

Endobronchial Photodynamic Therapy for Lung Cancer

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Background and Objective: Endobronchial photodynamic therapy (PDT) is a minimally invasive technique for the palliation of major airway obstruction from lung cancer, and for the treatment of endobronchial microinvasive lung cancer.

Study Design: Results of reported clinical trials were compared, and the author's preliminary results with second generation photosensitizers were also reviewed.

Results: A review of the clinical experience with endobronchial PDT is provided. Potential advantages of PDT include the duration of palliation achieved through the delayed cellular effects of PDT within tumor. Side-effects from FDA-approved photosensitizer (Photofrin, Porfimer sodium, Axcan Scandipharm, Montreal, Quebec) include skin photosensitivity. HPPH (2-[1-hexyloxyethyl]-2 devinyl pyropheophorbide) is an example of a second-generation photosensitizer that shows promise in the treatment of lung cancer, and appears to be free from significant skin photosensitivity.

Conclusion: PDT is an effective tool for the palliation of endobronchial lung cancers which obstruct the central airways and is also effective for the treatment of central microinvasive carcinoma and carcinoma in situ of the central airways. *Lasers Surg. Med.* 38:364–370, 2006.

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Key words: bronchoscopy; carcinoma in situ; central airway obstruction; HPPH, 2-[1-hexyloxyethyl]-2 devinyl pyropheophorbide; microinvasive carcinoma; lung cancer; palliation; PDT

INTRODUCTION

Lung cancer is an international epidemic, with an estimated yearly incidence of 1.2 million new cases worldwide [1]. It is the leading cause of cancer death in North America. Despite therapeutic advances with minimally invasive surgical techniques, improved radiotherapy dosing with 3-dimensional planning, new chemotherapy agents and targeted therapy, the overall survival at 5 years is poor. This is largely because 85% of lung cancer is advanced at the time of diagnosis. The first-line conventional treatment for localized lung cancer is surgery, with radiation as the second-line therapy for curative intent.

Photodynamic therapy (PDT), like radiation and surgery, is a local therapy. Because the PDT reaction is dependant on direct light administration to the tumor, the use of PDT in the arena of lung cancer has been primarily

limited to lung cancer that is localized in the central airways where it is accessible to fiber optic instruments. This sort of central airway lung cancer represents about 1/3 of all lung cancer. PDT has been used to treat *early* central airway lung cancers (micro invasive disease) for curative intent [2–5] but these lung cancers are relatively rare. PDT has also been used to palliate advanced central airway lung cancers when symptomatic obstruction of the airway occurs [6,7].

PDT relies on the interaction between visible light and a photo sensitizer within tumor cells, and it employs a light absorbing molecule (photo sensitizer) that produces cytotoxic oxygen species upon illumination. Photosensitizers are relatively innocuous compounds in the absence of light [8]. Illumination-mediated cytotoxicity occurs through the intracellular generation of reactive oxygen species, predominantly singlet oxygen in a Type II photo-oxidation reaction. The clinical observation of delayed tumor regression in endobronchial lung cancer may be seen because of such local vascular and inflammatory alterations in the cellular milieu. In cultured tumor and bronchial epithelial cells, PDT induces cross-linking of STAT3, which is primarily localized to the cytoplasm and is directly related to the light dose. The STAT3 cross-linking and inactivation of receptor functions renders surviving PDT-treated cells refractory to interleukin-6 and oncostatin M for at least 24 hours [9]. These cytokines are known to be elevated at site of tissue damage and inflammation. Vascular congestion and red cell extravasation also occur within tumor shortly after light exposure [10,11]. Tumor selectivity is obtained through a therapeutic gradient of photosensitizer concentration between tumor and (most) normal tissues, but selectivity is also augmented when light exposure itself can be targeted specifically within the tumor.

Porfimer sodium (Photofrin, Axcan Pharma, Quebec, Canada) is the first-generation photosensitizer that obtained US regulatory approval for the treatment of both early and late stage endobronchial lung cancer among other indications. Hematoporphyrin derivative (HPD), an investigational first-generation photosensitizer was

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used for lung cancer PDT prior to the isolation of Photofrin as the active component [12].

MATERIALS AND METHODS

Endobronchial PDT: Clinical Technique

Photofrin is given intravenously at a dose of 2 mg/kg, and is preferentially retained in malignant cells, skin, liver and spleen [13]. Photofrin is retained in the skin for up to 6 weeks, and patients are required to observe sunlight precautions with avoidance of full-spectrum light during this time [11]. When doses lower than 2 mg/kg are used, the initial tumor response to PDT is effective, but the likelihood of early recurrence at 30 days post-therapy is increased [14], and the likelihood of photosensitivity is not reduced. Approximately 48 hours after Photofrin administration, bronchoscopy is performed, and the visible endobronchial tumor is exposed to red laser light at 630 nm through a quartz fiber that is advanced through the working channel of the bronchoscope. The fiber may be positioned along side of the tumor when it is flat, or the fiber may be used to impale the tumor when it is bulky and exophytic. The light is usually delivered through a quartz fiber with a cylindrical tip that transilluminates light in 360 degrees within the tumor, or within the airway. Prior to light administration, the length of the tumor is assessed with bronchoscopy, and a suitable light fiber length is selected to transilluminate the tumor. Fibers for the treatment of endobronchial cancer are commercially available, and generally 1, 2, and 2.5 cm tip lengths are adequate for tumor necrosis within the central airways. Within lung and tumor tissue, 630 nm light will penetrate to a depth of 5–10 mm from the point of origin, depending on power density and the length of fiber [15]. The FDA-approved light dose for the treatment of endobronchial lung cancers with Photofrin is 200 J/linear cm (400 mw/linear cm of fiber), but light dosages between 200 and 300 J/cm² have been safely used and are effective for the treatment of endobronchial tumor. The light exposure time for this dose range typically lasts for 8–12 minutes per fiber placement. For large endobronchial tumors, multiple fiber placements may be necessary. Although the Argon-pumped dye laser has been traditionally used as a light source, a new diode-based system (Diomed Ltd., Andover MA) is now commercially available as a compact and less expensive alternative.

Although rapid tumor vascular stasis is observed, the cytotoxicity and cellular death of tumor cells is delayed. Necrotic debris eventually forms at the site of treatment over the next 48 hours, and this debris is tenacious and difficult or impossible to expectorate. Necrotic tumor slough and secretions from bulky tumors may potentially cause respiratory distress, atelectasis or pneumonia. For this reason, a second bronchoscopy is required in 48 hours to remove necrotic debris from the airway. Occasionally local edema and mucous formation from *surrounding normal tissues* may result in transient bronchitic symptoms including cough and dyspnea. PDT may be done under local anesthesia with sedation, or general anesthesia. The decision to treat an individual patient on an outpatient

(vs. inpatient) basis is made based on the degree of central airway obstruction, the underlying lung function, and the patient's projected ability to tolerate a transient increase in respiratory secretions.

Other potential complications of endobronchial PDT include mild pleuritic post-treatment chest pain that responds well to minor analgesics. In earlier series, [16] fatal hemoptysis was reported, and was attributed to tumor erosion into the central major vessels. Major hemoptysis is now prevented by careful case selection, and PDT is avoided when there is tumor encasement of the central great vessels proximate to the area to be treated. Bronchopleural fistulas have been reported in association with intrapleural PDT for mesothelioma [17], but not with endobronchial therapy. Airway stenosis may occur following PDT, as with electrocautery and YAG laser resection [18] but is uncommon.

The most common complication of PDT is sunburn from cutaneous photosensitivity and inadequate sunlight precautions. Incidence ranges from 0 to 20% in published series, sensitivity to sunlight may persist after administration for 6 weeks or longer. Sunburn may be completely prevented with careful instruction and patient compliance to sunlight avoidance. Skin burn has been described following PDT from prolonged exposure to pulse oximetry [19], and care must be taken to move the finger pulse oximeter no less than every 2 hours, and to avoid using skin pulse oximeters on areas where the skin is thin. Patients should be routinely instructed to avoid full-spectrum light, and to wear a hat, gloves, long sleeves, and sunglasses while outside, immediately after Porfimer has been administered. Photobleaching of the Photofrin occurs with ambient low intensity light, and slowly increasing exposure to sunlight is tested at 3–4 weeks from administration. If reaction still occurs, weekly tests are continued until negative. Occasionally, Photofrin may result in permanent darkening of the skin, particularly in patients of African and Asian descent.

RESULTS

PDT for Palliation of Advanced Endobronchial Lung Cancer

Central airway obstruction from lung cancer is a common complication of lung cancer, and local failure with endobronchial recurrence is of locally advanced lung cancer is frequently seen in patients who have been previously treated with radiotherapy or chemoradiotherapy. Prior surgery, chemotherapy or radiation does not preclude the use of PDT. In one series, 85% of patients treated for palliation with PDT had received prior chemoradiotherapy [20]. The symptoms of endobronchial obstruction include progressive dyspnea, cough with occasional severe cough paroxysms, wheezing, atelectasis, and post-obstructive pneumonia. Malignant central airway obstruction may occur through a variety of mechanisms [21] and a variety of endobronchial techniques may be applied to specific scenarios. PDT is most suitable for patients with airway obstruction from tumor *within* the lumen of the major airways [22], sometimes referred to as mucosal tumor. PDT is not suitable for high-grade upper airway obstruction at

TABLE 1. PDT for Palliation of Endobronchial Obstruction: Selected Studies

Reference	Patients (n)	Drug	Palliation	Complications
Kato, 1998 [43]	111	HPD	74%	Sunburn 21.5%
Balchum, 1984 [44]	22	HPD	OR 21/22	Pneumothorax 9%, Pneumonia 13%
Lam, 1986 [45]	24	Photofrin	79%	None
Zwirewich, 1988 [22]	20	Photofrin	89% OR in patients with intraluminal tumor	None
LoCicero, 1990 [46]	10	HPD	100% palliation of symptoms	Sunburn 20%
Moghissi, 1993 [47]	15	Photofrin	RT plus PDT versus YAG	None
Moghissi, 1997 [27]	17	Photofrin	YAG plus PDT 100% palliation of symptoms	Sunburn 5.8%
Dougherty, 2002 [25]	106	Photofrin	PDT superior to YAG at 1 month	Sunburn 20%
Diaz-Jimenez, 1999 [26]	31	Photofrin	PDT improved survival over YAG	Sunburn 28%
Moghissi, 1999 [20]	100	Photofrin	100% palliation of symptoms ^a	Sunburn 5%
Jones, 2001 [30]	10	Photofrin	100%	None

OR, overall response rate (e.g., % relief of endobronchial obstruction).

^a, included small cell lung cancer cases.

the trachea or main carina when respiratory distress is present, because of the 72 hour delay between drug administration and tumor removal. In patients who are not in respiratory distress however, PDT has been used for successful palliation of central airway symptoms in patients with lung cancer, as shown in Table 1. Patients who have developed frank respiratory failure and have been stabilized with mechanical ventilation may benefit from PDT as a method of re-establishing durable airway patency, leading to extubation [23], (Fig. 1).

One important advantage of PDT over other palliative techniques for malignant central airway obstruction appears to be its durability. A median time to relapse of 22 weeks is reported for patients with mucosal intraluminal tumor [45]. A comparative, multi-center PDT trial using Photofrin as sensitizer compared PDT with tumor ablation by Nd: YAG laser. The endpoint of the trial was palliation of the obstructed airway. In this phase III study for FDA approval, there were 141 patients in the European group and 70 patients in the US/Canada group [24,25]. The PDT study group showed significantly enhanced and longer lasting tumor response and symptom relief at 1 month. Adverse events were comparable between PDT and the Nd: YAG treatment arm, with the exception of skin photosensitivity seen in the PDT arm. Although initial post-treatment bronchitis and dyspnea were higher in the PDT group, most cases of bronchitis which occurred within 1 week of treatment, were mild or moderate in intensity, and resolved within 10 days with antibiotic therapy. Any treatment-related worsening of dyspnea in the PDT group was generally transient, resolving with removal of exu-

dates and necrotic tissue with cleanout bronchoscopy. In all, PDT of obstructing endobronchial tumor was safe and effective, providing significantly longer lasting tumor response and symptomatic relief than Nd-YAG. In another randomized trial for central airway obstruction which compared PDT to Nd: YAG laser therapy [26], both the median survival and time until treatment failure and were significantly longer in the PDT group.

PDT has been combined with other endobronchial techniques for palliation of malignant central airway obstruction. When *combined* with YAG laser, relief of airway obstruction is rapid *and* durable [27]. When compared with external beam radiotherapy (EBR), PDT plus EBR provided more sustained relief of respiratory symptoms than EBR alone [28]. PDT has been combined in a sequential manner with HDR brachytherapy for palliation of bulky tumor central airway obstruction [29], but HDR brachytherapy has not been compared directly with PDT. When PDT was combined with endobronchial stents in series of 10 patients with lung cancer [30], it resulted in 100% palliation of obstruction, as well as relief of hemoptysis and improvement of dyspnea.

PDT for Curative Intent for Early Central Endobronchial Lung Cancer

The current staging system for lung cancer widely separates carcinoma in situ (CIS) from stage Ia lung cancer [31], and does not distinguish between the broad differences that are observed between varieties of stage Ia endobronchial lung cancer. For example, microinvasive squamous cell lung cancer will typically present as a flat

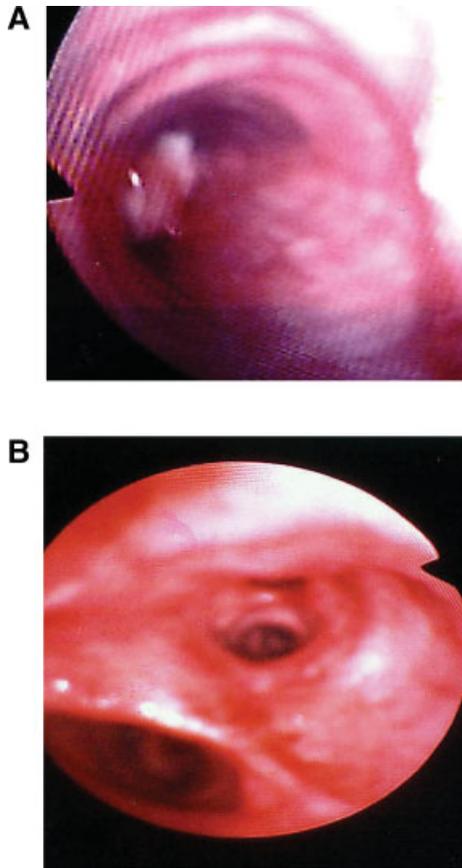


Fig. 1. A 48-year-old male who presented with L lung atelectasis and respiratory failure necessitating mechanical ventilation. **A:** Endobronchial obstruction of the *distal* left main bronchus not suitable for ND: YAG. **B:** Close-up view of distal left main bronchus post-PDT, with erythema. Following debriement, the left lung re-expanded and the patient was weaned from the ventilator within 24 hours.

endobronchial lesion, a few cells in thickness, with invasion of the basement membrane. In the AJCC staging system, such an early lesion with basement membrane invasion is classified exactly the same as a 2.9 cm intraluminal tumor (stage Ia) despite the probable differences of prognosis and differences in potential benefit from endobronchial therapy. Photofrin is used widely for the treatment of CIS, even though in the US it is technically only approved for the treatment of microinvasive (usually squamous) carcinoma. Clinical trials which have used PDT to treat early lung cancer have included stage I lung cancer, microinvasive lung cancer, and CIS, and the true overall response rates in these trials may be obscured by the actual tumor volume. Fujimura and colleagues have proposed that PDT should only be considered in lesions that are less than 10 mm in diameter with visible margins [32], and that larger lesions should be considered for surgical resection with segmentectomy. Although CIS by definition does not invade

cartilage, microinvasive squamous cell carcinoma may invade the cartilage and evade therapeutic light penetration, making PDT ineffectual [33]. Endobronchial ultrasound has been shown to be superior to CT for the determination of depth of microinvasive disease [33,34], and is recommended where it is available.

Attempts have been made to increase the yield of bronchoscopy for the early detection of CIS and microinvasive carcinoma of the central airways. In general, autofluorescence bronchoscopy (AFB) exploits the native fluorescence of the epithelium of the central airways, which is not a feature of surface cancers that are otherwise invisible during white light bronchoscopy. AFB significantly increases the detection of intraepithelial neoplasia compared with white-light bronchoscopy alone [35,36], including premalignant central airway lesions. In one series of heavy smokers or former smokers with sputum atypia, the CIS rate was 1.6% with moderate to severe dysplasia occurring in another 19% of patients; CIS lesions in this population were relatively small, and over half measured less than 1.6 mm in greatest dimension [37]. Commercially available AFB systems in the US include the D-Light (Storz Tittlingen, Germany) and the Onco-Life (Xillix, Canada). It is likely that with the growing availability of AFB, the detection rate of CIS and microinvasive squamous carcinoma will increase, expanding the need for PDT for the treatment of these early lesions.

Some authors have suggested that because PDT is relatively nonselective based on histopathological changes [18], that other endobronchial strategies are preferable for the treatment of early central lung cancers. PDT as a biophysical treatment holds a theoretical advantage for the treatment of flat superficial endobronchial tumors when compared to other endobronchial physical treatments (electrocautery, APC, HDR brachytherapy, cryotherapy) because intraluminal PDT is diffuse rather than focal. This advantage is particularly important for CIS which is difficult to visualize under conventional white light bronchoscopy (Fig. 2).

Over 600 reported cases of PDT for early lung cancer may be found in the literature [24]. Comparison between studies is difficult when CIS, flat superficial microinvasive carcinoma, and stage I lung cancer or greater are included in these reports, and as expected, response rates vary depending on stage and thickness of disease. Selected series of PDT for early superficial endobronchial lung cancers are shown in Table 2. The highest response rates and longest disease-free survival are found in CIS cases, and in superficial flat microinvasive carcinomas less than 1 cm in diameter. Despite this generalization, long-term disease control and potential cure may be also seen in larger lesions, and PDT should not be withheld in the treatment of lesions > 1 cm, if surgery and external beam radiation are not feasible because of underlying medical conditions. Patients who are medically unfit for lung resection or external beam radiation therapy will often tolerate bronchoscopy and PDT without difficulty. As AFB becomes more established for the surveillance of high-risk patients with COPD [38], the scenario of stage 0 or microinvasive

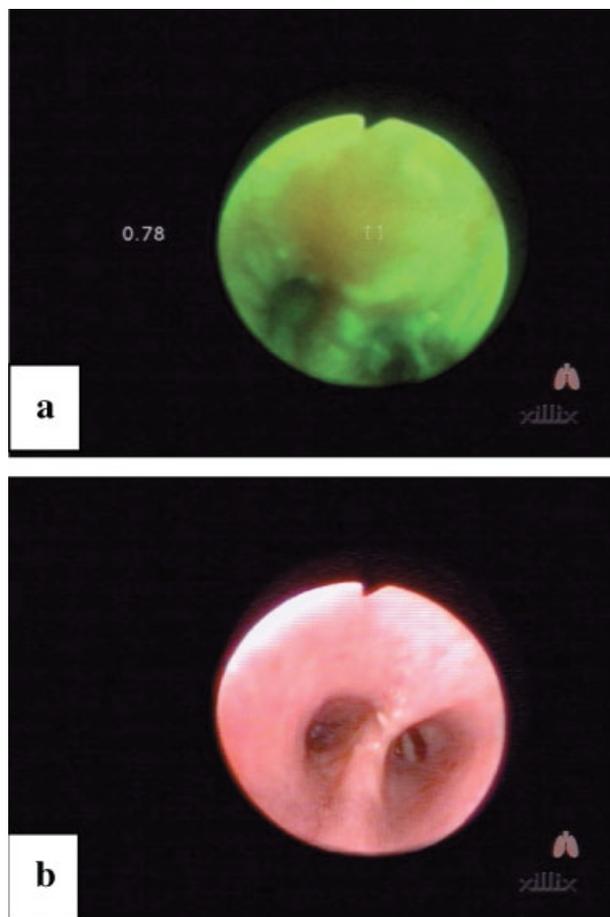


Fig. 2. Superficial microinvasive squamous cell carcinoma bronchus intermedius. (a) Shows the lesion prior to treatment on white light bronchoscopy, and (b) shows the lesion with autofluorescence imaging. The diffuse effect of intraluminal PDT resulted in a complete pathologic response (documented with AF bronchoscopy).

carcinoma in medically unfit patients is likely to become more common.

Second-Generation Photosensitizers for Endobronchial Cancer

While PDT with the FDA-approved drug Photofrin is a highly effective treatment modality, the persistence of Photofrin in skin and associated photosensitization necessitates complete protection from sunlight and other sources of bright light for periods typically of 30–60 days. Further, Photofrin is activated by light at 630 nm, which is suboptimal for tissue penetration. These drawbacks have led to a search for other photosensitizers without these limitations [39]. Second-generation photosensitizers that have been studied for PDT in the treatment of lung cancer include tin etiopurpurin, lutetium texaphyrin, meta-tetrahydroxyphenylchlorin, and polyhematoporphyrin [8]. In addition, the PDT Center at Roswell Park Cancer Institute has evaluated over 400 new photosensitizers as possible successors to Photofrin. One of these compounds, HPPH (2-[1-hexyloxyethyl]-2 devinyl pyropheophorbide or Photochlor), proved to be the most effective photosensitizer among a series of homologues with different numbers of methylene groups on the ether function in a preclinical quantitative structure-activity relationship study [40]. This compound strongly absorbs light at 665 nm, so that penetration into tumor tissue is increased beyond what is possible at 630 nm with Porfimer sodium.

HPPH has been entered into phase I trials at Roswell Park Cancer Institute for early and late stage lung cancer. An IND was also obtained for treatment of partially obstructing esophageal carcinoma, high grade dysplasia in Barrett's esophagus, and basal cell carcinoma of the skin. Pharmacokinetics studies in 25 cancer patients revealed estimated half-lives (95% confidence intervals) of 7.77 hours (3.46–17.6 hours) and 596 hours (120–2951 hours), respectively [41]. No metabolites were detected in serum. Although low concentrations of HPPH could be detected in plasma several months after a single infusion, only 3 of 80 patient reported any degree of cutaneous photosensitivity, and the actually relationship to HPPH was unclear. A more extensive study of skin photosensitivity in 48 patients with

TABLE 2. PDT for Curative Intent in Early Endobronchial Lung Cancer: Selected Studies

Reference	Patients (n)	Drug	Response	Stage
Kato, 1996 [3]	95	Photofrin	83% CR ^a	Stage 0-Ia
Ono, 1992 [48]	36	HPD	31% CR	ROLC ^b
Imamura, 1994 [49]	29	HPD	64% CR	ROLC ^b
Patelli, 1999 [50]	23	Photofrin	62% CR	Stage 0 plus superficial squamous cell
Sutedja, 1992 [51]	11	Photofrin	90% CR	Stage I
Lam, 1998 [35]	102	Photofrin	78% CR	CIS, Ia and Ib
Edell, 1987 [52]	13	HPD	100% CR	ROLC ^a , <3 cm and superficial

^aComplete Response (pathologic).

^bRadiographically occult lung cancer.

TABLE 3. Phase I Results of HPPH PDT for Endobronchial Lung Cancer

Dosimetry cohort	Patients/lesions N)/n	Response by Lesion (CR/PR)	Adverse events
75 J	(3) 4	(3/1)	Gr. II debris, Gr. I sunburn
85 J	(3) 3	(2/0) 1 unevaluable	Gr. I debris, Gr. IV MI 1 week after treatment ^a
100 J	(3) 3	(2/1)	Gr. II fever
110 J	(3) 3	(3/0)	Gr. I sunburn, Gr. II exacerbation of COPD
130 J	(1) 1	(0/1)	Gr. I sunburn ^b
150 J	(3) 5	(4/0) 1 no response	Gr. III debris, Gr. I erythema

PR, partial response; CR, complete response.

^aJudged unrelated to PDT.

^bMild transient burning sensation of skin on exposure to sunlight without erythema.

HPPH (Photochlor)-PDT, receiving drug doses of 2.5–6 mg/m² and solar simulator light doses from 44.4–133.2 J/cm², has demonstrated that even 1 day after drug administration the highest drug and light doses elicited a response of only erythema without edema [42]. Even these mild responses declined over a few days. A total of 16 lung cancer patients have been treated with HPPH-based PDT (Table 2); all patients except one have had complete or partial responses, and skin photosensitivity has been negligible (Table 3).

CONCLUSIONS

Despite the effectiveness and apparent advantages of PDT as a biophysical treatment modality for endobronchial lung cancer, other physical endobronchial treatment methods (YAG laser, electrocautery, and cryotherapy) have also gained popularity because of their availability and affordability. Randomized controlled trials are needed to compare these modalities with PDT. Such comparisons are particularly relevant because of the economical diode-based light sources for PDT, and with the eventual advent of cheaper, generic photosensitizers. Second-generation photosensitizers that have improved efficacy without photosensitivity could also improve the practical utility of PDT for palliative care of endobronchial lung cancer. The growing use of AFB will ultimately result in increased detection of microinvasive central squamous cell lung cancer, which is best suited for treatment with PDT. Ultimately, however, the future of PDT in lung cancer depends on the availability of training for physicians who desire to integrate it into their bronchoscopy practice.

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