Bronchoscopic Laser Ablation of Solid Peripheral Lung Tumors followed by Surgical Resection (BLAST-SR Trial)

Background and Rationale

[redacted]

[redacted]

[redacted]

Study Objectives

Primary objective

1. To assess the pathologic changes that result from bronchoscopic laser ablation of peripheral lung tumors focusing on the degree of tumor ablation which will be categorized as complete, quasi-complete, or incomplete.

Secondary Objectives

2a. To assess the safety of this technique by describing both procedure-related complications such as bleeding or pneumothorax and post-procedure adverse effects such as fever or pneumonitis.

2b. To assess the pathologic changes observed in the lung tissue surrounding the treated lung tumor.

2c. To assess radiographic changes observed by cone-beam CT immediately after the application of bronchoscopic laser ablation.

DESIGN AND PROCEDURE

Overall Study Description

[redacted]

[redacted]

Study Design

This is a prospective observational pilot study in which patients with peripheral lung tumors will undergo bronchoscopic laser ablation followed by surgical resection and pathologic evaluation of ablative changes.

Study Setting

The University of Texas MD Anderson Cancer Center.

Study Population

Inclusion Criteria:

- Written informed consent
- Performance status 0-2 (Eastern Cooperative Oncology Group classification)
- ≥ 18 years old
- Subject is considered a candidate for bronchoscopy
- Subject is considered a candidate for surgery (either lobar or sub-lobar resection) based on radiographic staging and functional evaluation

- Lung lesion that is either biopsy-proven cancer or is suspicious for cancer
- Both non-small cell lung cancer (including carcinoid tumors) and metastatic disease
- The lesions should be: ≤ 3 cm, located in the outer 2/3 of the lung, and leave ≥1 cm of tumor-free lung parenchyma between target tumor and pleura or fissure

Exclusion Criteria:

- Tumors greater than 3 cm, located in the inner 1/3 of the lung, invading a major vessel, or located < 1 cm from the pleural or fissure
- Tumors qualified as non-resectable
- Tumors that cannot be reached bronchoscopically
- Patients declared non-surgical candidates
- Patients who are not candidates for bronchoscopy
- Patients with lung cancer who are found to have N2-3 disease
- Patient with lung metastases who are found to have any malignant mediastinal lymph node
- Patients in which the target lesion is confirmed as benign or small cell lung cancer
- Patients without a prior diagnosis of the target lesion whose diagnosis cannot be made during bronchoscopy
- Patients who have received chemotherapy within 60 days prior to bronchoscopic laser ablation
- Patients who were previously treated for the target lesion
- Pregnant patients

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Statistical Considerations and Sample Size Justification

The primary outcome of the trail will be the pathologic changes that result from bronchoscopic laser ablation of peripheral lung tumors, and will be categorized into three groups: 1. Complete Ablation: absence of staining (MAB 1273 or NADH, or both) of tumor cells. 2. Quasi-Complete Ablation: positive staining of ≤10% of tumor cells. 3. Incomplete ablation: positive staining in > 10% of tumor cells. The secondary outcomes include the safety of this ablative procedure which will be measured by serious adverse effects (SAE), defined as pneumothorax requiring chest tube, bleeding requiring balloon tamponade or leading to respiratory failure, and hypoxemia (SpaO2 < 90% for > 1 min) during bronchoscopy, post-bronchoscopy pneumonitis with need of supplemental oxygen., as well as pathologic changes observed in the lung tissue surrounding the treated lung tumor, and radiographic changes observed by cone-beam CT immediately after the application of bronchoscopic laser ablation.

Only patients who undergo bronchoscopic tumor ablation will be included in the analysis.

We will conduct extensive descriptive analyses of the data collected. We will calculate the appropriate summary statistics and 90% confidence intervals (CIs) for the measures of interest described in primary and secondary objectives. For example, we will obtain frequencies and proportions of the three tumor ablation outcome categories (complete, quasi-complete, and incomplete) for the primary objective, and record the number of each type of SAE at each level of laser power. Our goal is to simply assess the magnitude and obtain preliminary estimates of this technique to proceed to our next project which is the development of a large multicenter randomized trial comparing the effectiveness of this new bronchoscopic laser ablative technique vs. the standard of care for these patients, SBRT, in patients with medically inoperable early lung cancer.

Sample Size Justification. This is a pilot trial to assess whether a new technique can be delivered safely to humans and provide complete ablation of lung tumors, and is not powered for significance in statistical comparison as there is insufficient existing evidence to predict the likely outcomes. A total of 15 patients will be recruited from UT MD Anderson Cancer Center. With this sample size, the 90% confidence interval for an expected 70% of complete ablation rate can be estimated with a maximum width of 0.195. This power was based on nQuery Advisor.

Toxicity Monitoring

We will monitor patients for unacceptable toxicity in cohorts of size 5 [11]. An unacceptable toxicity in this study is defined as pneumothorax requiring chest tube, bleeding requiring balloon tamponade or leading to respiratory failure, and hypoxemia (SpaO2 <90% for > 1 min) during bronchoscopy, post-bronchoscopy pneumonitis with need of supplemental oxygen.

If we find $\Pr[\pi_T > 0.3 \mid \text{data}] > 0.85$, where π_T is the true proportion of patients who experience unacceptable toxicities and follows a beta(0.6, 1.4) distribution, we will stop the trial for toxicity.

The stopping boundaries for toxicity are found in Table 1. Table 2 shows the operating characteristics for this design. The stopping boundaries and operating characteristics were created based upon 1,000 simulations using Multc Lean Desktop V2.1.

[redacted]

Other Considerations

[redacted]

[redacted]

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017 Jan;67(1):7-30.

2. Gould MK, Tang T, Liu IL, Lee J, Zheng C, Danforth KN, Kosco AE, Di Fiore JL, Suh DE. Recent Trends in the Identification of Incidental Pulmonary Nodules. Am J Respir Crit Care Med. 2015 Nov 15;192(10):1208-14.

3. Berman AT, Thukral AD, Hwang WT, Solin LJ, Vapiwala N. Incidence and patterns of distant metastases for patients with early-stage breast cancer after breast conservation treatment. Clin Breast Cancer 2013 Apr;13(2):88-94.

4. Boily G, Filion E, Rakovich G, et al. Stereotactic Ablative Radiation Therapy for the Treatment of Early-stage Non-Small-Cell Lung Cancer: CEPO Review and Recommendations. J Thorac Oncol. 2015;10:872-882.

5. Cornwell LD, Echeverria AE, Samuelian J, **Casal RF**, Bakaeen FG, Omer S, Preventza O, Mai W, Chen G, Simpson KH, Moghanaki D, Zhu AW. Video-assisted thoracoscopic lobectomy is associated with greater recurrence-free survival than stereotactic body radiotherapy for clinical stage I lung cancer. J Thorac Cardiovasc Surg. 2017 Aug 16. doi: 10.1016/j.jtcvs.2017.07.065. [Epub ahead of print]

6. **Casal RF**, Tam AL, Eapen GA. Radiofrequency ablation of lung tumors. Clin Chest Med. 2010 Mar;31(1):151-63

7. Jahangeer S, Forde P, Soden D, Hinchion J. Review of current thermal ablation treatment for lung cancer and the potential of electrochemotherapy as a means for treatment of lung tumours. Cancer Treat Rev. 2013 Dec;39(8):862-71.

8. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-Analysis of Guided Bronchoscopy for the Evaluation of the Pulmonary Nodule. Chest 2012 Aug;142(2):385-393.

9. Khemasuwan D, Mehta AC, Wang KP. Past, present, and future of endobronchial laser photoresection. J Thorac Dis. 2015 Dec;7(Suppl 4):S380-8.

10. **Casal RF**, Walsh G, McArthur M, Hill L, et al. Bronchoscopic Laser Interstitial Thermal Therapy (BLITT): An Experimental Study in Normal Porcine Lung Parenchyma. Journal of Bronchology and Interventional Pulmonology 2018 (in-press)

11. Thall PF, Simon RM, Estey, EH. (1995). Bayesian Sequential Monitoring Designs for Single-Arm Clinical Trials with Multiple Outcomes. Statistics in Medicine 14: 357-379.