Original Article

Bibliometric and visual analysis of photodynamic therapy for lung cancer from 2010 to 2022

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Background: A growing body of research shows that photodynamic therapy (PDT) has become an important mode of treatment in the field of lung cancer (LC) in recent years. Although numerous papers related to PDT in LC have been published, no bibliometric studies have been conducted to summarize the research prospects and highlight the research trends and hotspots in this field. This bibliometric analysis was conducted to investigate and provide a systematic understanding of the development of PDT research for LC over the past 13 years with the aim of providing a reference for new directions and strategies in the field of PDT for LC.

Methods: In May 2023, relevant publications from the Web of Science Core Collection were downloaded, and CiteSpace and VOSviewer were used to conduct the scientometrics analysis in this study.

Results: A total of 2,932 articles and reviews that met the inclusion criteria were retrieved, with China dominated the volume of publications from 2010 to 2022 and the most prolific institution was Shanghai Jiao Tong University.

Conclusions: PDT can be utilized for the diagnosis and treat LC. Bronchoscopic fluorescence diagnosis using photosensitizers helps to detect tumor changes in the large bronchial mucosa. In the future, we should actively explore the use of new photosensitizers, including the development of nanomaterials, in addition, PDT combined with other treatments can significantly prolong survival. This combination therapy may also be the direction of future research.

Keywords: Photodynamic therapy (PDT); lung cancer (LC); bibliometrics visualization analysis; CiteSpace; VOSviewer

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Introduction

Lung cancer (LC) is the most common cancer in the world and has become one of the malignant tumors with the highest morbidity and mortality (1,2). Globally, an estimated 2.2 million new cases of LC occur each year, accounting for about 11.4% of all cancer cases (3). More than half of the patients with LC die within 1 year after diagnosis, and the 5-year survival rate is less than 18% (4). Tobacco products cause approximately 90% of LC cases, but other factors such as radon, asbestos, air pollution exposure, and chronic infections can also contribute to LC (5). Patients usually choose conventional surgery to remove the tumor, and this may be combined with chemotherapy, radiotherapy, gene targeted therapy, or other adjunctive therapy to reduce the risk of cancer recurrence (6). However, conventional treatments such as surgery, chemotherapy, and radiotherapy cannot cure the disease, and the toxic effect is substantial, afflicting patients with considerable pain (7).

Photodynamic therapy (PDT) (8) is a well-established therapy approved by U.S Food and Drug Administration (FDA) and other regulatory agencies for the ablation of pulmonary endobronchial tumors. PDT is a precise, cell-targeting therapy that involves administering photosensitizers intravenously or locally under a specific laser wavelength to stimulate the accumulation of photosensitizers in tumor tissue. After a variable time interval, with the participation of oxygen in biological tissues, oxygen-free radicals and singlet oxygen are generated. Fixed wavelength light is specifically focused on the target lesion site, leading to the selective excitation of photosensitizers and inducing photophysical and photochemical effects for cancer treatment (9-11). Since 1993, various countries have approved PDT for the treatment of LC (12), and PDT has been used to treat LC for more than 15 years (13). Compared with other conventional treatments such as radiotherapy, surgery, and chemotherapy, PDT is more selective, can directly kill tumor cells, and has relatively low toxicity, without side effects such as drug resistance, bone marrow suppression, and liver and kidney damage (14,15). A single-center prospective pilot study evaluated the palliative efficacy and safety of PDT as a part of multimodal therapy, and the results showed significant improvements in lung capacity and function and significantly improved survival in all the participating patients with LC (16). In addition, PDT is being increasingly recommended in clinical practice guidelines for LC (17), and it can be used as an option or as part of combination therapy for LC treatment. Nonetheless, PDT is currently being underutilized in clinic (18,19).

Via mathematical and statistical measurement techniques, bibliometric analysis uses the characteristics of the literature as its research object to evaluate and predict the current state of science and technology (20,21). By examining and evaluating the quantity and quality of scientific literature related to a particular topic, bibliometric evaluation can objectively assess the state and level of development of a given field (22). In recent years, there has been a growing abundance of literature on the use of PDT in patients. However, there is no quantitative analysis of PDT for LC, and thus this study was conducted to discern the research trends, hotspots and research frontiers of PDT for LC. The results of this work will contribute to further research in the field.

Highlight box

Key findings

- The focus of the field of photodynamic therapy may be the development of novel photosensitizers and the combination of photodynamic therapy with other methods in treating lung cancer. Future directions in this field may include exploring the use of nanomaterials as photosensitizers.

What is known and what is new?

- There is an abundance of evidence demonstrating that photodynamic therapy is an important mode of treatment in the field of lung cancer.

What is the implication, and what should change now?

- In the future, we should actively explore the development of nanomaterials, conduct more clinical development to verify their reliability, and further explore the combined treatment of lung cancer to improve the quality of life of patients with lung cancer.

Methods

Given the quality of the eligible literature and the requirement for an appropriate reference format, we adopted the Science Citation Index-Expanded of Web of Science Core Collection (WoSCC; https://www.webofscience.com/wos/) as the data source. The WoSCC, covering more than 12,000 of high-quality scientific journals, is known to harbor a relatively reliable database and to be the optimal database in previous bibliometric studies (23,24). The search strategy was conducted as follows: (TS(Topic)=("photodynamic therapies" OR "photochemotherapy" OR "photosensitizer" OR "PDT" OR "light sensitive agent" OR "light" OR "phototherapy"

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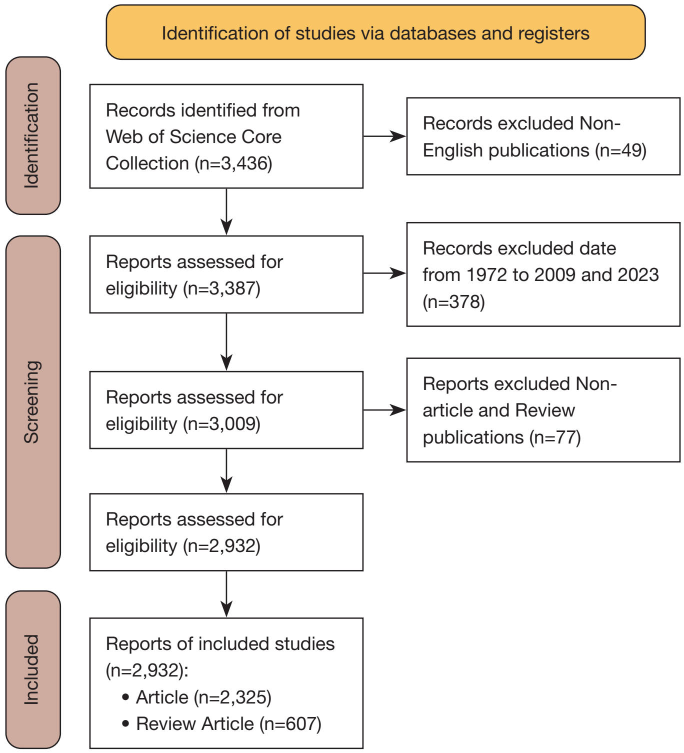

Figure 1 Flowchart of literature retrieval.

OR "hematoporphyrin in photoradiation")) AND TS=("lung cancer" OR "carcinoma of lung" OR "pulmonary carcinoma" OR "lung neoplasms" OR "adenocarcinoma of Lung" OR "carcinoma, non-small-cell lung" OR "small-cell lung carcinoma" OR "squamous cell carcinoma of the lungs" OR "adenocarcinoma of the lung" OR "large-cell carcinoma of the lung" OR "pulmonary neoplasms" OR "cancer of lung"). We chose 2010–2022 as our search period. The publication types were restricted to original articles and reviews, and only English language literature was included. The flowchart of the study is presented in *Figure 1*.

Data acquisition

Two authors (Z.G. and L.W.) independently conducted the main search. Any differences were discussed with a third investigator (M.H.) before reaching a consensus. The data collected included number of publications, titles, authors, countries, institutions, journals, highly cited articles, and keywords. WoSCC data were converted to text format and imported into CiteSpace 6.R6 and VOSviewer 1.6.18.

Data analysis

CiteSpace is a free program used for analyzing, identifying, and visualizing trends and patterns in the scientific literature. We chose to use CiteSpace to conduct our analysis (25). The details of the CiteSpace setup for this study were as follows: 1 year for each time period from 2010 to 2022, with link (intensity: cosine; range: within slice) and term source (title, abstract, author keywords, and keyword plus sign) set to the default values. In a network, links between nodes represent cooperative or common reference relationships, and different node sizes and colors represent different items and years (26). VOSviewer was also used in this study to create network visualization maps (27). The h-index, originally devised by Jorge Hirsch (28), is defined as the number of papers that have received at least h citations and is used to measure the cumulative impact of a country's literature output. The impact factor (IF) was derived from the 2021 Journal Citation Reports (JCR).

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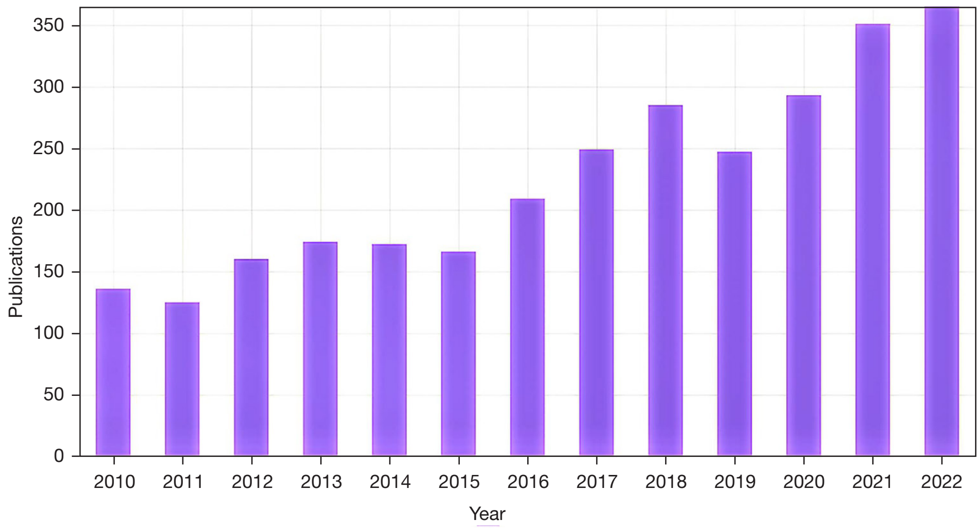

Figure 2 Global publication trend chart.

Table 1 Top five countries according to publishing volume

Rank	Count	Country	Percentage	Citations
1	1,054	China	35.94	24,976
2	758	United States	25.85	32,480
3	193	Japan	6.58	6,378
4	174	Italy	5.93	6,910
5	150	India	5.11	4,355

Results

Global publication results

From 2010 to 2022, a total of 2,932 pieces of literature were retrieved from the WoSCC, including 2,325 articles (79.30%) and 607 reviews (20.70%). The total number of citations for the retrieved papers was 88,899 (87,311 times cited without self-citations), and the average citations per document was 30.32. The h-index of all the selected publications related to PDT for LC was 115. *Figure 2* shows the number of articles published each year. Over the past 13 years, the overall trend has increased. The highest number of papers was published in 2022, with 365 articles. This shows that research related to PDT of LC has become a hotspot and is garnering worldwide attention.

Distribution of countries

Statistics from the countries that reported publications related to LC and PDT demonstrate the stage of photodynamic development in each country. According to the WoSCC, many countries have participated in this field over the past 14 years. *Table 1* lists the top five most productive countries in this field. China published the most papers (n=1,054), accounting for 33.01% of the total publication count, followed by the United States (n=758), Japan (n=193), Italy (n=174), and India (n=150). However, the number of citations in China was lower than that of the United States.

The circles in the VOSviewer (*Figure 3*) map were used to represent countries, and the lines to represent the connections between them. The larger the area of the circle is, the greater the contribution of these countries to this field. We found that China made significant contributions to PDT in treating LC followed by the United States and Japan. However, The United States has the most citations (n=32,480). This shows that China is deepening its research in this field.

Institutional distribution

The top five institutions by number of articles over the past 13 years are listed in *Table 2*. Shanghai Jiao Tong University (n=54) was the most prolific institution in this regard, followed by Sun Yat-sen University (n=51). Meanwhile, the National Cancer Institute from the United States had the most citations (n=2,506).

The combined consortium network diagram shown in *Figure 4* has 381 nodes and 1,069 links. The line thickness

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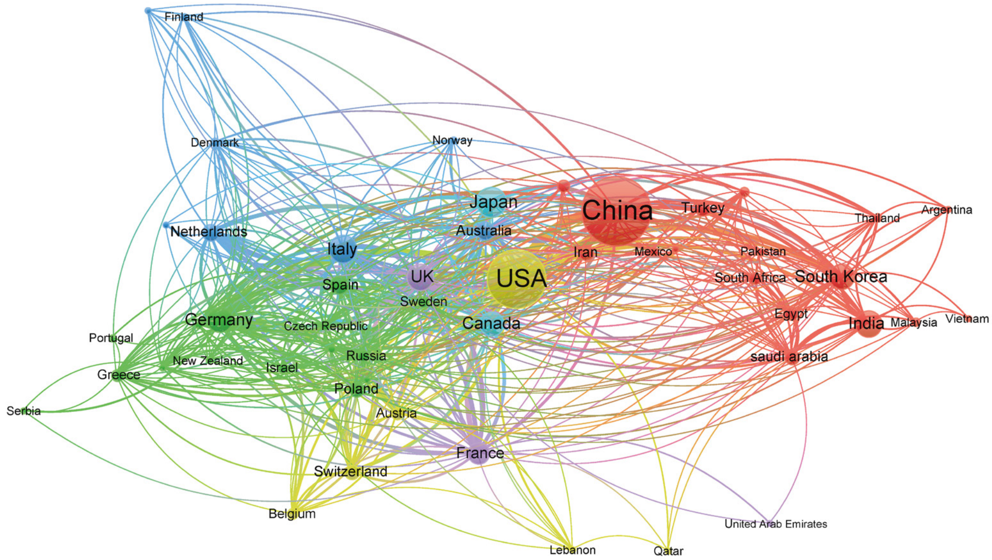

Figure 3 Contribution map by country.

Table 2 Top five institutions according to publishing volume

Rank	Count	Institution	Percentage	Citations
1	54	Shanghai Jiao Tong University	1.84	1,933
2	51	Sun Yat-sen Institute	1.73	1,344
3	40	National Cancer Institute	1.36	2,506
4	36	University of Toronto	1.22	1,602
5	33	Memorial Sloan Kettering Cancer Center	1.12	638

indicates the strength of the cooperation. The network density is only 0.0148, suggesting that the cooperation between these institutions is not sufficiently intense.

VOSviewer can map the collaboration between institutions (*Figure 5*). *Figure 5* shows the timeline of collaboration between the institutes from 2015 to 2019, with the node colors on this map corresponding to the average appearing year of cooperation for each institution. Based on the color gradient in the lower right corner, institutions from China appear as newer entries, including Shanghai Jiao Tong University, Sun Yat-sen Institute, Fudan University, and Sichuan University.

Author distribution

The top five authors by number of published articles over the past 13 years are listed in *Table 3*. Abrahamse was the most prolific author (n=18), followed by Usuda (n=12). Moreover, Abrahamse also had also the most citations (n=320). The number of publications published by the author can represent the author's research activities in a field, but we cannot know the specific contributions of these authors to these articles, and these authors have the potential to contribute to the future development of the field.

Journal distribution

The top five journals according to number of publications are listed in *Table 4* and *Figure 6*. These top five journals published 186 papers. *Lung Cancer* (IF=6.081) was the most prolific journal with 47 articles. This journal is an

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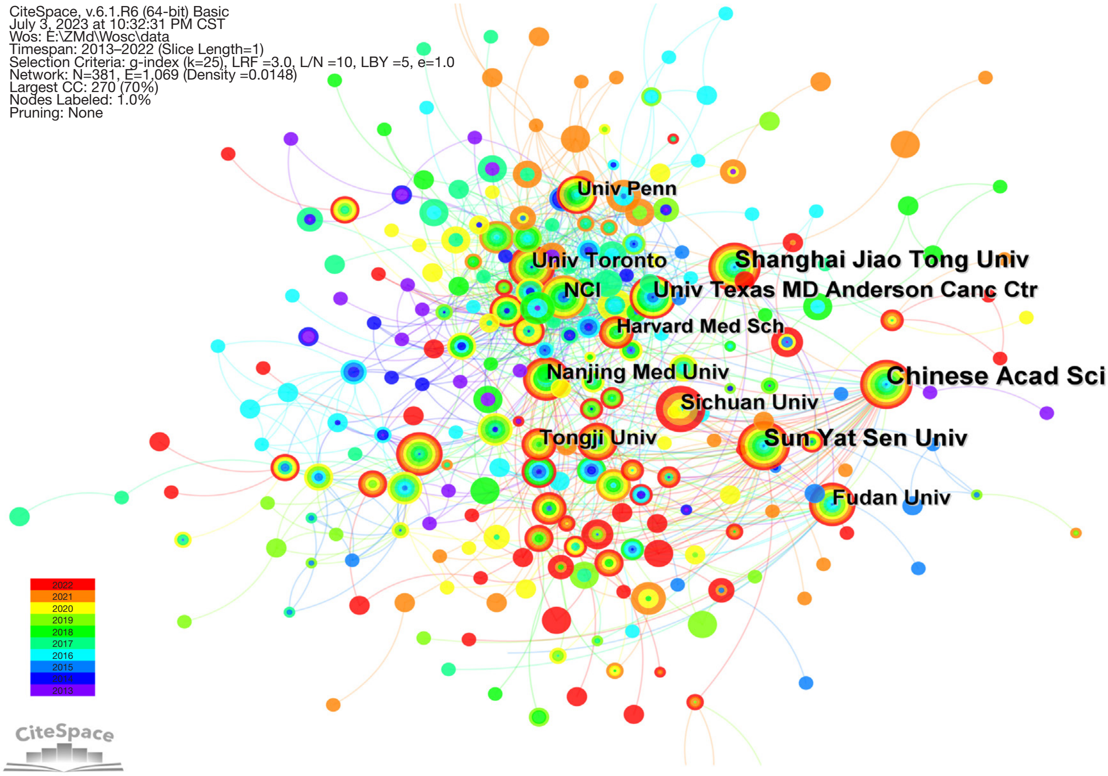

Figure 4 Institutional cooperation network diagram.

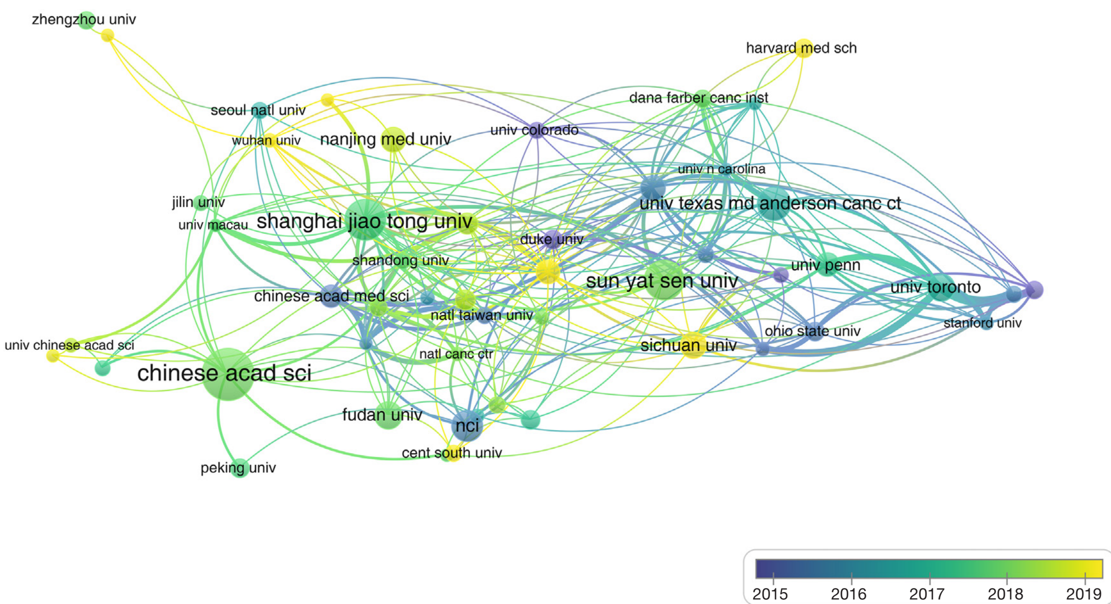

Figure 5 Institutional cooperation timeline.

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Table 3 Top five authors according to publishing volume

Rank	Count	Author	h-index	Citations
1	18	Abrahamse, Heidi	40	320
2	12	Usuda, Jitsuo	31	233
3	11	Sato, Kazuhide	29	299
4	11	Ikeda, Norihiko	39	222
5	10	Ohtani, Keishi	16	205

international publication covering the clinical, translational, and basic science of malignancies of the lung and chest region, as well as the prevention, epidemiology and etiology, basic biology, pathology, clinical assessment, surgery, chemotherapy, radiotherapy, combined treatment modalities, and other treatment modalities and outcomes of LC. A review published in the journal *Lung Cancer* titled "Advanced bronchoscopic techniques for the diagnosis and treatment of peripheral lung cancer" (29) provides

Table 4 Top five journals according to publishing volume

Rank	Journal	Articles	Citations	2021 journal impact factor
1	*Lung Cancer*	47	1,503	6.081
2	*International Journal of Molecular Science*	45	1,020	6.208
3	*Photodiagnosis and Photodynamic Therapy*	34	570	3.577
4	*Journal of Thoracic Oncology*	31	4,669	20.400
5	*Journal of Thoracic Disease*	29	533	3.005

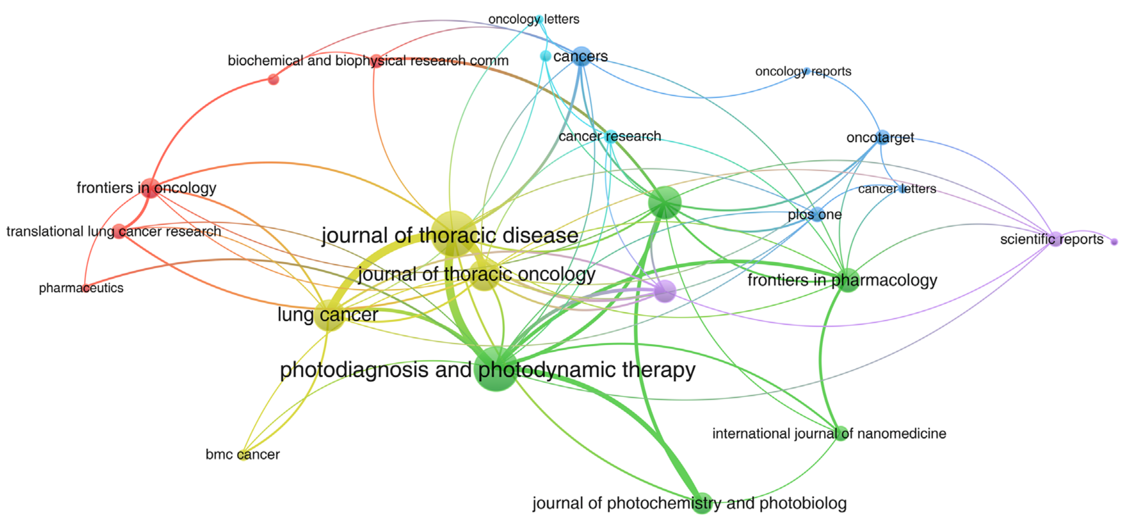

Figure 6 Journal network analysis diagram.

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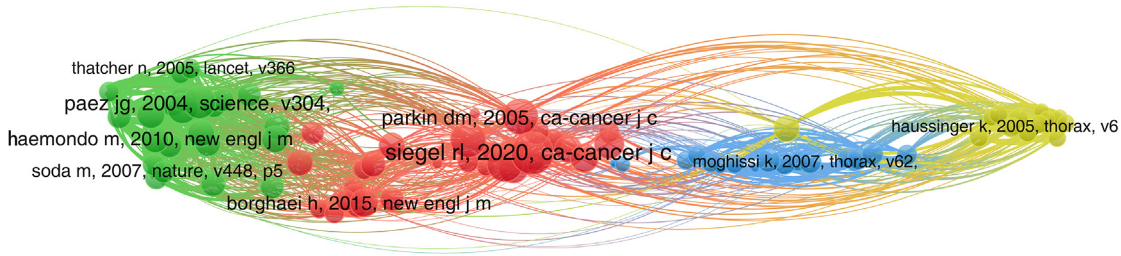

Figure 7 Commonly cited references.

Table 5 Top five most frequently cited articles

Rank	Article title	Journal	2021 impact factor	Citations
1	Cancer Statistics, 2020	*CA: A Cancer Journal for Clinicians*	286.13	97
2	Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib	*The New England Journal of Medicine*	176.082	94
3	EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy	*Science*	63.832	92
4	Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma	*The New England Journal of Medicine*	176.082	78
5	Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial	*Lancet Oncology*	54.433	54

a brief overview of advanced bronchoscopy techniques for the diagnosis and treatment of LC and was cited 102 times. Second in terms of most articles published was the *International Journal of Molecular Science* (IF=6.208) with 45 articles.

Commonly cited references

We analyzed the references using VOSviewer, the result is shown in *Figure 7*, and the top five articles according to the number of citations are shown in *Table 5*. Among them, "Cancer Statistics, 2020" from the journal *CA: A Cancer Journal for Clinicians* was the article with the most citations (n=97). This article provides the number of cancer cases and deaths in the United States in 2020, both nationally and in each state. This article likely has the most citations due to it being used for background information in articles related to LC and PDT. The other four articles all mentioned gefitinib or epidermal growth factor (EGF), which may be because researchers are investigating how to further promote LC tumor apoptosis through the targeting of EGF receptors.

Keyword analysis

Keywords are often considered to be important indicators of research frontiers and hotspots of a given topic (30). The results of analyzing the content in the title and abstract of the included articles are shown in *Figure 8*.

Lung cancer, as the topic of this paper, represents the largest circle. In addition, the keywords closely surrounding LC and PDT are apoptosis, photosensitizers, epithelial mesenchyme, and nanoparticles, among others. This shows that the main focus in the field of PDT may be the development and utilization of new photosensitizers. As research progresses, a greater number and variety of photosensitizers are being developed, and more of these are being used to target mitochondrial action and promote

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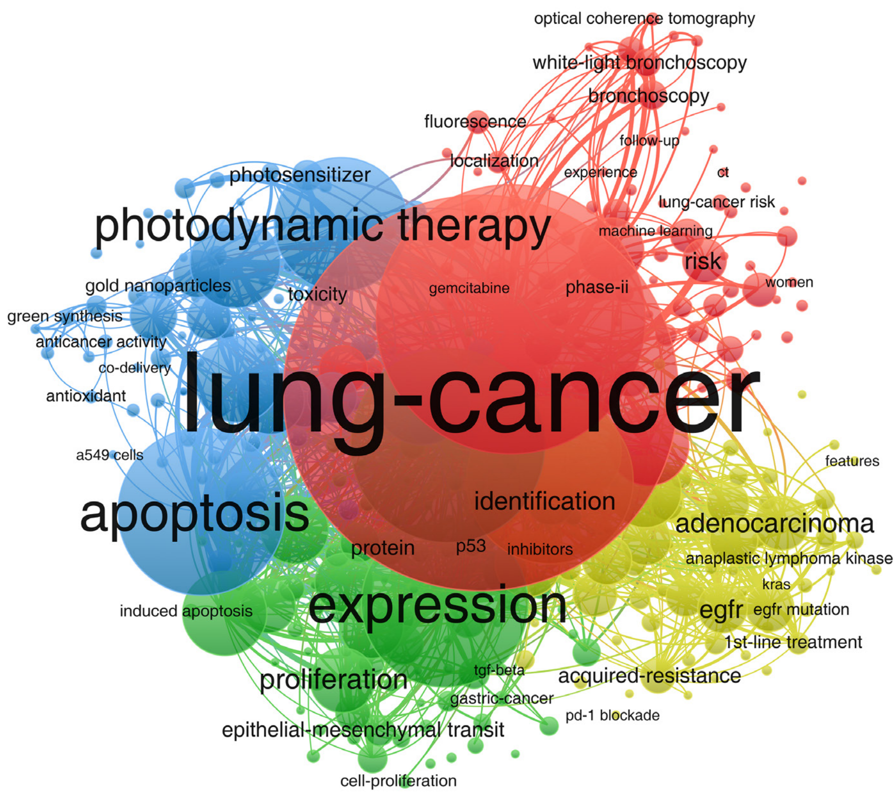

Figure 8 Keyword emergence.

apoptosis.

Figure 9 shows the top 18 keywords according to keyword frequency. The most common keywords (n=8.84) were white light bronchoscopy, followed by growth factor receptor (n=6.82), with risk factors, autofluorescence bronchoscopy, and white light bronchoscopy continuing to appear from 2013 to 2017, showing the longest duration.

Discussion

Chemotherapy and radiation therapy are the standard of treatment methods for patients with cancer. However, the resistance of malignancies to these treatments and the occurrence of major organ damage severely limit their benefits (31). PDT is a form of optical therapy based on the use of photosensitizers. Tumor tissue accumulates photosensitizers, which can produce reactive oxygen species (mostly singlet oxygen) when exposed to light in the presence of molecular oxygen. Reactive oxygen species can impair the tumor-associated vasculature, which causes vascular occlusion and bleeding, resulting in apoptosis, necrosis, or autophagy and ultimately cell death (32,33). PDT offers several advantages over traditional cancer therapies, including a less invasive than surgery, precise tumor targeting, minimal systemic toxicity, and availability of repeat treatments, making it an attractive choice for patients with LC (34,35).

PDT for the diagnosis of LC

According to keyword analysis, we found the diagnosis of LC may be a hotspot area of research.

The 5-year survival rate for LC is only 18%, and this is partly due to patients only being diagnosed at an advanced stage (36). The early detection of tumor is an important opportunity for reducing mortality, and existing technologies are mainly used to screen selected patients at high risk of LC via the use of low-dose chest computed tomography (LDCT) (37). However, there is considerable uncertainty concerning LDCT in that it may lead to patients passively receiving radiation exposure during scanning. Additionally, the benefits and costs of LDCT

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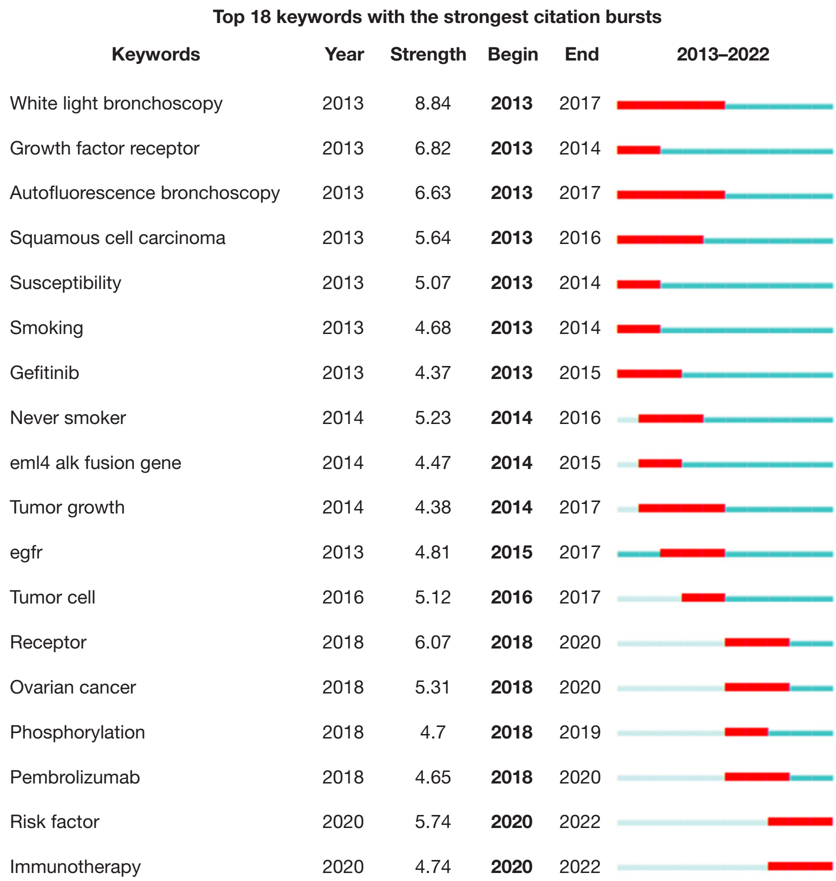

Figure 9 Top 18 keywords that appear most frequently.

are not proportional to conventional thresholds (38). Bronchoscopic fluorescence diagnosis using photosensitizers and other instrumental systems can facilitate the early revelation of tumor changes in the large bronchial mucosa, and the development of PDT technology performed under fluorescence control can contribute to the realization of personalized treatment and is considered to be a photodynamic therapeutic diagnostics technique (39). PDT diagnostics has exciting potential in LC management, and compared with traditional bronchoscopic methods that only have a 30% sensitive for early detection (40), fluorescence bronchoscopy has significantly higher specificity and sensitivity. It can thus can enhance the detection of preinvasive lesions and early invasive carcinoma involving the central airway and directly observe the course of the disease, effectively improving the prognosis of patients with LC (41,42).

PDT for the treatment of LC

Renewal of photosensitizer research

Photosensitizers are a key factor in PDT. Currently, Photofrin is commonly used in the medical institutions and is routinely injected intravenously at a dose of 2 mg/kg and delivered through a fiber optic catheter to produce singlet oxygen that forces tumor ablation under the irradiation of a 630-nm laser (43). However, the biggest issue with this generation of photosensitizers is that the penetration depth is limited and the infiltration poor, resulting in an inability to completely cure tumors outside the radiation range and prolonged skin phototoxicity. Researchers are actively developing novel photosensitizers and irradiation devices to solve such problems. Second-generation photosensitizers such as Laserphyrin (NPe6) have strong absorption at 664 nm and faster skin clearance than do first-generation

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photosensitizers (44). Phthalocyanine derivatives are also commonly used in PDT second-generation photosensitive molecules, and researchers have found that after 24 hours of zinc phthalocyanine irradiation (680 nm; 5 J/cm²), the tumor cell apoptosis (45). However, these second-generation photosensitizers still have unavoidable challenges such as an Immunosuppressive tumor microenvironment. An important feature of tumor development is the regulatory role of metabolic plasticity in maintaining mitochondrial oxidative phosphorylation and the glycolytic balance of cancer cells. Therefore, research on novel photosensitizers mainly focuses on cell therapy and strategies for targeting mitochondria.

Nanotechnology is widely used for cancer treatment, and these ultrasmall nanoparticles (metal nanoparticles, liposomes, hydrogels and polymers, etc.) can achieve penetration into deeper tumor tissues and are preferentially retained in mitochondria as the main source of reactive oxygen species in cells, maintaining a more negative membrane potential than normal cells. Strategies targeting mitochondria can maximize the efficiency of cancer PDT, stimulate intercellular signaling, induce apoptosis, successfully inhibit tumor cell proliferation, and selectively ablate LC (46,47). Effective metal nanomaterial photosensitizers include graphene, gold, and other nanomaterials (48-50). These metal nanoparticles have excellent biocompatibility and photothermal conversion ability, have no obvious toxicity to normal cells or major organs, and can completely eliminate tumor xenogeneic cells without damaging normal tissues. Liposomes, as an advanced drug delivery system, have been shown to enhance drug permeability (51). Most of the hydrogels are associated with reactive oxygen species response junctions through nanoparticles and programmed death ligand 1 antibodies. Through laser mediation, they can not only induce tumor cell death but also destroy reactive oxygen species response junctions to prevent tumor metastasis (52). In addition, hydrogels can also be used as fungicides in PDT, and *in vitro* and *in vivo* results have shown that hydrogels can promote fibrinogen formation at an early stage of the tissue rebuilding process to accelerate scab formation (53). Nanopolymers include various semiconductor polymers, enzymes, etc., which can reprogram the tumor immune microenvironment under near-infrared light to effectively inhibit tumor cells and control lung cell metastasis (54). The combination of nanomaterials and biomedicine represent a new avenue of research for the medical community, but the application of nanomaterials is limited, and many of them are still in the stage of animal experiments, with more clinical trials being needed to verify their reliability. While celebrating the benefits of nanomaterials, we should also reasonably estimate their potential risks. Nanomaterials are potentially toxic to lung surfactants, the alveolar epithelium, and the immune system. Nonetheless, we are at the brink of a new era of nanomaterials era, and this innovative nanotechnology should be actively explored to benefit patients and alleviate the pain of those with LC.

PDT in combination with other therapies to control tumor metastasis

Immune checkpoint inhibitors prevent cancer cells from evading immune detection by inhibiting programmed death ligands 1 and 2. They are monoclonal antibodies specific to immune system suppression targets. In this way, immune checkpoint inhibitors reverse the negative regulatory signals between immune cells and tumor cells, improving the survival rate of patients, but their efficacy is limited by the immune-inhibitory tumor microenvironment (55). In addition, the treatment of immune checkpoint inhibitors is expensive, the cost of pabolizumab is high, and systemic adverse reactions are prone to occur (6). PDT can enhance the immune effect after treatment by activating immune cells (neutrophils, natural killer cells, macrophages, etc.), and prevent lung metastasis (56). Therefore, the combination of these two approaches seems to be an effective strategy to combat LC metastasis.

By using nanoparticles, Song *et al.* (57) designed a chimeric peptide that integrates photosensitizers and immune checkpoint inhibitors to achieve a synergistic cascade effect, inducing LC cell apoptosis and promoting tumor antigen production under 630-nm light irradiation; this thereby triggers an immune response and activates lymphocytes, effectively preventing tumor cell metastasis. Yu *et al.* (58) loaded chloroprotein e6 (ce6) onto glucose-linked iron oxide nanoparticles, which are more phototoxic to LC cells under near-infrared light and can damage LC cell DNA, activating cell expression and promoting LC cell immunogenicity and the phagocytosis of tumor metastasis cells.

Limitations

Some limitations to this study should be addressed. To begin, our selection was based on bibliometric tools, and the study data were only retrieved from the WoSCC

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database, while data from other relevant search engines (such as PubMed, Embase, and Cochrane Library) were ignored. Therefore, it was difficult to accurately obtain all relevant literature in this field. Due to the low frequency of citations, some newly published and potentially high-impact studies might not have been included in our analysis. Therefore, the trends and hotspots of LC photodynamic research may change with the update of the bibliometric data. Finally, our study was limited to the past 10 years, and some notable articles or authors were ignored because they were not in our time frame.

Conclusions

PDT shows promise as an antitumor treatment, but its application involves several considerations. In the future, new strategies for the synergistic treatment of PDT with sonodynamic therapy, magnetic hyperthermia, and immunotherapy should be further explored. Determining how to make the elements of these combinations greater than the sum of their parts should be the aim of basic research and clinical application. The rationale, effectiveness, and mechanism of the standardized combination of PDT and other treatments still need to be clarified by a large number of experiments. In addition, the innovation of optical PDT technology and the development of novel photosensitizers require further clinical verification. We surmise that the promising areas of research are nanomaterials, nanomedicine, epithelial mesenchyme, tumor microenvironment, and targeting. We believe that with the development of PDT and medical technology in the future, the survival rate and quality of life of patients with LC can be further improved.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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