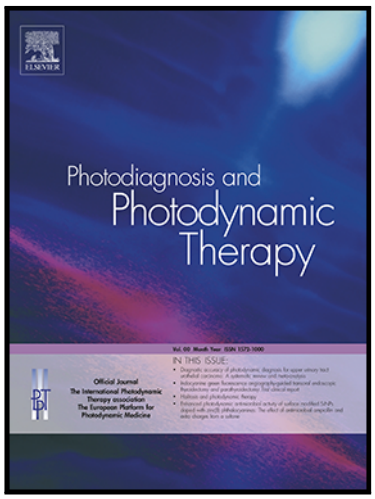
Journal Pre-proof



Three Decades of Photodynamic Therapy for Glioblastoma: A Comprehensive Scientometric Analysis

Jiheng Zhang , Xiuwei Yan , Xin Gao , Jiahe Hu , Hongtao Zhao , Chengyun Yang , Lei Xu , Yapeng Niu , Mo Geng , Nan Wang , Shaoshan Hu

PII: S1572-1000(25)00063-8
DOI: https://doi.org/10.1016/j.pdpdt.2025.104533
Reference: PDPDT 104533

To appear in: *Photodiagnosis and Photodynamic Therapy*

Received date: 13 December 2024
Revised date: 9 February 2025
Accepted date: 26 February 2025

Please cite this article as: Jiheng Zhang , Xiuwei Yan , Xin Gao , Jiahe Hu , Hongtao Zhao , Chengyun Yang , Lei Xu , Yapeng Niu , Mo Geng , Nan Wang , Shaoshan Hu , Three Decades of Photodynamic Therapy for Glioblastoma: A Comprehensive Scientometric Analysis, *Photodiagnosis and Photodynamic Therapy* (2025), doi: https://doi.org/10.1016/j.pdpdt.2025.104533

Highlights

- PDT for GBM has achieved notable advancements, with research interest reaching its peak in 2022.
- The United States and China are major contributors to research on PDT for GBM, which is continually being advanced through innovative research by several leading academic institutions and researchers.
- Current research is focused on innovative strategies like nanotechnology and combination therapies.
- Despite promising developments, further exploration is needed to overcome clinical translation challenges.

Three Decades of Photodynamic Therapy for Glioblastoma: A Comprehensive Scientometric Analysis

Jiheng Zhang[1], Xiuwei Yan[1], Xin Gao[1], Jiahe Hu[1], Hongtao Zhao[1], Chengyun Yang[1], Lei Xu[1], Yapeng Niu[1], Mo Geng[1], Nan Wang[2,3*], Shaoshan Hu[1*]

1 Cancer Center, Department of Neurosurgery, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, China
2 Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
3 Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

* Correspondence:
Shaoshan Hu, Cancer Center, Department of Neurosurgery, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, China. Present: No.158 Shangtang Road, Hangzhou, China. Tel: +0571-85893451; E-mail: shaoshanhu421@163.com
Nan Wang, Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China. Present: No. 119, South Fourth Ring West Road, Fengtai District, Beijing, China. Tel: + 01069152530; E-mail: wangnan20200807@163.com

ABSTRACT

Background: Photodynamic therapy (PDT) has emerged as a promising adjunctive treatment for glioblastoma (GBM), yet a comprehensive bibliometric analysis of this field is lacking. This study explores research trends, major contributors, and hotspots in PDT for GBM to provide an integrated overview of its development.

Methods: Literature from 1993 to 2024 was retrieved from the Web of Science Core Collection. Bibliometric tools, including CiteSpace, analyzed publication trends, collaborations, and keyword co-occurrence to identify influential authors, institutions, and journals.

Results: A total of 799 publications showed a growing research interest, peaking in 2022. The United States and China were leading contributors, with prominent institutions like the University of California System and Centre National de la Recherche Scientifique. Influential figures, such as Jiro Akimoto and Walter Stummer, advanced clinical applications and fluorescence-guided techniques. Early studies of photodynamic therapy for GBM have focused on evaluating its efficacy and potential side effects, transitioning towards innovative strategies like targeted drug delivery, nanotechnology, and combination therapies. However, the similarities between early and recent studies are in the search for safe and reliable photosensitizers. Keyword analysis highlighted "5-aminolevulinic acid", "in vitro", and "polyethylene glycol

compounds" as key areas, while timeline analysis revealed shifts from foundational photosensitizer research to approaches addressing tumor heterogeneity and resistance.
Conclusions: This study provides a systematic overview of PDT research for GBM, spotlighting breakthroughs and collaborative networks. The findings emphasize the importance of preclinical innovation and clinical translation to fully realize PDT's potential in GBM therapy.
Keywords: Photodynamic Therapy, Photosensitizer Development, glioblastoma, Bibliometric Analysis, Research Trends

1. Introduction

Glioblastoma (GBM) is one of the deadliest tumours in the central nervous system, with a survival rate survival of no more than 1 year, and about 5% of patients surviving more than 5 years [1]. Although the clinical prognosis of patients with GBM has improved in recent years with advances in diagnostic techniques and therapeutic options, precision surgical resection, adjuvant radiotherapy, and chemotherapy remain the mainstay of treatment [2, 3]. However, a large body of clinical evidence suggests that the presence of residual tumour, even after standard treatment, leads to a high recurrence rate and rapid malignant progression in GBM. This is mainly attributed to the highly aggressive nature of GBM and the significant resistance of its cells to the apoptosis-inducing mechanisms of conventional chemotherapy [4]. Therefore, the development of innovative combination therapies that target the mechanisms of tumour recurrence and progression is particularly urgent.

In recent years, immunotherapy including CAR-T cell therapy and PD-1 inhibitors, photodynamic therapy (PDT), and novel treatments such as electric field therapy have gradually attracted attention [5-8]. As a minimally invasive and low-toxicity treatment, the potential of PDT in cancer therapy has been widely confirmed by preclinical and clinical studies, and its application areas cover gastric cancer [9], lung cancer [10], bladder cancer [11], squamous cell skin cancer [12], and glioma [13]. Photodynamic therapy works by irradiating specifically aggregated photosensitizers (PSs) in the tumour tissue with specific wavelengths of excitation light, which releases reactive oxygen species (ROS) and directly kills the tumour cells. In addition, PDT further enhances its therapeutic effect by destroying the local vascular structure and modulating the anti-tumour immune response [14]. This feature makes PDT particularly suitable for tumour areas that are difficult to completely resect by conventional surgery, while causing minimal damage to healthy brain tissue, thus promising to improve the prognosis of GBM patients [15]. However, despite the promising future of PDT in GBM treatment, its research direction, development trend, and research hotspots have not been systematically analysed by bibliometric methods.

Bibliometrics, as a scientific assessment tool, can quantitatively analyse the existing literature and reveal the trajectory and key trends in specific research areas [16]. By introducing visualisation tools, bibliometrics' ability to explore complex relationships and trends in large-scale datasets has been significantly enhanced [17-19]. To fill the research gap in the field of PDT in GBM, this study systematically

reviewed the research literature related to PDT in GBM over the past 30 years using bibliometric analysis and visualisation techniques. We aimed to reveal the key research contributors, important findings, and emerging research trends in the field. The results of this study will provide valuable insights for researchers and clinicians to understand the current research landscape, identify future research directions, and promote multidisciplinary collaboration and innovation, ultimately contributing to the further development of the field of GBM treatment.

2. Method

2.1 Data Sources and Search Strategy

The literature data analysed were obtained from the Web of Science Central Dataset (WoSCC), the most comprehensive database for scientometric analysis [20]. A comprehensive systematic search strategy was elaborated, and the total search equation for the search strategy was #1: TS=("glioblastoma*" OR "glioblastoma multiform" OR "glioblastoma multiforme" OR "spongioblastoma" OR "glioblastoma cells" OR "human glioblastoma" OR "malignant glioma" OR "GBM"); #2: TS= ("photodynamic therapy*" OR "photodynamics therapy" OR photodynamic* OR "tumor photodynamic therapy" OR photochemotherapy OR "photodynamic therapy treatment" OR "phtodynamic therapy" OR "photodynamic therapy" OR "PDT")

The criteria for the inclusion of sources in this study were: (1) the literature search period was from 1 January 1993 to 27 October 2024; (2) the type of literature selected was ‘article’ and ‘review’; and (3) the language selected was English. In addition, the exclusion criteria included: (1) articles not related to PDT and GBM; (2) formats such as letters, reports, preprints, short articles, or abstracts; and (3) redundant literature. (4) withdrawn literature. The bibliometric process is shown in flowchart **Figure 1**. Finally, 799 literature materials were retrieved from WoS.

2.2 Data Extraction and Analyses

To analyze PDT and GBM-related publications, we conducted a bibliometric analysis, visualizing a variety of characteristics, with units of measurement including authors, journals, references, countries, institutions, and keywords. Microsoft Excel plotted the temporal distribution of annual and cumulative publications. The analysis of major institutions, core authors, journal distribution, citation keyword analysis, and co-cited reference analysis involved CiteSpace (6.2.2), which is widely used in bibliometrics [21-23]. In the visual network maps, each node represents a specific parameter, such as country, institution, or keyword. The size of each node is proportional to its parameter weight, with larger nodes indicating higher weights. Both nodes and connecting lines are coloured according to their assigned clusters.

CiteSpace uses sigma, a unified metric combining betweenness centrality and citation burstiness, to assess the potential influence of works: sigma is calculated as (centrality + 1) * burstiness, with higher values indicating greater impact [19, 24]. The modularity score (Q score) measures the extent to which a network can be divided into distinct clusters, with values above 0.3 suggesting a significant structure [25]. The silhouette score (S score) evaluates cluster consistency from -1 to 1, where

coefficients over 0.3, 0.5, and 0.7 represent homogeneous, reasonable, and highly credible clusters, respectively. A score near +1 may indicate relative cluster isolation. Cluster labels were derived from noun phrases in the keywords of cited articles through the likelihood ratio test ($p < 0.001$) and were refined by the authors to ensure relevance and accuracy based on their expertise [26].

3. Result

3.1 Annual Research Trends and Disciplinary Distribution

From 1993 to 2024, a total of 799 articles focusing on PDT in GBM were indexed in the WoS, comprising 614 original research articles and 155 reviews. Among these, original research articles constituted the majority, accounting for 76.84% of the total publications, while reviews represented 23.15% (**Figure 2A**). Over the study period, the number of publications exhibited a fluctuating growth trend, with annual publications not exceeding 100. The year 2022 marked the peak in publication activity, with 79 papers published. Using an exponential time prediction model, the publication trend was characterized by the equation $y = 8.3831e^{0.1581x}$, demonstrating a statistically significant relationship between the publication year and the cumulative number of papers ($R^2 = 0.9774$), indicative of a strong model fit (**Figure 2B**). This increasing trend highlights a progressive, albeit modest, research focus on PDT for GBM over the decades. However, the relatively low overall publication volume underscores the need for further exploration in this field.

The primary research domains for PDT in GBM include oncology, biochemistry and molecular biology, chemistry, neuroscience and neurology, materials science, surgery, pharmacology and pharmacy, biophysics, and engineering. Of particular note is the integration of materials science and PSs, which have provided innovative therapeutic strategies (**Figure 2C**). This interdisciplinary approach highlights the potential of leveraging advanced materials to enhance the efficacy of PDT in GBM treatment.

3.2 Co-occurring Author Keywords Networks

Using CiteSpace for bibliometric analysis, we identified the top 11 most prolific authors in the field of PDT for GBM research (**Table 1**). The leading contributors to this field include Stummer Walter with 26 publications, Hirschberg Henry with 20 publications, and Akimoto Jiro and Stepp Herbert each with 19 publications. Following them are Barberi-Heyob Muriel and Frochot Celine, each having 14 publications. Among the top four contributors, Stummer made significant early contributions in 1998, publishing three highly-cited articles with 557, 220, and 214 citations, respectively. Stummer's research laid the groundwork for assessing the accuracy and safety of PDT for malignant gliomas [27, 28]. By using 5-aminolevulinic acid (5-ALA) to effectively label malignant gliomas in clinical practice, he enhanced the completeness of tumor resection [29]. This improved accuracy was verified through animal experiments using rat models. Subsequently, Stummer and his colleagues analyzed the impact of fluorescence-guided resection on postoperative magnetic resonance imaging and survival rates in a cohort of surgical

patients. Their findings demonstrated that the intraoperative assessment of residual tissue fluorescence during surgery correlated with postoperative MRI results and survival outcomes in GBM patients. The use of 5-ALA-induced tumor fluorescence has proven valuable in guiding tumor resection, as supported by imaging standards [30]. Hirschberg Henry, the second most prolific author in this field, has significantly impacted PDT research for GBM through two widely-cited papers with Stummer in 2007 and 2018. Their work highlighted the use of 5-ALA for intraoperative fluorescence-guided surgery, demonstrating that selective fluorescent protoporphyrin IX accumulation in tumor cells allows precise visualization without expensive imaging tools. This advancement boosts resection accuracy and lays the groundwork for next-generation PDT methods, such as postoperative or interstitial PDT [31]. Further, advancements in 3-D treatment planning have addressed challenges like non-selective PS accumulation, allowing precise treatment volume calculation and effective light diffuser placement. Combining 5-ALA interstitial PDT (iPDT) with 3-D planning has shown to be a safe and feasible therapy, promising new directions in GBM management [32].

The Author Collaboration Network Analysis highlights key contributors to the field of PDT in GBM. In **Figure 3A**, red nodes indicate emergent authors who have rapidly published a significant number of papers. Mordon Serge (burst=5.1744) published 12 papers between 2015–2021, Hirschberg Henry (burst=4.7895) and Madsen Steen J (burst=4.426) each published 11 papers from 2001–2009, Reyns Nicolas (burst=4.3934) had a volume of 9 publications from 2017–2021, and Sun Chung-Ho (burst=3.5462) published 10 papers between 2000–2014. These authors rank in the top five by burst value (**Figure 3B-F**). In **Figure 3G**, the co-citation network shows nodes representing authors, with size corresponding to co-citation frequency. Stummer, Stupp R, and Eljamel MS are central figures, having the largest nodes which reflect their major influence and connectivity in the research landscape. **Figure 3H** displays the top 25 authors with the strongest citation bursts, ranked by burst strength and shown with time intervals to indicate their periods of impact. **Table 2** details the top 10 co-cited authors, along with their h-indices, offering insights into their academic influence. The top five authors are Stummer (count=294), Stupp R (count=195), Eljamel MS (count=132), Dougherty TJ (count=107), and Joseph Sarkis (count=91). A higher h-index highlights their substantial and sustained impact. These findings underscore the collaborative and interdisciplinary nature of PDT research in GBM, with key contributors and their significant works driving the advancement of this therapeutic field.

3.3 Analysis of cooperation networks across countries/regions and institutions

A total of 398 organisations from 58 countries or regions have made significant contributions to PDT in GBM field. The top ten contributing countries span three continents, including Europe (4 countries), Asia (3 countries), and North America (2 countries). The United States leads with 188 publications (17.33%), followed by China (129, 11.89%), Germany (117, 10.78%), and Japan (92, 8.48%) (**Table 3**). While the United States has maintained its leadership with early and sustained

contributions, China has shown a notable rise in impactful publications in recent years. In terms of centrality, which reflects a country's role in facilitating knowledge dissemination, Germany has the highest value (0.81), highlighting its influential position in this research area. The collaboration network reveals that the United States and China dominate international collaborations. However, the overall connections between countries are relatively weak, as indicated by the darker colors of the network lines (**Figure 4A**). This suggests limited intensity and strength of cooperation in this domain, particularly in recent years. Despite the prominence of a few leading nations, the findings indicate an urgent need to strengthen global collaboration to further advance research in PDT for GBM.

The analysis of research institutions reveals that the top 18 contributors to the field, as presented in **Table 4**, include notable institutions such as the University of California System (32 publications), Centre National de la Recherche Scientifique (CNRS) (32), University of Munich (28), and Harvard University (26). Other key contributors include Harvard Medical School (23), the University of Oslo (23), Institut National de la Sante et de la Recherche Medicale (Inserm) (22), and the Chinese Academy of Sciences (22). When assessing mediated centrality, the University of California System and the University of Toronto lead with a centrality score of 0.14, followed by CNRS at 0.13. This measure indicates these institutions' significant influence and connectivity within the research network. Additionally, burst detection highlights institutions with strong emergent growth potential. The top institutions with the highest burst values include the University of Oslo, Inserm, University of California Irvine, the Nevada System of Higher Education, and CHU Lille. As visualized in **Figure 4B**, these institutions are poised to play increasingly critical roles in advancing the field, reflecting their capacity for innovation and contribution to emerging trends.

3.4 Knowledge areas, evolution, and emerging trends

A keyword is a generalization of a research area. We performed keyword co-occurrence using CiteSpace (**Figure 5A**). Keyword co-occurrence analysis can be used to identify research hotspots in a scientific field. Nodes indicate literature keywords, the larger the node, the more often the keyword occurs, the color of the circle contained in the node indicates different time ranges, and the darker the color of the node's periphery indicates the higher centrality of the keyword. The ring width of the rings indicates the frequency of keyword occurrence in a certain time range. The color of the connecting line represents the time when the keyword first co-occurred, and the thickness represents the amount of times/likelihood of co-occurrence. To get a clearer picture of the specifics of the keywords, keywords with the same meaning were combined, and the keywords with a frequency of more than 22 were made into **Table 5**. As can be seen from the figure and table, "photodynamic therapy, 5 aminolaevulinic acid, malignant gliomas, glioblastoma multiforme, cancer, brain tumors, and in vitro" have a frequency of more than 100, which mainly constitute the representative terms in the field. In vitro has the highest mediator centrality of 0.18, indicating that the keyword has an important mediating or bridging role in a specific

research field, and plays an important role in the overall network structure connection and information transfer plays a key role. The keywords with a mediator centrality greater than 0.1 are, in descending order, in vitro, cancer, 5 aminolaevulinic acid, brain tumors, and glioblastoma are the most important keywords with a centrality of mediator greater than or equal to 0.1.

In order to improve the accuracy of summarizing the research field, this study performs clustering by Log-Likelihood Rate (LLR) algorithm for the keyword network and takes the name of the feature word with the highest value of LLR operator in the class as the name of the cluster, and obtains the clustering results as shown in **Figure 5B** and a total of 10 clusters are obtained. CiteSpace is based on the structure of the network and clustering CiteSpace provides two metrics, modularity Q and mean silhouette, when the Q value is > 0.3, the clustering structure is significant, and when the S value reaches 0.7315, the clustering is convincing. The Q value of the graph is 0.7315 and the S value is 0.863, the data are within a reasonable range, which indicates that the clustering in this study is significant, and the results are convincing. **Figure 5C** presents a graph of high-frequency research topics from 1993 to 2024. Initially, research focused on PDT, then shifted to using 5-ALA as a PS for clinical surgical navigation. Subsequently, attention turned to immunity, techniques for breaching the blood-brain barrier, and combination chemotherapy to treat GBM and suppress recurrent gliomas. To visualize the evolution of research trends over time, we generated a keyword timeline view (**Figure 5D**). This timeline maps keywords into their respective clusters in chronological order, with node sizes indicating frequency of occurrence and connecting lines illustrating topic evolution. Notably, photodynamic diagnostics (#4) was a highly cited topic early on but saw a decline in attention after 2015. More recent research hotspots include polyethylene glycol compounds (#15), targeting malignant glioma survival (#7), human leukemia cells (#3), tissue factor release (#5), hyperthermia sensitization (#0), human glioma spheroids (#12), and current glioblastoma studies (#13). These trends highlight the dynamic and evolving nature of the field.

3.5 Refences and Clusters of Research

The network consists of 1204 nodes and 4664 links, as per CiteSpace analysis. After clustering the cited networks, 18 clusters were obtained. A profile > 0.7 in these clusters indicates the interpretability of the clustering results. We generated reference co-citation maps and corresponding clusters to extract landmark reference and research clusters (**Figure 6A**). Cluster numbers are ordered by node size. The smaller the number in the numbering, the more the literature has been cited. The connecting lines between nodes indicate co-citation relationships, and their thickness indicates co-citation strength. The colour corresponds to the time of the first co-citation of the node. From the sudden increase in the number of citations, emerging trends in science can be inferred from them. We have listed the 10 strongest references by the intensity of citation bursts. The research published by Stummer in 2006 was far-reaching [33]. It is worth noting that the research directions of Cramer SW [34], Eljamel MS [35],

Mahmoudi K [36], Quirk BJ [37], Akimoto J [38], Vermandel M [39], Stepp H [31], Bechet D [40], Teng L [41] have also made an impact on the field(**Figure 6B**).

We generated journal co-citation maps to detect and assess resounding journals that are responsible for contributing to the development of research on PDT therapy for GBM and to some extent act as a knowledge base. As shown in **Figure 7A**. The CiteSpace configuration was set as follows: top N = 30, LRF = 3, L/Y = 10. By pruning the sliced and merged network, 386 nodes and 2287 links were obtained. Based on the citation frequency of the data (i.e., node size), the most cited journals PHOTOCHEM PHOTOBIOL (432), J NEUROSURG (406), and J NEURO-ONCOL (394) (**Table 6**). In terms of centrality between citing journals (nodes with purple circles), the following journal with a centrality of more than 0.1 is CANCER RES (0.15), which suggests that it connects other journals to a large extent. In addition, **Figure 7B** shows the top 25 journals in terms of citations. The top 5 journals are CANCERS (strength 50.5), SCI REP-UK (strength 37.62), NAT COMMUN (strength 37.59), FRONT ONCOL (strength 35.46) and INT J MOL SCI (strength 32.38), representing the strong connection strength between these journals and other journals, and the recent year of appearance of these journals, suggesting that these journals may become one of the influential and representative journals in the field of PDT treatment GBM in the future.

4. Discussion

In this study, we conducted a systematic literature search using the WoSCC database and applied bibliometric and information visualization techniques to perform a comprehensive analysis of 799 articles published between 1993 and 2024 on the application of PDT in GBM. To the best of our knowledge, this is an early bibliometric study that systematically explores the research trends, major contributors, and knowledge structure of PDT in the context of GBM. By providing a multidimensional overview of the current state of research, this study provides a foundational framework for understanding the current state of the field while also identifying gaps and opportunities for future exploration. The results of the multi-dimensional study provide perspectives on emerging trends, collaborative networks, and the evolving research priorities of PDT at GBM.

The number of papers related to PDT for the treatment of GBM has shown fluctuation and growth, especially peaking in 2022, This surge reflects the scientific community's increasing interest in PDT as a promising therapeutic strategy. A plausible explanation for this peak is that the approval of 5-ALA by the US FDA in 2017 has greatly facilitated clinical research and applications involving PDT. 5-ALA, the first optical imaging agent approved for intraoperative visualization of high-grade gliomas, produces the metabolite PPIX, which possesses both fluorescent and photosensitizing properties [32, 42]. This dual functionality allows PDT to enhance tumor control in challenging-to-resect GBM. Additionally, advancements in PSs, improvements in precision therapy techniques, and the pressing need for effective GBM treatments have contributed to the research momentum [43]. However, despite this growing interest, the overall volume of research in PDT for GBM remains modest

compared to other cancer types, such as lung and skin cancers [44, 45]. This suggests that PDT research in GBM is still in its early stages and has yet to produce large-scale breakthroughs or establish itself as a prominent research focus.

The field of research on PDT for GBM focuses on biochemistry, molecular biology, oncology, and materials science. These disciplines underpin the exploration of PDT mechanisms and the optimization of therapeutic strategies for GBM. In particular, the development of PSs rooted in materials science has emerged as a key area of innovation. For instance, Quinlan et al. introduced a carrier-free nanomedicine, "NanoVP," designed to address the limitations of traditional PSs like vitepofungin (VP), which rely on liposomal carriers that often hinder intracellular accumulation. The NanoVP formulation, with its adjustable size and higher drug-loading capacity, demonstrated a twofold increase in cellular uptake and superior PDT efficacy compared to liposomal VP. In mouse models, NanoVP-PDT not only significantly suppressed tumor growth and prolonged survival but also safely opened the blood-brain barrier, enhancing drug delivery to the brain [46]. To tackle the challenge of insufficient tumor accumulation of PSs in GBM, Xu et al. proposed an innovative drug delivery system utilizing platelets as carriers for PS complexes. These complexes comprised chlorin e6 (Ce6) as the PS, combined with boron nitride nanoparticles coated with polyglycerol and adriamycin. Upon laser irradiation, the system enabled photo-controlled release of the PS and robust ROS generation, effectively inducing tumor cell death [47]. This interdisciplinary approach not only advances the development of highly effective PSs but also facilitates the optimization of PDT modalities. Such strategies are expected to significantly enhance the therapeutic efficacy of PDT for GBM in the future. Nonetheless, substantial challenges remain in translating these promising research findings into clinical applications. Bridging the gap between basic research and clinical practice will require continued interdisciplinary collaboration, robust preclinical validation, and well-designed clinical trials to ensure safety and efficacy.

Regarding the major authors and their contributions, several key researchers have played a crucial role in advancing both the clinical and preclinical applications of PDT in the treatment of GBM. Herwig Kostron is recognized as one of the pioneering figures in the application of PDT in neurosurgery, with his contributions serving as a foundation for the development of this innovative therapeutic approach. Since the 1980s, Kostron has been extensively involved in the clinical translation of photodynamic therapy. Under his leadership, photodynamic therapy was applied to the treatment of GBM [48]. In their 1988 report, they explored the application of PDT in the treatment of malignant brain tumors, particularly GBM, malignant meningioma, and metastatic melanoma. A total of 20 patients underwent PDT, which involved the administration of hematoporphyrin derivative followed by irradiation with 630 nm light at a dose of 40-120 J/cm^2. The results indicated a median survival of 5 months for patients with recurrent glioblastoma, with some surviving up to 22 months. The treatment was well tolerated, with phototoxicity being the only observed side effect. These preliminary findings suggest that PDT holds significant potential as an adjunctive therapy for malignant gliomas. This marked a significant milestone in the

treatment of malignant brain tumors [49]. In the following years, Kostron also pioneered the introduction of fluorescence-guided resection (FGR) for intraoperative visualisation of malignant brain tumours using second-generation PSs such as m-tetrahydroxyphenyl chloride (m-THPC) and 5-ALA. This technique is widely recognised for improving surgical accuracy and reducing tumour burden [50]. Kostron's research has demonstrated that PDT, as an adjunct to standard therapies, offers enhanced median survival for patients with primary and recurrent GBM compared to conventional treatments alone. One of their meta-analyses revealed median survival times of 22 months for primary GBM and 9 months for recurrent cases following PDT, compared to 15 and 3 months, respectively, with standard approaches [51]. These outcomes highlight the potential of PDT to selectively destroy tumor cells while sparing healthy tissues, making it an invaluable addition to the neuro-oncology therapies.

Akimoto Jiro's work on clinical trials has demonstrated the potential of PDT as part of intraoperative combination therapy to significantly improve OS in patients with newly diagnosed and recurrent GBM. A pivotal Phase II clinical study enrolled 22 patients with histopathologically confirmed malignant brain tumors, including 13 newly diagnosed GBM patients. Among these, the study reported a 12-month OS rate and a 6-month progression-free survival (PFS) rate of 100%, underscoring PDT's effectiveness in improving survival outcomes. Importantly, the study utilized a single-arm design without a randomized control group, with results compared primarily to historical benchmarks such as the Stupp protocol. This limitation highlights the need for further randomized clinical trials to validate these findings. Nevertheless, Akimoto's work demonstrates the potential of PDT in enhancing local tumor control, particularly in cases of aggressive and difficult-to-resect tumors [52]. In addition, Akimoto’s team examined three patients with GBM who received additional PDT treatment. Preoperative MRI showed no tumor recurrence within the PDT-treated area. Histopathological analysis revealed a treatment depth ranging from 9 to 18 mm (mean depth: 12.7 mm), within which the tissue exhibited characteristics of gliotic scarring, accompanied by infiltration of T lymphocytes and macrophages, as well as mild degeneration of small vessel walls. However, tumor tissue was still present beyond the treatment depth. This suggests that PDT effectively prevents early local recurrence, potentially through immune mechanism activation, though tumor tissue remains outside the treated depth [53]. Furthermore, Akimoto’s team also conducted foundational research on PDT. They explored the effects of PDT using talaporfin sodium (NPe6) as the PS on the death mechanisms of human GBM T98G cells. The study found that NPe6-PDT induced necroptosis, as evidenced by increased lactate dehydrogenase (LDH) leakage. This process was inhibited by the necroptosis inhibitor necrostatin-1 and the downregulation of necroptosis-related proteins (RIP1, RIP3, and MLKL). Moreover, at lower concentrations (25 μg/ml), NPe6-PDT induced autophagy, whereas at higher concentrations (50 μg/ml), this process was not observed. The findings suggest that necrotic cell death induced by NPe6-PDT is partially mediated by the necroptotic pathway, providing new insights into the mechanisms of PDT for GBM treatment [54].

Similarly, Kaneko's research team in Japan extensively discussed the clinical applications of PDT in malignant gliomas, particularly in GBM. They highlighted the results of a meta-analysis of observational studies on PDT in high-grade gliomas (HGGs), which included over 1,000 patients. This analysis reported a median OS of 16.1 months for newly diagnosed GBM patients and a median OS of 10.3 months for patients with recurrent GBM. Although PDT showed promising outcomes in some studies, Kaneko and colleagues emphasized that the evidence from controlled trials assessing its survival benefit remains limited. The main adverse effects identified for PDT were transient photosensitivity of the skin and retina, which can be managed with appropriate protective measures. Based on these findings, the team concluded that PDT is a safe and effective adjuvant therapy, with aggressive tumor resection being crucial for maximizing its therapeutic efficacy [55]. Furthermore, the team also emphasized the clinical applications of ALA and fluorescein (FLCN) in HGG. FGR, as a revolutionary advancement, has been crucial for achieving more complete glioma resection. This technique significantly enhances tumor resection rates, especially in challenging GBM surgeries, by aiding in the identification of tumor boundaries during the procedure [56, 57].

Professor Kaye and his team in Australia have made significant progress in the study of PDT for gliomas, contributing both clinical and laboratory-based research. They discussed the selective cytotoxicity of PDT in gliomas, highlighting its ability to target infiltrating tumour cells through tumour-specific uptake and light-activated PSs, leading to a reduction in tumour cells [58, 59]. Clinical studies further demonstrated that PDT, as an adjunct to surgery, positively impacted survival rates in patients with GBM and anaplastic astrocytoma, with higher laser doses (> 230 J/cm²) correlating with improved prognosis [60]. Additionally, their team systematically evaluated the performance of various PSs. HpD exhibited significantly higher absorption in HGGs compared to normal brain tissue, and its absorption level was positively correlated with the survival rate of GBM patients [61, 62]. A novel borated porphyrin (BOPP) demonstrated superior tumor-selective absorption in animal models compared to HpD, with a tumor-to-normal brain tissue ratio of 400:1. Moreover, BOPP showed potential for both PDT and Boron Neutron Capture Therapy (BNCT) [63, 64]. Phase I clinical trials confirmed the safety of BOPP, with the recommended dose being 4 mg/kg, and identified platelet reduction and photosensitivity as the primary toxicities [65]. Laboratory studies also explored other PSs, such as aluminum phthalocyanine (AISPc), which, when activated by 675 nm light, induced selective tumor necrosis but required strict dose control to avoid normal brain damage [66]. Furthermore, their team identified a porphyrin C analog, whose photoactivity was comparable to HpD but exhibited lower toxicity. In animal models, this analog achieved tumor cell death at a depth of 1.77 mm [67]. The physicochemical properties of PSs, such as their partition coefficient, were shown to influence tumor targeting, with neutral or cationic porphyrins performing better [67]. Kaye and colleagues also optimized PDT parameters, discovering that HpD doses greater than 1 mg/kg led to normal brain damage, while fractionated doses or low-power light (e.g., 3125 mW/cm²) did not significantly improve therapeutic outcomes, suggesting that current clinical protocols

may require adjustment [68]. In terms of combination therapies, the chemotherapeutic agent MX2 enhanced the cytotoxicity of PDT, providing a basis for multimodal treatment strategies [69]. While PDT has shown potential in glioma treatment, Kaye et al. emphasized the need for large-scale clinical trials to validate its efficacy and further optimize PSs and irradiation protocols [70, 71].

Muller and colleagues from Toronto conducted a study investigating the application of FGR combined with PDT in brain tumor treatment using a rabbit brain tumor model. The study utilized ALA-induced protoporphyrin IX (PpIX) fluorescence imaging in conjunction with low-dose, prolonged light exposure. Experimental groups included a control group, an FGR-only group, and an FGR+PDT group. The results demonstrated that PDT selectively induced apoptosis in tumor cells without causing bacterial infections. This study established an experimental model for FGR-assisted PDT in brain tumor therapy and emphasized the need for optimization of drug administration and illumination parameters to enhance therapeutic efficacy [72]. In clinical research, Muller et al. evaluated PDT in 112 patients with malignant gliomas, including 96 patients with supratentorial gliomas. The results showed a median OS of 42 weeks following PDT, with 1-year and 2-year survival rates of 40% and 22%, respectively. Notably, patients with a higher proportion of oligodendroglial components in their tumors exhibited prolonged survival. Additionally, 75% of patients did not experience severe postoperative complications, demonstrating the safety of Photofrin-based PDT and providing a basis for further dose optimization [73]. Furthermore, Muller and colleagues developed a multispectral fluorescence imaging system to improve intraoperative identification of residual glioma tissue during PDT. Their study confirmed that this system effectively detected postoperative residual tumor tissue with high clarity [74]. In a study involving 50 patients with malignant brain tumors, PDT resulted in a median OS of 8.6 months. Notably, patients who achieved complete or near-complete response, exhibited a significantly longer median OS of 17.1 months [75].

Eljamel and his team have conducted multiple studies on the application of PDT in glioma treatment, with a particular focus on the roles of photodynamic diagnosis (PDD) and PDT in improving tumor resection rates, prolonging survival, and enhancing patient outcomes [76]. Early studies demonstrated that PDD and PDT significantly extended the time to tumor progression, reduced local recurrence rates, and increased the rate of gross total resection (GTR). These techniques were well tolerated and showed potential in prolonging patient survival, highlighting the need for further investigation into their role as adjuvant postoperative treatment modalities [77]. In a single-center randomized controlled trial, Eljamel evaluated the efficacy of ALA- and Photofrin-FGR combined with PDT in patients with GBM. The results indicated that the experimental group achieved a mean OS of 52.8 weeks, significantly longer than the 24.6 weeks observed in the control group ($p < 0.01$). Additionally, patients in the experimental group exhibited a 20-point improvement in Karnofsky Performance Score ($p < 0.05$), and the time to tumor progression was extended to 8.6 months compared to 4.8 months in the control group ($p < 0.05$). These findings suggest that this combination therapy can significantly improve the survival

of GBM patients without increasing surgical risks [35]. Eljamel further explored the applications of PSs, such as ALA and Photofrin, and laser parameters in the treatment of aggressive brain tumors. His findings demonstrated that PDD exhibited 100% specificity and over 80% sensitivity in detecting occult tumor nests, enabling precise intraoperative identification of residual tumor tissue. Furthermore, PDT effectively destroyed residual tumor cells post-resection, thereby improving overall patient survival. The study suggested that PDT could potentially double patient survival time and underscored the need for further optimization to maximize its therapeutic potential [78]. Eljamel and colleagues also made significant contributions to FGR for HGG. Their research demonstrated that, compared to standard surgical techniques, ALA- or fluorescein (FLCN)-mediated fluorescence-guided imaging systems significantly increased the rate of GTR to 74.5% and 84.4%, respectively. Moreover, these techniques performed well in cost-effectiveness analyses, suggesting that they not only enhance surgical precision but also offer economic feasibility [56]. Eljamel's comprehensive review on PDT applications in GBM highlights its crucial role in improving treatment outcomes. ALA-guided fluorescence imaging allows accurate biopsy sampling of high-grade components in tumors that appear low-grade on MRI, with an 89% sensitivity. In observational studies and RCTs, FGR achieved >84% sensitivity and >65% complete resection, extending tumor-free survival ($p < 0.05$). PDT, supported by over 1000 patients in observational studies and RCTs, demonstrated high selectivity and safety, significantly improving survival quality and delaying tumor relapse ($p < 0.05$). Eljamel's work strongly supports integrating PDT as a selective, sensitive, and safe treatment modality for GBM [79, 80].

Stummer and Stepp Herbert's research, on the other hand, focuses on intra-operative fluorescence-guided surgery with 5-ALA for precise intra-operative visualisation. Notably, this technique has significant clinical applicability because it eliminates the need for expensive equipment and reduces operational complexity [31]. Other notable contributors include Mordon Serge, who has a strong focus on iPDT and 5-ALA. Between 2019 and 2021, Mordon published six articles with a combined two-year citation count of 176, reflecting his influence in the field. His collaborations with Reyns Nicolas have explored mesenchymal PDT for high-grade gliomas in preclinical models. While their studies found no significant differences in cell death or necrosis between experimental and control groups, they reported significantly lower levels of edema in the experimental group, highlighting the potential benefits of their treatment regimen [81]. Moreover, their work on parallelizing Monte Carlo methods using Graphics Processing Units offers a cost-effective solution for treatment planning [82]. Mordon has also proposed a standardized workflow for the clinical application of iPDT in GBM. This workflow integrates intraoperative imaging, a dedicated treatment planning system, and robot-assisted stereotactic fiber implantation. The comprehensive protocol has been validated in simulated operating theater conditions, marking a significant step towards clinical trials to assess the role of iPDT in GBM treatment [83]. He highlighted the efficacy and safety of 5-ALA as PS in iPDT seem to be both for the treatment of brain tumors (especially high-grade gliomas) [39, 84]. Hirschberg H published 3 in 2002 and 4 in 2006. He demonstrated

that ALA PDT treatment of high-grade gliomas prolonged the survival of experimental animals with glioblastoma [85]. Repeated PDT at relatively long intervals (several weeks) was more effective in inhibiting tumor growth than daily fractionated PDT or single treatment regimens [86]. In the brains of all animals treated with PDT, the survival rate of the group of animals treated with ALA PDT was significantly higher, with significant oedema in the center of the necrotic tumor as well as in the surrounding brain and white matter bundles [87]. Its study focused more on the zoological studies of PDT treatment of GBM, exploring the therapeutic effects of different energy densities in experimental animals, and reviewed the studies of ALA as an effective rate of PDT treatment of GBM [88]. Although Hirschberg H published his article earlier, the reliability of his experiment was widely recognized.

The results of the keyword co-occurrence analysis provide an in-depth view of the research hotspots and trends in the field. Notably, "in vitro" emerges as a critical bridging keyword in the network structure, reflecting the significant number of experimental studies conducted on PDT for GBM. This may stem from the fact that there has been a large number of experimental articles on improving PSs in recent years. With the firestorm of nanomaterials and disciplinary crossover, this has led to a growing interest in designing and optimising PSs by many researchers. Bruno et al. conducted a series of in vitro experiments to explore the potential of pro-oxidant therapies, specifically focusing on the combination of doxorubicin and PDT with Me-ALA, for GBM treatment. The study aimed to leverage the elevated oxidative stress levels in GBM cells to induce selective cytotoxicity and overcome resistance to conventional therapies [89]. Banendu et al. developed and evaluated an advanced nanoplatform for enhancing PDT in GBM using *in vitro* experiments. Their work focused on addressing tumor hypoxia and improving the efficacy of combination phototherapy [90]. These studies have been pivotal in validating the efficacy of novel PSs, optimizing photodynamic effects, and exploring various therapeutic combinations. Additionally, the co-occurrence of other high-frequency keywords underscores the multidisciplinary nature of PDT research. The progression from basic research to clinical applications is evident, particularly through the integration of molecular biology, materials science, and photodynamics, which has driven continuous technological advancements in PDT. At the clinical level, the evolution of keywords from photodynamic diagnosis to targeting malignant glioma survival highlights the transition of PDT from diagnostic applications to therapeutic use, demonstrating its growing role in GBM management. However, our bibliometric analysis indicates a relative scarcity of articles focusing on clinical applications compared to the abundance of preclinical studies. PDT has indeed shown some clinical efficacy in glioma treatment. For instance, pioneering efforts by Perria et al. were reported as early as the 1980s [91], followed by preliminary trials by Kostron et al. using haematoporphyrin derivatives and light irradiation in patients [48]. In 1996, Kostron et al. summarized a series of phase I/II trials demonstrating the feasibility and potential of PDT, although these were limited by small sample sizes and variability in treatment protocols [92]. Advances such as 5-ALA fluorescence-guided surgery, introduced by Stummer et al., have paved the way for adjuvant light-guided therapies.

Nevertheless, these techniques primarily aim to enhance resection rather than serve as standalone treatments [33]. To validate the efficacy and safety of PDT in neurosurgery, larger multicenter clinical trials are essential. While adjuvant PDT has shown promise in extending survival, such trials often involve small cohorts and non-standardized protocols [84]. The lack of randomized controlled trials hinders broader clinical adoption. Variations in light dosimetry, PS selection, and delivery methods further complicate protocol standardization.

The cluster analysis results further reveal the diverse research interests within the field. For example, Cluster #7 (targeting malignant glioma survival) reflects recent shifts in research priorities, particularly in advancing targeted therapies and optimizing PS delivery strategies. The timeline view validates this by showing the changing state of the study in chronological order. Prior to 2010, research focused on traditional PDT techniques, tending towards basic theoretical explorations and initial clinical applications. The use of PDT as an adjunctive neurosurgical therapy was evaluated in a review by Kostron et al. They critically analysed data from more than 310 patients treated with haematoporphyrin derivative-mediated PDT in a phase I/II clinical trial and showed a trend towards increased median survival when PDT was combined with surgical resection [92]. During this timeframe, Stummer et al. extensively explored the clinical application of 5-ALA and its potential role in iPDT. While 5-ALA is primarily recognized for its fluorescence-guided surgical applications, Stummer et al. also highlighted its photosensitizing properties, which allow for selective tumor destruction when combined with light irradiation. Notably, their work demonstrated the feasibility and safety of 5-ALA-mediated PDT, offering a novel and effective strategy for treating recurrent and unresectable GBM [33, 93]. During 2010-2015, the focus shifted to in vitro studies and tissue factor release, marking an in-depth study of the molecular mechanisms of photochemotherapy and the pathways of PS response. For example, Berkovitch-Luria et al. investigated the potential of multifunctional 5-ALA to optimise cancer therapy by activating different cell death pathways and enhancing therapeutic outcomes [94]. Etminan et al. explored the immunostimulatory effects of 5-ALA-mediated PDT on dendritic cells (DCs) in a human GBM spheroid model. They focused their in vitro studies on the role of heat shock protein 70 in promoting adaptive immune input [95]. More recently (2016-present), research focus has shifted to innovative therapeutic strategies including thermosensitisation, nanomaterials and immune remodelling. Chen et al. developed a self-disassembling porphyrin lipoprotein-coated calcium peroxide nanoparticle designed to guide surgical interventions and enhance the efficacy of PDT using fluorescence. This novel nanoplatform addresses critical challenges in GBM treatment, including tumor residuals and hypoxia-induced drug resistance [96]. Similarly, Ge et al. have employed upconversion nanoparticles to create a new nanoplatform that combines PDT with carbon monoxide therapy, overcoming the limitations of conventional PDT like inadequate therapeutic efficacy and potential side effects [97]. These advancements underscore the potential of integrating PDT with other therapeutic modalities, such as thermal therapies and nanomaterial-based drug delivery systems, to tackle issues like therapeutic resistance and tumor

heterogeneity in GBM.

Overall, early research on PDT for GBM primarily focused on evaluating its feasibility, efficacy, and potential side effects. These studies investigated PDT's effectiveness in treating GBM across different brain regions [98], the impact of varying PDT dosages on neurological deficits using canine models [99], and the uptake and distribution of PSs during treatment [100]. However, the similarities between early and recent studies are in the search for safe and reliable PSs. Explorations of early PSs, including boronated porphyrins [64], monomeric and oligomeric porphyrins [101], and liposome-delivered photofrin [102], laid the groundwork for PDT as a therapeutic option. As PDT's efficacy became widely recognized, research shifted towards addressing key challenges, such as penetrating the blood-brain barrier [103, 104], while also focusing on innovative approaches to enhance therapeutic outcomes. Recent efforts include combining PDT with nanomaterials [105, 106], and oncolytic virotherapy [107], as well as evaluating its long-term efficacy through retrospective studies [108]. This evolution highlights a shift from validating PDT's basic mechanisms to developing advanced, integrated strategies aimed at overcoming clinical application barriers while maximizing therapeutic benefits for GBM patients. PDT has shown promising results in extending the survival of GBM patients. However, its limited clinical application in GBM treatment arises from several scientific, technical, and practical challenges. First, the invasive and infiltrative nature of GBM complicates the uniform uptake of PSs. Although advances in targeted agents have been made, their efficacy within the heterogeneous tumor microenvironment remains inconsistent. Haematoporphyrin derivatives, for example, still struggle to adequately cover the invasive tumor margins [91, 109]. Second, effectively crossing the blood-brain barrier remains a significant obstacle for PSs. While PSs combined with nanomaterials hold great potential, their clinical application is still limited. Furthermore, laser penetration in brain tissue is restricted to a depth of 1–2 mm, making it challenging to address deeper tumor areas. Approaches such as balloon light delivery and interstitial fiber optics provide partial solutions but are technically complex to implement. Another challenge lies in the potential adverse effects of PDT, including edema and inflammation in adjacent healthy brain tissue, which can increase the risk of brain herniation and functional damage. Finally, the lack of large-scale clinical trials with standardized protocols significantly hinders regulatory approval and broader adoption of PDT. While early studies have demonstrated survival benefits, variability in methodologies and patient populations limits their generalizability.

The future directions and research trends of PDT in GBM are focused on the following aspects. Firstly, the development of novel PSs is the focus and difficulty of the current field. Breaking the blood-brain barrier, overcoming the uneven distribution of drugs within the tumour, and coping with tumour drug resistance are urgent issues to be addressed [110, 111]. Exploration of novel PSs with high efficiency and specificity, especially nano- PSs and multifunctional PSs that can cross the blood-brain barrier, will provide new opportunities for the application of PDT. Second, the integration of multimodal therapies has significant potential. The molecular

mechanisms by which PDT modulates the immune microenvironment are complex and varied, and its effects are influenced by the type of PSs and the mechanism of cell death [112, 113]. The combination of PDT and immunotherapy can exploit the immune effects triggered by PDT to produce synergistic effects and thus enhance efficacy. For example, Vedunova et al. demonstrated that DCs vaccines loaded with glioblastoma cells undergoing immunogenic cell death induced by PS-based PDT robustly activated Th17-mediated antitumor immunity [7]. Similarly, Shimizu et al. developed an innovative photodynamic virotherapy using a clinical oncolytic herpes simplex virus expressing the KillerRed PS. Both in vitro and in vivo studies confirmed the superior efficacy of this combined approach compared to standalone treatments [107]. Third, personalized therapeutic strategies tailored to GBM heterogeneity are essential. Leveraging genomics and molecular biology to design individualized treatment plans that address specific tumor characteristics could significantly enhance therapeutic outcomes. Finally, efforts should focus on clinical translation and international collaboration. Despite the plethora of studies reporting new PSs, their clinical application remains limited. Strengthening the link between basic research and clinical trials is critical to validating efficacy and ensuring safety. Standardised management protocols and treatment guidelines are what will accelerate research progress.

5. Conclusion

This bibliometric analysis comprehensively examined the research landscape of PDT for GBM from 1993 to 2024, highlighting key trends, influential contributors, and emerging research hotspots. Our findings reveal a steadily growing interest in PDT, driven by advancements in PS development and interdisciplinary collaborations. Despite promising results in preclinical and early clinical studies, challenges such as drug delivery, tumor heterogeneity, and treatment resistance remain significant barriers to its widespread clinical adoption. Future efforts should prioritize innovative drug design, combination therapies, and robust translational studies to fully realize the potential of PDT in improving GBM patient outcomes. The integration of cutting-edge technologies, such as nanomedicine and artificial intelligence, combined with international cooperation, will be pivotal in shaping the future of PDT research for GBM.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

The literature for this study was obtained from the Web of Science Core Collection database, a public online site. For more information, please refer to the Methods section of the manuscript.

Competing interests

All authors declare that they have no conflicts of interest.

Acknowledgments

This study was supported by Talent Introduction Project of Zhejiang Provincial People's Hospital (No. C-2021-QDJJ03-01).

References

1. S Lapointe, Perry A, Butowski N A, Primary brain tumours in adults. Lancet. 2018; 392(10145):432-446. https://doi.org//10.1016/s0140-6736(18)30990-5.
2. L R Schaff, Mellinghoff I K, Glioblastoma and Other Primary Brain Malignancies in Adults: A Review. Jama. 2023; 329(7):574-587. https://doi.org//10.1001/jama.2023.0023.
3. S Xu, Tang L, Li X et al, Immunotherapy for glioma: Current management and future application. Cancer Lett. 2020; 476:1-12. https://doi.org//10.1016/j.canlet.2020.02.002.
4. P Y Wen, Weller M, Lee E Q et al, Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol. 2020; 22(8):1073-1113. https://doi.org//10.1093/neuonc/noaa106.
5. R G Majzner, Ramakrishna S, Yeom K W et al, GD2-CAR T cell therapy for H3K27M-mutated diffuse midline gliomas. Nature. 2022; 603(7903):934-941. https://doi.org//10.1038/s41586-022-04489-4.
6. T F Cloughesy, Mochizuki A Y, Orpilla J R et al, Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. Nat Med. 2019; 25(3):477-486. https://doi.org//10.1038/s41591-018-0337-7.
7. M Vedunova, Turubanova V, Vershinina O et al, DC vaccines loaded with glioma cells killed by photodynamic therapy induce Th17 anti-tumor immunity and provide a four-gene signature for glioma prognosis. Cell Death Dis. 2022; 13(12):1062. https://doi.org//10.1038/s41419-022-05514-0.
8. T Yan, Liao Q, Chen Z et al, β-Ketoenamine covalent organic framework nanoplatform combined with immune checkpoint blockade via photodynamic immunotherapy inhibit glioblastoma progression. Bioact Mater. 2025; 44:531-543. https://doi.org//10.1016/j.bioactmat.2024.10.029.
9. A Casas, Clinical uses of 5-aminolaevulinic acid in photodynamic treatment and photodetection of cancer: A review. Cancer Lett. 2020; 490:165-173. https://doi.org//10.1016/j.canlet.2020.06.008.
10. A L Akopov, Rusanov A A, Papayan G V et al, Endobronchial photodynamic therapy under fluorescence control: Photodynamic theranostics. Photodiagnosis Photodyn Ther. 2017; 19:73-77. https://doi.org//10.1016/j.pdpdt.2017.05.001.
11. M Kochergin, Fahmy O, Asimakopoulos A et al, Photodynamic Therapy: Current Trends and Potential Future Role in the Treatment of Bladder Cancer. Int J Mol Sci. 2024; 25(2)https://doi.org//10.3390/ijms25020960.
12. Y A Algarin, Jambusaria-Pahlajani A, Ruiz E et al, Advances in Topical Treatments of Cutaneous Malignancies. Am J Clin Dermatol. 2023; 24(1):69-80.

https://doi.org//10.1007/s40257-022-00731-x.
13. X Li, Geng X, Chen Z et al, Recent advances in glioma microenvironment-response nanoplatforms for phototherapy and sonotherapy. Pharmacol Res. 2022; 179:106218. https://doi.org//10.1016/j.phrs.2022.106218.
14. P Agostinis, Berg K, Cengel K A et al, Photodynamic therapy of cancer: an update. CA Cancer J Clin. 2011; 61(4):250-281. https://doi.org//10.3322/caac.20114.
15. T Hsia, Small J L, Yekula A et al, Systematic Review of Photodynamic Therapy in Gliomas. Cancers (Basel). 2023; 15(15)https://doi.org//10.3390/cancers15153918.
16. T He, Zou J, Sun K et al, Global research status and frontiers on autophagy in hepatocellular carcinoma: a comprehensive bibliometric and visualized analysis. Int J Surg. 2024; 110(5):2788-2802. https://doi.org//10.1097/js9.0000000000001202.
17. C Chen, Searching for intellectual turning points: progressive knowledge domain visualization. Proc Natl Acad Sci U S A. 2004; 101 Suppl 1(Suppl 1):5303-5310. https://doi.org//10.1073/pnas.0307513100.
18. C Chen, Song M, Visualizing a field of research: A methodology of systematic scientometric reviews. PLoS One. 2019; 14(10):e0223994. https://doi.org//10.1371/journal.pone.0223994.
19. C Chen, CiteSpace II: Detecting and visualizing emerging trends and transient patterns in scientific literature. Journal of the American Society for Information Science and Technology. 2005; 57(3):359-377. https://doi.org//10.1002/asi.20317.
20. P Mongeon, Paul-Hus A, The journal coverage of Web of Science and Scopus: a comparative analysis. Scientometrics. 2016; 106:213-228.
21. Y Gao, Qu B, Shen Y et al, Bibliometric profile of neurogenic bladder in the literature: a 20-year bibliometric analysis. Neural Regen Res. 2015; 10(5):797-803. https://doi.org//10.4103/1673-5374.156985.
22. G Isola, Polizzi A, Serra S et al, Relationship between periodontitis and systemic diseases: A bibliometric and visual study. Periodontol 2000. 2025; https://doi.org//10.1111/prd.12621.
23. Z Jiang, Wu C, Hu S et al, Research on neck dissection for oral squamous-cell carcinoma: a bibliometric analysis. Int J Oral Sci. 2021; 13(1):13. https://doi.org//10.1038/s41368-021-00117-5.
24. C Chen, Ibekwe‐SanJuan F, Hou J, The structure and dynamics of cocitation clusters: A multiple‐perspective cocitation analysis. Journal of the American Society for information Science and Technology. 2010; 61(7):1386-1409.
25. M Sabe, Pillinger T, Kaiser S et al, Half a century of research on antipsychotics and schizophrenia: A scientometric study of hotspots, nodes, bursts, and trends. Neurosci Biobehav Rev. 2022; 136:104608. https://doi.org//10.1016/j.neubiorev.2022.104608.
26. C Chen, Science Mapping: A Systematic Review of the Literature. Journal of Data and Information Science. 2017; 2(2):1-40. https://doi.org//doi:10.1515/jdis-2017-0006.
27. W Stummer, Stocker S, Wagner S et al, Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. Neurosurgery.

1998; 42(3):518-525; discussion 525-516. https://doi.org//10.1097/00006123-199803000-00017.
28. W Stummer, Stepp H, Möller G et al, Technical principles for protoporphyrin-IX-fluorescence guided microsurgical resection of malignant glioma tissue. Acta Neurochir (Wien). 1998; 140(10):995-1000. https://doi.org//10.1007/s007010050206.
29. W Stummer, Stocker S, Novotny A et al, In vitro and in vivo porphyrin accumulation by C6 glioma cells after exposure to 5-aminolevulinic acid. J Photochem Photobiol B. 1998; 45(2-3):160-169. https://doi.org//10.1016/s1011-1344(98)00176-6.
30. W Stummer, Novotny A, Stepp H et al, Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients. J Neurosurg. 2000; 93(6):1003-1013. https://doi.org//10.3171/jns.2000.93.6.1003.
31. H Stepp, Stummer W, 5-ALA in the management of malignant glioma. Lasers Surg Med. 2018; 50(5):399-419. https://doi.org//10.1002/lsm.22933.
32. T J Beck, Kreth F W, Beyer W et al, Interstitial photodynamic therapy of nonresectable malignant glioma recurrences using 5-aminolevulinic acid induced protoporphyrin IX. Lasers Surg Med. 2007; 39(5):386-393. https://doi.org//10.1002/lsm.20507.
33. W Stummer, Pichlmeier U, Meinel T et al, Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol. 2006; 7(5):392-401. https://doi.org//10.1016/s1470-2045(06)70665-9.
34. S W Cramer, Chen C C, Photodynamic Therapy for the Treatment of Glioblastoma. Front Surg. 2019; 6:81. https://doi.org//10.3389/fsurg.2019.00081.
35. M S Eljamel, Goodman C, Moseley H, ALA and Photofrin fluorescence-guided resection and repetitive PDT in glioblastoma multiforme: a single centre Phase III randomised controlled trial. Lasers Med Sci. 2008; 23(4):361-367. https://doi.org//10.1007/s10103-007-0494-2.
36. K Mahmoudi, Garvey K L, Bouras A et al, 5-aminolevulinic acid photodynamic therapy for the treatment of high-grade gliomas. J Neurooncol. 2019; 141(3):595-607. https://doi.org//10.1007/s11060-019-03103-4.
37. B J Quirk, Brandal G, Donlon S et al, Photodynamic therapy (PDT) for malignant brain tumors--where do we stand? Photodiagnosis Photodyn Ther. 2015; 12(3):530-544. https://doi.org//10.1016/j.pdpdt.2015.04.009.
38. J Akimoto, Photodynamic Therapy for Malignant Brain Tumors. Neurol Med Chir (Tokyo). 2016; 56(4):151-157. https://doi.org//10.2176/nmc.ra.2015-0296.
39. M Vermandel, Dupont C, Lecomte F et al, Standardized intraoperative 5-ALA photodynamic therapy for newly diagnosed glioblastoma patients: a preliminary analysis of the INDYGO clinical trial. J Neurooncol. 2021; 152(3):501-514. https://doi.org//10.1007/s11060-021-03718-6.
40. D Bechet, Mordon S R, Guillemin F et al, Photodynamic therapy of malignant brain tumours: a complementary approach to conventional therapies. Cancer Treat

Rev. 2014; 40(2):229-241. https://doi.org//10.1016/j.ctrv.2012.07.004.
41. L Teng, Nakada M, Zhao S G et al, Silencing of ferrochelatase enhances 5-aminolevulinic acid-based fluorescence and photodynamic therapy efficacy. Br J Cancer. 2011; 104(5):798-807. https://doi.org//10.1038/bjc.2011.12.
42. C G Hadjipanayis, Stummer W, 5-ALA and FDA approval for glioma surgery. J Neurooncol. 2019; 141(3):479-486. https://doi.org//10.1007/s11060-019-03098-y.
43. X Wang, Peng J, Meng C et al, Recent advances for enhanced photodynamic therapy: from new mechanisms to innovative strategies. Chem Sci. 2024; 15(31):12234-12257. https://doi.org//10.1039/d3sc07006a.
44. Z Gu, Wu L, Li J et al, Bibliometric and visual analysis of photodynamic therapy for lung cancer from 2010 to 2022. Transl Cancer Res. 2024; 13(2):738-751. https://doi.org//10.21037/tcr-23-1238.
45. J Sun, Zhao H, Fu L et al, Global Trends and Research Progress of Photodynamic Therapy in Skin Cancer: A Bibliometric Analysis and Literature Review. Clin Cosmet Investig Dermatol. 2023; 16:479-498. https://doi.org//10.2147/ccid.S401206.
46. J A Quinlan, Inglut C T, Srivastava P et al, Carrier-Free, Amorphous Verteporfin Nanodrug for Enhanced Photodynamic Cancer Therapy and Brain Drug Delivery. Adv Sci (Weinh). 2024; 11(17):e2302872. https://doi.org//10.1002/advs.202302872.
47. H Z Xu, Li T F, Ma Y et al, Targeted photodynamic therapy of glioblastoma mediated by platelets with photo-controlled release property. Biomaterials. 2022; 290:121833. https://doi.org//10.1016/j.biomaterials.2022.121833.
48. H Kostron, Grunert V, [Photodynamic therapy of malignant brain tumors]. Wien Klin Wochenschr. 1987; 99(11):389-392.
49. H Kostron, Fritsch E, Grunert V, Photodynamic therapy of malignant brain tumours: a phase I/II trial. Br J Neurosurg. 1988; 2(2):241-248. https://doi.org//10.3109/02688698808992675.
50. A Zimmermann, Ritsch-Marte M, Kostron H, mTHPC-mediated photodynamic diagnosis of malignant brain tumors. Photochem Photobiol. 2001; 74(4):611-616. https://doi.org//10.1562/0031-8655(2001)074<0611:Mmpdom>2.0.Co;2.
51. H Kostron, Photodynamic diagnosis and therapy and the brain. Methods Mol Biol. 2010; 635:261-280. https://doi.org//10.1007/978-1-60761-697-9_17.
52. Y Muragaki, Akimoto J, Maruyama T et al, Phase II clinical study on intraoperative photodynamic therapy with talaporfin sodium and semiconductor laser in patients with malignant brain tumors. J Neurosurg. 2013; 119(4):845-852. https://doi.org//10.3171/2013.7.Jns13415.
53. J Akimoto, Fukami S, Suda T et al, First autopsy analysis of the efficacy of intra-operative additional photodynamic therapy for patients with glioblastoma. Brain Tumor Pathol. 2019; 36(4):144-151. https://doi.org//10.1007/s10014-019-00351-0.
54. Y Miki, Akimoto J, Moritake K et al, Photodynamic therapy using talaporfin sodium induces concentration-dependent programmed necroptosis in human glioblastoma T98G cells. Lasers Med Sci. 2015; 30(6):1739-1745.

https://doi.org//10.1007/s10103-015-1783-9.
55. S Kaneko, Fujimoto S, Yamaguchi H et al, Photodynamic Therapy of Malignant Gliomas. Prog Neurol Surg. 2018; 32:1-13. https://doi.org//10.1159/000469675.
56. S Kaneko, Eljamel M S, Fluorescence image-guided neurosurgery. Future Oncol. 2017; 13(26):2341-2348. https://doi.org//10.2217/fon-2017-0194.
57. S Kaneko, Kaneko S, Fluorescence-Guided Resection of Malignant Glioma with 5-ALA. Int J Biomed Imaging. 2016; 2016:6135293. https://doi.org//10.1155/2016/6135293.
58. E A Popovic, Kaye A H, Hill J S, Photodynamic therapy of brain tumors. Semin Surg Oncol. 1995; 11(5):335-345. https://doi.org//10.1002/ssu.2980110503.
59. E A Popovic, Kaye A H, Hill J S, Photodynamic therapy of brain tumors. J Clin Laser Med Surg. 1996; 14(5):251-261. https://doi.org//10.1089/clm.1996.14.251.
60. S S Stylli, Kaye A H, MacGregor L et al, Photodynamic therapy of high grade glioma - long term survival. J Clin Neurosci. 2005; 12(4):389-398. https://doi.org//10.1016/j.jocn.2005.01.006.
61. A H Kaye, Hill J S, Photodynamic therapy of brain tumours. Ann Acad Med Singap. 1993; 22(3 Suppl):470-481.
62. S S Stylli, Howes M, MacGregor L et al, Photodynamic therapy of brain tumours: evaluation of porphyrin uptake versus clinical outcome. J Clin Neurosci. 2004; 11(6):584-596. https://doi.org//10.1016/j.jocn.2004.02.001.
63. J S Hill, Kahl S B, Kaye A H et al, Selective tumor uptake of a boronated porphyrin in an animal model of cerebral glioma. Proc Natl Acad Sci U S A. 1992; 89(5):1785-1789. https://doi.org//10.1073/pnas.89.5.1785.
64. J S Hill, Kahl S B, Stylli S S et al, Selective tumor kill of cerebral glioma by photodynamic therapy using a boronated porphyrin photosensitizer. Proc Natl Acad Sci U S A. 1995; 92(26):12126-12130. https://doi.org//10.1073/pnas.92.26.12126.
65. M A Rosenthal, Kavar B, Hill J S et al, Phase I and pharmacokinetic study of photodynamic therapy for high-grade gliomas using a novel boronated porphyrin. J Clin Oncol. 2001; 19(2):519-524. https://doi.org//10.1200/jco.2001.19.2.519.
66. S Stylli, Hill J, Sawyer W et al, Aluminium phthalocyanine mediated photodynamic therapy in experimental malignant glioma. J Clin Neurosci. 1995; 2(2):146-151. https://doi.org//10.1016/0967-5868(95)90008-x.
67. G Karagianis, Hill J S, Stylli S S et al, Evaluation of porphyrin C analogues for photodynamic therapy of cerebral glioma. Br J Cancer. 1996; 73(4):514-521. https://doi.org//10.1038/bjc.1996.89.
68. S H Tudge, Kaye A H, Hill J S, Modulation of light delivery in photodynamic therapy of brain tumours. J Clin Neurosci. 1999; 6(3):227-232. https://doi.org//10.1016/s0967-5868(99)90508-8.
69. M Kabuto, Kaye A H, Hill J S et al, Antitumour effect of MX2, a new morpholino anthracycline against C6 glioma cells and its cytotoxic effect in combination with photodynamic therapy. J Clin Neurosci. 1994; 1(1):47-52. https://doi.org//10.1016/0967-5868(94)90010-8.
70. S S Stylli, Kaye A H, Photodynamic therapy of cerebral glioma - a review. Part II - clinical studies. J Clin Neurosci. 2006; 13(7):709-717.

https://doi.org//10.1016/j.jocn.2005.11.012.
71. S S Stylli, Kaye A H, Photodynamic therapy of cerebral glioma--a review Part I--a biological basis. J Clin Neurosci. 2006; 13(6):615-625. https://doi.org//10.1016/j.jocn.2005.11.014.
72. A Bogaards, Varma A, Collens S P et al, Increased brain tumor resection using fluorescence image guidance in a preclinical model. Lasers Surg Med. 2004; 35(3):181-190. https://doi.org//10.1002/lsm.20088.
73. P J Muller, Wilson B C, Photodynamic therapy of brain tumors--a work in progress. Lasers Surg Med. 2006; 38(5):384-389. https://doi.org//10.1002/lsm.20338.
74. V X Yang, Muller P J, Herman P et al, A multispectral fluorescence imaging system: design and initial clinical tests in intra-operative Photofrin-photodynamic therapy of brain tumors. Lasers Surg Med. 2003; 32(3):224-232. https://doi.org//10.1002/lsm.10131.
75. P J Muller, Wilson B C, Photodynamic therapy of malignant brain tumours. Can J Neurol Sci. 1990; 17(2):193-198. https://doi.org//10.1017/s0317167100030444.
76. M S Eljamel, Photodynamic assisted surgical resection and treatment of malignant brain tumours technique, technology and clinical application. Photodiagnosis Photodyn Ther. 2004; 1(1):93-98. https://doi.org//10.1016/s1572-1000(04)00014-6.
77. M S Eljamel, Brain PDD and PDT unlocking the mystery of malignant gliomas. Photodiagnosis Photodyn Ther. 2004; 1(4):303-310. https://doi.org//10.1016/s1572-1000(05)00008-6.
78. M S Eljamel, New light on the brain: The role of photosensitizing agents and laser light in the management of invasive intracranial tumors. Technol Cancer Res Treat. 2003; 2(4):303-309. https://doi.org//10.1177/153303460300200404.
79. S Eljamel, Photodynamic applications in brain tumors: a comprehensive review of the literature. Photodiagnosis Photodyn Ther. 2010; 7(2):76-85. https://doi.org//10.1016/j.pdpdt.2010.02.002.
80. M S Eljamel, Brain photodiagnosis (PD), fluorescence guided resection (FGR) and photodynamic therapy (PDT): past, present and future. Photodiagnosis Photodyn Ther. 2008; 5(1):29-35. https://doi.org//10.1016/j.pdpdt.2008.01.006.
81. M Vermandel, Quidet M, Vignion-Dewalle A S et al, Comparison of different treatment schemes in 5-ALA interstitial photodynamic therapy for high-grade glioma in a preclinical model: An MRI study. Photodiagnosis Photodyn Ther. 2019; 25:166-176. https://doi.org//10.1016/j.pdpdt.2018.12.003.
82. C Dupont, Baert G, Mordon S et al, Parallelized Monte-Carlo dosimetry using graphics processing units to model cylindrical diffusers used in photodynamic therapy: From implementation to validation. Photodiagnosis Photodyn Ther. 2019; 26:351-360. https://doi.org//10.1016/j.pdpdt.2019.04.020.
83. H A Leroy, Baert G, Guerin L et al, Interstitial Photodynamic Therapy for Glioblastomas: A Standardized Procedure for Clinical Use. Cancers (Basel). 2021; 13(22)https://doi.org//10.3390/cancers13225754.
84. H A Leroy, Guérin L, Lecomte F et al, Is interstitial photodynamic therapy for

brain tumors ready for clinical practice? A systematic review. Photodiagnosis Photodyn Ther. 2021; 36:102492. https://doi.org//10.1016/j.pdpdt.2021.102492.
85. E Angell-Petersen, Spetalen S, Madsen S J et al, Influence of light fluence rate on the effects of photodynamic therapy in an orthotopic rat glioma model. J Neurosurg. 2006; 104(1):109-117. https://doi.org//10.3171/jns.2006.104.1.109.
86. H Hirschberg, Sørensen D R, Angell-Petersen E et al, Repetitive photodynamic therapy of malignant brain tumors. J Environ Pathol Toxicol Oncol. 2006; 25(1-2):261-279. https://doi.org//10.1615/jenvironpatholtoxicoloncol.v25.i1-2.170.
87. H Hirschberg, Spetalen S, Carper S et al, Minimally invasive photodynamic therapy (PDT) for ablation of experimental rat glioma. Minim Invasive Neurosurg. 2006; 49(3):135-142. https://doi.org//10.1055/s-2006-932216.
88. S Madsen, Hirschberg H, Photodynamic therapy and detection of high-grade gliomas. J Environ Pathol Toxicol Oncol. 2006; 25(1-2):453-466. https://doi.org//10.1615/jenvironpatholtoxicoloncol.v25.i1-2.290.
89. B A Cesca, Caverzan M D, Lamberti M J et al, Enhancing Therapeutic Approaches in Glioblastoma with Pro-Oxidant Treatments and Synergistic Combinations: In Vitro Experience of Doxorubicin and Photodynamic Therapy. Int J Mol Sci. 2024; 25(14)https://doi.org//10.3390/ijms25147525.
90. B S Dash, Lu Y J, Chen J P, Enhancing Photothermal/Photodynamic Therapy for Glioblastoma by Tumor Hypoxia Alleviation and Heat Shock Protein Inhibition Using IR820-Conjugated Reduced Graphene Oxide Quantum Dots. ACS Appl Mater Interfaces. 2024; 16(11):13543-13562. https://doi.org//10.1021/acsami.3c19152.
91. C Perria, Capuzzo T, Cavagnaro G et al, Fast attempts at the photodynamic treatment of human gliomas. J Neurosurg Sci. 1980; 24(3-4):119-129.
92. H Kostron, Obwegeser A, Jakober R, Photodynamic therapy in neurosurgery: a review. J Photochem Photobiol B. 1996; 36(2):157-168. https://doi.org//10.1016/s1011-1344(96)07364-2.
93. W Stummer, Beck T, Beyer W et al, Long-sustaining response in a patient with non-resectable, distant recurrence of glioblastoma multiforme treated by interstitial photodynamic therapy using 5-ALA: case report. J Neurooncol. 2008; 87(1):103-109. https://doi.org//10.1007/s11060-007-9497-x.
94. G Berkovitch-Luria, Weitman M, Nudelman A et al, Multifunctional 5-aminolevulinic acid prodrugs activating diverse cell-death pathways. Invest New Drugs. 2012; 30(3):1028-1038. https://doi.org//10.1007/s10637-011-9669-6.
95. N Etminan, Peters C, Lakbir D et al, Heat-shock protein 70-dependent dendritic cell activation by 5-aminolevulinic acid-mediated photodynamic treatment of human glioblastoma spheroids in vitro. Br J Cancer. 2011; 105(7):961-969. https://doi.org//10.1038/bjc.2011.327.
96. Y Chen, Ma Y, Shi K et al, Self-Disassembling and Oxygen-Generating Porphyrin-Lipoprotein Nanoparticle for Targeted Glioblastoma Resection and Enhanced Photodynamic Therapy. Adv Mater. 2024; 36(15):e2307454. https://doi.org//10.1002/adma.202307454.
97. J Ge, Zuo M, Wang Q et al, Near-infrared light triggered in situ release of CO for

enhanced therapy of glioblastoma. J Nanobiotechnology. 2023; 21(1):48. https://doi.org//10.1186/s12951-023-01802-9.

98. P J Muller, Wilson B C, Photodynamic therapy for recurrent supratentorial gliomas. Semin Surg Oncol. 1995; 11(5):346-354. https://doi.org//10.1002/ssu.2980110504.
99. H T Whelan, Schmidt M H, Segura A D et al, The role of photodynamic therapy in posterior fossa brain tumors. A preclinical study in a canine glioma model. J Neurosurg. 1993; 79(4):562-568. https://doi.org//10.3171/jns.1993.79.4.0562.
100. T C Origitano, Reichman O H, Photodynamic therapy for intracranial neoplasms: development of an image-based computer-assisted protocol for photodynamic therapy of intracranial neoplasms. Neurosurgery. 1993; 32(4):587-595; discussion 595-586. https://doi.org//10.1227/00006123-199304000-00015.
101. R Sreenivasan, Muruganandham M, Sharma M et al, Binding of monomeric and oligomeric porphyrins to human glioblastoma (U-87MG) cells and their photosensitivity. Cancer Lett. 1997; 120(1):45-51. https://doi.org//10.1016/s0304-3835(97)00290-5.
102. F Jiang, Lilge L, Grenier J et al, Photodynamic therapy of U87 human glioma in nude rat using liposome-delivered photofrin. Lasers Surg Med. 1998; 22(2):74-80. https://doi.org//10.1002/(sici)1096-9101(1998)22:2<74::aid-lsm2>3.0.co;2-t.
103. C Christie, Madsen S J, Peng Q et al, Macrophages as a photosensitizer delivery system for photodynamic therapy: Potential for the local treatment of resected glioblastoma. Photodiagnosis Photodyn Ther. 2024; 45:103897. https://doi.org//10.1016/j.pdpdt.2023.103897.
104. T G Nguyen Cao, Kang J H, Kang S J et al, Brain endothelial cell-derived extracellular vesicles with a mitochondria-targeting photosensitizer effectively treat glioblastoma by hijacking the blood–brain barrier. Acta Pharm Sin B. 2023; 13(9):3834-3848. https://doi.org//10.1016/j.apsb.2023.03.023.
105. F Zhang, Wen C, Peng Y et al, Biomimetic lipid nanoparticles for homologous-targeting and enhanced photodynamic therapy against glioma. Eur J Pharm Sci. 2023; 190:106574. https://doi.org//10.1016/j.ejps.2023.106574.
106. H S Borges, Gusmão L A, Tedesco A C, Multi-charged nanoemulsion for photodynamic treatment of glioblastoma cell line in 2D and 3D in vitro models. Photodiagnosis Photodyn Ther. 2023; 43:103723. https://doi.org//10.1016/j.pdpdt.2023.103723.
107. K Shimizu, Kahramanian A, Jabbar M et al, Photodynamic augmentation of oncolytic virus therapy for central nervous system malignancies. Cancer Lett. 2023; 572:216363. https://doi.org//10.1016/j.canlet.2023.216363.
108. M Foglar, Aumiller M, Bochmann K et al, Interstitial Photodynamic Therapy of Glioblastomas: A Long-Term Follow-up Analysis of Survival and Volumetric MRI Data. Cancers (Basel). 2023; 15(9)https://doi.org//10.3390/cancers15092603.
109. J S Hill, Kaye A H, Sawyer W H et al, Selective uptake of hematoporphyrin derivative into human cerebral glioma. Neurosurgery. 1990; 26(2):248-254. https://doi.org//10.1097/00006123-199002000-00011.
110. H J Liu, Xu P, Strategies to overcome/penetrate the BBB for systemic

nanoparticle delivery to the brain/brain tumor. Adv Drug Deliv Rev. 2022; 191:114619. https://doi.org//10.1016/j.addr.2022.114619.

111. O van Tellingen, Yetkin-Arik B, de Gooijer M C et al, Overcoming the blood-brain tumor barrier for effective glioblastoma treatment. Drug Resist Updat. 2015; 19:1-12. https://doi.org//10.1016/j.drup.2015.02.002.

112. L E Ibarra, Vilchez M L, Caverzán M D et al, Understanding the glioblastoma tumor biology to optimize photodynamic therapy: From molecular to cellular events. J Neurosci Res. 2021; 99(4):1024-1047. https://doi.org//10.1002/jnr.24776.

113. D Kessel, Oleinick N L, Cell Death Pathways Associated with Photodynamic Therapy: An Update. Photochem Photobiol. 2018; 94(2):213-218. https://doi.org//10.1111/php.12857.

Figure Legend and Table

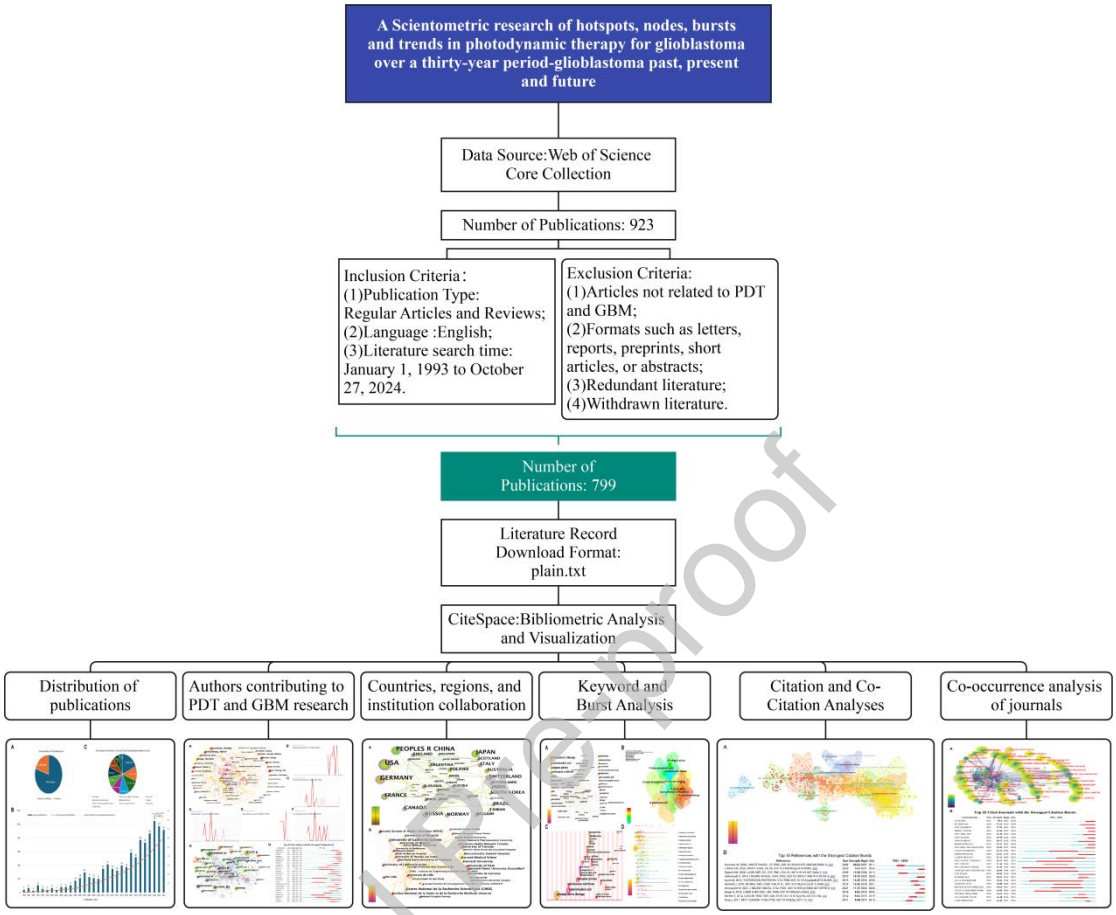


Figure 1 Workflow of the study.

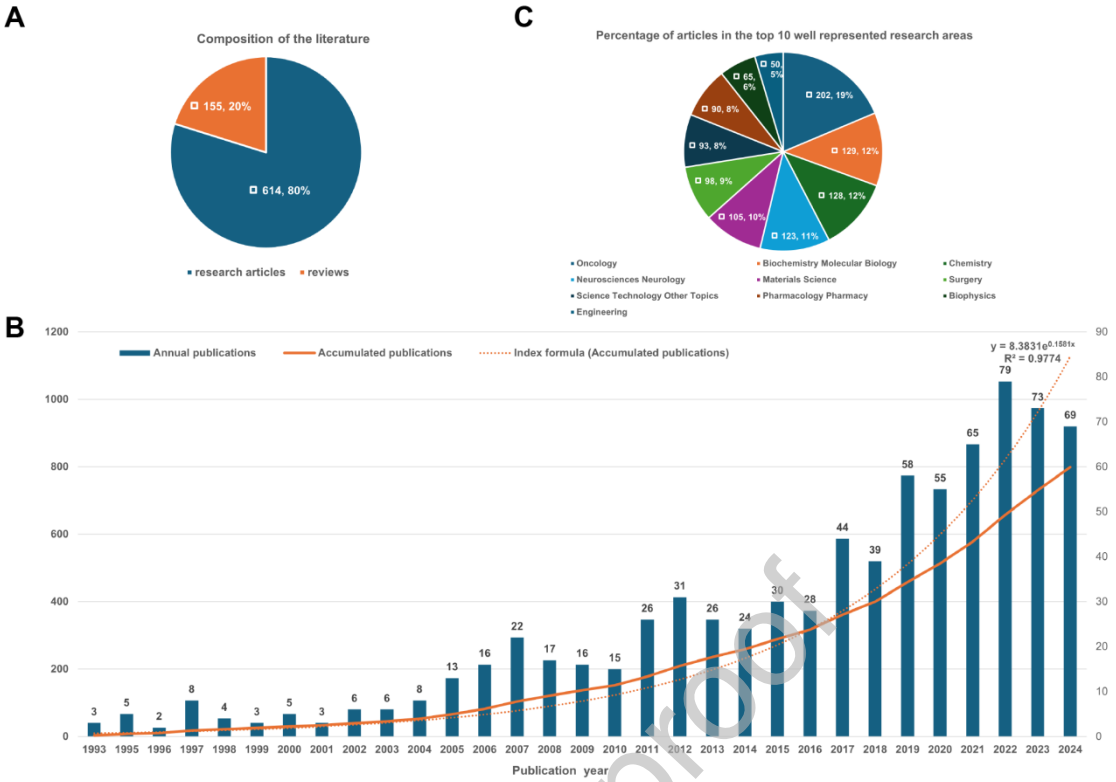


Figure 2 Literature publication trends and major research areas. (**A**) Percentage of each of 614 original research articles and 155 reviews. (**B**) Distribution of publications and their citations from 1993 to 2024. Blue bars indicate annual publications, while yellow lines indicate cumulative publications. The left axis shows cumulative publication data and the right axis shows annual publication data. (**C**) Research areas covered by published literature. The fan chart shows the top 10 scientific disciplines and their respective number and percentage of publications.

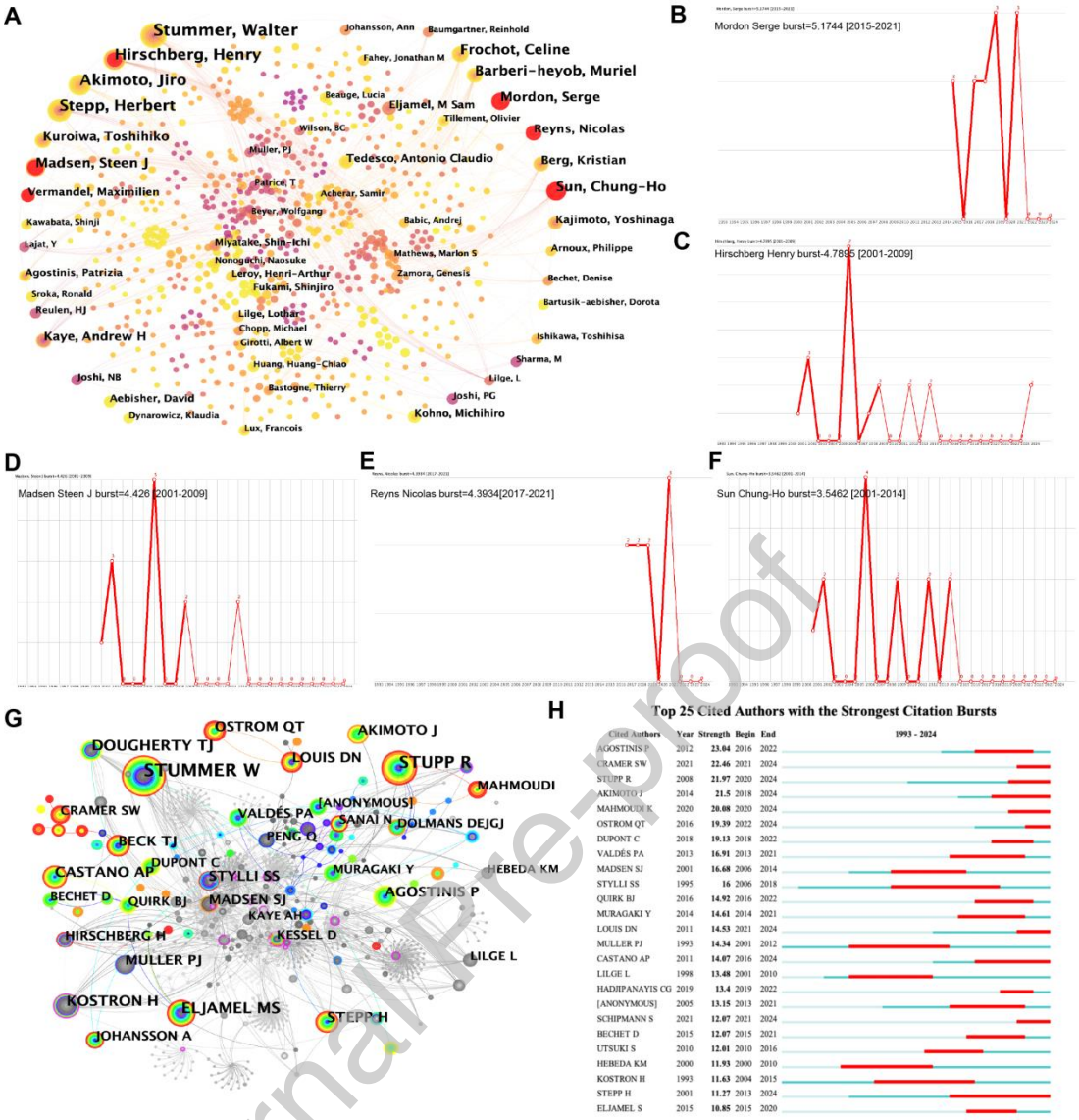


Figure 3 Authors contributing to PDT for GBM research. (**A**) Author's coupling network analysis. Top five with the highest burst Index. The authors are, in order, (**B**) Mordon Serge, (C) Hirschberg Henry, (**D**) Madsen Steen J, (**E**) Reyns Nicolas, and **(F**) Sun Chung-Ho. (**G**) Author co-citation analyses. Each node represents a cited author, and each link between two nodes represents a co-citation relationship between two authors. The size of the node represents the author cited. Network map of authors that were co-cited in more than 5 publications. (**H**) Top 25 Cited Authors with the Strongest Citation Bursts.

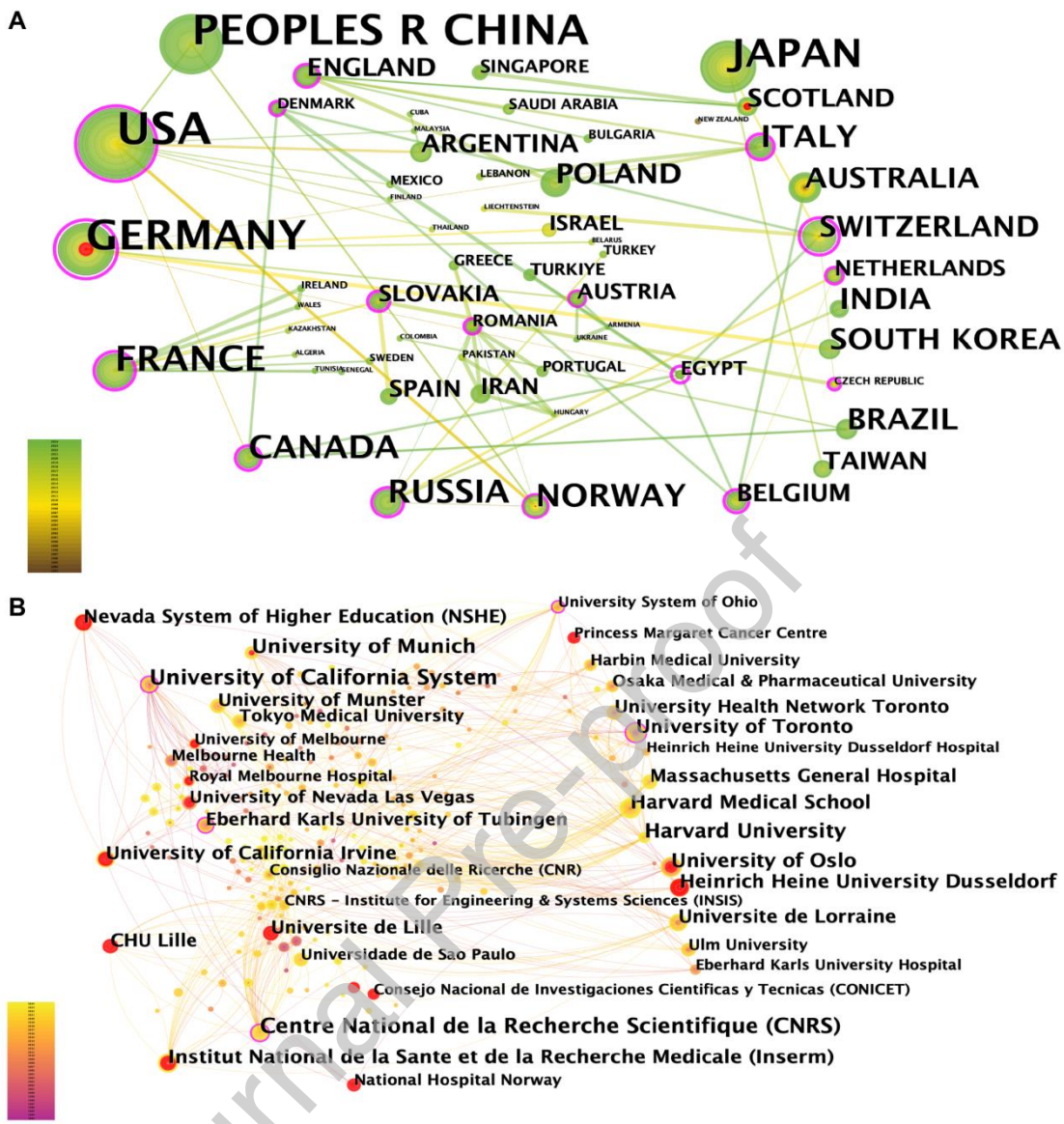


Figure 4 Countries, regions, and institution collaboration networks involved in publishing papers on PDT for GBM from 1993 to 2024. (**A**) The country or region collaboration network: each node represents the influence of a country, organized by betweenness centrality normalized to the interval [0,1]. Nodes with high betweenness centrality typically connect multiple large node clusters and have a significant impact on the network. The thickness of purple borders indicates the strength of the centrality. Nodes are limited to the top 50 countries. (**B**) Institution collaboration network diagram: node size corresponds to the centrality value.

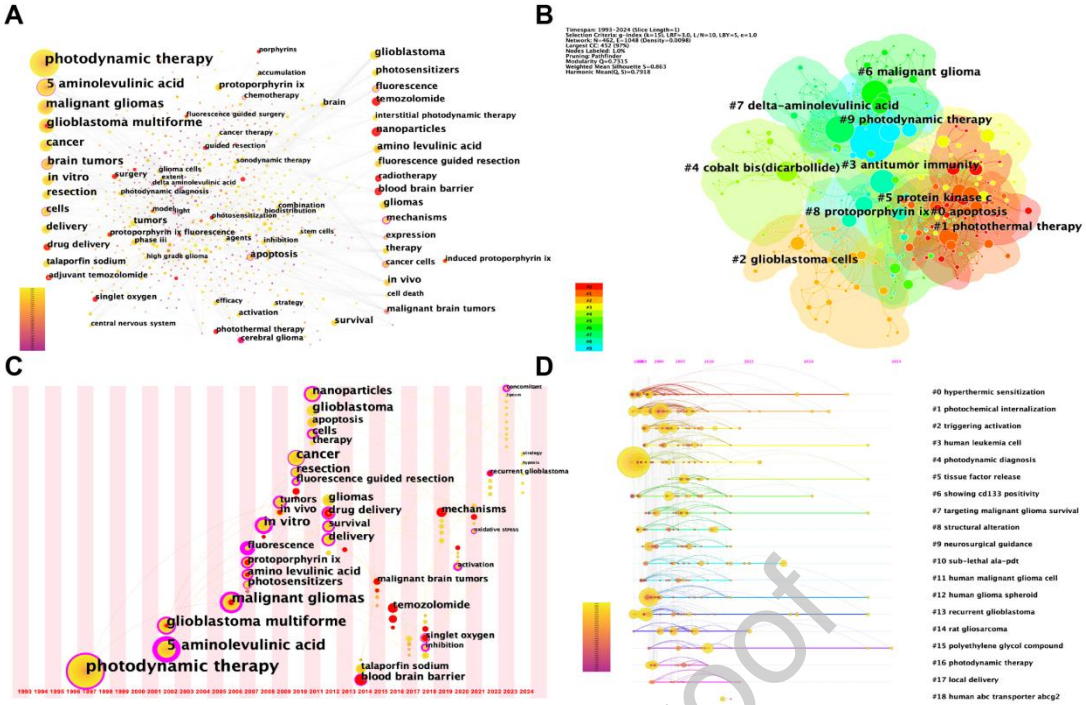
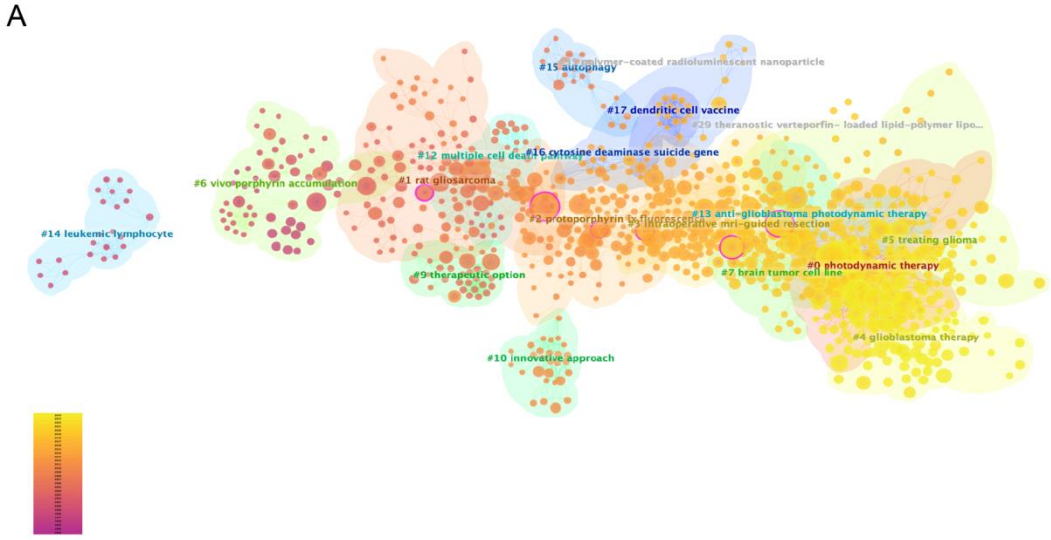


Figure 5 Keyword and Burst Analysis. (**A**) Keyword co-occurrence map. (**B**) The 10 largest clusters. (**C**) Timeline visualization of co-occurring keyword networks from 1993 to 2024. Note: Nodes represent keywords, with colors indicating the average publication year of each node. The size of the cross is proportional to the burstiness of keyword co-occurrence. Co-occurrence networks are weighted by the total link strength between keyword nodes and scored according to the average publication year. (**D**) This timeline arranges the keywords in chronological order of occurrence and persistence of the clustered keywords. Each node represents a keyword, node size indicates frequency of occurrence, and connecting lines indicate topic evolution.

A

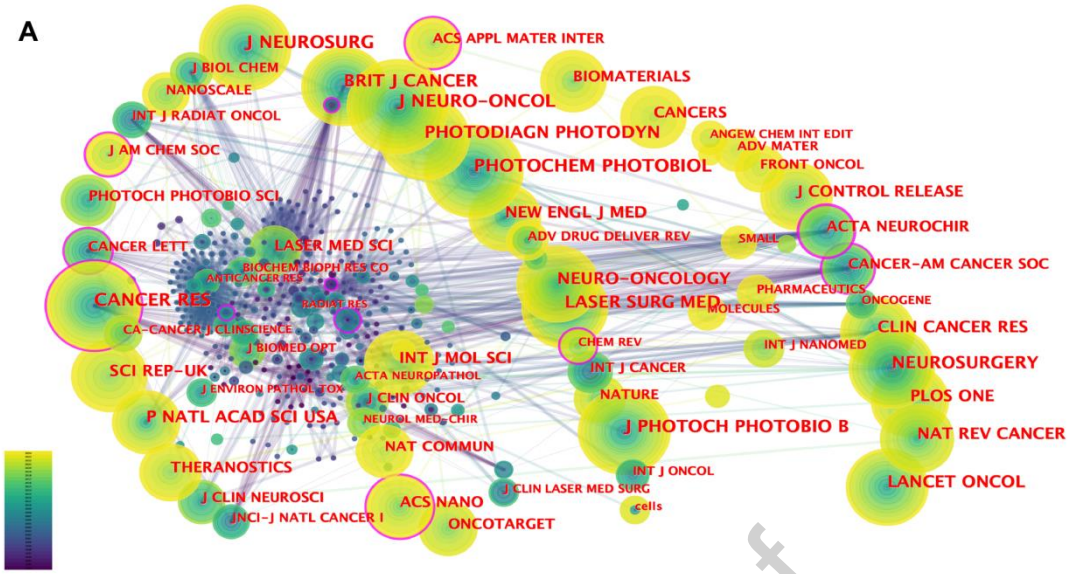


B

Top 10 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	1993 - 2024
Stummer W, 2006, LANCET ONCOL, V7, P392, DOI 10.1016/S1470-2045(06)70665-9, DOI	2006	20.22	2007	2011	
Cramer SW, 2020, FRONT SURG, V6, P0, DOI 10.3389/fsurg.2019.00081, DOI	2020	16.4	2021	2024	
Eljamel MS, 2008, LASER MED SCI, V23, P361, DOI 10.1007/s10103-007-0494-2, DOI	2008	15.56	2008	2013	
Mahmoudi K, 2019, J NEURO-ONCOL, V141, P595, DOI 10.1007/s11060-019-03103-4, DOI	2019	14.72	2020	2024	
Quirk BJ, 2015, PHOTODIAGN PHOTODYN, V12, P530, DOI 10.1016/j.pdpdt.2015.04.009, DOI	2015	13.25	2016	2020	
Akimoto J, 2016, NEUROL MED-CHIR, V56, P151, DOI 10.2176/nmc.ra.2015-0296, DOI	2016	12.42	2018	2021	
Vermandel M, 2021, J NEURO-ONCOL, V152, P501, DOI 10.1007/s11060-021-03718-6, DOI	2021	11.37	2022	2024	
Stepp H, 2018, LASER SURG MED, V50, P399, DOI 10.1002/lsm.22933, DOI	2018	9.65	2019	2024	
Bechet D, 2014, CANCER TREAT REV, V40, P229, DOI 10.1016/j.ctrv.2012.07.004, DOI	2014	9.62	2015	2019	
Teng L, 2011, BRIT J CANCER, V104, P798, DOI 10.1038/bjc.2011.12, DOI	2011	9.48	2013	2016	

Figure 6 Citation and Co-Citation Analyses. (**A**) Literature clustering graph. (**B**) Top 10 References with the Strongest Citation Bursts



B

Top 25 Cited Journals with the Strongest Citation Bursts

Cited Journals	Year	Strength	Begin	End	1993 - 2024
CANCERS	2021	**50.5**	2021	2024	
SCI REP-UK	2018	**37.62**	2019	2024	
NAT COMMUN	2021	**37.59**	2021	2024	
FRONT ONCOL	2022	**35.46**	2022	2024	
INT J MOL SCI	2016	**32.38**	2020	2024	
ADV MATER	2022	**29.98**	2022	2024	
ONCOTARGET	2016	**28.73**	2018	2024	
BIOMATERIALS	2015	**25.47**	2022	2024	
ACS APPL MATER INTER	2019	**24.99**	2021	2024	
J CLIN NEUROSCI	1996	**23.74**	2006	2017	
THERANOSTICS	2018	**23.51**	2018	2024	
LASER MED SCI	1995	**22.12**	2009	2020	
JNCI-J NATL CANCER I	1993	**21.61**	2001	2015	
INT J ONCOL	2003	**21.46**	2004	2013	
INT J RADIAT ONCOL	1995	**21.36**	1995	2016	
CANCER-AM CANCER SOC	1995	**20.98**	1998	2017	
ACS NANO	2015	**20.83**	2018	2024	
NANOSCALE	2018	**20.62**	2018	2021	
ACTA NEUROCHIR	1995	**19.02**	1998	2019	
CANCER LETT	1995	**18.88**	2008	2018	
PHOTOCH PHOTOBIO SCI	2003	**18.02**	2007	2019	
J CLIN LASER MED SURG	2000	**16.85**	2000	2010	
NEUROL MED-CHIR	2010	**16.63**	2018	2020	
CA-CANCER J CLIN	2013	**16.48**	2016	2021	
J AM CHEM SOC	2010	**16.38**	2021	2022	

Figure 7 Co-occurrence analysis of journals. (**A**) Mapping of journals. Each node represents a journal, the link between nodes represents the co-citation intensity, and different colors represent different clusters. (**B**) Top 25 Cited Journals with the Strongest Citation Bursts.

Table 1 The top 11 authors with most articles about PDT for GBM

Number	Count	Centrality	Year	Cited Authors	Index of H	Citations
1	294	0.01	1998	STUMMER W	55	14,783
2	195	0.04	2008	STUPP R	89	63,524
3	132	0.04	2004	ELJAMEL MS	24	1,520
4	107	0.08	1993	DOUGHERTY TJ	60	26,575
5	91	0.21	1993	KOSTRON H	24	2,522
6	88	0.01	2011	CASTANO AP	21	7,101
7	88	0.01	2001	STEPP H	43	7,506
8	80	0.05	2011	BECK TJ	50	8,449
9	78	0.02	2012	AGOSTINIS P	87	42,258
10	74	0.01	1995	STYLLI SS	32	3,091

Table 2 The top 10 cited authors with most articles about PDT for GBM.

Number	Count	Year	Authors
1	26	1998	Stummer Walter
2	20	2001	Hirschberg Henry
3	19	2008	Akimoto Jiro
4	19	1998	Stepp Herbert
5	14	2006	Barberi-heyob Muriel
6	14	2006	Frochot Celine
7	13	2001	Sun Chung-Ho
8	13	2001	Madsen Steen J
9	12	2015	Mordon Serge
10	10	1993	Kaye Andrew H
11	10	2007	Kuroiwa Toshihiko

Table 3 The top 10 countries/regions in terms of number of articles.

Number	Count	Centrality	Year	Countries
1	188	0.56	1993	USA
2	129	0	2002	PEOPLES R CHINA
3	117	0.81	1998	GERMANY
4	92	0.07	1998	JAPAN
5	59	0.45	1997	FRANCE
6	38	0.57	1993	CANADA
7	36	0.42	2001	RUSSIA
8	35	0.18	2001	NORWAY
9	31	0.44	2003	ITALY
10	28	0.07	2004	BRAZIL

Table 4 The top 18 institutions contributing to publications in PDT for GBM.

Number	Count	Centrality	Year	Institutions

1	32	0.14	1995	University of California System
2	32	0.13	2006	Centre National de la Recherche Scientifique
3	28	0.07	1998	University of Munich
4	26	0.07	1997	Harvard University
5	23	0.05	2009	Harvard Medical School
6	23	0.02	2001	University of Oslo
7	22	0.04	2007	Institut National de la Sante et de la Recherche Medicale
8	22	0.01	2016	Chinese Academy of Sciences
9	21	0.14	1993	University of Toronto
10	21	0.01	1998	Heinrich Heine University Dusseldorf
11	20	0.01	2001	University of California Irvine
12	20	0	2006	Universite de Lorraine
13	19	0	2001	Nevada System of Higher Education
14	17	0.01	2014	CHU Lille
15	17	0.01	2015	Universite de Lille
16	17	0.01	1993	University Health Network Toronto
17	17	0.03	2009	Massachusetts General Hospital
18	17	0.1	2010	University of Munster

Table 5 The top 20 most used keywords.

Number	Count	Centrality	Year	Keywords
1	548	0.05	1993	photodynamic therapy
2	235	0.12	1998	5 aminolevulinic acid
3	199	0.07	1995	malignant gliomas
4	177	0.08	2001	glioblastoma multiforme
5	130	0.15	1997	cancer
6	120	0.11	1995	brain tumors
7	109	0.18	2002	in vitro
8	85	0.05	1993	resection
9	85	0.1	1993	glioblastoma
10	73	0.08	1998	amino levulinic acid
11	66	0.08	1999	cells
12	65	0.03	2011	nanoparticles
13	62	0.04	2006	delivery
14	61	0.04	1997	gliomas
15	60	0.09	2000	in vivo
16	58	0.04	2006	blood brain barrier
17	57	0.06	1996	photosensitizers
18	54	0.08	1998	protoporphyrin IX
19	53	0.09	1998	fluorescence
20	51	0.07	2001	apoptosis
20	51	0.05	1995	survival

20	51	0.02	2008	temozolomide

Table 6 The top 15 journal co-citations on PDT for GBM research.

Number	Count	Centrality	Year	Cited Journals
1	432	0	1993	PHOTOCHEM PHOTOBIOL
2	406	0.01	1993	J NEUROSURG
3	394	0.08	1993	J NEURO-ONCOL
4	389	0.15	1993	CANCER RES
5	358	0	1998	J PHOTOCH PHOTOBIO B
6	326	0.04	1993	BRIT J CANCER
7	323	0	2008	PHOTODIAGN PHOTODYN
8	318	0.06	1993	NEUROSURGERY
9	300	0.01	1993	LASER SURG MED
10	274	0.01	2002	NEURO-ONCOLOGY
11	261	0	2007	LANCET ONCOL
12	247	0.01	1995	P NATL ACAD SCI USA
13	240	0.07	1999	CLIN CANCER RES
14	231	0.01	2012	PLOS ONE
15	216	0.02	1995	NEW ENGL J MED