Peer Review File

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Reviewer A

The manuscript describes a statistical analysis of photodynamic therapy research on lung cancer using knowledge graphs and bibliometric methods. Authors conclude that Chinese researchers publish the most papers; The most prolific institution was Shang Hai Jiao Tong University. The terms "pembrolizumab", and "Phosphorylation" are now hot research topics related to photodynamic therapy in lung cancer.

The statistics used are appropriate and the conclusions derived from these and the interpretations of the figures and tables are consistent and sound. I look forward to seeing it in print.

Reply for reviewer A:

On behalf of all the authors, I would like to thank you for your recognition of the article, thank you for your efforts to recognize us, thank you for your time and energy in reviewing this article, and we will definitely redouble our efforts in the future to achieve higher achievements in this field.

Reviewer B

Comment 1

There is a collection of sentence fragments in the Abstract, e.g., lines 30-31, 40-41.

Reply 1: Thank you for your correction, lines 30-31 and 40-41 have been changed.

Changes in the text: lines 30-31: This Bibliometric analysis aims to investigate and have a systematic understanding of the development of photodynamic therapy research over the past ten years for lung cancer, to provide new directions and reference strategies for photodynamic therapy in the field of lung cancer (See Page 2). Lines 40-41: Through the statistical analysis of lung cancer photodynamic therapy, we found that the current research focus may be the development and utilization of new photosensitizers (See Page 2).

Comment 2

It is not clear how s discussion of high-frequency keywords is useful, especially since 'immunotherapy' seems to be the first. Of the key findings, pembrolizumab and phosphorylation do not relate to photodynamic therapy. The first (also known as Keytrudta) is a monoclonal antibody and an immune checkpoint inhibitors that does not involve photodynamic therapy (PDT). It is not clear how publication of numbers of reports is relevant.

The topic of this report is said (in the title) to be photodynamic therapy not immunotherapy, although there may be a immune response to photodamaged tissues. This is also true for therapies involving phosphorylation. These are not related to anything involved in PDT.

The claim in lines 290-282 relating to Keytruda and phosphorylation is untrue. These topics bear no relationship to the elements of PDT.

It is concluded that a greater focus on cellular responses is needed. What is really needed, in the context of lung cancer, are [1] identification of optimal light sources and irradiation devices for treatment protocols, and [2] a better appreciation of where PDT might be the

treatment of choice. We already know about cellular responses relating to PDT. Keytruda and phosphorylation are irrelevant.

Reply 2: Thanks for your criticism and correction. we have re-discussed our results after carefully reviewing the manuscript. We think the current research focus may be the diagnosis of lung cancer and the development of new photosensitizers, and the future may focus on the development and application of nanomaterials.

Changes in the text: 4.2 Photodynamic therapy for Treatment of lung cancer

4.2.1 Renewal of Photosensitizers

Photosensitizers are a key factor in photodynamic therapy. Currently, Photofrin is commonly used in the medical institutions, which is routinely injected intravenously at a dose of 2mg/kg and delivered through a fiber optic catheter to produce singlet oxygen that forces tumor ablation under the irradiation of a 630nm laser(43). However, the biggest problem of this generation of photosensitizers is that the penetration depth is limited, the infiltration is poor, resulting in tumors outside the radiation range can not be completely cured, and will produce prolonged skin phototoxicity. Researchers are actively looking for new photosensitizers and irradiation devices to solve such problems. Second-generation photosensitizers such as Laserphyrin(NPe6) have strong absorption at 664nm and faster skin clearance than first-generation photosensitizers(44). In addition, phthalocyanine derivatives are also commonly used in PDT second-generation photosensitive molecules, the researchers found that after 24 hours of zinc phthalocyanine irradiation (680nm; 5J/cm^2), the tumor cell apoptosis(45). But these second-generation photosensitizers still have unavoidable challenges such as tumor inhibition microenvironment. An important feature of tumor development is the regulatory role of metabolic plasticity in maintaining mitochondrial oxidative phosphorylation and 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 ultra-small 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 (ROS) in cells, maintaining more negative membrane potential than normal cells. Strategies targeting mitochondria can maximize the efficiency of cancer photodynamic therapy, stimulate intercellular signaling, induce apoptosis, successfully inhibit tumor cell proliferation and selectively ablate LC(46, 47). Effective metal nanomaterials 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 and 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 ROS response junctions through nanoparticles and programmed death ligand 1 antibodies. Through laser mediation, they can not only induce tumor cell death, but also destroy ROS response junctions to prevent tumor metastasis(52). In addition, hydrogels can also be used as fungicides in photodynamic therapy, 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). Nano-polymers 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 provide a new idea for the medical community, but the application of nanomaterials is limited, many of them are still in the stage of animal experiments, and more

clinical trials are needed to verify their reliability. While enjoying the benefits of nanomaterials, we should also reasonably estimate the potential risks of nanomaterials. Nanomaterials have potential toxicity to lung surfactants, alveolar epithelium, and immune system. A new nanomaterials era is coming to us, and the future should also continue to actively explore the development of innovative nanotechnology to alleviate the pain of LC patients.

4.2.2 Photodynamic therapy combine with other therapies 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 inhibitory tumor immune 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, NK cells and macrophages, etc.), and prevent lung metastasis(56). So the combination of these two approaches seems to be an effective strategy to combat LC metastasis.

By using nanoparticles, Song(57) and his team designed a chimeric peptide PpIX-1MT that integrates photosensitizer and immune checkpoint inhibitor to achieve a synergistic cascade effect, inducing LC cell apoptosis and promoting tumor antigen production under 630 nm light irradiation, thereby triggering an immune response and activating lymphocytes, effectively preventing tumor cell metastasis; Yu(58) and team loaded chloroprotein e6 (ce6) onto glucose-linked iron oxide nanoparticles, which were more phototoxic to LC cells under near-infrared light, while damaging LC cell DNA, activating cell expression, enhancing LC cell immunogenicity, and phagocytosis of tumor metastasis cells.(See pages 12-15 in the manuscript)

Comment 3

The use of statistics to evaluate progress in a field can be misleading. If any author is often cited, this could be in the context of 'we were unable to verify the work of . . . ', 'in contrast to studies reported by . . . ' or something similar. This is the problem with uncritical summaries.

Reply 3: Thank you for your criticism, and we strongly agree that this article needs a critical summary, We have added to the limitations of this article.

Changes in the text: Although our research has found some results, our selection was based on bibliometric tools, and the study data were only retrieved from the WoSCC database, while data from other relevant search engines (such as PubMed, Em base 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 may not be included in our analysis. Therefore, the scientific trends and hot spots of LC photodynamic research may change with the update of the bibliometric data. Finally, our study was limited to the last 10 years, and some high-contribution articles or authors were ignored because they were not in our time frame (Part 5, page 16).

Comment 4

Material discussed in section 4.3 is mainly irrelevant to clinical PDT. Some of this might have been relevant to PDT as it was practiced 40 years ago

Reply 4: We sincerely thank you for your suggestion, we have deleted this part of the content.

Comment 5

PDT. Fig. 1 nowhere discusses relevance, only numbers

Reply 5: Thanks for the reminder, and after careful consideration, we have corrected the text.

Changes in the text: The flowchart of the study is presented in Figure 1.(Part 2. Methods and Materials, page 6).

Comment 6

A significant fraction of the PDT literature involves agents with no known clinical efficacy.

Reply 6: Thanks for your careful review, we have changed the content of the discussion section and added some agents with known clinical efficacy.

Changes in the text: Photosensitizers are a key factor in photodynamic therapy. Currently, Photofrin is commonly used in the medical institutions, which is routinely injected intravenously at a dose of 2mg/kg and delivered through a fiber optic catheter to produce singlet oxygen that forces tumor ablation under the irradiation of a 630nm laser(43). However, the biggest problem of this generation of photosensitizers is that the penetration depth is limited, the infiltration is poor, resulting in tumors outside the radiation range can not be completely cured, and will produce prolonged skin phototoxicity. Researchers are actively looking for new photosensitizers and irradiation devices to solve such problems. Second-generation photosensitizers such as Laserphyrin(NPe6) have strong absorption at 664nm and faster skin clearance than first-generation photosensitizers(44). In addition, phthalocyanine derivatives are also commonly used in PDT second-generation photosensitive molecules, the researchers found that after 24 hours of zinc phthalocyanine irradiation (680nm; 5J/cm^2), the tumor cell apoptosis(45). But these second-generation photosensitizers still have unavoidable challenges such as tumor inhibition microenvironment. An important feature of tumor development is the regulatory role of metabolic plasticity in maintaining mitochondrial oxidative phosphorylation and glycolytic balance of cancer cells. Therefore, research on novel photosensitizers mainly focuses on cell therapy and strategies for targeting mitochondria.

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Comment 7

The sites where research is done, along with journals involved may be of some interest but in no way relates to relevance of data

Reply 7: Thank you for your suggestions, and after careful discussion with us, we have made changes to the content (location and journal) of your concern

Changes in the text: Add: This shows that China is deepening its research in this field.(Part 3.2 Distribution of countries, the last sentence, page 8). A review, published in the journal lung cancer, is called advanced bronchoscopic techniques for the diagnosis and treatment of peripheral lung cancer provides a brief overview of advanced bronchoscopy techniques for the diagnosis and treatment of LC, cited 102 times.(Part 3.5 Journal Distribution, page 9)

Comment 8

It is perhaps not surprising (Fig 8) that in a list of reports on lung cancer, the words 'lung cancer' might occur most often. The relevance of this information is obscure.

Reply 8: We quite agree with your suggestion, so we have made changes to the manuscript.

Changes in the text: LC, as the topic of this paper, represents the largest circle. In addition, the keywords closely surrounding LC and PDT are apoptosis, photosensitizers, epithelial mesenchyme, nanoparticles and other keywords. This shows that the main focus in the field of PDT may be the development and utilization of new photosensitizers. As research progresses, more and more

photosensitizers are developed, and more photosensitizers are selected to target mitochondrial action to promote apoptosis.
Figure 9 shows the top eighteen keywords referenced by the outbreak. The strongest keyword burst (n=8.84) was "white light bronchoscopy", followed by growth factor receptor "(n=6.82), and" risk factors "and "autofluorescence bronchoscopy" and "white light bronchoscopy" continued to appear from 2013 to 2017, with the longest duration.(Part 3.7 Keywords Analysis, page 10)

Comment 9
This is also true for the 'top five authors', none of whom is associated with any significant advance in the field. The major contributor is likely to have been Prof. Hayata and his name is never mentioned.
Reply 9: We are very sorry for our carelessness, thank you very much for your suggestion. We have made corresponding modifications to the text
Changes in the text: The number of publications published by the author can represent the author's research activities in the field, but we cannot know the contribution of these authors to the article, these authors have the potential to contribute to the future development of the field. (Part 3.4 Author distribution, page 9)

Comment 10
None of the papers cited in Table 5 relate to PDT
Reply 10: Thank you for your patient review, we think you raised constructive comments, we have added some content.
Changes in the text: This article provides the number of cancer cases and deaths in the United States in 2020, both nationally and in each state. Analyzing the reason why it is cited most often may be as the background introduction of articles related to LC and PDT. The long-term decline in LC mortality may be due to the fact that PDT is a new treatment for LC, which prolongs the survival of LC patients. The remaining 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.(Part 3.6 Commonly cited references, page10).