ORIGINAL ARTICLE

# First-In-Human Computer-Optimized Endobronchial Ultrasound-Guided Interstitial Photodynamic Therapy for Patients With Extrabronchial or Endobronchial Obstructing Malignancies

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## ABSTRACT

**Objective:** Patients with inoperable extrabronchial or endobronchial tumors who are not candidates for curative radiotherapy have dire prognoses with no effective long-term treatment options. To reveal that our computer-optimized interstitial photodynamic therapy (I-PDT) is safe and potentially effective in the treatment of patients with inoperable extra or endobronchial malignancies inducing central airway obstructions.

**Methods:** High-spatial resolution computer simulations were used to personalize the light dose rate and dose for each tumor. Endobronchial ultrasound with a transbronchial needle was used to place the optical fibers within the tumor according to an individualized plan. The primary and secondary end points were safety and overall survival, respectively. An exploratory end point evaluated changes in immune markers.

**Results:** Eight patients received I-PDT with planning, and five of these received additional external beam PDT. Two

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additional patients received external beam PDT. The treatment was declared safe. Three of 10 patients are alive at 26.3, 12, and 8.3 months, respectively, after I-PDT. The treatments were able to deliver a prescribed light dose rate and dose to 87% to 100% and 18% to 92% of the tumor volumes, respectively. A marked increase in the proportion of monocytic myeloid-derived suppressor cells expressing programmed death-ligand 1 was measured in four of seven patients.

**Conclusions:** Image-guided light dosimetry for I-PDT with linear endobronchial ultrasound transbronchial needle is safe and potentially beneficial in increasing overall survival of patients. I-PDT has a positive effect on the immune response including an increase in the proportion of programmed death-ligand 1–expressing monocytic myeloid-derived suppressor cells.



*Keywords:* Malignant central airway obstruction; Personalized cancer treatment; Image guided; Interstitial photodynamic therapy; Endobronchial ultrasound; Clinical trial

## Introduction

Malignant central airway obstructions (MCAOs) are a highly morbid complication in a variety of malignancies with a median overall survival (OS) of only 1 to 7 months.[1–5] Locally advanced bronchogenic lung cancer is the most common cause of MCAOs, but a variety of extrapulmonary malignancies can also obstruct the central airway.[3,6] These airway obstructions can manifest as intrinsic (only endobronchial tumor growth), extrinsic (only extrabronchial tumor compression), or mixed obstructions.[2,3,7] Endobronchial obstructions have many treatment options because the tumor within the airway can often be removed by mechanical or thermal treatments followed by airway stenting.[2,8–10] Therapeutic options for extrabronchial and endobronchial and extrabronchial (mixed) compression are currently limited to balloon dilation and stent placement.[2] In radiation-naive patients, external beam radiation is also a consideration,[8] but such treatments are associated with potentially considerable side effects, including radiation-induced bronchitis, fistula formation, infection, and normal tissue radiation exposure.[11,12] Extrabronchial and mixed obstruction are associated with a shorter median survival than mixed or intrinsic airway obstruction in multiple studies.[8,13] At present, additional treatment options are needed to treat patients with extrabronchial disease, with the goal of improving the tumor response and survival.

Photodynamic therapy (PDT) is one therapeutic option for inoperable lung cancer. The U.S. Food and Drug Administration (FDA) has approved the use of PDT with porfimer sodium (Photofrin, Pinnacle Biologics Inc., Bannockburn, IL) to palliatively treat locally advanced, partially obstructing endobronchial lung cancer. The PDT involves the activation of a light-sensitive drug (photosensitizer) by a laser with visible light wavelengths that initiate a phototoxic reaction.[14,15] After the absorption of photons, the photosensitizer reacts with oxygen to produce singlet molecular oxygen, a reactive oxygen species that results in cell death.[16,17] Tumor retention of Photofrin, along with the delivery of therapeutic light in a targeted manner to the tumor and surrounding margins, allows for the preferential destruction of tumor tissue.[14,18] The FDA-approved application uses external beam illumination for PDT (i.e., EB-PDT) 48 hours after intravenous (IV) injection of Photofrin. To treat deeply seated and locally advanced large tumors, we use interstitial PDT (I-PDT), where cylindrical light diffuser fibers (CDFs) are inserted into the tumor to provide intratumoral illumination.[18]

Preclinical and clinical studies have revealed that safe and effective I-PDT requires image-based treatment planning using computer simulations to guide the placement of CDFs and compute the light dose rate (irradiance, $mW/cm^2$) and dose (fluence, $J/cm^2$).[18–23] In previous clinical studies, treatment plans for I-PDT have been limited to simple anatomies using parallel CDFs inserted through a fixed grid.[18,19,21,22] Nevertheless, this approach is not suitable for I-PDT in extrabronchial tumors, because of the space constraints within the airway. We have developed a novel high-spatial resolution image-based treatment planning system for I-PDT of tumors next to critical organs in the head and neck and central airways.[18,20,23–26] In our treatment plan, the distances and angles between adjacent CDFs vary according to the tumor location and anatomy. Using a nonuniform fiber distribution, we simulate the light propagation and compute the irradiance and fluence within the target tumor and at blood vessels.[25] We have recently reported that our treatment plan and dosimetry system can define and deliver a target irradiance and fluence within the tumor and margins that will result in a 70% to 90% cure rate and complete tumor response in Photofrin-mediated I-PDT of locally advanced cancer in mice and rabbits.[20,23] To test whether this approach can be used to administer safe and potentially effective I-PDT in human patients, we used our treatment plan to translate the knowledge gained from preclinical light dosimetry into a pilot clinical study. The image-based treatment plan for I-PDT with Photofrin was used to

identify the laser settings required to deliver the target irradiance and fluence. We used linear endobronchial ultrasound (EBUS) to guide the CDFs into target tumors according to the individualized treatment plans. Here, the results are reported from this first clinical study in patients with extrabronchial or mixed MCAOs.

## Materials and Methods

This was a single-arm, single-center, phase 1 study. The primary objective was to evaluate the safety of the new image-based treatment planning technique for I-PDT, and secondary objectives were to evaluate the tumor responses and OS. As an exploratory aim, we also evaluated changes in immune markers. The study interventions were all approved by the Roswell Park Comprehensive Cancer Center Institutional Review Board (IRB). All patients signed an IRB-approved informed consent form before receiving study-related intervention. A detailed description of inclusion and exclusion criteria is provided in the online Supplementary Materials. Initially, only patients with airway obstruction due to NSCLC were included in the study; however, after perceiving the need for effective therapies in metastatic extrapulmonary disease, the authors broadened the inclusion criteria to treat any malignancy causing a central airway obstruction. Only patients with an Eastern Cooperative Oncology Group performance status of less than or equal to 3 and no severe thrombocytopenia or other biochemical bleeding risks were considered potentially eligible. Notable exclusion criteria included recent radiotherapy to the target tumor area and evidence of major vascular invasion on planning computed tomography (CT) imaging. A high-resolution CT with IV contrast was obtained in the days before the procedure, and the CT images were reviewed by the treating physician and bioengineer. The target tumor, surrounding central airway, and major vasculature were marked by using finite element analysis software, and a computer simulation was performed to determine the treatment parameters. Further details are provided in the online Supplementary Materials. Porfimer sodium (Photofrin, Pinnacle Biologics Inc., Bannockburn, IL), the only photosensitizer approved by the FDA for treating endobronchial NSCLC, was administered by IV injection at a dose of 2 mg/kg body weight at 48 $\pm$ 4 hours before light delivery. Extrabronchial cancer was treated with I-PDT by using the treatment planning results, and endobronchial cancer was treated with FDA-approved EB-PDT by using a standard cylindrical diffuser (OPTIGUIDE Fiber-Optic, Pinnacle Biologics Inc., Bannockburn, IL).

On the treatment day, the malignancy was again confirmed by using EBUS and rapid on-site cytology, and this was followed by treatment at sites where the tumor was confirmed and not in direct proximity to major vasculature. Treatment was performed by using the EBUS scope and EBUS needle to insert the CDF into the tumor, followed by needle retraction while the CDF remained within the tumor. Treatment was then initiated as per the preprocedure plans. Details of this treatment technique are provided in the online Supplementary Materials, as are details regarding immune studies. Safety measures were evaluated in all patients by using a 3 + 3 study design to evaluate adverse events (AEs) greater than or equal to grade 4. The objective tumor response was measured by the Response Evaluation Criteria in Solid Tumors version 1.1, and OS was measured from the date of treatment.

## Results

### *Patient Characteristics*

A total of 10 patients were treated in this study. Table 1 summarizes the patient characteristics. Patients were of an older age (56–82 y) and predominantly female (7 of 10); seven were previous smokers, whereas one was a current smoker. Table 2 summarizes the disease and stage, the use of prior and concurrent therapies, and the obstruction location. Most patients had NSCLC adenocarcinoma and squamous cell carcinoma and previously had received chemotherapy and radiation therapy but had experienced disease recurrence. Of 10 patients, four were receiving concurrent therapy. All patients had locally advanced or metastatic disease at the time of entry into the study.

### *Treatment Procedures*

A total of 10 patients were treated. Three patients received I-PDT only, five patients received I-PDT followed by EB-PDT, and two patients received EB-PDT only. Treatments were administered in the endoscopy suite at Roswell Park Comprehensive Cancer Center under general anesthesia. When indicated, any intrinsic airway obstruction was managed with therapeutic bronchoscopy, including mechanical debridgement, argon plasma coagulation, and cryoextraction. After establishing airway patency, the EBUS scope was used to identify extrabronchial tumor tissue (i.e., tumor tissue that cannot be visualized within the airway). Color Doppler was used to demarcate vasculature.

An example of our image-based treatment planning for I-PDT in a patient with an extrabronchial tumor inducing an MCAO is illustrated in Figure 1*A–D*. The detailed plan includes the precise location of the CDFs within the airway, distance from the main carina, and degree of scope flexion and rotation in a clock face

**Table 1.** Patient Characteristics

| Patient Characteristics | Range |
|---|---|
| Age, average (range) in y | 69.7 (56-82) |
| Sex | 7 Females, 3 males |
| Tobacco use | Current 1 |
| | Former 7 |
| | Never 2 |
| Eastern Cooperative Oncology Group status | 0-3 |
| Race | White |

orientation. The I-PDT was administered to treat extrabronchial malignancy or regions that are more than 5 mm deep in patients with endo or extrabronchial MCAO. Additional EB-PDT was administered within few minutes after the I-PDT or at 48 hours later during the bronchoscopy cleanout. In patients 2 and 3 where I-PDT was planned but could not be performed owing to the firmness of the tumor and lack of sufficient stiffness of the initial fiber model used (RD250 CDF, Medlight SA, Ecublens, Switzerland), an EB-PDT only was accomplished to treat the endobronchial malignancy in endo or extrabronchial tumors. After treating these two patients, we obtained another CDF with greater rigidity (PB900 CDF, Pinnacle Biologics Inc., Bannockburn, IL) that allowed for fiber insertion without difficulty in all other subsequent patients. In addition to the above-mentioned two patients who received EB-PDT only, five patients received both I-PDT followed by EB-PDT as described previously. This was at the discretion of the treating clinician. In all such patients, visible endobronchial disease (a pattern of mixed endobronchial and extrinsic obstruction) was the indication for such treatment.

### *Treatment Safety*

Table 3 summarizes all AEs that occurred within 30 days of the I-PDT with or without concomitant EB-PDT. Five patients had no reportable AEs. The first three study patients had no grade 4 or above AEs that were probably, possibly, or definitely related to the I-PDT with or without concomitant EB-PDT, and thus, the study was allowed to continue. Patient 3 experienced atrial fibrillation (judged to be a possibly related grade 3 AE). This patient received a rate control intervention and nonischemic cardiology evaluation and was discharged home from the endoscopy suite. Patient 4 developed pneumonia and a chronic obstructive pulmonary disease exacerbation requiring readmission several days after the treatment; this patient recovered without difficulty. Patient 5 required admission for hypoxic respiratory failure (judged definitely related). After a cleanout bronchoscopy 2 days later, the patient experienced immediate improvement and was discharged home without hypoxia on the following day. Patient 8 had a massive hemoptysis during a second treatment that was conducted 48 hours after the I-PDT. This serious AE was judged to be probably related to the therapy. The treatment was halted, and the airway bleeding was managed with balloon tamponade, suctioning, and selective left mainstem intubation. He was admitted to the intensive care unit and extubated on the following day. The patient was monitored for 3 days in the intensive care unit before being discharged home and required 1 U of packed red blood cells. No further transfusions were necessary in the successive checks. At the last follow-up in the medical oncology clinic, the patient had improved. Nevertheless, at 22

**Table 2.** Disease Pathology and Stage, Prior and Concurrent Therapies, and Obstruction Location

| Patient Number | Disease Pathology and Stage | Prior Therapy | Concurrent Therapy | Obstruction Location |
|---|---|---|---|---|
| 1[a] | NSCLC-A IIb | Chemoradiation | None | RMS & BI |
| 2 | NSCLC-A IVa | Chemoradiation | None | RMS & BI |
| 3 | NSCLC-PD IVb | None | Chemotherapy | BI |
| 4 | NSCLC-S IIIa | Chemotherapy | Immunotherapy with pembrolizumab | Distal trachea & RMS & BI |
| 5[a] | Endometrial IVb | Chemoradiation | Immunotherapy with pembrolizumab | Distal trachea & RMS & BI |
| 6 | Melanoma IV | Surgery and interferon | None | Distal BI & basilar takeoffs |
| 7 | Large cell neuroendocrine IVa | None | Chemotherapy | Distal trachea & RMS & BI |
| 8 | NSCLC-S IVa | Chemoradiation | None | RMS & BI & left upper lobe takeoff |
| 9 | NSCLC-S IIb | Surgery, chemotherapy, Immunotherapy | None | Left mainstem |
| 10 | Recurrent NSCLC-S | Surgery and radiation | None | Right upper lobe takeoff |

[a]Patients treated on IRB compassionate care use, while receiving the same treatment as the others.
BI, bronchus intermedius; IRB, institutional review board; NSCLC-A, NSCLC adenocarcinoma; NSCLC-S, NSCLC squamous cell carcinoma; NSCLC-PD, poorly differentiated NSCLC; RMS, right mainstem.

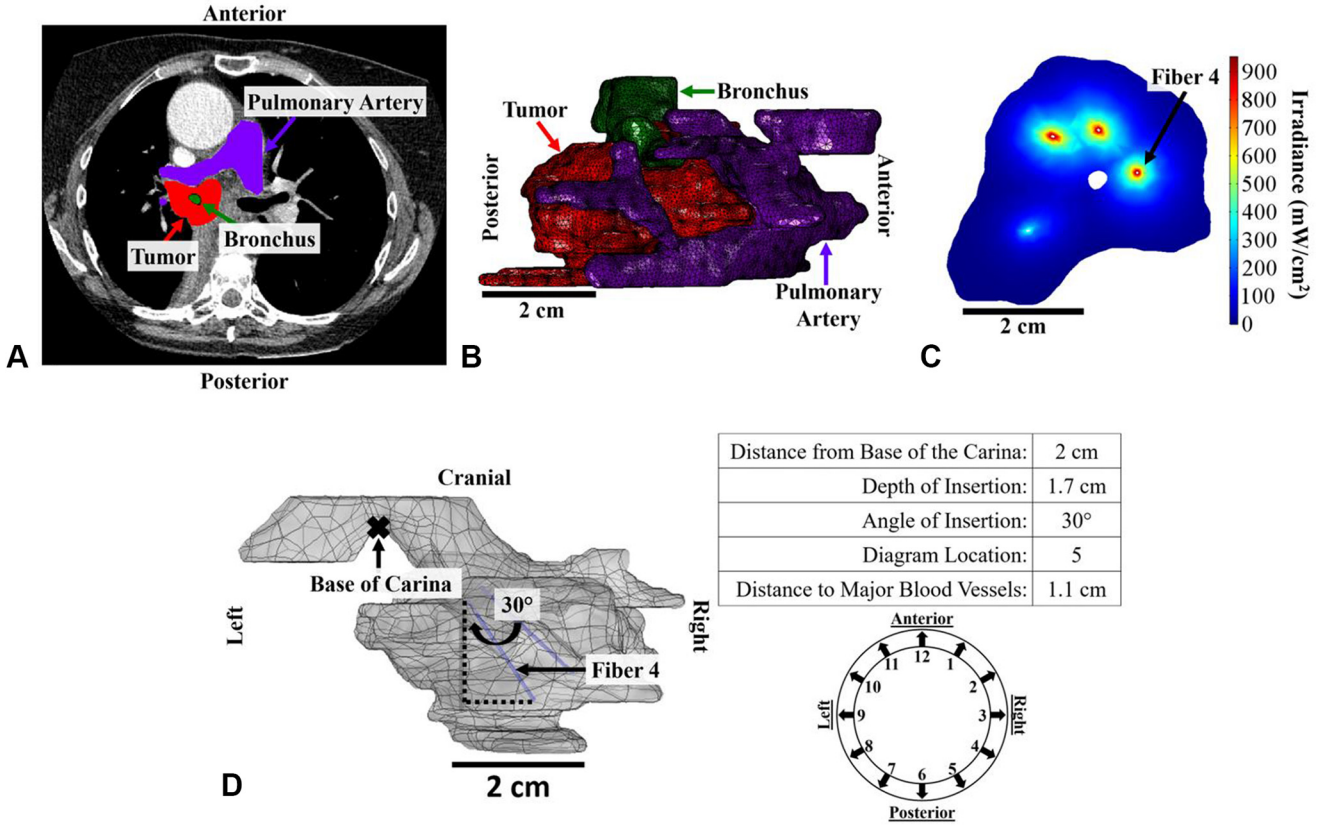


**Figure 1.** Image-based treatment plan for I-PDT of inoperable NSCLC with an airway obstruction. (*A*) A CT scan with outlines of the tumor and pulmonary artery. (*B*) Digital mesh demarcating the tumor (red), pulmonary artery (purple), and airway (green). (*C*) Cross section of the irradiance distribution from the light diffuser fibers. Range of irradiance, 0.4 to 955 mW/cm$^2$. (*D*) Treatment plan for placement of fiber 4. Fiber 4 was placed 2.0 cm from the base of the carina and inserted into the tumor at a 30° angle off the base of the carina and at a depth of 1.7 cm into the target tumor tissue. Fiber 4 was placed at the 5 o'clock position in relation to 12 o'clock as being directly anterior. CT, computed tomography; I-PDT, interstitial photodynamic therapy.

days post-treatment, the patient had a fatal massive airway hemorrhage that was judged to be probably related to the treatment.

### *Treatment Outcomes and Survival Statistics*

Table 4 summarizes treatment outcomes. During I-PDT, the delivered light intensity was 100 to 160 mW/cm

**Table 3.** AEs and Range of Intratumoral Light Irradiance and Fluence at Adjacent Major Blood Vessels

| Patient Number | AEs Within 30 d Post-Treatment | Maximum Irradiance at Adjacent Major Blood Vessels, mW/cm$^2$ | Maximum Fluence at Adjacent Major Blood Vessels, J/cm$^2$ |
|---|---|---|---|
| 1 | Cutaneous phototoxicity (AE grade 1, definitely related) | 14.9 | 9.5 |
| 2 | Pleural effusion (AE grade 4, unrelated) | EB-PDT only | EB-PDT only |
| 3 | Atrial fibrillation (AE grade 3, possibly related) | EB-PDT only | EB-PDT only |
| 4 | COPD exacerbation pneumonia (AE grade 4 unrelated) | 19 | 9.6 |
| 5 | Hypoxia that required admission (AE grade 4, definitely related) | 4.7 | 4.2 |
| 6 | None | 7.2 | 5.4 |
| 7 | None | 7.8 | 6.4 |
| 8 | Massive hemoptysis at 48 h during cleanup bronchoscopy and EB-PDT. Fatal airway hemorrhage at day 22 (AE grade 5, possibly related) | 10.3 | 12.2 |
| 9 | None | 6.9 | 5.7 |
| 10 | None | 16.3 | 8.2 |

AE, adverse event; COPD, chronic obstructive pulmonary disease; EB-PDT, external beam illumination for PDT; PDT, photodynamic therapy.

and the energy was 40 to 75 J/cm for seven of eight patients. In one patient (patient 1), high light intensity of 400 and 280 mW/cm and corresponding energy of 200 and 140 J/cm were used. The treatment planning calculations suggest that in two patients (4 and 9) the entire tumor was illuminated with the target irradiance ($\geq$8.6 mW/cm$^2$). In the other six patients, at least 87% of the tumor volume was illuminated with the target irradiance. None of the treated tumors received the target fluence throughout 100% of the volume of the tumor. This was a result of the need to limit the fluence because of the proximity to the adjacent vasculature.

Target tumor responses at day 90 were assessed in seven patients. One patient had a complete response, three patients had a partial response, three patients had stable disease, and three were not able to be evaluated.

Three patients treated with I-PDT are alive at 26.3, 12, and 8.3 months (Table 4). This includes patient 1 with NSCLC-A IIb, patient 9 with NSCLC-S IIB, and patient 10 with recurrent NSCLC-S. Our simulations suggest that 99% of the tumor volume received the target irradiance and 91.6% received the target fluence in patient 1 alive at 26.3 months. Figures 2*A–D* and 3*A–D* present the treatment plan and bronchoscopic/CT imaging for this patient.

The median OS was 3.75 months (with 95% confidence interval of 0.72, no upper limit). There was no significant relationship detected between OS and the patients' body mass index ($p = 0.14$) or Eastern Cooperative Oncology Group status ($p = 0.086$).

Although the sample size is small, we did not detect a difference between the treatment outcomes or AEs in the patients with metastatic extrapulmonary malignancies and those with pulmonary malignancies.

### *Effect of PDT on a Patient's Immune Status*

Blood samples were analyzed immediately before and at various times after I-PDT in seven patients. See Supplementary Materials for details. Of seven patients, three had an increase in the proportion of circulating CD8$^+$ T cells with tumoricidal potential as measured by expression of perforin.[27] In addition, four of seven patients had a marked increase in the proportion of monocytic myeloid-derived suppressor cells (mMDSCs) expressing programmed death-ligand 1 (PD-L1), a hallmark of a hot tumor characterized by a dense T cell infiltrate and improved response to immunotherapy.[28]

## Discussion

In this pilot study, we used an image-based treatment planning technique to guide Photofrin-mediated I-PDT during the treatment of extrabronchial tumors inducing MCAOs. The treatment plan was used to calculate the irradiance and fluence within the tumor and at adjacent blood vessels. Thus, our treatment planning technique allows for personalized cancer treatment according to the tumor size and location. In our approach, the treatment plan is implemented by using a linear EBUS bronchoscope with a transbronchial needle to position optical CDFs. The EBUS allowed for insertion of the CDFs within $\pm$5 mm of the planned depth, and we found in a previous computational study that errors in the depth of insertion of up to 13 mm from the plan will have only a minor effect on the total light dose that will be delivered to the tumors.[26] Use of the image-based treatment planning with EBUS was successful as the treatment approach was declared safe, and we observed potential efficacy by achieving a median OS of 3.75 months with three patients (of 10) alive at 26.3, 12, and 8.3 months.

### *Treatment Safety*

Previous reports indicate that MCAOs are associated with high rates of morbidity and mortality of up to 21% to 34% within 30 days of intervention.[4,29–31] In a recent study, extrinsic obstruction was associated with an adjusted risk of death of 2.12. This gave extrinsic obstruction a higher risk of death than age, medical comorbidities, intubated status before the procedure, and even histologic type of malignancy.[5]

Among the 10 patients in this study, five patients had AEs less than or equal to grade 2, one patient had a grade 3 AE that was possibly related, two patients had unrelated and one had a related grade 4 AE, and one patient had a probably related grade 5 AE. We therefore suggest that I-PDT alone or in combination with EB-PDT with Photofrin is not associated with undue risk in comparison with other endobronchial ablative tumors. Endobronchial brachytherapy is associated with a 7.5% risk of massive fatal hemoptysis,[32] and Nd-YAG laser therapy for endobronchial obstruction is associated with a rate of 6% of massive bleeding.[33]

Tumor ablation next to a major blood vessel carries a risk of excessive bleeding. We did not treat tumors where vascular invasion was suggested on CT scan. There is a theoretical possibility that I-PDT or EB-PDT of the vessel walls could weaken a blood vessel after treatment of an area invaded by cancer cells that could not be found in the CT. To minimize this risk, we used the treatment planning to determine the laser settings that would produce an effective intratumoral irradiance and fluence to a significant volume of the target tumor while yielding subtherapeutic illumination at adjacent major blood vessels. According to our calculations for all patients, the maximum irradiance and fluence at blood vessels (4.7–19 mW/cm$^2$ and 4.2–12.2 J/cm$^2$, respectively) were well below the therapeutic levels for

**Table 4.** Treatment Data

| Patient Number | Tumor Volume ($cm^3$) | I-PDT | EB-PDT | Percent of Tumor Volume at $\geq$8.6 mW/$cm^2$, % | Percent of Tumor Volume at $\geq$45 J/$cm^2$, % | Tumor Response at 90 d | Overall Survival (d) |
|---|---|---|---|---|---|---|---|
| 1 (CC1) | 12.7 | L1: 400 mW/cm, 200 J/cm, 2 cm CDF<br>L2: 280 mW/cm, 140 J/cm, 3 cm CDF | No EB-PDT | 99.0 | 91.6 | PR | >800 (alive) |
| 2 (RP1) | 6.5 | No I-PDT | L1, L2: 400 mW/cm, 200 J/cm, 2.5 cm CDF | No I-PDT | No I-PDT | NE | 71 |
| 3 (RP3) | 20.4 | No I-PDT | L1: 400 mW/cm, 200 J/cm, 5 cm CDF<br>At 48 h post I-PDT:<br>L1: 400 mW/cm, 200 J/cm, 2.5 cm CDF<br>L2: 400 mW/cm, 200 J/cm, 2.5 cm CDF | No I-PDT | No I-PDT | SD | 166 |
| 4 (RP4) | 1.0 | L1: 106 mW/cm, 53 J/cm, 1.5 cm CDF | No EB-PDT | 100 | 70.3 | SD | 93 |
| | 2.0 | L1: 106 mW/cm, 53 J/cm, 1.5 cm CDF | | 90.5 | 34.3 | | |
| 5 (CC2) | 6.7 | L1: 100 mW/cm, 50 J/cm, 1.5 cm CDF<br>L2: 80 mW/cm, 40 J/cm, 1 cm CD | At 48 h post I-PDT:<br>L1: 400 mW/cm, 200 J/cm, 5 cm CDF<br>L2: 400 mW/cm, 200 J/cm, 2.5 cm CDF | 94.2 | 48.1 | NE | 94 |
| 6 (RP5) | 0.35 | L1: 100 mW/cm, 75 J/cm, 1 cm CDF | L1: 400 mW/cm, 200 J/cm, 5 cm CDF | 95.2 | 57.5 | PR | 134 |
| 7 (RP7) | 39 | L1, L2, L3, and L4: 160 mW/cm, 120 J/cm, 1.5 cm CDF | L1: 400 mW/cm, 200 J/cm, 5 cm CDF | 89.4 | 45 | SD | 78 |
| 8 (RP6) | 17.4 | L1, L2, L3, and L4: 160 mW/cm, 120 J/cm, 1.5 cm CDF | L1: 400 mW/cm, 200 J/cm, 2.5 cm CDF | 99.99 | 78.2 | NE | 22 |
| 9 (RP8) | 3.1 | L1, L2: 100 mW/cm, 50 J/cm, 1.5 cm CDF | No EB-PDT | 100 | 85.5 | PR | >365 (alive) |
| 10 (RP9) | 0.56 | L1: 100 mW/cm, 75 J/cm, 1.0 cm CDF | L1, L2: 400 mW/cm, 200 J/cm, 2.5 cm CDF | 87.4 | 18.3 | CR | >254 (alive) |

CDF, cylindrical diffuser fiber; CR, complete response; EB-PDT, external beam illumination for PDT; I-PDT, interstitial PDT; NE, not able to be evaluated; PDT, photodynamic therapy; PR, partial response; SD, stable disease. *Note*. Columns indicate the target tumor volume; I-PDT light settings, including number of illuminations (L1–4), light intensity (mW/cm), energy per centimeter (J/cm) of the diffuser length, and length of the CDF; and EB-PDT light settings administered immediately and 48 hours after I-PDT. Also illustrated is the calculated percent of tumor volume that received more than or equal to 8.6 mW/$cm^2$ and more than or equal to 45 J/$cm^2$ during I-PDT, and the corresponding response and overall survival for each patient.

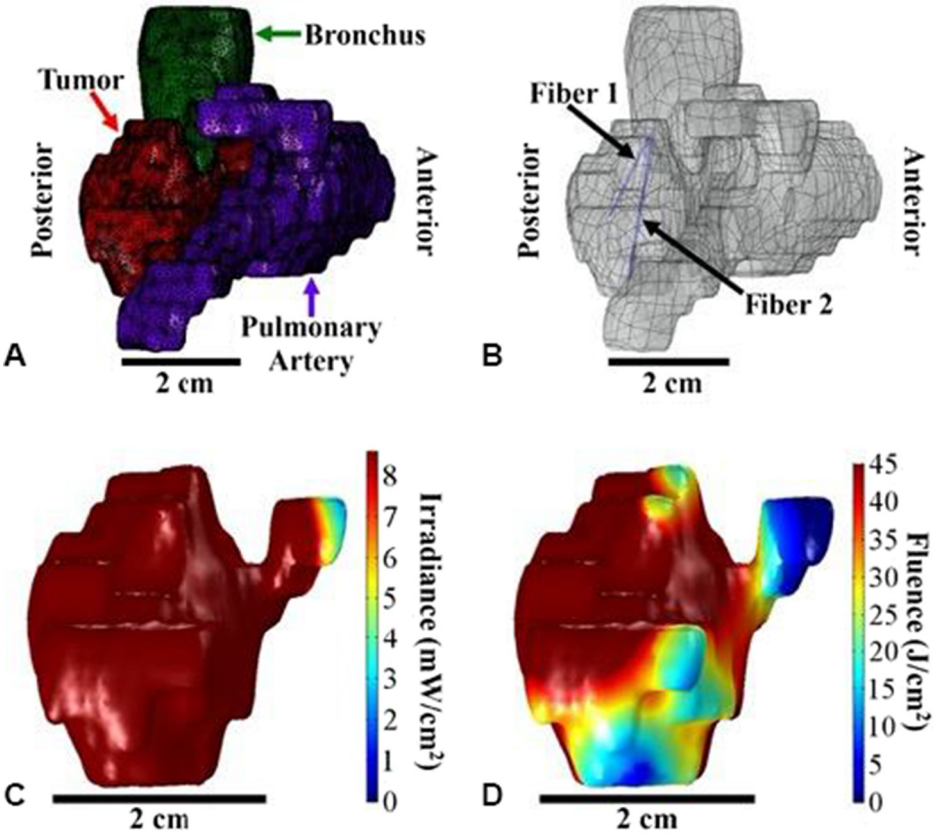


**Figure 2.** Image-based treatment plan for I-PDT of inoperable NSCLC with an MCAO, illustrated in Figure 3. (*A*) The 3D reconstruction of the CT scans with outlines of the target tumor (red, 12.7 $cm^3$), pulmonary artery (purple), and airway (green). (*B*) Tumor geometry with locations for the planned insertion of laser fibers. (*C*) Simulated irradiance within the target tumor suggesting that 99% of the tumor volume will receive the target threshold irradiance of 8.6 $mW/cm^2$. (*D*) Simulated fluence within the target tumor suggesting that 91.6% of the tumor volume will receive the target threshold fluence of 45 $J/cm^2$. 3D, three dimensional; CT, computed tomography; I-PDT, interstitial photodynamic therapy; MCAO, malignant central airway obstruction.

Photofrin-mediated PDT, that is, 100 to 150 $mW/cm^2$ and 50 to 100 $J/cm^2$, respectively.[14] In the patient who experienced a fatal bleeding incident, the calculated maximum fluence at the vessel was 12.2 $J/cm^2$. In the patient who had the best response, with no reportable AEs, the maximum fluence at a major vessel was 9.5 $J/cm^2$, whereas the maximum calculated irradiance at this vessel was 14.9 $mW/cm^2$. Hence, we recommend minimizing the fluence to less than or equal to 9.5 $J/cm^2$ while keeping the irradiance at less than or equal to 14.9 $mW/cm^2$ at adjacent major blood vessels.

We recorded the patients' concurrent therapies to assess the potential risk of adding I-PDT and EB-PDT to standard-of-care therapies. One patient had a possibly related grade 4 AE (hypoxia) that was fully resolved after the cleanout bronchoscopy, and the patient was discharged home without needing supplemental oxygen. This patient was on a concurrent immunotherapy. The patient who experienced a grade 5 AE had received no concurrent therapy at the time of the I-PDT. The other patients who received prior or concurrent therapy had no reportable AEs. Several papers have reported no added toxicity or serious AEs where Photofrin-mediated EB-PDT was used with or after chemotherapy in patients with advanced esophageal cancer or unresectable cholangiocarcinoma.[34–37] We therefore suggest that I-PDT can be added to standard oncologic therapies but emphasize caution with systemic therapies causing thrombocytopenia.

## *Treatment Outcomes*

The response to Photofrin-mediated I-PDT depends primarily on Photofrin retention, light irradiance, and tumor volume, as we reported in extensive preclinical studies.[20,23] In those studies, we used our image-based treatment planning and found that there is a 92.7% probability of achieving a cure during Photofrin-mediated I-PDT of locally advanced murine tumors illuminated with 630 nm light at a minimal intratumoral irradiance of 8.6 $mW/cm^2$ and fluence of 45 $J/cm^2$.[23] These preclinical studies also revealed that the irradiance is the critical parameter for effective tumor

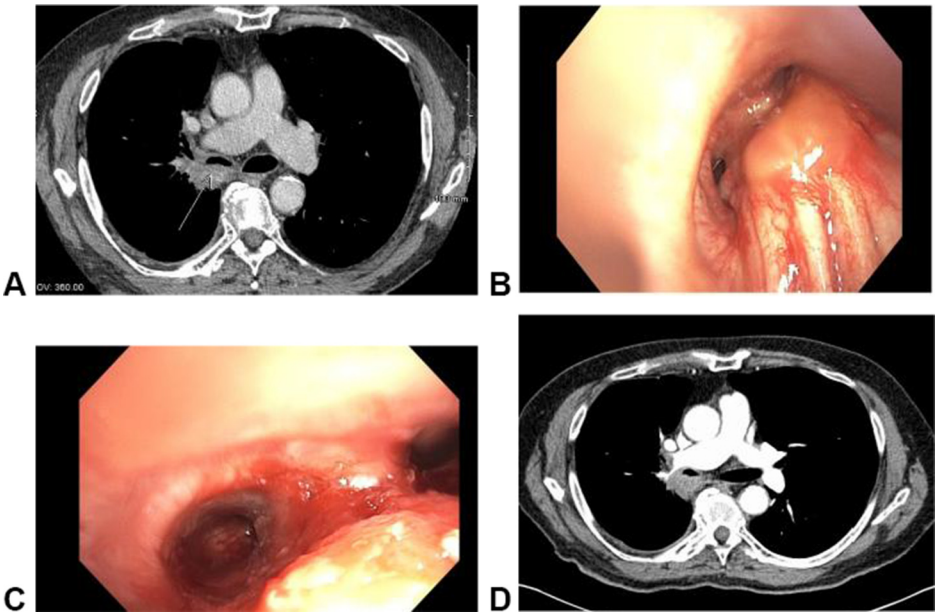


**Figure 3.** The CT and clinical photographs of a patient's tumor that was treated with I-PDT only according to the plan illustrated in Figure 2. This patient had endobronchial and extrabronchial NSCLC-S that recurred after standard chemotherapy and radiation. (*A*) A CT scan that was used for the pretreatment planning. (*B*) Clinical image of the right mainstem on the day of I-PDT before treatment. (*C*) The right mainstem 2 days after treatment and cleanup. The treatment included endobronchial tumor debulking and extrabronchial I-PDT. (*D*) A CT scan 3 months after I-PDT; the reduction in the extent of the airway obstruction had persisted. The patient was alive 24.5 months after the I-PDT at the time of the last follow-up. CT, computed tomography; I-PDT, interstitial photodynamic therapy.

ablation. In the clinical study reported herein, we translated our pretreatment planning findings from the experimental animal studies to guide light delivery within target tumors of patients. Our treatment plan calculations suggest that we administered the target irradiance to more than 90% of the tumor volume in seven of eight patients treated with I-PDT. Nevertheless, the small sample size (10 patients) does not allow for a determination of how the calculated intratumoral irradiance is related to the therapy response and OS. Although anecdotal, the best response ($>$26.3 mo OS with AE $\leq$1) was associated with the delivery of the target irradiance in 99% of the tumor volume of patient 1, who was alive at the end of the study. In addition to this patient, in two more patients who are still alive, the target irradiance was delivered to 100% and 87.4% of the target tumor. This may suggest that the irradiance is a critical parameter for obtaining effective outcomes in the clinical setting, which is in agreement with the results of our preclinical studies.

Patients with MCAOs have dire prognoses with a median OS of 1 to 7 months.[1–5] A recent article suggested that addition of clinically approved PDT (i.e., EB-PDT) to standard-of-care chemotherapy and radiation can be beneficial, in terms of survival, for patients with stage III or IV NSCLC.[38] Other available methods of palliative ablation, including external beam radiotherapy with or without stent placement, were found to have median OS rates of 3 weeks to 3 months.[39–41] Our measured 3.75 months of median OS, with three patients still alive (26.3, 12, and 8.3 mo), suggests that patients with extrabronchial tumors inducing MCAOs who are not candidates for other curative treatments may benefit from our image-based Photofrin-mediated I-PDT where the target irradiance is delivered to 90% of the target tumor. Although our pilot study was not designed to detect the effects of I-PDT on OS, it nevertheless compares favorably to these published rates. These results represent a potential benefit to patients who receive I-PDT and warrant a future phase 2 study.

In this study, we included two patients with extrapulmonary malignancies that had spread to the airways causing central airway obstruction. We treated both with combinations of I-PDT and EB-PDT with good effect. We observed no undue long-term risk in either patient, and their survival was on par with other patients within the study. The effect on the patient with endometrial cancer was considered not able to be evaluated, and a partial treatment response was observed in the patient with metastatic melanoma. More patients with extrapulmonary malignancies will need to be included in future larger studies to determine whether AEs, treatment effect, or survival differs between these groups.

In this study, we added the FDA-approved EB-PDT with Photofrin to treat superficial endobronchial disease

immediately or 48 hours after I-PDT in five patients. The EB-PDT affects tumor and tissue that are 3 to 5 mm deep in the bronchus. In I-PDT, however, we inserted the treatment fibers in the extrabronchial malignancy or deeper parts of endobronchial/extrabronchial tumors. The intensity and energy of the EB-PDT and I-PDT are expected not to be additive as they will treat different parts of the target tumor with minimal or no overlap. The addition of EB-PDT to I-PDT seemed to be safe. The response in the two patients who received EB-PDT only suggests that the EB-PDT affects treatment efficacy. We therefore suggest that I-PDT can be used with EB-PDT in patients where endobronchial disease is also present.

Multiple studies have revealed that Photofrin can be used to treat a wide variety of cancers, such as esophageal, bile duct, ovarian, brain, pancreatic, and head and neck, including NSCLC and SCLC.[14,18,42] The presence of Photofrin was detected in all tumor pathology specimens treated in this study. Therefore, in the follow-up phase 2 study, we used the FDA-approved photosensitizer (Photofrin) in I-PDT with or without EB-PDT for the treatment of patients with primary lung cancer and metastatic malignancies inducing MCAOs.

### *Immune Responses*

Patients with cancer generally have an immunosuppressed immune contexture, which may be associated with elevated levels of circulating regulatory T cells, MDSCs, PD-1–expressing T cells, and PD-L1–expressing MDSCs.[43–45] Several studies have reported that EB-PDT can activate antitumor immunity.[46] To date, no study has evaluated the effects of I-PDT on the immune response. In this study, we found that I-PDT had a positive effect on the immune response as measured by an increase in circulating $CD8^+$ T cells with tumoricidal potential. We also intriguingly found an increase in the proportion of mMDSCs expressing PD-L1. Increased PD-L1 expression on myeloid cells is associated with high T cell infiltrate[47] and positively associates with survival outcomes to immune checkpoint blockade in several cancers, suggesting I-PDT stimulates antitumor immunity by turning cold tumors to hot ones. Although PDT significantly increases tumor PD-L1 levels through activation of HIF-1$\alpha$,[48] the mechanism by which PDT increases the proportion of PD-L1–expressing mMDSCs remains less well defined. Of the three surviving patients, two had immune markers that were monitored. The first, patient RP-8, had a decrease in PD-L1–expressing mMDSCs, whereas the second, RP-9, had a marked increase in the proportion of PD-L1–expressing mMDSCs. This patient was chemotherapy and immune therapy naive. The small number of patients and the various diseases preclude a conclusive assessment of whether I-PDT stimulates an immune response. Nevertheless, these data support the need for further studies to determine the effects of I-PDT on immunity in this disease setting.

### *Study Limitations and Future Directions*

The main limitations of this study are the small number of patients and the heterogeneity of their diseases. Therefore, the phase 1 study reported in this article is being followed by an IRB-approved phase 2 study to evaluate the efficacy of EBUS guided I-PDT with and without EB-PDT. The phase II study will enroll similar patients to those treated in the pilot study. The primary objectives of the phase 2 study are to assess the tumor responses and changes in quality of life and performance, whereas the secondary objectives are to determine the progression-free survival and to evaluate new commercially dedicated treatment planning software for I-PDT. An exploratory aim will include changes in immune markers owing to the I-PDT.

In conclusion, our image-based treatment plan for I-PDT can assist the physician in the treatment of patients with extrabronchial tumors that induce MCAOs and are not amenable to any other standard-of-care ablative treatment. The EBUS can be used for the placement of the CDFs in arrangements more complex than previously possible according to the individual plan. The Photofrin-mediated EB-PDT can be added to I-PDT. A follow-up phase 2 study is warranted to assess the efficacy, the antitumor immunity, and the impact on quality of life.

## CRediT Authorship Contribution Statement

**Nathaniel M. Ivanick**: Conceptualization, Data curation, Investigation, Methodology, Writing—original draft preparation, Writing—review and editing.

**Emily R. Oakley**: Data curation, Methodology, Software, Validation, Writing—original draft preparation, Writing—review and editing.

**Rajesh Kunadharaju**: Investigation, Writing—original draft, Writing—review and editing.

**Craig Brackett**: Data curation, Investigation, Writing—review and editing.

**David A. Bellnier**: Data curation, Investigation, Writing—review and editing.

**Lawrence M. Tworek**: Data curation, Methodology, Resources, Project administration, Writing—review and editing.

**Sergei N. Kurenov**: Methodology, Resources, Writing—review and editing.

**Sandra O. Gollnick**: Investigation, Methodology, Writing—review and editing, Funding acquisition.

**Alan D. Hutson**: Data curation, Formal Analysis, Methodology, Writing—review and editing.

**Theresa M. Busch:** Validation, Writing—review and editing.

**Gal Shafirstein:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Roles/writing—original draft, Writing—review and editing.

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## Ethics Approval

The clinical study was approved by Roswell Park's Institutional Review Board in accordance with the Declaration of Helsinki. All participants signed an Institutional Review Board-approved consent form before taking part in the study. The study was exempt from federal investigational new drug application or investigational device exemption requirements.

## Data Sharing

The following data will be shared: participants' data that motivate the results reported in this article, after deidentification (text, tables, and figures). The data will be available beginning 9 months and ending 36 months after article publication. The data will be provided to researchers who provide a methodologically sound proposal, to achieve aims in the approved proposals. The proposals should be directed to Nathaniel Ivanick, MD, at Nathaniel.Ivanick@RoswellPark.org and Gal Shafirstein, DSc. at Gal.Shafirstein@RoswellPark.org. The data will be provided through an agreement with the Roswell Park Comprehensive Cancer Center.

## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at http://doi.org/10.1016/j.jtocrr.2022.100372.

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