Chapter

Clinical Usage of Photodynamic Therapy

Niral M. Patel and Ali I. Musani

Abstract

This chapter will provide a brief overview of the fundamentals of photodynamic therapy with an emphasis on its use in a clinical setting. Beginning with the history and fundamental science underlying photodynamic therapy and delving into clinical uses. There will be a primary focus on understanding the use of photodynamic therapy under currently approved clinical indications along with their limitations. There are a number of approved therapeutic indications for photodynamic therapy, but there are important limitations and contraindications when applying this therapy. Photodynamic therapy, as applied to the clinical treatment of cancer will be the primary focus with further emphasis on endoluminal and specifically endobronchial cancer as the primary case study.

Keywords: photodynamic therapy, lung cancer, esophageal cancer, Barrett's esophagus, interventional pulmonology, interventional gastroenterology

1. Introduction

Photodynamic therapy is a minimally invasive approach for the treatment of malignancy [1, 2]. It involves selective uptake of a photosensitizing agent, which is then activated by specific wavelengths of light [3, 4]. This results in oxidative damage to the cells by the production of reactive oxygen species [5, 6]. This results in targeted cellular destruction [5, 6]. Along with this direct cellular destruction, there are local inflammatory effects as well as vascular thromboemboli formation, which allow for a further delayed therapeutic effect [5, 6]. The thromboemboli effect blocks blood flow to the target and thereby results in ischemia [5–7]. Photodynamic therapy has been approved across the world for a number of different clinical indications [5, 6]. This chapter will review the mechanisms and clinical utility of photodynamic therapy.

A photosensitizer in this context is an agent, often a porphyrin which reacts to light in the 500–800 nanometer range depending upon the specific agent utilized [7]. The earliest described photodynamic effect was in 1900 by Raab, Von Tappeiner coined the term photodynamic therapy [3, 5]. Over time, hematoporphyrins were noted to result in tumor fluorescence [3]. This was gradually studied further and refined until the nature of the porphyrins was better understood. Light exposure following cellular uptake resulted in cellular damage and destruction [6]. Over time the fundamentals of this damage were better understood. Depending upon the exact photosensitizer, different mechanisms of damage have been proposed. The major mechanisms of damage are singlet oxygen and free radical formation inducing: apoptosis, autophagy, and necrosis [6, 8, 9]. Apoptosis is a form of

controlled cellular death which in this case is induced when photosensitizers cause damage to mitochondria or the proteins of bcl-2 [6]. These are major regulators of the cellular death pathway. Autophagy allows for the gradual destruction of cellular components in an ordered manner [8]. However, necrosis is a less orderly effect and can often result in unintended tissue damage due to the disorganized manner of tissue destruction [6, 8].

Over time, many different photosensitizers have been discovered, but of these, only a few have seen broad clinical approval and use [5, 6, 10]. Each photosensitizer is reactive at a specific wavelength of light. Hematoporphyrin (HPD) was the first photosensitizer approved by the FDA in 1995 for the indication of esophageal cancer. HPD was a hematoporphyrin mixture containing monomers and chains of varying lengths [3, 5, 6]. Photofrin (porfimer sodium) is a refined version of HPD with monomers removed, and it is one of the most common clinically used agents, see **Figure 1** [3, 5, 6]. Photosensitizers are primarily porphyrin-based and contain multiple ring structures [3, 5, 6, 11]. These can be applied locally or injected systemically, and over a period of time they will be selectively taken up by cells [3, 5, 6, 11]. Porfimer sodium is part of the first generation of photosensitizers developed in the 1970s and early 1980s [5, 10, 12]. Later generations were developed as the characteristics of the agents were chemically refined [5, 10, 12]. These later generation agents also tended to have decreased duration of systemic photosensitivity [3, 5, 6, 11]. The second generation has been refined to target longer wavelengths of light, thus allowing for deeper tissue penetration of the activating wavelength of light and, therefore greater effect [5, 6, 11]. In conjunction with the increased penetration of longer wavelengths of light, the light source can be embedded into the tissue to allow for an alternative way to increase the effect [6, 11].

Photodynamic therapy has approved indications for superficial or early-stage malignancies as well as late-stage malignancies [5, 6]. These indications intuitively make sense as light penetration is a vital component of this therapy. Given that later stages of malignancy typically spread systemically via blood or lymphatic spread, photodynamic therapy has limited utility in those cases unless it is for a local effect. For example, photodynamic therapy has been well described as an alternative therapy in addressing central airway obstructions in lung cancer [13]. Central airway obstructions are typically manifestations of late-stage cancer, but photodynamic

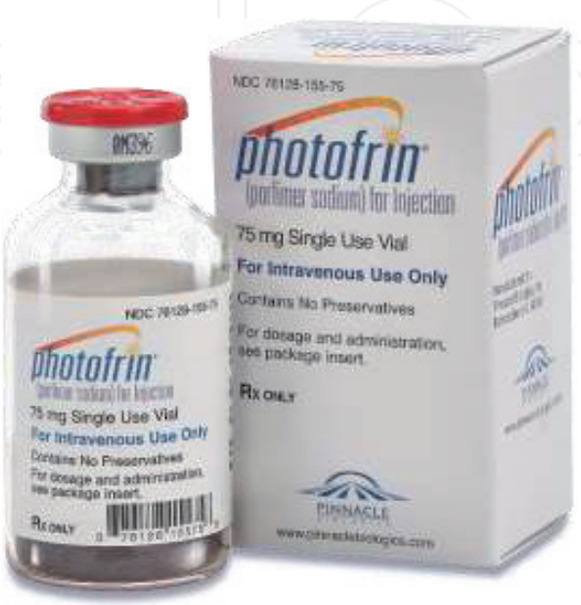

Figure 1.
Comercially available porfimer sodium. Photo used with permission from Pinnacle Biologics.

therapy can be used to clear the tumor obstructing the airway even when it does not have the ability to affect the entirety of the metastatic tumor burden [1, 2, 13]. In many ways, this focused local effect is a significant advantage over alternative treatments which can have greater side effects [1, 2, 13]. These cases of central airway obstruction can be challenging and having an option to provide a delayed and gradual effect that specifically targets tumor cells can be a vital therapeutic intervention. Skin and endoluminal malignancy treatment are approved indications for photodynamic therapy, but this chapter will primarily focus on endoluminal malignancy and especially endobronchial malignancy. Of the photosensitizing agents commercially available, Protomir sodium is the most well studied and widely available, and the best understood.

Photodynamic therapy usage in lung cancer is used as the primary example for a few reasons. The primary being that in many ways. it is the most challenging application. The esophagus consists of a single cylindrical region where the therapy is applied, and blockage of it is not life threatening. Utilization of photodynamic therapy on the skin similarly has limited side effects. However, utilization of photodynamic therapy within the pulmonarysystem is limited to only some surfaces, and damage to this tissue has the potential for life threatening complications. Therefore, understanding the practical applications of photodynamic therapy within the context of lung cancer can be extrapolated to other vital organs.

2. Contraindications of photodynamic therapy

Photodynamic therapy and porfimer sodium, in particular, has a set of contraindications that are worth noting. Porfimer sodium and really any photodynamic therapy cannot be used therapeutically in individuals with porphyria [14, 15]. These individuals have one of a group of diseases that allow for an increased accumulation of porphyrins utilized by the human body in hemoglobin production, and these porphyrins increase photosensitivity [16]. Given the foundation of photodynamic therapy is localized photosensitivity by means of porphyrins, this contraindication is reasonable [3]. Other contraindications are existing tracheoesophageal/bronchoesophageal fistulas [17]. These are abnormal connections between the airway and the esophagus. Tumor eroding into the airway are also contraindicated given the risks that will be described below [17]. Additionally, given the delayed time scale of photodynamic therapy, usage in emergency situations when therapy must be delivered immediately would not be optimal [17].

3. Fundamentals of lung cancer

Throughout the world, lung cancer is one of the most prevalent cancers worldwide; it is the most commonly occurring cancer in men and the third most common in women [18]. The best treatment responses to lung cancer are early detection, diagnosis, and treatment [18, 19]. Photodynamic therapy has a robust role in both early and late-stage lung cancers [20]. Lung cancer has significant morbidity and mortality, and there has been strong interest and research in identifying treatments to improve the morbidity and mortality associated with this disease process [18, 19, 21]. Frequently, management of lung cancer is discussed in local meetings at tumor boards allow physicians of different specialties to determine the optimal next stage of diagnosis or treatment [21]. Knowing the risks and benefits of photodynamic therapy in this context can allow for discussion of the optimal role it can play in treatment.

4. Fundamentals of photodynamic therapy for lung cancer

In the United States, the FDA has approved the usage of photodynamic therapy (porfimer sodium) for endobronchial malignancy [17]. Within the airway, this treatment is applied to non-small cell lung cancer that is not otherwise treatable by surgery or radiation therapy [17]. Beyond this, the limitation to therapy is solely the ability to illuminate the desired areas of disease with the correct wavelength of light [3, 6, 11, 22]. This, therefore limits therapy to lesions that are primarily visible on bronchoscopy. Standard bronchoscopy is able to visualize airways out to the fourth or fifth generation of airways [23]. The airways of the human go out past twenty generations which can limit utility to only the larger central airways [24]. There have been preliminary studies utilizing electromagnetic navigational bronchoscopic approaches to treat more distal malignancies, but these are still early studies [25]. There are also tools now available, including robotic bronchoscopic platforms that allow for navigation, direct visualization, and intervention down to the ninth generation of airways [26]. Although not directly studied with photodynamic therapy, these recent developments could greatly expand the role of photodynamic therapy in lung cancer.

Currently, the major roles for photodynamic therapy in lung cancer are utilizing it early-stage carcinoma in situ or in central airway lesions [1, 2, 13, 20, 27]. There have been multiple off-label uses and case series reporting success in other disease processes, such as in tracheal papillomatosis [28]. This is a relatively benign but recurrent papillomatosis disease of the trachea causing partial obstruction overtime with significant risk for malignant transformation of the underlying papillomas [28]. Although not directly approved for this indication, as will be discussed, endoluminal obstruction in an early or premalignant disease process is not too far from the currently approved indications [28].

Photodynamic therapy can also target the vasculature that feeds areas of malignancy [5]. This can require illumination with the appropriate wavelength of light up to 30 minutes after exposure/injection to the photosensitizer [5, 7]. This ensures the photosensitizers are still circulating and in the vasculature near the target malignant cells [5, 7]. This approach is more often used in ocular conditions such as macular degeneration to target neovascularization as well as cutaneous lesions of the skin [5]. Photodynamic therapy targeting vasculature has demonstrated efficacy in animal models of solid tumors [7]. However, additional studies need to be performed.

There has been increasing interest in the local injection of photosensitizers directly into tumors [5, 12]. Although only early studies have been done, this has demonstrated efficacy in tumors as small as 8 mm in diameter [12]. However, again these are results from early studies. In general, there are many areas of research both clinical and in basic science for photodynamic therapy. However, clinical utilization often has stringent criteria [17]. Therefore, the focus on the currently approved indications will be to better understand where growth in clinical utilization of this technique will need to occur. Given the requirements for safely delivering therapy to patients, understanding these limitations can help guide the future direction of clinical and translational research. Lung cancer will be utilized as a primary model given the unique characteristics of its prevalence and complexity, and esophageal cancer use will be contrasted to it.

5. Approach to photodynamic therapy in lung cancer

Airway lesions must first be identified then confirmed bronchoscopically to ensure the lesions can be reached and light can be applied to the desired areas.

Additionally, it is important to note the anatomy of the area surrounding the lesions. If the lesion location is adjacent to the large blood vessels surrounding the airway, the risk of massive hemoptysis should be considered prior to administering therapy [29]. This is also true for large central airway tumors that may have large vascular beds [29, 30]. As necrosis occurs, these perforating vessels can potentially lead to significant bleeding. The risk of further airway compromise in an already partially compromised airway (i.e. from the central airway tumor) is already significant in these scenarios. This is a greater consideration when there is malignancy both intrinsic and extrinsic to the airway. Additionally, there is a risk of fistula formation into the surrounding structures of the thorax such as: the esophagus, mediastinum, or blood vessels (pulmonary artery, superior vena cava, innominate vein, etc.) [31]. It should also be noted that mediastinal anatomy, especially airways and blood vessels will shift out of their traditional anatomic locations in the presence of large tumor burden. Being aware of these changes can be vital when reviewing a patient for consideration of photodynamic therapy. Depending upon the shape and course of the lesions, consideration should be given to the anticipated inflammatory effects during photodynamic therapy as the process of controlled and uncontrolled cell death occurs. The areas particularly at risk are the trachea, carina, and main stem bronchi [17, 29]. In these cases, long or circumferential tumors would be at a higher risk of obstructing the airway given the expansion associated with edema that would be anticipated with photodynamic therapy [17]. Additionally, individuals with impaired liver and/or renal function can have delayed clearance of porfimer sodium [17]. This delayed clearance can prolong the period of photosensitivity beyond 90 days when it would typically be ~30 days [5, 12, 28].

Skin/systemic photosensitivity is the most significant and common adverse effect associated with photodynamic therapy [17]. Following the injection of the photosensitizer, it is important to ensure that patients are able to protect their skin until the photosensitizer is fully cleared [17]. This can be as short as two weeks and sometimes as long as three months [5, 6, 12]. Ensuring patients remain indoors for this period to prevent serious collateral skin damage from occurring is vital to safely administering this therapy [17]. Porfimer sodium has not been extensively studied in pregnant and lactating women, but there are animal studies that have demonstrated adverse effects [17]. This has led to porfimer sulfate having an FDA pregnancy category of C, ie animal studies demonstrating adverse fetus effects without any well-controlled human studies, but the benefits may warrant consideration in this population. Similarly, there are no studies on lactation either, so it is not known if porfimer sulfate is secreted in breast milk [17].

Porfimer sodium is injected systemically at a dosage of 2 mg/kg intravenously over 3–5 minutes; this is considered time zero [2, 28]. From this point onwards, the patient will be extremely photosensitive and must wear protective clothing. Additionally, there can be ocular sensitivity, so it is important for patients to wear dark glasses that transmit <4% of white light over the next 30 days [17]. Over the next 2–3 days from time zero, the porfimer sodium will preferentially localize to the desired areas of malignancy over this period of time [5, 6]. Next, the patient will be brought in for a bronchoscopy for the second stage of the treatment [17]. This typically will occur 40–50 hours from time zero [1, 2]. Upon reidentification of the lesions of interest, here a laser light diffuser illuminating at a wavelength of 620 nm with 200 J/cm for the length of the diffuser is utilized, **Figure 2** shows available diffusers [17]. The duration of illumination is eight minutes and twenty seconds (five hundred seconds) [17]. If the tissue of the lesion is soft and allows, the fiber can be positioned interstitially, otherwise the fiber remains within the lumen of the airway for the five hundred seconds of illumination [17]. During this period all

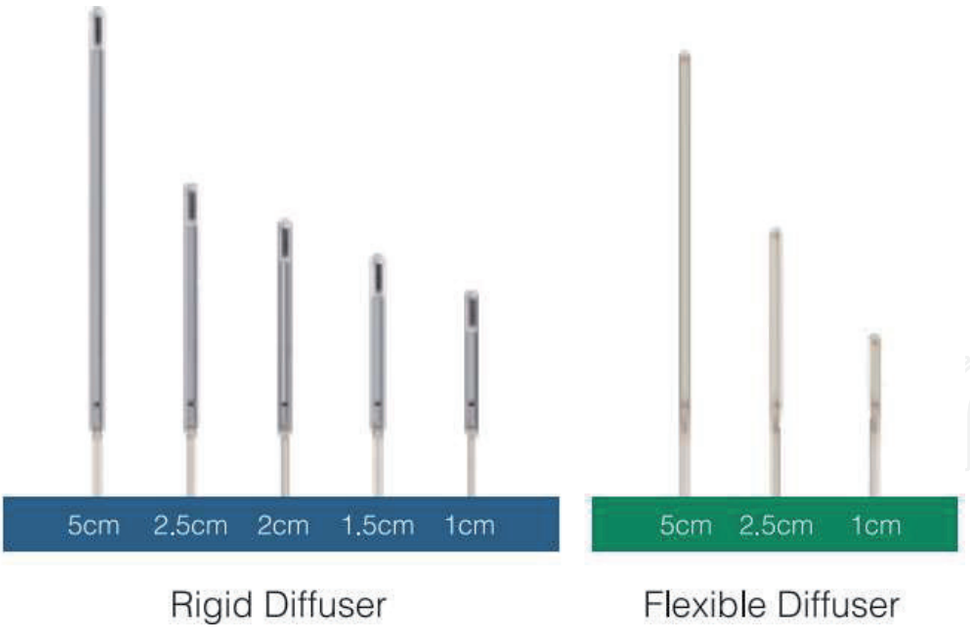

Figure 2.
Comercially available laser diffuser fibers for endobronchial use. Photo used with permission from Pinnacle Biologics.

individuals, including the patient receiving therapy, in the procedure room wear eye protection. Following endoillumination of the desired lesions, it is often advisable to have the patients hospitalized for observation [17]. As the tumor sloughs off, it can often be necessary to debride the necrotic tissue to prevent obstruction of the airway [17]. This is recommended to be done 48–72 hours after the light treatment, or 88–122 hours from time zero [17]. If it is clinically indicated a second light treatment can be performed 96–120 hours from time zero [17]. Given there is an overlap between when tissue debridement is performed and when a second light therapy can be indicated, they are sometimes performed simultaneously. Although the tumor debridement is recommended to be 48–72 hours from light therapy, there can often be a very robust tissue response, and the debridement may need to be done sooner and multiple times before the photodynamic effect is fully realized. Given that airway obstruction can be an emergent and life-threatening condition if not intervened upon quickly, there is a strong reason to keep patients hospitalized for the duration of this therapy.

Following the first injection of Porfimer sodium, subsequent injections and light exposures can be repeated as described above up to three times [17]. However, each treatment must be separated by thirty days. If radiation therapy was performed at any point there should be a period of approximately four weeks from the completion of radiation before photodynamic therapy is attempted [17]. After exposure to porfimer sodium, exposure to sunlight can cause a significant skin reaction, but indoor light can help clear the residual photosensitizer [17]. The duration of the of photosensitivity period can vary from patient to patient, and should be individualized, but a minimum of thirty days should be considered [17]. To determine if there is any residual photosensitivity, patients can be instructed to expose an area of skin to sunlight for approximately ten minutes and then observe for any skin reaction over the subsequent twenty-four hours. As it may be difficult to remember exactly where the exposure was, using a pen or marker to outline the sun-exposed area can help identify this area. Following treatment, chest discomfort secondary to the associated inflammatory effect may require temporary analgesia until the inflammation subsides [17].

6. Esophageal cancer and high-grade Barrett's esophagus

Similar to lung cancer, the dosing for porfimer sodium is 2 mg/kg [17]. The laser light diffuser utilized however, is different. In esophageal cancer a laser light diffuse of 200 J/cm is utilized, and in Barrett's esophagus, a laser light diffuser of 130 J/cm is used, see **Figure 2** for current available laser light diffusers [17]. High-grade Barrett esophagus is the final precancerous stage before progressing to esophageal cancer [32]. Typically, high- grade Barrett esophagus is treated by surgical resection [32]. Treatment of high-grade Barrett's esophagus is an approved indication for photodynamic therapy if surgical resection is not an option [17, 33]. Treatment of esophageal cancer is an approved treatment for photodynamic therapy if there is complete obstruction of the esophagus by tumor or a partial obstruction that cannot adequately be treated by laser therapy/debridement [17, 33]. Given that the esophagus travels just posterior to the trachea and mainstem bronchi, the risks of fistula formation are the same and primarily to the trachea, blood vessels, and mediastinum. Specifically, if a tumor has already spread into these structures, there is a higher risk of fistula formation as the malignant cells are destroyed from photodynamic therapy. Esophageal varices are veins within the esophagus that are enlarged. These veins are at high risk for bleeding and rupture at baseline, and photoactivation of the photosensitizer in these veins could lead to significant bleeding [17]. Specifically, if these varices are >1 cm in diameter, the risk is likely too great [17]. Following treatment of Barrett esophagus, there is a risk of esophageal strictures resulting in food dysphagia (inability to swallow) [34]. In research studies these strictures occurred in 38% of subjects within six months of initiating photodynamic therapy. This is typically treated with dilation of the stricture, but it may require other treatments, depending upon the severity [17].

In esophageal cancer the timeline from injection to photoactivation of the photosensitizer is the same as in lung cancer. The time of injection (time zero) to photoactivation (40–50 hours from time zero) to potential second photoactivation (96–120 hours) is the same [17]. However, the duration of the treatment is different, the exposure to light is 12.5 minutes (750 seconds) [17]. A minimum of 30 days between injections of porfimer sodium is recommended with similar distancing between radiation therapy and photodynamic therapy [17]. Additionally, just as in lung cancer, endoscopic re-evaluation between treatments is recommended to ensure no complications have occurred such as fistula formation [17]. Barrett's esophagus has similar injection to photoactivation of the photosensitizer is the same as in lung cancer and esophageal cancer [17]. The time of injection (time zero) to photoactivation (40–50 hours from time zero) is the same [17]. The duration of treatment with light can however vary depending upon the length of the laser light diffuser utilized to deliver therapy with a maximum length of 7 cm treated at any one time [17]. In high-grade Barrett's esophagus, the time interval between injections of porfimer sodium is a minimum of 90 days [17].

7. Building a photodynamic therapy program

In building a program that utilizes photodynamic therapy, a collaborative and team-based approach is often vital. This is especially true in cases immediately after light exposure when interventions may need to be done at any hour of the day depending upon the reaction to photdynamic therapy. In the world of Oncology, there are frequent meetings amongst local specialists to discuss how best to diagnose and treat suspected cancers. These tumor boards meet regularly to review

patient cases and determine next steps [21]. Given that photodynamic therapy uses similar equipment, it is reasonable to share equipment across a single institution to maximize utility. Depending upon the country/locale it is administered cost of the drug, approval by insurance/regulatory agencies, and equipment costs can easily add up significantly. Porfimer sodium is sold commercially as Photofirin and is sold by Concordia Healthcare Corporation. Its retail cost in the United States is > $20,000 per dose. Between the cost of the drug, facility fees, physician fees, and the need for frequent short term follow up the upfront costs may be high. The upfront costs of utilizing this therapy can be difficult to overcome, but a shared resource model can help overcome this given the benefits provided. With a robust clinical program, there is always room to expand the research aspect of photodynamic therapy, whether it is basic research, translational research, or clinical research.

8. Conclusion

In the years since photodynamic therapy was first discovered and developed through today, it has gone through numerous iterations. From the early identification of fluorescence to the discovery of selective uptake and tissue destruction with light exposure, the field of photodynamic therapy has had great potential. The number of publications has increased year over year, and there are no signs of this decreasing in the near future. From a biochemical perspective, its mechanism of action is unique and it shows great promise for the future as a scientific tool as well as a therapeutic one. However, as a therapeutic instrument there are currently limited indications, and even amongst these indications there are both obvious and subtle advantages and disadvantages in its use. Fully understanding the limitations of the current clinical role of photodynamic therapy can allow for future research and development to better address the current shortcomings and allow for even more widespread use of this technology.

Author details

Niral M. Patel[1,2*] and Ali I. Musani[2]

1 Division of Pulmonary Diseases and Critical Care Medicine, University of California Irvine, Orange, CA, USA

2 Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado, Denver, CO, USA

*Address all correspondence to: niral.patel@uci.edu

References

[1] Bilaceroglu, S., *Endobronchial Ablative Therapies.* Clin Chest Med, 2018.**39**(1): p. 139-148.

[2] Seaman, J.C. and A.I. Musani, *Endobronchial ablative therapies.* Clin Chest Med, 2013.**34**(3): p. 417-25.

[3] Kessel, D., *Photodynamic Therapy: A Brief History.* J Clin Med, 2019.**8**(10).

[4] Kessel, D., *Components of hematoporphyrin derivatives and their tumor-localizing capacity.* Cancer Res, 1982.**42**(5): p. 1703-6.

[5] Dolmans, D.E., D. Fukumura, and R.K. Jain, *Photodynamic therapy for cancer.* Nat Rev Cancer, 2003. **3**(5): p. 380-7.

[6] dos Santos, A.F., et al., *Photodynamic therapy in cancer treatment - an update review.* Journal of Cancer Metastasis and Treatment, 2019. **5**: p. 25.

[7] Huang, Z., et al., *Photodynamic therapy for treatment of solid tumors--potential and technical challenges.* Technol Cancer Res Treat, 2008. **7**(4): p. 309-20.

[8] Kessel, D., *Apoptosis, Paraptosis and Autophagy: Death and Survival Pathways Associated with Photodynamic Therapy.* Photochem Photobiol, 2019. **95**(1): p. 119-125.

[9] Agarwal, M.L., et al., *Photodynamic therapy induces rapid cell death by apoptosis in L5178Y mouse lymphoma cells.* Cancer Res, 1991. **51**(21): p. 5993-6.

[10] McFarland, S.A., et al., *Metal-based photosensitizers for photodynamic therapy: the future of multimodal oncology?* Curr Opin Chem Biol, 2020. **56**: p. 23-27.

[11] Dougherty, T.J., et al., *Photodynamic therapy.* J Natl Cancer Inst, 1998. **90**(12): p. 889-905.

[12] Huang, Z., et al., *Photodynamic therapy of cancer — Challenges of multidrug resistance.* Journal of Innovative Optical Health Sciences, 2015. **08**(01): p. 1530002.

[13] Diaz-Jimenez, J.P., et al., *Efficacy and safety of photodynamic therapy versus Nd-YAG laser resection in NSCLC with airway obstruction.* Eur Respir J, 1999. **14**(4): p. 800-5.

[14] Babes, A., et al., *Photosensitization in Porphyrias and Photodynamic Therapy Involves TRPA1 and TRPV1.* J Neurosci, 2016. **36**(19): p. 5264-78.

[15] Sylantiev, C., et al., *Acute neuropathy mimicking porphyria induced by aminolevulinic acid during photodynamic therapy.* Muscle Nerve, 2005. **31**(3): p. 390-3.

[16] Bissell, D.M., K.E. Anderson, and H.L. Bonkovsky, *Porphyria.* N Engl J Med, 2017. **377**(9): p. 862-872.

[17] *Pinnacle Biologics. Photofrin (porfimer sodium) [Injection Label]. U.S. Food and Drug Administration Revised 06/2008.*

[18] Dela Cruz, C.S., L.T. Tanoue, and R.A. Matthay, *Lung cancer: epidemiology, etiology, and prevention.* Clin Chest Med, 2011. **32**(4): p. 605-44.

[19] Colt, H.G., et al., *Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines.* Chest, 2013. **143**(5 Suppl): p. e437S-e454S.

[20] Simone, C.B., 2nd, et al., *Photodynamic therapy for the treatment of non-small cell lung cancer.* J Thorac Dis, 2012. **4**(1): p. 63-75.

[21] Kay, F.U., et al., *Revisions to the Tumor, Node, Metastasis staging of lung cancer (8(th) edition): Rationale, radiologic findings and clinical implications.* World J Radiol, 2017.**9**(6): p. 269-279.

[22] Minnich, D.J., et al., *Photodynamic laser therapy for lesions in the airway.* Ann Thorac Surg, 2010.**89**(6): p. 1744-8; discussion 1748-9.

[23] Leong, S., et al., *Diagnostic bronchoscopy--current and future perspectives.* J Thorac Dis, 2013. **5 Suppl 5**: p. S498-510.

[24] Patwa, A. and A. Shah, *Anatomy and physiology of respiratory system relevant to anaesthesia.* Indian J Anaesth, 2015. **59**(9): p. 533-41.

[25] Musani, A.I., et al., *Photodynamic therapy via navigational bronchoscopy for peripheral lung cancer in dogs.* Lasers Surg Med, 2018. **50**(5): p. 483-490.

[26] Murgu, S.D., *Robotic assisted-bronchoscopy: technical tips and lessons learned from the initial experience with sampling peripheral lung lesions.* BMC Pulm Med, 2019. **19**(1): p. 89.

[27] Jayadevappa, R., et al., *Outcomes of patients with advanced non-small cell lung cancer and airway obstruction treated with photodynamic therapy and non-photodynamic therapy ablation modalities.* J Thorac Dis, 2019. **11**(10): p. 4389-4399.

[28] Glisinski, K., et al., *Photodynamic therapy for the treatment of tracheobronchial papillomatosis: A multicenter experience.* Photodiagnosis Photodyn Ther, 2020. **30**: p. 101711.

[29] MacRosty, C.R., et al., *Fatal Hemoptysis in a Patient With Left Mainstem Bronchus Squamous Cell Carcinoma Treated With Photodynamic Therapy: A Case Report and Review of the Literature.* J Bronchology Interv Pulmonol, 2019. **26**(4): p. e60-e63.

[30] Johnstone, C. and S.E. Rich, *Bleeding in cancer patients and its treatment: a review.* Ann Palliat Med, 2018. **7**(2): p. 265-273.

[31] Liu, W. and J. Deslauriers, *Mediastinal divisions and compartments.* Thorac Surg Clin, 2011. **21**(2): p. 183-90, viii.

[32] Naini, B.V., R.F. Souza, and R.D. Odze, *Barrett's Esophagus: A Comprehensive and Contemporary Review for Pathologists.* Am J Surg Pathol, 2016. **40**(5): p. e45-66.

[33] Wu, H., T. Minamide, and T. Yano, *Role of photodynamic therapy in the treatment of esophageal cancer.* Dig Endosc, 2019. **31**(5): p. 508-516.

[34] Overholt, B.F., M. Panjehpour, and J.M. Haydek, *Photodynamic therapy for Barrett's esophagus: follow-up in 100 patients.* Gastrointest Endosc, 1999. **49**(1): p. 1-7.