The trends of uveal melanoma research in the past two decades and future perspectives.

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Research Article

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Abstract

PURPOSE Evaluation of the research trends in uveal melanoma in the past two decades.

METHODS Data were extracted from the Web of Science database website. VOSviewer and Citespace software were used to analyze the retrieved data.

RESULTS The leading country in terms of output and international collaboration is the United States. Research interest in genetic mutations, molecular pathways, and immunotherapy was remarkable in recent years. Most of the top ten journals are specialized in ophthalmology. In recent years the hotspots include future perspectives, BAB1 mutation, therapeutic target, and systematic reviews. The keywords with the strongest citation bursts are immunotherapy, outcome, and in situ hybridization.

CONCLUSION The output of uveal melanoma research increased during the past two decades. Future research foci may include exploring different mutations role, immunotherapy, molecular alterations, and finding ideal clinical biomarkers.

1. Introduction

The uveal tract structure includes the choroid, iris, and ciliary body. The melanoma of this structure is the most common intraocular malignancy in adults [1, 2]. The treatment options include local control using brachytherapy, surgical resection, or enucleation [3]. However, half of the uveal melanoma cases result in liver metastasis, which is associated with short survival [4]. The genetic and molecular alterations have a role in drive prognosis determination [5, 6]. In recent years many efforts have been directed toward examining the effectiveness of targeted therapy and immunotherapy on uveal melanoma metastasis with a view to improving survival [7, 8]. We tried to identify the change in research trends in uveal melanoma in the past two decades and to elaborate on future perspectives. Bibliometric indicators are useful in identifying the hotspots and researchers' output on a particular topic [9, 10]. Thus, our study using bibliometric tools aimed to identify the hotspots, future perspectives, changing trends, and the intellectual explain of these changes. This study also aimed to identify the countries' collaboration, the top-cited articles, the top journals, and the top institutes, as well as the keywords with the highest citations bursts in this topic.

2. Methods And Materials

The data have been extracted from the Web of Science database (Science Citation Index Expanded) on the 3rd of July 2020. We restricted documents type to articles and reviews. We restricted the results to the English language. We searched for topic terms in the title, abstract, and keywords fields within a record. The following terms were used: uveal melanoma or choroidal melanoma or ciliary body melanoma or iris melanoma or melanoma of the uvea or melanoma of the choroid or melanoma of the iris or melanoma of the ciliary body. The selected period was from 2000–2019. Full records and cited references were exported for the aim of analysis. The first two authors have run the same search plan independently to

make sure the outputs are uniform. We used the Citespace (version 5.6.R5) to identify the keywords that have strong citation burst in recent years. We selected the following parameters; term source from all options, the period was from 2000–2019, node type was the reference, selection criteria were the top 35 levels of most cited items from each slice, pathfinder pruning, and a static cluster visualization, log-likelihood test scoring was used for cluster labeling. We identified the keywords clusters through the VOSviewer (version 1.6.15) analysis of (keywords plus), using a full counting method. We prepared the network and overlay visualization maps for the aim of presentation and analysis. Because we are interested in recent years' trends, we selected the time period between 2011 and 2019 for the keyword burst detection, and selection criteria were the top 50 levels of most cited items for each slice. A fractional counting method was adopted in the analysis of countries' collaboration and keywords co-occurrence ranking. No ethical approval was needed because we used a public database (Web of Science) in our study.

3. Results

The results indicate that there are 3806 published papers on uveal melanoma during the period from (2000–2019). Its h-index was high (116), and the average citations per item were (25.42). There is a significant increase in publication with time. The year with the highest number of publications was 2019, with (322) documents. The pattern of publications count per year for the last two decades is shown in [Fig. 1].

3.1 Countries' productivity and collaboration in uveal melanoma research

The total number of countries that participated in uveal melanoma research is 66. The most productive country in uveal melanoma research is the United States, which accounted for 43% of all publications. The total number of its documents and counted citations is 1639 and 54007, respectively. The next two countries in productivity are Germany and England with (387 documents; 11658 citations), and (336 documents; 10004 citations), respectively. To evaluate countries' collaboration, we performed a fractional counting analysis of 39 countries, each of which contributed to 10 documents or more. The USA accounted for the highest total link strength and links count. It has been the common factor in all of the strongest eight collaboration links between countries. The strongest three links in addition to the USA involve England, PRC, and Germany, in descending order. According to the overlay map analysis, the average publication year for all countries ranges from (2009 to 2015.4), and the average is (2012). The average publication year for PRC is (2015.4), which indicates a prominent increase in the productivity of this country in recent years. The network and overlay visualization maps are shown in [Fig. 2].

3.2 Top journals, institutes, and authors in uveal melanoma research

The number of journals that participated in uveal melanoma research output was 688. The top ten active journals that participated in 30% of all total output and their impact factors are shown in [Table 1]. Investigative Ophthalmology Visual Science is the leading journals with the highest number of published documents (221) and total citations count (7534). Followed by British Journal of Ophthalmology with

(141) documents and (2752) total citations count.Thomas Jefferson University is the leading institute in terms of both documents (203) and citations count (6362). The second and third institutes are Leiden University (149 documents, 3699 citations) and the University of California San Francisco (92 documents, 4820 citations), respectively. The top ten active institutes that participated in 27% of all documents are also shown in [Table 1]. The geographical distribution of these institutes includes the United States, Netherlands, England, and France. Half of them are located in the United States.

The top author in terms of publications count is Shields CL, with 178 published documents. Shields JA and Damato B are the following two authors with 146 and 112 published documents, respectively. In terms of citation count, Shields CL also ranked the first with 5320 total citations count and is followed by Harbour JW and Shields JA with 4845 and 4840 total citations count, respectively. Of the top ten authors in terms of citations count, only two are from European countries, and the rest of them are from the United States. The top ten authors in terms of both citations and publications count are listed in [Table 2].

3.3 The top-cited articles and co-cited references in uveal melanoma research

To identify the hotspots in uveal melanoma research, we analyzed the co-cited references using Citespace software. The top sixteen clusters and co-cited articles are shown in [Fig. 3]. The modularity Q is 0.90, and the mean silhouette is 0.46. However, the mean silhouette of these top clusters is 0.94, indicating highly consistent contents of the cluster [11]. The largest cluster is labeled by #0 future prospective. Other main hotspots are #1 systematic review, #2 BRAF mutation, #3 BAB1 germline mutation, #4 and recurrent cancer, etc. The Mean year of the publication of the articles in the clusters designated by yellow color (#0,#1,#3,#7) ranges from (2013–2017), mean year of clusters designated by orange color (#5,#10,#11) ranges from (2010–2011), mean year of clusters designated by pink color (the rest of clusters) ranges from (2001–2008). The most cited article is about the GNAQ mutation in uveal melanoma, published in 2009, and has been cited 875 times [12]. The second most cited article is about the Hippo Pathway role, published in 2015, and has been cited 779 times [13]. The top-cited articles in uveal melanoma are shown in [Table 3].

3.4 Keyword burst detection and analysis

We identified the top 37 keywords with the strongest citation burst in recent years. The keyword "immunotherapy" has the strongest citation burst. The keywords with the strongest citations burst before 2015 are in situ hybridization, retinoblastoma, angiogenesis, and chromosome 3. The keywords with the strongest citations burst since 2015 are: immunotherapy, outcome, and gene expression. The keywords list is shown in [Fig. 4]. Of the 6002 keywords used in uveal melanoma research, 392 keywords occurred 12 times on a minimum. Seven clusters of keywords have been identified. The network and overlay visualization maps are presented in [Fig. 5]. The first cluster in yellow color is about mutations. The second cluster in light blue color is about chromosome 3 status and includes the keywords: monosomy-3, chromosome 3 status, gains, losses, gene expression profile, classification, needle aspiration biopsy, DNA, assay, microsatellite analysis, in situ hybridization, and pathology, prognosis and predicts. The third cluster in red color is about molecular alterations. The keywords in order of occurrence frequency are:

expression, cancer, metastasis, cells, growth, activation, breast cancer, progression, identification, apoptosis, and angiogenesis, etc. The fourth cluster in orange color is about immunotherapy includes the keywords: Ipilimumab, Nivolumab, Pembrolizumab, immunotherapy, efficacy, safety, responses, patient, and quality of life. The fifth cluster in green color is about management. The sixth cluster in dark blue color is about epidemiology, it comprises the keywords: tumors, risk factors, risk, United States, sun exposure, prevalence, ciliary body melanoma, iris melanoma, nevus, lesion, oculocuatneous melanoma, host factors, population, features, and epidemiological aspects. The last cluster in purple is about survival and encompasses the keywords: survival, liver metastasis, prognostic factors, and chemotherapy.

4. Discussion

The research output in uveal melanoma has increased in the past twenty years. The United States is the most productive country in uveal melanoma research and participated in nearly half of all publications. The United States is also distinguished by strong international collaboration. While the productivity of the PRC has been increased in recent years, it's still less than Germany and England, ranking the fourth on the publications count list. The Investigative Ophthalmology Visual Science journal and the British Journal of Ophthalmology are the leading journals and have published the highest number of related documents. Knowing the specialized journals in this topic is informative for authors, particularly in deciding where to submit articles. Most of the leading journals in this topic are specialized in ophthalmology, and only two of them are specialized in oncology. Thomas Jefferson University is the most active institute in this regard, which, as well as most of the top ten are located in the United States. Consistently, most of the top authors are from the United States. The top one is Shields CL, who has published the highest number of documents on uveal melanoma.

Based on the analysis of co-cited references and keywords citations burst, there is a change of research interest from studying radiation therapy and chromosomes abnormalities in the early years of the past two decades toward studying genetic mutations and immunotherapy outcomes in recent years. The main recent research themes are about therapeutic targets efficacy in the uveal melanoma treatment, BAB1 mutation role, future prospect, and systematic reviews. The older themes are about the whole-body positron emission, tumor cell plasticity, radiation therapy, and BRAF mutation.

The keyword burst detection is a useful bibliometric tool to identify research hotspot areas in a particular topic [22]. Therefore, we identified the keywords with the strongest citation burst in uveal melanoma research. The keyword "immunotherapy" achieved the strongest citation burst. There is a recent research attraction to themes of immunotherapy agents like (Pembrolizumab and Ipilimumab) and mutations like (GNA11 and BAB1).In comparison, before the year 2015, the keywords with the strongest burst were related mainly to carcinogenesis, therapy, and chromosome 3 status themes.

The first keywords cluster gathered those related to somatic mutations. The genetic mutational profile in uveal melanoma is different from other types of melanoma. A well-known one of these mutations is the

(BAP1) that is associated with a high potential of malignancy. Other mutations include GNAQ, GNA11, EIF1AX, and SF3B1 have received great attention in recent years. The first two are associated with the initiation and progression of uveal melanoma [23]. While that, the SF3B1 mutation is characterized primarily by being associated with the risk of metastasis. Though, the potential risk for metastasis is lower with SF3B1 mutation than for BAP1 mutation [24]. In the circle of this cluster, we also found several keywords related to somatic mutations, including (BRCA1, TERT promoter, NRAS, BRAF, and KIT). However, the last three have been identified in cutaneous rather than uveal melanomas [25].

In the second cluster, three elements of keywords were found: (1) chromosome 3, (2) classification, and (3) prognosis. These elements are closely related, as the microsatellite analyses and pathology examinations have been used to determine the classification and prognosis in a precise manner [26]. There are several chromosomes in which abnormalities, losses, or gains are associated with an increased risk of metastasis. Chromosome 3 abnormalities can be useful in prognosis prediction [27]. Structural abnormalities of chromosomes 6, 8, and 11 also play a role in the uveal melanoma oncogenesis [28]. Unfortunately, the probability of metastasis is high in uveal melanoma patients, reaching about 50 % [29]. However, this analysis indicates that there is still a quest to find an effective drug that can improve the survival rate in uveal melanoma patients.

The third and the largest cluster gathering keywords related to cellular pathways and inflammatory cells involved in molecular alterations. The role of encountered immune cells such as (T-cells, lymphocytes, tumor-infiltrating lymphocytes, macrophages, and melanocytes) and cytokines such as (VEGF) in tumor promotion had been studied extensively. Unfortunately, they are associated with a bad prognosis in uveal melanoma [30]. Epithelial-mesenchymal transition (EMT) program and its role in uveal melanoma have got a focus of attention in recent years as turned out by the overlay map analysis. Although the role of this program has been known for a long time in the development of several tumors, it has recently emerged in the research of uveal melanoma. Research indicates that EMT transcription factors like ZEB1 are overexpressed in uveal melanoma cell lines and associated with a higher risk of metastasis. Downregulation of these factors is thought to be a potential treatment target [31].

The need for a non-invasive method for prognosis determination encourages scientists to find ideal biomarkers. Recently several biomarkers have been examined, including ME20-S serum level, microRNAs, exosomes, circulating tumor DNA, and circulating tumor cells [32–34]. The analysis of the overlay visualization map showed that the average publication year for biomarker keyword was in 2016. Thus this indicates an increasing interest in this field recently, comparing to other keywords with the same occurrence frequency.

Due to the role of inflammatory processes in uveal melanoma, it is not surprising that we found research interest in immunotherapy such as (Ipilimumab), (Nivolumab) and (Pembrolizumab), as shown in the overlay map analysis. Given the side effects of these drugs, the search on the (1) *efficacy*, the (2) identification of *suitable patients* to receive these drugs, and (3) finding *alternatives* that are associated with fewer complications is still under development. These novel immunotherapy agents thought to have

marginal benefits in selected patients [35, 36]. However, contrary to cutaneous melanoma, there are no randomized clinical trials in uveal melanoma that have approved the benefit of these agents.

The mainstay of management includes radiotherapy options, surgical resection or enucleation. They have represented by large nodes in the network visualization maps because they had occurred a lot. The American Association of Physicists in Medicine (AAPM) guidelines emerged in the arena of uveal melanoma management recently and are getting focus of attention in recent years [37]. Most of the publications that are concerned with the role of Bevacizumab and the outcome of agents have been published in the past decade. The previously mentioned observation is obtainable from the overlay visualization map and keywords burst detection.

Some of the keywords that have been represented by large nodes in the epidemiology cluster are risk factors, sun exposure, and the United States. Several studies indicate that sun exposure is not a significant risk factor for uveal melanoma. On the other hand, they found that ethnicity is the most important factor [38–40]. The high output of uveal melanoma research in the United States and Europe may be attributed in some way to the incidence variation of uveal melanoma between ethnic groups. "Survival" is represented by the largest node in the seventh cluster. Ample studies evaluated the benefit of chemotherapy agents such as Dacarbazine, Cisplatin. However, none have been approved to improve the survival rate, which has been stable for decades [41].

Our study's limitations include the adoption of a single database (Web of Science) in data extraction, which is a common practice in bibliometric studies [42–44]. The other limitation is the due acquisition of only English written articles. However, more than (95 %) of all uveal melanoma articles are in the English language. A third limitation is that only articles published between the years (2000 and 2019) were included, while those older articles were excluded.

5. Conclusion

In view of the above, the research trends are changing with time. We expect that research on immunotherapy, biomarkers, and genetic alterations of uveal melanoma will continue to expand in the coming years. Up to our knowledge, this is the first bibliometric analysis of uveal melanoma research. Future analyses can rely on this study to explore the change in research hotspots and output.

Declarations

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Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

[Table 1] T**he top 10 journals and institutes in the research field of uveal melanoma.**

Journal	Documents, (%)	Impact Factor* (2019)	Institute	Count, (%)	Country
Investigative halmology Visual Science	221,(5.8)	3.47	Thomas Jefferson University	203, (5.3)	USA
itish Journal Of phthalmology	141,(3.7)	3.61	Leiden University	153, (4.0)	Netherlands
anoma Research	134,(3.5)	2.75	Royal Liverpool University Hosp	93, (2.4)	England
phthalmology	130,(3.4)	8.47	University of California San Francisco	92, (2.42)	USA
erican Journal Of phthalmology	103,(2.7)	4.01	Memorial Sloan Kettering Cancer Center	89, (2.34)	USA
Archives Of phthalmology	96,(2.5)	4.40	University of Liverpool	87, (2.29)	England
ıa The Journal Of ıal And Vitreous Diseases	(2.4),93	3.65	Harvard University	80, (2.1)	USA
efes Archive For Clinical And Experimental phthalmology	80,(2.1)	2.40	Institut Curie	75, (1.97)	France
rnational Journal adiation Oncology iology Physics	71,(1.9)	5.86	University of Texas MD Anderson Cancer Center	71, (1.87)	USA
Plos One	67,(1.8)	2.74	Washington University	68, (1.79)	USA

Data are from the **2019 edition of Journal Citation Reports.*

[Table 2]**Top ten authors in uveal melanoma research.**

Rank	Author	Citations	H-index	Country	Author	(%) ,Documents count
1	Shields CL	5320	73	USA	Shields CL	(4.68) ,178
2	Harbour JW	4845	7	USA	Shields JA	(3.83) ,146
3	Shields JA	4840	67	USA	Damato B	(2.99) ,112
4	Bastian BC	3545	62	USA	Jager MJ	(2.89) ,110
5	Damato B	3456	41	England	Singh AD	(2.23), 85
6	Worley LA	2940	22	USA	Harbour JW	(2.04) ,77
7	Jager MJ	2918	37	Netherlands	Coupland SE	(1.81) ,69
8	Singh AD	2757	18	USA	Finger PT	(1.76) ,67
9	Onken MD	2465	24	USA	Luyten GPM	(1.55) ,59
10	Hendrix M	2259	75	USA	Pe'er J	(1.42) ,54

[Table 3] **The most cited articles in uveal melanoma research.**

Title	1st Author	Journal Title	Publication Year	Total Citations	Average per Year
quent somatic mutations GNAQ in uveal melanoma and blue naevi[12]	Van Raamsdonk, Catherine D.;	Nature	2009	857	71.42
ippo Pathway in Organ Size Control, Tissue neostasis, and Cancer[13]	Yu, Fa-Xing;	Cell	2015	779	129.83
Mutations in GNA11 in Uveal Melanoma[14].	Van Raamsdonk, Catherine D.;	New England Journal Of Medicine	2010	764	69.45
quent Mutation of BAP1 n Metastasizing Uveal Melanomas[15]	Harbour, J. William;	Science	2010	736	66.91
sculogenic mimicry and tumour-cell plasticity: sons from melanoma[16]	Hendrix, MJC;	Nature Reviews Cancer	2003	584	32.44
elatonin - Nature's most rsatile biological signal? [17]	Pandi-Perumal, S. R.;	Febs Journal	2006	554	36.93
rmline BAP1 mutations redispose to malignant mesothelioma[18]	Testa, Joseph R.;	Nature Genetics	2011	543	54.3
sculogenic mimicry and umor angiogenesis[19]	Folberg, R;	American Journal Of Pathology	2000	484	23.05
urvey of 1264 patients ith orbital tumors and mulating lesions - The 02 Montgomery Lecture, Part 1[20]	Shields, JA;	Ophthalmology	2004	481	28.29
nase I pharmacokinetic pharmacodynamic study the oral, small-molecule togen-activated protein ase kinase 1/2 inhibitor 06244 (ARRY-142886) in atients with advanced cancers[21]	Adjei, Alex A.;	Journal Of Clinical Oncology	2008	455	35

Figures

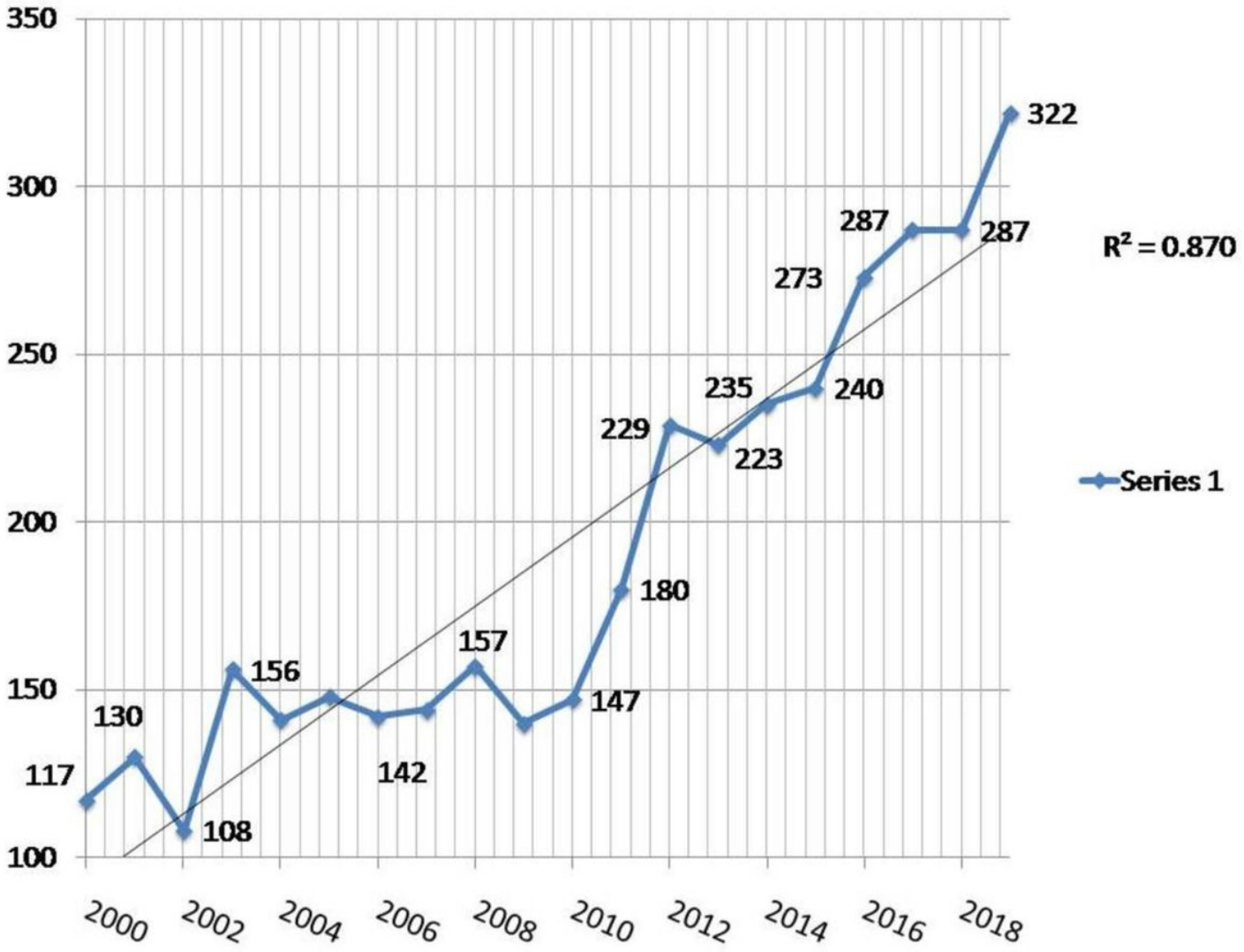

Figure 1

Publications count per year. Highest number of publication was in 2019 (322 articles). Number of published articles per year was increasing with time. The value of R2, the coefficient of determination, is 0.8703. The P-Value is < .00001. The result is statistical significant at p < .05.

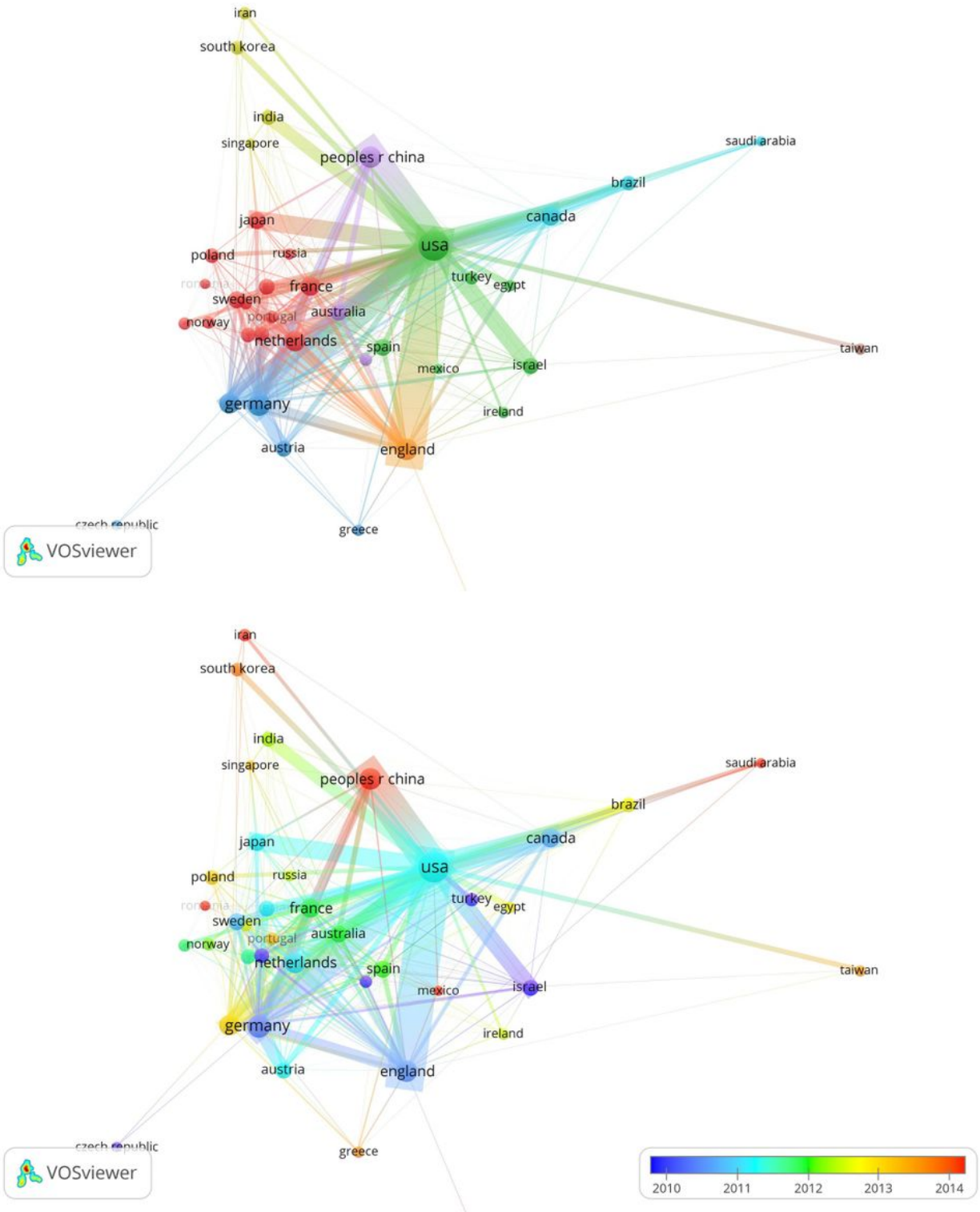

Figure 2

The network and overlay visualization maps for the countries colla boration in uveal melanoma research. In the network map larger nodes indicates higher total link strength, wider link indicates stronger link between two countries, each cluster of co-authorship coded by a color. In the overlay map the warm color indicates that average publication year is 2014, and the cold color indicates that average publication year is 2010.

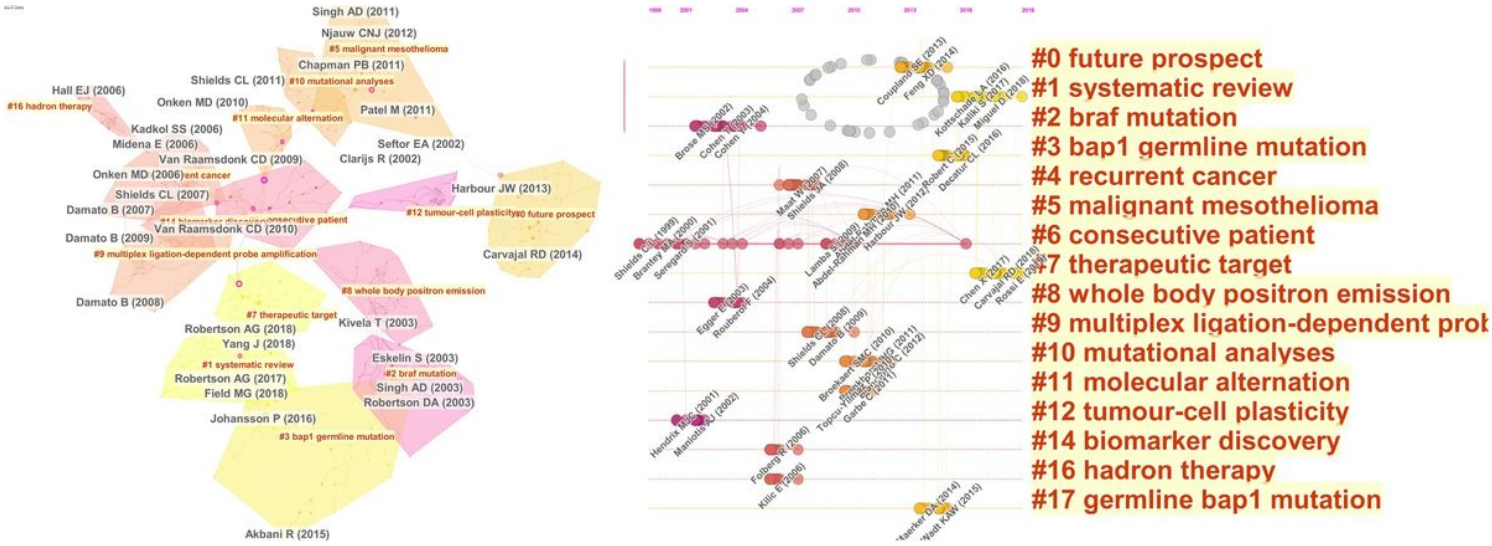

Figure 3

The top hotspots and co-cited references. The top 16 hotspots in the uveal melanoma research. The Mean year of the publication of the articles in the clusters designated by yellow color (#0,#1,#3,#7) ranges from (2013-2017), mean year of clusters designated by orange color (#5,#10,#11) ranges from (2010-2011), mean year of clusters designated by pink color (the rest of clusters) ranges from (2001-2008).

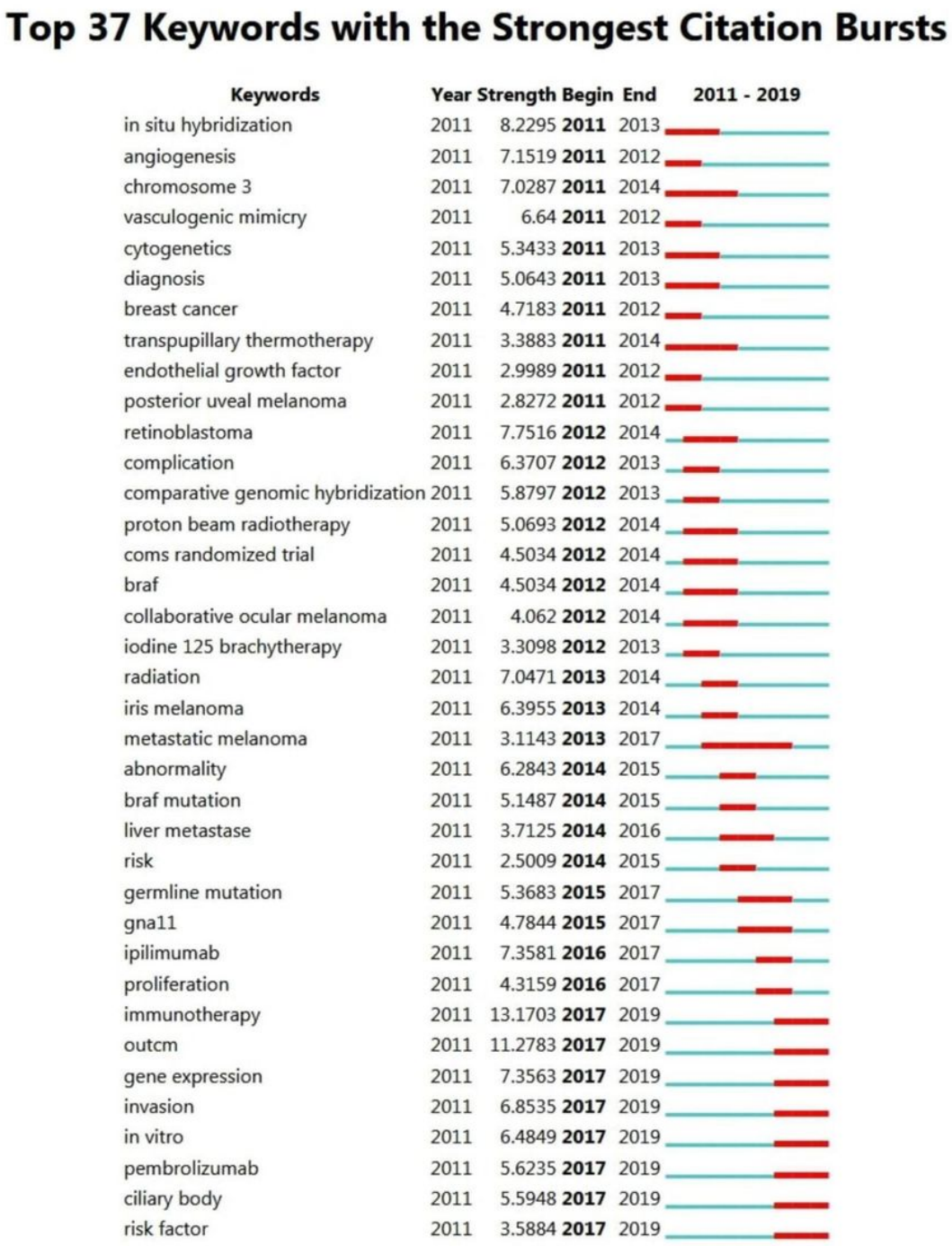

Figure 4

The top keywords with the strongest citation bursts.

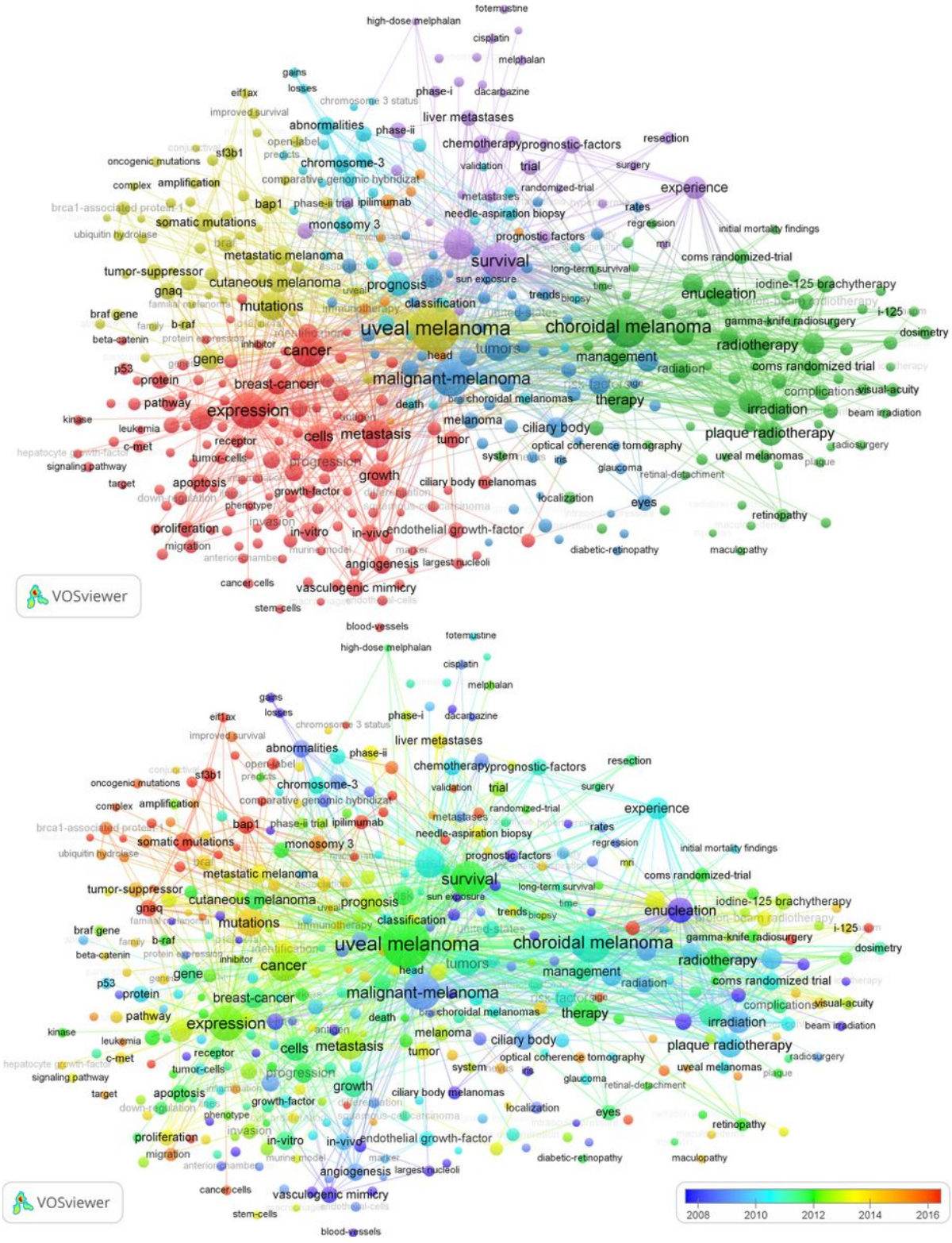

Figure 5

The network and overlay visualization maps of the highly co-occurred keywords in the uveal melanoma research. Seven clusters of keywords, each designated by a color. Labels with red color indicate that the average publication year is 2016; labels with dark blue color indicate that the average publication year is 2008. The size of the node represents a positive relationship with the occurrence count. A larger node indicates higher times of occurrence.