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Clinical Trial NCT03735095

Endobronchial Ultrasound Transbronchial Needle guided Interstitial Photodynamic Therapy for Palliation of Locally Advanced Lung Cancer and Advanced Cancers Obstructing the Airway -Phase I/IIa Study

Study Key Investigators:

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Assistant Professor Clinical Oncology

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Director of Photodynamic Therapy Clinical Research
Professor of Oncology

What is Photodynamic Therapy?

Photodynamic therapy involves a light activated medicine called a photosensitizer; a light source (usually a laser) and oxygen. The photosensitizer is given at a set time before the treatment, usually 48 hours. The laser light is used to activate the photosensitizer that reacts with oxygen to trigger a cascade of events that result in a generation of reactive oxygen species that causes tumor cell death. This cell death can also cause immune system activation, which may help to prime the immune system against the cancer.

Conventional photodynamic therapy involves shining a light in the lumen of the airway. Usually, we do this with a cylindrical diffuser, which makes a cylindrical ray of light in all directions. This is the usual way that photodynamic therapy is delivered, but it does not work as well when the tumor is underneath normal tissue but still causing airway blockage, or when the tumor is so large that it is greater than a 0.5 cm in depth. In this case we use interstitial photodynamic therapy that involves insertion of the cylindrical diffuser laser fiber directly into the tumor, to illuminate the tumor from the inside. This method can be used to treat large tumors and is termed interstitial PDT or I-PDT.

How we choose a specific photosensitizer for this study?

In this study we chose to use a photosensitizer (Photofrin®) that has been approved to treat cancerous tumors. We decided to use Photofrin® for several reasons. Photofrin® PDT is currently FDA approved for treating esophageal cancer, and lung cancer within the airway as well as Barrett's esophagus.
It has a predictable pharmacokinetic pattern. Thus, we know where and how Photofrin® is taken up by cancer cells, and how it is excreted by the body. We know that it takes 24 to 48 hours to preferentially be retained by the tumor, and it remains in the tumor for about 5-7 days. As a result, more than one treatment can be delivered within a week. Importantly, 48 hours after the administration of Photofrin® it does not remain in the bloodstream and so the risk of bleeding is somewhat lessened. Finally, because Photofrin® is a fairly nonspecific drug, it is retained in different cancer tumors and therefore can be used to treat a wide variety of cancers. This is important when treating cancer in the airway (the goal of this study) as often these cancers in the lung may have originated from different parts of the body, including breast, endometrial, renal, melanoma of the skin, head and neck and others.

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What does the Endobronchial Ultrasound Guided Interstitial Photodynamic Therapy in Treating Patients with Locally Advanced Lung Cancer (NCT03735095 study) entail?

- In this study we use ultrasound system (Endobronchial Ultrasound, EBUS**)** to image the tumor and guide fiber insertions into the tumor to treat the tumor with interstitial PDT (I-PDT). Prior to treatment (7-14 days) we obtain a CT scan of the chest, with contrast, when possible. This scan gets imported into a treatment planning algorithm developed by the study team. The treatment is designed with the goal of treating the greatest volume of the tumor with the least amount of exposure to the major blood vessels. In this way we aim to treat as safely and effectively as possible.
- Two days before treatment the patient receives a Photofrin® infusion through a vein.
- On the day of the procedure, the patient is placed under general anesthesia and intubated. We take biopsies of the treatment locations to reconfirm that the tumor is indeed cancer (i.e., malignant tumor). If a certain location has no cancer cells, we do not treat that site. In a malignancy is confirmed, we use the EBUS to guide the insertion of the light diffuser fiber into the target tumor, according to the treatment plan. The procedure of the fiber insertion is shown in the **Figure 1** below. Typically, the treatment is completed within about 1-3 hours

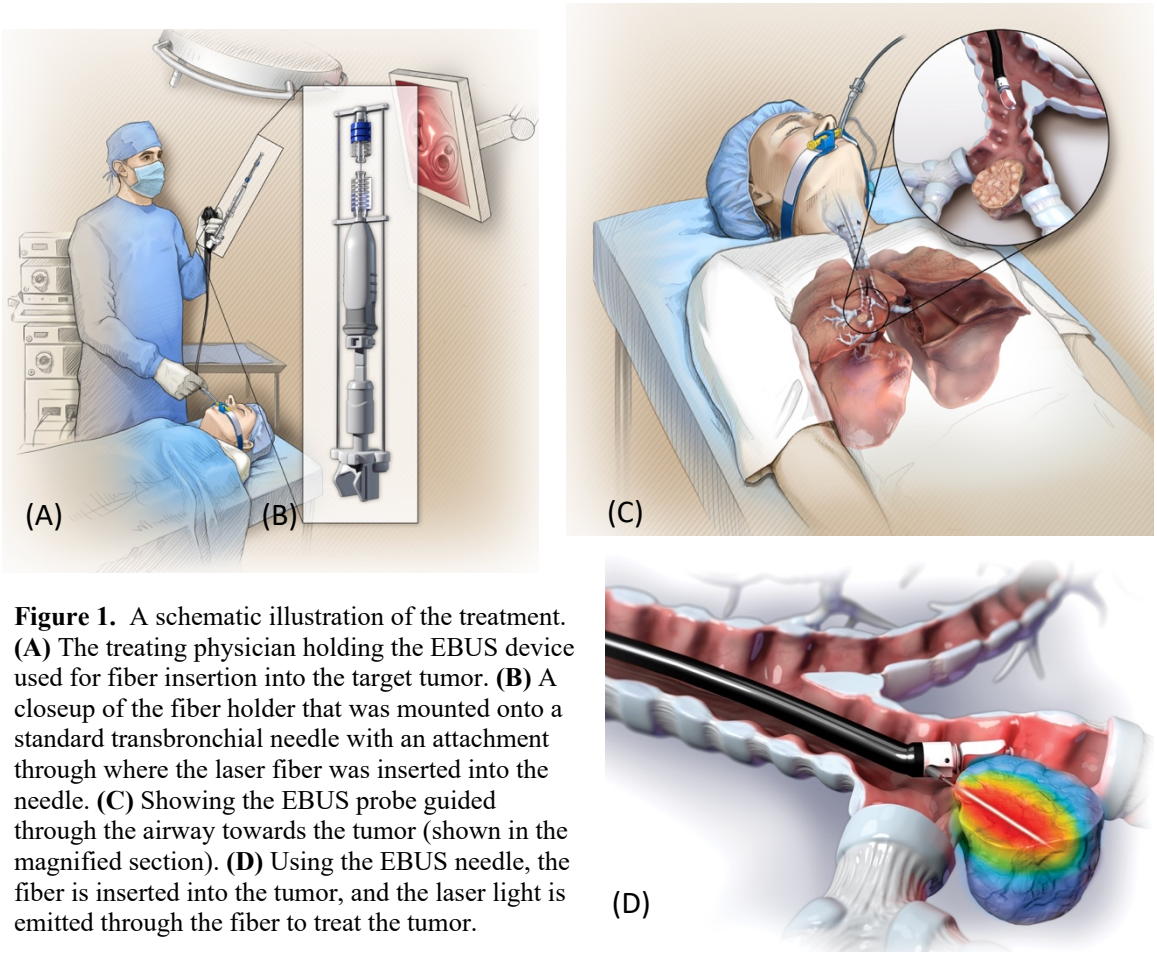

Figure 1. A schematic illustration of the treatment. **(A)** The treating physician holding the EBUS device used for fiber insertion into the target tumor. **(B)** A closeup of the fiber holder that was mounted onto a standard transbronchial needle with an attachment through where the laser fiber was inserted into the needle. **(C)** Showing the EBUS probe guided through the airway towards the tumor (shown in the magnified section). **(D)** Using the EBUS needle, the fiber is inserted into the tumor, and the laser light is emitted through the fiber to treat the tumor.

- Two days after the treatment we again place the patient under general anesthesia and perform bronchoscopy. This is because tumors slough off dead cells and these can block off the airway unless removed. At this time, we may place a stent to help protect the airway.
- We perform repeat CT scan and repeat bronchoscopy at one month after the initial treatment. This allows us to see if the treatment has been effective in alleviating airway obstruction. We then repeat CT scans and symptom review at 2 and 3 months after treatment. After three months the patient has completed the study.

Who is a candidate for the NCT03735095 study?

- A patient may be a candidate for this study if it has a tumor that is not suitable for surgical resection, and this tumor presses the central airway to compromise breathing. In this study the tumor can press the airway from the outside or block the airway from the inside. There are no good therapies to treat tumors that pressing the airway from the outside. ***The uniqueness of this study is that in addition to treating tumors that block the airways, the EBUS guided I-PDT can also be used to treat tumors that are pressing the airway from the outside.*** The central airways include the windpipe (trachea), right and left mainstream bronchi (the branch point immediately after the windpipe) and the bronchus intermedius (further within the main airway on the right side). A CT scan of the chest (ideally with contrast agent) can identify the airway, the tumor and any amount of blockage that may be presented. The CT scan is also used to verify that the tumor is not invading a major blood vessel that would be a contraindication, because if one treats such a tumor it could weaken the vessel wall and lead to major bleeding. The EBUS guided I-PDT can be used to treat one or more tumors. The physician (Dr. Ivanick) decides what needs to be treated and discuss with the scientist (Dr. Shafirstein) the treatment plan. Dr. Ivanick MD, always has the final say if and what to treat, taking into account patient safety and potential efficacy, to maximize the potential benefits over the risks.
- Patients can receive other therapies while partaking in this study, including chemotherapy and immunotherapy. Patients can receive radiation therapy to the lungs but need to receive it more than one month before or after treatment. This is so that we can determine the effect of the study treatment.
- This is a Phase I/IIa clinical trial conducted at Roswell Park Comprehensive Cancer Center. This means that we are testing safety of the study protocol primarily. The Phase I part of the protocol was deemed safe, based upon our pre-determined criteria in the first three patients. The initial study number was set at 6 patients; however, we chose to expand the study to a Phase IIa and treat additional 18 patients and broaden the inclusion criteria to all patients with any time of malignant central airway obstruction. This includes lung cancer as well as any other solid cancers that have metastasized to the lungs.

What are the major reasons that someone would not be a candidate for the NCT03735095 study?

— If the tumor is close to the edge of the lung and could not be accessed through the main airways, then it could not be treated in the study. This can be determined with the use of a CT scan of the Chest, or from bronchoscopy reports.

— If the tumor encases or invades a blood vessel within the lungs. This might include bronchial arteries, pulmonary arteries, and pulmonary veins. Because photodynamic therapy destroys tumor tissue, if the tumor is blocking a bleeding vessel but then dies away this could result in a major bleed.

Why would a patient choose to be a part of the NCT03735095 study and not get conventional or interstitial PDT outside of a study?

There are several reasons that patients might consider enrolling in this trial.

1. We believe that I-PDT delivered after pre-treatment planning offers the greatest chance of successful treatment with the lowest risk to a patient. This is because we can determine what areas to treat and what areas to avoid.
2. We can treat extrinsic compression (pressure from outside of the airway causing narrowing and blockage within the airway). Currently the only generally accepted therapy in these cases is balloon dilation and stenting, but neither is a complete fix for extrinsic compression. The EBUS guided I-PDT may benefit these instances.
3. Roswell Park Comprehensive Cancer Center has one of the greatest institutional experiences with PDT of any cancer center. Dr. Thomas Dougherty who worked at Roswell Park helped to develop this therapy over 40 years ago and helped to develop Photofrin®. Dr. Shafirstein (Co-PI on this study) has experience in the use of Photofrin® in treating a multitude of malignancies with Photofrin® and has written novel articles on pre-treatment planning and finite element modeling in the use of PDT. Dr. Ivanick is a board-certified interventional pulmonologist with experience treating airway obstruction with a variety of ablative modalities.

What can a patient expect from the NCT03735095 study?

- Our goal within the study is to demonstrate local tumor control, defined by keeping the airways open with lower amounts of tumor within and surrounding the airway. This degree of this benefit has varied between different patients, and this is often reflected in their baseline degree of functional health. Some patients have persisted without symptoms for up to 1 year following the procedure, while others have not noticed a major benefit from the procedure. Patients who enter the trial at a greater baseline level of health seem to do better and have a longer lasting benefit. The underlying type of cancer may also play a role. So far, we have treated mostly lung cancers, as the study was initially designed to target this. We have also now treated melanoma, endometrial cancer, and large cell neuroendocrine tumors of the lung.

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