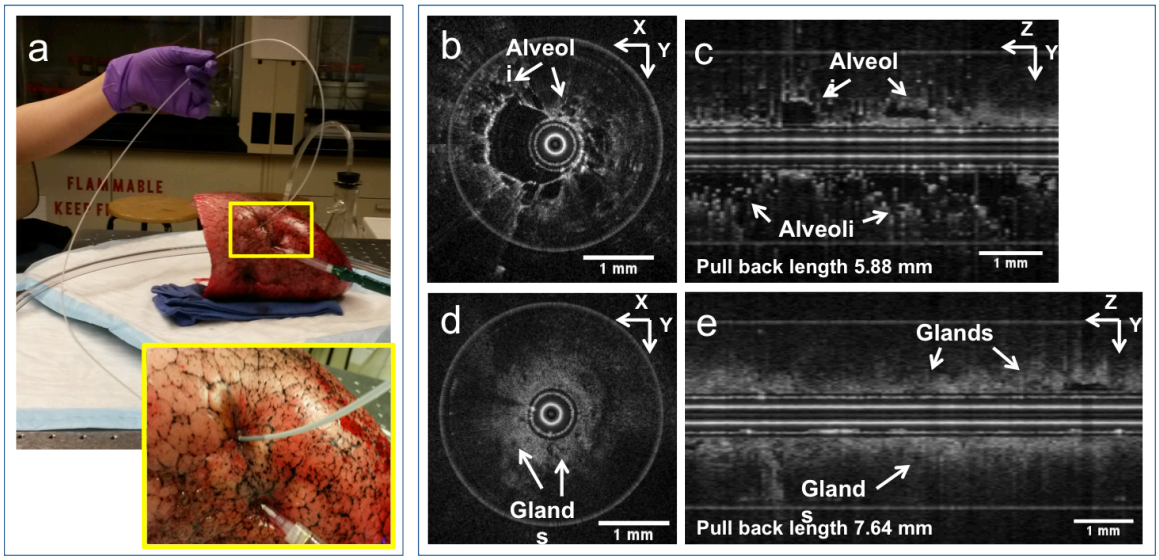
We subsequently conducted transbronchial tests of the EM-OCT catheter ex vivo swine and human lungs



Ex vivo testing of the EM-OCT catheter in inflated swine lungs ex vivo.



Ex-vivo swine lung, EM-OCT imaging through TBNA and airway wall *a) Endoscopic view of inflated swine lung ex-vivo of TBNA punctured through the airway wall in the lower lobe. b) According to a) obtained cross-sectional OCT image (3.44 x 3.25 mm) of lung tissue. Alveoli of the parenchyma tissue can be seen around the catheter. c) Longitudinal OCT image in the YZ plane (starting at the yellow dashed line) at pullback speed of 1 mm/s with a distance of 2.15 mm.*



Ex-vivo human lung, OCT imaging through TBNA in adenocarcinoma nodule *a) Photograph of inflated human lung (ex-vivo). Inset shows inflation site and TBNA puncturing through lung nodule. b) Cross-sectional OCT image of lung tissue. Alveoli's of the parenchyma tissue can be seen around the catheter. c) According to b) longitudinal OCT image in the YZ plane, pull back length of 5.88 mm. Arrows pointing at alveoli's typically seen in parenchyma tissues. d) Cross-sectional OCT image of adenocarcinoma nodule. e) According to d) longitudinal OCT image in the YZ plane, pull back length of 7.64 mm. Arrows pointing at visible glands typically seen in adenocarcinoms. Pullback speed of 1mm/s.*

EM testing

The measurement accuracy provided by NDI Medical is 1.2 mm in spatial position and 0.5° in orientation angle, both were root mean square (RMS) values. The measurement accuracy is better when the sensor is placed close to the center of tabletop field generator. Ferromagnetic materials within the measurement volume can also increase the measurement error. We measured the RMS values by placing the sensor in multiple positions within the measurement volume and recorded at least 300 data points for each position measurement. Our measurement results showed that the best position accuracy is as good as 0.01 mm in position and 0.01° in angle when the sensor is placed close to the field generator at center. The measurement accuracy deteriorates to 1.3 mm in position and 0.1° in angle when sensor was placed close to boundaries at top of the dome.

We also measured the position accuracy while moving the bare sensor with translational stage (Newport 423 series). The translational stage was ferromagnetic and was placed outside of field generator and sensor was mounted on an aluminum post for movement. The minimal movement step on the translational stage was 0.01 mm. We moved the sensor along X, Y, and Z axis separately and did the measurement accordingly. For each axis, we placed the sensor at two different spatial positions, and then moved the sensor in steps of 0.01, 0.05, 0.1 and 0.5 mm respectively. For each position, more than 300 data points were recorded for calculation. Table 1 shows the moving steps we set and the corresponding measured moving distances. We did manual adjustment on the translational stage, the error between the ideal set moving step and the measured movement is up to 0.021 mm.

Table 1. Characterization of spatial positions

Move with X(mm)			Move with Y(mm)			Move with Z(mm)		
Set	x=18.81, y=-43.69, z=-150.55	x=183.05, y=-43.25, z=-149.15	Set	x=9.91, y=-12.66, z=-150.34	x=10.92, y=-281.09, z=-147.37	Set	x=-19.05, y=-33.67, z=-155.92	x=-19.61, y=-36.18, z=-303.57
0.01	0.009 ±0.008	0.007 ±0.012	0.01	0.01 ±0.006	0.011 ±0.013	0.01	0.010 ±0.008	0.010 ±0.037
0.05	0.050 ±0.007	0.049 ±0.011	0.05	0.047 ±0.006	0.045 ±0.014	0.05	0.053 ±0.008	0.054 ±0.041
0.1	0.104 ±0.007	0.100 ±0.011	0.1	0.097 ±0.006	0.094 ±0.007	0.1	0.102 ±0.009	0.100 ±0.037
0.5	0.504 ±0.007	0.499 ±0.011	0.5	0.495 ±0.006	NA	0.5	0.521 ±0.009	0.516 ±0.036

The angle accuracy was calculated by measuring relative rotation angle. An angle rotation mount (Thorlabs CRM1) was used to mount a bare sensor, the minimal rotation angle step on the rotator was 2°. We rotated the mount with step rotation of 2° and 10° respectively, the sensor was placed close to position x = -55.41 mm, y = -48.08 mm, z = -228.37 mm. The rotation angle was calculated as the relative angle difference between measured angle and angle at initial position. The measured results are shown in table 2. The error between set rotation angle and the measured rotation is up to 0.21° including the error caused by manually moving the rotation mount.

Table 2. Characterization of orientation angle in XY plane

Set rotation (degree)	**Measured (degree)**	**Set rotation (degree)**	**Measured (degree)**
2	1.91 ± 0.004	10	10.02 ± 0.002
4	3.88 ± 0.003	20	20.02 ± 0.002
6	5.94 ± 0.003	30	30.05 ± 0.003
8	7.92 ± 0.004	40	40.13 ± 0.003
10	9.80 ± 0.004	50	50.17 ± 0.003
12	11.79 ± 0.003	60	59.81 ± 0.003
14	14.00 ± 0.003	70	69.83 ± 0.003
16	15.90 ± 0.004	80	79.87 ± 0.002

We also measured the accuracy after assembling the sensor into the catheter, and compared the measurement accuracy while placing the EM-OCT probe at multiple steady positions, and compared with a bare sensor used as above. Table 3 shows the measurement error of a bare sensor and EM-OCT probes close to spatial position of x = 15.3 mm, y = 121.1 mm, and z = 184.8 mm. We found assembling the sensor into the catheter and connecting the catheter to hybrid rotary junction did not influence the measurement accuracy. The measured accuracy in position and angle by EM-OCT probe is comparable to a bare sensor.

Table 3. Measurement error of EM-OCT probes compared to a bare sensor

	Bare sensor	*EM-OCT probe (non-spinning)*	*EM-OCT probe (spinning)*	*EM-OCT needle probe (non-spinning)*
X	*0.006*	*0.012*	*0.016*	*0.011*
Y	*0.007*	*0.012*	*0.021*	*0.012*
Z	*0.012*	*0.017*	*0.026*	*0.026*
Pitch	*0.007*	*0.008*	*0.008*	*0.008*
Yaw	*0.005*	*0.005*	*0.013*	*0.013*

Task 3: Design and develop navigational software to provide real time tracking of the catheter position within the tracheobronchial tree (months 6-18)

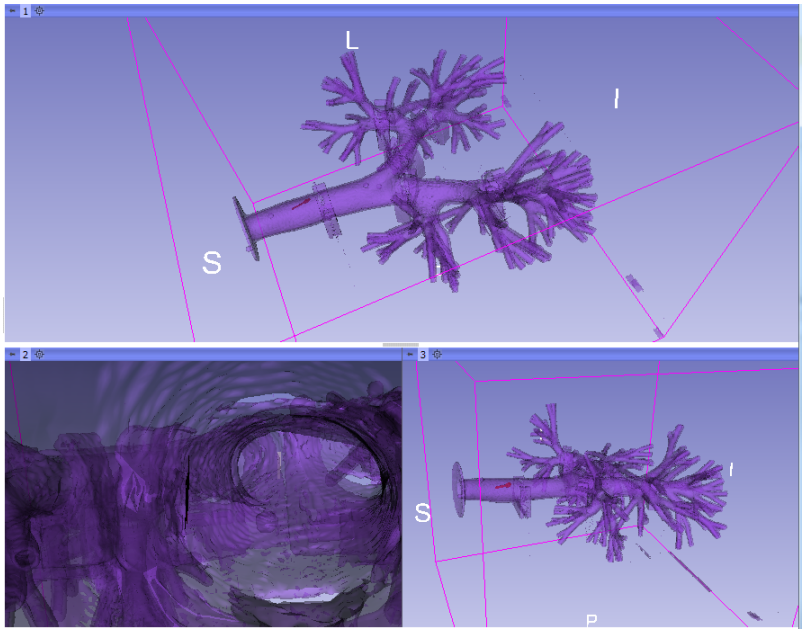
3a: Modify an existing OCT system to simultaneously record the catheter position data associated with each OCT image axial depth profile (month 6-7)

Completed

We synchronized two separate systems to ensure that we can maintain the necessary write speeds for both modalities. The OCT system sends a trigger to the Aurora Tracking system to commence saving and control of the EM-OCT catheter scanning. Software has been modified to display the position of the sensor within the tracheobronchial tree in real time.

3b: Modify existing electromagnetic navigation software to track the catheter position within the tracheobronchial tree using in real time (month 6-10)

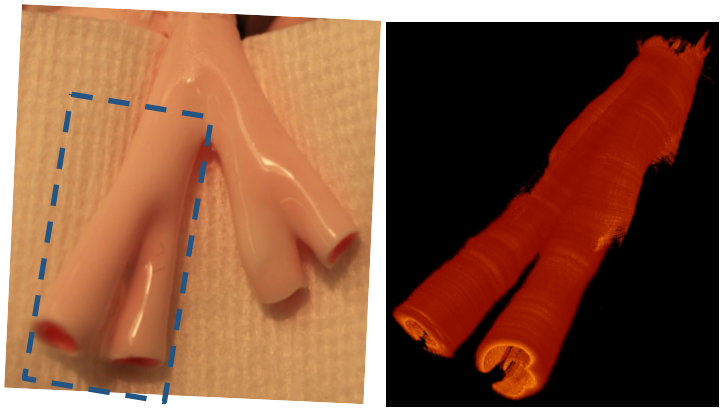
Completed



We have written software to track the sensor/catheter position within the 3D volume (rendered from CT) in real-time. Cursors show the position of the catheter.

3c: Develop software to construct multi-modality CT and OCT images of the airways using the registered datasets to provide a synergistic description of the lung and tumor environment and to precisely localize biopsy acquisition location. (month 6-18)

Completed



We have successfully used the EM information to perform accurate 3D renderings of the OCT images (see images above). However, we have not yet constructed multi-modality images.

<u>Aim 2:</u> Conduct a preclinical study to demonstrate feasibility of EM-OCT biopsy guidance of artificial SPN (aSPN) in living swine (n=6).

<u>Task 4: Validation and refinement of catheter tracking within fixed lungs</u>

Completed

Rather than using fixed lungs that would degrade over time, we elected to do our testing using a rubber airway phantom. We performed the EM navigated OCT imaging in the airway phantom. The figure below is a photograph of the experimental set-up. The airway phantom with the fiducial markers were placed on top of tabletop field generator. Both the airway phantom and sensor were registered with the virtual volume model and virtual sensor respectively by following steps described in section 2.4. The probe was placed inside the airway phantom and connected to both EM system and OCT systems in the proximal. There was 7 mm offset between the optical beam and the sensor and was compensated in the navigation software. Both the EM navigation and OCT imaging were updated in real-time. The volume model on Slicer was set with transparency of 0.6 so that the sensor model can be visualize through the airway. The navigation screen was recorded by screen recorder (Camstasia Recorder 8, TechSmith) at the same time when saving OCT raw data.

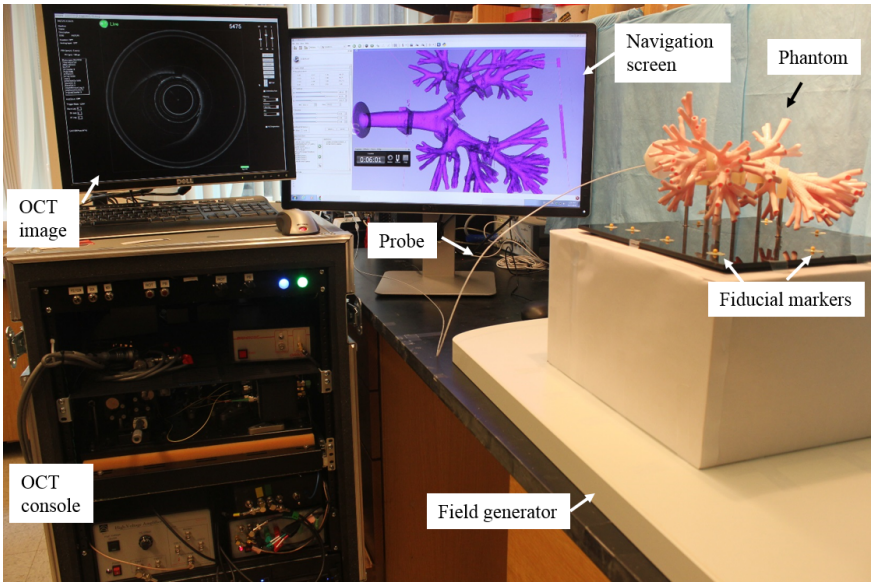


Figure: Experimental set-up. Airway phantom was placed on top of tabletop filed generator. The endobronchial EM-OCT probe was placed within the lung phantom and connects to EM system and OCT

system in the proximal. EM navigation and OCT imaging are running simultaneously on two different screens.

At each fiducial marker location as determined by the EM navigation, all the markers were additionally visible by OCT. As expected we found that the sensor was sensitive to fast movement or spinning of the catehter which caused a loss of EM signal, thus navigation to targets were performed prior to spinning the OCT catheter.

Task 5: Conduct swine studies to demonstrate the feasibility of EM-OCT transbronchial biopsy guidance and to determine the potential increase in the diagnostic yield over conventional biopsy approaches.

Incomplete

Though we did not complete the final step of this project during the award period, Dr Suter and her team are committed to completing the proposed preclinical studies using discretionary funds in the coming months.

4. KEY RESEARCH ACCOMPLISHMENTS

- *Developed the first clinical viable transbronchial OCT catheters.*
    - *Provided proof of principle of the design in ex vivo swine and human lungs*
- *Developed the first clinically viable endobronchial and transbronchial EM-OCT catheters to provide global macroscopic electromagnetic navigation to targeted regions in the lung in addition to local microscopic OCT confirmation of location (ie catheter residing in nodule).*
    - *Provided proof of principle in phantom lungs.*

5. CONCLUSION

We have accomplished many of the milestones outlined above for this research proposal. Though we have run into a number of challenges with the mechanical properties as outlined in this report we expect to complete the remaining tasks within the remaining months of this award under no cost extension.

Our objective is to develop, test and validate an EM-OCT biopsy guidance platform that is compatible with standard bronchoscopy techniques and greatly increases the diagnostic yield of bronchial biopsy. This objective is in line with the following LCRP Area of Emphasis: ***"Identification or development of non-invasive or minimally invasive tools to improve detection of the initial stages of lung cancer."*** *Increasing the diagnostic yield of transbronchial biopsy approaches may reduce the number of high-risk surgical diagnostic procedures performed, and when coupled with CT screening may increase the early detection of lung cancer.*

Specifically we envision that following the identification and gross localization of a nodule by CT, a low-risk transbronchial biopsy will be acquired for diagnosis using EM-OCT guidance rather than a higher-risk transthoracic or surgical diagnostic procedure. The EM-OCT biopsy guidance platform will (1) provide spatial guidance to the lesion through real-time tracking the location of the biopsy needle within the lung using the previously reconstructed CT roadmap of the tracheobronchial tree, and (2) will provide microscopic OCT guidance to ensure that the needle is positioned within the lesion prior to biopsy acquisition.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS

Abstract/Oral Presentations:

1. Wang Y, Jagadeesan J, Adams DC, Miller AJ, Hariri LP, Vosburg K, Suter MJ. Electromagnetic optical coherence tomography for assessment of the pulmonary airways. SPIE Photonics West; 2014 February, San Francisco, CA USA: 8927-41.

2. Wang Y, Shishkov M, Vosburgh KG, Hariri LP, Adams DC, Miller AJ, San-Jose Estepar R, Lanuti M, Bouma BE, Suter MJ. Electromagnetic optical coherence tomography guided needle biopsy of lung nodules. SPIE Photonics West; 2015 February, San Francisco, CA, USA: 9304-120.
3. Holz JA, Wang Y, Shishkov M, Adams DC, Hariri LP, Channick CL, Keyes CM, Lanuti M, Suter MJ. Needle catheter optical coherence tomography in lung tissue. SPIE Photonics West; 2016 February, San Francisco, CA, USA: 9691-51

7. INVENTIONS, PATENTS AND LICENSES

Nothing to report.

8. REPORTABLE OUTCOMES

Nothing to report.

9. OTHER ACHIEVEMENTS

Nothing to report.

10. REFERENCES

None.

11. APPENDICES

None.