

The Application of Photodynamic Therapy in the Treatment of Metastatic Endobronchial Disease

Cynthia M. Magro, MD,¹ Abbas E. Abbas, MD,² and Patrick Ross, Jr., MD, PhD^{2*}

¹Department of Pathology, The Ohio State University, Columbus, Ohio

²Division of Cardiothoracic Surgery, The Ohio State University, Columbus, Ohio

Background and Objective: We utilized photodynamic therapy (PDT) for palliation of metastatic endobronchial tumors employing sensitization with synthetic porphyrin, application of non-thermal light, and endoscopic debridement of necrotic tumor.

Study Design/Materials and Methods: Nine patients with symptomatic endobronchial metastasis from carcinomas of the colon(3), breast(3), kidney(2), and tongue(1) received PDT.

Results: After two PDT treatments, patients showed substantial response, which was complete in all but one. One patient had perioperative complications and expired 2 days after developing massive hemoptysis during tumor debridement. Patient survival was 6.38 months (mean) and 4.2 months (median). Most patients died from advanced metastatic disease. One patient with metastasis limited to the airway is still alive 24 months following endobronchial presentation.

Conclusions: PDT ameliorates symptoms of metastatic airway obstruction, is easy to apply, has low morbidity and improves the quality of life. *Lasers Surg. Med.* 38:376–383, 2006. © 2006 Wiley-Liss, Inc.

Key words: bronchial metastasis; lung cancer; laser

INTRODUCTION

Photodynamic therapy (PDT) represents a specific treatment modality among the armamentarium for treating primary bronchogenic neoplasia and metastatic disease of the airway. However, it is not as widely implemented as other forms of therapy, at least based on a comparative assessment of literature citations. The principle behind the efficacy of PDT in this setting rests on a firm understanding of its pathophysiologic basis. In brief, subsequent to pharmacological sensitization with a systemically administered synthetic porphyrin, visible non-thermal light at 630 nm wavelength (i.e., in the red light spectrum) is applied to the region of neoplasia. The light directed at the porphyrin produces direct and indirect cell necrosis. The direct effect occurs as the light energy evokes the generation of oxygen free radicals, the latter having direct tumoricidal properties. Oxidation of cross-linking of membranes followed by cell lysis is the probable mode of cell death [1]. The indirect effect is a consequence of small vessel thrombosis producing tissue ischemia. In addition,

PDT may enhance cytotoxic immunity directed against the tumor through up-regulation of those inflammatory cytokines potentially involved in tumor surveillance [2].

PDT has an advantage over other endoluminal treatment modalities by virtue of its minimal effects on surrounding tissue due to reduced retention of porphyrin by adjacent normal tissue [3]. The mechanism involved in the preferential distribution of these photosensitizers to tumors has not been fully elucidated, however, a decreased pH or elevated low-density protein receptors may be of pathogenic significance [3]. PDT is especially suited for the treatment of tracheobronchial disease due to the resistance of collagen and cartilage to PDT. From a historical perspective, the first documented application of PDT in the treatment of endobronchial disease was 22 years ago, in the context of an anecdotal case report in a patient at the Tokyo Medical College. After undergoing PDT, the patient had complete eradication of a small upper airway bronchial squamous cell carcinoma [4].

We have used PDT as a mainstay of palliative therapy in the setting of symptomatic metastatic endobronchial disease. Patients with this form of endobronchial neoplasia manifest intractable and progressive dyspnea, cough, and hemoptysis, all of which clearly impact the quality of their life and may be potentially lethal due to airway compromise. We review our experience using PDT in the palliation of nine patients with malignant airway obstruction attributable to metastatic endobronchial disease.

MATERIALS AND METHODS

All patients who have undergone PDT for the treatment of symptomatic endobronchial malignancies from non-bronchogenic primaries were identified from the database of the division of Thoracic Surgery, Ohio State University. The patients were all assessed and treated by one of the authors (PR) over a time period of April 2000–November 2003. During this same time period, 300 additional patients with other forms of symptomatic airway disease were seen

*Correspondence to: Patrick Ross, Jr., MD, PhD, Division of Cardiothoracic Surgery, The Ohio State University, N839 Doan Hall, 410 West 10th Avenue, Columbus, Ohio 43210.

E-mail: patrick.ross@osumc.edu

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by this author. The synthetic hematoporphyrin utilized for the study was PHOTOFRIN[®]. The dosing was 2 mg/kg administered intravenously via freely flowing intravenous line with 0.5N saline and 5% glucose. Forty-eight hours following the injection, light generated by a tunable dye laser was delivered through cylindrical diffusing tip quartz fibers passed through the biopsy channel of a flexible bronchoscope. The light was administered at a wavelength of 630 nm and a power density of 400 mW/cm fiber length. The light applicators provided surface illumination or interstitial therapy to tumor masses with the average light doses to the area being 200 Joules cm². All patients received general anesthesia to facilitate accurate positioning of the quartz fiber.

A bronchoscopic assessment of treatment efficacy was performed 2 days after the delivery of the initial light energy; PDT results in a visual response detectable by endoscopic evaluation. Necrotic tissue was removed with irrigation and biopsy forceps. All debridement specimens were assessed pathologically to determine the effects of PDT on tumor viability. A response to treatment was based on bronchoscopic inspection of the airway and symptomatic improvement. If mechanical obstruction was still visible and or if the patient continued to be symptomatic, additional PDT treatments were given 2 days apart to a maximum of three light therapy sessions. The light energy was adjusted on subsequent treatments.

RESULTS

Demographic Information

Endobronchial PDT was administered to nine patients (five males, four females) with endobronchial metastatic disease using the technique as outlined above. The patients ranged in age from 34 to 69 with five patients being under the age of 45 (Table 1).

Indications and Treatment Protocols

Among the indications for PDT were hemoptysis in three and symptomatic endobronchial obstruction in seven, manifesting as progressive dyspnea and post-obstructive pneumonia with atelectasis. Seven patients required two light treatments to achieve luminal patency while two patients required three treatments. Twenty-four to forty-eight hours lapsed between consecutive treatments (Table 1).

Sites of Primary Malignancy

All primary tumors represented carcinomas being of colonic origin in three (33%), breast in three (33%), kidney in two (22%), and larynx (11%). The endobronchial lesions frequently assumed a polypoid and or pedunculated appearance; hyperemia was characteristic of metastatic renal cell carcinoma (Fig. 1, Table 1).

Sites of Endobronchial/Endotracheal Metastatic Disease

The lesions were located in the right mainstem bronchus in five of the cases, bronchus intermedius in two of the

cases, the left mainstem bronchus in one case, and trachea with carinal extension in one case (Table 1).

Time Between Initial Diagnosis of Primary and Subsequent Endobronchial Metastasis and Extent of Metastatic Disease Elsewhere

In all cases the endobronchial disease occurred meta-chronously to the primary tumor.

The dates between the diagnosis of the initial malignancy and the subsequent endobronchial metastasis ranged from 12 months to 7 years (53.7 months). In seven of nine cases metastatic disease to other organs presaged the endobronchial metastasis with the most frequent site being lung, comprising a metastatic site in seven of nine patients. By 12 months from the initial diagnosis of the tumor, the probability of not metastasizing was 0.57, by 24 months, it was 0.43, and by 36 months 0.29 (Table 1).

Post-Operative Complications/Morbidity

One patient (Patient 9) with endobronchial renal cell carcinoma developed massive hemoptysis upon tumor debridement resulting in progressive hypoxemia and cardiac arrest; the patient was successfully resuscitated although he required mechanical ventilation due to inadequate oxygenation. He died 2 days later due to respiratory insufficiency. In Patient 5, there was a bronchopleural fistula recognized at bronchoscopy. It was later established that the patient had massive intrapulmonary carcinomatosis and necrosis with no viable lung tissue separating the pleural space from the bronchus. This patient died 1 month later of progressive respiratory failure. In the remaining cases there were no intraoperative or immediate post-operative complications. All patients had received general anesthesia to allow better airway control and surveillance and in all cases oxygenation throughout the procedure and post-extubation was very well maintained. No patient developed photosensitivity.

Subjective and Objective Improvement Following PDT

All patients prior to PDT had significant endoluminal obstruction (Fig. 1) which in all nine patients was clinically very symptomatic be it in the context of hemoptysis and or progressive dyspnea. All patients experienced a striking subjective amelioration of the initial airway symptoms. In addition, there was a gross reduction in the extent of endoluminal obstruction as assessed bronchoscopically in all cases. As well post-obstructive radiographic findings showed significant improvement following PDT (Figs. 2 and 3). In no case, however, were post-PDT pulmonary function studies carried out. In seven patients, after two or at most three PDT treatments, there was a complete response as determined by a patent bronchus with no discernible obstruction. In Patient 5, the response was only partial; however, his unstable pulmonary condition due to massive lung necrosis with bronchopleural fistula precluded further therapy. In one patient (Patient 7), the residual tumor after the second PDT treatment was

TABLE 1. Summary of History of Primary Tumor and Metastatic Disease Including Endobronchial Presentation

	Age	Sex	Primary malignancy	Date primary malignancy diagnosed	Location in endobronchus	Date of endobronchial presentation	Symptoms of airway disease	Metastases to other organs	Date other metastases diagnosed
1	69	M	Colon	4/98	Right mainstem	11/02	Hemoptysis	Liver, lung	4/98
2	42	M	Kidney	9/96	Right mainstem	8/02	Hemoptysis	Lung, pleura, brain, lymph nodes, stomach, bowel, spleen, pancreas, bone	Not known
3	61	F	Breast, bilateral	4/97, 1/99	Right mainstem	4/04	Obstruction	Lung, right upper, and lower lobes	Not known
4	62	M	Colon	2/01	Right mainstem	9/02	Obstruction	Lung, right upper, and lower lobes	2/02
			Colon		Right distal mainstem/bronchus intermedius	6/03	Obstruction		
5	41	M	Floor of mouth	3/96	Bronchus intermedius	2/00	Obstruction	Right lung	Not known
6	34	M	Breast	6/97	Bronchus intermedius, left distal mainstem	1/00, 2/00	Obstruction	Bilateral lungs, pleura, recurrent right breast, left breast	9/99, 10/99
7	46	F	Breast	1/93	Endotracheal extending to carina	12/00	Obstruction	Recurrent right breast, bilateral lungs, lymph node, liver, pleura, brain	1/98, 9/99, 7/00, 8/00, 1/01
8	43	F	Colon	9/94	Bronchus intermedius	4/00	Obstruction	Liver, lung	5/95
9	42	M	Kidney	1/95	Right mainstem	6/00	Hemoptysis/obstruction	Lung	6/00

F, female; M, male.

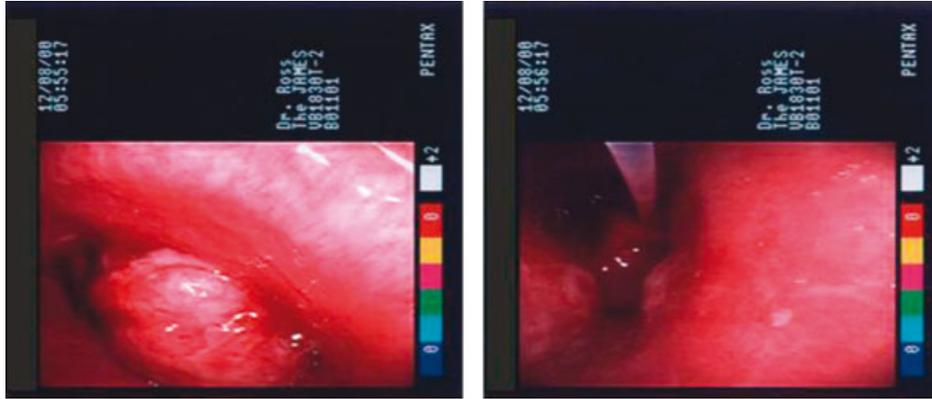


Fig. 1. There is a pedunculated mass with striking neovascularity occluding the right upper lobe orifice. The patient had a history of multiorgan metastatic renal cell carcinoma (Patient 2). [Figure can be viewed in color online via www.interscience.wiley.com.]

surgically resected endoluminally, resulting in complete luminal patency. In all cases the post-PDT pathology revealed extensive tumor cell necrosis compatible with treatment response (Fig. 4). All patients had a sustained response to PDT; there were no documented recurrences between the period of the initial PDT sessions and date of death.

Mortality

Eight of nine patients died within 2 days to 13 months following PDT [2 days (1), 21 days (1), 1 month (1), 2 months (1), 3 months (2), 4 months (1), 8 months (1), 13 months (1)]. The mean survival was 6.38 months with a median survival of 4.2 months; there was a probability of survival of 0.11 at 12 months. In one patient who died 2 days after PDT the cause of death was respiratory insufficiency triggered by massive intraoperative hemoptysis (see above). In the remaining patients who died, the cause of death was

attributable to the advanced state of the metastatic disease albeit in two the immediate cause of death was respiratory failure due to extensive lung necrosis with bronchopleural fistula in one and pleural carcinomatosis in another. In the one patient with more limited metastatic disease confined to the bronchus and lung, he is still alive 24 months after his last PDT. He has had metastectomies of his lung tumors and has undergone an additional PDT treatment for recurrent endobronchial disease (Patient 4).

DISCUSSION

PDT defines an interesting treatment modality that has found its application in a variety of clinical settings utilizing a synthetic photosensitizer in concert with light energy. To date there are a limited number of series addressing its use as end stage palliation in patients presenting with malignant airway obstruction due to metastatic endobronchial disease [5–9]. In this series along



Fig. 2. A radiograph from 10/12/02 prior to the administration of PDT shows right upper lobe atelectasis (Patient 4). The patient had metastatic adenocarcinoma of the colon to the right mainstem bronchus.



Fig. 3. A post-PDT radiograph (10/14/02) shows resolution of the atelectasis (Patient 4).

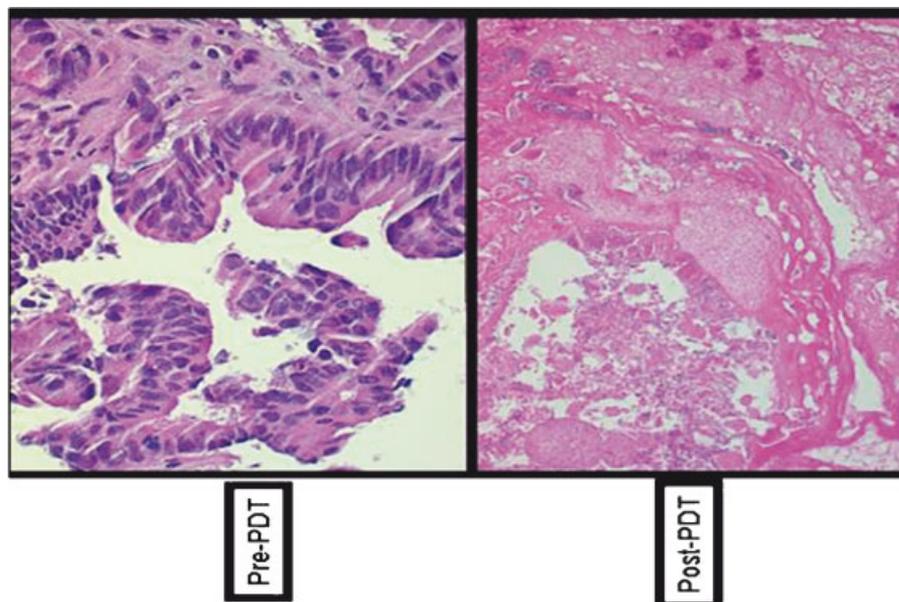


Fig. 4. Pre-PDT: The biopsy of the bronchial lesion shows fragments of moderately differentiated adenocarcinoma compatible with metastatic colonic adenocarcinoma (200 \times , hematoxylin and eosin) (Patient 4). Post-PDT: There is extensive necrosis with fibrin deposition. Viable tumor is not identified (200 \times , hematoxylin and eosin). [Figure can be viewed in color online via www.interscience.wiley.com.]

with other published works, hemoptysis and or obstruction related to metastatic endobronchial disease can be substantially alleviated with PDT. While eight of the nine patients died of their disease the sustained amelioration of their airway symptoms improved their quality of life. In our series, the most common primary tumors were similar to that described in other publications and included colonic adenocarcinoma, breast adenocarcinoma, and renal carcinoma. The affinity of these specific tumors for the bronchus is unclear; however, it is known that select primary malignancies have a tendency to deposit preferentially at certain distant organ sites.

As with the other reported series, we found endobronchial metastatic disease to be indicative of late stage metastatic disease with an average of at least 4 years between the initial primary malignancy diagnosis and the subsequent presentation of metastatic endobronchial disease. While years could pass between the initial diagnosis of the primary malignancy and the subsequent endobronchial metastasis, the survival following interventional palliation with PDT is short, with survival beyond 12 months being exceptional. The poor survival statistics reflects the advanced state of their metastatic disease as the majority of the patients in our series manifested metastatic disease at other sites prior to the development of symptomatic malignant airway disease. However, at least in our experience when the extent of metastatic disease is more limited, especially in the context of endobronchial confined disease, survival beyond 12 months may not be uncommon, a point that will be discussed further.

There are only five prior series utilizing PDT as a palliative and/or therapeutic measure for the treatment of

endobronchial disease [5–9]. The limited literature precedent clearly indicates that its use in this setting while recognized does not appear to be common practice despite its many advantages. Five patients reported in the 1984 series by Balchum et al. had metastatic disease in the bronchi, originating in the thyroid, colon, and breast. Although all experienced subjective relief of obstructive symptoms, none survived more than 14 months [5]. Another series of 13 patients by McCaughan [6] reported endobronchial metastases originating in decreasing of frequency from uterus, colon, breast, gallbladder, kidney, and bladder. The mean percent obstruction due to metastatic non-pulmonary tumors diminished from 85% endoluminal narrowing to 13% with almost 50% of patients experiencing complete response and as well there was statistically significant improvement in the level of dyspnea, hemoptysis, and cough. The median survival was 14 months, which is the longest reported in any of the series to date [6].

The most recent series examining the efficacy of PDT in the treatment and palliation of metastatic endobronchial disease was by Little et al. [8]. In their series comprising 27 patients, the predominant primary tumor was renal cell carcinoma, representing 44% of all cases. Endobronchial metastases presented metachronously with other extra-bronchial metastases in three-quarters of patients. As with our own experience, most patients had received two PDT treatments, with symptomatic relief and an objective response to therapy including extensive tumor cell necrosis. The median survival time after PDT was comparable to our median survival, being 4 months. Of interest the patients who survived longer (up to 30 months) had

metastatic disease largely limited to the airways [8]. Similarly in our series the one patient with more limited metastatic disease confined to lungs and regional lymph nodes is still alive 33 months after his endobronchial presentation and 24 months after his last photodynamic treatment. Both patients had underlying colonic adenocarcinoma. They reported a longer survival in patients with renal carcinoma; however, in our experience both patients with renal carcinoma died within days to months following PDT and in one it was due to hemoptysis. Extensive bleeding from metastatic renal cell carcinomas is a therapeutic dilemma encountered in other organ sites [10–12]. McCaughan [6] reported the median survival for patients with renal cell carcinoma as 6 months; of interest it was longest in those patients with metastatic uterine leiomyosarcoma, being 24 months.

In the Little [8] series the most significant factor contributing to morbidity and mortality was hypoxemia with 15% of their patients requiring intubation or bronchoscopy within 24 hours of PDT and seven patients dying of respiratory failure within 6 weeks following PDT. Balchum and co-workers did not report any complication during the procedure or post-PDT debridement. Four of the patients died of hemoptysis 4–5 weeks following PDT; however, the authors could not attribute the hemoptysis to the PDT *per se* [5]. Vincent and Dougherty reported that 14 of their 17 patients developed significant post-PDT complications with eight of these patients requiring intubation following the procedure. They described excessive mucosal sloughing and bronchial secretions affecting over 50% of their patients receiving PDT [7]. Taber et al. [9] described hypoxemia and respiratory failure requiring intubation in 6 of 19 patients receiving PDT. In our series one patient developed massive intraoperative hemoptysis from a metastatic renal cell carcinoma leading to progressive and rapid hypoxemia; he succumbed to progressive respiratory failure 2 days after his third PDT treatment. Two other patients in our series succumbed to respiratory failure including in the context of one patient who died 21 days after PDT; however, in neither case could the cause of death be directly attributable to PDT intervention but rather was on the basis of massive tumor infiltration of the lung in one and malignant progressive pleural carcinomatosis in another.

In regards to the technique of PDT administration, one parameter that does differ in our series compared to other previously reported series was the implementation of general anesthesia in all cases. General anesthesia ensured precise delivery of the light energy to the discrete tumor sites. Additionally several anesthesia facilitated the debridement process and protected the airway in cases where bleeding occurred. Morbidity and/or mortality that could be directly attributable to the administration of general anesthesia were not encountered in our patient cohort.

Other forms of endoluminal therapy have been used for the palliation of metastatic endobronchial disease, the spectrum comprising laser vaporization, endobronchial brachytherapy, cryotherapy, and mechanical stent placement. Laser therapy and stent replacement are among the

more frequently implemented ones. Thermal laser vaporization treatment using the neodymium: yttrium–aluminum garnet laser (Nd:YAG laser) has been reported as a successful method of relieving airway obstruction secondary to malignancy with the majority of patients experiencing moderate to marked symptomatic relief of dyspnea and hemoptysis [13]. There was associated mortality when the obstruction was bilateral and morbidity, including laryngeal edema requiring intubation, atrial fibrillation, bronchospasm, and acute pulmonary edema. The series by Taber et al. [9] provides a comparative outcome analysis between the Nd:YAG laser and PDT. The two modalities were similar in terms of successful short-term symptom palliation, morbidity, and mortality. Of the 102 patients who were suitable for review, 83 were treated the Nd:YAG laser while PDT was administered to 19 patients. Morbidity rates and 30-day mortality rates related to hypoxemia and massive hemoptysis were similar in both groups. In regards to the two patients who received PDT and then died within 30 days, one had an acute myocardial infarct while the other patient died of massive hemoptysis related to an undiagnosed fistula between the bronchus and a pulmonary vessel that was made larger by the PDT. Others have reported upon this complication with PDT in the setting of obstructing esophageal cancer. There is a growing body of literature describing complications associated with Nd:YAG laser treatment primarily in the intraoperative setting. Among these complications are creating a perforation in the bronchial wall if there is obscuration visually between tumor and bronchial wall, intraluminal fire, smoke plume, and explosion [9,13,14]. When a fire or explosion occurs during the use of the Nd:YAG laser it is usually fatal to the patient and hazardous to the operating room personnel. The smoke plume also referred to as electrosurgical smoke caused by the thermal reaction laser can make treatment difficult due to obscuration of the tumor area and associated unintentional injury to the bronchus [14]. The laser also penetrates much deeper than what is discernible on gross inspection and hence an overzealous treatment by a less experienced operator may have deleterious and potentially fatal consequences.

Endobronchial stenting has been implemented in the palliative management of airway stenosis and in fact is the only form of endoluminal therapy available for extrinsic compression. Stenting prior to the induction of tumor-specific therapy may result in significant clinical improvement of respiratory symptoms, after a mean interval of 26 days from initial placement. The main disadvantage is one of stent migration [15–17].

The antitumor effect of PDT has been attributed to various mechanisms including promotion of apoptosis, direct vascular endothelial injury, induction of a strong inflammatory response via alteration of the cytokine milieu and its inherent indirect adaptive immune effects. Apoptosis following PDT loss of mitochondrial membrane potential, photodamage to Bcl-2, and activation of p38 MAP kinase and is independent of Bax activation [18–20]. PDT leads to selective cytotoxicity of vascular endothelial cells through production of oxidative radicals. It has been shown

that tumor cells co-incubated with photophrin exhibit enhanced cell surface expression and release of heat shock protein (HSP) 70 from treated cells. The HSP triggers Toll receptor transduction resulting in the production of tumor necrosis factor alpha, hence promoting apoptosis [21]. Other non-immune cytokine effects are the enhancement of local and systemic interleukin-6 production subsequent to photophyrin administration, the sequelae of which is neutrophilic infiltration [22]. In the same vein photophyrin upregulation of E selection and ICAM 1 expression by endothelial cells have a similar effect on the induction of neutrophil migration [23]. Neutrophils migrating to the site may contribute to cell death through the release of proteases and other chemokines. PDT results in an immediate downregulation of signaling by receptors for epidermal growth factor, an effect that may interfere with survival of residual tumor cells [24]. With respect to the immunomodulatory attributes of PDT, the effects are in essence indirect. For example, the enhanced expression of surface HSP and higher levels of complement opsonization in PDT treated tumors have been shown to enhance significantly the adaptive humoral and cellular immune response to tumor [24]. Tumor initially defined by an antigenic repertoire, which is "self," becomes altered by the effects of PDT to become neoantigenic. The addition of antiangiogenic factors (e.g., receptor tyrosine kinase inhibitor) has been used experimentally to enhance the antiangiogenic activity and antitumor efficacy by PDT [25–27]. A counter suppressive factor of PDT may relate to a transient loss (48–72 hours following PDT) of responsiveness to cytokines that mediate an inhibitory effect on epithelial cell growth including oncostatin and interleukin-6 [28].

The complex series of events related to photofrin activation account for the immediate local effect and suggest a mechanism for systemic effect.

In conclusion, PDT defines an attractive treatment modality for symptomatic endobronchial disease, comparing favorably with other endoluminal palliative measures. It is a very reasonable treatment option in patient with malignant airway obstruction due to metastatic disease, resulting in improved survival time and quality of life in these patients. Furthermore, in patients with limited metastatic disease, long-term survival may be possible especially if the palliated endobronchial metastasis is the only site of metastatic disease, potentially allowing the option of definitive surgical resection following airway clearing.

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