



A bibliometric analysis and visualization of photothermal therapy on cancer

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Background: Cancer is one of the most lethal diseases in the world, and photothermal therapy was reported recently as a new and effective therapy for cancer. This study offers the bibliometric and visualization analysis of photothermal therapy on cancer.

Methods: A record of 6,233 papers in this field from 1995 to 2019 was obtained based on the Web of Science Core Collection (WoSCC). And CiteSpace was used to analyze the annual trends of publications, countries, institutions, journals, co-cited references, and keywords in the field of photothermal therapy on cancer.

Results: We identified that the number of publications continually increased over the time. The most productive country and institution in this field was China and Chinese Academy of Sciences, respectively. The ACS Appl Mater Interfaces was the most active journal. Co-cited references analysis revealed the top landmark articles in the field. Co-occurrence keywords and their clustered network were analyzed, revealing that materials, especially nanomaterials, used in photothermal therapy, remained the hotspots in this research field. Timezone view and burst detection of keywords showed that nanomaterials were always the hotspots and the frontier topics in this field.

Conclusions: The current study revealed that photothermal therapy has become a subject of growing study and a very important research area. In addition, the research of materials in photothermal therapy, especially nanomaterials, which were applied in photothermal therapy to treat cancer effectively, is the foci and the frontier topic in this field.

Keywords: Photothermal therapy; cancer; CiteSpace; visualization analysis; nanomaterials

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Introduction

Cancer overtook heart disease and became an important reason of death all over the world (1,2). It was estimated that there were 18.1 million new cancer cases and 9.6 million

deaths of cancer, according to the International Agency for Research on Cancer (IARC) estimated in 2018 (3). On the other side, surgery, radiotherapy, and chemotherapy are the main ways to treat clinical cancer at present. Unfortunately,

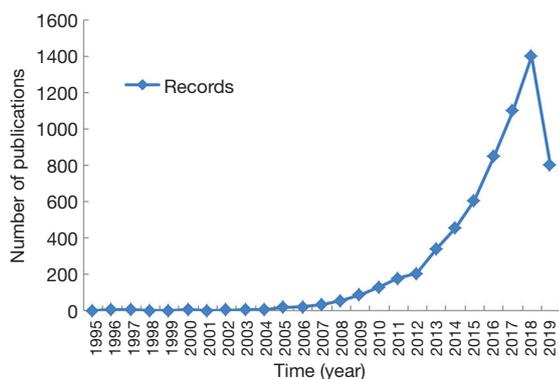


Figure 1 The annual trends of publications of photothermal therapy on cancer.

patients have to suffer the drawbacks of these traditional treatments, such as normal cells killed, the immune system destroyed, and the risk of a second cancer increased (4-6). Photothermal therapy is becoming a better treatment on cancer due to its high targeting and effectiveness (7). Both photothermal therapeutic (PTT) agent accumulation and localized near-infrared (NIR) laser irradiation were used in photothermal therapy, making its therapeutic effects occur only at the sites of the tumor, therefore it can avoid the drawbacks of traditional treatments mentioned above. Compared with traditional techniques, photothermal therapy has many other advantages including simple operation, fewer complications, quicker recovery, and shorter length of stay in hospital (8).

Meanwhile, nanotechnology is extensively explored for drug delivery. Nanocarrier delivery offered a great opportunity to improve the bioactivity of drugs and the biocompatibility of tumor therapy (9-11). Nanomaterials, such as nanoparticles, nanoshell, and nanorods, had strong near-infrared absorption ability. Hence, they are able to convert near-infrared laser into heat effectively by photothermal process. Recently, nanomaterials have become the hot spot in photothermal therapy, especially in designing new nanoparticle-drug conjugates, which produce the photothermally activated physical and biological effects, to treat cancer effectively (12-16).

In this study, the quantity and quality of global publications of photothermal therapy on cancer from 1995 to 2019 were assessed with bibliometric analysis. The objective of our research was to study and analyze the global scientific outputs of photothermal therapy on cancer research and to estimate the research trends and hotspots

of this field. We found that the continuous advances of this field and application of novel nanomaterials would enhance the future development of cancer photothermal therapy.

Methods

Data acquisition

A record of 6,233 papers published between 1995 and 2019 from the Web of Science Core Collection (WoSCC) was obtained. The WoSCC is the most frequently used source of scientific information. We used the term # 1 (TS= “photothermal” and “cancer”) or # 2 (TS= “photothermal” and “tumor”) to search the related articles, and removed the duplicates. The final record was obtained on July 23, 2019.

Statistical analysis

We used the WoSCC and CiteSpace V 5.0R1 SE to analyze the annual trends of publications, countries, institutions, co-cited articles, and keywords in cancer photothermal therapy field (17,18). The parameters of CiteSpace were as follows: time slicing [1995–2019], years per slice (1), term source (all selection), node type (choose one at a time), and pruning (pathfinder, Pruning the merged network, Pruning Sliced Networks).

Results

The annual trends of publications of photothermal therapy on cancer

The web of science collection provided 5,866 documents with topic words of “photothermal and cancer” in different format of publications and provided 2,033 files with the topic words of “photothermal and tumor”. After removing the duplicates, 6,233 publications were obtained. As shown in *Figure 1*, the number of published articles of photothermal therapy on cancer increased steadily from 1995 to 2010, and the number of publications increased rapidly from 2,011 onwards. From 2017 to 2018, the activity of photothermal therapy on cancer reached a peak.

The distribution of countries and institutions

We analyzed the distribution of countries in the research field of photothermal therapy on cancer. There were 72 different countries ranked. Among them, the top 10 countries were China, USA, South Korea, India, Singapore,

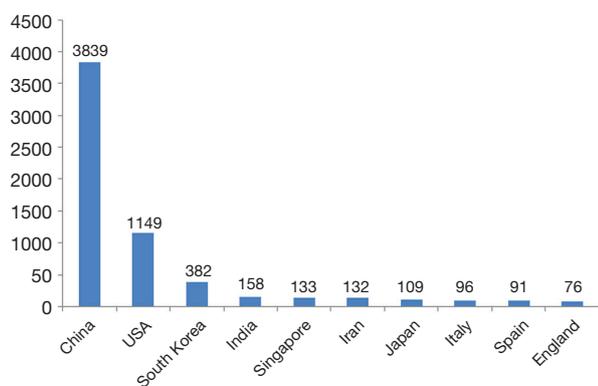


Figure 2 The top 10 countries of publications of photothermal therapy on cancer.

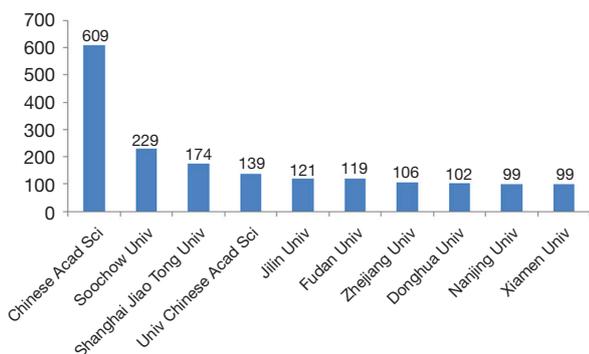


Figure 3 The top 10 institutes of publications of photothermal therapy on cancer.

Iran, Japan, Italy, Spain, and England (Figure 2). The results showed that china was the country with the largest number of publications in this field.

Figure 3 showed the top 10 institutions among 277 institutions in the world, which published the largest number of articles of photothermal therapy on cancer. Chinese Academy of Sciences (Chinese Acad Sci) published the most papers, with 609 papers, accounting for 9.63% of the total published papers in this field. The second one was the Soochow University with 229 publications, followed by Shanghai Jiao Tong University [174], the University Chinese Academy of Sciences [139], Jilin University [121], Fudan University [119], Zhejiang University [106], Donghua University [102], Nanjing University [99] and Xiamen University [99]. Most interestingly, all top 10 institutes were from China, consistent with the statistical analysis of national publication of photothermic therapy on cancer.

Analysis of journals of publications of photothermal therapy on cancer

A total of 112 journals published 6,233 articles of photothermal therapy on cancer. The characteristics of the top 10 active journals were shown in Table 1. Among the top 10 publishers of the journals, three were from American, three were from British, two were from German journals, one was Netherlands journal and one was New Zealandian journal. The largest number of articles in this area was

Table 1 The top 10 journals of publications on photothermal therapy for cancer

Rank	Journal	Frequency	Country	JCR	Impact factor [2018]
1	<i>ACS Appl Mater Interfaces</i>	417	USA	Q1	8.456
2	<i>Nanoscale</i>	299	England	Q1	6.97
3	<i>Biomaterials</i>	290	Netherlands	Q1	10.273
4	<i>J Mater Chem B</i>	281	England	Q2	5.047
5	<i>ACS Nano</i>	242	USA	Q1	13.903
6	<i>RSC Advances</i>	176	England	Q3	3.049
7	<i>Small</i>	152	Germany	Q1	10.856
8	<i>Adv Funct Mater</i>	149	Germany	Q1	15.621
9	<i>Adv Mater</i>	137	USA	Q1	25.809
10	<i>Int J Nanomedicine</i>	137	New Zealand	Q2	4.471

JCR, journal citation reports.

published on *ACS Applied Materials and Interfaces*, followed by *Nanoscale and Biomaterials*. The journal with highest impact factor was *Adv Mater*, followed by *Adv Funct Mater*.

Analysis of the co-cited references

The clustered network consists of those references with higher centrality and citation counts was shown in *Figure 4*. Visualization of co-cited references showed a total of 646 nodes and 1,578 links. Each node represents a cited article. The link lines between the nodes represent the relationships between the articles. The area of each node was proportional to the total co-citation frequency of the associated publications.

Table 2 showed the top 10 co-cited references, including their authors, year, journal, cited frequency and title. The author Robinson (19) published in *J Am Chem Soc* had the highest number of citations (611 citations), followed by Yang (20) in *Nano Lett* (604 citations), and Cheng (9) in *Chem Rev* (595 citations). These ten references were often considered fundamental in the research field of photothermal therapy on cancer.

Analysis of co-occurrence keywords and burst keywords

Keywords co-occurrence can effectively reflect the research hotspots in the field, and burst keywords could indicate frontier topics (27). To explore research hotspots and frontier topics, we analyzed the distribution of keywords. The keywords co-occurrence network map, the top 10 keywords, clustered network of co-occurrence keywords, the keywords timezone view, and keywords with the strongest citation bursts of publications in this field were presented.

The keyword co-occurrence network of publications of photothermal therapy on cancer was constructed with 6,233 articles (*Figure 5*). The nodes in the map represented the corresponding keywords, the node size represented the number of publications in the field of photothermal therapy that include the keywords. The link lines between the nodes represented the relationships between the keywords. For example, a great many of connection lines were observed between cancer and other keywords nodes, indicating that the keyword “cancer” has a close relationship with other keywords in this field. From these keywords, we obtained the top 10 co-occurrence keywords (*Table 3*) according to their frequency occurred in the publications. The hot keywords were photothermal therapy, nanoparticle, drug delivery, *in vivo*, cancer, cancer therapy, gold nanoparticle, photodynamic therapy, cell, and therapy.

We mapped 6,233 publications of photothermal therapy on cancer via a clustered network in hierarchical order (*Figure 6*). Different co-occurrence keywords were represented by the nodes and a distinct specialty or a thematic concentration was represented by the clusters. The co-occurrence keywords knowledge map revealed keywords with higher centrality and occurrence counts. The area of each node was proportional to the total co-occurrence frequency of the associated reference. The co-occurrence keywords could be clustered into eleven main sub-clusters including #0discrete particle model, #1liposome, #2optical property, #3nanostructure, #4optical property, #5performance liquid chromatography, #6laser immunotherapy, #7nanostructure, #8reduced graphene oxide, #9multifunctional germanium nanoparticle, and #10near infrared responsive.

Figure 7 displayed a timezone view of co-occurrence keywords. From *Figure 7* we can demonstrated that, before 2000, the research of photothermal therapy on cancer was little and the keywords in that time were concentrated on “tumor”, “photodynamic therapy” and “cancer”, etc. Since 2000, the research in this field began to increase, and the field of key words became extensive, such as “photothermal therapy”, “*in vivo*”, “cell”, “nanoparticle” and “drug delivery”, etc. Since 2010, the publications of photothermal therapy increased rapidly. Many new nanomaterials, like “nanomaterial graphene”, “mesoporous silica nanoparticle” and “iron oxide nanoparticle”, were employed in photothermal therapy. The link between these keywords in *Figure 7* was concentrated and progressive, revealing the close connection of these keywords in the field.

So-called “burst words” represent words that are cited frequently over a period of time. CiteSpace was used to detect burst keywords, which were considered to be indicators of research frontier topics over time (27). In this study, we detected bursts from 1995 to 2019 based on analysis of 6,233 original articles. The timeline was depicted as a blue line, and the time interval that a subject was found to have a burst was shown as a red segment on the blue timeline. It indicated the beginning year, the ending year, and the duration of the burst. Among the top 65 keywords with the highest burst strength, we were particularly interested in those keywords with research significance which indicated the evolution trend of the photothermal therapy research field (*Table 4*). The keywords with more stronger citation bursts in photothermal therapy articles were laser [1997–2013], optical property [2005–2014], gold nanoparticle [2006–2014], nanoshell [2006–2014], size [2007–2011], metal nanoparticle [2007–2013], shape

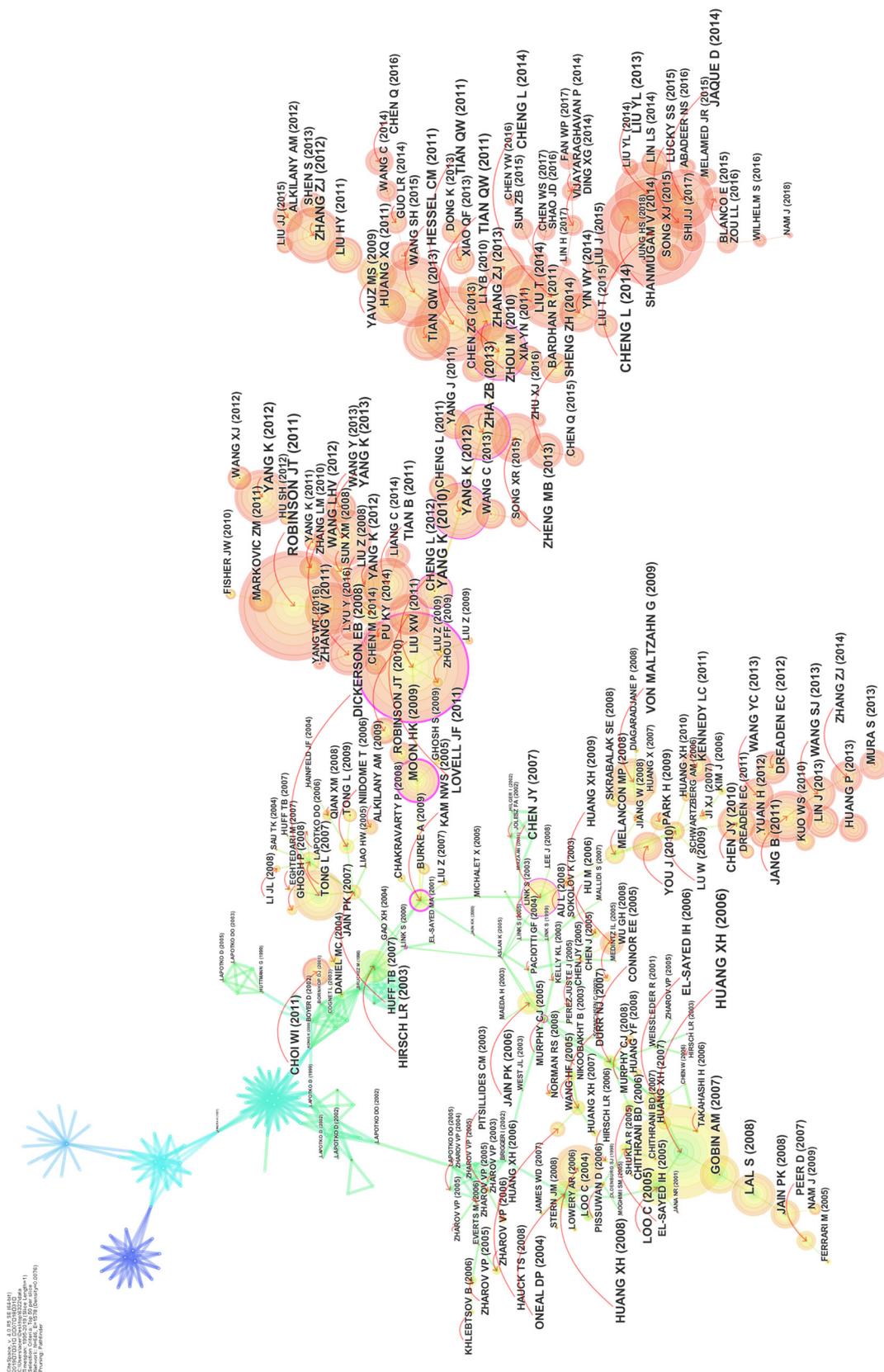


Figure 4 Co-cited references network of publications of photothermal therapy on cancer.

Table 2 The top 10 co-cited references of photothermal therapy on cancer

Authors	Years	Journal	Cited frequency	Title
Robinson (19)	2011	<i>J Am Chem Soc</i>	611	Ultrasmall reduced graphene oxide with high near-infrared absorbance for photothermal therapy
Yang (20)	2010	<i>Nano Lett</i>	604	Graphene in mice: ultrahigh <i>in vivo</i> tumor uptake and efficient photothermal therapy
Cheng (9)	2014	<i>Chem Rev</i>	595	Functional nanomaterials for phototherapies of cancer
Huang (21)	2006	<i>J Am Chem Soc</i>	532	Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods
Tian (22)	2011	<i>ACS Nano</i>	426	Hydrophilic Cu ₉ S ₅ nanocrystals: a photothermal agent with a 25.7% heat conversion efficiency for photothermal ablation of cancer cells <i>in vivo</i>
Hessel (23)	2011	<i>Nano Lett</i>	397	Copper selenide nanocrystals for photothermal therapy
Liu (24)	2013	<i>Adv Mater</i>	366	Dopamine-melanin colloidal nanospheres: an efficient near-infrared photothermal therapeutic agent for <i>in vivo</i> cancer therapy
Cheng (25)	2014	<i>Adv Mater</i>	365	PEGylated WS ₂ nanosheets as a multifunctional theranostic agent for <i>in vivo</i> dual-modal CT/photoacoustic imaging guided photothermal therapy
Jaque (10)	2014	<i>Nanoscale</i>	335	Nanoparticles for photothermal therapies
Yang (26)	2013	<i>Chem Soc Rev</i>	323	Nano-graphene in biomedicine: theranostic applications

[2007–2014], nanorod [2008–2012], tumor cell [2009–2012], photothermal cancer therapy [2009–2013], nanomaterial graphene [2009–2014], nanocage [2010–2014], multifunctional nanoparticle [2010–2014]. Since 2015, many researches in cancer photothermal therapy filed have focused on conversion efficiency [2015–2016] and guided photothermal therapy [2015–2019].

Discussion

In the present study, we used information visualization methods to analyze the publications of photothermal therapy on cancer between 1995 and 2019. The annual trends of publications of photothermal therapy on cancer (*Figure 1*) showed that there were more and more scientific research publications over the past 20+ years. Of note, publications increased rapidly after 2010. Before 2010, there were only 381 publications collectively in this field, accounting for 6.11% of the total number of publications. The reason of the above results was that the doctors firstly observed the beneficial effects of thermal therapy for the treatment of cancer in the 19th century (28). And photothermal therapy was firstly reported by professor Halas from Rice University in 2003, as a new therapy on cancer (29). We found that

photothermal therapy has become a subject of growing study and an increasingly important area of cancer research.

Secondly, we investigated the distribution of countries and institutions in this field. Based on the top 10 countries and institutes of publications of photothermal therapy on cancer (*Figures 2,3*), we identified that China contributed most to the number of articles on photothermal therapy and China was in a leading position in this field, followed by USA. The incidence and mortality of cancer have been increased rapidly year after year. Cancer incidence and mortality in China were the highest compared with other countries in the world. Therefore, it has made cancer the leading cause of death since 2010 and a major public health problem in China (3,30). From then on, China has to face huge challenges in managing the large and increasing burden of cancer. And China urgently requires concerted efforts and commitment from all levels of government and nongovernment organizations. Thus, more and more Chinese researchers focused on the cancer and cancer treatment research area.

Thirdly, the top 10 journals which published the greatest number of articles of photothermal therapy on cancer (*Table 1*) were mostly journals in material science and bioengineering, such as *ACS Appl Mater Interfaces*, *Nanoscale*,

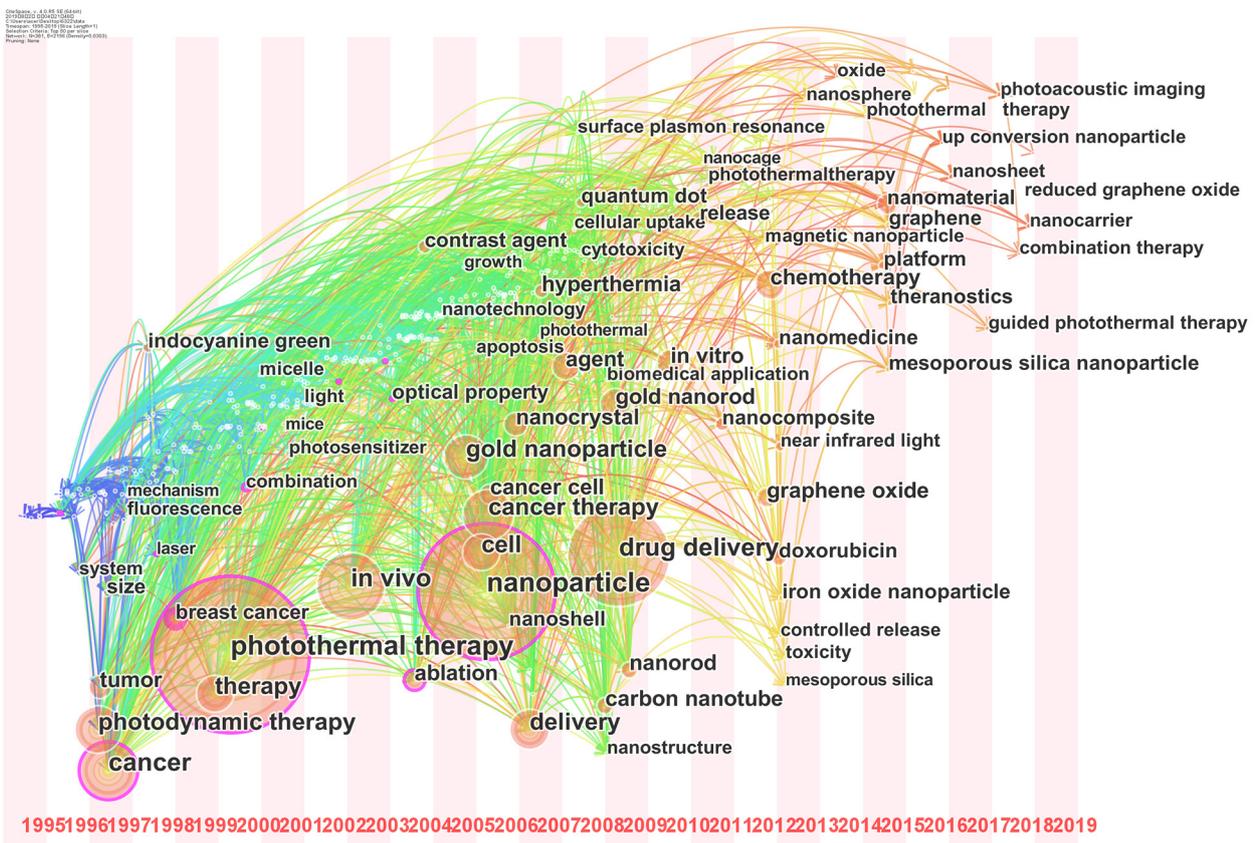


Figure 7 Co-occurrence keywords timezone view of publications of photothermal therapy on cancer.

Table 4 Keywords with more stronger citation bursts in articles of photothermal therapy on cancer published during 1995–2019

Keyword	Strength	Begin	End	1995–2019
Laser	18.0519	1997	2013	-----
Optical property	30.2728	2005	2014	-----
Gold nanoparticle	14.5017	2006	2014	-----
Nanoshell	40.0504	2006	2014	-----
Size	7.7664	2007	2011	-----
Metal nanoparticle	17.7269	2007	2013	-----
Shape	13.6039	2007	2014	-----
Nanorod	11.3306	2008	2012	-----
Tumor cell	13.7501	2009	2012	-----
Photothermal cancer therapy	14.8022	2009	2013	-----
Nanomaterial graphene	30.3168	2009	2014	-----
Nanocage	20.6233	2010	2014	-----
Multifunctional nanoparticle	8.0976	2010	2014	-----
Conversion efficiency	6.3367	2015	2016	-----
Guided photothermal therapy	6.2703	2016	2019	-----

and biocompatibility in 2011. Almost at the same time, Hessel *et al.* (23) found that Cu(2-x)Se nanocrystals as an photothermal therapy materials, could lead to the human colorectal cancer cell (HCT-116) destruction. And in November, 2011, Tian *et al.* (22) developed hydrophilic plate-like Cu₉S₅ nanocrystals as a new photothermal agent, and demonstrated that under the irradiation of 980 nm laser with the conservative and safe power density over a short period, the photothermal effects of the Cu₉S₅ NCs could efficiently kill cancer cells *in vivo*. After that, Liu *et al.* (24) investigated the dopamine-melanin colloidal nanospheres, as efficient near-infrared PTT materials for *in vivo* cancer treatment in 2013. Recently, Cheng *et al.* (25) developed a new photothermal theranostic agents, PEGylated WS2 nanosheets, which could completely ablate the tumors in 2014.

The remaining 3 co-cited references are reviews. Among them, two articles reviewed the present status of the use of nanoparticles for photothermal therapy in details, the advantages and disadvantages of the different heating nanoparticles were discussed (9,10). And the last one focused on nano-graphene in photothermal treatment, summarizing the latest progress in this rapidly growing field, discussing the future prospects and challenges of using graphene-based materials for theranostic applications (26). The above results suggested that the applications of nanomaterials in photothermal therapy, for example gold nanorods, nano-graphene and Cu(2-x) Se nanocrystals, etc., was burst and hot in this research field, all of which are identical with those conclusions of analyzing the journals.

Lastly, but most importantly, we analyzed the distribution of keywords in the field of photothermal therapy on cancer. To reflect hot topics, the high frequency co-occurrence keywords (Figure 5 and Table 3) and co-occurrence keywords clustered network (Figure 6) were analyzed. The results suggested that photothermal therapy as a new effective cancer treatment, its materials, especially nanomaterials, remained the hotspots in this research field. To explore frontier topics, we studied the co-occurrence keywords timezone view (Figure 7) and the keywords with more stronger citation bursts (Table 4). Photothermal therapy, in which nanomaterials embedded within tumors generate heat in response to exogenously applied laser light, has been well documented as an independent strategy for highly selective cancer treatment (31-33). Therefore, nanomaterials are always the hotspots and the frontier topics in this field. Different nanomaterials, like gold nanoparticle, nano-graphene and Cu(2-x) Se nanocrystals, etc, are widely used

in this field, including in the diagnosis, monitoring, and treatment of diseases. The shapes of the nanomaterials are varied, showing as nanoshell, nanoparticles, nanorub, nanocrystal and nanotube. And different shapes showed different properties in physical and chemical. Overall, these characteristics could make benefits to the photothermal therapy on cancer (34-36).

“Gold nanoparticle” was the keyword with strongest citation bursts. Gold nanoparticles were the main agent used in photothermal therapy because the following reasons. First, they have good biocompatibility and efficient light-to-heat conversion. Next, they are tuned to absorb near-infrared light, which penetrates tissue more deeply than other wavelengths of light. Again, they offer simple gold-thiol bioconjugation chemistry for the attachment of desired molecules. Finally, they exist small diameters that enable tumor penetration upon systemic delivery (31,37,38).

Another keyword was the nanomaterial graphene, which is a hot study in photothermal therapy. Graphene and its derivatives exhibit unique physical and chemical properties, hence they are useful vehicles for photothermal therapy-based cancer treatment, including enhancement of multimodalities, guided imaging, enhanced chemotherapy and low-power efficient photothermal therapy for optimum therapeutic efficiency. Graphene-based nanomaterials, with NIR absorption properties, can provide successful thermal ablation in cancer cells. In the recent years, advances in graphene-based photothermal therapy have produced efficient and efficacious tumor inhibition via nanomaterial structural design and different functionalization of graphene-derived nanocomposites (19,39-41).

Of note, we found that photothermal therapy is mostly applied in epidermic tumors, such as breast cancer and skin tumors, due to the poor penetration ability of the infrared light. As a result, there is a lack of researches for treatment of solid tumors in the deep layers of the body using photothermal therapy, which needs to be deeply studied in the future.

From 2015 onwards, the investigation of carrier materials to guide photothermal therapy and the development of materials were concerned, by analyzing the keywords “guided photothermal therapy” and “conversion efficiency”. Conversing more efficiency from exogenously applied laser light have been become the frontier topics in this field. We predict the photothermal therapy will be frequently employed in cancer treatment, not only for treating superficial tumors, such as breast cancer, but also for treating other solid tumor. Researchers should pay more attention on surmounting the defects of current photothermal therapy, developing better

materials applied in photothermal therapy to treat cancers.

Conclusions

There is no doubt that photothermal therapy on cancer has significantly advanced over the past 20+ years. With the help of information visualization, we were able to identify research foci and overall trends in the field. The results of our study could offer gathered information for future research. The development of better materials, applied in photothermal therapy to destroy cancer cells targetingly and effectively, is always the foci in this research field in present and in future. However, the side effects and cell toxicity of the materials should be pay more attention when using the materials in humans (15,16).

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-2961>). The authors have no conflicts of interest to declare.

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

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