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Factors influencing the efficacy of photodynamic therapy in tracheobronchial lung cancer

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Abstract

Objective: This study aimed to identify factors associated with heterogeneous therapeutic responses to photodynamic therapy (PDT) in patients with tracheobronchial lung cancer.

Methods: We retrospectively analyzed data from patients with tracheobronchial lung cancer who underwent PDT followed by combined immunotherapy and chemotherapy over the past 12 years. We evaluated lesion location, histopathological type, bronchoscopic findings, PDT-related treatment parameters, and follow-up outcomes. These clinical data were integrated with evidence from the literature to evaluate key factors affecting treatment efficacy.

Results: PDT efficacy may be influenced by anatomical location, pathological type, photosensitizer distribution, drug dose, irradiation timing, irradiation parameters, patient-specific factors, bronchoscopic technique, and combination-treatment strategies.

Conclusion: PDT efficacy is determined by the interplay of multiple factors. Patients with central, superficial lesions and squamous cell carcinoma may be more likely to benefit from PDT. PDT may be valuable for improving local disease control and creating favorable conditions for subsequent multimodal therapy. Larger studies are needed to validate these findings.

1. Introduction

Lung cancer remains one of the most common and lethal malignancies worldwide [9]. Because early-stage lung cancer often lacks specific symptoms, most patients are diagnosed at locally advanced or advanced stages. Such delayed diagnosis substantially reduces the opportunity for curative treatment [19]. In addition to the disease burden itself, patients often experience substantial psychological distress and financial strain[57, 77]. Despite advances in surgery, chemoradiotherapy, targeted therapy, and immunotherapy, some patients remain ineligible for standard treatment. These limitations may be attributable to advanced age, comorbidities, tumor anatomical location, or poor treatment tolerance [22, 60, 88]. Therefore, minimally invasive, low-toxicity, and repeatable therapies that provide effective local control are of considerable clinical value [89].

Photodynamic therapy (PDT) is a local therapeutic approach based on the interaction of a photosensitizer, wavelength-specific laser irradiation, and oxygen. This interaction generates reactive oxygen species (ROS), selectively damages tumor tissue, and minimizes injury to adjacent normal tissues [17, 83, 88]. With advances in bronchoscopy, PDT has been increasingly used to treat early central lung cancer and malignant airway obstruction. PDT is now regarded as an important local treatment modality for selected patients [89]. Previous studies have shown that PDT offers controllable tissue injury, improved preservation of normal tissue, repeatability, fewer systemic adverse events, and potential synergy with other treatments [1, 14, 49]. For properly selected central early-stage lesions, complete response rates of 73%–100% have been reported. PDT can also relieve airway obstruction and improve quality of life [48, 81]. Recent studies have further explored PDT in early lesions, locally

advanced disease, and combination-treatment settings. These findings provide additional support for the clinical utility of PDT [41, 65, 82].

However, in clinical practice, PDT efficacy shows substantial interindividual variability. Some patients achieve durable remission, whereas others show limited responses or recurrence and require repeated PDT. These differences suggest that PDT efficacy may be modulated by multiple factors [28, 83]. Prior studies indicate that tumor morphology, invasion depth, photosensitizer distribution, and irradiation parameters may influence the therapeutic response [41, 86]. Existing studies have mainly focused on single factors or small-sample observations and have not systematically evaluated the combined effects of multiple factors. Integrated clinical evidence remains particularly limited for patients with tracheobronchial lung cancer. A systematic analysis of clinical factors affecting PDT efficacy in tracheobronchial lung cancer may provide a basis for individualized treatment planning.

2. Analysis of influencing factors

2.1 Anatomical location

Tumor location within the respiratory tract is an important determinant of PDT efficacy, and substantial evidence indicates that PDT can be effective as curative-intent treatment for early, superficial, centrally located tracheobronchial lung cancer [29, 62, 80]. Central airway tumors are usually located in the tracheobronchial mucosa or submucosa, where photosensitizers can selectively accumulate in superficial tumor tissue, making direct bronchoscopic irradiation feasible [16, 56, 83]. In contrast, peripheral lung cancers are usually located deep within the lung parenchyma, where narrow and anatomically complex distal bronchial branches make optical-fiber manipulation difficult. Studies indicate that effective tissue penetration is typically approximately 2–3 mm at 630 nm and 5–6 mm at longer wavelengths [47, 50]. Therefore, deeply invasive tumors may receive insufficient light exposure, oxygen supply, and photosensitizer accumulation, thereby reducing ROS production and increasing the risk of residual disease or local recurrence [24, 36, 53]. In addition, necrotic tissue generated after PDT in peripheral lesions is often difficult to clear, which may lead to airway obstruction or secondary infection [12, 88]. For peripheral or deeply located tumors, PDT alone is generally not recommended as the primary therapeutic approach.These anatomical and optical factors are summarized in Figure1.

2.2 Pathological type

This study suggests that patients with lung squamous cell carcinoma may be more likely to benefit from PDT; similarly, a previous study [59] reported that squamous cell carcinoma is more sensitive to hematoporphyrin derivative-mediated photodynamic therapy (HpD-PDT) than adenocarcinoma and small-cell lung cancer. Several mechanisms may explain this observation. First, from the perspective of tissue optical properties, tumor tissues of different pathological types differ in light scattering and absorption characteristics. Under certain conditions, squamous cell carcinoma tissue may exhibit more favorable effective light-penetration characteristics, which may expand the range of the photodynamic reaction[38] . Second, with respect to organelle distribution, squamous cell carcinoma cells are relatively

enriched in mitochondria and lysosomes, which are major intracellular sites of photosensitizer localization. After photoactivation, HpD generates ROS within these organelles, triggering mitochondrial dysfunction, lysosomal membrane permeabilization, and subsequent apoptosis or other programmed cell-death pathways[45, 69]. Third, the tumor microenvironment may also contribute, because PDT depends on molecular oxygen to generate singlet oxygen. Central squamous cell carcinoma is usually located in the bronchial mucosa or submucosa, where improved accessibility and local oxygenation may enhance PDT efficacy compared with deeper peripheral lesions[29]. Taken together, the tissue optical characteristics, organelle localization, and local microenvironment of squamous cell carcinoma suggest that this subgroup may be particularly responsive to PDT; however, further clinical studies are needed to validate this possibility.

2.3 Photosensitizer, drug dose, and irradiation timing

The type and pharmacokinetic profile of the photosensitizer are important determinants of PDT efficacy. In this study, all patients received Xipo hematoporphyrin derivative, namely Hematoporphyrin Injection (HpD; Chongqing Mile Bio-Pharmaceutical Co., Ltd.), as the photosensitizer during clinical treatment. At present, first-generation photosensitizers remain the most widely used agents for clinical PDT in lung cancer; however, they have limited tumor selectivity, restricted tissue penetration, and pronounced skin phototoxicity [11]. Second-generation photosensitizers generally provide deeper tissue penetration and higher singlet-oxygen generation efficiency, but further improvements are needed in tumor selectivity, phototoxicity, delivery methods, and clinical translation [71, 75, 76] . Third-generation photosensitizers remain under development and optimization and have not yet been widely adopted in routine clinical practice. Wei et al.[90] showed that HpD-PDT induced apoptosis and autophagic cell death in esophageal squamous cell carcinoma while inhibiting tumor-cell migration. Prior research[55] found that HpD-PDT regulated Bax, Caspase-9, and Bcl-2 expression, induced apoptosis in H446 and BEAS-2B cells, and enhanced tumor-cell killing. These studies indicate that HpD is supported by both clinical feasibility and experimental evidence. Beyond the photosensitizer itself, drug dose and irradiation timing are also critical determinants of PDT efficacy. The commonly used clinical photosensitizer dose is 2.5–5 mg/kg, and an early study [46] recommended that the HpD dose above 2.5 mg/kg but below 5 mg/kg to balance efficacy and phototoxicity. Animal data further showed that PDT can effectively inhibit tumor growth at 3 mg/kg [79]. A drug-light interval of 48–50 hours after HpD administration may represent a suitable window for tumor irradiation. In a previous study[56] involving 20 patients with bronchogenic lung cancer treated with PDT, irradiation was performed 48 hours after photosensitizer administration. In contrast, an animal study showed that the optimal irradiation window in mice was 6–24 hours after photosensitizer administration [51]. This discrepancy may be attributable to pharmacokinetic differences[68, 85]. Thus, rational optimization of drug dose and irradiation timing is essential for balancing tumor killing with normal-tissue protection.

2.4 Irradiation parameters and irradiation methods

During PDT, irradiation wavelength, power density, irradiation duration, and delivery method collectively determine local ROS-generation efficiency and the extent of tissue injury. In this study, PDT was performed using intermittent 630-nm irradiation at a power density of 100 mW/cm² for 1000 seconds. Shafirstein et al.[73] reported that 630-nm irradiation at 100 mW/cm² achieved a 90% cure rate in a rabbit model of neck squamous cell carcinoma. This wavelength is close to the excitation absorption peak of many clinically used porphyrin photosensitizers, enabling effective excitation of photosensitizers and subsequent interaction with oxygen molecules to generate singlet oxygen[23]. Irradiance selection is also critical. Excessive irradiance can rapidly deplete local oxygen and induce transient hypoxia, thereby reducing ROS-generation efficiency; by contrast, appropriately reduced irradiance may preserve tumor oxygenation, improve light-energy utilization, and promote permanent tumor vascular injury. If irradiance is too low, photosensitizer activation may be insufficient, making the desired therapeutic effect difficult to achieve[30, 33, 37]. Thus, clinical parameter settings should not simply maximize light intensity; rather, they should balance photosensitizer excitation efficiency, tissue oxygen preservation, and normal-tissue protection. In our study, PDT was delivered as surface-based fractionated irradiation for 16–20 minutes, corresponding to approximately 1000 seconds. Previous studies[72] indicate that surface irradiation is primarily suitable for superficial or intraluminal tumors. For deep or bulky tumors, clinicians may first reduce tumor burden through debulking before PDT or insert the fiber directly into the tumor to achieve effective photosensitizer activation. Agostinis et al.[1] proposed that fractionated irradiation can promote local oxygen reperfusion between irradiation intervals, thereby improving ROS-generation efficiency. Continuous high-intensity irradiation may rapidly deplete local oxygen and increase the risk of acute phototoxic injury. Other studies suggest that fractionated irradiation may also promote inflammatory responses and immune-cell infiltration, thereby enhancing subsequent antitumor immune effects[5, 15, 20]. Thus, the irradiation method may influence both local cytotoxicity and post-treatment immune-microenvironment remodeling.

2.5 Individual factors

Patient-specific factors also influence PDT efficacy. Previous treatment history, local tumor blood supply, oxygenation status, and overall health may all influence the response to PDT. Studies have shown that radiotherapy before PDT may reduce PDT sensitivity by altering tumor microvascular structure and oxygen supply [91]. Moreover, the synergistic effect between PDT and chemotherapy has a certain sequence dependent. One study [52] found that the synergistic antitumor effect of HpD-PDT and cisplatin showed clear sequence dependence, with PDT followed by chemotherapy significantly increasing apoptosis in lung adenocarcinoma cells. Sun et al.[78]found that, even at the same light dose, ROS concentrations may differ significantly among patients and even among different regions within the same patient. This variability mainly results from tissue heterogeneity, including differences in tumor structure, optical properties, oxygen supply, and photosensitizer distribution [3]. Comorbidities such as chronic obstructive pulmonary disease (COPD) may influence tumor progression and therapeutic response through chronic inflammation, microbiome imbalance, oxidative DNA damage, and impaired

immune surveillance [8, 26, 31, 63]. Therefore, previous treatment, pulmonary function, and comorbidities should be comprehensively evaluated in clinical practice to optimize treatment strategies.

2.6 Bronchoscopic procedural technique

The effectiveness of PDT depends not only on the photosensitizer and irradiation parameters but also on the quality of the bronchoscopic procedure. Bronchoscopy combined with white-light or fluorescence imaging helps improve the recognition of mucosal lesions in early central lung cancer, define lesion extent, and improve the accuracy of PDT irradiation targeting [66]. This is consistent with the findings reported by Ali et al [4] . An appropriately sized optical fiber should cover the visible tumor and extend the irradiation field 1–2 cm beyond the proximal and distal tumor margins, thereby including suspicious margins and reducing the risk of residual disease or recurrence. This approach is consistent with previous procedural principles recommending complete coverage of visible lesions with an adequate peripheral margin [92]. In this study, necrotic tissue was promptly removed bronchoscopically after treatment to prevent airway obstruction, and regular bronchoscopic follow-up was used to assess mucosal recovery and determine whether repeat PDT was needed, consistent with the findings of Shah et al. [74]. Clinically, this indicates that PDT is not merely drug administration followed by light irradiation, but rather a continuous treatment process that depends on preoperative assessment, precise intraoperative technique, and dynamic postoperative follow-up. Higher procedural quality increases the likelihood that the theoretical advantages of PDT will translate into actual clinical benefits. The key bronchoscopic procedural steps are summarized in Figure 2.

2.7 Combination therapy strategies

In recent years, combination strategies incorporating surgery, radiotherapy, chemotherapy, or immunotherapy have been increasingly used to enhance PDT efficacy, improve local control, and reduce the risk of recurrence [39, 44]. PDT can be used as neoadjuvant therapy to reduce tumor volume and can also be applied intraoperatively or postoperatively to eliminate microscopic residual tumor cells [35, 42, 43, 61]. This is consistent with findings reported by Akopov [2]. PDT combined with radiotherapy also demonstrates a clear synergistic antitumor effect. Pogue et al.[67] showed that this combination produced stronger cytotoxic effects than either PDT or radiotherapy alone. In a clinical series of 32 patients with bronchial tumors, Freitag et al.[27] found that PDT combined with brachytherapy was safe and effective. This synergistic effect may be explained by the distinct targets of the two treatments: PDT mainly acts on cell membranes and tumor microvasculature, whereas radiotherapy primarily induces DNA damage [40, 87]. PDT can modulate the tumor immune microenvironment and enhance the efficacy of immune checkpoint inhibitors [58]. Mechanistically, PDT-induced immunogenic cell death promotes the release of tumor antigens and damage-associated molecular patterns, facilitates dendritic-cell maturation, and activates $CD8^+$ T cell-mediated antitumor immune responses [84]. In addition, PDT can affect tumor vascular permeability, T-cell infiltration, and immunosuppressive cellular components, thereby increasing sensitivity to anti-PD-1 therapy [18, 32, 34, 58, 70, 84]. PDT combined with chemotherapy can exert both local and systemic therapeutic effects [10]. A palliative-treatment study in patients with

advanced lung cancer and airway obstruction showed that PDT combined with chemotherapy could relieve airway obstruction and improve symptoms [48]. Potential mechanisms may include ROS-mediated enhancement of tumor-cell sensitivity to chemotherapeutic drugs, PDT-induced increases in tumor vascular permeability that promote drug penetration, and possible reversal of chemoresistance [54, 64]. Therefore, in some patients, the value of PDT may not lie in achieving complete remission after a single treatment; moreover, based on the data from this study, final efficacy cannot be fully attributed to PDT itself. Rather, PDT likely contributed to local tumor debulking, restoration of airway patency, and improvement of the local microenvironment, thereby creating more favorable conditions for subsequent systemic therapy and demonstrating potential value as a bridging treatment.

3. Discussion

The efficacy of PDT depends on the synergistic interaction of three elements: laser light, oxygen, and a photosensitizer. After preferential accumulation in tumor tissue, the photosensitizer is activated by laser light at a specific wavelength and reacts with molecular oxygen to generate ROS. These ROS exert antitumor effects by directly killing tumor cells, damaging tumor microvessels, and inducing host antitumor immune responses [20, 21, 25, 65, 82]. Therefore, the core determinants of PDT efficacy are whether light can effectively reach the lesion, whether oxygen can be continuously supplied during treatment, and whether the photosensitizer can sufficiently accumulate and be activated within the tumor. The results of this study suggest that PDT can improve airway patency and achieve local disease control in selected patients with central tracheobronchial lung cancer. PDT may be particularly suitable for patients with central, superficial squamous cell carcinoma that is accessible by bronchoscopy.

Efficient light delivery is fundamental to PDT activity. Central airway lesions are mostly located in the mucosa or submucosa and can be directly accessed by bronchoscopy. The optical fiber can more easily cover the lesion and its margins, facilitating delivery of an adequate and uniform effective light dose. Previous studies have shown that PDT provides favorable local control in bronchoscopically visible, early, superficial central lesions [66, 83, 86]. In contrast, peripheral or deep lesions are constrained by limited light penetration, difficult fiber positioning, and impaired clearance of necrotic debris; therefore, PDT may not be suitable as a routine primary treatment for these lesions. However, in recent years, advances in navigational bronchoscopy, radial endobronchial ultrasound, hybrid bronchoscopes, interstitial PDT, and lipiodol-assisted light delivery have improved the feasibility of PDT for peripheral lung cancer[6, 12, 47]. Current evidence is derived mainly from small-sample studies and remains insufficient to support PDT as a routine treatment for peripheral lung cancer.

Oxygen supply directly affects ROS-generation efficiency. If local oxygenation is insufficient or excessive irradiance rapidly consumes oxygen during PDT, treatment efficacy may decrease even when laser power and photosensitizer dose remain unchanged [30, 33, 37, 72]. This study used intermittent irradiation, which allows time for local tissue reoxygenation and thereby enhances the photodynamic reaction. Prior radiotherapy, chronic inflammation, COPD, impaired pulmonary function, and tumor microvascular changes may all alter PDT responses by affecting local blood flow, oxygenation, and the immune

microenvironment [8, 26, 31, 63, 91]. In recent years, nanoplatforms capable of detecting and responding to the hypoxic tumor microenvironment or directly supplying oxygen, as well as intelligent nano-delivery systems that regulate the tumor microenvironment, have provided new directions for alleviating oxygen depletion during PDT [7]. However, their safety and clinical benefits in PDT for tracheobronchial lung cancer require further validation.

Adequate tumor accumulation and effective activation of the photosensitizer are essential for PDT efficacy. First-generation photosensitizers such as HpD and Photofrin have a long history of clinical use; however, they are limited by relatively poor tumor selectivity, pronounced skin phototoxicity, and restricted depth of action [11]. In clinical practice, patients are advised to avoid light exposure for 4 weeks after treatment to reduce photosensitivity reactions. In recent years, liposomes, polymer nanoparticles, conjugated polymers, oxygen-regulating nanophotosensitizers, and tumor microenvironment-responsive nanophotosensitizers have improved photosensitizer tumor accumulation, prolonged circulation time, and alleviated tumor hypoxia to some extent. Some multifunctional nanoplatforms can also simultaneously carry photosensitizers, chemotherapeutic drugs, immunomodulatory components, or radiosensitizing materials, thereby more closely integrating PDT with systemic therapy [44]. However, the safety, delivery efficiency, and actual clinical benefits of these technologies in bronchoscopic treatment for lung cancer need to be confirmed in large-scale studies.

Beyond these three core elements, combination therapy may further expand the clinical utility of PDT. Local tumor debulking, cryotherapy, and bronchoscopic removal of necrotic tissue can improve airway patency and facilitate light delivery. Radiotherapy, chemotherapy, and immunotherapy may synergize with PDT through complementary damage targets, enhanced ROS-related stress, and promotion of antitumor immune responses, whereas X-ray-induced PDT offers a potential strategy to overcome the penetration limitations of visible light [56,79–87]. For patients with locally advanced tumors or airway obstruction, PDT may be more valuable for local debulking, airway recanalization, and bridging to subsequent therapy than for achieving curative remission after a single treatment.

In summary, central, superficial squamous cell carcinoma accessible by bronchoscopy may be particularly suitable for PDT. This suitability may be explained by more effective light delivery, maintenance of local oxygen supply, photosensitizer activation, and post-treatment clearance of necrotic tissue in these lesions. Nevertheless, the risks of local edema, necrotic-tissue sloughing, and airway obstruction after PDT require attention; adequate preoperative risk assessment, postoperative bronchoscopic clearance, and close follow-up are therefore necessary[13, 92]. With advances in navigational bronchoscopy, robotic bronchoscopy, interstitial PDT, real-time dosimetry, oxygenation monitoring, and novel photosensitizers, the indications for PDT may further expand. Given the limited sample size of this study and the use of comprehensive treatments, including combined immunotherapy and chemotherapy, final efficacy cannot be fully attributed to PDT itself. Therefore, the results of this study should be regarded as exploratory observations that may inform subsequent optimization of individualized PDT parameters, candidate selection, and combination-treatment design.

4. Conclusion

The efficacy of PDT for tracheobronchial lung cancer may be influenced by multiple interacting factors, including anatomical location, pathological type, photosensitizer distribution, drug dose, irradiation timing, irradiation parameters, patient-specific factors, bronchoscopic technique, and combination-treatment strategies. Based on our case observations and previous literature, patients with central, superficial lesions and squamous cell carcinoma may be more likely to benefit from PDT. This study was limited by a small sample size, lack of statistical analysis, and absence of comparison groups with other pathological types or anatomical sites. Larger clinical studies and more in-depth mechanistic investigations are needed to confirm these conclusions.

Declarations

Author Contribution

Author Contributions:Dan Yang,Lian Li and Cunzhi Lin conceived and designed the study.Dan Yang and Lian Li performed data analysis and drafted the manuscript.Shuyun Zheng, Jinfeng Li and Lina Wang contributed to the experimental methodology.Cunzhi Lin contributed to the revision of the manuscript.All authors read and approved the final manuscript.

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